Abstract:

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Language:

English

No.

Applicants

(including


Declarations under Rule 4.17:

— of inventorship (Rule 4.1.7(iv))

Published:

— with international search report (Art. 21(3))

— before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))

Title: ACETAMIDE COMPOUNDS, THEIR PROCESS AND PHARMACEUTICAL APPLICATION

IN)

Chemical and Biotechnological Applications

WO 2012/020357 A1

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(43) International Publication Date

16 February 2012 (16.02.2012)

(19) World Intellectual Property Organization

International Bureau

PCT

WO 2012/020357 A1

[IN/IN]; Quantum Towers, Plot No. 9, Rajiv Gandhi Infotech Park, Phase I, Hinjewadi, 411 057 Pune (Maharashtra) (IN). PALLE, Venkata Poornapragnacharyulu [US/IN]; Quantum Towers, Plot No. 9, Rajiv Gandhi Infotech Park, Phase I, Hinjewadi, 411 057 Pune (Maharashtra) (IN).

(10) International Publication Number

WO 2012/020357 A1

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(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(21) International Application Number:

PCT/IB2011/053473

(22) International Filing Date:

4 August 2011 (04.08.2011)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

2278/CHE/2010 9 August 2010 (09.08.2010) IN

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(54) Title: ACETAMIDE COMPOUNDS, THEIR PROCESS AND PHARMACEUTICAL APPLICATION

(57) Abstract: This disclosure relates to a series of acetamide compounds of formula (I), their stereoisomers, tautomers, prodrugs, pharmaceutically acceptable salts, polymorphs, solvates and formulations thereof. The disclosure also relates to process of preparation of the acetamide compounds. The compounds of the present disclosure are identified as Glucokinase activators or modulators.
Field of the invention

This disclosure relates to a series of acetamide compounds, their stereoisomers, tautomers, prodrugs, pharmaceutically acceptable salts, polymorphs, solvates and formulations thereof. The disclosure also relates to process of preparation of the acetamide compounds. The compounds of the present disclosure are identified as Glucokinase activators or modulators, which are beneficial for the prophylaxis, management, treatment, control of progression, or adjunct treatment of diseases and/or medical conditions where the activation of glucokinase would be beneficial, such as diabetes, metabolic syndrome, and/or diabetes-related complications including retinopathy, nephropathy, neuropathy, ischemic heart disease, arteriosclerosis, β-cell dysfunction, and as therapeutic and/or prophylactic agents for obesity.

Background of the invention

Diabetes mellitus is a metabolic disorder characterized by recurrent or persistent hyperglycemia (high blood glucose) and other signs, as distinct from a single disease or condition. Glucose level abnormalities can result in serious long-term complications, which include beta-cell dysfunction, glucotoxicity, cardiovascular disease, chronic renal failure, retinal damage, nerve damage (of several kinds), microvascular damage, macrovascular damage, adipocyte inflammation, vascular inflammation and obesity.

Type 1 diabetes, also known as Insulin Dependent Diabetes Mellitus (IDDM), is characterized by loss of the insulin-producing β-cells of the islets of Langerhans of the pancreas leading to a deficiency of insulin. Type-2 diabetes previously known as adult-onset diabetes, maturity-onset diabetes, or Non-Insulin Dependent Diabetes Mellitus (NIDDM) - is due to a combination of increased hepatic glucose output, defective insulin secretion, and insulin resistance or reduced insulin sensitivity (defective responsiveness of tissues to insulin).

Glucokinase (GK), also known as hexokinase IV or D, is one of four glucose-phosphorylating enzymes called hexokinases that catalyze the first step of glycolysis, the conversion of glucose to glucose 6-phosphate (G6P), in vertebrate tissues. GK functions in a dual role, with distinct functions in the pancreas and liver; (a) as a molecular glucose sensor in the insulin-producing pancreatic β-cells, and (b) as the high-capacity enzymatic step initiating the storage of glucose in the form of glycogen in the liver and uptake of glucose during hyperglycemia. Therefore, GK plays a central role in glucose homeostasis, through the phosphorylation of glucose in the liver, and the modulation of insulin secretion in the pancreas (Postic, C. et al (1999) J. Biol. Chem. 274: 305-315). GK also functions as a sensor in other neuroendocrine cells of the gastrointestinal tract and in various brain cells including specific cells in the hypothalamus (Jetton, T. A. et al (1994) J. Biol. Chem. 269: 3641-3654).
The physiological concentration of glucose in human plasma is approximately 5.5 mM under fasting conditions, and increases to about 12 mM in the fed state. This concentration is dependent on and maintained by the activity of GK, which senses glucose and controls metabolic flux in key cell types. The glucose concentration, at which GK activity is at half of its maximal velocity or \( V_{\text{max}} \), is defined as its \( S_{0.5} \). The \( S_{0.5} \) of GK for glucose lies in the middle of the physiological glucose concentration range at approximately 8 mM, allowing this enzyme to act as a molecular glucose sensor crucial for glucose homeostasis. The limited tissue distribution and unique kinetic properties of GK allow it to play a critical role in pancreatic \( \beta \)-cell insulin secretion and hepatic glucose utilization. GK differs from the other members of the mammalian hexokinase family in its unique sigmoidal kinetics with respect to glucose, a high \( S_{0.5} \) that lies in the physