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(54) Title: USES OF PROTEIN TYROSINE PHOSPHATASE RECEPTOR KAPPA INHIBITORS

(57) Abstract: This application discloses Protein Tyrosine Phosphatase Receptor Kappa (PTPRK) inhibitors for use in medicine, in particular for use in the treatment and/or prevention of a condition selected from the group consisting of overweight, obesity, hyperglycaemia, diabetes, hyperlipidaemia, a non-alcoholic fatty liver disease (NAFLD), hepatocellular carcinoma, and combinations thereof. Also disclosed is a pharmaceutical composition comprising a PTPRK inhibitor or a combination of PTPRK inhibitors for use in the treatment and/or prevention of a condition selected from the group consisting of overweight, obesity, hyperglycaemia, diabetes, hyperlipidaemia, a non-alcoholic fatty liver disease (NAFLD), hepatocellular carcinoma, and combinations thereof.

USES OF PROTEIN TYROSINE PHOSPHATASE RECEPTOR KAPPA INHIBITORS

FIELD OF THE INVENTION

The invention is broadly in the medical field, particularly in the fields of treatment or prevention of obesity, hyperglycaemia, diabetes, hyperlipidaemia, non-alcoholic fatty liver diseases, hepatocellular carcinoma and combinations thereof, as well as in the field of non-therapeutic methods to control certain aspects of body physiology.

BACKGROUND OF THE INVENTION

The rapid transition of modern lifestyle in human societies presents a chronic challenge to the ancestral mechanisms employed by the cells to adapt to excessive availability of energy-dense nutrients. The alarming prevalence of overweight and obesity, effecting more than 1.9 billion individuals worldwide, severely impact on metabolic homeostasis. The consumption of highly processed industrialized foods with high caloric density, coupled with reduced energy expenditure due to sedentary behaviours, leads to a state of nutrient and energy overload. In response to this excess energy, cells adapt by storing energy mainly in the form of triglycerides, resulting in the expansion of adipose tissues and ectopic fat deposition in organs such as muscles and the liver. The presence of a lipid-rich environment in these organs gives rise to deleterious pathological consequences, comprising insulin resistance, dyslipidemia, non-alcoholic fatty liver disease (NAFLD), and a spectrum of malignancies intrinsically linked to obesity.

Obesity-associated health implications, such as NAFLD and hepatocellular carcinoma (HCC), have become major concerns. NAFLD, currently also known as metabolic dysfunction-associated steatotic liver disease (MASLD) has emerged as the leading cause of HCC, a highly heterogeneous and aggressive malignancy. HCC accounts for 90% of primary liver cancers and is refractory to nearly all currently available anti-cancer therapies with a 5-year survival rate of nearly 15%. Over the last 20 years, the incidence of HCC has been rapidly increasing in economically developed nations and is mostly attributable to hepatitis C virus (HCV), alcoholic, and non-alcoholic fatty liver disease (NAFLD).

The hallmark of NAFLD is the accumulation of fat in hepatocytes. Indeed, the main risk factors of NAFLD are obesity and type-2 diabetes (steatosis occurs in >75% of all obese individuals and prevalence increases by a factor 4.6 if BMI $\geq$ 30 kg/m^2) which can progress to fibrosis, cirrhosis, non-alcoholic steatohepatitis (NASH; currently also known as metabolic dysfunction-associated steatohepatitis, MASH) and HCC. There are ~1.6 billion overweight adults (BMI>25 kg/m^2) worldwide of whom > 650 million are obese (BMI>30 kg/m^2). This is predicted to rise in the near future and to be

largely unabated by lifestyle intervention (WHO). Obesity is associated with a state of chronic low-grade inflammation.

Hepatic expression of protein tyrosine phosphatases (PTPs) is affected in steatotic livers and NASH. PTPs were conventionally perceived as effectors responsible for terminating or modulating signals initiated by tyrosine kinases but accumulating evidence reveals their potential as propagators of signals themselves. For example, it was previously shown that non-receptor type protein tyrosine phosphatase 2 (PTPN2) facilitates signaling through both STAT1 and STAT3, exerting different influences on NASH and HCC development (Grohmann et al., Cell 2018, 175: 1289-1306). Also oxidative inactivation of PTPN2 was shown to activate the insulin-STAT5-IGF-1-GH pathway in a condition of insulin resistance, contributing to obesity progression in high-fat-fed mice (Gurzov et al., Cell Metab. 2014, 20: 85-102).

Receptor-type protein tyrosine phosphatases (RPTPs or PTPRs) represent a subclass of transmembrane proteins among the classical PTPs. RPTPs are distinguished by the features of their extracellular domains, adapted to detect and transduce extracellular sensing into intracellular catalytic events. It has been demonstrated that expression of PTPRG is induced by inflammatory signalling and upregulated in obesity. PTPRG deletion enhances hepatic insulin sensitivity, while hepatic overexpression of PTPRG induces insulin resistance in mice (Brenachot et al., Nat Commun. 2017, 8(1)). Nevertheless, the role of other PTPRs in metabolic diseases or liver diseases is currently unknown.

SUMMARY

The present invention is at least in part based on the inventor's discovery that protein tyrosine phosphatase receptor kappa (PTPRK) is increased in humans and mice with liver steatosis and non-alcoholic steatohepatitis and positively correlates with PPARγ-induced lipogenic signalling. The inventors further demonstrate that absence of PTPRK in mice reduces fat accumulation in adipose tissue and liver after obesogenic diet feeding, whereas overexpression of PTPRK increases glycolytic capacity in mouse hepatocytes. Finally, treatment with PTPRK inhibitors resulted in reduced body weight, reduced liver fat and reduced glucose levels in mice that are on obesogenic diet.

Accordingly, an aspect of the invention provides a PTPRK inhibitor for use in the treatment and/or prevention of a condition selected from the group consisting of overweight, obesity, hyperglycaemia, diabetes, hyperlipidaemia, a non-alcoholic fatty liver disease (NAFLD), hepatocellular carcinoma, and combinations thereof in a subject. In certain embodiments the therapy and/or prevention may employ a combination of PTPRK inhibitors.

A further aspect provides the non-therapeutic use of a PTPRK inhibitor for reduction of body weight, blood glucose level, blood lipid levels, or a combination thereof, in a subject; preferably for reduction

of body weight in a subject. In certain embodiments, the non-therapeutic use may employ a combination of PTPRK inhibitors.

A further aspect provides a pharmaceutical composition comprising a PTPRK inhibitor or a combination of PTPRK inhibitors for use in the treatment and/or prevention of a condition selected from the group consisting of overweight, obesity, hyperglycemia, diabetes, hyperlipidaemia, a non-alcoholic fatty liver disease (NAFLD), hepatocellular carcinoma, and combinations thereof in a subject.

Another aspect provides a method of preventing and/or treating a condition selected from the group consisting of overweight, obesity, hyperglycaemia, diabetes, hyperlipidaemia, a non-alcoholic fatty liver disease (NAFLD), hepatocellular carcinoma, and combinations thereof in a subject in need of such treatment, comprising administering to said subject a therapeutically or prophylactically effective amount of a PTPRK inhibitor or a pharmaceutical composition comprising a PTPRK inhibitor. In certain embodiments, a combination of PTPRK inhibitors or a pharmaceutical composition comprising a combination of PTPRK inhibitors may be administered.

A further aspect provides a non-therapeutic method for the reduction of body weight, blood glucose level, blood lipid levels or a combination thereof in a subject; preferably for reduction of body weight in a subject, wherein said method includes administering to said subject in need for such reduction a PTPRK inhibitor as disclosed herein to said subject. In certain embodiments, a combination of PTPRK inhibitors as disclosed herein may be administered.

In some embodiments, the PTPRK inhibitor is a compound of formula I or formula II, or a stereoisomer, enantiomer, tautomer, solvate, hydrate, pharmaceutically acceptable salt, or prodrug thereof, as taught elsewhere in this specification. In some embodiments, the PTPRK inhibitor as disclosed herein is a compound of formula III or formula IV or a stereoisomer, enantiomer, tautomer, solvate, hydrate, pharmaceutically acceptable salt, or prodrug thereof, as taught elsewhere in this specification. In some embodiments, the PTPRK inhibitor as disclosed herein is a compound of formula III. In some embodiments, the PTPRK inhibitor as disclosed herein is a compound of formula IV.

Another aspect of the invention provides a PTPRK inhibitor for use in medicine. In certain embodiments the invention provides a PTPRK inhibitor for use in medicine, wherein the inhibitor is a compound of formula I, formula II or a stereoisomer, enantiomer, tautomer, solvate, hydrate, pharmaceutically acceptable salt, or prodrug thereof, as taught elsewhere in this specification. In some embodiments, the invention provides a PTPRK inhibitor for use in medicine wherein the inhibitor is a compound of formula III, formula IV or a stereoisomer, enantiomer, tautomer, solvate, hydrate, pharmaceutically acceptable salt, or prodrug thereof, as taught elsewhere in this specification.

In a further aspect, a combination of a PTPRK inhibitor that is a compound of formula III, or a stereoisomer, enantiomer, tautomer, solvate, hydrate, pharmaceutically acceptable salt, or prodrug

thereof and a PTPRK inhibitor that is a compound of formula IV or a stereoisomer, enantiomer, tautomer, solvate, hydrate, pharmaceutically acceptable salt, or prodrug thereof, is provided.

Another aspect provides a method of preventing and/or treating a condition selected from the group consisting of overweight, obesity, hyperglycaemia, diabetes, hyperlipidaemia, a non-alcoholic fatty liver disease (NAFLD), hepatocellular carcinoma, and combinations thereof in a subject in need of such treatment, comprising administering to said subject a therapeutically or prophylactically effective amount of a PTPRK inhibitor, a combination of PTPRK inhibitors, or a pharmaceutical composition as disclosed herein.

A related aspect relates to the use of a PTPRK inhibitor, or a combination of PTPRK inhibitors as disclosed herein for the manufacture of a medicament for the treatment of a condition selected from the group consisting of overweight, obesity, hyperglycaemia, diabetes, hyperlipidaemia, a non-alcoholic fatty liver disease (NAFLD), hepatocellular carcinoma, and combinations thereof.

A related aspect relates to use of a PTPRK inhibitor, or a combination of PTPRK inhibitors as disclosed herein for the treatment of a condition selected from the group consisting of overweight, obesity, hyperglycaemia, diabetes, hyperlipidaemia, a non-alcoholic fatty liver disease (NAFLD), hepatocellular carcinoma, and combinations thereof.

In some embodiments, the non-alcoholic fatty liver disease (NAFLD) is selected from the group consisting of liver fibrosis, non-alcoholic steatohepatitis (NASH), NASH with liver fibrosis, and NASH with live cirrhosis.

In some embodiments, the subject is a human subject.

BRIEF DESCRIPTION OF DRAWINGS

Figure 1. Enhanced PTPRK expression in human livers with steatosis and non-alcoholic steatohepatitis (NASH). **(A)** Methodological approach schematic illustrating the quantification of protein tyrosine phosphatase (PTP) profile and total proteome in human livers. **(B)** Quantification of lipid metabolism-related proteins using label-free quantification (LFQ). **(C)** Schematic representation of PTP families and their characteristic domains. **(D)** Heat map displaying the hepatic PTP profile. **(E)** Spectral counts of total PTPs and the proportional contribution of receptor and non-receptor PTPs among the identified PTPs. **(F)** The proportional contribution of PTPRK and other receptor PTPs to the total identified PTPs. **(G)** Data extracted from the human protein atlas. **(H)** Correlation analysis between PTPRs and Pparg mRNA levels in the E-GEOD-48452 dataset. **(I)** mRNA levels of PTPRs in the E-MEXP-3291 dataset. **(J)** Representative immunohistochemistry (IHC) images displaying PTPRK staining and quantitative results for nuclear PTPRK. Data are the mean of independent experiments and

presented as mean±SEM. Statistical significance is denoted as * $p<0.05$, ** $p<0.01$, *** $p<0.001$ based on t-test or One-way ANOVA.

Figure 2. Hepatocyte PTPRK is induced by Notch signaling and LPS, correlating positively with PPARγ in obese mouse models and primary hepatocytes. 8 weeks old C57BL6N mice were fed either a high-fat diet (HFD) or a high-fat high-fructose high-cholesterol diet (HFHFHCD) for a duration of 12 weeks. Subsequently, various measurements were performed including (**A**) assessment of body weight, (**B**) analysis of body composition, and (**C**) measurement of fasting insulinemia. Moreover, the mice underwent (**D**) glucose and (**E**) insulin tolerance tests. (**F**) Primary hepatocytes, inguinal white adipose tissue (iWAT), epididymal white adipose tissue (eWAT), and gastrocnemius (muscle) were harvested for immunoblot analysis of PTPRK. (**G**) To evaluate hepatic changes, the livers were extracted and assessed for liver weight and composition. Additionally, histological analysis was conducted to quantify the vacuolation area, serving as an indicator of lipid inclusions (**H**). (**I**) Immunoblot analysis was carried out to determine the levels of PTPRK and PPARγ (Peroxisome Proliferator-Activated Receptor Gamma). 8 weeks old C57BL6N mice receiving a CHOW (control) diet were were transduced with an adenoviral vector to induce overexpression of PTPRK (AdV-PTPRK). Two weeks later, immunoblot analysis was performed in liver samples to assess the levels of PTPRK and PPARγ (**J**). Furthermore, primary mouse hepatocytes were cultured overnight under standard conditions and fixed at different time points (0, 4, 8, and 24 hours) for nile red staining to visualize lipid droplets (**K**). Immunoblot analysis of PTPRK and PPARγ was conducted on primary mouse hepatocytes collected at various time points (0, 4, 8, 24, and 48 hours) (**L**). To explore the influence of Notch signaling, primary mouse hepatocytes were cultured overnight and treated with different concentrations of the Notch signaling inhibitor GSIXX for 24 hours. Immunoblot analysis was employed to evaluate the expression levels of PTPRK and PPARγ (**M**). Additionally, primary mouse hepatocytes were cultured overnight and treated with lipopolysaccharide (LPS) for 24 hours. The expression of tumor necrosis factor-alpha (Tnfα), Ptprk, and Pparγ was analyzed using both quantitative PCR (qPCR) and immunoblot techniques (**N**, **O**). Primary mouse hepatocytes were cultured overnight and treated with dimethyloxalylglycine (DMOG), an inhibitor of 2-oxoglutarate-dependent dioxygenases required for hypoxia-inducible factor (HIF) degradation, for 24 hours. Immunoblot analysis was performed to examine the expression of HIF2α, PTPRK, and PPARγ (**P**). Data are the mean of independent experiments and presented as mean±SEM. Statistical significance is denoted as * $p<0.05$, ** $p<0.01$, *** $p<0.001$ based on t-test or One-way ANOVA.

Figure 3. PTPRK deletion confers protection against diet-induced obesity, insulin resistance, and hepatic steatosis. Male (♂) and female (♀) C57BL6N wild-type mice (*Ptprk*$^{+/+}$) and PTPRK knock-out mice (*Ptprk*$^{-/-}$), at the age of eight weeks, were subjected to a high-fat high-fructose high-cholesterol diet (HFHFHCD) for a period of 12 weeks. Rigorous measurements were performed to evaluate alterations in (**A, D**) body weight, (**B, E**) body composition, and (**C, F**) insulinemia, and glucose and insulin tolerance tests (**G, H**). Subsequent to the experimental timeline, insulin was administered to the

mice five minutes prior to liver collection. The obtained liver samples were analyzed to determine **(L, M)** liver weight and composition, and a histological assessment **(J, K)** and total lipids extraction **(N, O)** was conducted. Immunoblot analysis was employed to examine the expression of pIR and pAKT in the liver **(I)**. The reported data represents the average of multiple independent experiments and is depicted as mean±SEM. Significance levels are denoted as $*p < 0.05$, $**p < 0.01$, $***p < 0.001$ based on t-test or One-way ANOVA.

Figure 4. PTPRK orchestrates the hepatic expression of metabolic enzymes and transcription factors promoting steatosis in mice fed an obesogenic diet. Eight-week-old male (♂) and female (♀) C57BL6N wild-type mice (*Ptprk*$^{+/+}$) and PTPRK knock-out mice (*Ptprk*$^{-/-}$) were exposed to a high-fat high-fructose high-cholesterol diet (HFHFHCD) for a duration of 12 weeks. **(A, B)** Liver samples were analyzed to examine the levels of PTPRK, PPARγ (Peroxisome Proliferator-Activated Receptor Gamma), ACC (Acetyl-CoA Carboxylase), FASN (Fatty Acid Synthase), SREBP1 (Sterol Regulatory Element-Binding Protein 1), and ChREBP (Carbohydrate Response Element-Binding Protein). Additionally, subcutaneous (inguinal fat, **C** and **D**) white adipose tissues were collected for immunoblot analysis of PPARγ. Liver mRNA expression of Ptprk, Pparγ, Acc, Fasn, Scd1 (Stearoyl-CoA Desaturase 1), and Acly (ATP Citrate Lyase) was assessed **(E)**. **(F)** To investigate the impact of PTPRK overexpression, wild-type mice were administered an adenoviral vector to induce PTPRK overexpression (AdV-PTPRK), and after a two-week period, liver samples were collected for immunoblot analysis of PTPRK and PPARγ. **(G)** PTPRK knock-out mice were subjected to HFHFHCD for four weeks and subsequently injected with AdV-PTPRK. After an additional two weeks on the obesogenic diet, body weight was measured, and liver samples were obtained for the evaluation of liver weight, composition, and **(H)** histological assessment. The presented data represents the average of multiple independent experiments and is represented as mean±SEM. Statistical significance is indicated as $*p < 0.05$, $**p < 0.01$, $***p < 0.001$ based on t-test.

Figure 5. Comprehensive analysis of the transcriptome, proteome, and protein phosphorylation changes in primary hepatocytes isolated from livers of wild-type (*Ptprk*$^{+/+}$) and PTPRK knock-out (*Ptprk*$^{-/-}$) mice. **(A)** Methodological approach schematic illustrating the isolation of primary hepatocytes from mice fed HFHFHCD for 12 weeks, followed by separation based on cell density into hepatocytes with high-fat content and hepatocytes with low-fat content. **(B)** Immunoblot analysis revealing protein expression profiles of hepatocytes with high-fat content. **(C)** RT-qPCR analysis depicting changes in the expression of lipid metabolism-related genes. **(D)** RNA-Seq heatmap displaying alterations in PPAR pathway-related genes. **(E)** RNA-Seq KEGG pathway enrichment analysis comparing wild type (*Ptprk*$^{+/+}$) low-fat vs. high-fat hepatocytes (left side) and the same comparison in PTPRK knock-out (*Ptprk*$^{-/-}$) (right side). **(F)** Total proteome global heatmap presenting significantly altered proteins. **(G)** Total proteome KEGG pathway enrichment analysis. **(H)** Volcano plot illustrating the changes in the total proteomic profile between *Ptprk*$^{+/+}$ and*Ptprk*$^{-/-}$ high-fat hepatocytes. **(I)** Phosphoproteome global heatmap highlighting significantly changed phosphoproteins.

(**J**) Phosphoproteome KEGG pathway enrichment analysis. (**K**) Volcano plot displaying the quantification of tyrosine phosphosites in *Ptprk*$^{-/-}$ and *Ptprk*$^{+/+}$ hepatocytes. Phosphosites with over 30% increase in *Ptprk*$^{-/-}$ cells are marked in red ($p<0.05$). (**L**) Heatmap showcasing the significantly changing phosphopeptides in fructose-1,6-bisphosphatase 1. NA represents missing values. (**M**) Schematic representation of different F16P1/FBP1 amino acid sequences, indicating distinct boxes for interaction mapping experiments. Predicted helical regions are depicted in the three-dimensional structure on the right side. (**N**) Conservation mapping of the PTPRK-FBP1 interface, illustrating the PTPRK-D2 complex (red, blue, and grey surface representation of their electrostatic surface potential) interacting with the FBP1 dimer (light green and light blue) and the proximity of the PTPRK catalytic site and increased FBP1 phosphotyrosine residues observed in PTPRK knock-out mice (highlighted in red), and the D1 domain of PTPRK is shown in grey surface representation. (**O**) Immunoblot analysis of pervanadate-treated mouse hepatocyte lysates incubated with or without the recombinant PTPRK-ICD (ICD: intracellular domain) prior to analysis of pFBP1 (Y265) (**P**) Immunoblot analysis of pFBP1 (Y265) in livers from *Ptprk*$^{+/+}$ and *Ptprk*$^{-/-}$ mice fed HFHFHCD for 12 weeks. The presented data represents the average of multiple independent biological replicates. Statistical significance in panels **B**, **C**, and **P** is indicated as * $p<0.05$, ** $p<0.01$, *** $p<0.001$ based on t-test (panel **B** and **P**) or 2-way ANOVA (panel **C**) and the data is represented as mean±SEM.

Figure 6. Influence of PTPRK in hepatocellular carcinoma (HCC). (**A**) Total proteome profiling was conducted on human livers encompassing various stages of obesity-associated liver dysfunction and hepatocarcinogenesis, including normal liver, non-alcoholic steatohepatitis (NASH), cirrhotic livers, peritumor regions, and hepatocellular carcinoma (HCC) tumors. The focus was on examining the expression levels of receptor-type protein tyrosine phosphatases (PTPs), as illustrated in the total proteome heatmap depicting PTPRK and other receptor PTPs. (**B**) Based on the expression levels of PTPRK, the samples were categorized as high or low, and the normalized counts of genes involved in glycolysis/gluconeogenesis and lipid metabolism/lipogenesis were analyzed accordingly. (**C**) Total proteome KEGG pathway enrichment analysis was performed specifically on tumor samples with low or high PTPRK expression levels, shedding light on potential pathways associated with PTPRK in hepatocarcinogenesis. To explore the role of PTPRK in hepatocarcinogenesis, male and female wild-type (*Ptprk*$^{+/+}$) and PTPRK knock-out (*Ptprk*$^{-/-}$) mice were subjected to diethylnitrosamine (DEN) induction of liver cancer at 2 weeks of age. Tumor development was assessed when the animals reached 40 weeks of age. (**D, G**) Measurements of final body weight, fat body mass, liver weight, and fat liver mass were recorded in the experimental mice. (**E, H**) Tumors on the hepatic lobes were quantified and measured, considering tumors larger than 0.2 mm. The results are presented as the number of tumors per liver and the average tumor size. Additionally, microscopic tumors were quantified through histological analysis. (**F, I**) Liver samples were collected, and the area of identified microscopic nodes in H&E stained sections was measured and presented as a percentage of the total area of liver sections captured at the same magnification (quantifications displayed in the last graph of panel **E**). Furthermore,

human hepatoma cell lines HepG2 (**J**) and HLE (**K**) were transfected with siRNA control or siRNAs targeting PTPRK to investigate the impact of PTPRK downregulation on colony-forming capacity. Immunoblot analysis confirmed the efficiency of transfection, and crystal violet staining was employed to visualize and quantify the colonies. The reported data are presented as mean±SEM. Statistical significance is indicated as * $p<0.05$, ** $p<0.01$, *** $p<0.001$ based on the t-test.

Figure 7. Biochemical screening of potential PTPRK inhibitors and their biological effects. Our study aimed to identify and evaluate potential inhibitors targeting the catalytic sites of PTPRK. Through in silico analysis, we selected two compounds with high molecular affinity and stability, named Inhibitor 1 and Inhibitor 2. (**A**) The structures of Inhibitor 1 and Inhibitor 2 are shown, with Inhibitor 1 on the right and Inhibitor 2 on the left. Docking simulations demonstrated the binding of both inhibitors to the interaction surface of the PTPRK catalytic D2 domain. The inserted table presents the calculated MM|PBSA free energy values for the Inhibitor 1-PTPRK and Inhibitor 2-PTPRK complexes. Positive values indicate strong and stable binding, while negative values suggest unstable or no binding. (**B**) Molecular dynamics simulations were performed to analyze the trajectories of Inhibitor 1 (top) and Inhibitor 2 (bottom) binding to the PTPRK catalytic site (red trace) or other PTPRs, including PTPRM (light blue trace), PTPRU (dark blue trace), PTPRB (purple trace), PTPN2 (light green trace), PTPRT (yellow trace), and PTPRF (dark green trace), over a 200 ns time period. (**C**) Enzymatic activity assays were conducted using recombinant PTPRK intracellular domain (PTPRK-ICD). The reactions were performed in the presence of Inhibitor 1 or Inhibitor 2, and the initial velocities were measured. PTPRK-ICD activity was plotted and normalized to the vehicle (DMSO). Similar analyses were performed using PTPN2 instead of PTPRK (bottom graphs). (**D**) Extracellular acidification rates were quantified in HepG2, HLE, and Huh6 human hepatoma cell lines using Seahorse Xf Analyzer. The cells were treated with increasing concentrations of PTPRK Inhibitor 1 and Inhibitor 2. ECAR values were normalized to the basal ECAR levels (before the first injection of PTPRK inhibitors). Bar graphs show the differences at a final concentration of 50 μM. (**E**) HepG2, HLE, and Huh6 human hepatoma cell lines were transfected with HYlight to monitor fructose 1,6-bisphosphate dynamics. After treatment with PTPRK Inhibitor 2 and glucose starvation, sequential injections of 10 mM glucose and 50 mM 2-deoxyglucose (2-DG) were performed, and fluorescence ratios (ΔR/R0) were calculated. An example of fluorescence ratiometric images in HLE cells (upper) and quantification (bottom graphs) of the ΔR/R ratio for HepG2, HLE, and Huh6 cells is presented, normalized to the glucose-starved state at the start of each experiment. Solid lines represent the mean across cells, while dots represent the mean±SEM. (**F**) Immunoblot analysis of PPARγ expression was conducted in *Ptprk*$^{+/+}$ primary mouse hepatocyte cultures treated with PTPRK Inhibitor 1 and Inhibitor 2 at indicated concentrations (10 μM and 50 μM). (**G**) Immunoblot analysis of PPARγ expression was performed in *Ptprk*$^{-/-}$ primary mouse hepatocyte cultures treated with PTPRK Inhibitor 1 and Inhibitor 2 for 24 hours. (**H**) *In vivo* testing of PTPRK Inhibitor 2 was conducted in C57Bl/6 male mice. The mice were treated with vehicle or 50 mg/kg PTPRK Inhibitor 2 for 5 days. Body composition was measured before and after the treatment, and

glycemia levels were assessed daily. After sacrifice, liver composition analysis was performed. The reported data are presented as mean±SEM. Statistical significance is indicated as * $p<0.05$, ** $p<0.01$, *** $p<0.001$ based on the t-test.

Figure 8. Impact of PTPRK inhibitor 2 on C57BL/6N mice fed a high-fat, high-fructose, high-cholesterol diet. (A) C57BL/6N mice were fed a high-fat, high-fructose, high-cholesterol diet for 4 weeks, followed by weekly injections of 50 mg/kg of Inhibitor 2 for 5 weeks. Body weight changes were recorded weekly. **(B)** Body composition analysis was performed before and after the treatment with Inhibitor 2. **(C)** Weekly measurements of blood glucose levels during the treatment period. **(D)** C57BL/6N mice were fed the same high-fat, high-fructose, high-cholesterol diet for 4 weeks and then received weekly injections of 50 mg/kg of Inhibitor 2 for two weeks and then the treatment was interrupted. Body weight changes were recorded weekly. Statistical analyses were done using two-tailed unpaired Student's t test two-tailed unpaired Student's t test. Statistical significance is indicated as *$p<0.05$.

DESCRIPTION OF EMBODIMENTS

As used herein, the singular forms "a", "an", and "the" include both singular and plural referents unless the context clearly dictates otherwise.

The terms "comprising", "comprises" and "comprised of" as used herein are synonymous with "including", "includes" or "containing", "contains", and are inclusive or open-ended and do not exclude additional, non-recited members, elements or method steps. The terms also encompass "consisting of" and "consisting essentially of", which enjoy well-established meanings in patent terminology.

The recitation of numerical ranges by endpoints includes all numbers and fractions subsumed within the respective ranges, as well as the recited endpoints.

The terms "about" or "approximately" as used herein when referring to a measurable value such as a parameter, an amount, a temporal duration, and the like, are meant to encompass variations of and from the specified value, such as variations of +/-10% or less, preferably +/-5% or less, more preferably +/-1% or less, and still more preferably +/-0.1% or less of and from the specified value, insofar such variations are appropriate to perform in the disclosed invention. It is to be understood that the value to which the modifier "about" refers is itself also specifically, and preferably, disclosed.

Whereas the terms "one or more" or "at least one", such as one or more members or at least one member of a group of members, is clear per se, by means of further exemplification, the term encompasses *inter alia* a reference to any one of said members, or to any two or more of said members, such as, e.g., any ≥3, ≥4, ≥5, ≥6 or ≥7 etc. of said members, and up to all said members. In another example, "one or more" or "at least one" may refer to 1, 2, 3, 4, 5, 6, 7 or more.

The discussion of the background to the invention herein is included to explain the context of the invention. This is not to be taken as an admission that any of the material referred to was published, known, or part of the common general knowledge in any country as of the priority date of any of the claims.

Throughout this disclosure, various publications, patents and published patent specifications are referenced by an identifying citation. All documents cited in the present specification are hereby incorporated by reference in their entirety. In particular, the teachings or sections of such documents herein specifically referred to are incorporated by reference.

Unless otherwise defined, all terms used in disclosing the invention, including technical and scientific terms, have the meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. By means of further guidance, term definitions are included to better appreciate the teaching of the invention. When specific terms are defined in connection with a particular aspect of the invention or a particular embodiment of the invention, such connotation is meant to apply throughout this specification, i.e., also in the context of other aspects or embodiments of the invention, unless otherwise defined.

In the following passages, different aspects or embodiments of the invention are defined in more detail. Each aspect or embodiment so defined may be combined with any other aspect(s) or embodiment(s) unless clearly indicated to the contrary. In particular, any feature indicated as being preferred or advantageous may be combined with any other feature or features indicated as being preferred or advantageous.

Reference throughout this specification to "one embodiment", "an embodiment" means that a particular feature, structure or characteristic described in connection with the embodiment is included in at least one embodiment of the present invention. Thus, appearances of the phrases "in one embodiment" or "in an embodiment" in various places throughout this specification are not necessarily all referring to the same embodiment, but may. Furthermore, the particular features, structures or characteristics may be combined in any suitable manner, as would be apparent to a person skilled in the art from this disclosure, in one or more embodiments. Furthermore, while some embodiments described herein include some but not other features included in other embodiments, combinations of features of different embodiments are meant to be within the scope of the invention, and form different embodiments, as would be understood by those in the art. For example, in the appended claims, any of the claimed embodiments can be used in any combination.

Similarly, it should be appreciated that in the description of exemplary embodiments of the invention, various features of the invention are sometimes grouped together in a single embodiment, figure, or description thereof for the purpose of streamlining the disclosure and aiding in the understanding of one or more of the various inventive aspects.

Unless otherwise defined, all terms used in disclosing the invention, including technical and scientific terms, have the meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. By means of further guidance, definitions for the terms used in the description are included to better appreciate the teaching of the present invention.

The present inventors have demonstrated that hepatic PTP expression is linked to liver dysfunction progression and that PTPRs accumulate in subjects with liver steatosis and NASH. Further, and as corroborated in the experimental section herein, the inventors found a positive correlation between PTPR kappa (PTPRK) expression and PPARγ-induced lipogenic signalling. It was also found that PTPRK knockout mice have reduced fat accumulation in adipose tissue and liver after obesogenic diet feeding, whereas PTPRK overexpression increased glycolytic capacity in mouse hepatocytes. Finally, the inventors have demonstrated that inhibition of PTPRK resulted in reduced body weight, reduced liver fat accumulation and reduced glucose levels in mice that are on an obesogenic diet.

Accordingly, an aspect of the invention relates to a PTPRK inhibitor for use in the treatment and/or prevention of a condition selected from the group consisting of overweight, obesity, hyperglycaemia, diabetes, hyperlipidaemia, a non-alcoholic fatty liver disease (NAFLD), hepatocellular carcinoma, and combinations thereof in a subject. In certain embodiments the therapy and/or prevention may employ a combination of PTPRK inhibitors. In some embodiments, the invention provides a PTPRK inhibitor for use in the treatment of a condition selected from the group consisting of overweight, obesity, hyperglycaemia, diabetes, hyperlipidaemia, a non-alcoholic fatty liver disease (NAFLD), hepatocellular carcinoma, and combinations thereof in a subject.. In some embodiments, the invention provides a PTPRK inhibitor for use in the prevention of a condition selected from the group consisting of overweight, obesity, hyperglycaemia, diabetes, hyperlipidaemia, a non-alcoholic fatty liver disease (NAFLD), hepatocellular carcinoma, and combinations thereof in a subject. In some embodiments, the invention provides a PTPRK inhibitor for use in the treatment and/or prevention of overweight and/or obesity, in particular for use in the treatment of overweight and/or obesity. In some embodiments, the invention provides a PTPRK inhibitor for use in the treatment and/or prevention of hyperglycaemia and/or diabetes, in particular for use in the treatment of hyperglycaemia and/or diabetes. In some embodiments, the invention provides a PTPRK inhibitor for use in the treatment and/or prevention of hyperlipidaemia in a subject, in particular for use in the treatment of hyperlipidaemia in a subject. In some embodiments, the invention provides a PTPRK inhibitor for use in the treatment and/or prevention of a non-alcoholic fatty liver disease (NAFLD) in a subject, in particular for use in the treatment of a non-alcoholic fatty liver disease (NAFLD) in a subject. In some embodiments, the invention provides a PTPRK inhibitor for use in the treatment and/or prevention of hepatocellular carcinoma. In some embodiments, the invention provides a PTPRK inhibitor for use in the treatment of hepatocellular carcinoma.

Another aspect relates to the non-medical use of a PTPRK inhibitor for reduction of body weight, blood glucose level, blood lipid levels, or a combination thereof in a subject. In certain embodiments the non-medical use may employ a combination of PTPRK inhibitors. In certain embodiments, the non-medical use of a PTPRK inhibitor is for reduction of body weight. In some embodiments, the non-medical use of a PTPRK inhibitor is for reduction of blood glucose level. In some embodiments, the non-medical use is for reduction of blood lipid levels.

A further aspect relates to a pharmaceutical composition comprising a PTPRK inhibitor or a combination of PTPRK inhibitors for use in the treatment and/or prevention of a condition selected from the group consisting of overweight, obesity, hyperglycemia, diabetes, hyperlipidaemia, a non-alcoholic fatty liver disease (NAFLD), hepatocellular carcinoma, and combinations thereof in a subject. In some embodiments, the pharmaceutical composition comprises a PTPRK inhibitor or combination of PTPRK inhibitors as defined herein. In some embodiments, the invention provides a pharmaceutical composition comprising a PTPRK inhibitor or a combination of PTPRK inhibitors as defined herein for use in the treatment of overweight and/or obesity in a subject. In some embodiments, the invention provides a pharmaceutical composition comprising a PTPRK inhibitor or a combination of PTPRK inhibitors as defined herein for use in the prevention of overweight and/or obesity in a subject. In some embodiments, the invention provides a pharmaceutical composition comprising a PTPRK inhibitor as defined herein for use in the treatment of hyperglycaemia and/or diabetes in a subject. In some embodiments, the invention provides a pharmaceutical composition comprising a PTPRK inhibitor or a combination of PTPRK inhibitors as defined herein for use in the prevention of hyperglycaemia and/or diabetes in a subject. In some embodiments, the invention provides a pharmaceutical composition comprising a PTPRK inhibitor or a combination of PTPRK inhibitors as defined herein for use in the treatment of hyperlipidaemia in a subject. In some embodiments, the invention provides a pharmaceutical composition comprising a PTPRK inhibitor or a combination of PTPRK inhibitors as defined herein for use in the prevention of hyperlipidaemia in a subject. In some embodiments, the invention provides a pharmaceutical composition comprising a PTPRK inhibitor or a combination of PTPRK inhibitors as defined herein for use in the treatment of a NAFLD in a subject. In some embodiments, the invention provides a pharmaceutical composition comprising a PTPRK inhibitor or a combination of PTPRK inhibitors as defined herein for use in the prevention of a NAFLD in a subject. In some embodiments, the invention provides a pharmaceutical composition comprising a PTPRK inhibitor or a combination of PTPRK inhibitors as defined herein for use in the treatment of hepatocellular carcinoma in a subject. In some embodiments, the invention provides a pharmaceutical composition comprising a PTPRK inhibitor or a combination of PTPRK inhibitors as defined herein for use in the prevention of hepatocellular carcinoma in a subject.

Another aspect provides a method of preventing and/or treating a condition selected from the group consisting of overweight, obesity, hyperglycaemia, diabetes, hyperlipidaemia, a non-alcoholic fatty liver disease (NAFLD), hepatocellular carcinoma, or combinations thereof in a subject in need of such treatment, comprising administering to said subject a therapeutically and/or prophylactically effective amount of a PTPRK inhibitor or a combination of PTPRK inhibitors as defined herein or of a pharmaceutical composition comprising a PTPRK inhibitor or a combination of PTPRK inhibitors as defined herein. In some embodiments, the method is for preventing a condition selected from the group consisting of overweight, obesity, hyperglycaemia, diabetes, hyperlipidaemia, a non-alcoholic fatty liver disease (NAFLD), hepatocellular carcinoma, or combinations thereof in a subject in need of such treatment. In some embodiments, the method is for treating a condition selected from the group consisting of overweight, obesity, hyperglycaemia, diabetes, hyperlipidaemia, a non-alcoholic fatty liver disease (NAFLD), hepatocellular carcinoma, or combinations thereof in a subject in need of such treatment. In some embodiments, the method is for treating and/or preventing overweight and/or obesity, in particular for treating overweight and/or obesity. In some embodiments, the method is for treating and/or preventing of hyperglycaemia and/or diabetes, in particular for treating hyperglycaemia and/or diabetes. In some embodiments, the method is for treating and/or preventing of hyperlipidaemia; in particular for treating hyperlipidaemia. In some embodiments, the method is for treating and/or preventing of a NAFLD; in particular for treating of a NAFLD. In some embodiments, the method is for treating and/or preventing of hepatocellular carcinoma; in particular for treating of a hepatocellular carcinoma.

A further aspect provides a non-therapeutic method for the reduction of body weight, blood glucose level, blood lipid levels or a combination thereof in a subject, wherein said method includes administering to said subject in need for such reduction a PTPRK inhibitor or a combination of PTPRK inhibitors as disclosed herein to said subject. In certain embodiments, a combination of PTPRK inhibitors as disclosed herein may be administered. In some embodiments, the non-therapeutic method is for the reduction of body weight in a subject. In some embodiments, the non-therapeutic method is for the reduction of the blood glucose level in a subject. In some embodiments, the non-therapeutic method is for the reduction of blood lipid levels in a subject.

The term “PTPs”, short for protein tyrosine phosphatases refers to a group of enzymes that remove phosphate groups from phosphorylated tyrosine residues on proteins. Protein tyrosine phosphorylation is a common post-translational modification that can create novel recognition motifs for protein interactions and cellular localization, affect protein stability, and regulate enzyme activity. PTPs catalyse the removal of a phosphate group attached to a tyrosine residue, using a cysteinyl-phosphate enzyme intermediate. PTPs are known to be signalling molecules that regulate a variety of cellular processes including cell growth, differentiation, mitotic cycle, and oncogenic transformation.

The term "PTPRs", short for protein tyrosine phosphatase receptors or receptor-type protein tyrosine phosphatases, abbreviated as "RPTPs" represent a subclass of transmembrane proteins among the classical protein tyrosine phosphatases (PTPs). PTPRs are distinguished by the features of their extracellular domains, adapter to detect and transduce extracellular sensing into intracellular catalytic events.

The term "PTPRK", short for protein tyrosine phosphatase receptor kappa or protein tyrosine phosphatase receptor type K, is a member of the PTPR family. PTPRK is also known as RPTP-kappa or R-PTP-kappa. PTPRK is a transmembrane receptor belonging to the R2B subfamily of PTPRs, known to engage in homophilic interaction to respond to cell-cell contacts, possible through the interaction with beta- and gamma-catenin at adherens junctions. PTPRK possesses an extracellular region, a single transmembrane region, and two tandem catalytic domains. PTPRK was shown to mediate homophilic interactions to respond to cell-cell contacts. The regulation of PTPRK protein involves a proteolytic cascade (furin, ADAM10, and γ-secretase), potentially releasing the intracellular catalytic PTPRK domain to interact and dephosphorylate proteins far away from the transmembrane microdomains.

By means of further guidance, the human PTPRK gene is annotated and available under NCBI Gene ID no. 5796. The messenger RNA (mRNA) reference sequence of *Homo sapiens* PRPRK is annotated in NCBI Genbank accession number NM_002844.4, with transcript variants NM_001135648.3 (variant 1), NM_001291981.2 (variant 2), NM_001291982.2 (variant 3), NM_001291983.2 (variant 4), and NM_001291984.2 (variant 5).

The reference human PTPRK protein sequence is annotated under NCBI Genbank accession number NP_002835.2, with transcript variants NP_001129120.1 (variant 1, isoform a), NP_001278910.1 (variant 2, isoform b), NP_001278911.1 (variant 3, isoform c), NP_001278912.1 (variant 4, isoform d), and NP_001278913.1 (variant 5, isoform e). The canonical human PTPRK protein sequence annotated in Uniprot (www.uniprot.org) is accession number Q15262-1 (sequence version 2) and is by means of example reproduced below (SEQ ID NO: 1)

MDTTAAAALPAFVALLLLSPWPLLGSAQGQFSAGGCTFDDGPGACDYHQDLYDDFEWVHV
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LNILVRVNKGPLANPIWNVTGFTGRDWLRAELAVSTFWPNEYQVIFEAEVSGGRSGYIAIDDI
QVLSYPCDKSPHFLRLGDVEVNAGQNATFQCIATGRDAVHNKLWLQRRNGEDIPVAQTKNI
NHRRFAASFRLQEVTKTDQDLYRCVTQSERGSGVSNFAQLIVREPPRPIAPPQLLGVGPTYLLI
QLNANSIIGDGPIILKEVEYRMTSGSWTETHAVNAPTYKLWHLDPDTEYEIRVLLTRPGEGGT
GLPGPPLITRTKCAEPMRTPKTLKIAEIQARRIAVDWESLGYNITRCHTFNVTICYHYFRGHNE
SKADCLDMDPKAPQHVVNHLPPYTNVSLKMILTNPEGRKESEETIIQTDEDVPGPVPVKSLQG

TSFENKIFLNWKEPLDPNGIITQYEISYSSIRSFDPAVPVAGPPQTVSNLWNSTHHVFMHLHPG
TTYQFFIRASTVKGFGPATAINVTTNISAPTLPDYEGVDASLNETATTITVLLRPAQAKGAPISA
YQIVVEELHPHRTKREAGAMECYQVPVTYQNAMSGGAPYYFAAELPPGNLPEPAPFTVGDN
RTYQGFWNPPLAPRKGYNIYFQAMSSVEKETKTQCVRIATKAATEEPEVIPDPAKQTDRVVK
IAGISAGILVFILLLLVVILIVKKSKLAKKRKDAMGNTRQEMTHMVNAMDRSYADQSTLHAE
DPLSITFMDQHNFSPRYENHSATAESSRLLDVPRYLCEGTESPYQTGQLHPAIRVADLLQHINL
MKTSDSYGFKEEYESFFEGQSASWDVAKKDQNRAKNRYGNIIAYDHSRVILQPVEDDPSSDY
INANYIDGYQRPSHYIATQGPVHETVYDFWRMIWQEQSACIVMVTNLVEVGRVKCYKYWP
DDTEVYGDFKVTCVEMEPLAEYVVRTFTLERRGYNEIREVKQFHFTGWPDHGVPYHATGLL
SFIRRVKLSNPPSAGPIVVHCSAGAGRTGCYIVIDIMLDMAEREGVVDIYNCVKALRSRRINM
VQTEEQYIFIHDAILEACLCGETAIPVCEFKAAYFDMIRIDSQTNSSHLKDEFQTLNSVTPRLQ
AEDCSIACLPRNHDKNRFMDMLPPDRCLPFLITIDGESSNYINAALMDSYRQPAAFIVTQYPLP
NTVKDFWRLVYDYGCTSIVMLNEVDLSQGCPQYWPEEGMLRYGPIQVECMSCSMDCDVIN
RIFRICNLTRPQEGYLMVQQFQYLGWASHREVPGSKRSFLKLILQVEKWQEECEEGEGRTIIH
CLNGGGRSGMFCAIGIVVEMVKRQNVVDVFHAVKTLRNSKPNMVEAPEQYRFCYDVALEY
LESS (SEQ ID NO: 1)

A skilled person can appreciate that any sequences represented in sequence databases or in the present specification may be of precursors of peptides, polypeptides, proteins, or nucleic acids and may include parts which are processed away from mature molecules.

The term "protein" as used throughout this specification generally encompasses macromolecules comprising one or more polypeptide chains, i.e., polymeric chains of amino acid residues linked by peptide bonds. As used herein, the term may encompass proteins that carry one or more co- or post-expression-type modifications of the polypeptide chain(s), such as, without limitation, glycosylation, acetylation, phosphorylation, sulfonation, methylation, ubiquitination, signal peptide removal, N-terminal Met removal, conversion of pro-enzymes or pre-hormones into active forms, etc. The term further also includes protein variants or mutants which carry amino acid sequence variations vis-à-vis corresponding native proteins, such as, e.g. amino acid deletions, additions and/or substitutions. The term contemplates both full-length proteins and protein parts or fragments, e.g., naturally-occurring protein parts that ensue from processing of such full-length proteins.

The term "polypeptide" as used throughout this specification generally encompasses polymeric chains of amino acid residues linked by peptide bonds. Hence, especially when a protein is only composed of a single polypeptide chain, the terms "protein" and "polypeptide" may be used interchangeably herein to denote such a protein. The term is not limited to any minimum length of the polypeptide chain. Without limitation, protein, polypeptides or peptides can be produced recombinantly by a suitable host

or host cell expression system and isolated therefrom (e.g., a suitable bacterial, yeast, fungal, plant or animal host or host cell expression system), or produced recombinantly by cell-free transcription and/or translation, or non-biological protein, polypeptide or peptide synthesis.

The term "nucleic acid" as used throughout this specification typically refers to a polymer (preferably a linear polymer) of any length composed essentially of nucleoside units. A nucleoside unit commonly includes a heterocyclic base and a sugar group. Heterocyclic bases may include *inter alia* purine and pyrimidine bases such as adenine (A), guanine (G), cytosine (C), thymine (T) and uracil (U) which are widespread in naturally-occurring nucleic acids, other naturally-occurring bases (e.g., xanthine, inosine, hypoxanthine) as well as chemically or biochemically modified (e.g., methylated), non-natural or derivatised bases.

The term "nucleic acid" further preferably encompasses DNA, RNA and DNA/RNA hybrid molecules, specifically including hnRNA, pre-mRNA, mRNA, cDNA, genomic DNA, amplification products, oligonucleotides, and synthetic (e.g., chemically synthesised) DNA, RNA or DNA/RNA hybrids. RNA is inclusive of RNAi (inhibitory RNA), dsRNA (double stranded RNA), siRNA (small interfering RNA), mRNA (messenger RNA), miRNA (micro-RNA), tRNA (transfer RNA, whether charged or discharged with a corresponding acylated amino acid), and cRNA (complementary RNA). A nucleic acid can be naturally occurring, e.g., present in or isolated from nature, can be recombinant, i.e., produced by recombinant DNA technology, and/or can be, partly or entirely, chemically or biochemically synthesized. A naturally occurring variant of a given sequence refers to all variants of the sequence which encode the same functional protein and that are present in or can be isolated from nature. Typically, this includes all variants of the sequence encountered in mammals, more particularly humans. It will be understood that variants from closely related species will have a higher sequence identity than variants from evolutionary more distant species. In particular embodiments, the natural variant of a given sequence has at least 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%; 90% or 95% sequence identity with the given sequence.

Without limitation, nucleic acids can be produced recombinantly by a suitable host or host cell expression system and isolated therefrom (e.g., a suitable bacterial, yeast, fungal, plant or animal host or host cell expression system), or produced recombinantly by cell-free transcription, or non-biological nucleic acid synthesis. A nucleic acid can be double-stranded, partly double-stranded, or single-stranded. Where single-stranded, the nucleic acid can be the sense strand or the antisense strand. In addition, the nucleic acid can be circular or linear.

The reference to any peptide, polypeptide, or nucleic acid, corresponds to the peptide, polypeptide, protein, or nucleic acid, commonly known under the respective designations in the art. The terms encompass such peptides, polypeptides, proteins, or nucleic acids, of any organism where found, and

particularly of animals, preferably warm-blooded animals, more preferably vertebrates, yet more preferably mammals, including humans and non-human mammals, still more preferably of humans.

Depending on the nature of the subject under consideration, the PTPRK inhibitor targets a PTPRK peptide, polypeptide, protein, or nucleic acid which is of animal origin, preferably warm-blooded animal origin, more preferably vertebrate origin, yet more preferably mammalian origin, including human origin and non-human mammalian origin, still more preferably human origin.

Unless otherwise apparent from the context, reference herein to any peptide, polypeptide, protein, or nucleic acid, or fragment thereof may generally also encompass modified forms of said marker, peptide, polypeptide, protein, or nucleic acid, or fragment thereof, such as bearing post-expression modifications including, for example, phosphorylation, glycosylation, lipidation, methylation, cysteinylation, sulphonation, glutathionylation, acetylation, oxidation of methionine to methionine sulphoxide or methionine sulphone, and the like.

The terms "inhibitor of PTPRK", "PTPRK inhibitor", "protein tyrosine phosphatase receptor kappa inhibitor", "PTP receptor kappa inhibitor" or "inhibitor" ma be used interchangeably herein and refer to any agent that can be regarded to have an inhibitory effect on PTPRK. It is known to a skilled person that an inhibitor can act in different ways and methods to determine whether an agent has an inhibitory effect on PTPRK are within the skill set of a person skilled in the art. Hence, a PTPRK inhibitor according to the invention may be effective in any possible manner, i.e. said inhibitor can either act on DNA level, RNA level, or protein level. In preferred embodiments, the PRPRK inhibitor acts on protein level. By means of guidance and not limitation, the inhibitor may inhibit, reduce, or decrease the activity of the PTPRK protein.

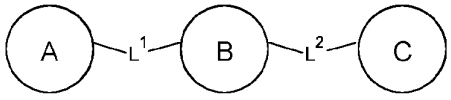
In some embodiments, the PTPRK inhibitor as disclosed herein is a specific PTPRK inhibitor, also referred to as a selective PTPRK inhibitor. A "selective PTPRK inhibitor" or a "specific PTPRK inhibitor" is an inhibitor that selectively inhibits PTPRK, while it does not inhibit any other PTPRs, or inhibits other PTPRs to a much lower extent. For examples, a specific PTPRK inhibitor will inhibit PTPR kappa but not other PTPRs, or it will be more active towards PTPRK. Particularly, a selective or specific PTPRK inhibitor will be, for example in an in vitro experiment, 5 times more active towards the targeted PTPRK than to other PTPRs, or 10 times more active, or 50 times more active, or 100 times more active, or 1000 times more active, or even more than 10^4 times more active, than to other PTPRs.

The compounds of the present invention have been found to specifically act on PTPRK, in particular to inhibit PTPRK. In preferred embodiments, the compounds of the invention act on the PTPRK protein level. In some preferred embodiments, the compounds of the invention inhibit, reduce, or decrease the activity of the PTPRK protein.

Any meaningful extent of inhibition of the expression and/or activity of PTPRK is envisaged. Hence, the terms "inhibit" or "inhibited", or "downregulate" or "downregulated", or "reduce" or "reduced", or "decrease" or "decreased" may in appropriate contexts, such as in experimental or therapeutic contexts, denote a statistically significant decrease relative to a reference. The skilled person is able to select such a reference. An example of a suitable reference may be the PTPRK expression and/or activity when exposed to a 'negative control' molecule, such as a molecule of similar composition but known to have no effects on PTPRK. For example, such decrease may fall outside of error margins for the reference (as expressed, for example, by standard deviation or standard error, or by a predetermined multiple thereof, e.g., ±1xSD, ±2xSD, or ±1xSE, ±2xSE). By means of an illustration, the expression and/or activity of PTPRK may be considered reduced when it is decreased by at least 10%, such as by at least 20% or by at least 30%, preferably by at least 40%, such as by at least 50% or by at least 60%, more preferably by at least 70%, such as by at least 80% or by at least 90% or more, as compared to the reference, up to and including a 100% decrease (i.e., absent activity as compared to the reference).

PTPRK is a transmembrane protein adapted to detect and transduce extracellular sensing into intracellular events. Accordingly, the present PTPRK inhibitor may in certain embodiments inhibit one or more of the various molecular functions and activities of PTPRK. By means of example and not limitation, one or more of the following can be inhibited: adhesion of the extracellular domain to cell adhesion proteins, signalling capacity of the intracellular catalytic domain, and/or catalytic activity of PTPRK. A skilled person can design *in vitro* or cell assays to measure such one or more activity of PTPRK.

In some embodiments, the PTPRK inhibitor as disclosed herein is a compound of Formula I or Formula II, or a stereoisomer, enantiomer, tautomer, solvate, hydrate, pharmaceutically acceptable salt, or prodrug thereof:



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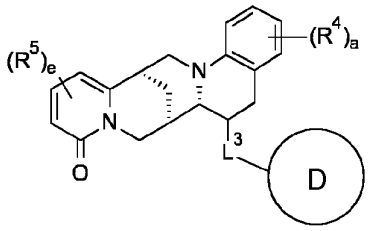
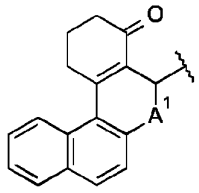
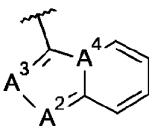
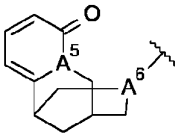
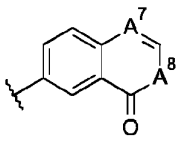
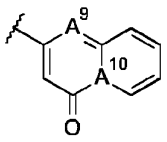
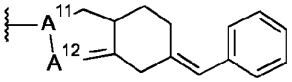
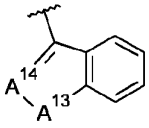
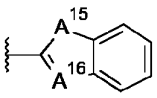
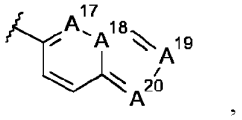
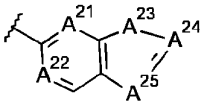
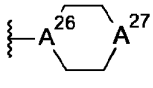


II

wherein,

cycle A is selected from the group consisting of C_{6-12}aryl, C_{3-12}cycloalkyl, C_{3-12}cycloalkenyl,












, and ;

wherein the wavy line (〰) indicates the point of attachment of cycle A to the rest of the molecule, wherein said groups can be unsubstituted or substituted with one or more R^A;

each of A^1, A^8, A^{13}, A^{15}, A^{23}, and A^{27} is independently selected from the group consisting of NR^A, CHR^A, S, $S(O)_2$ and O;

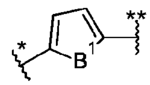
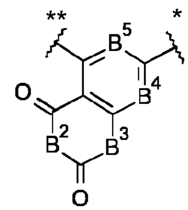
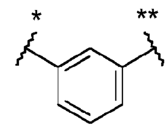
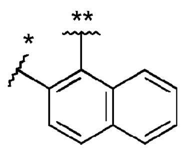
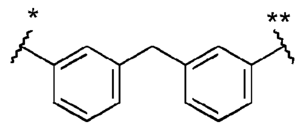
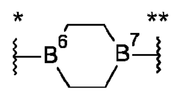
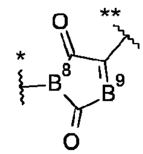
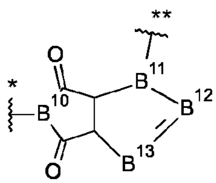
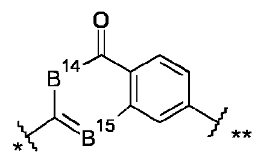
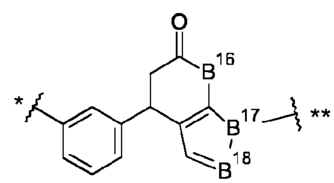
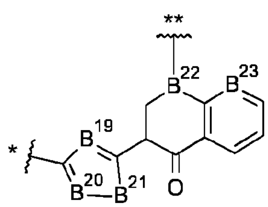
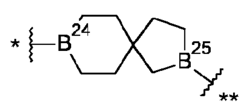
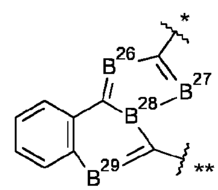
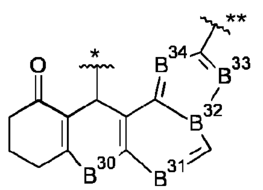
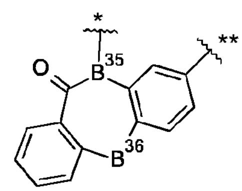
each of A^2, A^3, A^4, A^5, A^6, A^7, A^9, A^{10}, A^{11}, A^{12}, A^{14}, A^{16}, A^{17}, A^{18}, A^{19}, A^{20}, A^{21}, A^{22}, A^{24}, A^{25},and A^{26} is independently selected from N or CR^A;

each R^A is independently selected from the group consisting of hydrogen, halogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, haloC_{1-6}alkyl, haloC_{1-6}alkyloxy, cyanoC_{1-6}alkyl, C_{1-6}alkoxy, nitro, cyano, hydroxy, $-NR^1R^2$, $-NR^1R^2S(O)_2R^3$, $-NR^1R^2C(O)_2R^3$, $-C(O)R^3$, $-C(O)_2R^3$, $-S(O)_2R^3$, C_{6-12}aryl, and C_{1-6}alkylC_{6-12}aryl; wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, or C_{6-12}aryl can be unsubstituted or substituted with one, two or three halogen, nitro, hydroxy or C_{1-6}alkyl;

L^1 is a linker moiety selected from the group consisting of a single bond, -C(O)-, -NHC(O)-, -C(O)NH-, $-(CH_2)$n-, $-CH_2C(O)-$, $-C(O)CH_2-$, $-CH(CH_3)C(O)-$, $-C(O)CH(CH_3)-$, $-CH_2C(O)NH-$, $-NHC(O)CH_2-$, $-CH_2-O-$, $-O-CH_2-$, $-CH_2-S-$, $-S-CH_2-$, -O-, -S-, $-S-CH_2C(O)NH-$, $-NHC(O)CH_2-S-$, $-C(O)NH(CH_2)$g- and -CH=N-NH-C(O)-;

n is an integer selected from 1, 2, 3 or 4;

g is an integer selected from 1, 2, 3 or 4;

cycle B is selected from the group consisting of  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and  ;

wherein * represents where cycle B is bound to L^1; and ** represents where cycle B is bound to L^2; wherein said groups can be unsubstituted or substituted with one or more R^B;

each of B^1, B^2, B^3, B^{14}, B^{16}, B^{21}, B^{30}, and B^{36} is independently selected from the group consisting of NR^B, CHR^B, S, $S(O)_2$ and O;

each of B^4, B^5, B^6, B^7, B^8, B^9, B^{10}, B^{11}, B^{12}, B^{13}, B^{15}, B^{17}, B^{18}, B^{19}, B^{20}, B^{22}, B^{23}, B^{24}, B^{25}, B^{26}, B^{27}, B^{28}, B^{29}, B^{31}, B^{32}, B^{33}, B^{34}, and B^{35} is independently selected from N or CR^B;

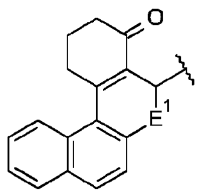
each R^B is independently selected from the group consisting of hydrogen, halogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, haloC_{1-6}alkyl, haloC_{1-6}alkyloxy, cyanoC_{1-6}alkyl, C_{1-6}alkoxy, nitro, cyano, hydroxy, $-NR^1R^2$, $-NR^1R^2S(O)_2R^3$, $-NR^1R^2C(O)_2R^3$, $-C(O)R^3$, $-C(O)_2R^3$, $-S(O)_2R^3$, C_{6-12}aryl, and C_{1-6}alkylC_{6-12}aryl; wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, or C_{6-12}aryl can be unsubstituted or substituted with one, two or three halogen, nitro, hydroxy or C_{1-6}alkyl;

L^2 is a linker moiety selected from the group consisting of a single bond, -C(O)-, -NHC(O)-, -C(O)NH-, -(CH_2)m-, -CH_2C(O)-, -C(O)CH_2-, -CH(CH_3)C(O)-, -C(O)CH(CH_3)-, -CH_2C(O)NH-, -NHC(O)CH_2-, -CH_2-O-, -O-CH_2-, -CH_2-S-, -S-CH_2-, -O-, -S-, -S-CH_2C(O)NH-, -NHC(O)CH_2-S-, -C(O)NH(CH_2)i- and -CH=N-NH-C(O)-;

m is an integer selected from 1, 2, 3 or 4;

i is an integer selected from 1, 2, 3 or 4;

cycle C is selected from the group consisting of C_{6-12}aryl, C_{3-12}cycloalkyl, C_{3-12}cycloalkenyl,



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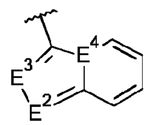

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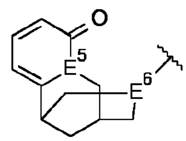

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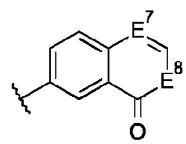

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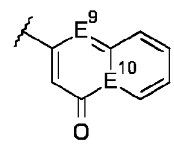

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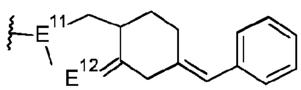

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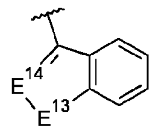

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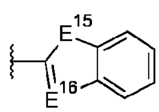

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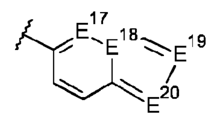

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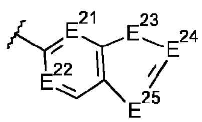

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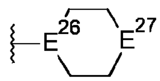


;

wherein the wavy line (〰) indicates the point of attachment of cycle C to the rest of the molecule, wherein said groups can be unsubstituted or substituted with one or more R^C;

each of E^1, E^8, E^{13}, E^{15}, E^{23}, and E^{27} is independently selected from the group consisting of NR^C, CHR^C, S, $S(O)_2$ and O;

each of E^2, E^3, E^4, E^5, E^6, E^7, E^9, E^{10}, E^{11}, E^{12}, E^{14}, E^{16}, E^{17}, E^{18}, E^{19}, E^{20}, E^{21}, E^{22}, E^{24}, E^{25},and E^{26} is independently selected from N or CR^C;

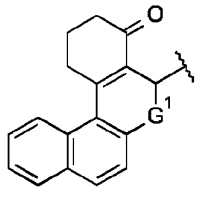
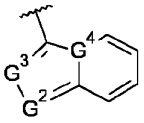
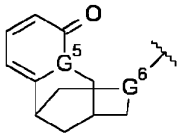
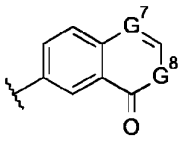
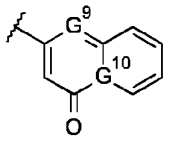
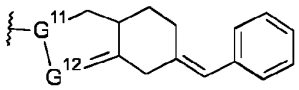
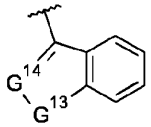
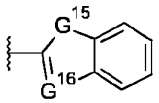
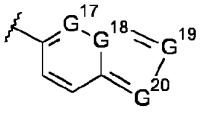
each R^C is independently selected from the group consisting of hydrogen, halogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, haloC_{1-6}alkyl, haloC_{1-6}alkyloxy, cyanoC_{1-6}alkyl, C_{1-6}alkoxy, nitro, cyano, hydroxy, -NR^1R^2, -$NR^1R^2S(O)_2R^3$, -$NR^1R^2C(O)_2R^3$, -C(O)R^3, -$C(O)_2R^3$, -$S(O)_2R^3$, C_{6-12}aryl, and C_{1-6}alkylC_{6-12}aryl; wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, or C_{6-12}aryl can be unsubstituted or substituted with one, two or three halogen, nitro, hydroxy or C_{1-6}alkyl;

L^3 is a linker moiety selected from the group consisting of a single bond, -C(O)-, -NHC(O)-, -C(O)NH-, -(CH_2)j-, -CH_2C(O)-, -C(O)CH_2-, -CH(CH_3)C(O)-, -C(O)CH(CH_3)-, -CH_2C(O)NH-, -NHC(O)CH_2-, -CH_2-O-, -O-CH_2-, -CH_2-S-, -S-CH_2-, -O-, -S-, -S-CH_2C(O)NH-, -NHC(O)CH_2-S-, -C(O)NH(CH_2)q- and -CH=N-NH-C(O)-;

j is an integer selected from 1, 2, 3 or 4;

q is an integer selected from 1, 2, 3 or 4;

cycle D is selected from the group consisting of C_{6-12}aryl, C_{3-12}cycloalkyl, C_{3-12}cycloalkenyl,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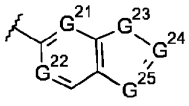
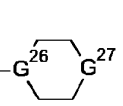


, and ;

wherein the wavy line (〰) indicates the point of attachment of cycle D to the rest of the molecule, wherein said groups can be unsubstituted or substituted with one or more R^D;

each of G^1, G^8, G^{13}, G^{15}, G^{23}, and G^{27} is independently selected from the group consisting of NH, NR^D, CHR^D, S, $S(O)_2$ and O;

each of G^2, G^3, G^4, G^5, G^6, G^7, G^9, G^{10}, G^{11}, G^{12}, G^{14}, G^{16}, G^{17}, G^{18}, G^{19}, G^{20}, G^{21}, G^{22}, G^{24}, G^{25}, and G^{26} is independently selected from N or CR^D;

each R^D is independently selected from the group consisting of hydrogen, halogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, haloC_{1-6}alkyl, haloC_{1-6}alkyloxy, cyanoC_{1-6}alkyl, C_{1-6}alkoxy, nitro, cyano, hydroxy, $-NR^1R^2$, $-NR^1R^2S(O)_2R^3$, $-NR^1R^2C(O)_2R^3$, $-C(O)R^3$, $-C(O)_2R^3$, $-S(O)_2R^3$, C_{6-12}aryl, and C_{1-6}alkylC_{6-12}aryl; wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, or C_{6-12}aryl can be unsubstituted or substituted with one, two or three halogen, nitro, hydroxy or C_{1-6}alkyl;

each R^1 is independently selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, and C_{6-12}aryl, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, or C_{6-12}aryl can be unsubstituted or substituted with one, two or three halogen, nitro, hydroxy or C_{1-6}alkyl;

each R^2 is independently selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, and C_{6-12}aryl, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, or C_{6-12}aryl can be unsubstituted or substituted with one, two or three halogen, nitro, hydroxy or C_{1-6}alkyl;

each R^3 is independently selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, and C_{6-12}aryl, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, or C_{6-12}aryl can be unsubstituted or substituted with one, two or three halogen, nitro, hydroxy or C_{1-6}alkyl.

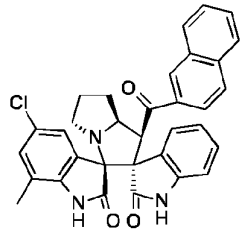
a is an integer selected from 1, 2, 3 or 4;

each R^4 is independently selected from the group consisting of hydrogen, halogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, haloC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkoxy, nitro, cyano, hydroxy, $-NR^1R^2$, $-NR^1R^2S(O)_2R^3$, $-NR^1R^2C(O)_2R^3$, $-C(O)R^3$, $-C(O)_2R^3$, $-S(O)_2R^3$, C_{6-12}aryl, and C_{1-6}alkylC_{6-12}aryl;

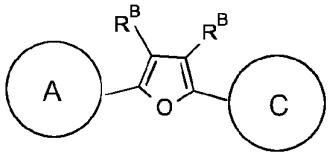
wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, or C_{6-12}aryl can be unsubstituted or substituted with one, two or three halogen, nitro, hydroxy or C_{1-6}alkyl;

e is an integer selected from 1, 2, or 3;

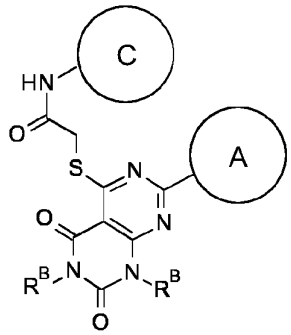
each R^5 is independently selected from the group consisting of hydrogen, halogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, haloC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkoxy, nitro, cyano, hydroxy, $-NR^1R^2$, $-NR^1R^2S(O)_2R^3$, $-NR^1R^2C(O)_2R^3$, $-C(O)R^3$, $-C(O)_2R^3$, $-S(O)_2R^3$, C_{6-12}aryl, and C_{1-6}alkylC_{6-12}aryl; wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, or C_{6-12}aryl can be unsubstituted or substituted with one, two or three halogen, nitro, hydroxy or C_{1-6}alkyl;

or the inhibitor is a compound of formula  , or a stereoisomer, enantiomer, tautomer, solvate, hydrate, pharmaceutically acceptable salt, or prodrug thereof.

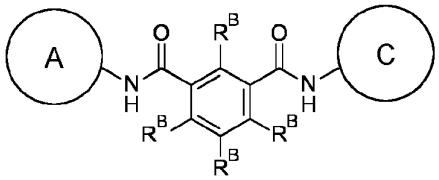
In some embodiments, the PTPRK inhibitor according to the present invention is a compound of Formula I-1, I-2, I-3, I-4, I-5, I-6, I-7, I-8, I-9, I-10, I-11, I-12, I13, I-14, I-15 or I-16, or a stereoisomer, enantiomer, tautomer, solvate, hydrate, pharmaceutically acceptable salt, or prodrug thereof,



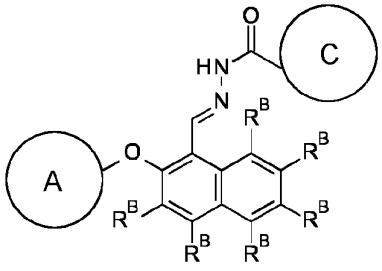
I-1



I-2



I-3



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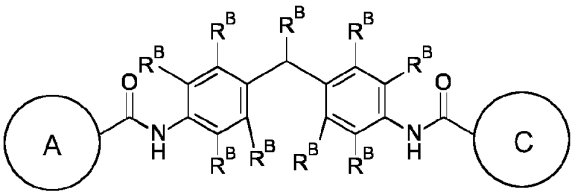
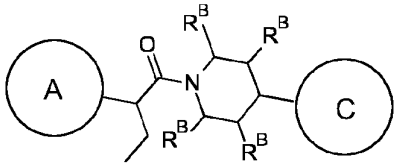
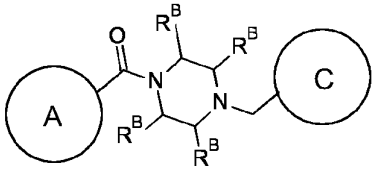


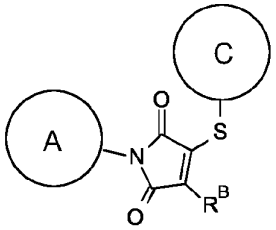
I-5



I-6



I-7



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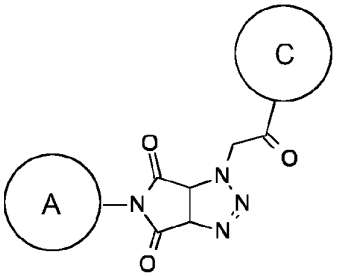

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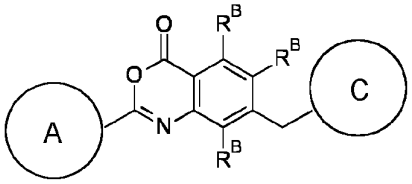

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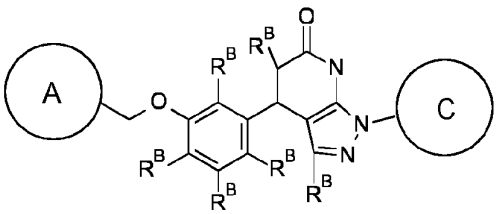

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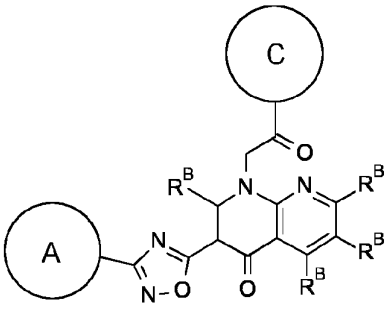
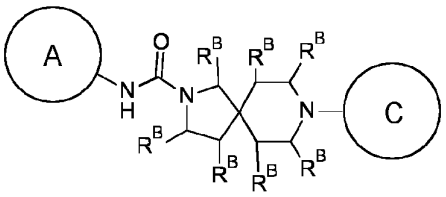


I-12



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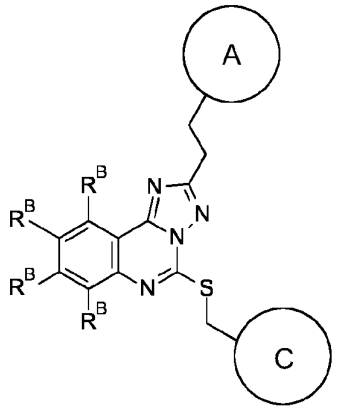
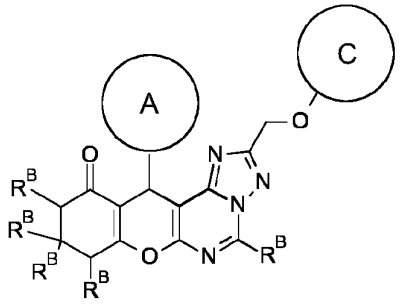
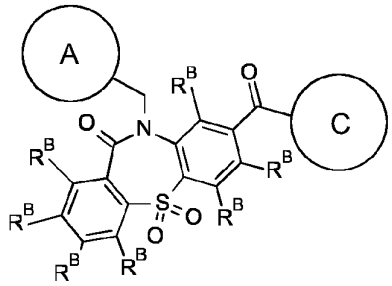


I-14



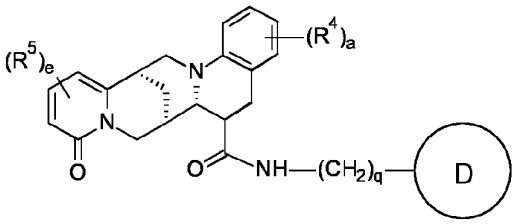
I-15



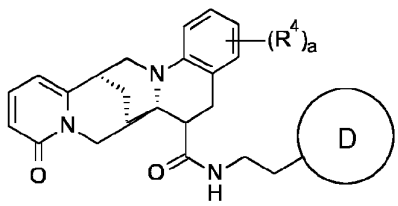
I-16

wherein cycle A, cycle C and R^B are as defined herein.

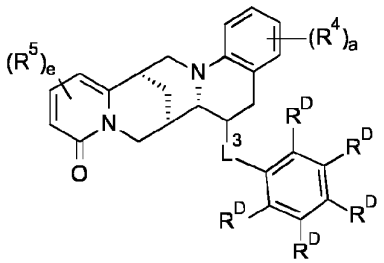
In some embodiments, the PTPRK inhibitor according to the present invention is a compound of Formula II-1, II-2 II-3, II-4 or II-5, or a stereoisomer, enantiomer, tautomer, solvate, hydrate, pharmaceutically acceptable salt, or prodrug thereof,

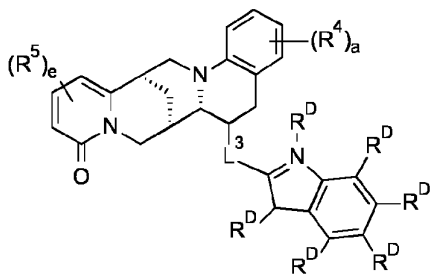


II-1

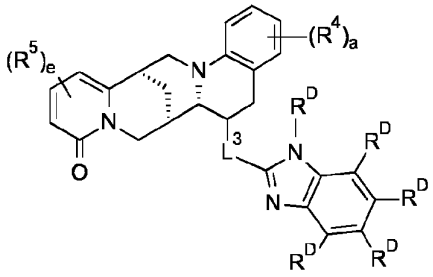


II-2





II-3 II-4

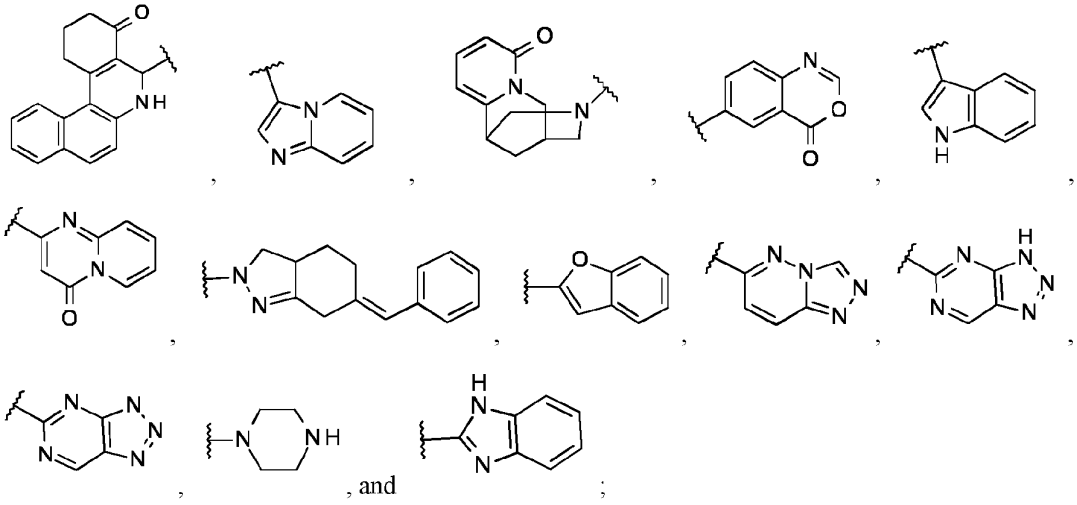


II-5,

wherein cycle D, a, e, q, R^4, R^5, R^D and L^3 are as defined herein.

In some embodiments, the PTPRK inhibitor according to the present invention is a compound of Formula I or Formula II, or a stereoisomer, enantiomer, tautomer, solvate, hydrate, pharmaceutically acceptable salt, or prodrug thereof, wherein,

cycle A is selected from the group consisting of C_{6-12}aryl, C_{3-12}cycloalkyl, C_{3-12}cycloalkenyl,



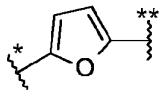
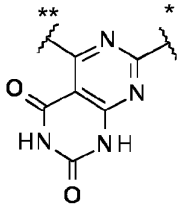
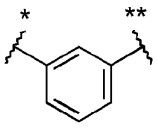
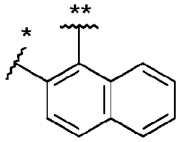
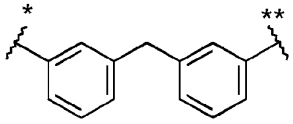
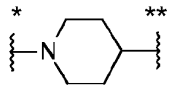
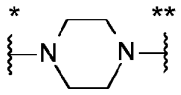
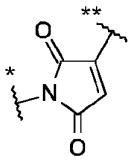
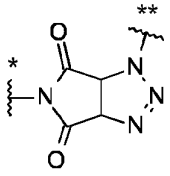
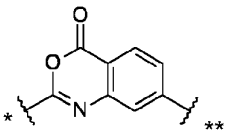
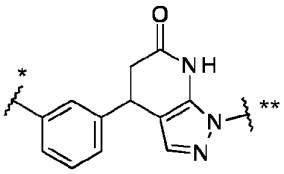
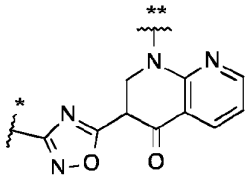
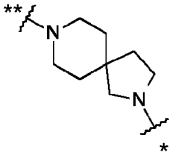
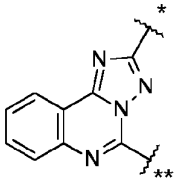
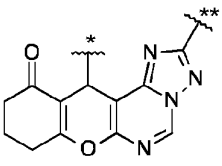
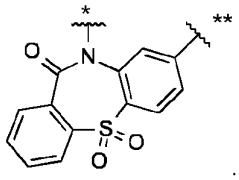
wherein the wavy line (〰) indicates the point of attachment of cycle A to the rest of the molecule, wherein said groups can be unsubstituted or substituted with one or more R^A;

each R^A is independently selected from the group consisting of hydrogen, halogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, haloC_{1-6}alkyl, haloC_{1-6}alkyloxy, cyanoC_{1-6}alkyl, C_{1-6}alkoxy, nitro, cyano, hydroxy, $-NR^1R^2$, $-NR^1R^2S(O)_2R^3$, $-NR^1R^2C(O)_2R^3$, $-C(O)R^3$, $-C(O)_2R^3$, $-S(O)_2R^3$, C_{6-12}aryl, and C_{1-6}alkylC_{6-12}aryl; wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, or C_{6-12}aryl can be unsubstituted or substituted with one, two or three halogen, nitro, hydroxy or C_{1-6}alkyl;

L^1 is a linker moiety selected from the group consisting of a single bond, -C(O)-, -NHC(O)-, -C(O)NH-, $-(CH_2)$n-, $-CH_2C(O)$-, $-C(O)CH_2$-, $-CH(CH_3)C(O)$-, $-C(O)CH(CH_3)$-, $-CH_2C(O)NH$-, $-NHC(O)CH_2$-, $-CH_2$-O-, -O-CH_2-, $-CH_2$-S-, -S-CH_2-, -O-, -S-, -S-$CH_2C(O)NH$-, $-NHC(O)CH_2$-S-, $-C(O)NH(CH_2)$g- and -CH=N-NH-C(O)-;

n is an integer selected from 1, 2, 3 or 4;

g is an integer selected from 1, 2, 3 or 4;

cycle B is selected from the group consisting of  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and  ;

wherein * represents where cycle B is bound to L^1; and ** represents where cycle B is bound to L^2, wherein said groups can be unsubstituted or substituted with one or more R^B;

each R^B is independently selected from the group consisting of hydrogen, halogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, haloC_{1-6}alkyl, haloC_{1-6}alkyloxy, cyanoC_{1-6}alkyl, C_{1-6}alkoxy, nitro, cyano, hydroxy, $-NR^1R^2$, $-NR^1R^2S(O)_2R^3$, $-NR^1R^2C(O)_2R^3$, $-C(O)R^3$, $-C(O)_2R^3$, $-S(O)_2R^3$, C_{6-12}aryl, and C_{1-6}alkylC_{6-12}aryl; wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, or C_{6-12}aryl can be unsubstituted or substituted with one, two or three halogen, nitro, hydroxy or C_{1-6}alkyl;

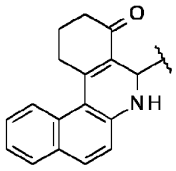
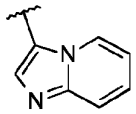
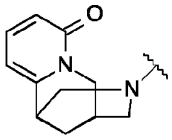
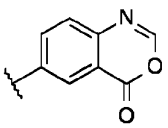
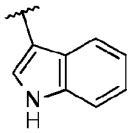
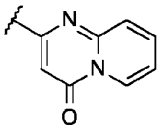
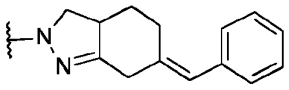
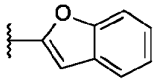
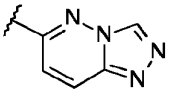
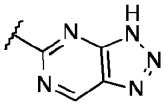
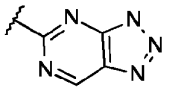
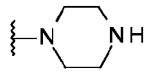
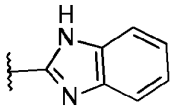
L^2 is a linker moiety selected from the group consisting of a single bond, -C(O)-, -NHC(O)-, -C(O)NH-, $-(CH_2)$m-, $-CH_2C(O)$-, $-C(O)CH_2$-, $-CH(CH_3)C(O)$-, $-C(O)CH(CH_3)$-, $-CH_2C(O)NH$-, $-NHC(O)CH_2$-

, -CH_2-O-, -O-CH_2-, -CH_2-S-, -S-CH_2-, -O-, -S-, -S-$CH_2C(O)NH$-, -$NHC(O)CH_2$-S-, -$C(O)NH(CH_2)$i- and -CH=N-NH-C(O)-;

m is an integer selected from 1, 2, 3 or 4;

i is an integer selected from 1, 2, 3 or 4;

cycle C is selected from the group consisting of C_{6-12}aryl, C_{3-12}cycloalkyl, C_{3-12}cycloalkenyl,














, and ;

wherein the wavy line ( ) indicates the point of attachment of cycle C to the rest of the molecule, wherein said groups can be unsubstituted or substituted with one or more R^C;

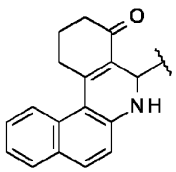
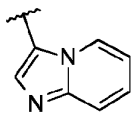
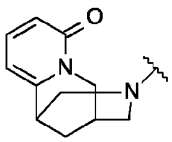
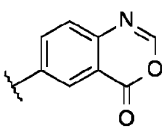
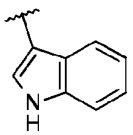
each R^C is independently selected from the group consisting of hydrogen, halogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, haloC_{1-6}alkyl, haloC_{1-6}alkyloxy, cyanoC_{1-6}alkyl, C_{1-6}alkoxy, nitro, cyano, hydroxy, -NR^1R^2, -$NR^1R^2S(O)_2R^3$, -$NR^1R^2C(O)_2R^3$, -$C(O)R^3$, -$C(O)_2R^3$, -$S(O)_2R^3$, C_{6-12}aryl, and C_{1-6}alkylC_{6-12}aryl; wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, or C_{6-12}aryl can be unsubstituted or substituted with one, two or three halogen, nitro, hydroxy or C_{1-6}alkyl;

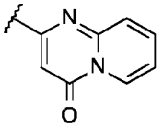
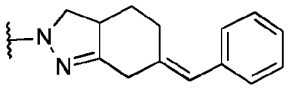
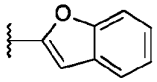
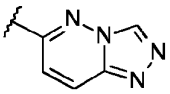
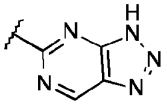
L^3 is a linker moiety selected from the group consisting of a single bond, -C(O)-, -NHC(O)-, -C(O)NH-, -(CH_2)j-, -$CH_2C(O)$-, -$C(O)CH_2$-, -$CH(CH_3)C(O)$-, -$C(O)CH(CH_3)$-, -$CH_2C(O)NH$-, -$NHC(O)CH_2$-, -CH_2-O-, -O-CH_2-, -CH_2-S-, -S-CH_2-, -O-, -S-, -S-$CH_2C(O)NH$-, -$NHC(O)CH_2$-S-, -$C(O)NH(CH_2)$q- and -CH=N-NH-C(O)-;

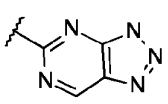
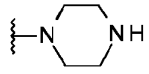
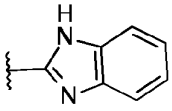
j is an integer selected from 1, 2, 3 or 4;

q is an integer selected from 1, 2, 3 or 4;

cycle D is selected from the group consisting of C_{6-12}aryl, C_{3-12}cycloalkyl, C_{3-12}cycloalkenyl,

 ,  ,  ,  ,  ,

 ,  , and  ;

wherein the wavy line (〰) indicates the point of attachment of cycle D to the rest of the molecule, wherein said groups can be unsubstituted or substituted with one or more R^D;

each R^D is independently selected from the group consisting of hydrogen, halogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, haloC_{1-6}alkyl, haloC_{1-6}alkyloxy, cyanoC_{1-6}alkyl, C_{1-6}alkoxy, nitro, cyano, hydroxy, $-NR^1R^2$, $-NR^1R^2S(O)_2R^3$, $-NR^1R^2C(O)_2R^3$, $-C(O)R^3$, $-C(O)_2R^3$, $-S(O)_2R^3$, C_{6-12}aryl, and C_{1-6}alkylC_{6-12}aryl; wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, or C_{6-12}aryl can be unsubstituted or substituted with one, two or three halogen, nitro, hydroxy or C_{1-6}alkyl;

each R^1 is independently selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, and C_{6-12}aryl, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, or C_{6-12}aryl can be unsubstituted or substituted with one, two or three halogen, nitro, hydroxy or C_{1-6}alkyl;

each R^2 is independently selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, and C_{6-12}aryl, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, or C_{6-12}aryl can be unsubstituted or substituted with one, two or three halogen, nitro, hydroxy or C_{1-6}alkyl;

each R^3 is independently selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, and C_{6-12}aryl, wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, or C_{6-12}aryl can be unsubstituted or substituted with one, two or three halogen, nitro, hydroxy or C_{1-6}alkyl;

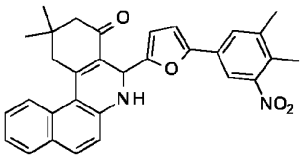
a is an integer selected from 1, 2, 3 or 4;

each R^4 is independently selected from the group consisting of hydrogen, halogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, haloC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkoxy, nitro, cyano, hydroxy, $-NR^1R^2$, $-NR^1R^2S(O)_2R^3$, $-NR^1R^2C(O)_2R^3$, $-C(O)R^3$, $-C(O)_2R^3$, $-S(O)_2R^3$, C_{6-12}aryl, and C_{1-6}alkylC_{6-12}aryl; wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, or C_{6-12}aryl can be unsubstituted or substituted with one, two or three halogen, nitro, hydroxy or C_{1-6}alkyl;

e is an integer selected from 1, 2, or 3;

each R^5 is independently selected from the group consisting of hydrogen, halogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, haloC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkoxy, nitro, cyano, hydroxy, $-NR^1R^2$, $-NR^1R^2S(O)_2R^3$, $-NR^1R^2C(O)_2R^3$, $-C(O)R^3$, $-C(O)_2R^3$, $-S(O)_2R^3$, C_{6-12}aryl, and C_{1-6}alkylC_{6-12}aryl; wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, or C_{6-12}aryl can be unsubstituted or substituted with one, two or three halogen, nitro, hydroxy or C_{1-6}alkyl.

In some embodiments the PTPRK inhibitor according to the present invention is a compound selected from: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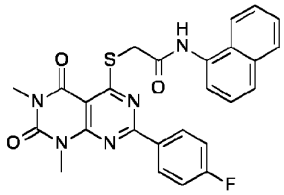
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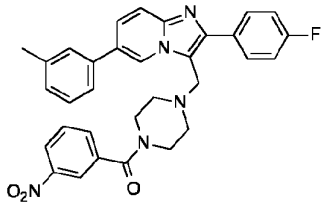
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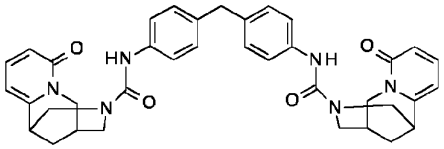
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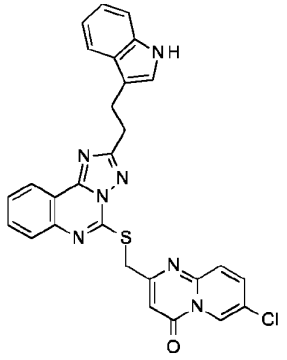
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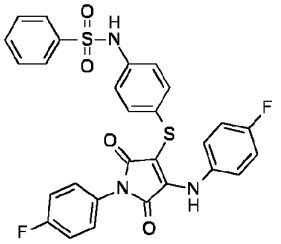
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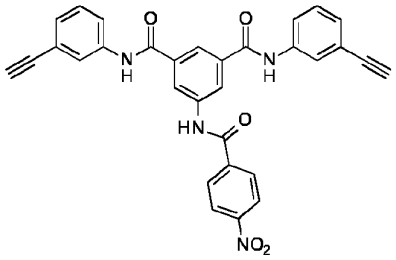
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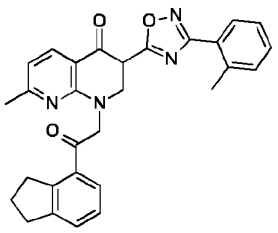
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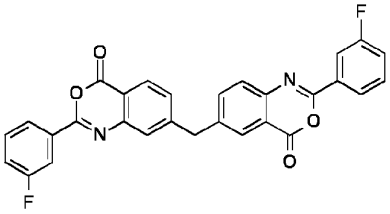
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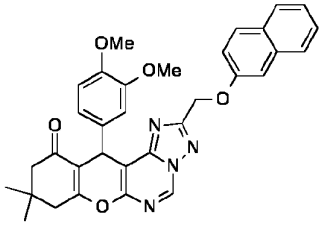
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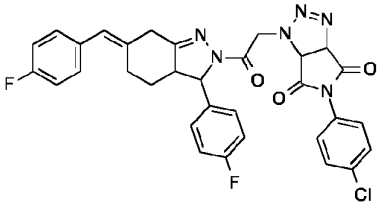
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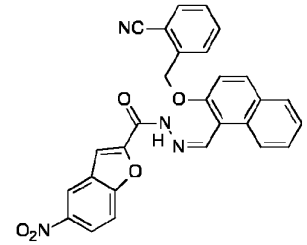
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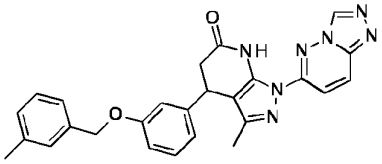
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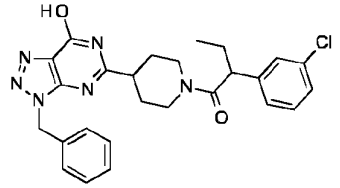
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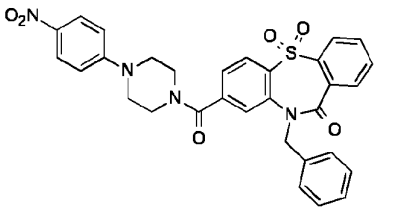
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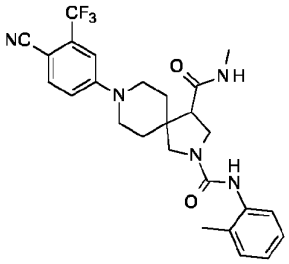
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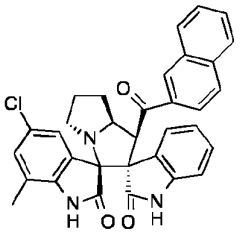
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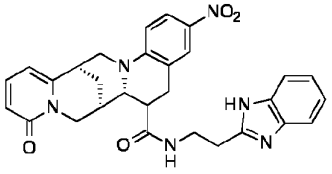
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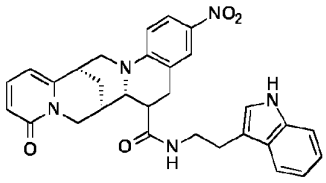
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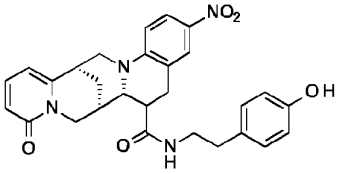
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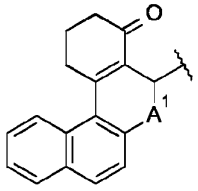
In some embodiments cycle A is from the group consisting of C_{6-12}aryl, C_{3-8}cycloalkyl, C_{3-8}cycloalkenyl, 
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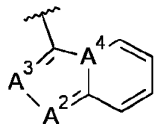
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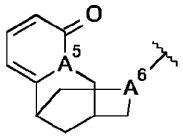
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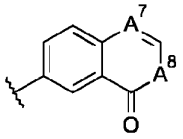
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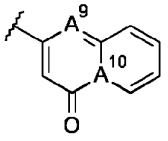
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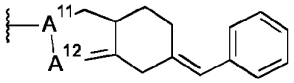
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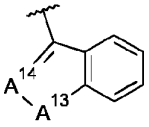
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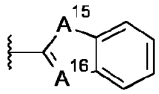
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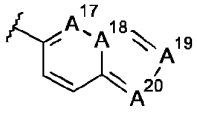
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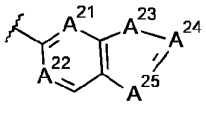
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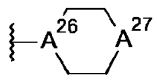
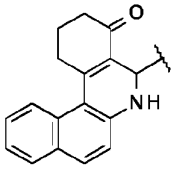

; preferably cycle A is C_{6-12}aryl, C_{3-10}cycloalkyl, C_{3-10}cycloalkenyl, 
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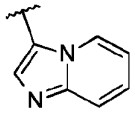
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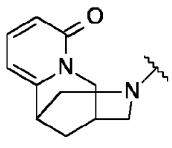
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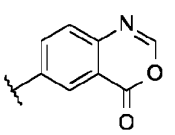
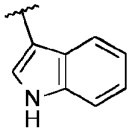
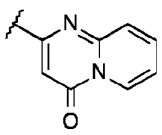
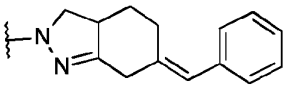
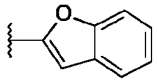
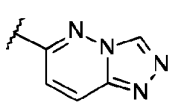
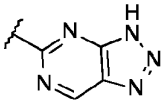
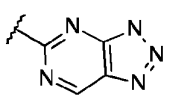
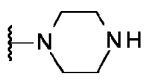
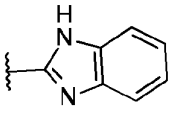
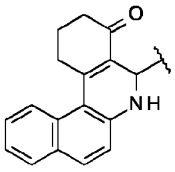
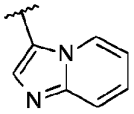
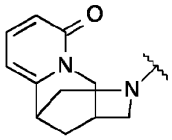
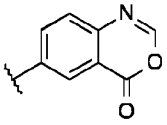
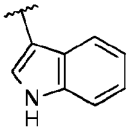
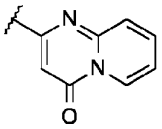
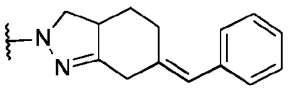
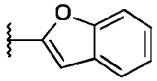
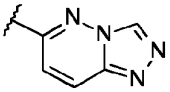
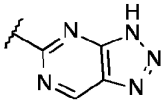
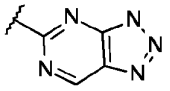
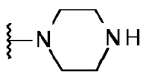
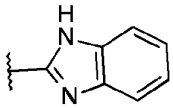











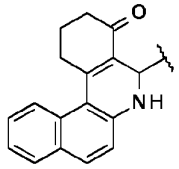
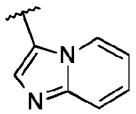
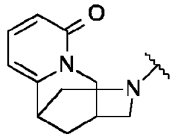
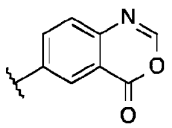
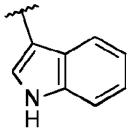
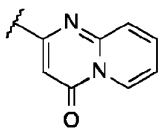
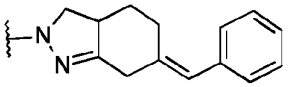
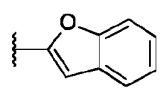
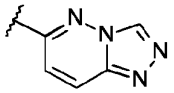
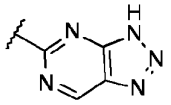
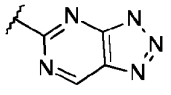
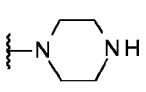
, and ;

preferably cycle A is phenyl, naphtyl, indanyl, anthracenyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkenyl,

, and ; preferably cycle A is phenyl, naphtyl,

indanyl, anthracenyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkenyl,

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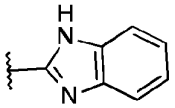
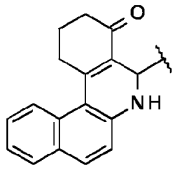
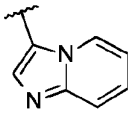
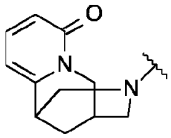
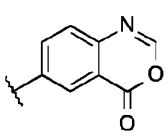
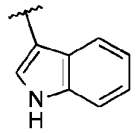
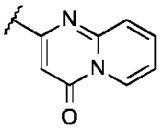
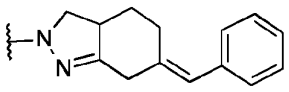
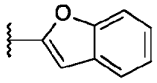
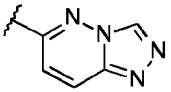
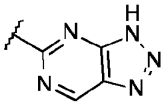
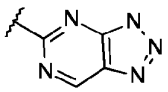
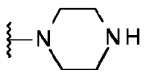
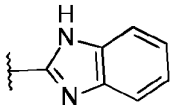
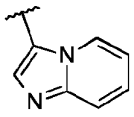
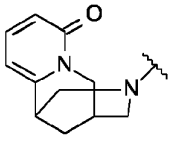
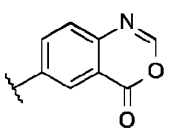
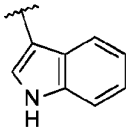
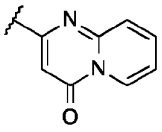
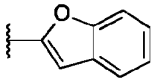
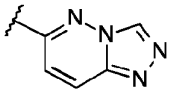
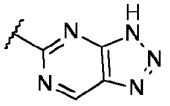
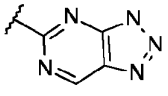
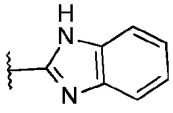


; preferably cycle A is phenyl, naphtyl, indanyl, anthracenyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicycle[2.2.1]heptan-2yl, (1S,4R)-norbornan-2-yl, (1R,4R)-norbornan-2-yl, (1S,4S)-norbornan-2-yl, (1R,4S)-norbornan-2-yl, 1-

adamantyl              and ; preferably cycle A is phenyl, naphtyl, indanyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicycle[2.2.1]heptan-2yl, (1S,4R)-norbornan-2-yl, (1R,4R)-norbornan-2-yl, 1-adamantyl          and  ;

wherein the wavy line (〰) indicates the point of attachment of cycle A to the rest of the molecule, wherein said groups can be unsubstituted or substituted with one or more R^A; preferably said groups can be unsubstituted or substituted with one, two, three or four R^A.

In some embodiments A^1 is selected from the group consisting of NR^A, CHR^A, and O.

In some embodiments A^2, and A^4 are N and A^3 is N or CR^A.

In some embodiments A^5 is N or CR^A and A^6 is N.

In some embodiments A^7 is N and A^8 is selected from the group consisting of NR^A, CHR^A, and O.

In some embodiments A^{10} is N or CR^A and A^9 is N.

In some embodiments A^{11} is N or CR^A and A^{12} is N.

In some embodiments A^{16} is CR^A and A^{15} is selected from the group consisting of NR^A, S, and O.

In some embodiments A^{16} is N and A^{15} is selected from the group consisting of NR^A, S, and O.

In some embodiments A^{17} and A^{19} are N or CR^A and A^{18} and A^{20} are N.

In some embodiments A^{17}, A^{18} and A^{19} are N or CR^A and A^{20} is N.

In some embodiments A^{18}, A^{19} and A^{20} are N or CR^A and A^{17} is N.

In some embodiments A^{21} and A^{25} are N or CR^A, A^{22} and A^{24} are N and A^{23} is selected from the group consisting of NR^A, CHR^A, and O.

In some embodiments A^{21}, A^{22} and A^{24} are N or CR^A, A^{25} is N and A^{23} is selected from the group consisting of NR^A, CHR^A, and O.

In some embodiments A^{27} is N, CR^A or O and A^{26} is N.

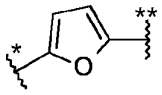
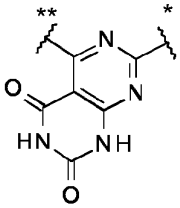
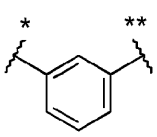
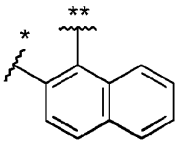
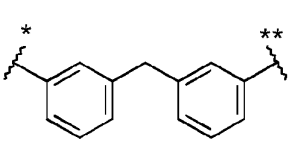
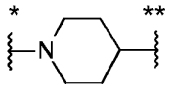
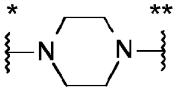
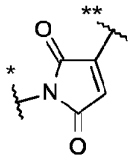
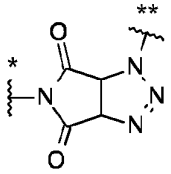
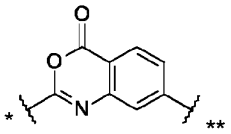
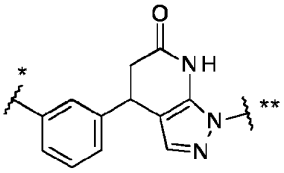
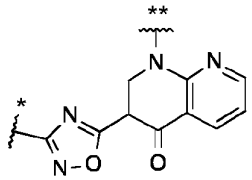
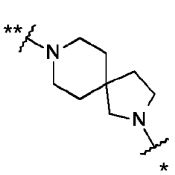
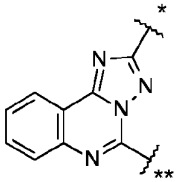
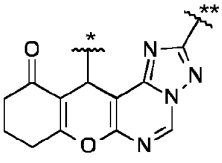
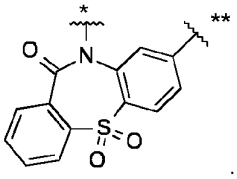
In some embodiments each R^A is independently selected from the group consisting of hydrogen, halogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, haloC_{1-6}alkyl, haloC_{1-6}alkyloxy, cyanoC_{1-6}alkyl, C_{1-6}alkoxy, nitro, cyano, hydroxy, amino, mono-C_{1-6}alkylamino, di-C_{1-6}alkylamino, mono-C_{6-12}arylamino, di-C_{6-12}arylamino, $-NR^1R^2S(O)_2R^3$, $-NR^1R^2C(O)_2R^3$, -C(O)H, C_{1-6}alkylcarbonyl, C_{6-12}arylcarbonyl, $-C(O)_2H$, C_{1-6}alkyloxycarbonyl, C_{6-12}aryloxycarbonyl, $-S(O)_2H$, C_{1-6}alkylsulfonyl, C_{6-12}arylsulfonyl, C_{6-12}aryl, and C_{1-6}alkylC_{6-12}aryl; preferably each R^A is selected from hydrogen, halogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, haloC_{1-6}alkyl, cyanoC_{1-6}alkyl, haloC_{1-6}alkyloxy, C_{1-6}alkoxy, nitro, cyano, hydroxy, amino, mono-C_{1-6}alkylamino, mono-C_{6-12}arylamino, $-NR^1R^2S(O)_2R^3$, $-NR^1R^2C(O)_2R^3$, C_{1-6}alkylcarbonyl, $-C(O)_2H$, C_{1-6}alkyloxycarbonyl, $-S(O)_2H$, C_{1-6}alkylsulfonyl, C_{6-12}aryl, and C_{1-6}alkylC_{6-12}aryl; preferably each R^A is selected from hydrogen, halogen, C_{1-4}alkyl, C_{2-4}alkynyl, haloC_{1-4}alkyl, haloC_{1-4}alkyloxy, cyanoC_{1-4}alkyl, C_{1-4}alkoxy, nitro, cyano, hydroxy, amino, mono-C_{1-4}alkylamino, mono-C_{6-12}arylamino, $-NR^1R^2S(O)_2R^3$, C_{1-4}alkylcarbonyl, $-C(O)_2H$, C_{1-4}alkyloxycarbonyl, $-S(O)_2H$, C_{1-4}alkylsulfonyl, C_{6-12}aryl, and C_{1-4}alkylC_{6-12}aryl; preferably each R^A is selected from hydrogen, fluroro, chloro, bromo, iodo, C_{1-4}alkyl, C_{2-4}alkynyl, haloC_{1-4}alkyl, cyanoC_{1-4}alkyl, C_{1-4}alkoxy, nitro, cyano, hydroxy, amino, mono-C_{1-4}alkylamino, mono-C_{6-12}arylamino, $-NR^1R^2S(O)_2R^3$, C_{6-12}aryl, and C_{1-4}alkylC_{6-12}aryl;

wherein said groups can be unsubstituted or substituted with one, two or three halogen, nitro, hydroxy or C_{1-6}alkyl;

In some embodiments, n is an integer selected from 1, 2 or 3.

In some embodiments, g is an integer selected from 1, 2 or 3.

In some embodiments L^1 is a linker moiety selected from the group consisting of a single bond, -C(O)-, -NHC(O)-, -C(O)NH-, $-CH_2-$, $-(CH_2)_2-$, $-(CH_2)_3-$, $-CH_2C(O)-$, $-C(O)CH_2-$, $-CH(CH_3)C(O)-$, $-C(O)CH(CH_3)-$, $-CH_2C(O)NH-$, $-NHC(O)CH_2-$, $-CH_2-O-$, $-O-CH_2-$, $-CH_2-S-$, $-S-CH_2-$, -O-, -S-, $-S-CH_2C(O)NH-$, $-NHC(O)CH_2-S-$, $-C(O)NHCH_2-$, $-C(O)NH(CH_2)_2-$, $-C(O)NH(CH_2)_3-$ and -CH=N-NH-C(O)-; preferably L^1 is selected from a single bond, -C(O)-, -NHC(O)-, -C(O)NH-, $-CH_2-$, $-(CH_2)_2-$, $-(CH_2)_3-$, $-CH_2C(O)-$, $-C(O)CH_2-$, $-CH(CH_3)C(O)-$, $-C(O)CH(CH_3)-$, $-CH_2-O-$, $-O-CH_2-$, $-CH_2-S-$, $-S-CH_2-$, -O-, -S-, $-S-CH_2C(O)NH-$, $-NHC(O)CH_2-S-$, and -CH=N-NH-C(O)-; preferably L^1 is selected from a single bond, -C(O)-, -NHC(O)-, -C(O)NH-, $-CH_2-$, $-(CH_2)_2-$, $-CH(CH_3)C(O)-$, $-C(O)CH(CH_3)-$, $-CH_2-O-$, $-O-CH_2-$, $-CH_2-S-$, $-S-CH_2-$, -O-, and -S-.

In some embodiments cycle B is selected from the group consisting of  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and ;

wherein * represents where cycle B is bound to L^1; and ** represents where cycle B is bound to L^2, wherein said groups can be unsubstituted or substituted with one, two, three or four R^B.

In some embodiments B^1 is selected from the group consisting of NR^B, S, and O.

In some embodiments B^4, and B^5 are N and B^2 and B^3 are selected from the group consisting of NR^B, S, and O.

In some embodiments B^7 is N or CR^B and A^6 is N.

In some embodiments B^9 is N or CR^B and B^8 is N.

In some embodiments B^{12} and B^{13} are N or CR^B and B^{10} and B^{11} are N.

In some embodiments B^{15} is N and B^{15} is selected from the group consisting of NR^B, S, and O.

In some embodiments B^{17}, and B^{18} are N and B^{16} is selected from the group consisting of NR^B, S, and O.

In some embodiments B^{20} and B^{23} are N or CR^B; B^{19} and B^{22} are N and B^{21} is selected from the group consisting of NR^B, S, and O.

In some embodiments B^{19} and B^{22} are N or CR^B; B^{20} and B^{23} are N and B^{21} is selected from the group consisting of NR^B, S, and O.

In some embodiments B^{31} and B^{33} are N or CR^B; B^{32} and B^{34} are N and B^{30} is selected from the group consisting of NR^B, S, and O.

In some embodiments B^{32} and B^{34} are N or CR^B; B^{31} and B^{33} are N and B^{30} is selected from the group consisting of NR^B, S, and O.

In some embodiments B^{35} is N and B^{36} is selected from the group consisting of NR^B, S, $S(O)_2$ and O.

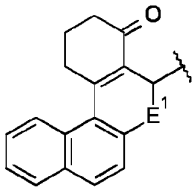
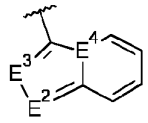
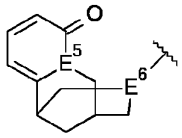
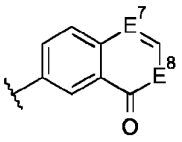
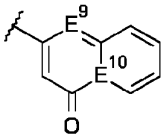
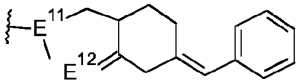
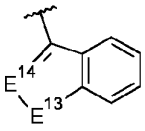
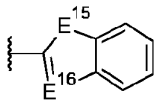
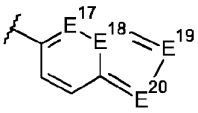
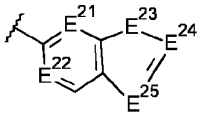
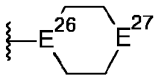
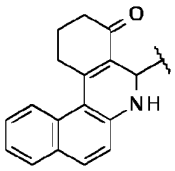
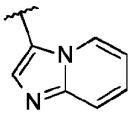
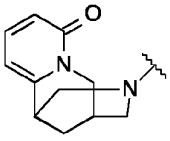
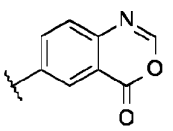
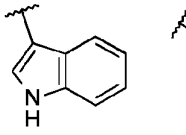
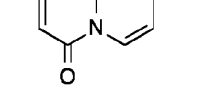
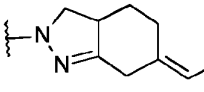
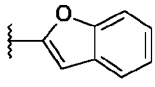
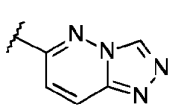
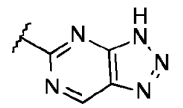
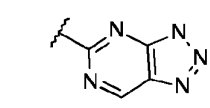
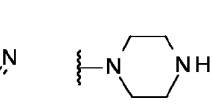
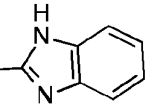
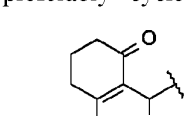
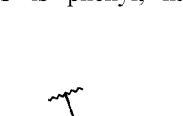
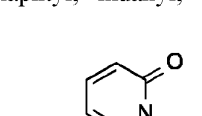
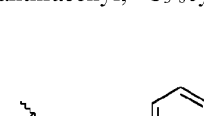
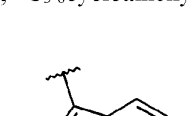
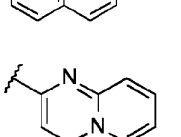
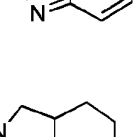
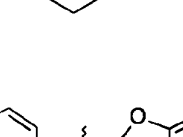
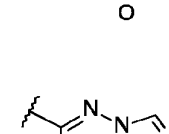
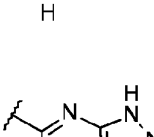
In some embodiments each R^B is independently selected from the group consisting of hydrogen, halogen, $C_{1\text{-}6}$alkyl, $C_{2\text{-}6}$alkenyl, $C_{2\text{-}6}$alkynyl, halo$C_{1\text{-}6}$alkyl, halo$C_{1\text{-}6}$alkyloxy, cyano$C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$alkoxy, nitro, cyano, hydroxy, amino, mono-$C_{1\text{-}6}$alkylamino, di-$C_{1\text{-}6}$alkylamino, mono-$C_{6\text{-}12}$arylamino, di-$C_{6\text{-}12}$arylamino, $-NR^1R^2S(O)_2R^3$, $-NR^1R^2C(O)_2R^3$, -C(O)H, $C_{1\text{-}6}$alkylcarbonyl, $C_{6\text{-}12}$arylcarbonyl, $-C(O)_2H$, $C_{1\text{-}6}$alkyloxycarbonyl, $C_{6\text{-}12}$aryloxycarbonyl, $-S(O)_2H$, $C_{1\text{-}6}$alkylsulfonyl, $C_{6\text{-}12}$arylsulfonyl, $C_{6\text{-}12}$aryl, and $C_{1\text{-}6}$alkyl$C_{6\text{-}12}$aryl; preferably each R^B is selected from hydrogen, halogen, $C_{1\text{-}6}$alkyl, $C_{2\text{-}6}$alkenyl, $C_{2\text{-}6}$alkynyl, halo$C_{1\text{-}6}$alkyl, cyano$C_{1\text{-}6}$alkyl, halo$C_{1\text{-}6}$alkyloxy, $C_{1\text{-}6}$alkoxy, nitro, cyano, hydroxy, amino, mono-$C_{1\text{-}6}$alkylamino, mono-$C_{6\text{-}12}$arylamino, $-NR^1R^2S(O)_2R^3$, $-NR^1R^2C(O)_2R^3$, $C_{1\text{-}6}$alkylcarbonyl, $-C(O)_2H$, $C_{1\text{-}6}$alkyloxycarbonyl, $-S(O)_2H$, $C_{1\text{-}6}$alkylsulfonyl, $C_{6\text{-}12}$aryl, and $C_{1\text{-}6}$alkyl$C_{6\text{-}12}$aryl; preferably each R^B is selected from hydrogen, halogen, $C_{1\text{-}4}$alkyl, $C_{2\text{-}4}$alkynyl, halo$C_{1\text{-}4}$alkyl, halo$C_{1\text{-}4}$alkyloxy, cyano$C_{1\text{-}4}$alkyl, $C_{1\text{-}4}$alkoxy, nitro, cyano, hydroxy, amino, mono-$C_{1\text{-}4}$alkylamino, mono-$C_{6\text{-}12}$arylamino, $-NR^1R^2S(O)_2R^3$, $C_{1\text{-}4}$alkylcarbonyl, $-C(O)_2H$, $C_{1\text{-}4}$alkyloxycarbonyl, $-S(O)_2H$, $C_{1\text{-}4}$alkylsulfonyl, $C_{6\text{-}12}$aryl, and $C_{1\text{-}4}$alkyl$C_{6\text{-}12}$aryl; preferably each R^B is selected from hydrogen, fluoro, chloro, bromo, iodo, $C_{1\text{-}4}$alkyl, $C_{2\text{-}4}$alkynyl, halo$C_{1\text{-}4}$alkyl, cyano$C_{1\text{-}4}$alkyl, $C_{1\text{-}4}$alkoxy, nitro, cyano, hydroxy, amino, mono-$C_{1\text{-}4}$alkylamino, mono-$C_{6\text{-}12}$arylamino, $-NR^1R^2S(O)_2R^3$, $C_{6\text{-}12}$aryl, and $C_{1\text{-}4}$alkyl$C_{6\text{-}12}$aryl;

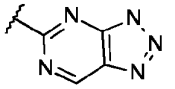
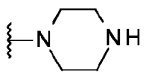
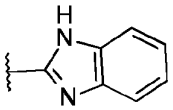
wherein said groups can be unsubstituted or substituted with one, two or three halogen, nitro, hydroxy or $C_{1\text{-}6}$alkyl;

In some embodiments, m is an integer selected from 1, 2 or 3.

In some embodiments, i is an integer selected from 1, 2 or 3.

In some embodiments L^2 is a linker moiety selected from the group consisting of a single bond, -C(O)-, -NHC(O)-, -C(O)NH-, $-CH_2-$, $-(CH_2)_2-$, $-(CH_2)_3-$, $-CH_2C(O)-$, $-C(O)CH_2-$, $-CH(CH_3)C(O)-$, $-C(O)CH(CH_3)-$, $-CH_2C(O)NH-$, $-NHC(O)CH_2-$, $-CH_2-O-$, $-O-CH_2-$, $-CH_2-S-$, $-S-CH_2-$, -O-, -S-, $-S-CH_2C(O)NH-$, $-NHC(O)CH_2-S-$, $-C(O)NHCH_2-$, $-C(O)NH(CH_2)_2-$, $-C(O)NH(CH_2)_3-$ and -CH=N-NH-C(O)-; preferably L^2 is selected from a single bond, -C(O)-, -NHC(O)-, -C(O)NH-, $-CH_2-$, $-(CH_2)_2-$, $-(CH_2)_3-$, $-CH_2C(O)-$, $-C(O)CH_2-$, $-CH(CH_3)C(O)-$, $-C(O)CH(CH_3)-$, $-CH_2-O-$, $-O-CH_2-$, $-CH_2-S-$, $-S-CH_2-$, -O-, -S-, $-S-CH_2C(O)NH-$, $-NHC(O)CH_2-S-$, and -CH=N-NH-C(O)-; preferably L^2 is selected from a single bond, -C(O)-, $-CH_2-$, $-(CH_2)_2-$, $-(CH_2)_3-$, $-CH_2C(O)-$, $-C(O)CH_2-$, $-CH_2-O-$, $-O-CH_2-$, $-CH_2-S-$, $-S-CH_2-$, -O-, -S-, $-S-CH_2C(O)NH-$, $-NHC(O)CH_2-S-$, and -CH=N-NH-C(O)-.

In some embodiments cycle C is from the group consisting of C_{6-12}aryl, C_{3-8}cycloalkyl, C_{3-8}cycloalkenyl,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and  ; preferably cycle C is C_{6-12}aryl, C_{3-10}cycloalkyl, C_{3-10}cycloalkenyl,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and ; preferably cycle C is phenyl, naphtyl, indanyl, anthracenyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkenyl,  ,  ,  ,  ,  ,  , ,  , , .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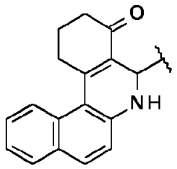
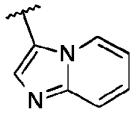
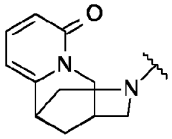
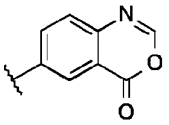
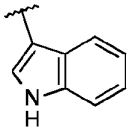
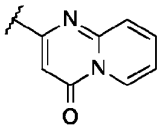
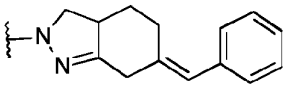
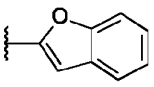
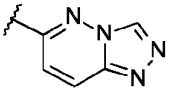
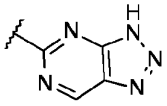
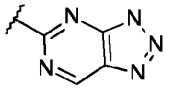
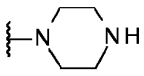
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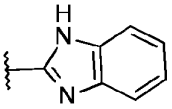
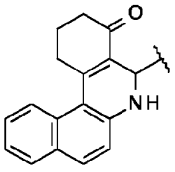
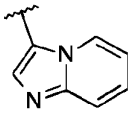
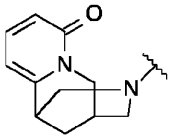
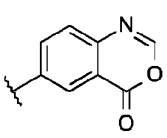
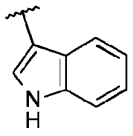
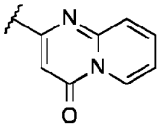
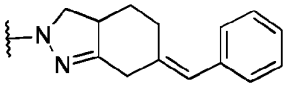
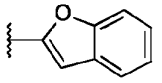
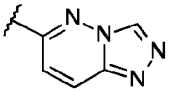
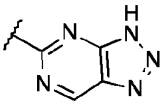
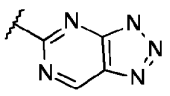
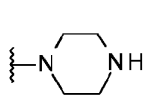
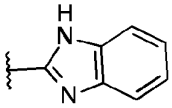

; preferably cycle C is phenyl, naphtyl, anthracenyl, indanyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicycle[2.2.1]heptan-2yl, (1S,4R)-norbornan-2-yl, (1R,4R)-norbornan-2-yl, (1S,4S)-norbornan-2-yl, (1R,4S)-norbornan-2-yl, 1-adamantyl













, and

;

wherein the wavy line ( ) indicates the point of attachment of cycle C to the rest of the molecule, wherein said groups can be unsubstituted or substituted with one or more R^C; preferably said groups can be unsubstituted or substituted with one, two, three or four R^C.

In some embodiments E^1 is selected from the group consisting of NR^C, CHR^C, and O.

In some embodiments E^2, and E^4 are N and E^3 is N or CR^C.

In some embodiments E^5 is N or CR^C and E^6 is N.

In some embodiments E^7 is N and E^8 is selected from the group consisting of NR^C, CHR^C, and O.

In some embodiments E^{10} is N or CR^C and E^9 is N.

In some embodiments E^{11} is N or CR^C and E^{12} is N.

In some embodiments E^{16} is CR^C and E^{15} is selected from the group consisting of NR^C, S, and O.

In some embodiments E^{16} is N and E^{15} is selected from the group consisting of NR^C, S, and O.

In some embodiments E^{17} and E^{19} are N or CR^C and E^{18} and E^{20} are N.

In some embodiments E^{17}, E^{18} and E^{19} are N or CR^C and E^{20} is N.

In some embodiments E^{18}, E^{19} and E^{20} are N or CR^C and E^{17} is N.

In some embodiments E^{21} and E^{25} are N or CR^C, E^{22} and E^{24} are N and E^{23} is selected from the group consisting of NR^C, CHR^C, and O.

In some embodiments E^{21}, E^{22} and E^{24} are N or CR^C, E^{25} is N and E^{23} is selected from the group consisting of NR^C, CHR^C, and O.

In some embodiments E^{27} is N, CR^C or O and E^{26} is N.

In some embodiments each R^C is independently selected from the group consisting of hydrogen, halogen, $C_{1\text{-}6}$alkyl, $C_{2\text{-}6}$alkenyl, $C_{2\text{-}6}$alkynyl, halo$C_{1\text{-}6}$alkyl, halo$C_{1\text{-}6}$alkyloxy, cyano$C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$alkoxy, nitro, cyano, hydroxy, amino, mono-$C_{1\text{-}6}$alkylamino, di-$C_{1\text{-}6}$alkylamino, mono-$C_{6\text{-}12}$arylamino, di-$C_{6\text{-}12}$arylamino, $-NR^1R^2S(O)_2R^3$, $-NR^1R^2C(O)_2R^3$, -C(O)H, $C_{1\text{-}6}$alkylcarbonyl, $C_{6\text{-}12}$arylcarbonyl, $-C(O)_2H$, $C_{1\text{-}6}$alkyloxycarbonyl, $C_{6\text{-}12}$aryloxycarbonyl, $-S(O)_2H$, $C_{1\text{-}6}$alkylsulfonyl, $C_{6\text{-}12}$arylsulfonyl, $C_{6\text{-}12}$aryl, and $C_{1\text{-}6}$alkyl$C_{6\text{-}12}$aryl; preferably each R^C is selected from hydrogen, halogen, $C_{1\text{-}6}$alkyl, $C_{2\text{-}6}$alkenyl, $C_{2\text{-}6}$alkynyl, halo$C_{1\text{-}6}$alkyl, cyano$C_{1\text{-}6}$alkyl, halo$C_{1\text{-}6}$alkyloxy, $C_{1\text{-}6}$alkoxy, nitro, cyano, hydroxy, amino, mono-$C_{1\text{-}6}$alkylamino, mono-$C_{6\text{-}12}$arylamino, $-NR^1R^2S(O)_2R^3$, $-NR^1R^2C(O)_2R^3$, $C_{1\text{-}6}$alkylcarbonyl, $-C(O)_2H$, $C_{1\text{-}6}$alkyloxycarbonyl, $-S(O)_2H$, $C_{1\text{-}6}$alkylsulfonyl, $C_{6\text{-}12}$aryl, and $C_{1\text{-}6}$alkyl$C_{6\text{-}12}$aryl; preferably each R^C is selected from hydrogen, halogen, $C_{1\text{-}4}$alkyl, $C_{2\text{-}4}$alkynyl, halo$C_{1\text{-}4}$alkyl, halo$C_{1\text{-}4}$alkyloxy, cyano$C_{1\text{-}4}$alkyl, $C_{1\text{-}4}$alkoxy, nitro, cyano, hydroxy, amino, mono-$C_{1\text{-}4}$alkylamino, mono-$C_{6\text{-}12}$arylamino, $-NR^1R^2S(O)_2R^3$, $C_{1\text{-}4}$alkylcarbonyl, $-C(O)_2H$, $C_{1\text{-}4}$alkyloxycarbonyl, $-S(O)_2H$, $C_{1\text{-}4}$alkylsulfonyl, $C_{6\text{-}12}$aryl, and $C_{1\text{-}4}$alkyl$C_{6\text{-}12}$aryl; preferably each R^C is selected from hydrogen, fluroro, chloro, bromo, iodo, $C_{1\text{-}4}$alkyl, $C_{2\text{-}4}$alkynyl, halo$C_{1\text{-}4}$alkyl, cyano$C_{1\text{-}4}$alkyl, $C_{1\text{-}4}$alkoxy, nitro, cyano, hydroxy, amino, mono-$C_{1\text{-}4}$alkylamino, mono-$C_{6\text{-}12}$arylamino, $-NR^1R^2S(O)_2R^3$, $C_{6\text{-}12}$aryl, and $C_{1\text{-}4}$alkyl$C_{6\text{-}12}$aryl;

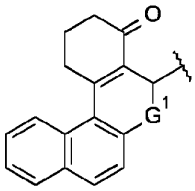
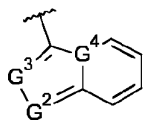
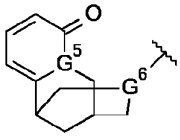
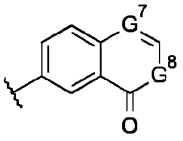
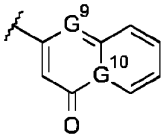
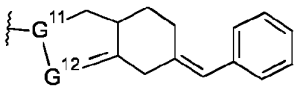
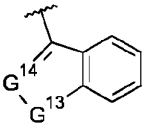
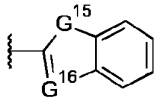
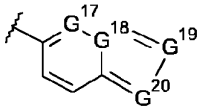
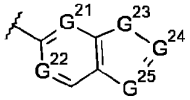
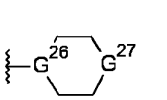
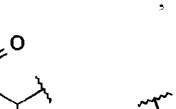
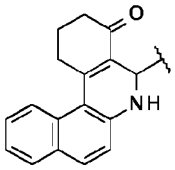
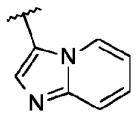
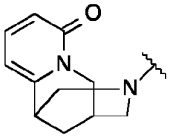
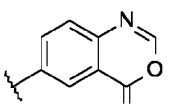
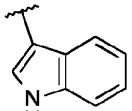
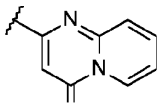
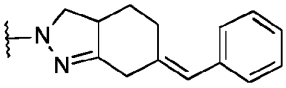
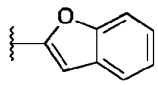
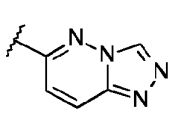
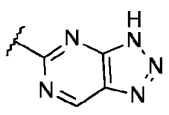
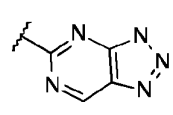
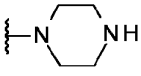
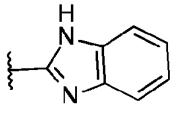
wherein said groups can be unsubstituted or substituted with one, two or three halogen, nitro, hydroxy or $C_{1\text{-}6}$alkyl;

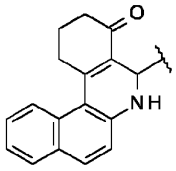
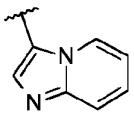
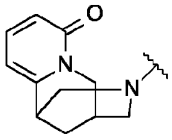
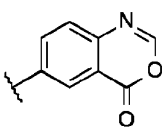
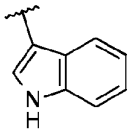
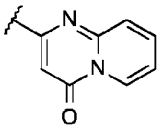
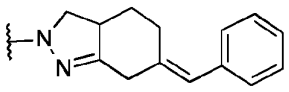
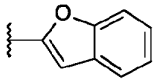
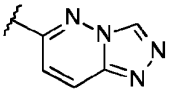
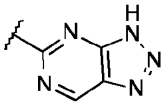
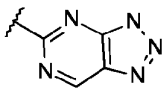
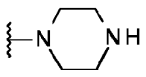
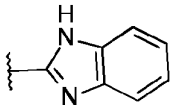
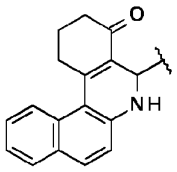
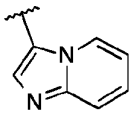
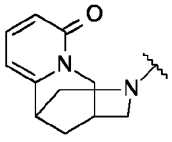
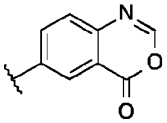
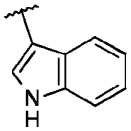
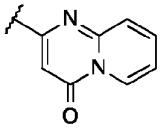
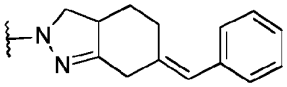
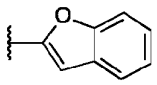
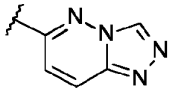
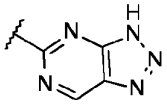
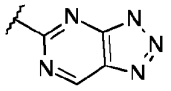
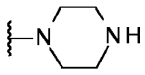
In some embodiments, j is an integer selected from 1, 2 or 3.

In some embodiments, q is an integer selected from 1, 2 or 3.

In some embodiments L^3 is a linker moiety selected from the group consisting of a single bond, -C(O)-, -NHC(O)-, -C(O)NH-, $-CH_2-$, $-(CH_2)_2-$, $-(CH_2)_3-$, $-CH_2C(O)-$, $-C(O)CH_2-$, $-CH(CH_3)C(O)-$, $-C(O)CH(CH_3)-$, $-CH_2C(O)NH-$, $-NHC(O)CH_2-$, $-CH_2-O-$, $-O-CH_2-$, $-CH_2-S-$, $-S-CH_2-$, -O-, -S-, -S-

$CH_2C(O)NH$-, -$C(O)NHCH_2$-, -$C(O)NH(CH_2)_2$-, -$C(O)NH(CH_2)_3$- and -CH=N-NH-C(O)-; preferably L^3 is selected from -C(O)-, -NHC(O)-, -C(O)NH-, -$(CH_2)_2$-, -$(CH_2)_3$-, -$CH_2C(O)$-, -$C(O)CH_2$-, -$CH(CH_3)C(O)$-, -$C(O)CH(CH_3)$-, -$CH_2C(O)NH$-, -$NHC(O)CH_2$-, -S-$CH_2C(O)NH$-, -$NHC(O)CH_2$-S-, -$C(O)NHCH_2$-, -$C(O)NH(CH_2)_2$-, -$C(O)NH(CH_2)_3$- and -CH=N-NH-C(O)-; preferably L^3 is selected from - -NHC(O)-, -C(O)NH-, -$(CH_2)_2$-, -$(CH_2)_3$-, -$CH_2C(O)$-, -$C(O)CH_2$-, -$C(O)CH(CH_3)$-, -$CH_2C(O)NH$-, -$NHC(O)CH_2$-, -S-$CH_2C(O)NH$-, -$NHC(O)CH_2$-S-, -$C(O)NHCH_2$-, -$C(O)NH(CH_2)_2$-, and -$C(O)NH(CH_2)_3$-.

In some embodiments cycle D is from the group consisting of C_{6-12}aryl, C_{3-8}cycloalkyl, C_{3-8}cycloalkenyl,               , and ; preferably cycle D is C_{6-12}aryl, C_{3-10}cycloalkyl, C_{3-10}cycloalkenyl,              , and ; preferably cycle D is phenyl, naphtyl, indanyl, anthracenyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkenyl,














, and ; preferably cycle D is phenyl, naphtyl, indanyl, anthracenyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkenyl,












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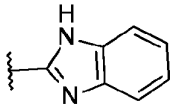
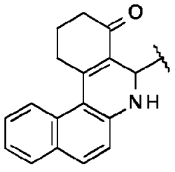
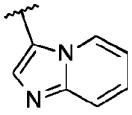
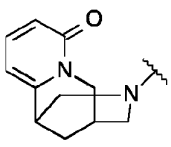
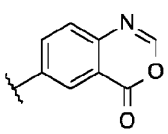
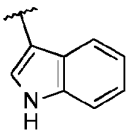
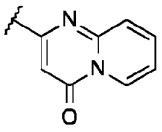
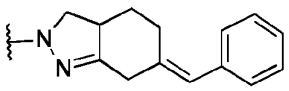
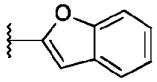
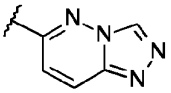
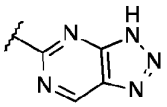

; preferably cycle D is phenyl, naphtyl, anthracenyl, indanyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicycle[2.2.1]heptan-2yl, (1S,4R)-norbornan-2-yl, (1R,4R)-norbornan-2-yl, (1S,4S)-norbornan-2-yl, (1R,4S)-norbornan-2-yl, 1-adamantyl










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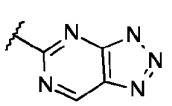
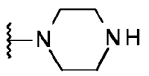
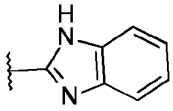
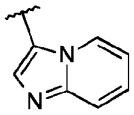
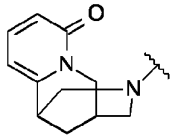
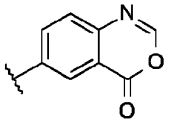
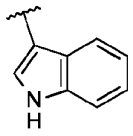
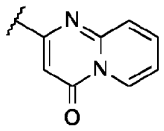
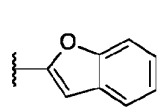
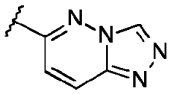
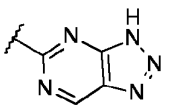
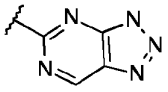
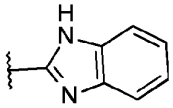
 ,  , and  ; preferably cycle A is phenyl, naphtyl, indanyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicycle[2.2.1]heptan-2yl, (1S,4R)-norbornan-2-yl, (1R,4R)-norbornan-2-yl, 1-adamantyl

 ,  ,  ,  ,  ,

 ,  ,  ,  , and  ;

wherein the wavy line (〰) indicates the point of attachment of cycle D to the rest of the molecule, wherein said groups can be unsubstituted or substituted with one or more R^D; preferably said groups can be unsubstituted or substituted with one, two, three or four R^D.

In some embodiments G^1 is selected from the group consisting of NR^D, CHR^D, and O.

In some embodiments G^2, and E^4 are N and G^3 is N or CR^D.

In some embodiments G^5 is N or CR^D and G^6 is N.

In some embodiments G^7 is N and G^8 is selected from the group consisting of NR^D, CHR^D, and O.

In some embodiments G^{10} is N or CR^D and G^9 is N.

In some embodiments G^{11} is N or CR^D and G^{12} is N.

In some embodiments G^{16} is CR^D and G^{15} is selected from the group consisting of NR^D, S, and O.

In some embodiments G^{16} is N and G^{15} is selected from the group consisting of NR^D, S, and O.

In some embodiments G^{17} and G^{19} are N or CR^D and G^{18} and G^{20} are N.

In some embodiments G^{17}, G^{18} and G^{19} are N or CR^D and G^{E0} is N.

In some embodiments G^{18}, G^{19} and G^{20} are N or CR^D and G^{17} is N.

In some embodiments G^{21} and G^{25} are N or CR^D, G^{22} and G^{24} are N and G^{23} is selected from the group consisting of NR^D, CHR^D, and O.

In some embodiments G^{21}, G^{22} and G^{24} are N or CR^D, G^{25} is N and G^{23} is selected from the group consisting of NR^D, CHR^D, and O.

In some embodiments G^{27} is N, CR^D or O and G^{26} is N.

In some embodiments each R^D is independently selected from the group consisting of hydrogen, halogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, haloC_{1-6}alkyl, haloC_{1-6}alkyloxy, cyanoC_{1-6}alkyl, C_{1-6}alkoxy, nitro, cyano, hydroxy, amino, mono-C_{1-6}alkylamino, di-C_{1-6}alkylamino, mono-C_{6-12}arylamino, di-C_{6-12}arylamino, $-NR^1R^2S(O)_2R^3$, $-NR^1R^2C(O)_2R^3$, -C(O)H, C_{1-6}alkylcarbonyl, C_{6-12}arylcarbonyl, $-C(O)_2H$, C_{1-6}alkyloxycarbonyl, C_{6-12}aryloxycarbonyl, $-S(O)_2H$, C_{1-6}alkylsulfonyl, C_{6-12}arylsulfonyl, C_{6-}

$_{12}$aryl, and C_{1-6}alkylC_{6-12}aryl; preferably each R^D is selected from hydrogen, halogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, haloC_{1-6}alkyl, cyanoC_{1-6}alkyl, haloC_{1-6}alkyloxy, C_{1-6}alkoxy, nitro, cyano, hydroxy, amino, mono-C_{1-6}alkylamino, mono-C_{6-12}arylamino, -$NR^1R^2S(O)_2R^3$, -$NR^1R^2C(O)_2R^3$, C_{1-6}alkylcarbonyl, -$C(O)_2H$, C_{1-6}alkyloxycarbonyl, -$S(O)_2H$, C_{1-6}alkylsulfonyl, C_{6-12}aryl, and C_{1-6}alkylC_{6-12}aryl; preferably each R^D is selected from hydrogen, halogen, C_{1-4}alkyl, C_{2-4}alkynyl, haloC_{1-4}alkyl, haloC_{1-4}alkyloxy, cyanoC_{1-4}alkyl, C_{1-4}alkoxy, nitro, cyano, hydroxy, amino, mono-C_{1-4}alkylamino, mono-C_{6-12}arylamino, -$NR^1R^2S(O)_2R^3$, C_{1-4}alkylcarbonyl, -$C(O)_2H$, C_{1-4}alkyloxycarbonyl, -$S(O)_2H$, C_{1-4}alkylsulfonyl, C_{6-12}aryl, and C_{1-4}alkylC_{6-12}aryl; preferably each R^D is selected from hydrogen, fluroro, chloro, bromo, iodo, C_{1-4}alkyl, C_{2-4}alkynyl, haloC_{1-4}alkyl, cyanoC_{1-4}alkyl, C_{1-4}alkoxy, nitro, cyano, hydroxy, amino, mono-C_{1-4}alkylamino, mono-C_{6-12}arylamino, -$NR^1R^2S(O)_2R^3$, C_{6-12}aryl, and C_{1-4}alkylC_{6-12}aryl;

wherein said groups can be unsubstituted or substituted with one, two or three halogen, nitro, hydroxy or C_{1-6}alkyl.

In some embodiments each R^1 is independently selected from the group consisting of hydrogen, C_{1-5}alkyl, C_{2-5}alkenyl, C_{2-5}alkynyl, and C_{6-12}aryl; preferably each R^1 is independently selected from the group consisting of hydrogen, C_{1-4}alkyl, C_{6-12}aryl;

wherein said groups can be unsubstituted or substituted with one, two or three halogen, nitro, hydroxy or C_{1-6}alkyl; preferably said groups can be unsubstituted or substituted with one, two or three halogen, nitro, hydroxy or C_{1-5}alkyl; preferably said groups can be unsubstituted or substituted with one, two or three halogen, nitro, hydroxy or C_{1-4}alkyl; preferably said groups can be unsubstituted or substituted with one, two or three halogen, nitro, hydroxy or C_{1-3}alkyl.

In some embodiments each R^2 is independently selected from the group consisting of hydrogen, C_{1-5}alkyl, C_{2-5}alkenyl, C_{2-5}alkynyl, and C_{6-12}aryl; preferably each R^2 is independently selected from the group consisting of hydrogen, C_{1-4}alkyl, C_{6-12}aryl;

wherein said groups can be unsubstituted or substituted with one, two or three halogen, nitro, hydroxy or C_{1-6}alkyl; preferably said groups can be unsubstituted or substituted with one, two or three halogen, nitro, hydroxy or C_{1-5}alkyl; preferably said groups can be unsubstituted or substituted with one, two or three halogen, nitro, hydroxy or C_{1-4}alkyl; preferably said groups can be unsubstituted or substituted with one, two or three halogen, nitro, hydroxy or C_{1-3}alkyl.

In some embodiments each R^3 is independently selected from the group consisting of hydrogen, C_{1-5}alkyl, C_{2-5}alkenyl, C_{2-5}alkynyl, and C_{6-12}aryl; preferably each R^3 is independently selected from the group consisting of hydrogen, C_{1-4}alkyl, C_{6-12}aryl;

wherein said groups can be unsubstituted or substituted with one, two or three halogen, nitro, hydroxy or C_{1-6}alkyl; preferably said groups can be unsubstituted or substituted with one, two or three halogen, nitro, hydroxy or C_{1-5}alkyl; preferably said groups can be unsubstituted or substituted with one, two or three halogen, nitro, hydroxy or C_{1-4}alkyl; preferably said groups can be unsubstituted or substituted with one, two or three halogen, nitro, hydroxy or C_{1-3}alkyl.

In some embodiments, a is an integer selected from 1, 2 or 3.

In some embodiments each R^4 is independently selected from the group consisting of hydrogen, halogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, haloC_{1-6}alkyl, haloC_{1-6}alkyloxy, cyanoC_{1-6}alkyl, C_{1-6}alkoxy, nitro, cyano, hydroxy, amino, mono-C_{1-6}alkylamino, di-C_{1-6}alkylamino, mono-C_{6-12}arylamino, di-C_{6-12}arylamino, $-NR^1R^2S(O)_2R^3$, $-NR^1R^2C(O)_2R^3$, -C(O)H, C_{1-6}alkylcarbonyl, C_{6-12}arylcarbonyl, $-C(O)_2H$, C_{1-6}alkyloxycarbonyl, C_{6-12}aryloxycarbonyl, $-S(O)_2H$, C_{1-6}alkylsulfonyl, C_{6-12}arylsulfonyl, C_{6-12}aryl, and C_{1-6}alkylC_{6-12}aryl; preferably each R^4 is selected from hydrogen, halogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, haloC_{1-6}alkyl, cyanoC_{1-6}alkyl, haloC_{1-6}alkyloxy, C_{1-6}alkoxy, nitro, cyano, hydroxy, amino, mono-C_{1-6}alkylamino, mono-C_{6-12}arylamino, $-NR^1R^2S(O)_2R^3$, $-NR^1R^2C(O)_2R^3$, C_{1-6}alkylcarbonyl, $-C(O)_2H$, C_{1-6}alkyloxycarbonyl, $-S(O)_2H$, C_{1-6}alkylsulfonyl, C_{6-12}aryl, and C_{1-6}alkylC_{6-12}aryl; preferably each R^4 is selected from hydrogen, halogen, C_{1-4}alkyl, C_{2-4}alkynyl, haloC_{1-4}alkyl, haloC_{1-4}alkyloxy, cyanoC_{1-4}alkyl, C_{1-4}alkoxy, nitro, cyano, hydroxy, amino, mono-C_{1-4}alkylamino, mono-C_{6-12}arylamino, $-NR^1R^2S(O)_2R^3$, C_{1-4}alkylcarbonyl, $-C(O)_2H$, C_{1-4}alkyloxycarbonyl, $-S(O)_2H$, C_{1-4}alkylsulfonyl, C_{6-12}aryl, and C_{1-4}alkylC_{6-12}aryl; preferably each R^4 is selected from hydrogen, fluroro, chloro, bromo, iodo, C_{1-4}alkyl, C_{2-4}alkynyl, haloC_{1-4}alkyl, cyanoC_{1-4}alkyl, C_{1-4}alkoxy, nitro, cyano, hydroxy, amino, mono-C_{1-4}alkylamino, mono-C_{6-12}arylamino, $-NR^1R^2S(O)_2R^3$, C_{6-12}aryl, and C_{1-4}alkylC_{6-12}aryl;

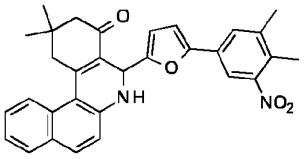
wherein said groups can be unsubstituted or substituted with one, two or three halogen, nitro, hydroxy or C_{1-6}alkyl.

In some embodiments, e is an integer selected from 1, 2 or 3.

In some embodiments each R^5 is independently selected from the group consisting of hydrogen, halogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, haloC_{1-6}alkyl, haloC_{1-6}alkyloxy, cyanoC_{1-6}alkyl, C_{1-6}alkoxy, nitro, cyano, hydroxy, amino, mono-C_{1-6}alkylamino, di-C_{1-6}alkylamino, mono-C_{6-12}arylamino, di-C_{6-12}arylamino, $-NR^1R^2S(O)_2R^3$, $-NR^1R^2C(O)_2R^3$, -C(O)H, C_{1-6}alkylcarbonyl, C_{6-12}arylcarbonyl, $-C(O)_2H$, C_{1-6}alkyloxycarbonyl, C_{6-12}aryloxycarbonyl, $-S(O)_2H$, C_{1-6}alkylsulfonyl, C_{6-12}arylsulfonyl, C_{6-12}aryl, and C_{1-6}alkylC_{6-12}aryl; preferably each R^5 is selected from hydrogen, halogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, haloC_{1-6}alkyl, cyanoC_{1-6}alkyl, haloC_{1-6}alkyloxy, C_{1-6}alkoxy, nitro, cyano, hydroxy, amino, mono-C_{1-6}alkylamino, mono-C_{6-12}arylamino, $-NR^1R^2S(O)_2R^3$, $-NR^1R^2C(O)_2R^3$, C_{1-6}alkylcarbonyl, $-C(O)_2H$, C_{1-6}alkyloxycarbonyl, $-S(O)_2H$, C_{1-6}alkylsulfonyl, C_{6-12}aryl, and C_{1-6}alkylC_{6-12}aryl; preferably each R^5 is selected from hydrogen, halogen, C_{1-4}alkyl, C_{2-4}alkynyl, haloC_{1-4}alkyl, haloC_{1-4}alkyloxy, cyanoC_{1-4}alkyl, C_{1-4}alkoxy, nitro, cyano, hydroxy, amino, mono-C_{1-4}alkylamino, mono-C_{6-12}arylamino, $-NR^1R^2S(O)_2R^3$, C_{1-4}alkylcarbonyl, $-C(O)_2H$, C_{1-4}alkyloxycarbonyl, $-S(O)_2H$, C_{1-4}alkylsulfonyl, C_{6-12}aryl, and C_{1-4}alkylC_{6-12}aryl; preferably each R^5 is selected from hydrogen, fluroro, chloro, bromo, iodo, C_{1-4}alkyl, C_{2-4}alkynyl, haloC_{1-4}alkyl, cyanoC_{1-4}alkyl, C_{1-4}alkoxy, nitro, cyano, hydroxy, amino, mono-C_{1-4}alkylamino, mono-C_{6-12}arylamino, $-NR^1R^2S(O)_2R^3$, C_{6-12}aryl, and C_{1-4}alkylC_{6-12}aryl;

wherein said groups can be unsubstituted or substituted with one, two or three halogen, nitro, hydroxy or C_{1-6}alkyl.

In some embodiments the PTPRK inhibitor according to the present invention is a compound of Formula III or Formula IV, or a stereoisomer, enantiomer, tautomer, solvate, hydrate, pharmaceutically acceptable salt, or prodrug thereof:



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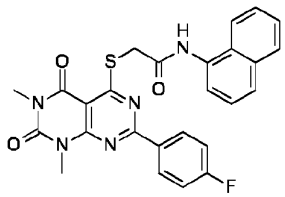
III



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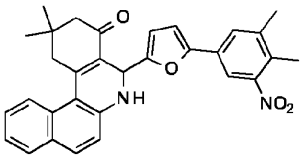
IV

In some embodiments the PTPRK inhibitor according to the present invention is a compound of Formula III or a stereoisomer, enantiomer, tautomer, solvate, hydrate, pharmaceutically acceptable salt, or prodrug thereof:



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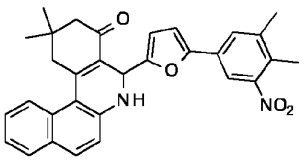
III

In some embodiments the PTPRK inhibitor according to the present invention is a compound of Formula III:



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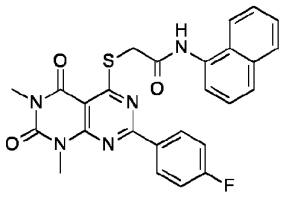
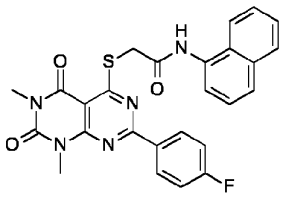
III

In some embodiments the PTPRK inhibitor according to the present invention is a compound of Formula IV or a stereoisomer, enantiomer, tautomer, solvate, hydrate, pharmaceutically acceptable salt, or prodrug thereof:



IV

In some embodiments the PTPRK inhibitor according to the present invention is a compound of Formula IV:



IV

Whenever the term "substituted" is used herein, it is meant to indicate that one or more hydrogen atoms on the atom indicated in the expression using "substituted" is replaced with a selection from the indicated group, provided that the indicated atom's normal valence is not exceeded, and that the substitution results in a chemically stable compound, i.e. a compound that is sufficiently robust to survive isolation from a reaction mixture.

Where groups can be substituted, such groups may be substituted with one or more, and preferably one, two or three substituents. Preferred substituents may be selected from but not limited to, for example, the group comprising halo, hydroxyl, alkyl, alkoxy, trifluoromethyl, trifluoromethoxy, cycloalkyl, aryl, arylalkyl, heterocyclyl, heteroaryl, cyano, amino, nitro, carboxyl, and mono- or dialkylamino.

The term "halo" or "halogen" as a group or part of a group is generic for fluoro, chloro, bromo, iodo.

The term "hydroxyl" or "hydroxy" as used herein refers to the group -OH.

The term "cyano" as used herein refers to the group -C≡N.

The term "amino" as used herein refers to the $-NH_2$ group.

The term "nitro" as used herein refers to the $-NO_2$ group.

The term "alkyl", as a group or part of a group, refers to a hydrocarbyl group of formula $-C_nH_{2n+1}$ wherein n is a number greater than or equal to 1. Alkyl groups may be linear or branched and may be

substituted as indicated herein. Generally, alkyl groups of this invention comprise from 1 to 6 carbon atoms, preferably from 1 to 5 carbon atoms, preferably from 1 to 4 carbon atoms, more preferably from 1 to 3 carbon atoms, still more preferably 1 to 2 carbon atoms. When a subscript is used herein following a carbon atom, the subscript refers to the number of carbon atoms that the named group may contain. For example, "C_{1-6}alkyl" includes all linear or branched alkyl groups with between 1 and 6 carbon atoms, and thus includes methyl, ethyl, n-propyl, i-propyl, butyl and its isomers (e.g. n-butyl, i-butyl and t-butyl); pentyl and its isomers, hexyl and its isomers. For example, "C_{1-5}alkyl" includes all includes all linear or branched alkyl groups with between 1 and 5 carbon atoms, and thus includes methyl, ethyl, n-propyl, i-propyl, butyl and its isomers (e.g. n-butyl, i-butyl and t-butyl); pentyl and its isomers. For example, "C_{1-4}alkyl" includes all linear or branched alkyl groups with between 1 and 4 carbon atoms, and thus includes methyl, ethyl, n-propyl, i-propyl, butyl and its isomers (e.g. n-butyl, i-butyl and t-butyl). For example "C_{1-3}alkyl" includes all linear or branched alkyl groups with between 1 and 3 carbon atoms, and thus includes methyl, ethyl, n-propyl, i-propyl.

The term "haloalkyl" as a group or part of a group, refers to a alkyl group having the meaning as defined above wherein one, two, or three hydrogen atoms are each replaced with a halogen as defined herein. Non-limiting examples of such haloalkyl groups include chloromethyl, 1-bromoethyl, fluoromethyl, difluoromethyl, trifluoromethyl, 1,1,1-trifluoroethyl, trichloromethyl, tribromomethyl, and the like.

The term "alkoxy" or "alkyloxy", as a group or part of a group, refers to a group having the formula –OR^b wherein R^b is alkyl as defined herein above. Non-limiting examples of suitable alkoxy include methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, pentyloxy and hexyloxy.

The term "cyanoC_{1-6}alkyl" as a group or part of a group, refers to a C_{1-6}alkyl group having the meaning as defined above wherein at least one hydrogen atom is replaced with at least one cyano group as defined herein. Non-limiting examples of such cyanoC_{1-6}alkyl groups include cyanomethyl, 1-cyanoethyl, 1-cyanopropyl and the like.

The term "cycloalkyl", as a group or part of a group, refers to a cyclic alkyl group, that is a monovalent, saturated, hydrocarbyl group having 1 or more cyclic structure, and comprising from 3 to 12 carbon atoms, more preferably from 3 to 9 carbon atoms, more preferably from 3 to 7 carbon atoms; more preferably from 3 to 6 carbon atoms. Cycloalkyl includes all saturated hydrocarbon groups containing 1 or more rings, including monocyclic or bicyclic groups. The further rings of multi-ring cycloalkyls may be either fused, bridged and/or joined through one or more spiro atoms. When a subscript is used herein following a carbon atom, the subscript refers to the number of carbon atoms that the named group may contain. For example, the term "C_{3-8}cycloalkyl", a cyclic alkyl group comprising from 3 to 8 carbon atoms. For example, the term "C_{3-6}cycloalkyl", a cyclic alkyl group comprising from 3 to 6 carbon atoms. Examples of C_{3-12}cycloalkyl groups include but are not limited to cyclopropyl, cyclobutyl,

cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicycle[2.2.1]heptan-2yl, (1S,4R)-norbornan-2-yl, (1R,4R)-norbornan-2-yl, (1S,4S)-norbornan-2-yl, (1R,4S)-norbornan-2-yl, 1-adamantyl.

The term "alkenyl" as a group or part of a group, refers to an unsaturated hydrocarbyl group, which may be linear, or branched, comprising one or more carbon-carbon double bonds. When a subscript is used herein following a carbon atom, the subscript refers to the number of carbon atoms that the named group may contain. For example, the term "C_{2-6}alkenyl" refers to an unsaturated hydrocarbyl group, which may be linear, or branched comprising one or more carbon-carbon double bonds and comprising from 2 to 6 carbon atoms. For example, C_{2-4}alkenyl includes all linear, or branched alkenyl groups having 2 to 4 carbon atoms. Examples of C_{2-6}alkenyl groups are ethenyl, 2-propenyl, 2-butenyl, 3-butenyl, 2-pentenyl and its isomers, 2-hexenyl and its isomers, 2,4-pentadienyl. and the like.

The term "cycloalkenyl", as a group or part of a group, refers to a cyclic alkeny group, that is a monovalent, with at least one unsaturation, hydrocarbyl group having 1 or more cyclic structure, and comprising from 5 to 12 carbon atoms, more preferably from 5 to 9 carbon atoms, more preferably from 5 to 7 carbon atoms; more preferably from 5 to 6 carbon atoms. Cycloalkenyl includes all unsaturated hydrocarbon groups containing 1 or more rings, including monocyclic or bicyclic groups. The further rings of multi-ring cycloalkenyls may be saturated or unsaturated. The further rings of multi-ring cycloalkyls may be either fused, bridged and/or joined through one or more spiro atoms. When a subscript is used herein following a carbon atom, the subscript refers to the number of carbon atoms that the named group may contain. For example, the term "C_{5-12}cycloalkenyl", a cyclic alkenyl group comprising from 5 to 12 carbon atoms. For example, the term "C_{5-6}cycloalkenyl", a cyclic alkenyl group comprising from 5 to 6 carbon atoms.

The term "alkynyl" by itself or as part of another substituent, refers to an unsaturated hydrocarbyl group, which may be linear, or branched, comprising one or more carbon-carbon triple bonds. When a subscript is used herein following a carbon atom, the subscript refers to the number of carbon atoms that the named group may contain. For example, the term "C_{2-6}alkynyl" refers to an unsaturated hydrocarbyl group, which may be linear, or branched comprising one or more carbon-carbon triple bonds and comprising from 2 to 6 carbon atoms. For example, C_{2-4}alkynyl includes all linear, or branched alkynyl groups having 2 to 4 carbon atoms. Non limiting examples of C_{2-6}alkynyl groups include ethynyl, 2-propynyl, 2-butynyl, 3-butynyl, 2-pentynyl and its chain isomers, 2-hexynyl and its chain isomers, and the like.

The term "aryl", as a group or part of a group, refers to a polyunsaturated, aromatic hydrocarbyl group having a single ring (i.e. phenyl) or multiple aromatic rings fused together (e.g. naphthyl), or linked covalently, typically comprising 6 to 12 carbon atoms; wherein at least one ring is aromatic, preferably comprising 6 to 10 carbon atoms, wherein at least one ring is aromatic. The aromatic ring may optionally include one to two additional rings (either cycloalkyl, heterocyclyl or heteroaryl) fused thereto. Examples of suitable aryl include C_{6-12}aryl, preferably C_{6-10}aryl, more preferably C_{6-8}aryl. Non-limiting

examples of aryl comprise phenyl, biphenylyl, biphenylenyl, or 1-or 2-naphthanelyl; 5- or 6-tetralinyl, 1-, 2-, 3-, 4-, 5-, 6-, 7- or 8-azulenyl, 4-, 5-, 6 or 7-indenyl, 4- or 5-indanyl, 5-, 6-, 7- or 8-tetrahydronaphthyl, 1,2,3,4-tetrahydronaphthyl, and 1,4-dihydronaphthyl; 1-, 2-, 3-, 4- or 5-pyrenyl. A "substituted aryl" refers to an aryl group having one or more substituent(s) (for example 1, 2 or 3 substituent(s), or 1 to 2 substituent(s)), at any available point of attachment.

The term "C_{6-12}arylC_{1-6}alkyl", as a group or part of a group, means a C_{1-6}alkyl as defined herein, wherein at least one hydrogen atom is replaced by at least one C_{6-12}aryl as defined herein. Non-limiting examples of C_{6-12}arylC_{1-6}alkyl group include benzyl, phenethyl, dibenzylmethyl, methylphenylmethyl, 3-(2-naphthyl)-butyl, and the like.

The term "mono- or di-alkylamino", as a group or part of a group, refers to a group of formula -N(R^o)(R^p) wherein R^o and R^p are each independently selected from hydrogen, or alkyl, wherein at least one of R^o or R^p is alkyl. Thus, alkylamino include mono-alkyl amino group (e.g. mono-C_{1-6}alkylamino group such as methylamino and ethylamino), and di-alkylamino group (e.g. di-C_{1-6}alkylamino group such as dimethylamino and diethylamino). Non-limiting examples of suitable mono- or di-alkylamino groups include *n*-propylamino, isopropylamino, *n*-butylamino, *i*-butylamino, *sec*-butylamino, *t*-butylamino, pentylamino, *n*-hexylamino, di-*n*-propylamino, di-*i*-propylamino, ethylmethylamino, methyl-*n*-propylamino, methyl-*i*-propylamino, *n*-butylmethylamino, *i*-butylmethylamino, *t*-butylmethylamino, ethyl-*n*-propylamino, ethyl-*i*-propylamino, *n*-butylethylamino, i-butylethylamino, *t*-butylethylamino, di-*n*-butylamino, di-*i*-butylamino, methylpentylamino, methylhexylamino, ethylpentylamino, ethylhexylamino, propylpentylamino, propylhexylamino, and the like.

The term "mono- or di-C_{6-12}arylamino", as a group or part of a group, refers to a group of formula -N(R^q)(R^r) wherein R^q and R^r are each independently selected from hydrogen, aryl, or alkyl, wherein at least one of R^q or R^r is C_{6-12}aryl.

The term "alkylcarbonyl", as a group or part of a group, refers to a group of formula –CO-R^b, wherein R^b is alkyl as defined herein.

The term "C_{6-12}arylcarbonyl", as a group or part of a group, refers to a group of formula –CO-R^b, wherein R^b is C_{6-12}aryl as defined herein.

The term "alkyloxycarbonyl", as a group or part of a group, refers to a group of formula –COO-R^b, wherein R^b is alkyl as defined herein.

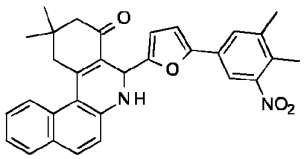
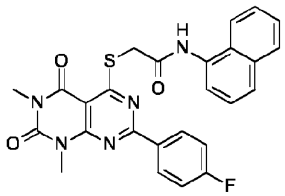
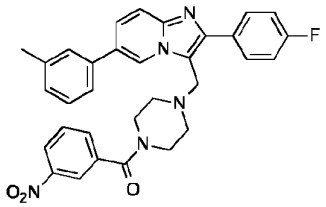
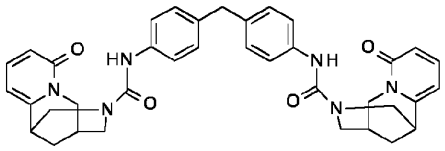
The term "C_{6-12}aryloxycarbonyl", as a group or part of a group, refers to a group of formula –COO-R^b, wherein R^b is C_{6-12}aryl as defined herein.

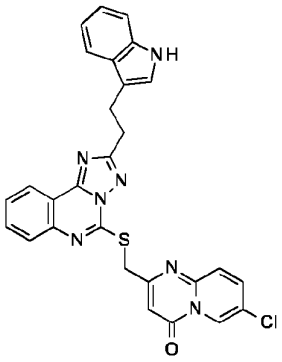
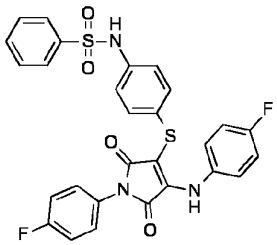
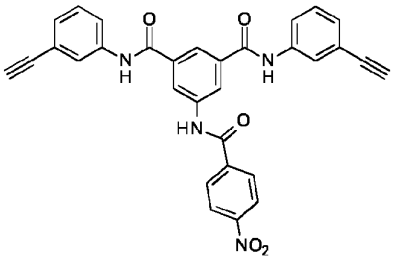
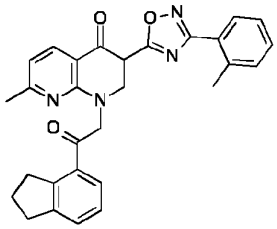
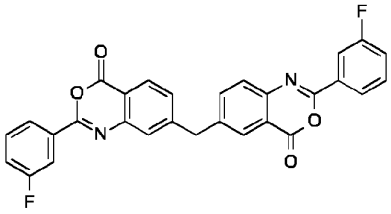
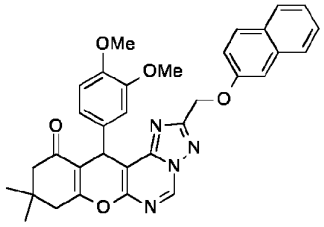
The term "C_{1-6}alkylsulfonyl", as a group or part of a group, refers to a group of formula –$S(O)_2$-R^b, wherein R^b is C_{1-6}alkylas defined herein.

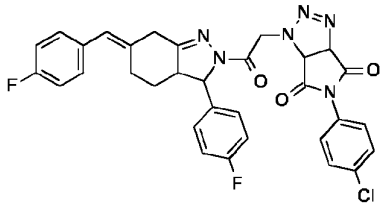
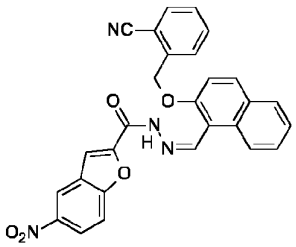
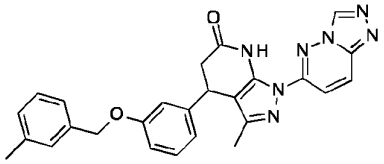
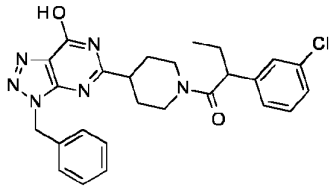
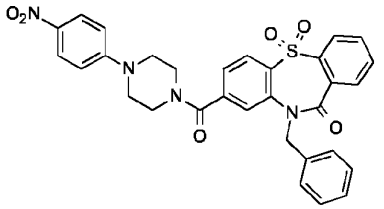
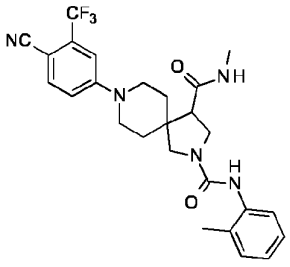
The term "C_{6-12}arylsulfonyl", as a group or part of a group, refers to a group of formula $-S(O)_2-R^b$, wherein R^b is C_{6-12}aryl as defined herein.

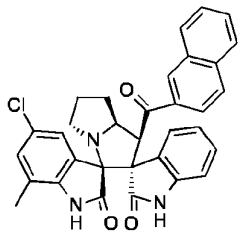
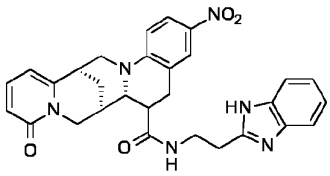
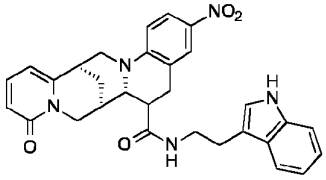
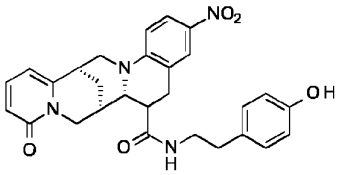
Whenever used in the present invention the term "compounds of the invention" or a similar term is meant to include the compounds of general formula I, II, I-1, I-2, I-3, I-4, I-5, I-6, I-7, I-8, I-9, I-10, I-11, I-12, I13, I-14, I-15, I-16, II-1, II-2 II-3, II-4, II-5 and any subgroup thereof. This term also refers to the compounds as depicted in Table 1 (compounds of Formula III - XXII) and their derivatives, N-oxides, salts, solvates, hydrates, tautomeric forms, analogues, pro-drugs, esters and metabolites, as well as their quaternized nitrogen analogues.

Table 1. Compounds according to some embodiments of the invention.

Formula	Compound
III	
IV	
V	
VI	

VII	
VIII	
IX	
X	
XI	
XII	

XIII	
VIX	
XV	
XVI	
XVII	
XVIII	

XIX	
XX	
XXI	
XXII	

As used herein and unless otherwise stated, the term ''stereoisomer'' refers to all possible different isomeric as well as conformational forms which the compounds of structural formula herein may possess, in particular all possible stereochemically and conformationally isomeric forms, all diastereomers, enantiomers and/or conformers of the basic molecular structure. Some compounds of the present invention may exist in different tautomeric forms, all of the latter being included within the scope of the present invention.

The present invention includes all possible stereoisomers of compounds of formula I or II and any subgroup thereof. When a compound is desired as a single enantiomer, such may be obtained by stereospecific synthesis, by resolution of the final product or any convenient intermediate, or by chiral chromatographic methods as each are known in the art. Resolution of the final product, an intermediate, or a starting material may be effected by any suitable method known in the art. See, for example, Stereochemistry of Organic Compounds by E. L. Eliel, S. H. Wilen, and L. N. Mander (Wiley-Interscience, 1994), incorporated by reference with regard to stereochemistry. A structural isomer is a type of isomer in which molecules with the same molecular formula have different bonding patterns and atomic organization. Where structural isomers are interconvertible via a low energy barrier, tautomeric isomerism ('tautomerism') can occur. This can take the form of proton tautomerism in

compounds of the invention containing, for example, an imino, keto, or oxime group, or so-called valence tautomerism in compounds which contain an aromatic moiety.

The term "prodrug" as used herein means the pharmacologically acceptable derivatives such as esters, amides and phosphates, such that the resulting in vivo biotransformation product of the derivative is the active drug. The reference by Goodman and Gilman (The Pharmacological Basis of Therapeutics, 8th Ed, McGraw-Hill, Int. Ed. 1992, "Biotransformation of Drugs", p 13-15) describing pro-drugs generally is hereby incorporated. Prodrugs of the compounds of the invention can be prepared by modifying functional groups present in said component in such a way that the modifications are cleaved, either in routine manipulation or in vivo, to the parent component. Typical examples of prodrugs are described for instance in WO 99/33795, WO 99/33815, WO 99/33793 and WO 99/33792 all incorporated herein by reference. Prodrugs are characterized by increased bio-availability and are readily metabolized into the active inhibitors in vivo. The term "prodrug", as used herein, means any compound that will be modified to form a drug species, wherein the modification may take place either inside or outside of the body, and either before or after the pre-drug reaches the area of the body where administration of the drug is indicated.

The compounds of the invention may be in the form of salts, preferably pharmaceutically acceptable salts, as generally described below. Some preferred, but non-limiting examples of suitable pharmaceutically acceptable organic and/or inorganic acids are as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, acetic acid and citric acid, as well as other pharmaceutically acceptable acids known per se (for which reference is made to the prior art referred to below).

When the compounds of the invention contain an acidic group as well as a basic group the compounds of the invention may also form internal salts, and such compounds are within the scope of the invention. When the compounds of the invention contain a hydrogen-donating heteroatom (e.g. NH), the invention also covers salts and/or isomers formed by transfer of said hydrogen atom to a basic group or atom within the molecule.

Pharmaceutically acceptable salts of the compounds of Formula I or II and any subgroup thereof include the acid addition and base salts thereof. Suitable acid addition salts are formed from acids which form non-toxic salts. Examples include the acetate, adipate, aspartate, benzoate, besylate, bicarbonate/carbonate, bisulfate/sulfate, borate, camsylate, citrate, cyclamate, edisylate, esylate, formate, fumarate, gluceptate, gluconate, glucuronate, hexafluorophosphate, hibenzate, hydrochloride/chloride, hydrobromide/bromide, hydroiodide/iodide, isethionate, lactate, malate, maleate, malonate, mesylate, methylsulphate, naphthylate, 2-napsylate, nicotinate, nitrate, orotate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, pyroglutamate, saccharate, stearate, succinate, tannate, tartrate, tosylate, trifluoroacetate and xinofoate salts. Suitable base salts are formed from bases which form non-toxic salts. Examples include the aluminium, arginine, benzathine, calcium, choline, diethylamine, diolamine, glycine, lysine, magnesium, meglumine,

olamine, potassium, sodium, tromethamine and zinc salts. Hemisalts of acids and bases may also be formed, for example, hemisulphate and hemicalcium salts. For a review on suitable salts, see Handbook of Pharmaceutical Salts: Properties, Selection, and Use by Stahl and Wermuth (Wiley-VCH, 2002), incorporated herein by reference.

The compounds of the invention may exist in a continuum of solid states ranging from fully amorphous to fully crystalline. The term 'amorphous' refers to a state in which the material lacks long range order at the molecular level and, depending upon temperature, may exhibit the physical properties of a solid or a liquid. Typically such materials do not give distinctive X-ray diffraction patterns and, while exhibiting the properties of a solid, are more formally described as a liquid. Upon heating, a change from solid to liquid properties occurs which is characterized by a change of state, typically second order ('glass transition'). The term 'crystalline' refers to a solid phase in which the material has a regular ordered internal structure at the molecular level and gives a distinctive X-ray diffraction pattern with defined peaks. Such materials when heated sufficiently will also exhibit the properties of a liquid, but the change from solid to liquid is characterized by a phase change, typically first order ('melting point').

Pharmaceutically acceptable salts of compounds of Formula I or II may be prepared by one or more of these methods:

(i) by reacting the compound of Formula I or II with the desired acid;

(ii) by reacting the compound of Formula I or II with the desired base;

(iii) by removing an acid- or base-labile protecting group from a suitable precursor of the compound of formula (I) or by ring-opening a suitable cyclic precursor, for example, a lactone or lactam, using the desired acid; or

(iv) by converting one salt of the compound of Formula I or II to another by reaction with an appropriate acid or by means of a suitable ion exchange column.

All these reactions are typically carried out in solution. The salt may precipitate from solution and be collected by filtration or may be recovered by evaporation of the solvent. The degree of ionization in the salt may vary from completely ionized to almost non-ionized.

The compounds of the invention may also exist in unsolvated and solvated forms. The term 'solvate' is used herein to describe a molecular complex comprising the compound of the invention and one or more pharmaceutically acceptable solvent molecules, for example, ethanol. The term 'hydrate' is employed when said solvent is water.

A currently accepted classification system for organic hydrates is one that defines isolated site, channel, or metal-ion coordinated hydrates - see Polymorphism in Pharmaceutical Solids by K. R. Morris (Ed. H. G. Britain, Marcel Dekker, 1995), incorporated herein by reference. Isolated site hydrates are ones in which the water molecules are isolated from direct contact with each other by intervening organic

molecules. In channel hydrates, the water molecules lie in lattice channels where they are next to other water molecules. In metal-ion coordinated hydrates, the water molecules are bonded to the metal ion.

When the solvent or water is tightly bound, the complex will have a well-defined stoichiometry independent of humidity. When, however, the solvent or water is weakly bound, as in channel solvates and hygroscopic compounds, the water/solvent content will be dependent on humidity and drying conditions. In such cases, non-stoichiometry will be the norm.

Also included within the scope of the invention are multi-component complexes (other than salts and solvates) wherein the drug and at least one other component are present in stoichiometric or non-stoichiometric amounts. Complexes of this type include clathrates (drug-host inclusion complexes) and co-crystals. The latter are typically defined as crystalline complexes of neutral molecular constituents which are bound together through non-covalent interactions, but could also be a complex of a neutral molecule with a salt. Co-crystals may be prepared by melt crystallization, by recrystallization from solvents, or by physically grinding the components together - see Chem Commun, 17, 1889-1896, by O. Almarsson and M. J. Zaworotko (2004), incorporated herein by reference. For a general review of multi-component complexes, see J Pharm Sci, 64 (8), 1269-1288, by Haleblian (August 1975), incorporated herein by reference.

The compounds of the invention may also exist in a mesomorphic state (mesophase or liquid crystal) when subjected to suitable conditions. The mesomorphic state is intermediate between the true crystalline state and the true liquid state (either melt or solution). Mesomorphism arising as the result of a change in temperature is described as 'thermotropic' and that resulting from the addition of a second component, such as water or another solvent, is described as 'lyotropic'. Compounds that have the potential to form lyotropic mesophases are described as 'amphiphilic' and consist of molecules which possess an ionic (such as -COO^-Na^+, -COO^-K^+, or -$SO_3^-Na^+$) or non-ionic (such as -$N^+N^+(CH_3)_3$) polar head group. For more information, see Crystals and the Polarizing Microscope by N. H. Hartshorne and A. Stuart, 4th Edition (Edward Arnold, 1970), incorporated herein by reference.

All references to compounds of Formula I or II or any subgroups thereof include references to salts, solvates, multi-component complexes and liquid crystals thereof and to solvates, multi-component complexes and liquid crystals of salts thereof.

The compounds of the invention include compounds of Formula I or II or any subgroups thereof as hereinbefore defined, including all polymorphs and crystal habits thereof, prodrugs and isomers thereof (including optical, geometric and tautomeric isomers) as hereinafter defined and isotopically-labeled compounds of Formula I or II.

In addition, although generally, with respect to the salts of the compounds of the invention, pharmaceutically acceptable salts are preferred, it should be noted that the invention in its broadest

sense also included non-pharmaceutically acceptable salts, which may for example be used in the isolation and/or purification of the compounds of the invention.

In some embodiments, the PTPRK inhibitor can be a PTPRK-binding protein, such as an antibody, an antibody fragment, an antibody-like protein scaffold or a PTPRK gene targeting nucleic acid.

In certain embodiments, the PTPRK inhibitor is a PTPRK binding antibody.

The term "antibody" as used herein is to be interpreted its broadest sense and generally refers to any immunologic binding agent. The term specifically encompasses intact monoclonal antibodies, polyclonal antibodies, multivalent (e.g., 2-, 3- or more-valent) and/or multi-specific antibodies (e.g., bi- or more-specific antibodies) formed from at least two intact antibodies, and antibody fragments insofar they exhibit the desired biological activity (particularly, ability to specifically bind an antigen of interest, i.e., antigen-binding fragments), as well as multivalent and/or multi-specific composites of such fragments. The term "antibody" is not only inclusive of antibodies generated by methods comprising immunisation, but also includes any polypeptide, e.g., a recombinantly expressed polypeptide, which is made to encompass at least one complementarity-determining region (CDR) capable of specifically binding to an epitope on an antigen of interest. Furthermore, the term "antibody" is indicative for antibodies described herein, regardless of whether they are produced *in vitro* or *in vivo*. In certain embodiments, the PTPRK inhibitor is a PTPRK binding antibody that directly binds at least one functional domain, or an epitope comprised in the PTPRK protein. In certain embodiments wherein the inhibitor of PTPRK is an antibody, binding to the PTPRK protein by the inhibitor induces PTPRK protein sequestering. In alternative embodiments wherein the inhibitor of PTPRK is an antibody, binding to the PTPRK protein by the inhibitor induces PTPRK protein precipitation. In particular embodiments, the antibody binds to a protein having SEQ ID NO:1.

An antibody may be any of IgA, IgD, IgE, IgG and IgM classes, and preferably IgG class antibody. An antibody may be a polyclonal antibody, e.g., an antiserum or immunoglobulins purified there from (e.g., affinity-purified). An antibody may be a monoclonal antibody or a mixture of monoclonal antibodies. Monoclonal antibodies can target a particular antigen or a particular epitope within an antigen with greater selectivity and reproducibility. By means of example and not limitation, monoclonal antibodies may be made by the hybridoma method described in the art and known to a skilled person (Kohler *et al.*, Continuous cultures of fused cells secreting antibody of predefined specificity., Nature, 1975). Alternatively, a skilled person is aware that antibodies can be made by recombinant DNA methods (Boss *et al.*, Assembly of functional antibodies from immunoglobulin heavy and light chains synthesised in *E. coli*, Nucleic Acids Research, 1984). As a further non-limiting example, monoclonal antibodies can also be generated by relying on the use of phage display libraries (Clarckson *et al.*, Making antibody fragments using phage display libraries, Nature 1991).

In certain embodiments, the PTPRK inhibitor is an antibody fragment. The term "antibody fragments" comprises a portion of an intact antibody, comprising the antigen-binding or variable region thereof. Methods to produce and purify antibody fragments are well established in the art (Bates and Power, David vs. Goliath: The Structure, Function, and Clinical Prospects of Antibody Fragments, Antibodies (Basel), 2019). By means of guidance and not limitation, examples of antibody fragments include Fab, Fab', F(ab')2, Fv and scFv fragments, single domain (sd) Fv, such as VH domains, VL domains and VHH domains; diabodies; linear antibodies; single-chain antibody molecules, in particular heavy-chain antibodies; and multivalent and/or multispecific antibodies formed from antibody fragment(s), e.g., dibodies, tribodies, and multibodies. The above designations Fab, Fab', F(ab')2, Fv, scFv etc. are intended to have their art-established meaning. In certain embodiments, the PTPRK inhibitor is an antibody fragment that directly binds at least one functional domain, or an epitope comprised in the PTPRK protein. In particular embodiments, the PTPRK protein is a protein having SEQ ID NO:1.

The term antibody includes antibodies originating from or comprising one or more portions derived from any animal species, preferably vertebrate species, including, e.g., birds and mammals. Without limitation, the antibodies may be chicken, turkey, goose, duck, guinea fowl, quail or pheasant. Also without limitation, the antibodies may be human, murine (e.g., mouse, rat, etc.), donkey, rabbit, goat, sheep, guinea pig, camel (e.g., *Camelus bactrianus* and *Camelus dromaderius*), llama (e.g., *Lama paccos*, *Lama glama* or *Lama vicugna*), horse, or shark.

A skilled person will understand that an antibody can include one or more amino acid deletions, additions and/or substitutions (e.g., conservative substitutions), insofar such alterations preserve its binding of the respective antigen. An antibody may also include one or more native or artificial modifications of its constituent amino acid residues (e.g., glycosylation, etc.).

Methods of producing polyclonal and monoclonal antibodies as well as fragments thereof are well known in the art, as are methods to produce recombinant antibodies or fragments thereof (see for example, Harlow and Lane, "Antibodies: A Laboratory Manual", Cold Spring Harbour Laboratory, New York, 1988; Harlow and Lane, "Using Antibodies: A Laboratory Manual", Cold Spring Harbour Laboratory, New York, 1999, ISBN 0879695447; "Monoclonal Antibodies: A Manual of Techniques", by Zola, ed., CRC Press 1987, ISBN 0849364760; "Monoclonal Antibodies: A Practical Approach", by Dean & Shepherd, eds., Oxford University Press 2000, ISBN 0199637229; Methods in Molecular Biology, vol. 248: "Antibody Engineering: Methods and Protocols", Lo, ed., Humana Press 2004, ISBN 1588290921).

In certain embodiments, the agent may be a Nanobody. The terms "Nanobody" and "Nanobodies" are trademarks of Ablynx NV (Belgium). The term "Nanobody" is well-known in the art and as used herein in its broadest sense encompasses an immunological binding agent obtained (1) by isolating the V_{HH} domain of a heavy-chain antibody, preferably a heavy-chain antibody derived from camelids; (2) by

expression of a nucleotide sequence encoding a V_{HH} domain; (3) by "humanization" of a naturally occurring V_{HH} domain or by expression of a nucleic acid encoding a such humanized V_{HH} domain; (4) by "camelization" of a V_H domain from any animal species, and in particular from a mammalian species, such as from a human being, or by expression of a nucleic acid encoding such a camelized V_H domain; (5) by "camelization" of a "domain antibody" or "dAb" as described in the art, or by expression of a nucleic acid encoding such a camelized dAb; (6) by using synthetic or semi-synthetic techniques for preparing proteins, polypeptides or other amino acid sequences known *per se*; (7) by preparing a nucleic acid encoding a Nanobody using techniques for nucleic acid synthesis known *per se*, followed by expression of the nucleic acid thus obtained; and/or (8) by any combination of one or more of the foregoing. "Camelids" as used herein comprise old world camelids (*Camelus bactrianus* and *Camelus dromaderius*) and new world camelids (for example *Lama paccos, Lama glama* and *Lama vicugna*). It is known to a person skilled in the art that, depending on the specific situation, nanobodies may display favourable characteristics compared to "traditional" antibodies, including but not limited to a high production yield in a broad variety of expression systems, minimal size, great stability, reversible refolding, and solubility in aqueous solutions.

In further embodiments the inhibitor of PTPRK is a polyclonal antibody, a monoclonal antibody, a chimeric antibody, a humanized antibody, a primatized antibody, a human antibody, a Nanobody, an intrabody, or any combination thereof. In further embodiments, the inhibitor of PTPRK is a concatenation of antibodies.

In certain embodiments, the PTPRK inhibitor is an antibody-like scaffoled or antibody mimetic. The term "antibody-like protein scaffolds" or "engineered protein scaffolds" broadly encompasses proteinaceous non-immunoglobulin specific-binding agents, typically obtained by combinatorial engineering (such as site-directed random mutagenesis in combination with phage display or other molecular selection techniques). Usually, such scaffolds are derived from robust and small soluble monomeric proteins (such as Kunitz inhibitors or lipocalins) or from a stably folded extra-membrane domain of a cell surface receptor (such as protein A, fibronectin or the ankyrin repeat). Methods and protocols to generate antibody-like protein scaffolds have been extensively reported in the art and are therefore known to a skilled person (inter alia in Skerra, Alternative non-antibody scaffolds for molecular recognition, Current opinion in biotechnology, 2007). Non-limiting examples of antibody-like protein scaffolds include affibodies, based on the Z-domain of staphylococcal protein A (Nygren, Alternative binding proteins: affibody binding proteins developed from a small three-helix bundle scaffold, Federation of European Biochemical Societies (FEBS) journal, 2008); engineered Kunitz domains based on a small (ca. 58 residues) and robust, disulphide-crosslinked serine protease inhibitor (Nixon and Wood, Engineered protein inhibitors of proteases, Current opinion in drug discovery & development, 2006); monobodies or adnectins based on the 10th extracellular domain of human fibronectin III (10Fn3) that adopt an Ig-like beta-sandwich fold with 2 to 3 exposed loops, but lack the

central disulphide bridge (Koide and Koide, Monobodies: antibody mimics based on the scaffold of the fibronectin type III domain, Methods in molecular biology, 2007); anticalins derived from the lipocalins, a diverse family of eight-stranded beta-barrel proteins that naturally form binding sites for small ligands by means of four structurally variable loops at the open end (Skerra, Alternative binding proteins: anticalins - harnessing the structural plasticity of the lipocalin ligand pocket to engineer novel binding activities, FEBS journal, 2008); DARPins, which are designed ankyrin repeat domains (Stumpp *et al.*, DARPins: a new generation of protein therapeutics, Drug Discovery Today, 2008); avimers (Silverman *et al.*, Multivalent avimer proteins evolved by exon shuffling of a family of human receptor domains, Nature Biotechnology, 2005); and cysteine-rich knottin peptides (Kolmar, Alternative binding proteins: Biological activity and therapeutic potential of cystine-knot miniproteins, FEBS journal, 2008).

In certain embodiments wherein the PTPRK inhibitor is a protein such as a PTPRK binding antibody, antibody fragment, or antibody-like scaffold, the inhibitor may further comprise additional amino acid sequences corresponding to a peptide or protein tag sequence, which optionally is a regulatory sequence, or a localization signal, preferably a nuclear localization signal. Tag sequences are routinely used in molecular biology and therefore their merits are known to a skilled person (. Non-limiting examples of commonly used peptide tag sequences are the AviTag, C-tag, calmodulin-tag, polyglutamate tag, E-tag, Flag-tag, HA-tag, His-tag, Myc-tag, NE-tag, Rho1D4-tag, S-tag, SBP-tag, Softag 1, Softag 3, Spot-tag, Strep-tag, TC tag, Ty tag, V5 tag, VSV-tag, Xpress tag, isopeptag, SpyTag, SnoopTag, DogTag, and the SdyTag. In certain embodiments, the inhibitor comprises multiple tag sequences. In further embodiments, the inhibitor comprises at least two distinct peptide or protein tag sequences. Likewise (nuclear) localization signals and methods to identify them have been reported in the art (Cokol *et al.*, Finding nuclear localization signals, EMBO reports, 2000). In certain embodiments, the inhibitor of PTPRK inhibits PTPRK by direct binding to the PTPRK protein and inducing precipitation of the protein. In certain embodiments, the inhibitor of PTPRK inhibits PTPRK by direct binding to the PTPRK protein and inducing oligomerization of the protein.

In an aspect of the invention, the PTPRK inhibitor or combinations of PTPRK inhibitors, or a stereoisomer, enantiomer, tautomer, solvate, hydrate, pharmaceutically acceptable salt, or prodrug thereof, as described herein may be formulated in a pharmaceutical composition. Such composition may contain, in addition to one or more active pharmaceutical ingredients, at least one pharmaceutically acceptable carrier, diluent or excipient and/or adjuvant.

A further aspect of the present invention thus provides a pharmaceutical composition comprising a compound of Formula I or II, or a combination thereof, or a stereoisomer, enantiomer, tautomer, solvate, hydrate, pharmaceutically acceptable salt or prodrug thereof, and a pharmaceutically acceptable carrier. In some embodiments, the pharmaceutical composition comprises a compound of Formula III or IV or

a combination thereof, or a stereoisomer, enantiomer, tautomer, solvate, hydrate, pharmaceutically acceptable salt or prodrug thereof, and a pharmaceutically acceptable carrier. In some embodiments, the pharmaceutical composition comprises a compound of Formula III or a stereoisomer, enantiomer, tautomer, solvate, hydrate, pharmaceutically acceptable salt or prodrug thereof, and a pharmaceutically acceptable carrier. In some embodiments, the pharmaceutical composition comprises a compound of Formula IV or a stereoisomer, enantiomer, tautomer, solvate, hydrate, pharmaceutically acceptable salt or prodrug thereof, and a pharmaceutically acceptable carrier. In some embodiments, the pharmaceutical composition comprises a compound of Formula III and a pharmaceutically acceptable carrier. In some embodiments, the pharmaceutical composition comprises a compound of Formula IV and a pharmaceutically acceptable carrier.

In an aspect, a combination of a PTPRK inhibitor that is a compound of formula III, or a stereoisomer, enantiomer, tautomer, solvate, hydrate, pharmaceutically acceptable salt, or prodrug thereof and a PTPRK inhibitor that is a compound of formula IV or a stereoisomer, enantiomer, tautomer, solvate, hydrate, pharmaceutically acceptable salt, or prodrug thereof, is provided. In some embodiments, said combination is comprised in a pharmaceutical composition. In some embodiments, the combination can be configured to allow for administration of the two compounds simultaneously, or to allow for administration of the two compounds sequentially in any order.

The term "pharmaceutically acceptable" as used herein is consistent with the art and means compatible with the other ingredients of a pharmaceutical composition and not deleterious to the recipient thereof. As used herein, "carrier" or "excipient" includes any and all solvents, diluents, buffers (such as, e.g., neutral buffered saline or phosphate buffered saline), solubilisers, colloids, dispersion media, vehicles, fillers, chelating agents (such as, e.g., EDTA or glutathione), amino acids (such as, e.g., glycine), proteins, disintegrants, binders, lubricants, wetting agents, emulsifiers, sweeteners, colorants, flavourings, aromatisers, thickeners, agents for achieving a depot effect, coatings, antifungal agents, preservatives, antioxidants, tonicity controlling agents, absorption delaying agents, and the like. The use of such media and agents for pharmaceutical active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active substance, its use in the therapeutic compositions may be contemplated.

Illustrative, non-limiting carriers for use in formulating the pharmaceutical compositions include, for example, oil-in-water or water-in-oil emulsions, aqueous compositions with or without inclusion of organic co-solvents suitable for intravenous (IV) use, liposomes or surfactant-containing vesicles, microspheres, microbeads and microsomes, powders, tablets, capsules, suppositories, aqueous suspensions, aerosols, and other carriers apparent to one of ordinary skill in the art.

Pharmaceutical compositions as intended herein may be formulated for essentially any route of administration, such as without limitation, oral administration (such as, e.g., oral ingestion or

inhalation), intranasal administration (such as, e.g., intranasal inhalation or intranasal mucosal application), parenteral administration (such as, e.g., subcutaneous, intravenous (I.V.), intramuscular, intraperitoneal or intrasternal injection or infusion), transdermal or transmucosal (such as, e.g., oral, sublingual, intranasal) administration, topical administration, rectal, vaginal or intra-tracheal instillation, and the like. In this way, the therapeutic effects attainable by the methods and compositions can be, for example, systemic, local, tissue-specific, etc., depending of the specific needs of a given application.

In some embodiments, the compound or the pharmaceutical composition as taught herein is administered parenterally. Preferably, the compound or the pharmaceutical composition as taught herein is administered intravenously, for example by infusion.

In some embodiments, the compound or the pharmaceutical composition as taught herein is administered orally.

Suitable administration forms – which may be solid, semi-solid or liquid, depending on the manner of administration – as well as methods and carriers, diluents and excipients for use in the preparation thereof, will be clear to the skilled person; reference is made to for instance US-A-6,372, 778, US-A-6,369,086, US-A-6,369,087 and US-A6,372,733, as well as the standard handbooks, such as the latest edition of Remington's Pharmaceutical Sciences.

Some preferred, but non-limiting examples of such preparations include tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols, ointments, cremes, lotions, soft and hard gelatin capsules, suppositories, drops, sterile injectable solutions and sterile packaged powders (which are usually reconstituted prior to use) for administration as a bolus and/or for continuous administration, which may be formulated with carriers, excipients, and diluents that are suitable per se for such formulations, such as lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, polyethylene glycol, cellulose, (sterile) water, methylcellulose, methyl- and propylhydroxybenzoates, talc, magnesium stearate, edible oils, vegetable oils and mineral oils or suitable mixtures thereof. The formulations can optionally contain other pharmaceutically active substances (which may or may not lead to a synergistic effect with the compounds of the invention) and other substances that are commonly used in pharmaceutical formulations, such as lubricating agents, wetting agents, emulsifying and suspending agents, dispersing agents, disintegrants, bulking agents, fillers, preserving agents, sweetening agents, flavoring agents, flow regulators, release agents, etc.. The compositions may also be formulated so as to provide rapid, sustained or delayed release of the active compound(s) contained therein, for example using liposomes or hydrophilic polymeric matrices based on natural gels or synthetic polymers. In order to enhance the solubility and/or the stability of the compounds of a pharmaceutical composition according to the

invention, it can be advantageous to employ α-, β- or γ-cyclodextrins or their derivatives. In addition, co-solvents such as alcohols may improve the solubility and/or the stability of the compounds.

The preparations may be prepared in a manner known per se, which usually involves mixing the at least one compound according to the invention with the one or more pharmaceutically acceptable carriers, and, if desired, in combination with other pharmaceutical active compounds, when necessary under aseptic conditions. Reference is again made to US-A-6,372,778, US-A-6,369,086, US-A-6,369,087 and US-A-6,372,733 and the further prior art mentioned above, as well as to the standard handbooks, such as the latest edition of Remington's Pharmaceutical Sciences.

The pharmaceutical preparations of the invention are preferably in a unit dosage form, and may be suitably packaged, for example in a box, blister, vial, bottle, sachet, ampoule or in any other suitable single-dose or multi-dose holder or container (which may be properly labeled); optionally with one or more leaflets containing product information and/or instructions for use. Generally, such unit dosages will contain between 1 and 1000 mg, and usually between 5 and 500 mg, of the at least one compound of the invention, e.g. about 10, 25, 50, 100, 200, 300 or 400 mg per unit dosage.

The compounds can be administered by a variety of routes including the oral, ocular, rectal, transdermal, subcutaneous, intravenous, intramuscular or intranasal routes, depending mainly on the specific preparation used and the condition to be treated or prevented, and with oral and intravenous administration usually being preferred. The at least one compound of the invention will generally be administered in an "effective amount", by which is meant any amount of a compound of the formula as taught herein that, upon suitable administration, is sufficient to achieve the desired therapeutic or prophylactic effect in the subject to which it is administered. The dosage or amount of the agent as taught herein, optionally in combination with one or more other active compounds to be administered, and therapeutic efficacy of the agent as described herein or pharmaceutical compositions comprising the same can be determined by known pharmaceutical procedures in, for example, cell cultures or experimental animals. These procedures can be used, e.g., for determining the LD50 (the dose lethal to 50% of the population) and the ED50 (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio LD50/ED50. Pharmaceutical compositions that exhibit high therapeutic indices are preferred. While pharmaceutical compositions that exhibit toxic side effects can be used, care should be taken to design a delivery system that targets such compounds to the site of affected tissue in order to minimize potential damage to normal cells (e.g., non-target cells) and, thereby, reduce side effects.

The data obtained from the cell culture assays and animal studies can be used in formulating a range of dosage for use in appropriate subjects. The dosage of such pharmaceutical compositions lies generally within a range of circulating concentrations that include the ED50 with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilised. For a pharmaceutical composition used as described herein, the therapeutically effective dose

can be estimated initially from cell culture assays. A dose can be formulated in animal models to achieve a circulating plasma concentration range that includes the IC50 (i.e., the concentration of the pharmaceutical composition which achieves a half-maximal inhibition of symptoms) as determined in cell culture. Such information can be used to more accurately determine useful doses in humans. Levels in plasma can be measured, for example, by high performance liquid chromatography.

The unit dose and regimen depend on the individual case and is, as is customary, to be adapted to the individual circumstances to achieve an optimum effect. Thus, the unit dose and regimen depend on the nature and the severity of the disorder to be treated, and also on factors such as the species of the subject, the sex, age, body weight, general health, diet, mode and time of administration, immune status, and individual responsiveness of the human or animal to be treated, efficacy, metabolic stability and duration of action of the compounds used, on whether the therapy is acute or chronic or prophylactic, or on whether other active compounds are administered in addition to the agent of the invention. In order to optimize therapeutic efficacy, the compound or the pharmaceutical composition as taught herein can be first administered at different dosing regimens. Typically, levels of the agent in a tissue can be monitored using appropriate screening assays as part of a clinical testing procedure, e.g., to determine the efficacy of a given treatment regimen. The frequency of dosing is within the skills and clinical judgement of medical practitioners (e.g., doctors, veterinarians or nurses). Typically, the administration regime is established by clinical trials which may establish optimal administration parameters. However, the practitioner may vary such administration regimes according to the one or more of the aforementioned factors, e.g., subject's age, health, weight, sex and medical status. The frequency of dosing can be varied depending on whether the treatment is prophylactic or therapeutic.

Usually, depending on the condition to be prevented or treated and the route of administration, such an effective amount will usually be between 0.01 to 1000 mg per kilogram, more often between 0.1 and 500 mg, such as between 1 and 250 mg, for example about 5, 10, 20, 50, 100, 150, 200 or 250 mg, per kilogram body weight day of the patient per day, which may be administered as a single daily dose, divided over one or more daily doses, or essentially continuously, e.g. using a drip infusion. The amount(s) to be administered, the route of administration and the further treatment regimen may be determined by the treating clinician, depending on factors such as the age, gender and general condition of the patient and the nature and severity of the disease/symptoms to be treated. Reference is again made to US-A-6,372,778,US-A-6,369,086, US-A-6,369,087 and US-A-6,372,733 and the further prior art mentioned above, as well as to the standard handbooks, such as the latest edition of Remington's Pharmaceutical Sciences.

In accordance with the method of the present invention, said pharmaceutical composition can be administered separately at different times during the course of therapy or concurrently in divided or single combination forms. The present invention is therefore to be understood as embracing all such

regimes of simultaneous or alternating treatment and the term "administering" is to be interpreted accordingly.

For an oral administration form, the compositions of the present invention can be mixed with suitable additives, such as excipients, stabilizers or inert diluents, and brought by means of the customary methods into the suitable administration forms, such as tablets, coated tablets, hard capsules, aqueous, alcoholic, or oily solutions. Examples of suitable inert carriers are gum arabic, magnesia, magnesium carbonate, potassium phosphate, lactose, glucose, or starch, in particular, corn starch. In this case, the preparation can be carried out both as dry and as moist granules. Suitable oily excipients or solvents are vegetable or animal oils, such as sunflower oil or cod liver oil. Suitable solvents for aqueous or alcoholic solutions are water, ethanol, sugar solutions, or mixtures thereof. Polyethylene glycols and polypropylene glycols are also useful as further auxiliaries for other administration forms. As immediate release tablets, these compositions may contain microcrystalline cellulose, dicalcium phosphate, starch, magnesium stearate and lactose and/or other excipients, binders, extenders, disintegrants, diluents and lubricants known in the art.

When administered by nasal aerosol or inhalation, these compositions may be prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other solubilizing or dispersing agents known in the art. Suitable pharmaceutical formulations for administration in the form of aerosols or sprays are, for example, solutions, suspensions or emulsions of the compounds of the invention in a pharmaceutically acceptable solvent, such as ethanol or water, or a mixture of such solvents. If required, the formulation can also additionally contain other pharmaceutical auxiliaries such as surfactants, emulsifiers and stabilizers as well as a propellant.

For subcutaneous or intravenous administration, the compound according to the invention, if desired with the substances customary therefore such as solubilizers, emulsifiers or further auxiliaries are brought into solution, suspension, or emulsion. The compounds of the invention can also be lyophilized and the lyophilizates obtained used, for example, for the production of injection or infusion preparations. Suitable solvents are, for example, water, physiological saline solution or alcohols, e.g. ethanol, propanol, glycerol, in addition also sugar solutions such as glucose or mannitol solutions, or alternatively mixtures of the various solvents mentioned. The injectable solutions or suspensions may be formulated according to known art, using suitable non-toxic, parenterally-acceptable diluents or solvents, such as mannitol, 1,3-butanediol, water, Ringer's solution or isotonic sodium chloride solution, or suitable dispersing or wetting and suspending agents, such as sterile, bland, fixed oils, including synthetic mono- or diglycerides, and fatty acids, including oleic acid.

When rectally administered in the form of suppositories, these formulations may be prepared by mixing the compounds according to the invention with a suitable non-irritating excipient, such as cocoa butter, synthetic glyceride esters or polyethylene glycols, which are solid at ordinary temperatures, but liquefy and/or dissolve in the rectal cavity to release the drug.

In some embodiments the composition is administered once a day, twice a day, three times a day or four times a day. In one embodiment, the administration of a dosage of 50 mg to 2 g/day/patient can be envisioned. More particularly, a dosage of about 250 mg to 750 mg/day, for example 500 mg/day, can be envisioned. It is particularly advantageous to formulate the pharmaceutical compositions envisioned in unit dosage regime form in order to facilitate administration and uniformity of the dosage regime. The unit dosage regime form in the present document refers to physically distinct units that can serve as unit doses, each unit containing a predetermined amount of active ingredient.

In some embodiments, the PTPRK inhibitor as taught herein is the main or only active ingredient of the pharmaceutical composition.

Except when noted, "subject" or "patient" are used interchangeably and refer to animals, preferably warm-blooded animals, more preferably vertebrates, even more preferably mammals, still more preferably primates, and specifically includes human patients and non-human mammals and primates. Preferred patients are human subjects including both genders and all age categories thereof. The subject or patient as envisaged herein may in particular require a treatment as taught herein. Particularly intended are subjects with overweight, obesity, hyperglycaemia, diabetes, hyperlipidaemia, a non-alcoholic fatty liver disease (NAFLD), hepatocellular carcinoma or a combination thereof. In some embodiments, the subjects have a non-alcoholic fatty liver disease that is selected from fatty liver, non-alcoholic steatohepatitis (NASH), NASH with liver fibrosis, and NASH with liver cirrhosis. In some embodiments, the subjects are diagnosed with hepatocellular carcinoma. In some embodiments, the subjects have overweight and/or obesity. In some embodiments, the subjects have diabetes, in particular type-2 diabetes. In some embodiments, the subject have increased blood glucose levels. In some embodiments, the subjects have hyperlipidaemia or increased blood lipid levels.

As used herein, a phrase such as "a subject in need of treatment" includes subjects that would benefit from treatment of a given condition, in particular a condition selected from the group consisting of overweight, obesity, hyperglycaemia, diabetes, hyperlipidaemia, a non-alcoholic fatty liver disease. Such subjects may include, without limitation, those that have been diagnosed with said condition, those prone to contract or develop said condition and/or those in whom said condition is to be prevented.

The terms "treat" or "treatment" encompass both the therapeutic treatment of an already developed disease or condition, such as the therapy of an already developed disease condition, as well as prophylactic or preventative measures, wherein the aim is to prevent or lessen the chances of incidence of an undesired affliction, such as to prevent the chances of contraction and progression of a retroviral infection. Beneficial or desired clinical results may include, without limitation, alleviation of one or more symptoms or one or more biological markers, diminishment of extent of disease, stabilised (i.e., not worsening) state of disease, delay or slowing of disease progression, amelioration or palliation of the disease state, and the like. "Treatment" can also mean prolonging survival as compared to expected survival if not receiving treatment. In a preferred embodiment, "treatment" in the light of the present invention implies reduction of overweight and obesity, reduction or normalization of blood glucose levels, treating diabetes, reduction of blood lipid levels, reduction of symptoms of a non-alcoholic fatty liver disease, and combinations thereof.

The term "prophylactically effective amount" refers to an amount of an active compound or pharmaceutical agent that inhibits or delays in a subject the onset of a disorder as being sought by a researcher, veterinarian, medical doctor or other clinician.

The term "therapeutically effective amount" as used herein, refers to an amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a subject that is being sought by a researcher, veterinarian, medical doctor or other clinician, which may include inter alia alleviation of the symptoms of the disease or condition being treated. Methods are known in the art for determining therapeutically and prophylactically effective doses for the present compounds.

As used herein, the term "obesity" refers to a medical condition in which excess body fat has accumulated to the extent that it may have a negative effect on health. In terms of a human (adult) subject, obesity can be defined as a body mass index (BMI) greater than or equal to 30 kg/m^3 (BMI $\geq$ 30 kg/m^2).

The term "overweight" refers to a medical condition in which the amount of body fat is higher than is optimally healthy. In terms of a human (adult) subject, obesity can be defined as a body mass index (BMI) greater than or equal to 25 kg/m^3 (e.g., 25 $kg/m^2 \leq$ BMI $<$ 30 kg/m^2).

The BMI is a simple index of weight-for-height that is commonly used to classify overweight and obesity in adults. It is defined as a person's weight in kilograms divided by the square of his/her height in meters (kg/m^2).

"Diabetes", also referred to as "diabetes mellitus", refers to a group of metabolic diseases characterized by high levels of blood glucose resulting from defects in insulin production, insulin action, or both. In one embodiment, diabetes is selected from the group consisting of type 1 diabetes, type 2 diabetes, gestational diabetes, late onset autoimmune diabetes in the adult (LADA), maturity onset diabetes of

the young (MODY) and other types of diabetes resulting from specific genetic conditions, drugs, malnutrition, infections and other illnesses. In a particular embodiment, diabetes is type 2 diabetes.

The current WHO diagnostic criteria for diabetes are as follows: fasting plasma glucose ≥ 7.0 mmol/l (126 mg/dL) or 2-h plasma glucose ≥ 11.1 mmol/l (200 mg/dL).

"Type-1 diabetes" (also known as insulin-dependent diabetes or juvenile diabetes) is a condition characterized by high blood glucose levels caused by total lack of insulin. This occurs when the body's immune system attacks the insulin producing beta cells in the pancreas and destroys them. The pancreas then produces little or no insulin. Pancreatic removal or disease may also lead to loss of insulin-producing beta cells. Type 1 diabetes accounts for between 5% and 10% case of diabetes.

"Type-2 diabetes" (also known as non-insulin-dependent diabetes or adult-onset diabetes) is a condition characterized by excess glucose production in spite of the availability of insulin, and circulating glucose levels remain excessively high as a result of inadequate glucose clearance (insulin action). Type 2 diabetes may account for about 90% to 95% of all diagnosed cases of diabetes.

The term "hyperglycaemia" refers to an excess of sugar (glucose) in the blood, in particular the term hyperglycaemia refers to a fasting glucose blood concentration that is above 140 mg/dl.

The term "hyperlipidaemia" refers to a disorder of lipoprotein metabolism, in particular to lipoprotein overproduction. Hyperlipidaemia may be manifested by elevation of total cholesterol, low-density lipoprotein (LDL) cholesterol and/or triglyceride concentrations, and/or a decrease in high-density lipoprotein (HDL) cholesterol concentration in the blood. As used herein, hyperlipidaemia in a human subject is present when one or more of the following applies: total cholesterol serum concentration above 200 mg/dl, HDL cholesterol serum concentration less than 40 mg/dl, non-HDL cholesterol serum concentration above 120 mg/dl, LDL cholesterol concentration above 130 mg/dl, and triglyceride serum concentration above 150 mg/dl.

As used herein, the "non-alcoholic fatty liver disease", or "NAFLD", encompasses a wide range of liver disorders associated with fatty liver, that occur when fat is deposited in the liver due to causes other than excessive alcohol use. As used herein, the term NAFLD is a synonym to "metabolic dysfunction-associated steatotic liver disease" (MASLD) or to "metabolic dysfunction-associated fatty liver disease" (MAFLD). The terms "non-alcoholic fatty liver disease", "NAFLD", "metabolic dysfunction-associated steatotic liver disease", "MASLD", "metabolic dysfunction-associated fatty liver disease", and "MAFLD" are thus considered as synonyms and can be used interchangeably. After all, a global consensus panel composed mostly of hepatology researchers and clinicians recommended a change of name of NAFLD to MASLD or MAFLD in 2023. NAFLD is the most common liver disorder in developed countries and it is generally associated with factors of the metabolic syndrome. NAFLD has several phases of disease progression which include: steatosis (also called fatty liver), non-alcoholic liver steatohepatitis (NASH), NASH with liver fibrosis, NASH with liver cirrhosis. In an ultimate stage,

NAFLD can even progress to hepatocellular carcinoma (HCC). In some embodiments, a NAFLD is thus selected from fatty liver (or steatosis), NASH, NASH with liver fibrosis, NASH with liver fibrosis, and NASH with liver cirrhosis.

"Liver steatosis" is also referred to as fatty liver and is characterized by deposits of fat in the liver that lead to liver enlargement. Subjects with liver steatosis do not always show disturbed liver function yet. Liver steatosis can progress into NASH with liver fibrosis.

"Non-alcoholic steatohepatitis" ("NASH") is a liver disease characterized by an accumulation of fat (lipid droplets), along with inflammation and degeneration of hepatocytes, resulting in a disturbed liver function. NASH is regarded as a major cause of liver cirrhosis, which is characterized by severe scarring or fibrosis of the liver, which prevents the liver from working properly. As used herein, the term NASH is a synonym of "metabolic dysfunction-associated steatohepatitis" or "MASH", and the terms "non-alcoholic steatohepatitis", "NASH", "metabolic dysfunction-associated steatohepatitis" and "MASH" can be used interchangeably. After all, a global consensus panel composed mostly of hepatology researchers and clinicians recommended a change of name of NASH to MASH in 2023.

Liver steatosis and NASH are known to progress to hepatocellular carcinoma (HCC) or liver cancer. As used herein, the term "hepatocellular carcinoma or "HCC" refers to a malignant tumour occurring in the liver. In some embodiments, the HCC is further specified as obesity-induced HCC.

In some embodiments, treatment with the PTPRK inhibitor or pharmaceutical composition comprising a PTPRK inhibitor as disclosed herein can result in the reduction of at least one point in severity of NAFLD or NASH grading scoring systems, including but not limited to, NALFD activity score (NAS), proposed by the NASH Clinical Research Network (established in 2002 by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)), a widely used scoring system.

The terms "treatment", "treating", "treat" and the like refer to obtaining a desired pharmacological and/or physiological effect. The effect may be prophylactic in terms of completely or partially preventing a disease or symptom thereof and/or may be therapeutic in terms of a partial or complete stabilization or cure for a disease and/or adverse effect attributable to the disease. "Treatment" covers any treatment of a disease in a mammal, particular a human, and includes: (a) preventing the disease or symptom but has not yet been diagnosed as having it; (b) inhibiting the disease symptoms, i.e. arresting its development: or (c) relieving the disease symptoms, i.e. causing regression of the disease or symptom. Beneficial or desired clinical results may include, without limitation, alleviation of one or more symptoms or one or more biological markers, diminishment of extent of disease, stabilised (i.e., not worsening) state of disease, delay or slowing of disease progression, amelioration or palliation of the disease state, and the like. "Treatment" can also mean prolonging survival as compared to expected survival if not receiving treatment. Non-limiting example of already available therapeutic treatment

options of liver steatosis, NAFLD, NASH and/or HCC are radiotherapy, chemotherapy, targeted drug therapy, immunotherapy and surgery.

In some aspects, the invention provides the non-therapeutic use of a PTPRK inhibitor as disclosed herein or a composition comprising a PTPRK inhibitor as disclosed herein for reduction of body weight, blood glucose levels, blood lipid levels or a combination thereof in a subject. In some embodiments, the non-therapeutic use of a PTPRK inhibitor or a composition comprising a PTPRK inhibitor is provided for reduction of body weight in a subject. In some embodiments, the non-therapeutic use of a PTPRK inhibitor or a composition comprising a PTPRK inhibitor as disclosed herein is provided for reduction of blood glucose levels in a subject. In some embodiments, the non-therapeutic use of a PTPRK inhibitor or composition comprising a PTPRK inhibitor as disclosed herein is provided for reduction of blood lipid levels in a subject. As used herein, the reduction of body weight, blood glucose levels or blood lipid levels in a subject is to be understood as a reduction of one or more of these parameters over time. As corroborated in the experimental section, the inventors have shown that administration of a PTPRK inhibitor resulted in reduced body weight, reduced blood glucose levels and reduced blood lipid levels over time.

As used herein, the non-therapeutic use as disclosed herein for reduction of blood glucose levels in a subject refers to the use in a non-therapeutic setting wherein the subject is a healthy subject and wherein the PTPRK inhibitor or composition comprising the PTPRK inhibitor is administered to reduce the blood glucose levels in said healthy subject. It is generally known that variations in blood glucose levels are common and are often dependent on the food consumption, also in healthy subjects. The non-therapeutic use as disclosed herein, hereby refers to the administration of a PTPRK inhibitor or composition comprising a PTPRK inhibitor in a healthy subject with the aim to reduce blood glucose levels, for example after the consumption of a carbohydrate-rich meal.

As used herein, the non-therapeutic use as disclosed herein for reduction of blood lipid levels in a subject refers to the use in a non-therapeutic setting wherein the subject is a healthy subject and wherein the PTPRK inhibitor or composition comprising the PTPRK inhibitor is administered to reduce the blood lipid levels in said healthy subject. It is generally known that variations in blood lipid levels are common and are often dependent on the food consumption, also in healthy subjects. The non-therapeutic use as disclosed herein, hereby refers to the administration of a PTPRK inhibitor or composition comprising a PTPRK inhibitor in a healthy subject with the aim to reduce blood lipid levels, for example after the consumption of a high-fat meal.

As used herein, the non-therapeutic use as disclosed herein for reduction of body weight in a subject refers to the use in a non-therapeutic setting wherein administration of the PTPRK inhibitor or composition comprising a PTPRK inhibitor as disclosed herein is to reduce body weight in said subject.

The subject can be a healthy subject, wherein the subject intends to reduce its body weight, but wherein the subject is not obese.

Another aspect provides a method of preventing and/or treating a condition selected from the group consisting of overweight, obesity, hyperglycaemia, diabetes, hyperlipidaemia, a non-alcoholic fatty liver disease (NAFLD), hepatocellular carcinoma, and combinations thereof in a subject in need of such treatment, comprising administering to said subject a therapeutically or prophylactically effective amount of a PTPRK inhibitor, a combination of PTPRK inhibitors, or a pharmaceutical composition as disclosed herein. In some embodiments, a method of treating a condition selected from the group consisting of overweight, obesity, hyperglycaemia, diabetes, hyperlipidaemia, a non-alcoholic fatty liver disease (NAFLD), hepatocellular carcinoma, and combinations thereof in a subject in need of such treatment is provided, said method comprising administering to said subject a therapeutically effective amount of a PTPRK inhibitor, a combination of PTPRK inhibitors, or a pharmaceutical composition as disclosed herein. In some embodiments, a method of preventing a condition selected from the group consisting of overweight, obesity, hyperglycaemia, diabetes, hyperlipidaemia, a non-alcoholic fatty liver disease (NAFLD), hepatocellular carcinoma, and combinations thereof in a subject in need of such treatment is provided, said method comprising administering to said subject a prophylactically effective amount of a PTPRK inhibitor, a combination of PTPRK inhibitors, or a pharmaceutical composition as disclosed herein.

A related aspect relates to the use of a PTPRK inhibitor, or a combination of PTPRK inhibitors as disclosed herein for the manufacture of a medicament for the treatment of a condition selected from the group consisting of overweight, obesity, hyperglycaemia, diabetes, hyperlipidaemia, a non-alcoholic fatty liver disease (NAFLD), hepatocellular carcinoma, and combinations thereof.

A related aspect relates to use of a PTPRK inhibitor, or a combination of PTPRK inhibitors as disclosed herein for the treatment of a condition selected from the group consisting of overweight, obesity, hyperglycaemia, diabetes, hyperlipidaemia, a non-alcoholic fatty liver disease (NAFLD), hepatocellular carcinoma, and combinations thereof.

As used herein, the sample may be any biological sample from the subject, in a particular a sample wherein glucose levels, lipid levels or a combination thereof can be determined. In preferred embodiments, the sample is a liquid sample, preferably a blood or a serum sample.

It is apparent that there have been provided in accordance with the invention products, methods, and uses, that provide for substantial advantages as set forth above. While the invention has been described in conjunction with specific embodiments thereof, it is evident that many alternatives, modifications, and variations will be apparent to those skilled in the art in light of the foregoing description.

Accordingly, it is intended to embrace all such alternatives, modifications, and variations as follows in the spirit and broad scope of the appended claims.

The above aspects and embodiments are further supported by the following non-limiting examples.

EXAMPLES

Materials and Methods

Reagents

Human Insulin solution, sodium pyruvate, sodium palmitate, oleic acid, bovine serum albumin, 2-deoxy-D-glucose, D-glucose, dimethyloxalylglycine (DMOG), and lipopolysaccharides (LSP) were obtained from Sigma-Aldrich. PeproTech provided Recombinant Murine IFN-γ (315-05-100ug), and Recombinant Human IL-6 Protein (206-IL-010) was obtained from R&D Systems. Insulin ProZinc (Boehringer Ingelheim, Rhein, Germany, NDC 0010-4499-01) was utilized for *in vivo* experiments. All other chemicals and reagents used were of the highest grade available.

Human samples

We studied 19 biopsy specimens of patients undergoing a liver biopsy for medical reasons in our institution. The clinical characteristics of these patients are shown in Table 2. Biopsies were collected after approval of the Hôpital Erasme Ethics Committee. Written informed consent was obtained from each participant.

Table 2. *Clinical and demographic characteristics of patients from whom liver biopsies were collected and used for mass spectrometry (MS) or PTPRK immunohistochemistry (IHC) analysis as shown in Figure 1.*

ID	Biopsy health status	Age	Weight (kg)	Height (cm)	BMI (kg/m^2)	Type 2 diabetes	Gender	Experiment
CHR01	Healthy liver	80	46	175	15	No	M	MS/IHC
CHR02	Healthy liver	66	62	150	28	No	F	MS/IHC
CHR03	Healthy liver	28	66	170	23	No	F	IHC
CHR04	Healthy liver	63	66	165	24	No	F	MS/IHC
CHR08	Steatosis	53	86	185	25	Yes	F	MS/IHC
CHR09	Steatosis	39	80	158	32	No	F	MS/IHC
CHR10	Steatosis	56	67	173	22	No	M	MS/IHC
CHR11	Steatosis	36	82	160	32	No	F	MS/IHC
CHR12	Steatosis	61	76	159	30	No	F	IHC
CHR13	Steatosis	68	115	168	41	Yes	M	IHC
CHR14	NASH/Cirrhosis	61	113	179	35	Yes	M	MS/IHC
CHR16	NASH/Cirrhosis	46	79	156	32	No	F	MS/IHC
CHR17	NASH/Cirrhosis	48	76	160	30	No	M	MS/IHC
CHR18	NASH/Cirrhosis	60	80	149	36	Yes	F	MS/IHC
CHR19	NASH	46	80	157	32	Yes	F	MS
CHR20	NASH	45	85	156	35	Yes	F	MS
CHR05	HCC	83	79	175	26	No	M	MS
CHR06	HCC	76	76	165	28	No	M	MS
CHR07	HCC	43	55	170	19	No	M	MS

Mice

Mice were housed and managed in compliance with the Belgian Regulations for Animal Care, and the animal protocols underwent approval from the Commision d'Ethicque du Bien-Être Animal (CEBEA), Faculté de Médecine, Université libre de Bruxelles (dossier No. 732). Animals were housed at 22°C on a 12:12-h light-dark cycle with ad libitum access to food and water.

Ptprk knockout mice were generated at The Jackson Laboratory (Ptprk-8356J-M669 project) by CRISPR/Cas9 technology and were bred on a pure C57BL/6N background. The strategy involved an intragenic deletion spanning 555 base pairs on Chromosome 10. This genetic alteration led to the excision of exon 3 within the Ptprk gene, accompanied by the removal of 283 base pairs from adjacent intronic sequences. The resulting mutation is predicted to induce an alteration in the amino acid sequence following residue 74 and an early truncation by 2 amino acids.

By breeding $Ptprk^{+/-}$ mice we obtained $Ptprk^{-/-}$ and $Ptprk^{+/+}$ males and females littermates. $Ptprk^{+/+}$ and $Ptprk^{-/-}$ mice, aged 8 weeks, were randomly assigned to experimental diet-induced obesity feeding with unrestricted access to the specific diets: a high-fat diet (HFD, 60 kcal% fat D09100310i), a high-fat, high-fructose high-cholesterol diet (HFHFHCD, 40 kcal% Fat, 20 kcal% Fructose, and 2% Cholesterol, D09100310i), or a control diet (10 kcal% Fat, D09100304i) obtained from Research Diets (New Brunswick, NJ, USA). The duration for which the animals were subjected to the experimental diets ranged from 4 to 24 weeks, as indicated in the specific experiment conducted.

Adenoviral-mediated hepatic PTPRK overexpression was obtained through retro-orbital injection with 1.8x10^9 PFU (ADV-269821) in 200 µL of PBS, and Adv-CMV-Null was used as control (Adv-control). The vectors were obtained from Vector Biolabs.

The *in vivo* effect of PTPRK inhibitor treatment was assessed in C57/BL6 male mice treated with vehicle of 50 mg/kg PTPRK inhibitor 2 for either 5 days or 5 weeks. When assessing the effect of the PTPRK inhibitor treatment during 5 weeks, mice were first fed a high-fat, high-fructose, high-cholesterol diet for 4 weeks, followed by weekly injections of 50 mg/kg of Inhibitor 2 for 5 weeks.

Metabolic measures

Evaluation of body and liver lean and fat mass was conducted using the EchoMRI™ 3-in-1 (NMR) body composition analyzer from EchoMedical Systems (Houston, TX, USA) at the indicated time points.

To conduct glucose tolerance tests (GTT), mice underwent a 6-hour fast and received intraperitoneal administration of glucose (2g D-Glucose/kg body weight). For pyruvate tolerance tests, mice were fasted overnight and administered pyruvate (2 g pyruvate/kg body weight). Similarly, insulin tolerance tests (ITT) were performed on mice fasted for 4 hours, involving the intraperitoneal injection of insulin (0.75 U/kg body weight). Fresh D-glucose, pyruvate or insulin solutions were prepared in PBS immediately before the injections. Blood glucose was measured before initiating the tolerance tests

(time 0) and subsequently at intervals of 15, 30, 45, 60, 90, and 120 minutes, allowing for continuous monitoring of glycemia over time. Blood samples were obtained from the tail tip, and the glycemia was measured using a glucometer (Accu-Check Performa, Roche, Basel, Switzerland). After the experimental diet feeding period, blood serum was collected in a fed state (9 am) and 6 hours after fasting (3 pm) and used for quantifying insulin levels through a commercially available Insulin ELISA kit (Crystal Chem Inc., Chicago, IL, USA; cat. #90080).

At 18 weeks of age, *Ptprk*$^{-/-}$ and *Ptprk*$^{+/+}$ mice fed a high-fat high-fructose and high-carbohydrate diet (HFHFHCD) for 10 weeks, were placed in metabolic cages TSE Phenomaster setup (TSE, Germany) for a duration of 72 hours. Following a 24-hour period of acclimatization, various metabolic parameters, including physical activity, energy expenditure, and substrate utilization were assessed through indirect calorimetry.

Lipid extraction

Total hepatic lipid content was evaluated by gravimetry after lipid extraction. Livers were promptly removed, immediately freeze-clamped in liquid nitrogen, and then stored at -80°C. The liver samples (100mg) were homogenized using a beads tissue homogenizer with cold methanol. After sonication, the homogenate was transferred to Falcon tubes. Chloroform was added, and the mixture was vortexed. Following agitation overnight at 4°C, the samples underwent centrifugation at 13,500g for 10 minutes. The organic phase was separated and allowed to air-dry at room temperature overnight, after which the resulting pellet was weighed for total fat quantification. The solid middle layer formed during centrifugation was similarly dried and weighed to determine the overall hepatic protein content. The results were expressed as mg of fat/100g of liver or g of fat/g of protein in the liver.

DEN-induced HCC

Liver tumour formation was induced by administering 25 mg/kg of diethylnitrosamine (DEN) (in PBS) via intraperitoneal injection into the underbelly region of 14-day-old mice. Throughout the experiment, the mice were maintained on a chow diet, and their body weights were recorded weekly. At 40 weeks of age, the mice were euthanized through cervical dislocation, and their livers were extracted for comprehensive analysis, including macroscopic and histological assessment of tumour number and size.

Histological analysis

Mouse liver tissues intended for histological analysis were collected from euthanized mice, dissected, and subsequently rinsed with PBS. The obtained tissue specimens were fixed in 4% buffered formaldehyde (pH 7.4) and embedded in paraffin blocks. The paraffin blocks were then sectioned into slices measuring 5-7 µm using a Leica rotator microtome. Hematoxylin and Eosin (H&E) staining was employed for the sections.

For immunohistochemistry analysis of PTPRK in human liver samples, 7 μm thick paraffin sections were situated on positively charged slides. Antigen unmasking was performed with a heated citrate buffer (10 mM, pH6.0). The sections were permeabilized utilizing triton (0.1%) and subsequently blocked with 2% milk for 15 minutes. A 30-minute incubation at room temperature was administered with 10% normal goat serum to prevent nonspecific binding. Primary antibodies were applied and allowed to incubate overnight at 4°C, followed by a 1-hour incubation with a goat anti-rabbit horseradish peroxidase (HRP) secondary antibody (P044801). Negative controls were established by subjecting specimen slices solely to the secondary antibody.

Lipid accumulation was assessed by Nile red staining (Sigma-Aldrich N3013). Primary hepatocytes were isolated and seeded onto chambered coverglass (IBIDI, 80806) at a density of 50,000 cells per well, 4h before adenoviral transfection for either PTPRK overexpression or silencing. After 24 hours of transfection, the culture medium was replaced with a BSA-conjugated FFAs (Palmitate acid 0.4mmol/L, Oleate acid 0.8mmol/L) or FFA-free 1% BSA control-enriched medium with 1% FBS. Following 24 hours of exposure to BSA-FFA, the hepatocytes were fixed in a 4% formaldehyde solution for 20 minutes and stained with a 5 μg/mL Nile red solution for a 20-minute incubation at room temperature. After this staining, the coverglass was mounted by VECTASHIELD Antifade Mounting Medium with DAPI (Lab Consult, VEC.H-1200). The stained cells were then observed using an inverted fluorescence microscope (Axio Observer D1, Carl Zeiss, Oberkochen, Germany). The same staining procedure was applied to hepatocytes with high-fat and low-fat content, fixed and stained following an overnight culture period.

Hepatic lipid content was assessed in frozen sections of both *Ptprk*$^{+/+}$ and *Ptprk*$^{-/-}$ livers through oil red O (ORO) (Sigma-Aldrich, O1391) staining, following a previously established protocol. Briefly, liver sections from cryostat cuts equilibrated for 30 minutes at room temperature in laminar flow hood. ORO working solution (0.3% ORO in 60% isopropanol) was applied to ensure complete coverage and incubated at 37°C for 15 minutes, and after counterstaining with hematoxylin, the sections and the images were then captured for analysis using NanoZoomer Digital Pathology (Hamamatsu Photonics K.K., version SQ 1.0.9) at 40x magnification.

Primary mouse hepatocyte isolation and culture and treatments

Mouse primary hepatocytes were isolated from *Ptprk*$^{+/+}$ and *Ptprk*$^{-/-}$ mice following overnight ad libitum feeding, utilizing a two-step collagenase perfusion method through the vena cava. The process was initiated by anaesthetizing the mice through an intraperitoneal injection of a ketamine (100mg/kg) and xylazine (10mg/kg) mixture, the peritoneum was opened, and the infrahepatic segment of the vena cava was cannulated for subsequent perfusion. The portal vein was cut to clear the blood from liver at the initiation of liver perfusion. In the first perfusion step, the liver was exposed to HBSS (no calcium, no magnesium, Thermo Fisher Scientific, #14170138) supplemented with 10 mM 4-(2-hydroxyethyl)-1-piperazine ethanesulfonic acid–NaOH (pH 7.4), saturated with O_2/CO_2 (95:5 vol/vol), at 37 °C for 10

minutes. The second step involved adding collagenase type IV (0.3 mg/mL) to William's E Medium (Thermo Fisher Scientific, #32551087) and further perfusing for 10 minutes, effectively softening the liver tissue. The softened liver was then transferred to a sterile plastic dish, and cells were dispersed using a coarse-toothed comb in a cold Williams medium, followed by filtration through a 100-µm cell filter to eliminate cell clumps. The resulting clump-free cell suspension was pelleted through centrifugation at 50g for 5 minutes at 4 °C and the pellet was resuspended in William's E Medium and layered onto Percoll solution (Millipore Sigma, # GE17-0891-01) (10ml Percoll + 1,25ml PBS 10X + 1,25ml H_2O.) and centrifuged for 10 minutes at 1000 RPM. The pellet was washed with William's E Medium (3 times). Viability assessment using the trypan blue exclusion test yielded around 15 million to 20 million cells with approximately 85% viability.

Additionally, to isolate hepatocytes with high-fat and low-fat content from steatotic livers, a technique was employed as follows: viable hepatocytes with different lipid content were separated from dead hepatocytes and non-parenchymal cell types in the cell suspension using Percoll gradient centrifugation. The hepatocytes were resuspended, washed, and assessed for cell number and viability using trypan blue and a hemocytometer and immediately pelleted and stored at -80°C for further RNA or protein extractions used in RNA-Seq and proteomics/phosphoproteomics analyses.

Cell culture

HepG2, HLE, and Huh6 cell lines were cultured using DMEM with 10% heat-inactivated FBS and 1% Pen-Strep. For mouse primary hepatocytes 100,000 cells/well in a P24 plate using attachment medium (William's Medium with Glutamax, Fetal Bovine Serum (FBS) at 10% final concentration, Penicillin-Streptomycin (P/S) at 1%, and HEPES at 10 mM). After attachment, the media was replaced with a Maintenance Medium (William's Medium with Glutamax, FBS at 10%, P/S at 1%, Non-Essential Amino Acids (NEAA) at 1%, HEPES at 10 mM, and Hydrocortisone at 5 µM). Cell death was measured using SYTOX green (ThermoFisher Scientific, Scientific, Gibco, UK).

Stem Cell Differentiation into Hepatocytes Like Cells (HLC)

The differentiation of stem cells into Hepatocytes Like Cells (HLCs) followed the protocol as described before. Briefly, laminin-coated plates were prepared and stem cells were gently detached, seeded into the laminin-coated plates, and allowed to reach optimal confluency before initiating the differentiation. Albumin was measured in the cell culture medium by ELISA (Merk) and in the cells by qPCR. The differentiated cells were used for glycolytic stress test and protein studies.

In vitro RNA interference and adenoviral treatment

To induce PTPRK knockdown, we transfected HepG2, HLE, and Huh6 cell lines with siRNAs targeting PTPRK or a Negative control siRNA (working concentration 30 nmol/L; QIAGEN, Venlo, the Netherlands). The delivery of the siRNA was achieved using Lipofectamine RNAiMAX (Invitrogen,

Carlsbad, CA) in Opti-mem medium (Invitrogen). The siRNA target sequences are detailed in Table 3 (siRNA PTPRK #1 sense sequence: SEQ ID NO 3; siRNA PTPRK #1 antisense sequence: SEQ ID NO 4; siRNA PTPRK #2 sense sequence: SEQ ID NO 5; siRNA PTPRK #2 antisense sequence: SEQ ID NO 6). In primary mouse hepatocytes, we used adenoviral vectors to achieve PTPRK overexpression (Adv-*Ptprk*, ADV-269821) and silencing (Adv-shRNA *Ptprk*, shAAV-269821, Vector Biolabs).

Table 3*. List of siRNAs for RNA interference in the present study.*

siRNA	Source or reference	Identifiers	Sense (5´->3´)	Antisense (5´->3´)
siRNA PTPRK #1	Ambion by Life Technologies	s11559	CCAGUAGCCCAG ACUAAGAtt	UCUUAGUCUGGG CUACUGGta
siRNA PTPRK #2	Ambion by Life Technologies	s11558	CAGCUAUAGCAG UAUAAGAtt	UCUUAUACUGCUA UAGCUGat
siRNA Control	Qiagen	1027281	-	-

Colony formation assay

48h after siRNA transfection, the cells underwent trypsinization to attain a single-cell suspension. For the colony formation assays, 2,000 cells were seeded into P6 plates. After 1-2 weeks, depending on the specific cell line, the resultant colonies were fixed with 4% PFA.

Dephosphorylation assay

The dephosphorylation assay employed lysates obtained from primary mouse hepatocytes that had been treated with pervanadate. After overnight culture, confluent primary hepatocyte cultures underwent pervanadate treatment. Freshly prepared sodium pervanadate was generated and used to treat primary mouse hepatocytes. Following the harvest of lysates, DTT was added and through centrifugation, the gathered supernatants were preserved by freezing. In the subsequent dephosphorylation assay, the lysates treated with pervanadate combined with a recombinant PTPRK domain (PTPRK-ICD, concentration) were allowed to incubate. The reaction was ceased after 90 minutes using SDS, and the resulting samples were subjected to immunoblot analysis of phospho-FBP1 (pY265).

Extracellular acidification rates measurement during glycolytic stress test

Glycolytic rates were evaluated using the XFp Flux Analyzer from Seahorse Bioscience (North Billerica, MA). The cells were plated and allowed to equilibrate in XF Base media (glucose-free, Seahorse Bioscience) at 37°C for one hour in a CO_2-depleted incubator and the medium was refreshed immediately before the experiment. The glycolytic stress test was conducted by adding glucose (10 mM), oligomycin (1.5 μM), and 2-DG (totalling 100 mM). For the experiments aiming to assess the impact of PTPRK inhibitors on the ECAR of HepG2, HLE, and Huh6 cell lines, the XF Base media

(Seahorse Bioscience) was supplemented with 1 mM pyruvate, 2 mM glutamine, and 10 mM glucose. The PTPRK inhibitors were then introduced through injections as specified.

Western blotting

RIPA buffer (Cell Signaling Technology) was used to extract total protein lysates from tissues, while cell total protein lysates were prepared using Cell Lysis Buffer (Cell Signaling Technology, 9803S). Both lysis buffers were supplemented with Halt protease and phosphatase inhibitor cocktail (Thermo Fisher, cat #78442). Protein quantification was performed using a BCA protein assay kit (Thermo Fisher; cat. #PI23227). Separated by polyacrylamide gels, 20–50 μg of protein lysate was subsequently transferred to a 0.22 μM nitrocellulose membrane (Bio-Rad, Hercules, CA, USA). Primary antibodies were applied on the membranes within a milk-blocking buffer. Detection of proteins employed goat anti-rabbit IgG (Dako Agilent, Santa Clara, CA, USA; cat. #P0448), goat anti-mouse IgG (Dako Agilent, Santa Clara, CA, USA; cat. #P0447), and Peroxidase AffiniPure Donkey Anti-Human IgG (Jackson ImmunoResearch, Code: 709-035-149) secondary antibodies. Immunoreactive bands were detected using a western blot imaging system (Amersham ImageQuant 800 western blot imaging system, Cytiva Life Science, Marlborough, MA, USA).

RNA extraction, qPCR, and transcriptomics analysis

For qPCR performed in cell cultures poly(A)+ mRNA extraction was performed with Dynabeads mRNA DIRECT kit (Invitrogen) according to the manufacturer's instructions; reverse transcription was carried out with a reverse transcriptase kit (Eurogentec, Seraing, Belgium). Quantitative real-time PCR was performed with a Bio-Rad CFX machine (Bio-Rad Laboratories, Hercules, CA) and SYBR Green reagent (Bio-Rad Laboratories). For tissues or freshly isolated hepatocytes with high-fat and low-fat content the total RNA was obtained with the use of QIAamp DNA Mini Kit (QIAGEN, Hilden, Germany) following the manufacturer's instructions. For the transcriptomics experiments, total RNA quality analysis, library preparation, and sequencing were performed by the BRIGHTcore facility (Brussels, Belgium). Sequencing was performed on an Illumina NovaSeq 600. An average of 25 million paired-end reads of 100 nucleotides long were obtained per sample. The list of up-/downregulated genes/transcripts and association with canonical pathways were determined with the use of the online Degust software with Limma/Voom and packages Bioconductor EGSEA and ComplexHeatmap in RStudio (Boston, MA).

Extraction of Proteins from Human Liver Biopsies, Enrichment of PTPs, and Proteomics Analyses

Frozen human liver biopsies were subjected to disruption using beads beating and sonication. Lysates were treated with a lysis buffer containing 10% glycerol, 1% NP-40, 1× complete EDTA-free protease inhibitor cocktail (Roche Diagnostics), and 1× phosphatase inhibitor (Sigma-Aldrich). After sonication, centrifugation at 20,000g for 1 hour at 4°C separated insoluble debris, retaining the supernatant for total

proteome analysis. The obtained lysates were enzymatically digested using trypsin, targeting C-terminal lysine and arginine residues (except when adjacent to a C-terminal proline). Purification of resulting peptides was performed using reverse-phase Sep-Pak C-18 cartridges, removing salts and buffers. By employing a strategy that explores the oxidation of the catalytic cysteine in the catalytic site of PTPs, peptides containing cysteine residues within the PTP signature motif HCX5R were enriched through immunoprecipitation. Immunoprecipitated peptides, resuspended in 0.2% formic acid, were injected in triplicate for LC-MS/MS analysis. A 40-minute reverse-phase gradient separation on UHPLC 1290 (Agilent) was followed by analysis on an Orbitrap Q Exactive HF mass spectrometer (Thermo Scientific), with MS scans spanning the 375–1500 m/z range at 60,000 resolution. Data were acquired in Data-Dependent Acquisition mode, selecting the top 7 precursor ions for HCD fragmentation, followed by MS/MS analysis at 30,000 resolution. MaxQuant (version 2.0.3.0) processed spectral files, searching the Homo sapiens Uniprot database with FDR restricted to 1%.

Mass spectrometry acquisition and data analysis for quantitative tyrosine phosphoproteomics and total proteomics

The liver tissue samples were lysed in cold HEN Buffer supplemented with PhosSTOP (Roche) and cOmplete™, Mini, EDTA-free Protease Inhibitor Cocktail (Roche). Frozen tissue was disrupted in lysis buffer using the TissueLyser II (Qiagen) and 1.4mm ceramic beads (Qiagen). Lysates were precipitated twice using methanol/chloroform precipitation (Sample:Methanol:Chloroform, 4:4:1). Pellets were resuspended using 2% SDS in 50mM HEPES, and protein concentration was performed using DC protein assay (Biorad). An equal amount of protein was subjected to reduction and alkylation by incubating the samples with 5mM DTT for 1h at 37°C, followed by 20mM iodoacetamide at room temperature for 30min. Pellets were dissolved using 6M Guanidine-HCl in digestion buffer (50mM ammonium bicarbonate, 1mM $CaCl_2$) and readjusted to the same concentration. 250µg of proteins were diluted to 0.3M Guanidine-HCl in digestion buffer and digested using Trypsin. Peptides were desalted on Supel™-Select HLB SPE Tube (Sigma). Eluates were evaporated under a vacuum until dryness. Peptides were dissolved in 80% acetonitrile and 0.1% TFA. Before enrichment, digestion quality control was performed using an Ultimate 3000 Nano Ultra High-Pressure Chromatography system with a PepSwift Monolithic® Trap 200 µm*5mm (Thermo Fisher Scientific). One part of the sample was kept aside and dried again for total proteomic analysis. The phosphorylated peptides enrichment was performed using Fe(III)-NTAcartridges (Agilent Technologies) using the AssayMAP Bravo Platform (Agilent Technologies). Cartridges were primed and equilibrated with 0.1% TFA in ACN and 0.1% TFA, 80% ACN (loading buffer) solutions, respectively. Samples were loaded onto the cartridges at a flow rate of 5µl/min. Cartridges were then washed with loading buffer and eluted using 1% NH_4OH. Peptides were immediately acidified using 10% Formic acid (FA) and dried in vacuum. Both total proteome and phosphorylated peptide enrichment were analyzed by high-resolution LC-MS/MS using an Ultimate 3000 Nano Ultra High-Pressure Chromatography system (Thermo Fisher Scientific)

coupled with an Orbitrap Eclipse™ Tribrid™ Mass Spectrometer via an EASY-spray (Thermo Fisher Scientific). For the total proteome analysis, Peptide separation was carried out with an Acclaim™ PepMap™ 100 C18 column (Thermo Fisher Scientific) using a 155min linear gradient from 3 to 35% of B (84% ACN, 0.1 % FA) at a flow rate of 250nL/min. The Peptide separation for the phospho-proteome analysis was carried out with an Acclaim™ PepMap™ 100 C18 column (Thermo Fisher Scientific) using a 155min non-linear gradient from 3 to 35% of B (0 min, 3% B; 135min, 30% B; 155min, 42% B; B:84 % ACN, 0.1 % FA) at a flow rate of 250 nL/min. Both were analyzed using the Orbitrap Eclipse™ operated in a DDA mode. MS1 survey scans were acquired from 300 to 1,500 m/z at a resolution 120,000 using the Orbitrap mode. MS2 scans were carried with high-energy collision-induced dissociation (HCD) at 32% using the Normal speed IonTrap mode. Data were evaluated with proteome discoverer software using 10ppm for precursor mass tolerance, 0.5Da for the fragment mass tolerance, specific tryptic digest, and a maximum of 3 missed cleavages. Carbamidomethylation (+57.021464Da) on C was added as a fixed modification. N-term Acetylation (+42.010565Da) and methionine oxidation (+15.994915Da) were added as variable modifications. Phosphorylation (+79.966331) on S, T, and Y was added as variable modification only for the phospho-proteome analysis in addition to other mentioned modifications. PSM and proteins were filtered at FDR 1%. Protein abundancies (total proteome) were normalized using TIC. Phosphorylated peptide abundancies were normalized using eigenMS with R studio.

Measurement of fructose 1,6-bisphosphate in cells using HYlight

We employed the HYlight biosensor to directly observe how glycolysis functions in real-time within live hepatic cells. This biosensor swiftly responds to changes in fructose 1,6-bisphosphate (FBP) levels. Cells were transfected with the HYlight plasmid as previously described and 1h before imaging, cultured primary hepatocytes from *Ptprk*$^{+/+}$ and *Ptprk*$^{-/-}$ mice, as well as HepG2, Huh6, and HLE cells, were subjected to glucose starvation using XF assay medium (seahorse, no glucose). For experiments using PTPRK inhibitor, cells were pre-incubated with 50 µM of PTPRK inhibitor 2 for 6h and also added during starvation and measurement times. Live-cell imaging was conducted on a Nikon Eclipse TiE inverted microscope equipped with a Yokogawa CSU-W1 spinning disk confocal unit and a 60× oil-based objective (NA 1.4, Plan Apo VC OFN 25) with the perfect focus system. The cells were excited at 488 nm and 405 nm, and emission was captured using a 525/25 nm emission filter. Imaging was carried out at 5% CO2 and 37 °C. Intracellular fructose-1,6-bisphosphate (FBP) within islets was visualized by exciting HYlight at 485 nm and capturing the emission at 515 nm. This was accomplished using either a Zeiss Axiozoom.V16 microscope with a 2.3/0.56 objective or a Zeiss Axioskop microscope with a 20/1.0 objective.

PTP activity assay

The pNPP phosphatase activity assay was conducted following a protocol described in the art. Briefly, recombinant PTPRK intracellular domain and PTPN2 were prepared in 50 µL volumes within a 96-well microplate format using assay buffer (50 mM Tris-HCl, pH 7.4, 150 mM NaCl, 5% glycerol, 5 mM DTT, 100 µg/ml BSA). Serial dilutions of pNPP substrate (0–40 mM, New England Biolabs) were prepared in assay buffer. Reaction plates containing enzyme and substrate dilutions were incubated at 30 °C for 30 minutes. Subsequently, 50 µL of pNPP substrate was added and mixed to initiate reactions. The formation of the reaction product was monitored for 15 minutes at 30 °C by measuring absorbance at 405 nm using a Spectramax M5 plate reader (Molecular Devices). The obtained data were fitted to a standard curve of known 4-nitrophenol (Sigma) concentrations, and initial enzymatic rates (V_0) were determined using linear regression in GraphPad Prism. V_0 values at different substrate concentrations underwent non-linear regression analysis to determine kinetic parameters (Vmax and Km), which were calculated using the Michaelis-Menten equation in GraphPad Prism. Lastly, kcat values were obtained using the formula kcat = Vmax/[ET].

Chemical libraries

The chemical formulae of all compounds in the chemical library used in this study were downloaded as SMILES from the MolPort FTP site (constructed with compounds commercially available in MolPort, https://www.molport.com/, and with a molecular weight below 700 Da). DATAWARRIOR 5.0 software was used to convert the SMILES into 3D SDF files. Chemical formulae of the compounds used in this study are also displayed in Table 1.

Protein structures

The crystallographic structure 2C7S.pdb available for PTPRK (UniProt code: Q15262, PTPRK_HUMAN) shows the WPDHGVP (SEQ ID NO: 2) loop displaced, which results in an "open conformation" without ligand of the catalytic pocket, and also presents several gaps, for these reasons the structure has been modelled for a "closed conformation" with ligand bound to the catalytic site, using the 2HO3.pdb structure as a template (Waterhouse et al., 2018). The structures of PTPN2 (UniProt code: P17706, PTN2_HUMAN), PTPRB (UniProt code: P23467, PTPRB_HUMAN), PTPRF (UniProt code: P10586, PTPRF_HUMAN), PTPRM (UniProt code: P28827, PTPRM_HUMAN), PTPRT (O14522, PTPRT_HUMAN) and PTPRU (UniProt code: Q92729, PTPRU_HUMAN) in their "closed conformation" for the catalytic site have also been modelled using the 2HO3.pdb structure as a template. The specific edition of protein structures was made using PyMol 2.0 software (PyMOL Molecular Graphics System, v2.3.3 Schrödinger, LLC, at http://www.pymol.org/) without further optimization. For each model, water molecules, ions, or inhibitors were removed.

Calculation of pharmacokinetic parameters and potential toxicity properties of candidates

Molecular descriptors, such as the topological polar surface area (TPSA), molecular weight (MW), the estimated logarithm (base 10) of the solubility measured in mol/L (cLogS), the estimated logarithm (base 10) of the partition coefficient between n-octanol and water (cLogP), the number of hydrogen bond acceptors (H-acceptors), the number of hydrogen bond donors (H-donors), number of rotable bonds, and the violations of Lipinski's rule of five (Ro5 violations) were calculated using DataWarrior v5.0.0 software (Allschwil, Switzerland). The in silico absorption, distribution, metabolism, excretion, and toxicity (ADMET) properties of all compounds were calculated using the admetSAR web application and the DataWarrior v5.0.0.

Molecular docking simulation

Molecular docking simulations were performed using YASARA structure v22.5.22 software (Vienna, Austria), running the AutoDock 4 algorithm with AMBER99 as the force field. A total of 100 flexible docking runs were set and clustered (7 Å) around the ligand-binding domain cavity, i.e., two complexed compounds belonged to different clusters if the ligand root-mean-square deviation of their atomic positions was greater than a minimum of 7 Å around certain hot spot conformations. The YASARA software has calculated the variation of the Gibbs free energy (ΔG, Kcal mol-1), taking into account that more positive energy values indicate stronger binding of the docked compound. To calculate this parameter, Autodock/Vina uses a force field scoring function that takes into account the strength of electrostatic interactions, hydrogen bonding between all atoms of the two binding partners in the complex, intermolecular van der Waals forces, and solvation and entropy contributions. Ligand-protein interactions were detected using the Protein-Ligand Interaction Profiler (PLIP) algorithm.

Molecular docking simulations were performed on the known catalytic sites of each protein in its closed conformation. The presence or absence of a compound in the catalytic pocket displaces a loop that closes or opens the structure. For each protein, the grid dimensions were 25 × 25 × 25. The appropriate pH 7.4 protonation state of each PTP protein side chains was created using the YASARA structure v22.5.22 software. YASARA software generated a file containing the molecular coordinates of different poses of the conformer docked to the binding site in the protein, as well as the Gibbs free energy variation (ΔG, kcal/mol) for each pose. YASARA's software was set up on a Linux cluster at Consortium des Équipements de Calcul Intensif (CÉCI). The figures were prepared using PyMol 2.6.0a0 software.

Molecular dynamics (MD) simulations

YASARA dynamics v22.5.22 (Vienna, Austria) was employed to carry out all the MD simulations with AMBER14 as a force field, similarly to the way it has been described in previous publications of the inventors. The simulation cell was allowed to include 20 Å surrounding the protein that was filled with water at a density of 0.997 g/mL. Initial energy minimization was carried out under relaxed constraints

using steepest descent minimization. Simulations were performed in water under constant pressure and constant temperature (25 °C) conditions. To mimic a physiological environment, counter ions were added to neutralize the system (Na^+ or Cl^- were added as a replacement for water to give a final NaCl concentration of 0.9% and the pH was maintained at 7.4). Hydrogen atoms were added to the protein structure at the appropriate ionizable groups according to both the calculated pKa and the simulation pH (i.e., a hydrogen atom was added if the computed pKa was higher than the pH). The pKa was computed for each residue according to the Ewald method (Krieger et al., 2006). Data were collected every 100 ps. Poisson-Boltzmann surface area calculations (MM/PBSA) were used to determine the free energy of binding of each compound to the catalytic site of each enzyme using the macro md_analyzebindenergy.mcr, as described in work from our group before.

Zebrafish Larvae Toxicity Assessment and Swimming Behavior Analysis

Zebrafish larvae were exposed to inhibitor 1 or 2 by submerging them in 6-well plates containing E3 medium (5 mM NaCl, 0.17 mM KCl, 0.33 mM CaCl2, 0.33 mM $MgSO_4$, 1 mM HEPES) for a duration of 3 to 5 days post-fertilization (dpf). Two concentrations, 5 μM and 10 μM, of the inhibitors were tested. Control groups consisted of a well containing only E3 medium and another with DMSO diluted in E3 medium. The exposure solutions were renewed daily. On the final day, the swimming behaviour of the zebrafish larvae was evaluated using the Daniovision system (ViewPoint Behavior Technology). Prior to the 20-minute swimming behavior analysis, the fish were individually placed in separate wells to ensure accurate observations.

LC-MS Analysis of Glycolytic, Tricarboxylic Acid (TCA) Cycle, and Pentose Phosphate Pathway (PPP) Intermediates

The metabolomics analysis was conducted at the VIB Metabolomics Core. In summary, polar metabolites were extracted using a two-phase methanol-water-chloroform method as described in the art. Briefly, dried metabolite samples were reconstituted in a solution of 60% acetonitrile and then transferred to LC-MS vials. For the analysis, an UltiMate 3000 LC System (Thermo Scientific) was coupled to a Q-Exactive Orbitrap mass spectrometer. Separation was achieved using a SeQuant ZIC/pHILIC Polymeric column (Merck Millipore). A gradient of solvent A (95% acetonitrile-H_2O, 2 mM ammonium acetate pH 9.3) and solvent B (2 mM ammonium acetate pH 9.3) was employed. Mass spectrometry was carried out in the negative ion mode, encompassing both full scans and a targeted Selected Ion Monitoring (SIM) approach. Data acquisition was managed using Xcalibur software (Thermo Scientific). The data is presented as raw abundances corrected for sample weight.

Statistical Analysis

Statistical significance was determined by a two-tailed paired Student's t-test or ANOVA with Tukey correction. The Correlation analyses were performed using the Pearson correlation test. P values <0.05 were considered statistically significant.

RESULTS

Human Hepatic PTPs Expression in Obesity-Related Liver Dysfunction

The global protein tyrosine phosphatome (PTPome) within the liver, in the context of NAFLD, remains largely unexplored. We conducted a comprehensive analysis of the total proteome and PTP expression patterns across different stages of liver disease using liquid chromatography-tandem mass spectrometry (LC-MS/MS) analysis of human liver samples (**Fig. 1A**). The cohort included liver biopsies obtained from individuals presenting varying degrees of liver disease, encompassing steatosis, non-alcoholic steatohepatitis (NASH), and hepatocellular carcinoma (HCC), as well as control samples from individuals without evidence of liver diseases (healthy liver). The heatmap illustrating the total proteome alterations (**data not shown**) shows variations in protein expression and sample heterogeneity across different stages of liver dysfunction. KEGG pathway analyses revealed that several protein modifications relate to metabolic dynamics. When comparing steatosis with healthy livers (**data not shown**), we observed activation of oxidative phosphorylation, starch and sucrose metabolism, and glutathione metabolism, alongside the suppression of the tight junction pathway. Comparing NASH with healthy livers (**data not shown**), reveals pathways associated with ECM receptor interaction, oxidative phosphorylation, and focal adhesion as activated in NASH while suppression in pathways related to the pentose phosphate pathway, purine metabolism, histidine metabolism, and cysteine and methionine metabolism is observed. In the comparison between NASH and steatosis (**data not shown**), oxidative phosphorylation is suppressed in NASH compared to steatosis, while ECM receptor interaction, focal adhesion, and ribosome pathways are activated in NASH. Through a full analysis of total protein lysates and PTP immunoprecipitates, we successfully identified 18 distinct PTPs out of the 37 PTP proteins expressed in the human body (**Fig. 1B**). Consistent with expected metabolic alterations common in NAFLD, complete proteome analysis showed that key enzymes involved in fatty acid uptake and metabolism, CD36, CPT1, and SCD, were significantly upregulated in steatosis and NASH samples, compared to healthy livers (**Fig. 1C**). The analysis of the PTPome revealed that samples within the same disease stage display similar expression patterns (**Fig. 1D**), while analysis of receptor protein tyrosine phosphatases (RPTPs) and non-receptor protein tyrosine phosphatases (PTPNs) revealed opposite patterns across the stages of fatty liver disease (**Fig. 1E**). Several PTPNs were downregulated with disease, in contrast, RPTPs generally exhibited low expression levels in healthy liver samples but showed a marked upregulation in steatosis and NASH. Specifically, PTPRK, PTPRE, PTPRM, PTPRF, and PTPRA demonstrated elevated expression levels in steatosis and NASH when compared to healthy livers (**Fig. 1F**). Single-cell RNA sequencing in healthy NASH livers revealed that PTPRK is the most abundant RPTP detected in hepatocytes, followed by PTPRG and PTPRM, with PTPRE mainly found in dendritic cells (**Fig. 1G; and data not shown**). Additionally, RPTP mRNA levels in the E-MEXP-3291 dataset displayed comparable transcription patterns (**Fig. 1H**). Correlation analysis showed that hepatic PTPRK, PTPRG, and PTPRE transcript levels positively correlate with PPARγ (**Fig. 1I**), a master regulator of lipid accumulation in hepatocytes. Immunohistochemistry (IHC) analyses in human

liver samples showed that PTPRK levels were higher in steatosis and NASH, while healthy liver tissues exhibited comparatively lower expression levels. PTPRK localized within various cellular regions, including the nucleus of steatotic hepatocytes (**Fig. 1J**). The striking remodelling of PTPomes with disease onset indicates a potential causative role in fat accumulation and liver dysfunction.

Hepatocyte PTPRK is induced in obesity and positively correlates with PPARγ in mouse models and primary hepatocytes.

To further investigate the relevance of PTPRK in obesity-related liver dysfunction, we employed diet-induced mouse models that mimic key features of human obesity and NAFLD. C57BL/6N mice were exposed to either a high-fat diet (HFD, ~5.2kcal/g, from which ~60% is derived from fat, 20% from carbohydrates and 20% from proteins) or a high-fat, high-fructose, high-cholesterol diet (HFHFHCD, ~4.5Kcal/g, from which ~40% derives from fat, 20% from carbohydrates and 20% proteins, enriched with 2% of cholesterol and around 50% of the carbohydrates is fructose) for 12 weeks. The results were compared with those obtained from mice fed a control diet (CON, ~3.8Kcal/g, from which ~70% is derived from carbohydrates, 20% from proteins and 10% from fat). Notably, both HFD and HFHFHCD regimens resulted in increased body weight gain (**Fig. 2A**), primarily attributed to increased body fat mass (**Fig. 2B**). This was accompanied by elevated fasting insulin levels (**Fig. 2C**), impaired glucose tolerance (**Fig. 2D**), and reduced insulin sensitivity (**Fig. 2E**). We next showed that among insulin-sensitive tissues that play important role in glucose homeostasis, PTPRK is expressed in hepatocytes, but not detected in subcutaneous and visceral adipose tissues or muscle (**Fig. 2F**). Mice fed with HFHFHCD exhibited a greater liver weight, liver-to-body weight ratio, and liver fat mass compared to the control group (**Fig. 2G**), indicating a more advanced stage of fatty liver development than that observed in HFD-fed mice after 12 weeks of feeding. Liver histological analysis (**Fig. 2H**) confirmed extensive steatosis in HFHFHCD-fed mice, while the HFD group displayed a milder form of fatty liver, resembling an early stage of the condition. PTPRK protein expression is enhanced in HFD and HFHFHCD-fed mice livers, accompanied by PPARγ upregulation (**Fig. 2I**). These results demonstrate in mice the observed patterns of PTPRK expression in human liver samples and suggest a conserved role for PTPRK in lipid metabolism and diet-induced liver dysfunction. Remarkably, we observed that adenovirus-mediated overexpression of PTPRK in the mouse livers resulted in a concomitant increase in PPARγ levels (**Fig. 2J**).

Subsequently, we investigated the direct association between PTPRK and PPARγ expressions in hepatocytes, employing cultured mouse primary hepatocytes for experimental analysis. It is noteworthy that primary hepatocytes undergo a loss of differentiation status during prolonged culture, leading to altered metabolic pathways due to limited representation of the complex liver microenvironment *in vitro*. Some of these time-dependent hepatocyte changes are observed *in vivo* along the progression of NAFLD. Within our culture conditions, we observed a gradual accumulation of lipid droplets in the cytosol of hepatocytes (**Fig. 2K**). This abundance of lipid droplets was accompanied by heightened

protein levels of PTPRK and PPARγ (**Fig. 2L**). This observation prompted us to dissect the possible signals mediating such upregulation. According to the "multiple hits" hypothesis, the pathogenesis of NAFLD involves a combination of various factors, including inflammation, hyperinsulinemia, lipotoxicity, oxidative stress and others. Acute and chronic treatments of primary hepatocytes with insulin or pro-inflammatory cytokines TNF-α, IL-6 or IFN-γ did not affect PTPRK expression (**data not shown**). We further observed that Notch2 levels are significantly increased in primary hepatocytes over time in culture (**data not shown**) and the administration of the Notch signalling inhibitor GSIXX effectively prevented the *in vitro* upregulation of both PTPRK and PPARγ in a dose-dependent manner (**Fig. 2M**). We further expanded our screening for factors inducing PTPRK expression in hepatocytes by testing the impact of lipopolysaccharide (LPS) treatment, a well-established inflammation and insulin resistance model. The results revealed that LPS treatment significantly increased both PTPRK transcript and protein levels (**Fig. 2N and 2O**), demonstrating the positive correlation between PTPRK and PPARγ as the PPARγ was also induced by LPS treatment. These findings suggest a potential cooperative regulatory mechanism between LPS-induced and Notch pathways to induce PTPRK expression in hepatocytes.

Our proteomics analysis of a small cohort of human HCC samples (n=3) revealed lack of PTPRK expression. It is known that solid tumors can be exposed to hypoxic microenvironment, which contributes to worsened disease outcomes. Cell adaptations to hypoxia largely rely on the stabilization and activation of hypoxia-inducible factors (HIFs) (Chen et al., 2019). To test if HIF-mediated signalling could affect PTPRK expression we treated primary mouse hepatocytes under normoxia by with DMOG, an inhibitor of 2-oxoglutarate-dependent dioxygenases required for HIF degradation. Remarkably, we observed an accumulation of HIF-2α reduced both PTPRK and PPARγ expression levels (**Fig. 2P**). Together, these experiments reveal compelling evidence of the interplay between PTPRK and PPARγ in coordinating lipid metabolism within hepatocytes, which can be differentially affected by diverse signalling pathways.

PTPRK deletion protects against diet-induced obesity, insulin resistance and hepatic steatosis in mice

To directly evaluate the metabolic relevance of PTPRK, we conducted loss-of-function studies using male and female 8-week-old *Ptprk*$^{-/-}$ and *Ptprk*$^{+/+}$ control mice subjected to either an HFHFHCD or a chow diet. PTPRK deficiency has minimal impact on body weight gain and fat accumulation in chow-fed males and females (**data not shown**). The glucose and insulin tolerance tests performed at 8 weeks of age showed no differences between *Ptprk*$^{+/+}$ and *Ptprk*$^{-/-}$ mice (**data not shown**), but at the age of 20 weeks, males and females *Ptprk*$^{-/-}$ showed increase sensitivity to insulin (**data not shown**). In males, at the age of 20 weeks, the glucose tolerance was also improved in *Ptprk*$^{-/-}$ mice and no differences were observed for females at the same age (**data not shown**), while the intake of chow diet

was similar in *Ptprk*$^{-/-}$ and *Ptprk*$^{+/+}$ males and females **(data not shown)**. After 12 weeks of HFHFHCD feeding, *Ptprk*$^{+/+}$ male and female mice developed obesity, characterized by substantial increases in body weight **(Fig. 3A and 3D)**, fat mass (**Fig. 3B and 3E**), circulating insulin levels and HOMA-IR **(Fig. 3C and 3F)**, glucose intolerance and insulin resistance **(Fig 3G and 3H)**. Strikingly, *Ptprk*$^{-/-}$ mice displayed resistance to HFHFHCD-induced obesity, as their body weight, fat mass, circulating insulin levels, and HOMA-IR, glucose sensitivity and insulin resistance were all significantly lower compared to *Ptprk*$^{+/+}$ mice. This protective effect was particularly prominent in female mice, where *Ptprk*$^{+/+}$ mice exhibited a two-fold increase in body weight gain and body adiposity compared to *Ptprk*$^{-/-}$ female mice. Consistent with our metabolic analyses, mice lacking PTPRK exhibited elevated energy expenditure, specifically during the dark cycle **(data not shown)**. *Ptprk*$^{-/-}$ mice also displayed increased VO_2 levels during the night-time, and the respiratory quotient (RER) showed a downward trend throughout both light and dark cycles **(data not shown)**. No significant disparities were noted in physical activity or water and food intake between wild-type and PTPRK-deficient mice, although there was a trend towards reduced food intake in *Ptprk*$^{-/-}$ mice (**data not shown**). The analysis of food intake over a span of 12 weeks revealed no disparities in males, but lower levels of food intake were observed in female *Ptprk*$^{-/-}$ mice compared to their wild-type counterparts, resulting in lower cumulative energy intake. The deficiency in PTPRK did not result in altered lipid excretion through faeces **(data not shown)**, suggesting that the reduced weight observed in *Ptprk*$^{-/-}$ mice is not related to changes in intestinal fat absorption. To further demonstrate the impact of PTPRK deletion on insulin sensitivity, we assessed insulin-induced signalling in mice fed HFHFHCD for 12 weeks. The results demonstrated that *Ptprk*$^{-/-}$ mice exhibited significantly higher induction of p-IR and p-AKT compared to *Ptprk*$^{+/+}$ mice, indicating enhanced insulin signalling in the absence of PTPRK (**Fig 3I**). The phosphorylation levels induced by insulin on IR and AKT displayed no discernible differences **(data not shown)**, indicating that PTPRK does not directly affect IR phosphorylation. We observed a significant reduction in hepatic lipid accumulation within the livers of *Ptprk*$^{-/-}$ mice **(Fig. 3J-O)** Collectively, these findings highlight that while PTPRK-deficiency exerts minimal influence on normal development, its deletion confers robust protection against diet-induced obesity and insulin resistance.

Hepatic PTPRK expression shapes nutrient-driven metabolic reprogramming in hepatocytes

Having established that PTPRK plays a major metabolic role in obesity, we next sought to define the lipogenic pathways in high-fat fed mice. Immunoblot analysis showed that *Ptprk*$^{-/-}$ mice exhibited lower levels of hepatic PPARγ **(Fig 4A and 4B)**, while no differences were observed in subcutaneous and visceral adipose tissue **(Fig. 4C and 4D and data not shown)**. We observed significantly reduced expression of PPARγ2 transcripts in *Ptprk*$^{-/-}$ mice, while PPARγ1 was unaffected (**Fig 4E**). Concomitantly, key lipogenic enzymes, namely Scd1, Acly, Acc, and Fasn, were downregulated in *Ptprk*$^{-/-}$ mice (**Fig. 4E**). Immunoblot analysis confirmed diminished levels of ACC and FASN in *Ptprk*$^{-/-}$ mice compared to their *Ptprk*$^{+/+}$ counterparts (**Fig 4A and 4B**). Additionally, transcription factors

governing fat metabolism, SREBP1c and ChREBP, also exhibited heightened expression in the livers of *Ptprk*$^{+/+}$ mice relative to *Ptprk*$^{-/-}$ mice (**Fig 4A and 4B**). Next, we used adenoviral-mediated upregulation of PTPRK in wild-type mice and observed a significant increase in hepatic PPARγ expression after two weeks of HFHFHCD feeding following the adenoviral infection (**Fig 4F**). Next, we used *Ptprk*$^{-/-}$ female mice fed an HFHFHCD for four weeks. Adenoviral overexpression of PTPRK reverted the hepatic phenotype of *Ptprk*$^{-/-}$mice, including increased liver weight, liver-to-body weight ratio, and liver fat mass (**Fig 4G**). Histological examination of liver sections and liver measurements revealed pronounced lipid deposition following PTPRK overexpression (**Fig 4H**). These results demonstrate that hepatic PTPRK overexpression effectively reverses key phenotypic characteristics observed in PTPRK-deficient mice. Primary hepatocytes with reduced PTPRK levels (heterozygous) or complete deletion (knockouts) showed reduced kinetics of STAT1 phosphorylation in response to IFN-γ (**data not shown**). STAT1 and Activator Protein 1 (AP-1) play a pivotal role in driving PPARγ expression and lipid accumulation within the liver. We observed significantly lower levels of c-Fos/AP-1 in *Ptprk*$^{-/-}$ fatty livers (**data not shown**). Taken together, our results suggest that PTPRK is upstream of transcriptional regulators of lipid metabolism and *de novo* lipogenesis in obesity.

Phosphoproteomic analysis reveals FBP1 as a PTPRK substrate in hepatocytes during steatosis

To explore the mechanisms by which PTPRK inactivation in hepatocytes might drive the development of steatosis, we performed unbiased transcriptome and proteomic analysis. Hepatocytes were isolated and separated based on their fat content (**Fig 5A**). Immunoblot analysis of high-fat content hepatocytes further underscored the direct correlation between PTPRK and PPARγ (**Fig 5B**). Steatotic PTPRK-deficient hepatocytes failed in recruiting PPARγ to engage CD36, a crucial protein in cellular fatty acid uptake (**Fig 5C**). In contrast, Cpt1, facilitating long-chain fatty acid transportation for mitochondrial beta-oxidation, displayed an opposing pattern, with higher expression in *Ptprk*$^{-/-}$ hepatocytes than in *Ptprk*$^{+/+}$ (**Fig 5C**). We performed RNA-Seq analysis in low/high fat *Ptprk*$^{-/-}$ and *Ptprk*$^{+/+}$ primary hepatocytes (**data not shown**). Volcano plot analysis unveiled that the predominant significant differences occurred among genes upregulated in low-fat hepatocytes compared to high-fat hepatocytes within the same genotype **(data not shown).** In contrast, only a limited number of genes exhibited significant transcriptional alterations resulting from PTPRK deletion in low-fat or high-fat hepatoctyes (**data not shown**). We also observed reduced PPAR signaling pathway in *Ptprk*$^{-/-}$ hepatocytes compared to *Ptprk*$^{+/+}$ hepatocytes (**Fig 5D**). Comparison of low-fat to high-fat *Ptprk*$^{+/+}$ hepatocytes revealed enriched pathways including cell adhesion molecules, MapK signaling, Pi3k-Akt signaling, cytokine interaction, chemokine signaling (**Fig 5E**). In *Ptprk*$^{-/-}$ hepatocytes, the same comparison highlighted pathways including gap junction, ECM receptor interaction, focal adhesion, cAMP signaling, Pi3k-Akt signaling, and Rap1 signaling. We subjected hepatocytes with high-fat content to proteomics and phosphoproteomics analysis (**data not shown**). The Venn diagram reveals that 1148 genes show modifications in both the phosphoproteomics and total proteome datasets. This occurs within a larger

context of 1993 proteins identified in the total proteome analysis and 1518 in the phosphoproteome analysis. This suggests a complex relationship between these protein datasets, indicating their interconnectedness and potential functional implications of regulatory mechanisms acting at the translational level and post-translationally through phosphorylation **(data not shown)**. The heatmap **(Fig 5F)** displays diverse protein changes between *Ptprk*$^{+/+}$ and *Ptprk*$^{-/-}$ hepatocytes, revealing their dynamic response. Enriched pathways **(Fig 5G)** include metabolism, phagosome, hepatocellular carcinoma, and oxidative stress. These pathways suggest impacts on core metabolism, potential involvement in liver diseases, chemical carcinogenesis-reactive oxygen species. In *Ptprk*$^{-/-}$ hepatocytes, an upregulation of specific proteins has been observed, reflecting a complex interplay of molecular events associated with altered mitochondrial function and redox balance, closely linked to cellular metabolic reprogramming **(Fig 5H)**. These observations collectively provide valuable insights into the dynamic molecular landscape of hepatocytes during metabolic reprogramming adding to our comprehension about the strategies employed by cells to adapt to altered metabolic conditions and how PTPRK can affect this process.

Phosphoproteomics revealed that PTPRK-deficiency increases phosphorylated residues across various proteins **(Fig 5I)**. These changes are directly associated with crucial pathways, including insulin signalling, mTOR pathway, AMPK signaling, insulin resistance, glucagon signaling, adherens junctions, biosynthesis of amino acids, and others **(Fig 5J)**. Interestingly, the prevalent phosphorylation sites predominantly involve serine and threonine residues, despite PTPRK being a tyrosine phosphatase. A total of 2572 phosphosites were significantly upregulated in *Ptprk*$^{-/-}$ hepatocytes compared with 258 found in lower levels **(data not shown)**. Phosphotyrosine residues CPSM(pY162), CH10(pY76), WASL(pY253), GSTP1(pY8), and F16P1(pY265, pY216) were increased in *Ptprk*$^{-/-}$ hepatocytes **(Fig 5K)**. The focused analysis of FBP1 revealed changes also at the positions pS273, pS248, pY265, pY245 and pY216 in *Ptprk*$^{-/-}$ steatotic hepatocytes **(Fig 5L)**. FBP1 is a key enzyme active in gluconeogenesis and glucose homeostasis. The structural analysis highlights conserved helical regions **(Fig 5M)** that engage with PTPRK's D2 domain **(Fig 5N)**, placing tyrosines near PTPRK's catalytic D1 domain. Computational simulations confirm PTPRK and tyrosine phosphorylated complex predictions with a range of different assemblies **(data not shown)**. Pervanadate-treated hepatocyte lysates, combined with recombinant PTPRK intracellular domain (PTPRK-ICD), demonstrate FBP1 dephosphorylation **(Fig. 5O)**. Liver analyses in female *Ptprk*$^{+/+}$ and *Ptprk*$^{-/-}$ mice following a 12-week HFHFHC diet showed high pFBP1(pY265) levels **(data not shown)**. We analysed FBP dynamics using the HYlight approach, a biosensor designed to track real-time changes in intracellular levels of FBP1's substrate, fructose-1,6 bisphosphate. We observed a reduction in FBP levels in *Ptprk*$^{-/-}$ hepatocytes compared to wild-types, particularly when stimulated with glucose to increase glycolytic rates **(Fig. 5P)**. Our results underscore the dynamic interplay between PTPRK and FBP1, significantly impacting glucose metabolism.

Deletion of PTPRK induces metabolic reprogramming in the liver during diet-induced obesity.

To assess the importance of hepatic PTPRK in glycolytic control, we cultured primary mouse hepatocytes with adenovirus-mediated PTPRK overexpression/silencing. Glucose-starved hepatocytes overexpressing PTPRK displayed heightened glycolytic activity after acute glucose injection and after mitochondrial respiration blockade by oligomycin (data not shown). Elevated glycolysis channels pyruvate toward acetyl-CoA synthesis, triggering de novo lipogenesis. Hepatocytes with PTPRK overexpression exhibited heightened lipid droplet accumulation **(data not shown)**. In addition, lipid droplet accumulation occurred to a greater extent in PTPRK overexpressing hepatocytes after free fatty acid administration (**data not shown**). Inhibition of glucose oxidation resulted in the suppression of PPARγ, while PTPRK expression was not affected **(data not shown)**. We next validated the results in human hepatocytes. *PTPRK*$^{-/-}$ and *PTPRK*$^{+/+}$ human embryonic stem cells were differentiated into hepatocyte-like cells (HLCs, **data not shown**). Deletion of PTPRK did not affect the ability of HLCs to produce and secrete albumin during their differentiation process **(data not shown)**. Consistent with mouse hepatocytes, PTPRK-deficient HLCs exhibited glycolytic rate following glucose stimulation **(data not shown)**. Together, these observations indicate that PTPRK leads to steatosis indirectly by stimulating glycolytic activity and directly by accelerating fatty acid esterification and lipid droplet formation in response to fatty acids.

To further explore hepatic metabolic changes, *Ptprk*$^{+/+}$ and *Ptprk*$^{-/-}$ mice were fed HFHFHCD for 12 weeks, and liver metabolites were quantified by mass spectrometry **(data not shown)**. *Ptprk*$^{-/-}$ livers showed decreased levels of dihydroxyacetone phosphate and glyceraldehyde-3-phosphate, with a corresponding reduction in the lactate/pyruvate ratio, reflecting restrained glycolytic rate. *Ptprk*$^{-/-}$ livers displayed elevated α-ketoglutarate levels and increased pyruvate, suggesting augmented demand for gluconeogenic substrates, aligning with gluconeogenesis being favoured over glycolysis in PTPRK absence. Despite elevated pyruvate levels, *Ptprk*$^{-/-}$ livers exhibited reduced concentrations of acetyl-CoA, but increased free coenzyme A compared to *Ptprk*$^{+/+}$, suggesting increased phosphorylation of pyruvate dehydrogenase in PTPRK deficient mice. This aligns with our findings of decreased levels of pyruvate dehydrogenase phosphatase in *Ptprk*$^{-/-}$ mice, while no differences were observed for pyruvate dehydrogenase kinase (**data not shown**). PTPRK deficiency also led to heightened PPP intermediates, particularly Ribulose-5-phosphate and Erythrose 4-phosphate. Enhancing PPP flux could fortify crucial reducing equivalent production, enhancing oxidative stress management. Parallel to shifts in lactate-to-pyruvate ratios, *Ptprk*$^{-/-}$ livers unveiled elevated GSSG and methionine sulfoxide levels, indicating an oxidized environment. The classical redox indicators NAD^+/NADH, NADP/NADPH, and GSSG/GSH remained unchanged, although the levels of NADP were significantly lower in *Ptprk*$^{-/-}$. No differences were found for phosphorylated adenine nucleotides (APT, ADP and AMP) and amino acids **(data not shown)**

We observed high expression of Pck1, a pivotal gluconeogenic driver, in *Ptprk*$^{-/-}$ livers **(data not shown)**, consistent with lower glycolysis. *Ptprk*$^{-/-}$ female mice, subjected to a 12-week HFHFHCD, exhibited elevated blood glucose levels compared to their *Ptprk*$^{+/+}$ counterparts after pyruvate injection, supporting a shift to a more gluconeogenic state upon PTPRK deletion **(data not shown)**. Taken together, our finding reveal that PTPRK plays a crucial role in controlling liver metabolislm through regulation of glycolytic intermediates shifts and altered lipid dynamics.

PTPRK contributes to hepatocyte transformation in obesity-associated HCC

Glycolytic and gluconeogenic proteins, including FBP1, contribute to HCC development (**data not shown**). Thus, we hypothesized that the impact of PTPRK on glycolysis can affect liver tumour growth. We observed a stratification pattern based on PTPRK mRNA expression levels in human samples (**Fig. 6A**) that bifurcated into two distinct clusters: one characterized by high PTPRK expression and the other marked by low PTPRK expression (**Fig 6B**). Normal liver samples uniformly exhibited low PTPRK expression, while in the context of NASH, peritumour, and tumour conditions, high PTPRK expression positively correlated with elevated hepatic expression of glycolytic genes. The analysis of all liver samples and the focused analysis of tumour samples revealed a positive correlation between elevated PTPRK expression and hepatic expression of lipogenic genes (**Fig 6B**). The enriched pathways associated with elevated PTPRK expression in liver tumour samples defined through KEGG pathway enrichment analysis, underscored the activation of key metabolic processes, including fatty acid metabolism, Type I diabetes mellitus, glycolysis/gluconeogenesis, TCA cycle, primary bile acid biosynthesis, biosynthesis of unsaturated fatty acids, PPAR signalling pathway, steroid biogenesis, and oxidative phosphorylation (**Fig 6C**).

To investigate the implications of PTPRK deletion in the context of liver cancer, diethylnitrosamine (DEN), a potent hepatocarcinogen, was administered via a single injection into both *Ptprk*$^{+/+}$ and *Ptprk*$^{-/-}$ mice at the age of two weeks. *Ptprk*$^{-/-}$ male mice showed a propensity for reduced body fat accumulation, while *Ptprk*$^{-/-}$ female exhibited diminished body weight and fat accumulation at the end of the experimental timeline compared with *Ptprk*$^{+/+}$ (**Fig. 6D and 6G**). Livers from *Ptprk*$^{-/-}$ male and female mice were smaller, and a thread of reduced hepatic lipid content, although the percentage of liver fat content remained unaltered (**Fig. 6D and 6G**). PTPRK deficiency did not affect the carcinogen's capacity to instigate tumour formation, as the tumour count remained unaffected in both genotypes (**Fig 6E and 6H**). However, macroscopic evaluation of tumour size showed reduced tumour dimensions in *Ptprk*$^{-/-}$ females (**Fig 6H**). This divergence was accentuated in histological analysis of liver tissue sections, where tumours within *Ptprk*$^{-/-}$ mice, regardless of sex, exhibited significantly diminished dimensions and reduced fat accumulation (**Fig. 6E and 6H**). In line with these findings, silencing of PTPRK using shRNA in HepG2, HLE, and Huh6 cell lines (**Fig 6J, 6K, and data not shown**) demonstrated a substantial attenuation in the colony-forming capacity of these hepatoma cells. Our observations support an oncogenic effect of PTPRK in rapid hepatic tumour growth.

In silico-identified PTPRK inhibitors reduced glycolysis and steatosis in pre-clinical models.

Having established the potential of PTPRK inhibition in obesity, we performed a screen through docking followed by dynamic simulations to identify potential inhibitors for PTPRK. Only two compounds (named here as PTPRK inhibitor 1, represented by Formula III and inhibitor 2, represented by Formula IV, **Fig 7A, top side)** showed an RMSD value lower than 5 Å throughout the MD simulation **(Fig 7B)**, and they also had an MM|PBSA value higher than 20 Kcal/mol against PTPRK and lower for the remaining PTPs. Analysis of the interactions of each compound on the catalytic site of PTPRK during the MD simulation shows that 'inhibitor 1' is mainly stabilized by hydrophobic interactions with the amino acids (Tyr916, Ile919, Arg992, Asp1050) of the catalytic site **(data not shown)**; whereas 'inhibitor 2' **(data not shown)**, in addition to hydrophobic interactions (Glu989, Lys994, Ala1084), establishes hydrogen bonds (Tyr916, Lys994, Asp1050) and π-stacking interactions (Tyr916).

Subsequently, these compounds underwent evaluation using the purified recombinant intracellular catalytic domain of PTPRK. We defined optimal concentrations of enzyme and pNPP for the assay and found 0.0003767 ΔOD405/s as Vmax and 2688uM as Km **(data not shown)**. We next used optimal conditions to test PTPRK inhibitors, and this approach unveiled that both compounds effectively suppressed PTPRK's catalytic activity with an IC_{50} of 37.39 μM for inhibitor 1 and 34.09 μM for inhibitor 2 **(data not shown)**. The inhibitors did not impact PTPN2 activity **(Fig 7C)**, known to regulate HCC development. In vitro experiments were performed in glycolytically active human hepatoma cell lines, demonstrated a marked reduction in ECAR levels upon inhibitor administration, indicating substantial suppression of glycolysis **(Fig. 7D)**. In addition, reduced FBP levels was observed in the cancer cell lines upon inhibitor addition during glucose stimulation of glycolytic rates.

PTPRK inhibitors reduced colony formation with minor effects on cell viability **(data not shown)**. In primary hepatocytes, PTPRK inhibitors led to a noticeable decrease in PPARγ expression **(Fig 7F)**. This was not observed in *Ptprk*$^{-/-}$ hepatocytes **(Fig 7G)**, which is consistent with our previous results. No toxicity of the compounds was noted in Zebrafish larvae **(data not shown)**. Thus, we treated obese mice with PTPRK inhibitor 2 (compound of Formula IV) daily and observed reduced weight and body fat **(Fig 7H)**. Livers were smaller with reduced levels of steatosis **(Fig 7H)**. The treated mice also had lower levels of glucose **(Fig 7H)**. We observed similar results in mice on the HFHFHCD for 5 weeks and treated with the PTPRK inhibitor 2 (compound of Formula IV) once a week **(data not shown)**. The effect of the inhibitor was reversible when the treatment was suppressed **(data not shown)**. In conclusion, we have identified two novel PTPRK inhibitors that phenocopy to a large extent the genetic deletion of PTPRK in mice fed an obesogenic diet.

PTPRK inhibitor treatment reduced body weight and fat body mass in mice fed with a high-fat, high-fructose, high-cholesterol diet.

Treatment with PTPRK inhibitor 2 (50 mg/kg; weekly) during 5 weeks resulted in a significant reduction of body weight and fat body mass in mice that were fed a high-fat, high-fructose, high-cholesterol diet for 4 weeks (**Fig 8 A-B**), and a slightly reduced blood glucose level (**Fig 8C**), as compared to non-treated mice that were fed the same diet. Treatment with PTPRK inhibitor 2 (50 mg/kg; weekly) during 2 weeks also resulted in a reduction of body weight. However, interruption of the treatment resulted in a rapid regain of body weight (**Fig 8 D**).

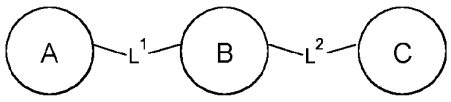
CLAIMS

1. A Protein Tyrosine Phosphatase Receptor Kappa (PTPRK) inhibitor for use in the treatment and/or prevention of a condition selected from the group consisting of overweight, obesity, hyperglycaemia, diabetes, hyperlipidaemia, a non-alcoholic fatty liver disease (NAFLD), hepatocellular carcinoma, and combinations thereof in a subject.

2. Non-therapeutic use of a PTPRK inhibitor for reduction of body weight, blood glucose level, blood lipid levels, or a combination thereof, in a subject; preferably for reduction of body weight in a subject.

3. The PTPRK inhibitor for use according to claim 1 or the use according to claim 2, wherein the inhibitor is a specific inhibitor of PTPRK.

4. The PTPRK inhibitor for use according to claim 1 or 3, or the use according to claim 2 or 3, wherein the inhibitor is a compound of Formula I or Formula II, or a stereoisomer, enantiomer, tautomer, solvate, hydrate, pharmaceutically acceptable salt, or prodrug thereof:



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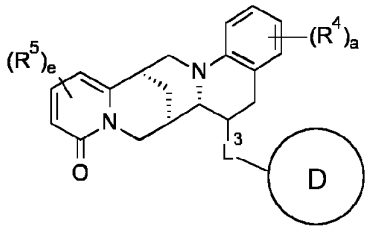
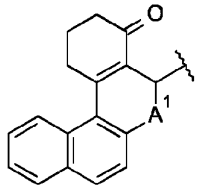


II

wherein,

cycle A is selected from the group consisting of C_{6-12}aryl, C_{3-12}cycloalkyl, C_{3-12}cycloalkenyl,



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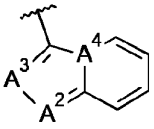

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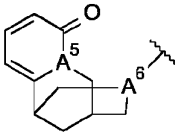

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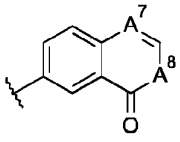

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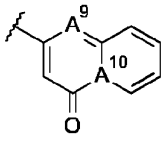

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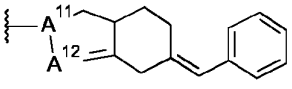

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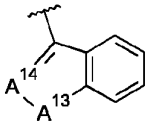

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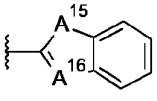

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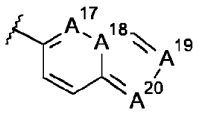

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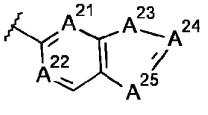

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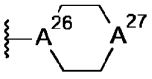

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wherein the wavy line (〰) indicates the point of attachment of cycle A to the rest of the molecule, wherein said groups can be unsubstituted or substituted with one or more R^A;

each of A^1, A^8, A^{13}, A^{15}, A^{23}, and A^{27} is independently selected from the group consisting of NR^A, CHR^A, S, $S(O)_2$ and O;

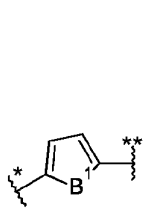
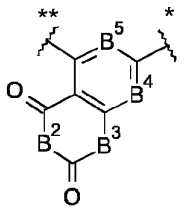
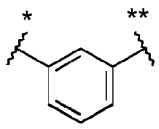
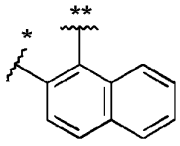
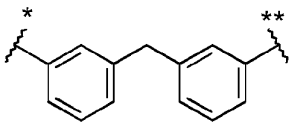
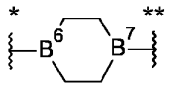
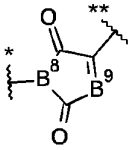
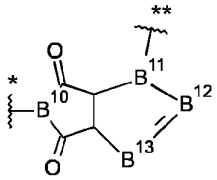
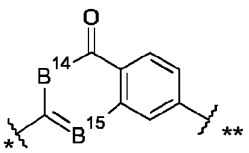
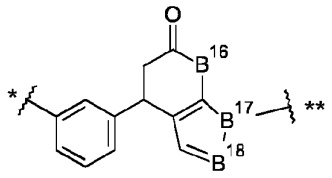
each of A^2, A^3, A^4, A^5, A^6, A^7, A^9, A^{10}, A^{11}, A^{12}, A^{14}, A^{16}, A^{17}, A^{18}, A^{19}, A^{20}, A^{21}, A^{22}, A^{24}, A^{25},and A^{26} is independently selected from N or CR^A;

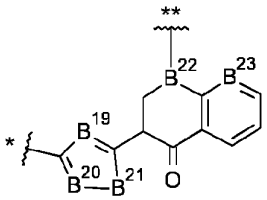
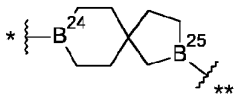
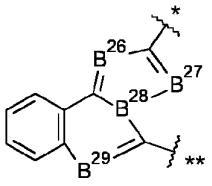
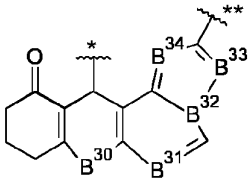
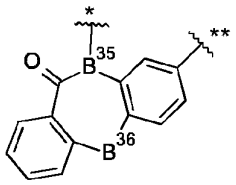
each R^A is independently selected from the group consisting of hydrogen, halogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, haloC_{1-6}alkyl, haloC_{1-6}alkyloxy, cyanoC_{1-6}alkyl, C_{1-6}alkoxy, nitro, cyano, hydroxy, $-NR^1R^2$, $-NR^1R^2S(O)_2R^3$, $-NR^1R^2C(O)_2R^3$, $-C(O)R^3$, $-C(O)_2R^3$, $-S(O)_2R^3$, C_{6-12}aryl, and C_{1-6}alkylC_{6-12}aryl; wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, or C_{6-12}aryl can be unsubstituted or substituted with one, two or three halogen, nitro, hydroxy or C_{1-6}alkyl;

L^1 is a linker moiety selected from the group consisting of a single bond, -C(O)-, -NHC(O)-, -C(O)NH-, $-(CH_2)n-$, $-CH_2C(O)-$, $-C(O)CH_2-$, $-CH(CH_3)C(O)-$, $-C(O)CH(CH_3)-$, $-CH_2C(O)NH-$, $-NHC(O)CH_2-$, $-CH_2-O-$, $-O-CH_2-$, $-CH_2-S-$, $-S-CH_2-$, -O-, -S-, $-S-CH_2C(O)NH-$, $-NHC(O)CH_2-S-$, $-C(O)NH(CH_2)g-$ and -CH=N-NH-C(O)-;

n is an integer selected from 1, 2, 3 or 4;

g is an integer selected from 1, 2, 3 or 4;

cycle B is selected from the group consisting of  ,  ,  ,  ,  ,  ,  ,  ,  ,  .

, and ;

wherein * represents where cycle B is bound to L^1; and ** represents where cycle B is bound to L^2; wherein said groups can be unsubstituted or substituted with one or more R^B;

each of B^1, B^2, B^3, B^{14}, B^{16}, B^{21}, B^{30}, and B^{36} is independently selected from the group consisting of NR^B, CHR^B, S, $S(O)_2$ and O;

each of B^4, B^5, B^6, B^7, B^8, B^9, B^{10}, B^{11}, B^{12}, B^{13}, B^{15}, B^{17}, B^{18}, B^{19}, B^{20}, B^{22}, B^{23}, B^{24}, B^{25}, B^{26}, B^{27}, B^{28}, B^{29}, B^{31}, B^{32}, B^{33}, B^{34}, and B^{35} is independently selected from N or CR^B;

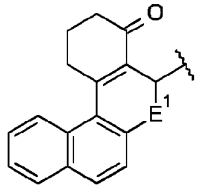
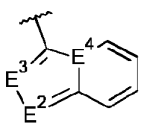
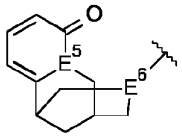
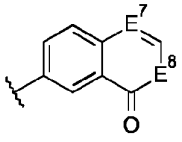
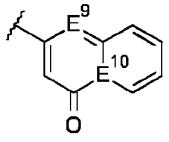
each R^B is independently selected from the group consisting of hydrogen, halogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, haloC_{1-6}alkyl, haloC_{1-6}alkyloxy, cyanoC_{1-6}alkyl, C_{1-6}alkoxy, nitro, cyano, hydroxy, $-NR^1R^2$, $-NR^1R^2S(O)_2R^3$, $-NR^1R^2C(O)_2R^3$, $-C(O)R^3$, $-C(O)_2R^3$, $-S(O)_2R^3$, C_{6-12}aryl, and C_{1-6}alkylC_{6-12}aryl; wherein said C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, or C_{6-12}aryl can be unsubstituted or substituted with one, two or three halogen, nitro, hydroxy or C_{1-6}alkyl;

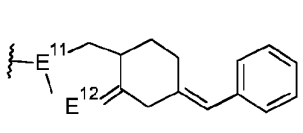
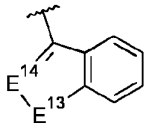
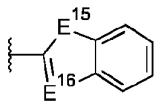
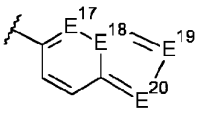
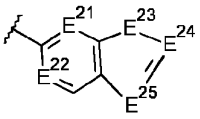
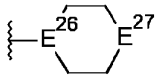
L^2 is a linker moiety selected from the group consisting of a single bond, -C(O)-, -NHC(O)-, -C(O)NH-, $-(CH_2)$m-, $-CH_2C(O)$-, $-C(O)CH_2$-, $-CH(CH_3)C(O)$-, $-C(O)CH(CH_3)$-, $-CH_2C(O)NH$-, $-NHC(O)CH_2$-, $-CH_2$-O-, -O-CH_2-, $-CH_2$-S-, -S-CH_2-, -O-, -S-, -S-$CH_2C(O)NH$-, $-NHC(O)CH_2$-S-, $-C(O)NH(CH_2)$i- and -CH=N-NH-C(O)-;

m is an integer selected from 1, 2, 3 or 4;

i is an integer selected from 1, 2, 3 or 4;

cycle C is selected from the group consisting of C_{6-12}aryl, C_{3-12}cycloalkyl, C_{3-12}cycloalkenyl,







, and ;

wherein the wavy line ( ) indicates the point of attachment of cycle C to the rest of the molecule, wherein said groups can be unsubstituted or substituted with one or more R^C;

each of E^1, E^8, E^{13}, E^{15}, E^{23}, and E^{27} is independently selected from the group consisting of NR^C, CHR^C, S, $S(O)_2$ and O;

each of E^2, E^3, E^4, E^5, E^6, E^7, E^9, E^{10}, E^{11}, E^{12}, E^{14}, E^{16}, E^{17}, E^{18}, E^{19}, E^{20}, E^{21}, E^{22}, E^{24}, E^{25}, and E^{26} is independently selected from N or CR^C;

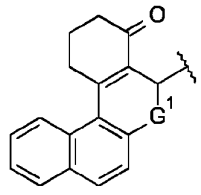
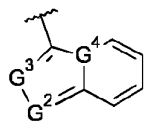
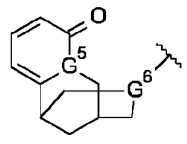
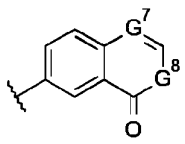
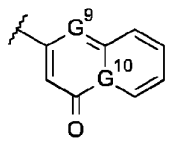
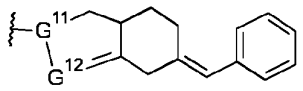
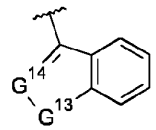
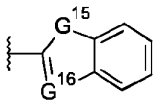
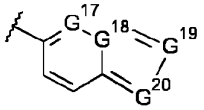
each R^C is independently selected from the group consisting of hydrogen, halogen, $C_{1\text{-}6}$alkyl, $C_{2\text{-}6}$alkenyl, $C_{2\text{-}6}$alkynyl, halo$C_{1\text{-}6}$alkyl, halo$C_{1\text{-}6}$alkyloxy, cyano$C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$alkoxy, nitro, cyano, hydroxy, $-NR^1R^2$, $-NR^1R^2S(O)_2R^3$, $-NR^1R^2C(O)_2R^3$, $-C(O)R^3$, $-C(O)_2R^3$, $-S(O)_2R^3$, $C_{6\text{-}12}$aryl, and $C_{1\text{-}6}$alkyl$C_{6\text{-}12}$aryl; wherein said $C_{1\text{-}6}$alkyl, $C_{2\text{-}6}$alkenyl, $C_{2\text{-}6}$alkynyl, or $C_{6\text{-}12}$aryl can be unsubstituted or substituted with one, two or three halogen, nitro, hydroxy or $C_{1\text{-}6}$alkyl;

L^3 is a linker moiety selected from the group consisting of a single bond, -C(O)-, -NHC(O)-, -C(O)NH-, $-(CH_2)j-$, $-CH_2C(O)-$, $-C(O)CH_2-$, $-CH(CH_3)C(O)-$, $-C(O)CH(CH_3)-$, $-CH_2C(O)NH-$, $-NHC(O)CH_2-$, $-CH_2-O-$, $-O-CH_2-$, $-CH_2-S-$, $-S-CH_2-$, -O-, -S-, $-S-CH_2C(O)NH-$, $-NHC(O)CH_2-S-$, $-C(O)NH(CH_2)q-$ and -CH=N-NH-C(O)-;

j is an integer selected from 1, 2, 3 or 4;

q is an integer selected from 1, 2, 3 or 4;

cycle D is selected from the group consisting of $C_{6\text{-}12}$aryl, $C_{3\text{-}12}$cycloalkyl, $C_{3\text{-}12}$cycloalkenyl,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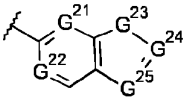
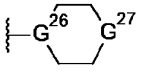


, and ;

wherein the wavy line (〰) indicates the point of attachment of cycle D to the rest of the molecule, wherein said groups can be unsubstituted or substituted with one or more R^D;

each of G^1, G^8, G^{13}, G^{15}, G^{23}, and G^{27} is independently selected from the group consisting of NH, NR^D, CHR^D, S, $S(O)_2$ and O;

each of G^2, G^3, G^4, G^5, G^6, G^7, G^9, G^{10}, G^{11}, G^{12}, G^{14}, G^{16}, G^{17}, G^{18}, G^{19}, G^{20}, G^{21}, G^{22}, G^{24}, G^{25}, and G^{26} is independently selected from N or CR^D;

each R^D is independently selected from the group consisting of hydrogen, halogen, $C_{1\text{-}6}$alkyl, $C_{2\text{-}6}$alkenyl, $C_{2\text{-}6}$alkynyl, halo$C_{1\text{-}6}$alkyl, halo$C_{1\text{-}6}$alkyloxy, cyano$C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$alkoxy, nitro, cyano, hydroxy, $-NR^1R^2$, $-NR^1R^2S(O)_2R^3$, $-NR^1R^2C(O)_2R^3$, $-C(O)R^3$, $-C(O)_2R^3$, $-S(O)_2R^3$, $C_{6\text{-}12}$aryl, and $C_{1\text{-}6}$alkyl$C_{6\text{-}12}$aryl; wherein said $C_{1\text{-}6}$alkyl, $C_{2\text{-}6}$alkenyl, $C_{2\text{-}6}$alkynyl, or $C_{6\text{-}12}$aryl can be unsubstituted or substituted with one, two or three halogen, nitro, hydroxy or $C_{1\text{-}6}$alkyl;

each R^1 is independently selected from the group consisting of hydrogen, $C_{1\text{-}6}$alkyl, $C_{2\text{-}6}$alkenyl, $C_{2\text{-}6}$alkynyl, and $C_{6\text{-}12}$aryl, wherein said $C_{1\text{-}6}$alkyl, $C_{2\text{-}6}$alkenyl, $C_{2\text{-}6}$alkynyl, or $C_{6\text{-}12}$aryl can be unsubstituted or substituted with one, two or three halogen, nitro, hydroxy or $C_{1\text{-}6}$alkyl;

each R^2 is independently selected from the group consisting of hydrogen, $C_{1\text{-}6}$alkyl, $C_{2\text{-}6}$alkenyl, $C_{2\text{-}6}$alkynyl, and $C_{6\text{-}12}$aryl, wherein said $C_{1\text{-}6}$alkyl, $C_{2\text{-}6}$alkenyl, $C_{2\text{-}6}$alkynyl, or $C_{6\text{-}12}$aryl can be unsubstituted or substituted with one, two or three halogen, nitro, hydroxy or $C_{1\text{-}6}$alkyl;

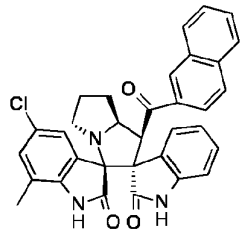
each R^3 is independently selected from the group consisting of hydrogen, $C_{1\text{-}6}$alkyl, $C_{2\text{-}6}$alkenyl, $C_{2\text{-}6}$alkynyl, and $C_{6\text{-}12}$aryl, wherein said $C_{1\text{-}6}$alkyl, $C_{2\text{-}6}$alkenyl, $C_{2\text{-}6}$alkynyl, or $C_{6\text{-}12}$aryl can be unsubstituted or substituted with one, two or three halogen, nitro, hydroxy or $C_{1\text{-}6}$alkyl.

a is an integer selected from 1, 2, 3 or 4;

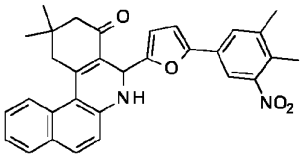
each R^4 is independently selected from the group consisting of hydrogen, halogen, $C_{1\text{-}6}$alkyl, $C_{2\text{-}6}$alkenyl, $C_{2\text{-}6}$alkynyl, halo$C_{1\text{-}6}$alkyl, cyano$C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$alkoxy, nitro, cyano, hydroxy, $-NR^1R^2$, $-NR^1R^2S(O)_2R^3$, $-NR^1R^2C(O)_2R^3$, $-C(O)R^3$, $-C(O)_2R^3$, $-S(O)_2R^3$, $C_{6\text{-}12}$aryl, and $C_{1\text{-}6}$alkyl$C_{6\text{-}12}$aryl; wherein said $C_{1\text{-}6}$alkyl, $C_{2\text{-}6}$alkenyl, $C_{2\text{-}6}$alkynyl, or $C_{6\text{-}12}$aryl can be unsubstituted or substituted with one, two or three halogen, nitro, hydroxy or $C_{1\text{-}6}$alkyl;

e is an integer selected from 1, 2, or 3;

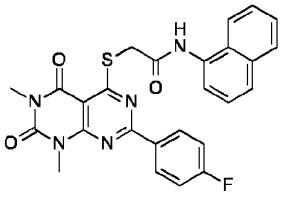
each R^5 is independently selected from the group consisting of hydrogen, halogen, $C_{1\text{-}6}$alkyl, $C_{2\text{-}6}$alkenyl, $C_{2\text{-}6}$alkynyl, halo$C_{1\text{-}6}$alkyl, cyano$C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$alkoxy, nitro, cyano, hydroxy, $-NR^1R^2$, $-NR^1R^2S(O)_2R^3$, $-NR^1R^2C(O)_2R^3$, $-C(O)R^3$, $-C(O)_2R^3$, $-S(O)_2R^3$, $C_{6\text{-}12}$aryl, and $C_{1\text{-}6}$alkyl$C_{6\text{-}12}$aryl; wherein said $C_{1\text{-}6}$alkyl, $C_{2\text{-}6}$alkenyl, $C_{2\text{-}6}$alkynyl, or $C_{6\text{-}12}$aryl can be unsubstituted or substituted with one, two or three halogen, nitro, hydroxy or $C_{1\text{-}6}$alkyl;

or the inhibitor is a compound of formula  , or a stereoisomer, enantiomer, tautomer, solvate, hydrate, pharmaceutically acceptable salt, or prodrug thereof.

5. The PTPRK inhibitor for use according to claim 4, or the use according to claim 4, wherein the inhibitor is a compound of Formula III or Formula IV, or a stereoisomer, enantiomer, tautomer, solvate, hydrate, pharmaceutically acceptable salt, or prodrug thereof:



III



IV.

6. A PTPRK inhibitor for use in medicine, optionally wherein the inhibitor is a compound of Formula I, Formula II, Formula III, Formula IV or a stereoisomer, enantiomer, tautomer, solvate, hydrate, pharmaceutically acceptable salt, or prodrug thereof.

7. The PTPRK inhibitor for use according to any one of claims 1 or 3 to 6, or the use according to any one of the claims 2 to 5, wherein the PTPRK inhibitor is a compound of formula III or a compound of formula IV.

8. A pharmaceutical composition comprising a PTPRK inhibitor or a combination of PTPRK inhibitors,such as a PTPRK inhibitor or a combination of PTPRK inhibitors as defined in any one of claims 3 to 7, for use in the treatment and/or prevention of a condition selected from the group consisting of overweight, obesity, hyperglycemia, diabetes, hyperlipidaemia, a non-alcoholic fatty liver disease (NAFLD), hepatocellular carcinoma, and combinations thereof in a subject.

9. The PTPRK inhibitor for use according to any one of claims 1 or 3 to 7 or the pharmaceutical composition for use according to claim 8, for use in the treatment and/or prevention of overweight or obesity in a subject.

10. The PTPRK inhibitor for use according to any one of claims 1 or 3 to 7 or the pharmaceutical composition for use according to claim 8, for use in the treatment and/or prevention of hyperglycaemia or diabetes in a subject.

11. The PTPRK inhibitor for use according to any one of claims 1 or 3 to 7 or the pharmaceutical composition for use according to claim 8, for use in the treatment and/or prevention of hyperlipidaemia in a subject.

12. The PTPRK inhibitor for use according to any one of claims 1 or 3 to 7 or the pharmaceutical composition for use according to claim 8, for use in the treatment a non-alcoholic fatty liver disease (NAFLD) or hepatocellular carcinoma.

13. The PTPRK inhibitor or the pharmaceutical composition for use according to claim 12 for use in the treatment of a NAFLD; in particular wherein the NAFLD is selected from the group consisting of fatty liver, non-alcoholic steatohepatitis (NASH), NASH with liver fibrosis, and NASH with liver cirrhosis.

14. The PTPRK inhibitor for use according to any one of claims 1, 3 to 7 or 9 to 13, or the pharmaceutical composition for use according to any one of claims 8 to 13, or the use according to any one of claims 2 or 7, wherein the subject is a human subject.

15. A combination of a PTPRK inhibitor that is a compound of formula III or a stereoisomer, enantiomer, tautomer, solvate, hydrate, pharmaceutically acceptable salt, or prodrug thereof and a PTPRK inhibitor that is a compound of formula IV or a stereoisomer, enantiomer, tautomer, solvate, hydrate, pharmaceutically acceptable salt, or prodrug thereof, optionally wherein the combination is comprised in a pharmaceutical composition.

Figure 1

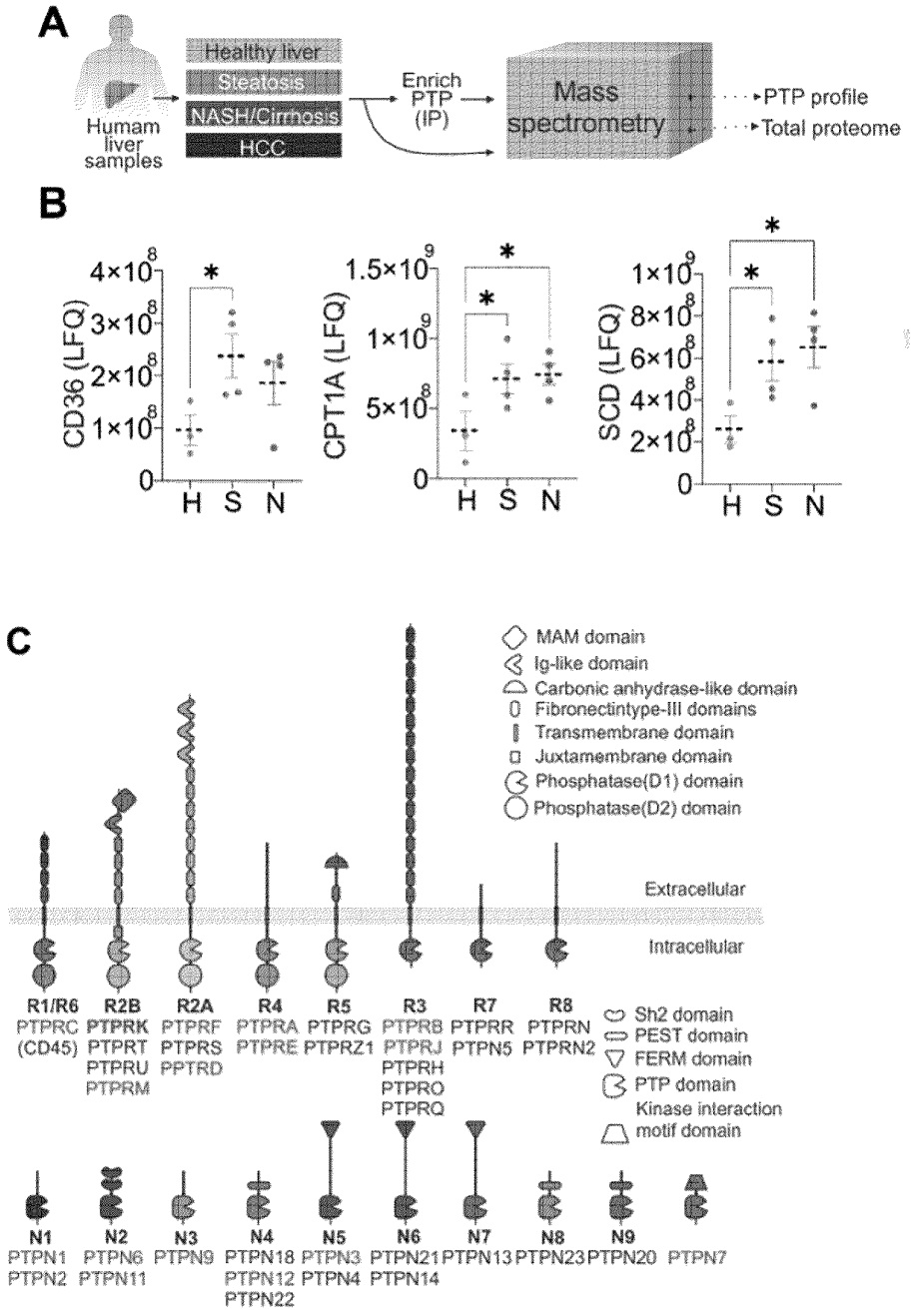

A
Humam liver samples
Healthy liver
Steatosis
NASH/Cirrhosis
HCC
Enrich PTP (IP)
Mass spectrometry
PTP profile
Total proteome
B
CD36 (LFQ)
CPT1A (LFQ)
SCD (LFQ)
H S N
C
MAM domain
Ig-like domain
Carbonic anhydrase-like domain
Fibronectintype-III domains
Transmembrane domain
Juxtamembrane domain
Phosphatase(D1) domain
Phosphatase(D2) domain
Extracellular
Intracellular
R1/R6 PTPRC (CD45)
R2B PTPRK PTPRT PTPRU PTPRM
R2A PTPRF PTPRS PPTRD
R4 PTPRA PTPRE
R5 PTPRG PTPRZ1
R3 PTPRB PTPRJ PTPRH PTPRO PTPRQ
R7 PTPRR PTPN5
R8 PTPRN PTPRN2
Sh2 domain
PEST domain
FERM domain
PTP domain
Kinase interaction motif domain
N1 PTPN1 PTPN2
N2 PTPN6 PTPN11
N3 PTPN9
N4 PTPN18 PTPN12 PTPN22
N5 PTPN3 PTPN4
N6 PTPN21 PTPN14
N7 PTPN13
N8 PTPN23
N9 PTPN20
PTPN7

Figure 1 - continued

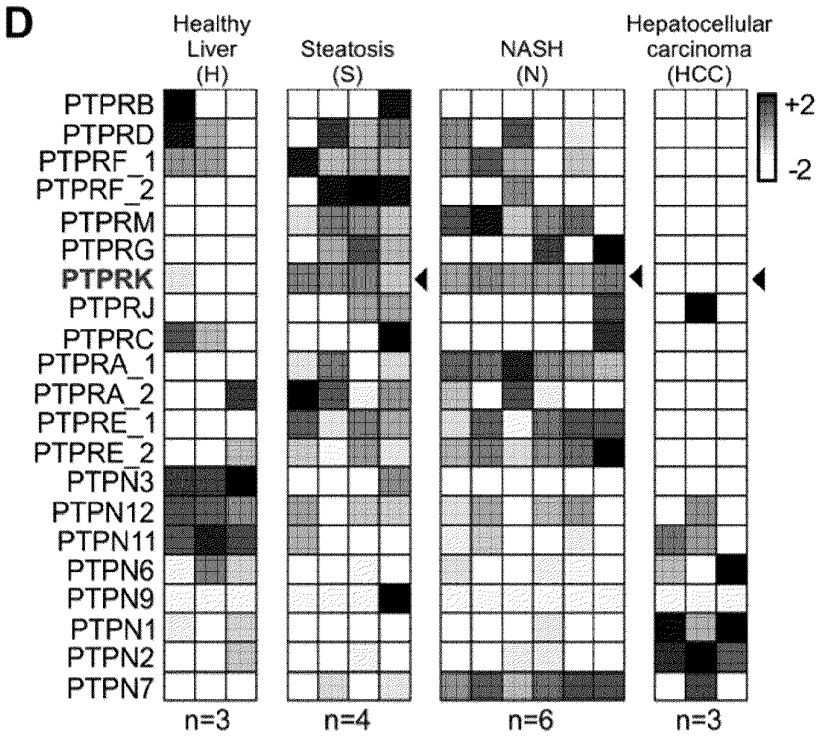


Figure 1 – continued

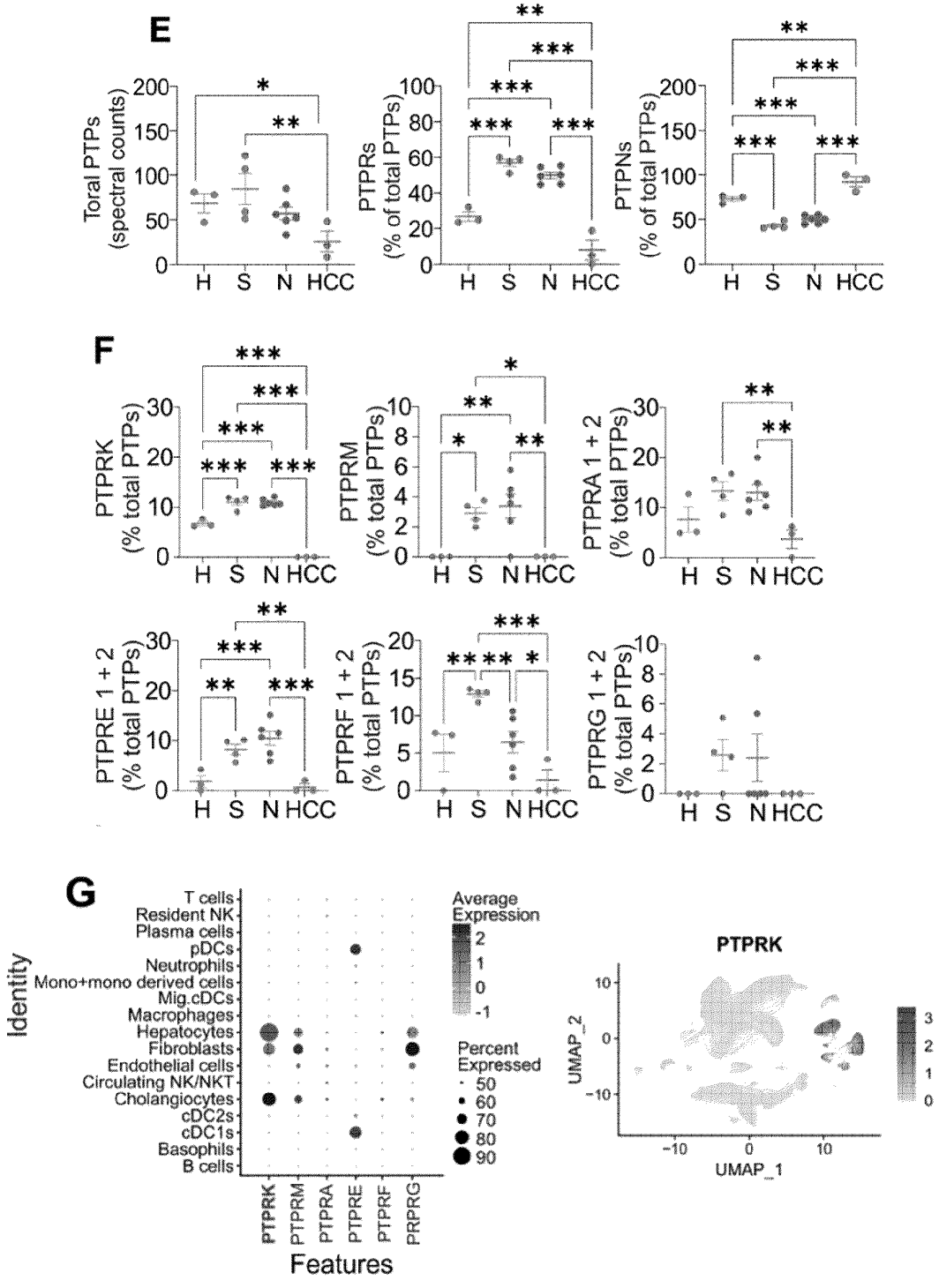


Figure 1 - continued

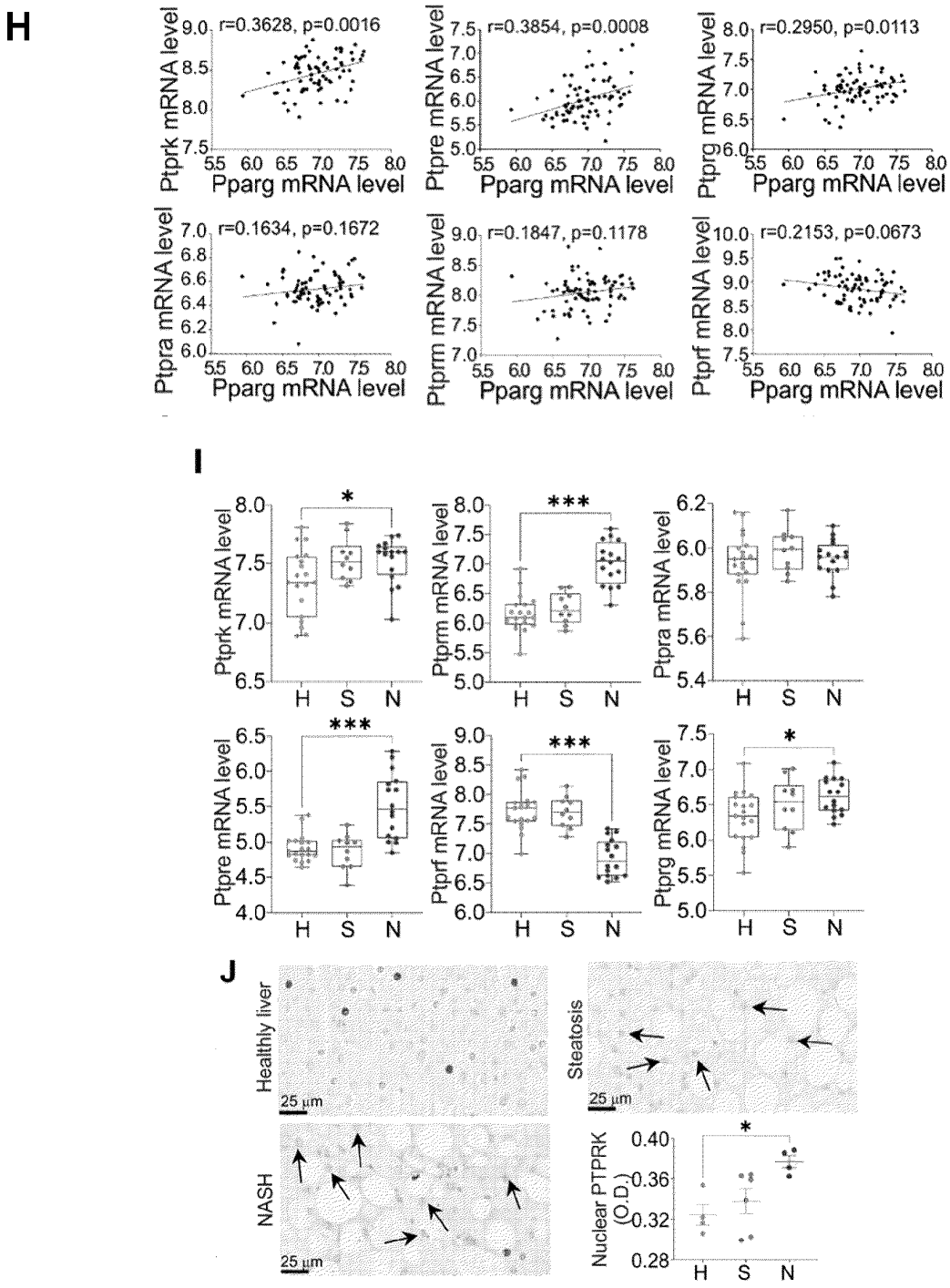


Figure 2

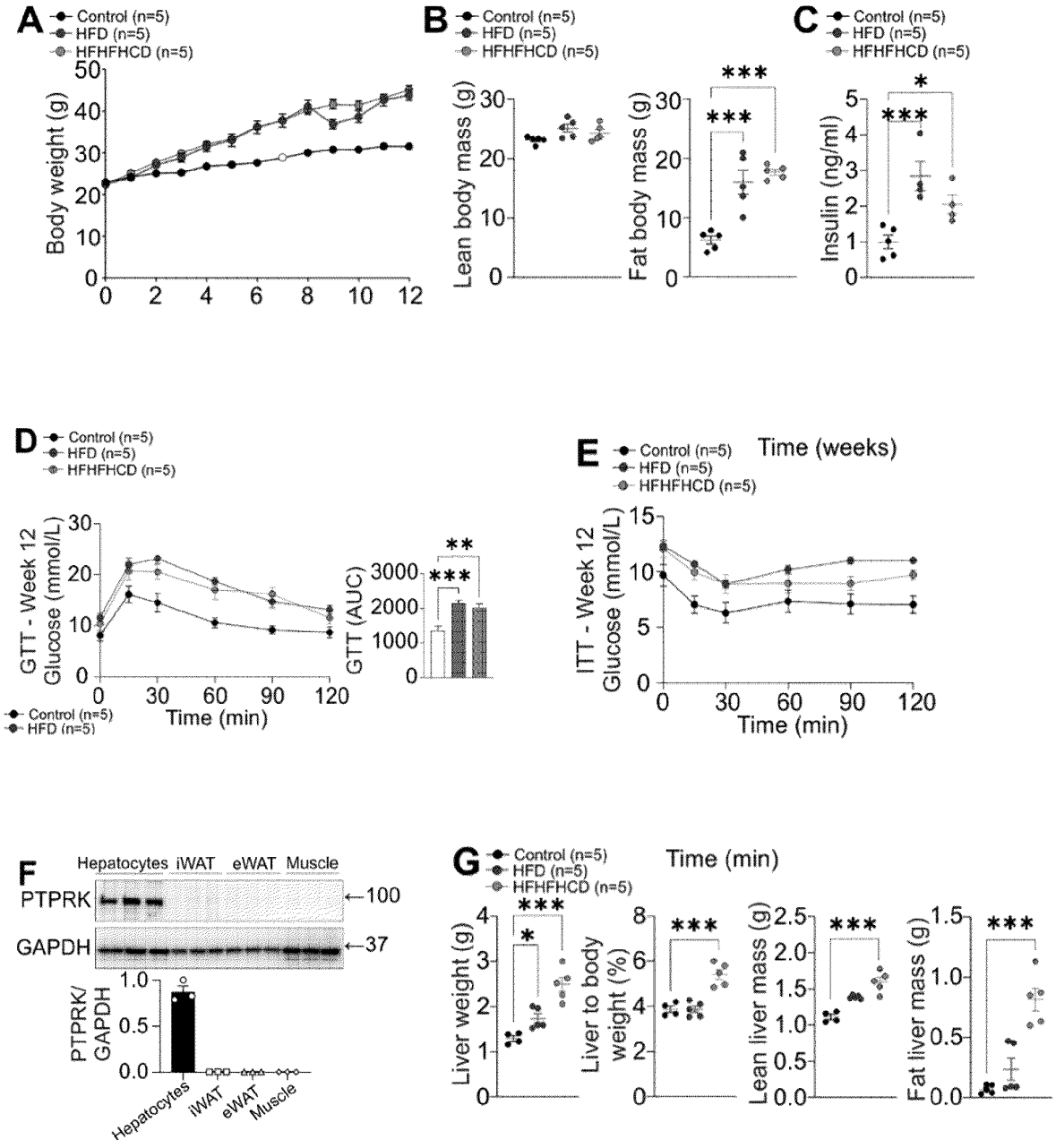

A
Control (n=5)
HFD (n=5)
HFHFHCD (n=5)
Body weight (g)
B
Lean body mass (g)
Fat body mass (g)
C
Insulin (ng/ml)
D
GTT - Week 12 Glucose (mmol/L)
Time (min)
GTT (AUC)
E
Time (weeks)
ITT - Week 12 Glucose (mmol/L)
F
Hepatocytes iWAT eWAT Muscle
PTPRK
GAPDH
PTPRK/ GAPDH
G
Time (min)
Liver weight (g)
Liver to body weight (%)
Lean liver mass (g)
Fat liver mass (g)

Figure 2 - continued

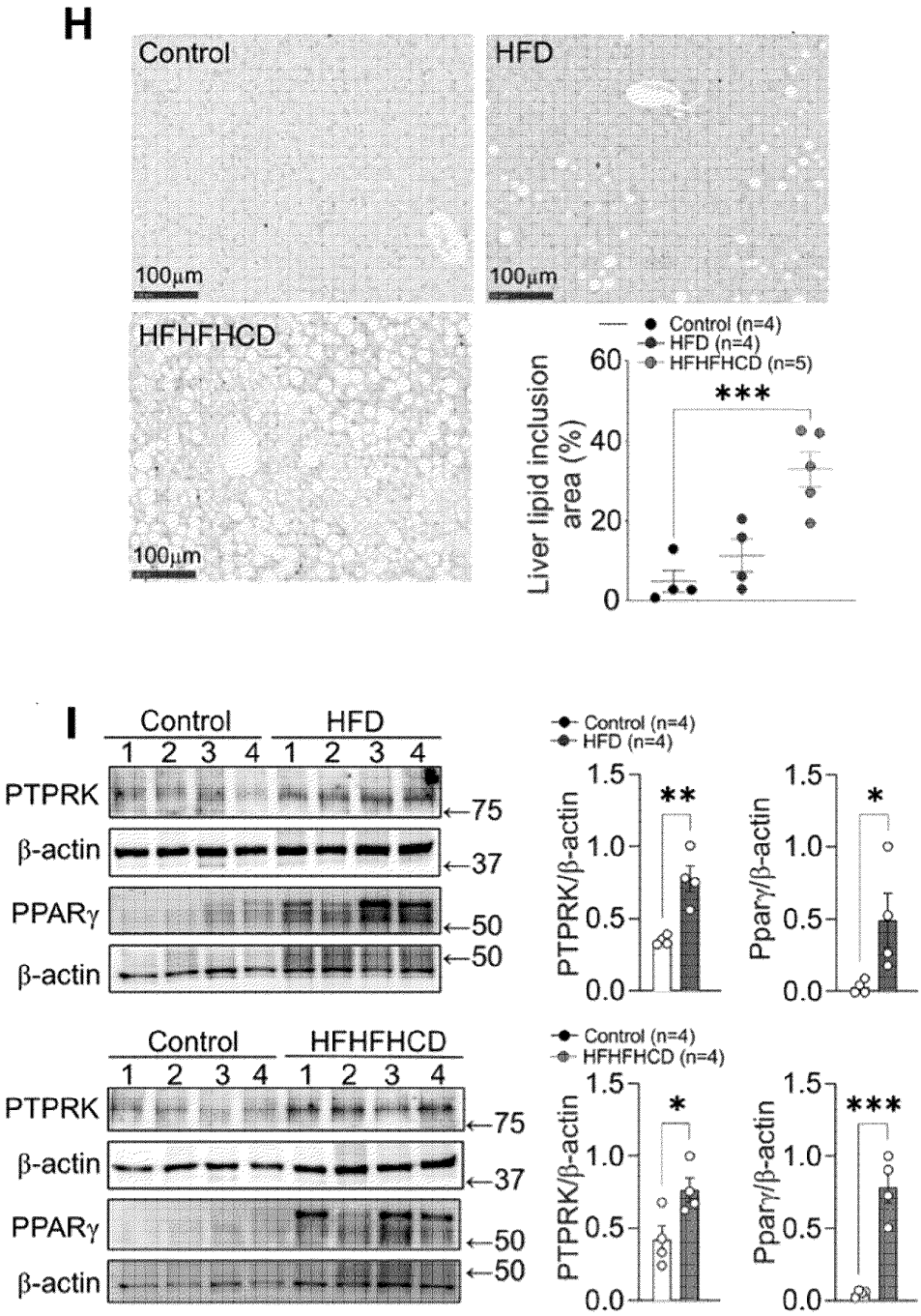


Figure 2 - continued

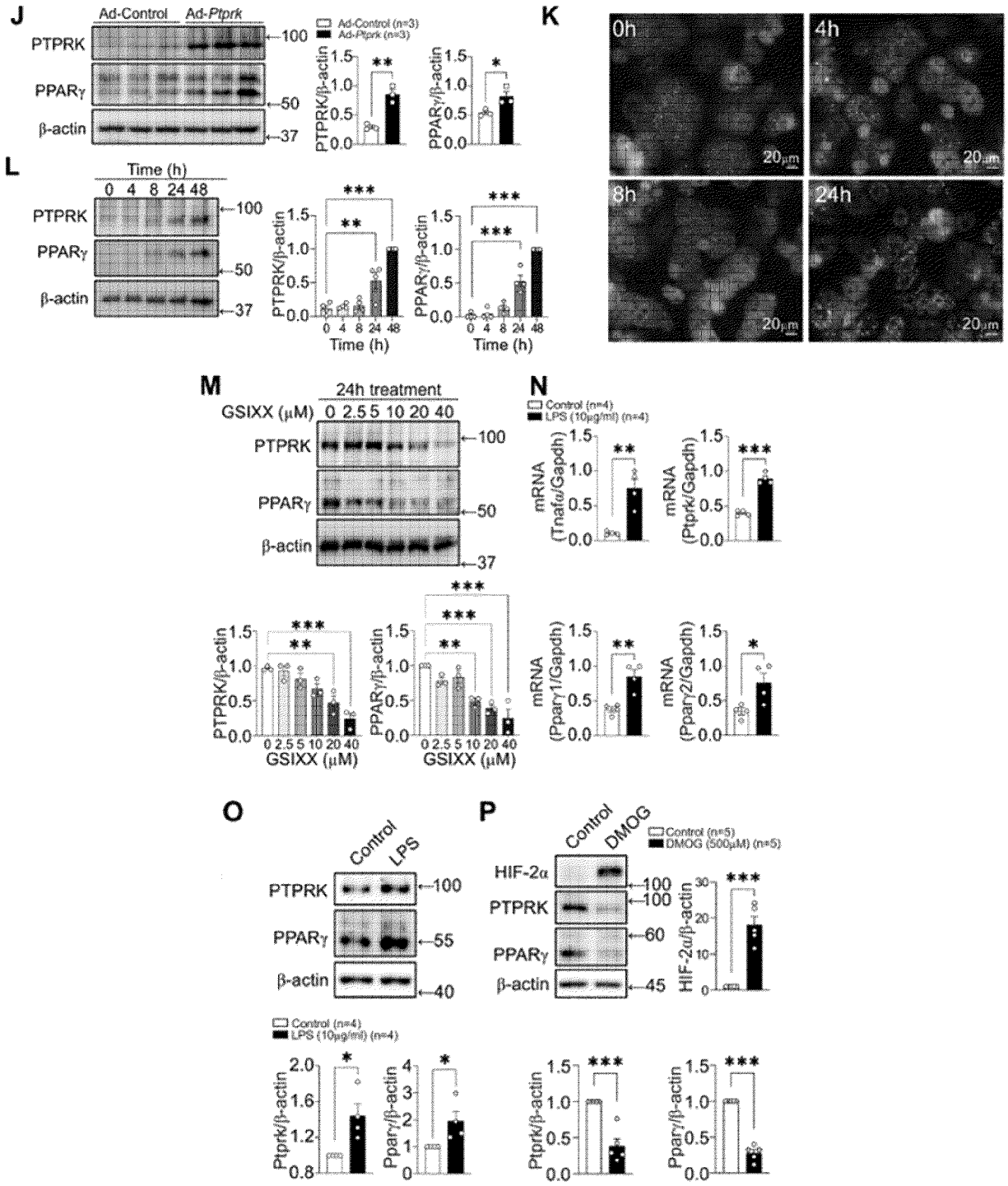


Figure 3

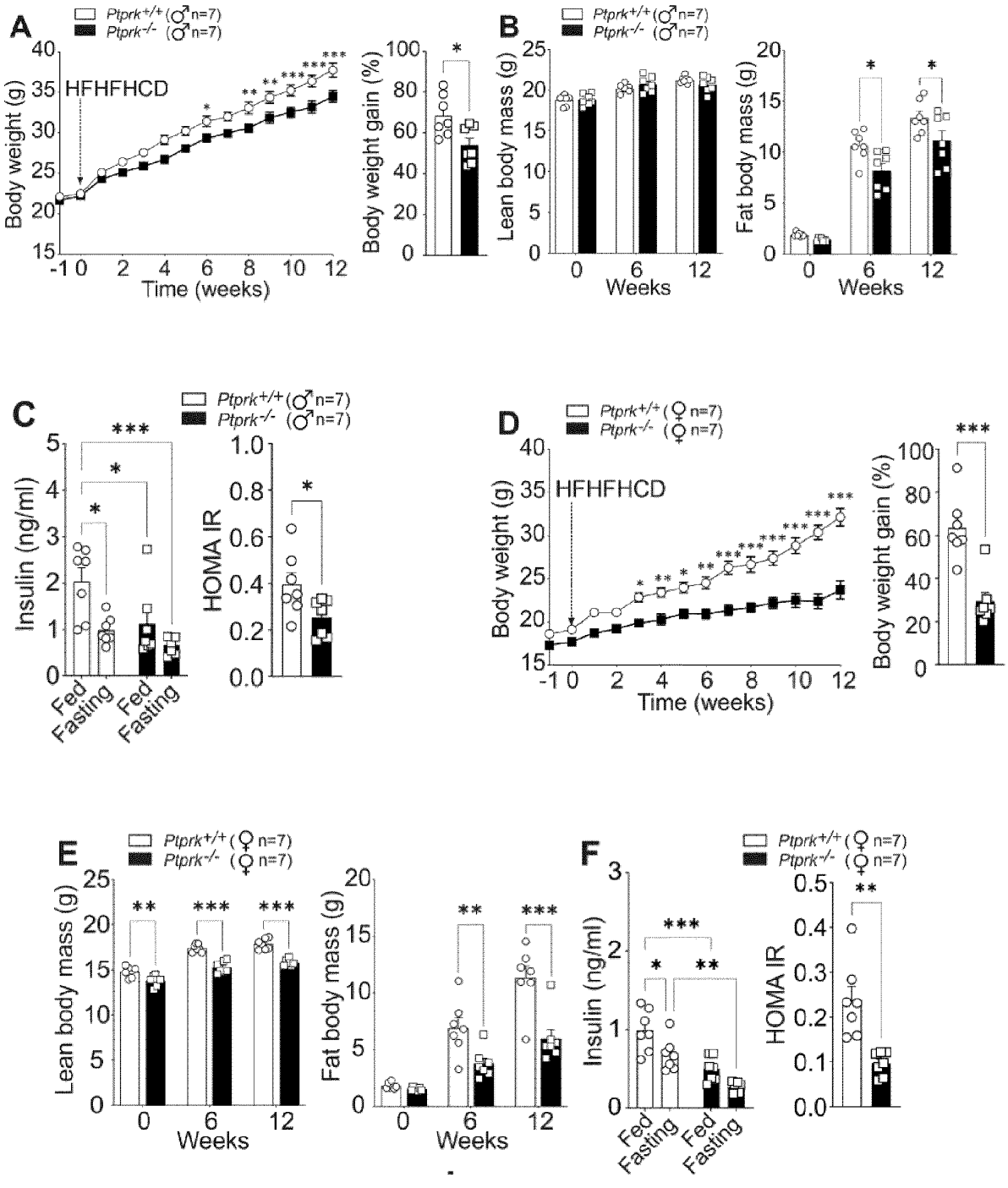

A
Ptprk+/+ (♂n=7)
Ptprk-/- (♂n=7)
HFHFHCD
Body weight (g)
Time (weeks)
Body weight gain (%)
B
Lean body mass (g)
Fat body mass (g)
Weeks
C
Insulin (ng/ml)
HOMA IR
Fed
Fasting
D
Ptprk+/+ (♀n=7)
Ptprk-/- (♀n=7)
E
F

Figure 3 - continued

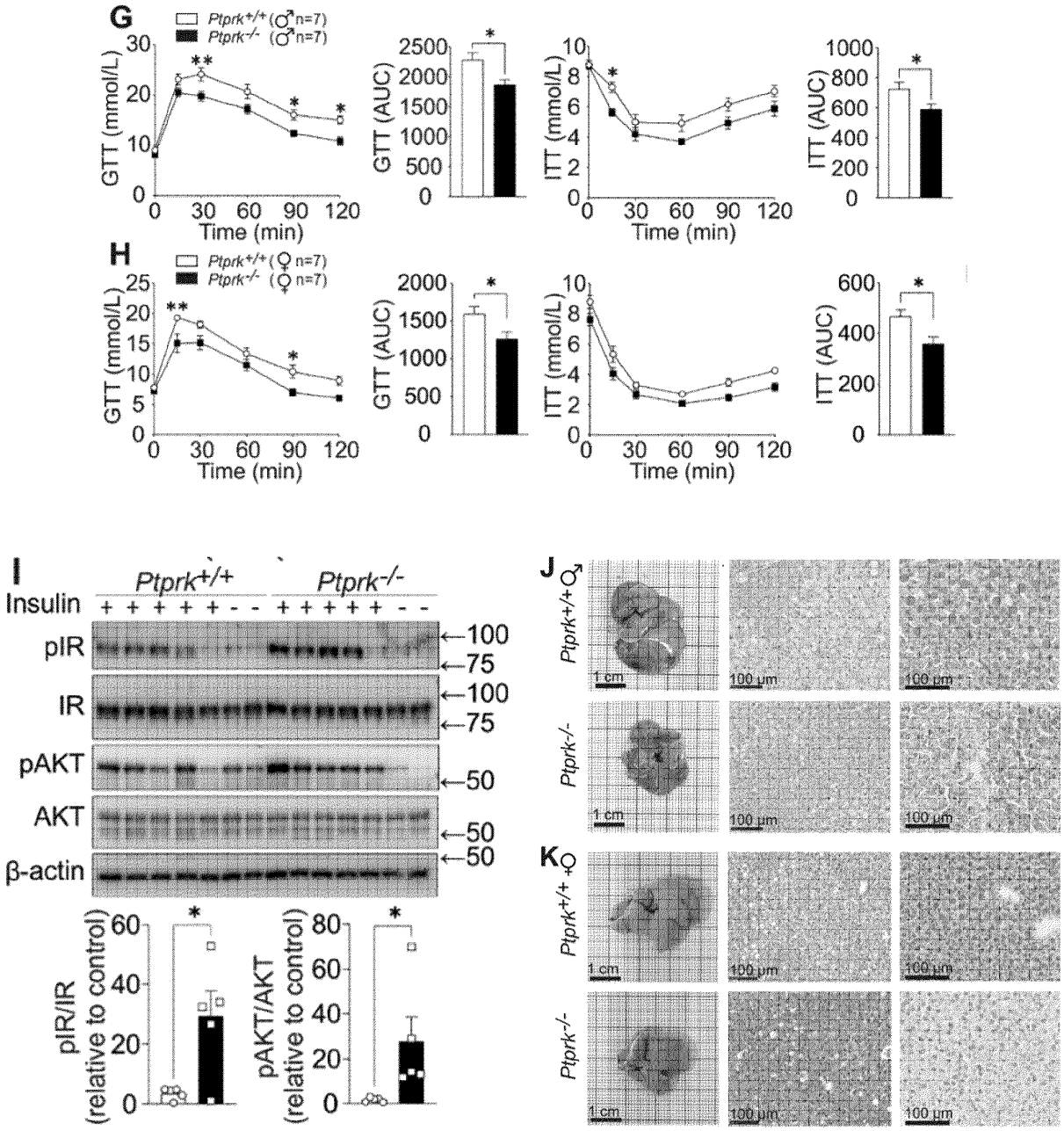


Figure 3 - continued

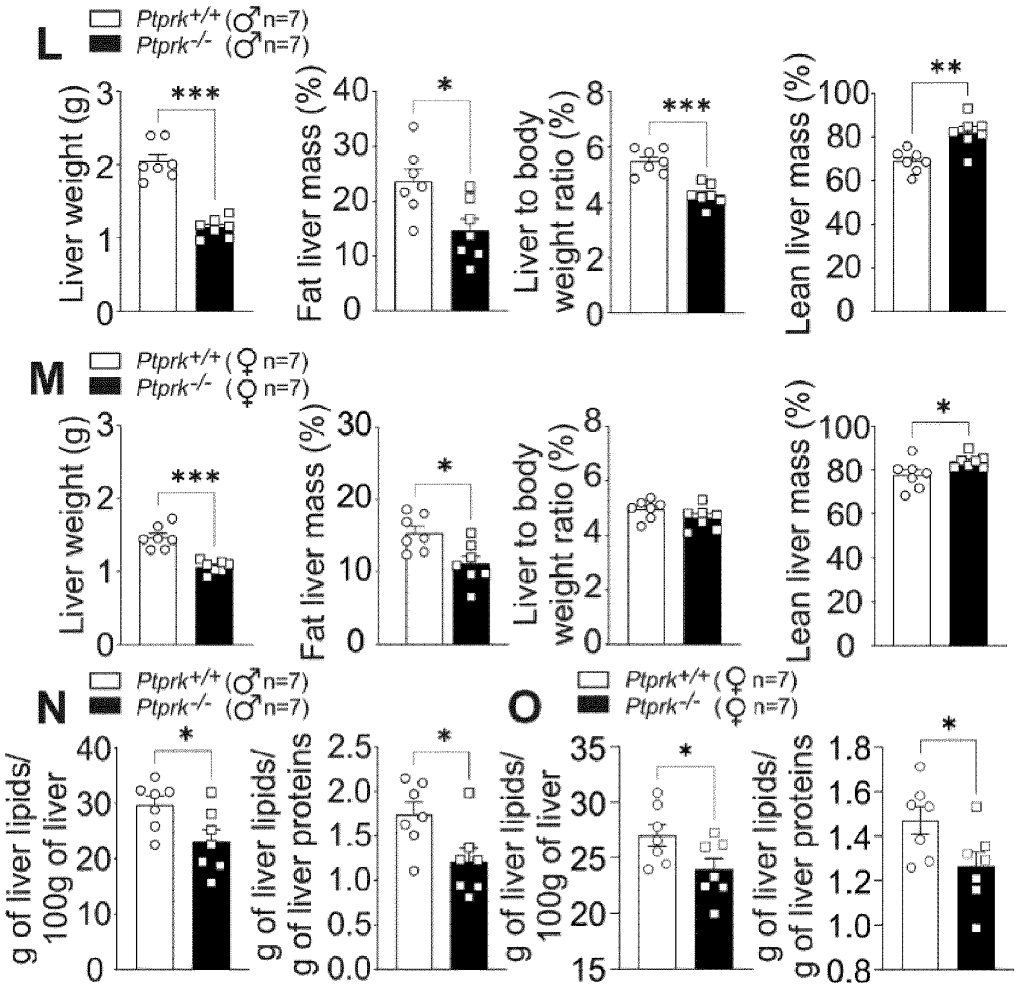


Figure 4

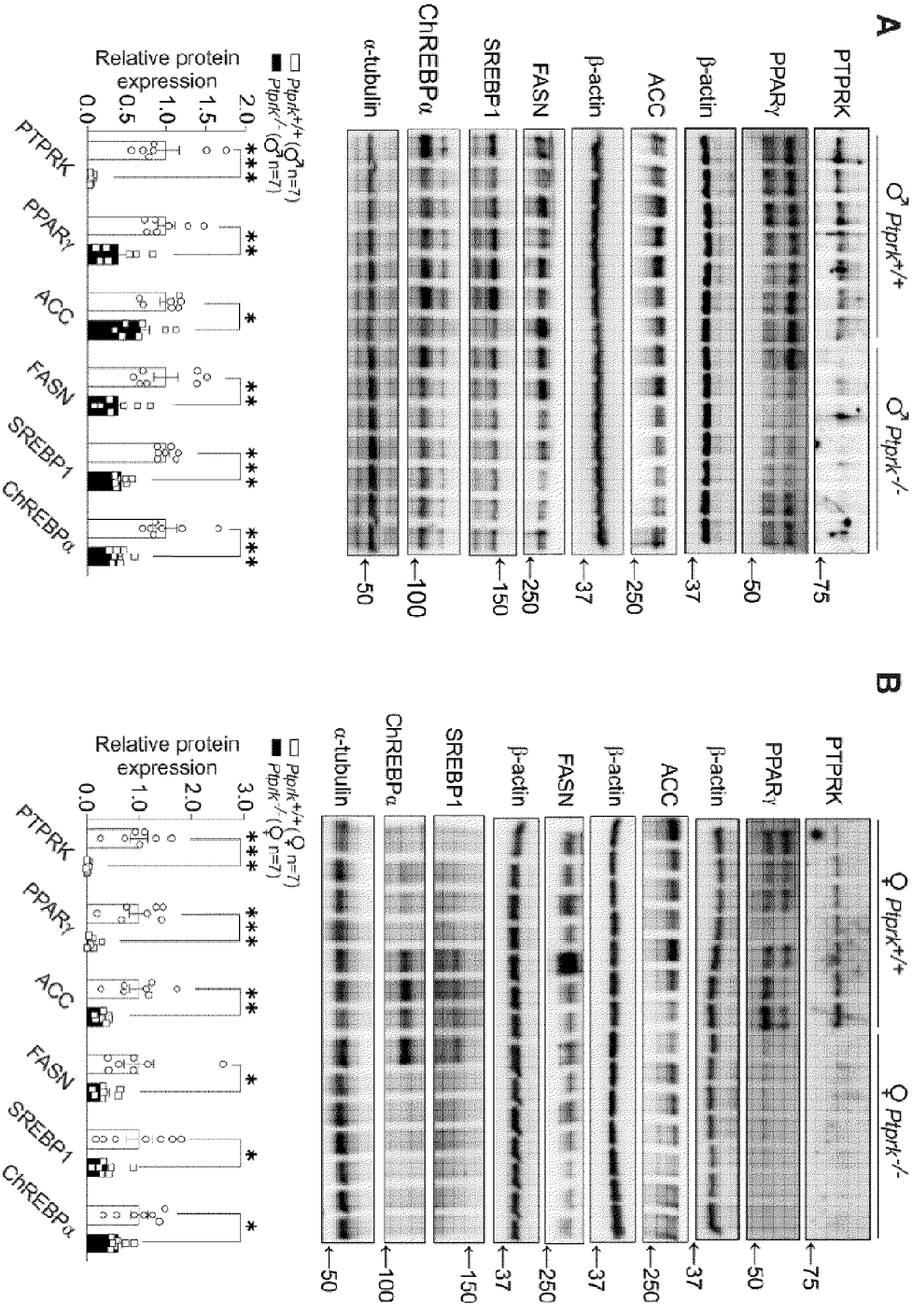

A
♂ Ptprk+/+
♂ Ptprk-/-
PTPRK
PPARγ
β-actin
ACC
β-actin
FASN
SREBP1
ChREBPα
α-tubulin
←75
←50
←37
←250
←37
←250
←150
←100
←50
Relative protein expression
Ptprk+/+ (♂ n=7)
Ptprk-/- (♂ n=7)
B
♀ Ptprk+/+
♀ Ptprk-/-
Ptprk+/+ (♀ n=7)
Ptprk-/- (♀ n=7)

Figure 4 - continued

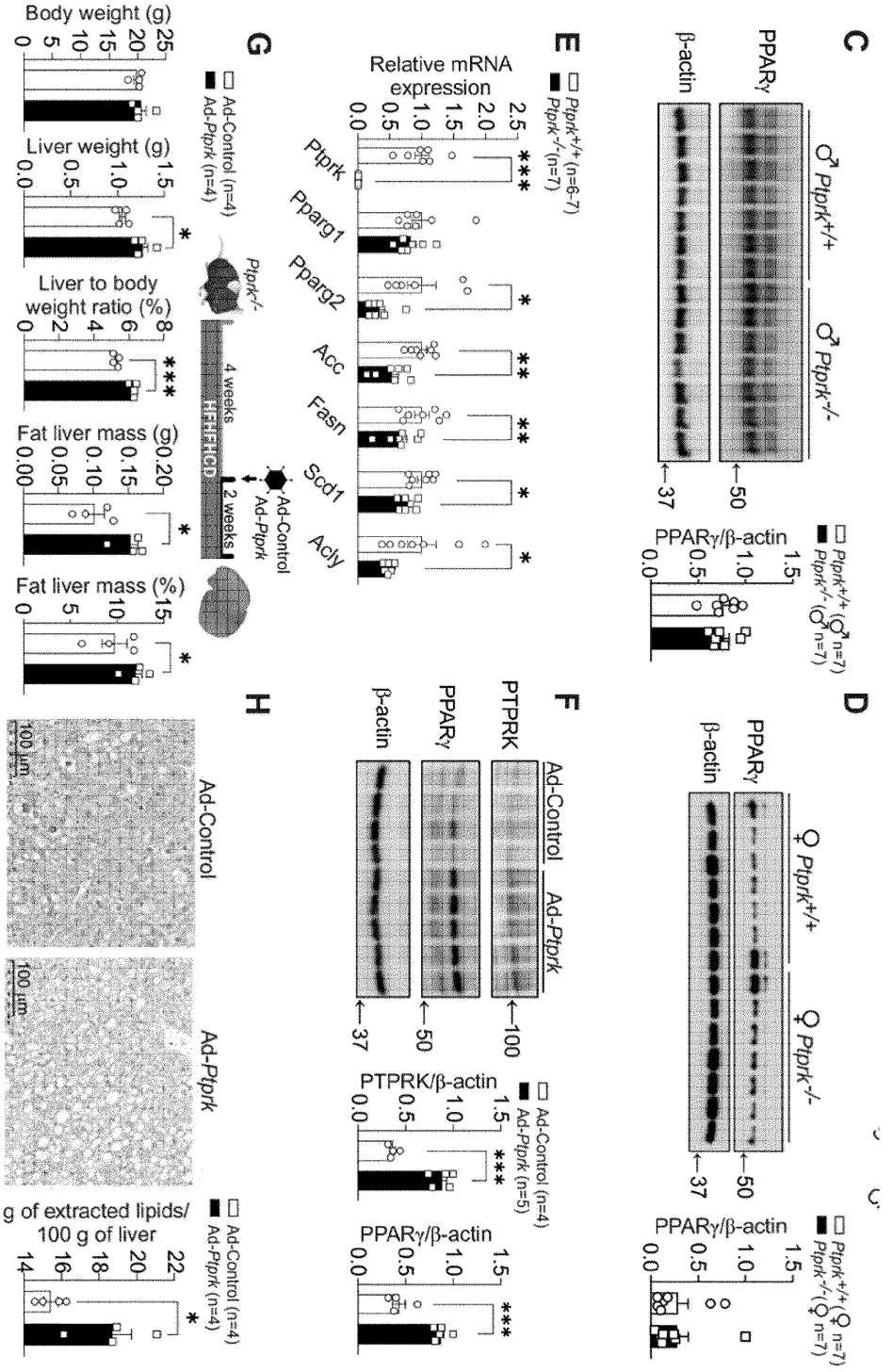


Figure 5

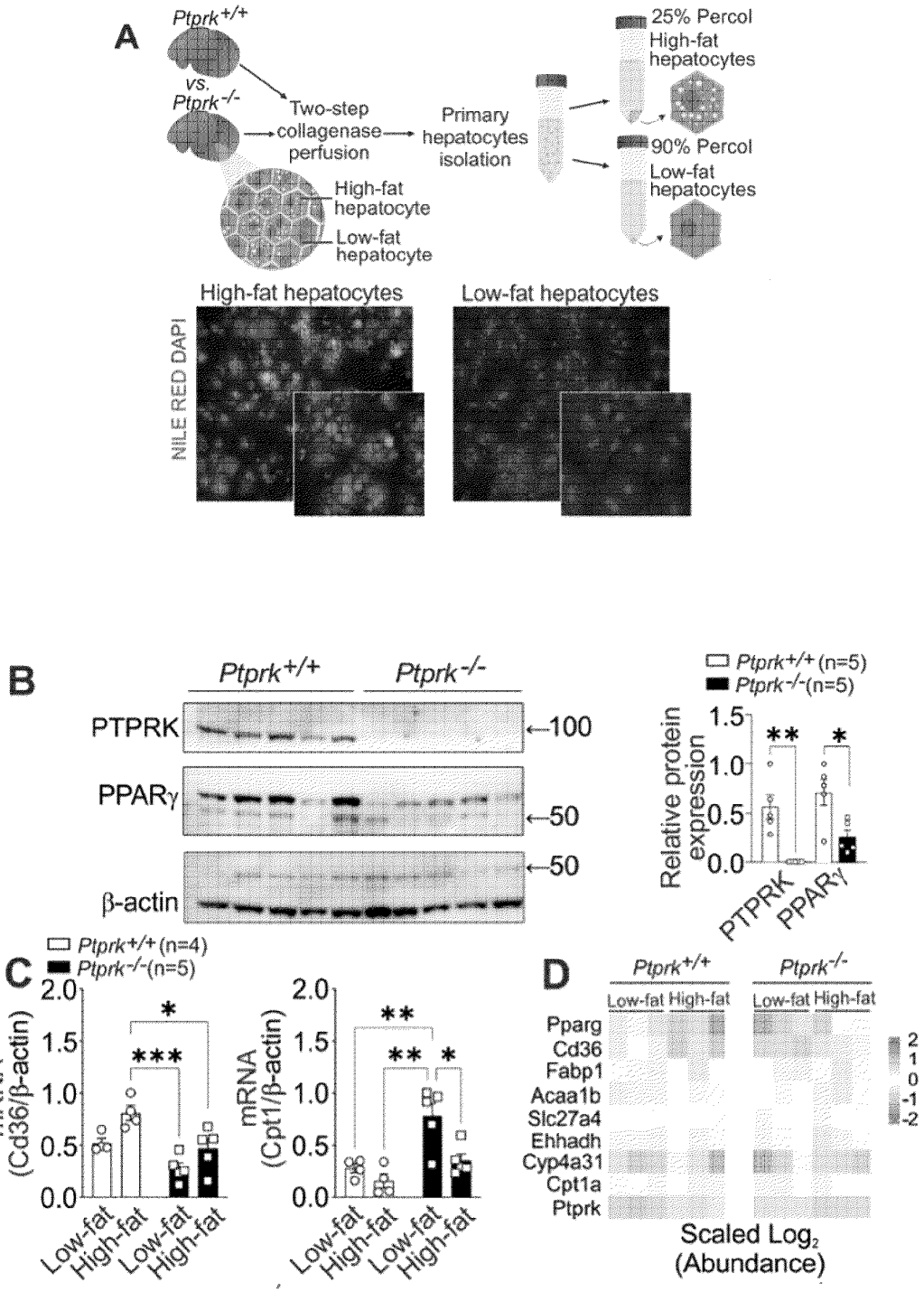

A
Ptprk+/+
vs.
Ptprk-/-
Two-step collagenase perfusion
Primary hepatocytes isolation
25% Percol
High-fat hepatocytes
90% Percol
Low-fat hepatocytes
High-fat hepatocyte
Low-fat hepatocyte
High-fat hepatocytes
Low-fat hepatocytes
NILE RED DAPI
B
Ptprk+/+
Ptprk-/-
PTPRK
PPARγ
β-actin
←100
←50
←50
Ptprk+/+ (n=5)
Ptprk-/-(n=5)
Relative protein expression
PTPRK
PPARγ
C
Ptprk+/+ (n=4)
Ptprk-/-(n=5)
mRNA (Cd36/β-actin)
mRNA (Cpt1/β-actin)
Low-fat
High-fat
D
Ptprk+/+
Ptprk-/-
Pparg
Cd36
Fabp1
Acaa1b
Slc27a4
Ehhadh
Cyp4a31
Cpt1a
Ptprk
Scaled Log2 (Abundance)

Figure 5 – continued

E

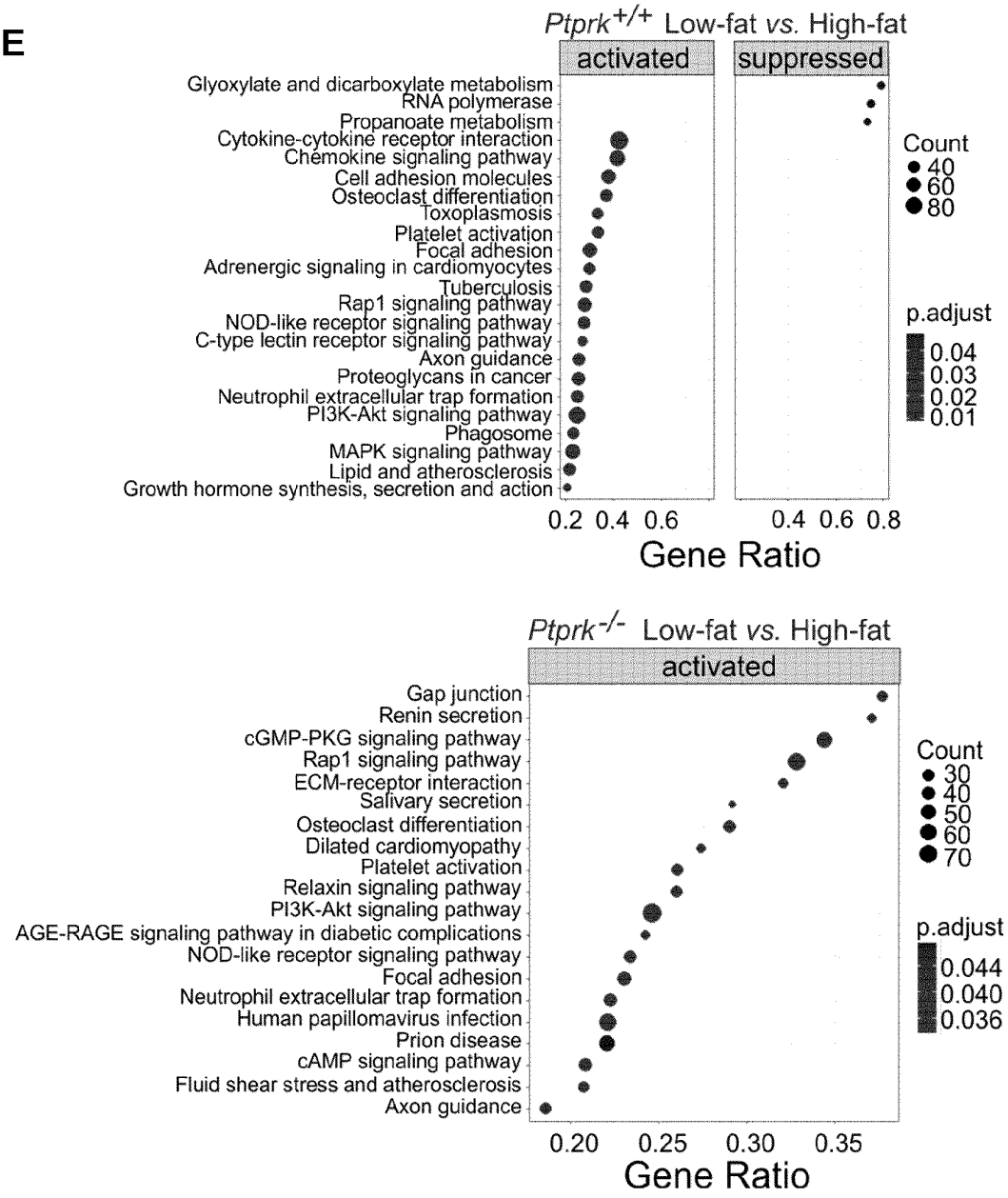


Figure 5 - continued

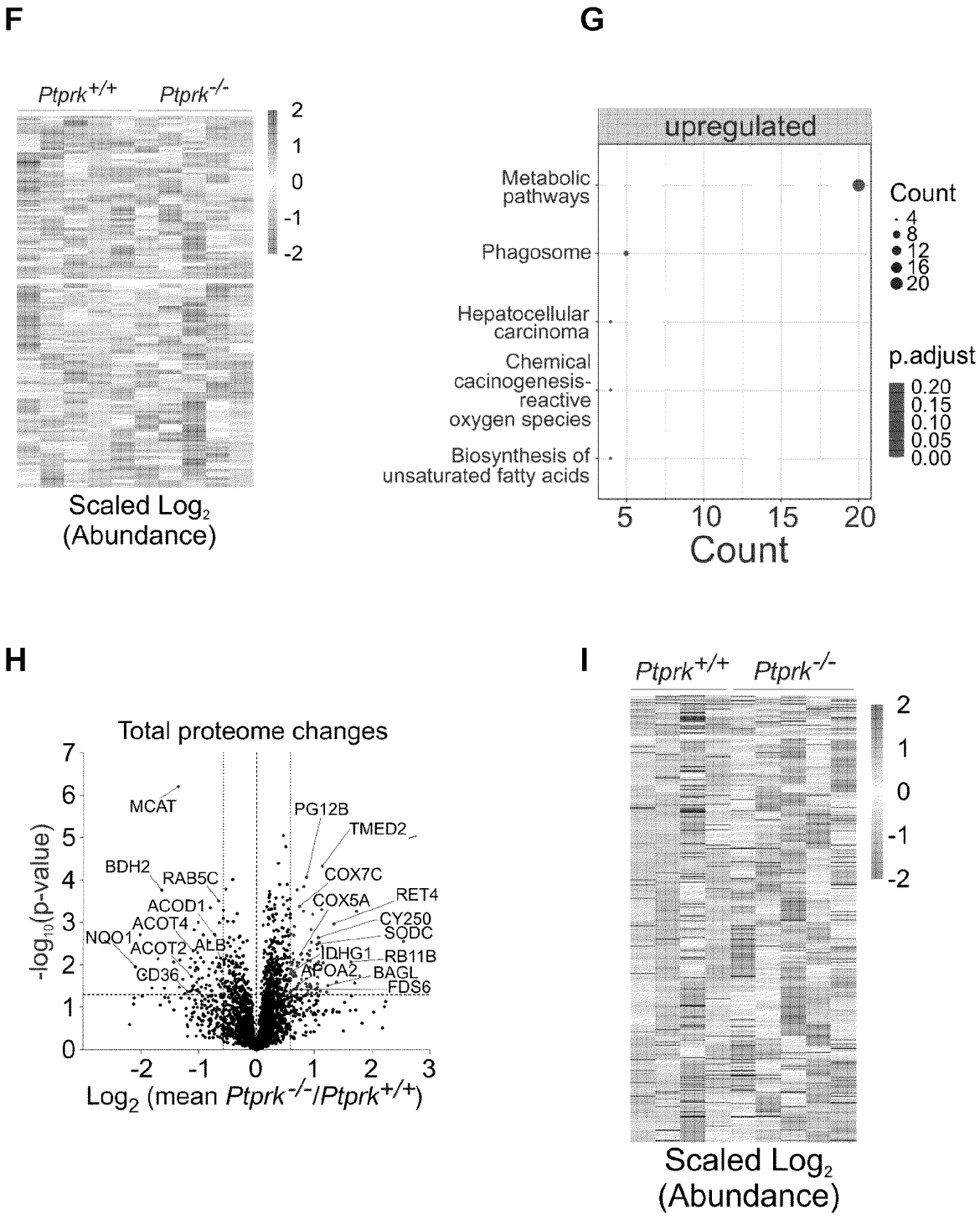


Figure 5 – continued

J

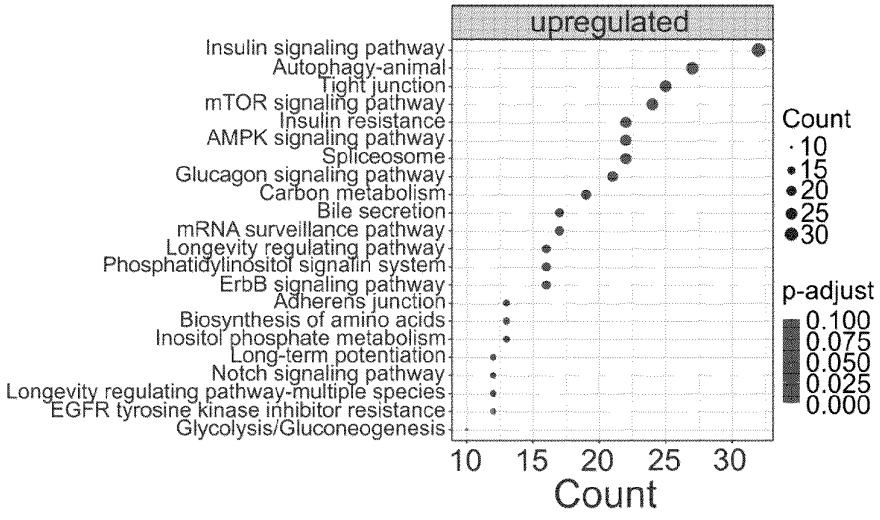


Figure 5 - continued

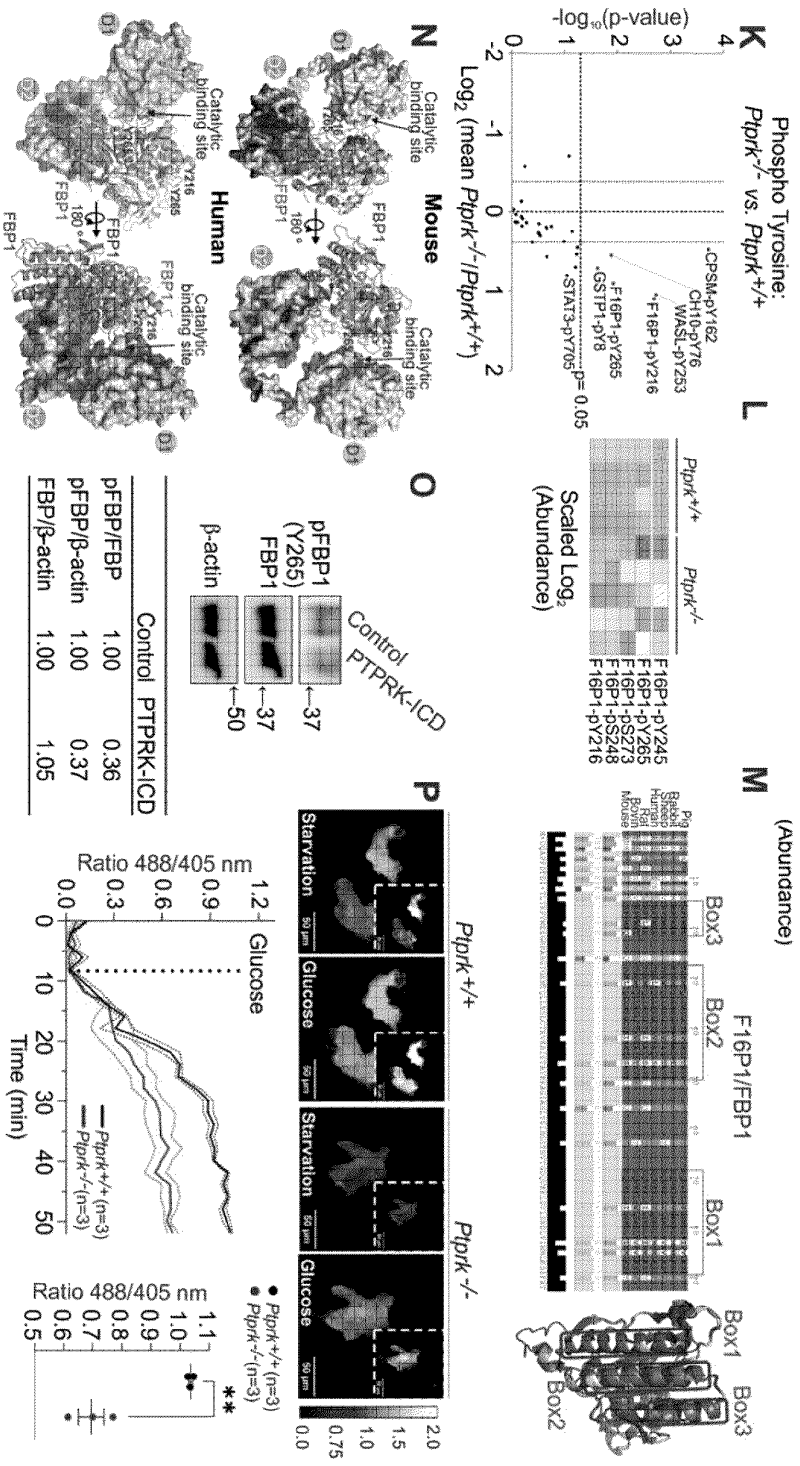


Figure 6

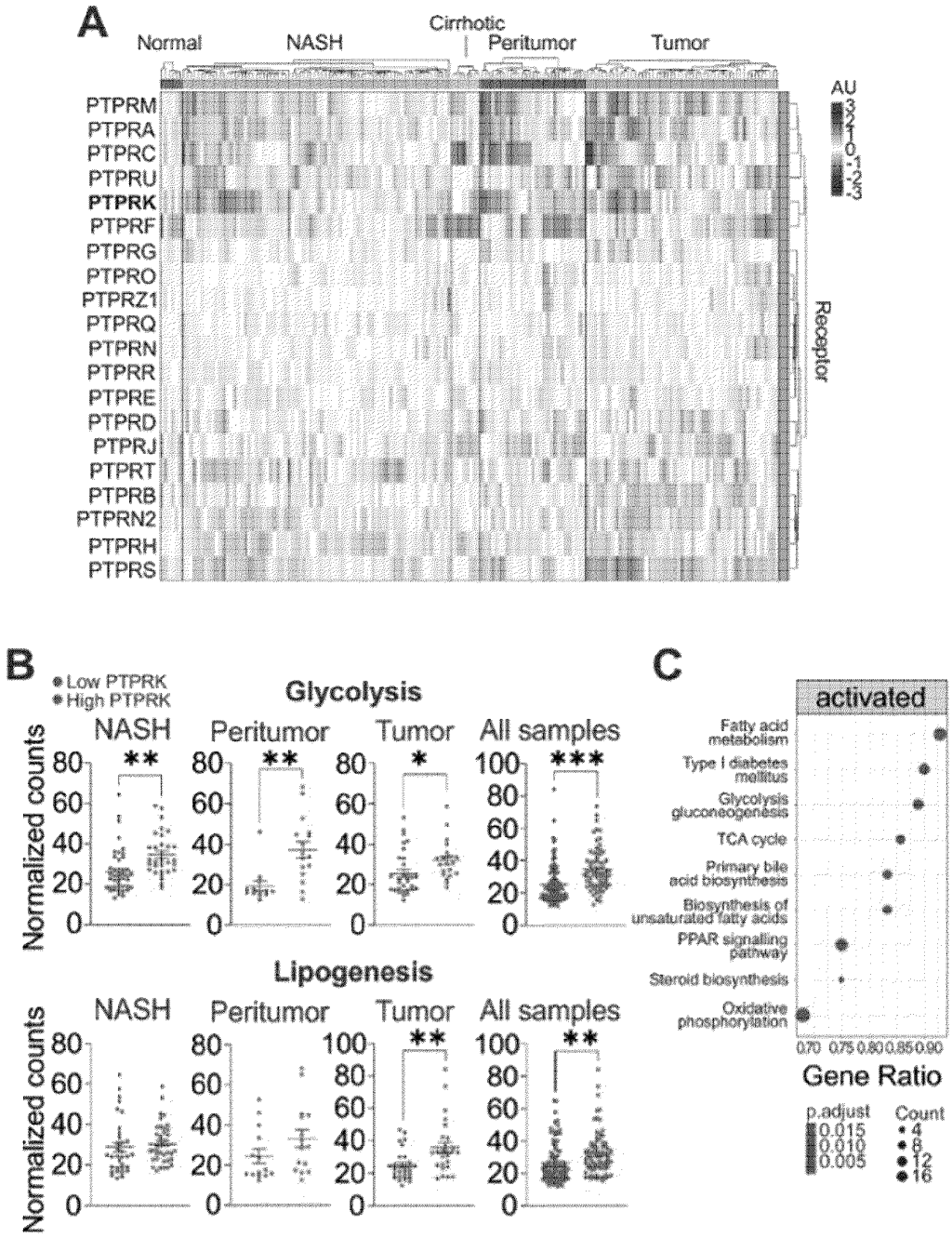

A
Normal
NASH
Cirrhotic
Peritumor
Tumor
AU
PTPRM
PTPRA
PTPRC
PTPRU
PTPRK
PTPRF
PTPRG
PTPRO
PTPRZ1
PTPRQ
PTPRN
PTPRR
PTPRE
PTPRD
PTPRJ
PTPRT
PTPRB
PTPRN2
PTPRH
PTPRS
Receptor
B
Low PTPRK
High PTPRK
Glycolysis
NASH
Peritumor
Tumor
All samples
Normalized counts
Lipogenesis
C
activated
Fatty acid metabolism
Type I diabetes mellitus
Glycolysis gluconeogenesis
TCA cycle
Primary bile acid biosynthesis
Biosynthesis of unsaturated fatty acids
PPAR signalling pathway
Steroid biosynthesis
Oxidative phosphorylation
Gene Ratio
p.adjust
Count

Figure 6 - continued

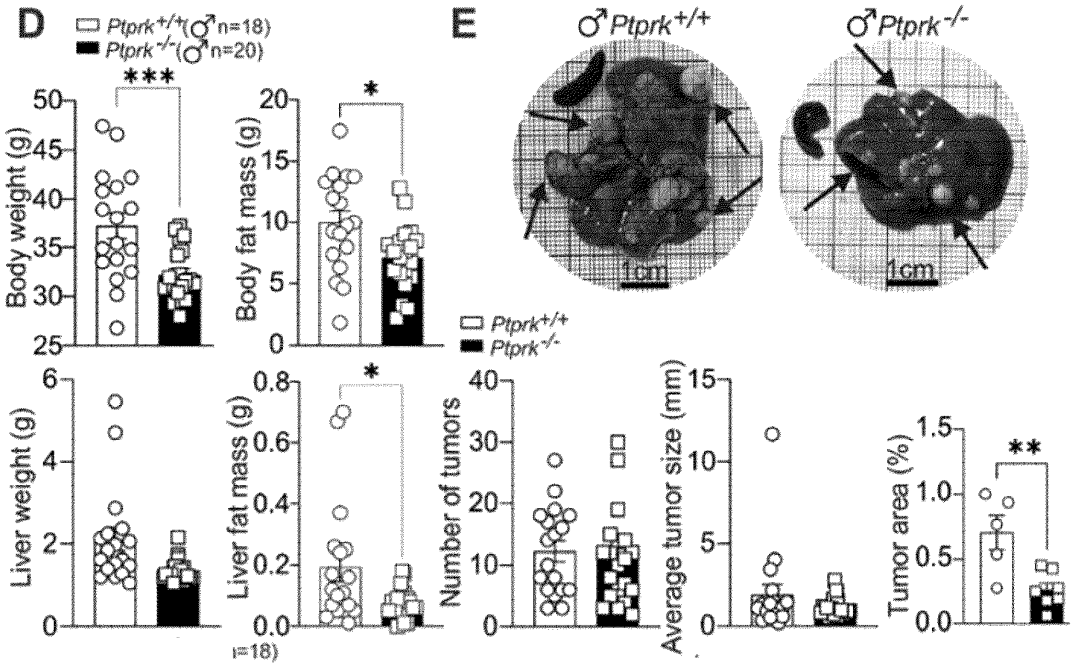
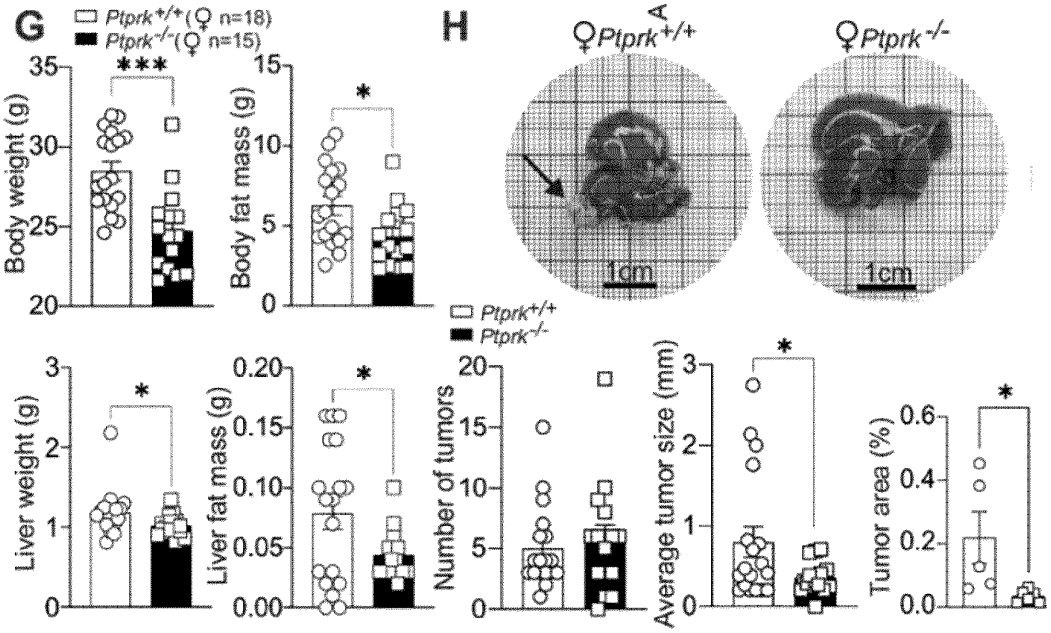


Figure 6 - continued



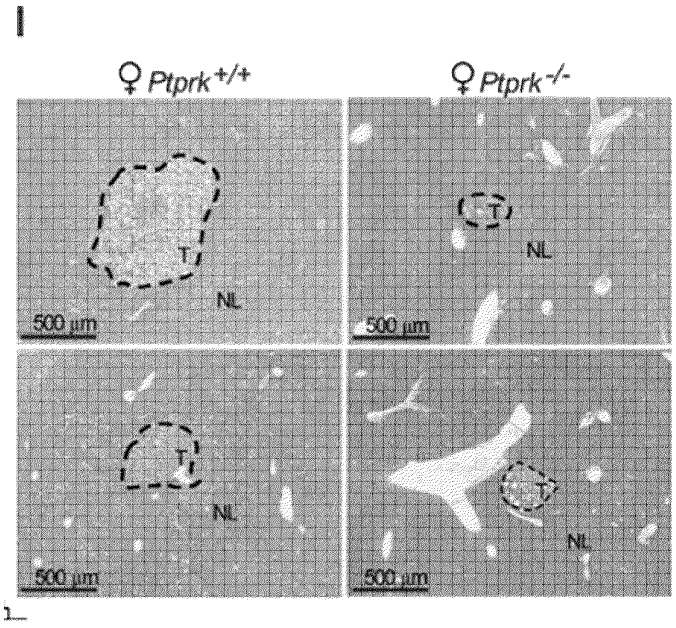


Figure 6 - continued

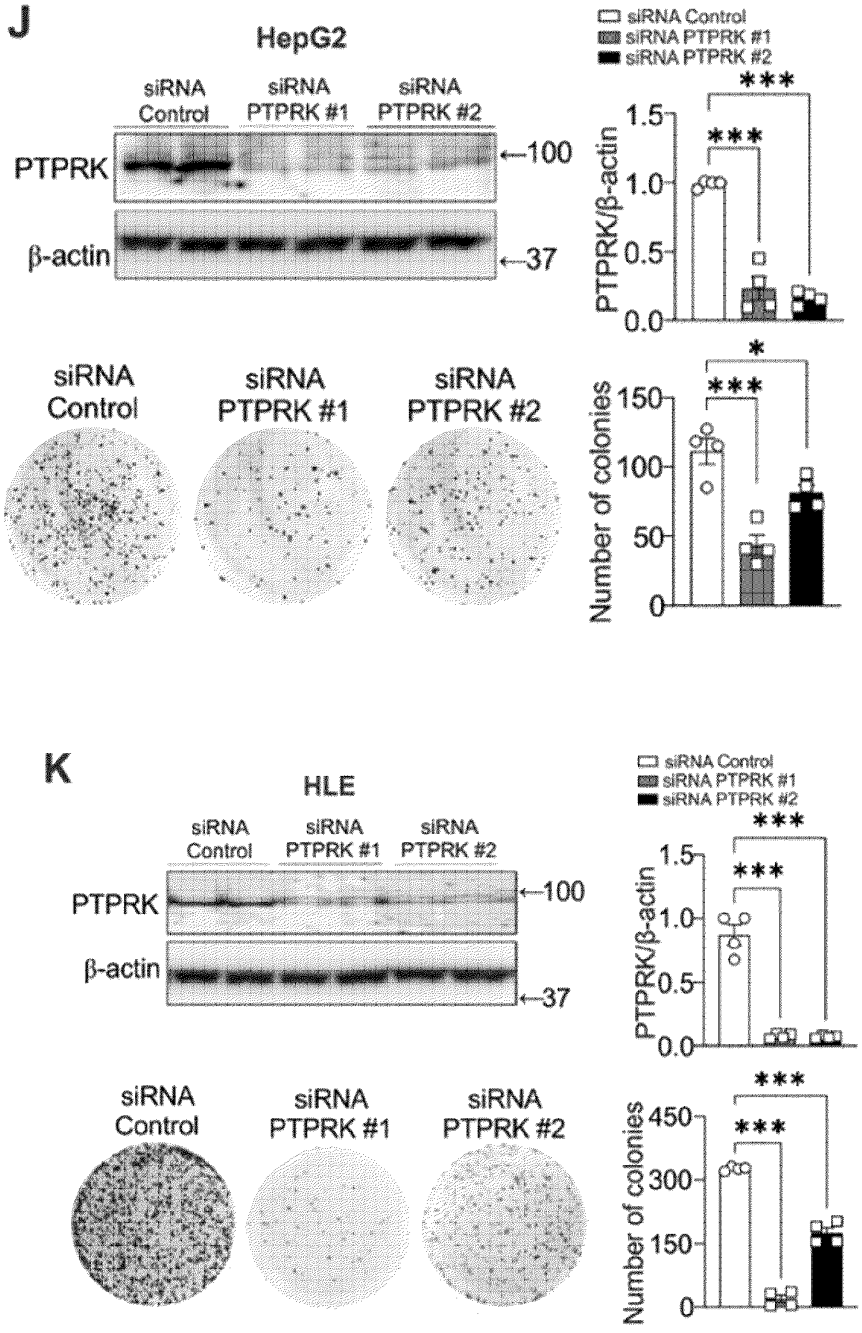


Figure 7

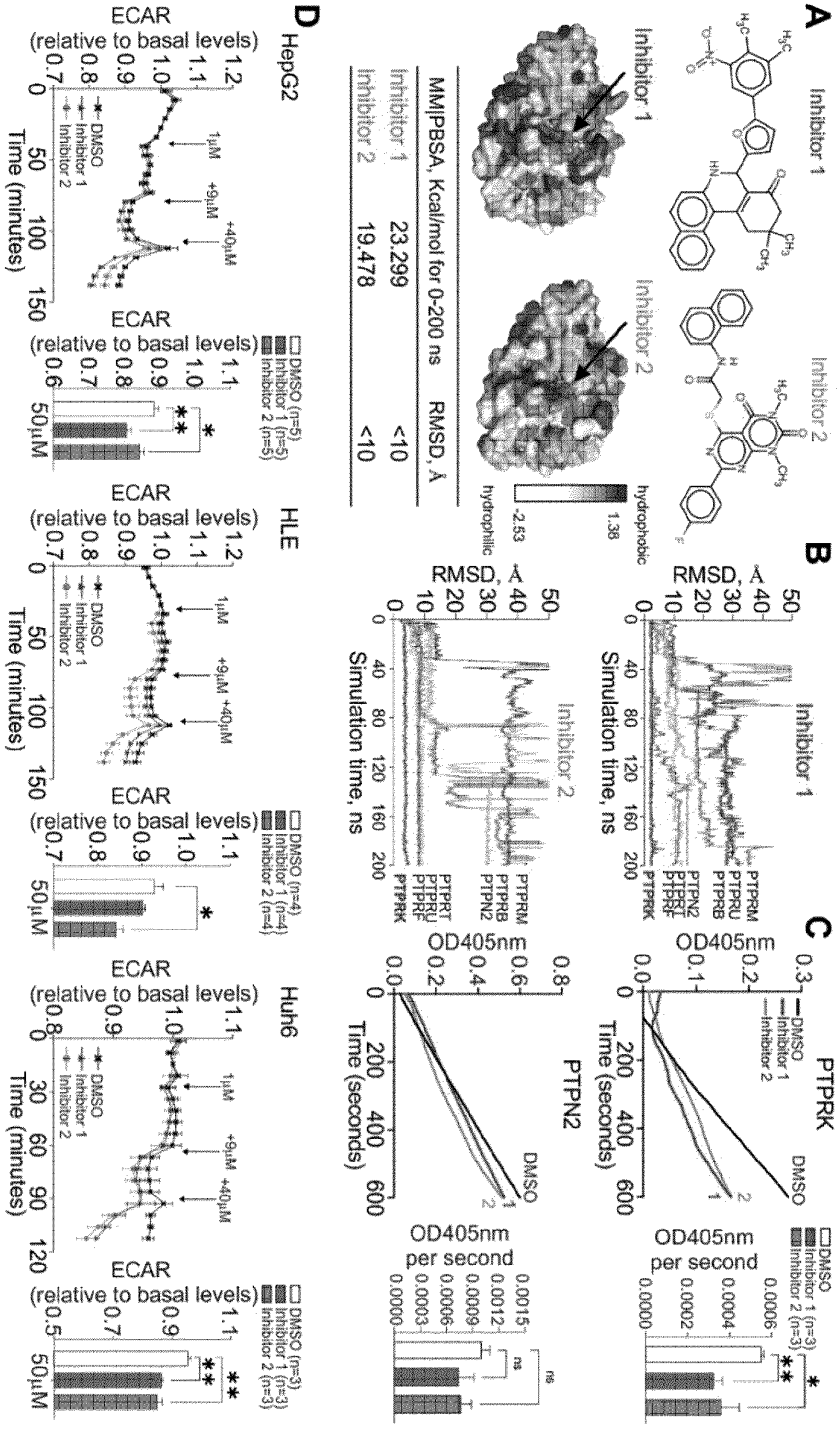

A
Inhibitor 1
Inhibitor 2
hydrophilic
hydrophobic
-2.53
1.38
MMPBSA, Kcal/mol for 0-200 ns
RMSD, Å
Inhibitor 1 23.299 <10
Inhibitor 2 19.478 <10
B
RMSD, Å
Simulation time, ns
PTPRM
PTPRU
PTPRB
PTPN2
PTPRT
PTPRJ
PTPRF
PTPRK
C
OD405nm
Time (seconds)
DMSO
Inhibitor 1
Inhibitor 2
PTPRK
PTPN2
OD405nm per second
ns
D
HepG2
HLE
Huh6
ECAR (relative to basal levels)
Time (minutes)
1μM
+9μM
+40μM
50μM
DMSO (n=5)
Inhibitor 1 (n=5)
Inhibitor 2 (n=5)
DMSO (n=4)
Inhibitor 1 (n=4)
Inhibitor 2 (n=4)
DMSO (n=3)
Inhibitor 1 (n=3)
Inhibitor 2 (n=3)

Figure 7 - continued

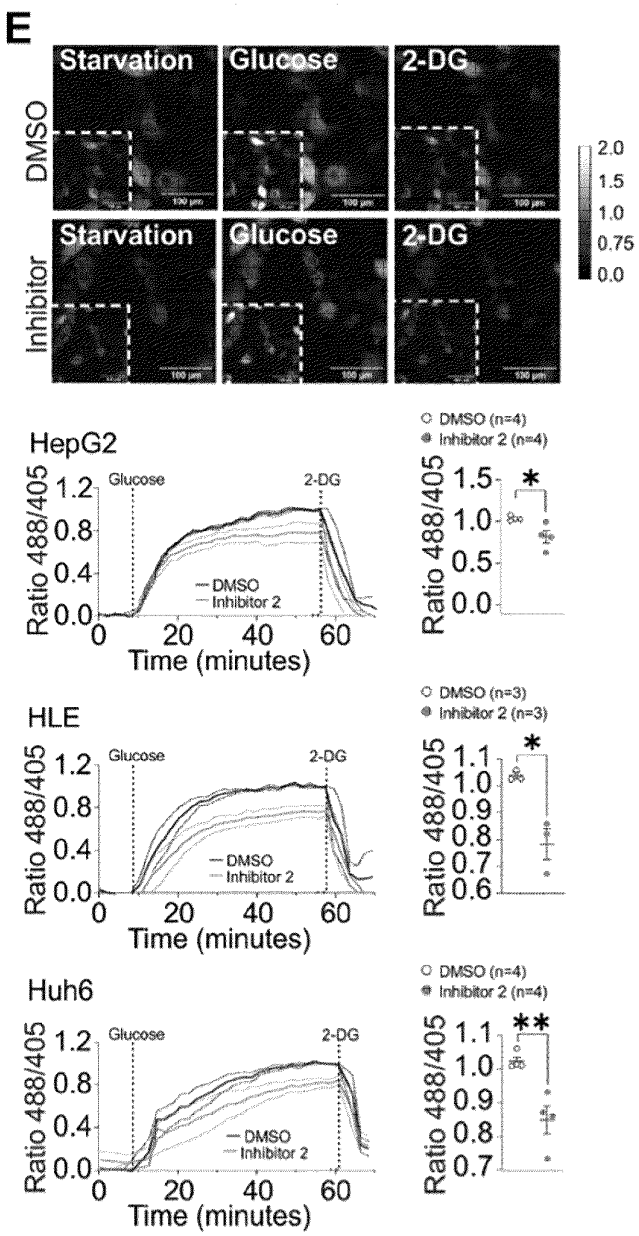
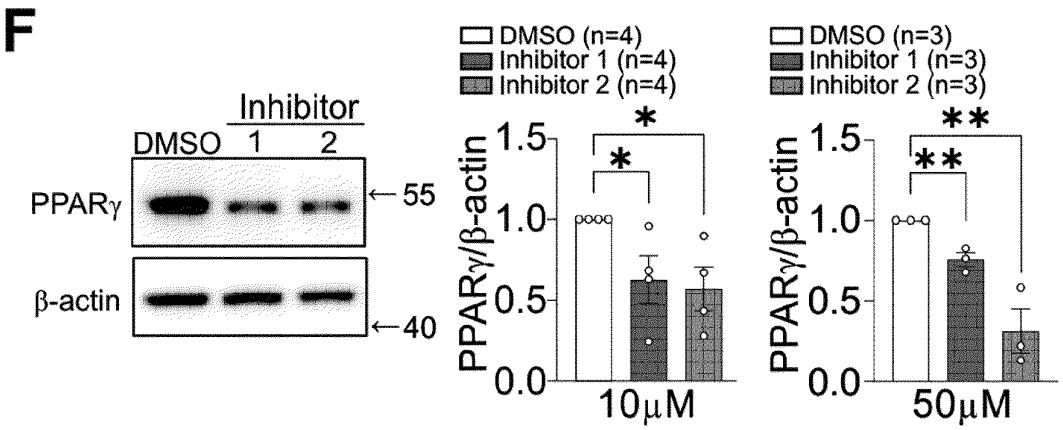


Figure 7 – continued



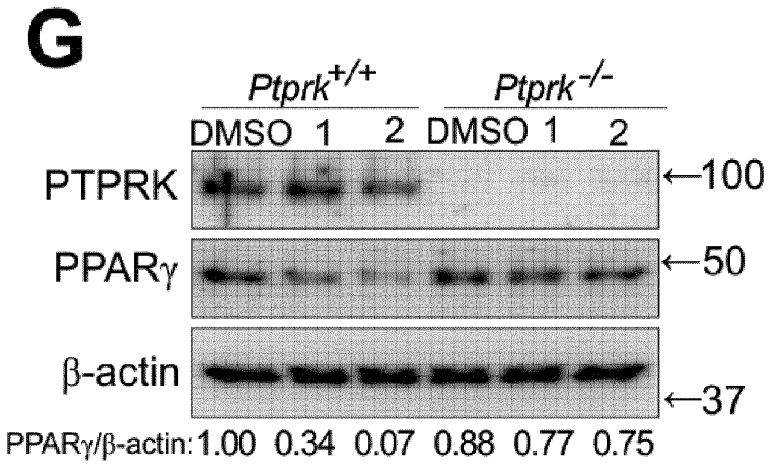


Figure 7 – continued

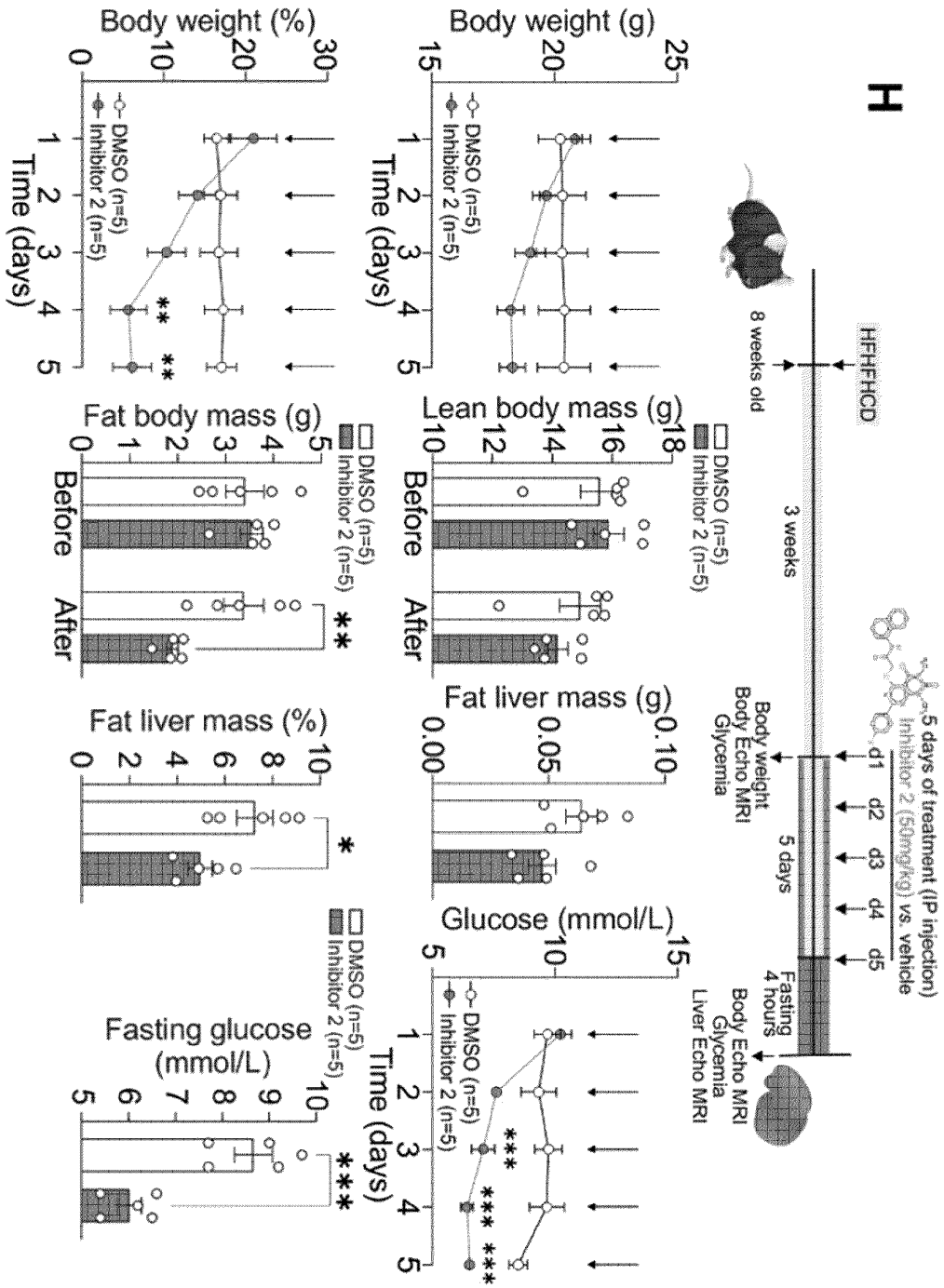
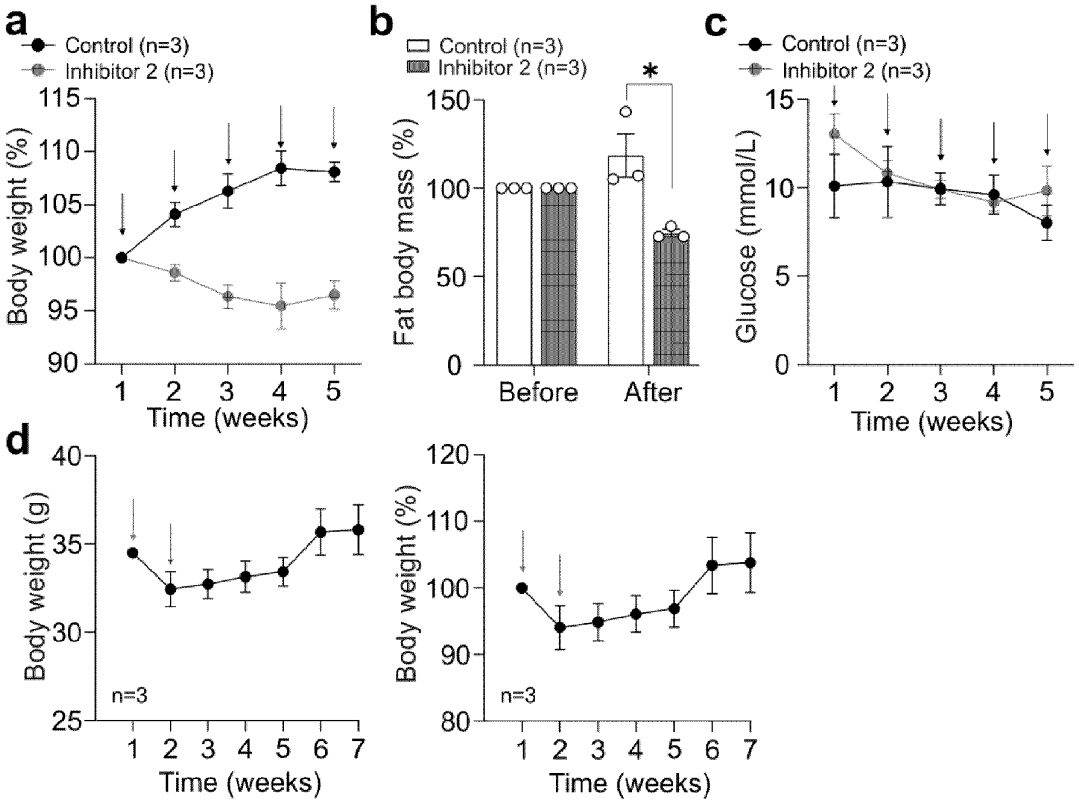


Figure 8


a
Control (n=3)
Inhibitor 2 (n=3)
Body weight (%)
115
110
105
100
95
90
1 2 3 4 5
Time (weeks)
b
Control (n=3)
Inhibitor 2 (n=3)
*
Fat body mass (%)
150
100
50
0
Before
After
c
Control (n=3)
Inhibitor 2 (n=3)
Glucose (mmol/L)
15
10
5
0
1 2 3 4 5
Time (weeks)
d
Body weight (g)
40
35
30
25
n=3
1 2 3 4 5 6 7
Time (weeks)
Body weight (%)
120
110
100
90
80
n=3
1 2 3 4 5 6 7
Time (weeks)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2024/082453

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:

   a. [X] forming part of the international application as filed.

   b. [ ] furnished subsequent to the international filing date for the purposes of international search (Rule 13*ter*.1(a)).

      [ ] accompanied by a statement to the effect that the sequence listing does not go beyond the disclosure in the international application as filed.

2. [ ] With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this report has been established to the extent that a meaningful search could be carried out without a WIPO Standard ST.26 compliant sequence listing.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2024/082453

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K31/407 A61K31/435 A61K31/519 A61P1/16 A61P3/04
A61P3/06 A61P3/10 A61P35/00

ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Gilglioni Eduardo: "33rd Meeting of the Belgian Endocrine Society October 20 & 21, 2023", BES meeting 2023, 21 October 2023 (2023-10-21), pages 1-12, XP093151250, DOI: 10.1530/endoabs.97.002 Retrieved from the Internet: URL:https://www.endocrine-abstracts.org/ea/0097/ea0097002 page 9 - page 10	1-4,6, 8-13

X	WO 2014/183062 A1 (JOLLA INST ALLERGY IMMUNOLOG [US]) 13 November 2014 (2014-11-13) claims 1-2, 14, 19-20	1,3,6,8, 10,14

	-/--	

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance;; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance;; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 January 2025	06/02/2025

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Matos de Brito, P

3

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2004/005312 A1 (ISIS PHARMACEUTICALS INC [US]; COWSERT LEX M [US]; FREIER SUSAN M [US]) 15 January 2004 (2004-01-15) page 3, line 12 - line 26; claims 1, 17, 19	1,3,6, 10,14
A	KRASNOV KONSTANTIN A. ET AL: "Stereodirected synthesis of alkaloid-like quinolizidine systems", NATURAL PRODUCT RESEARCH, vol. 34, no. 2, 10 November 2018 (2018-11-10), pages 269-277, XP093151367, GB ISSN: 1478-6419, DOI: 10.1080/14786419.2018.1528588 the whole document	4,6,8-14
A	WO 2022/152800 A1 (UNIV MADRID AUTONOMA [ES]; CONSEJO SUPERIOR INVESTIGACION [ES] ET AL.) 21 July 2022 (2022-07-21) the whole document	4,6,8-14
A	BOBKIEWICZ-KOZLOWSKA TERESA ET AL: "Hypoglycaemic effect of quinolizidine alkaloids - lupanine and 2-thionosparteine on non-diabetic and streptozotocin-induced diabetic rats", EUROPEAN JOURNAL OF PHARMACOLOGY, vol. 565, no. 1-3, 1 June 2007 (2007-06-01), pages 240-244, XP093151368, NL ISSN: 0014-2999, DOI: 10.1016/j.ejphar.2007.02.032 the whole document	4,6,8-14
A	GARCIA LOPEZ P M ET AL: "Quinolizidine alkaloids isolated from Lupinus species enhance insulin secretion", EUROPEAN JOURNAL OF PHARMACOLOGY, ELSEVIER SCIENCE, NL, vol. 504, no. 1-2, 3 November 2004 (2004-11-03), pages 139-142, XP004613500, ISSN: 0014-2999, DOI: 10.1016/J.EJPHAR.2004.09.008 the whole document	4,6,8-14

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2024/082453

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2014183062 A1	13-11-2014	US 2016122768 A1	05-05-2016
		WO 2014183062 A1	13-11-2014
WO 2004005312 A1	15-01-2004	AU 2003247400 A1	23-01-2004
		US 2004009597 A1	15-01-2004
		WO 2004005312 A1	15-01-2004
WO 2022152800 A1	21-07-2022	EP 4029500 A1	20-07-2022
		EP 4277620 A1	22-11-2023
		JP 2024507030 A	16-02-2024
		US 2023348482 A1	02-11-2023
		WO 2022152800 A1	21-07-2022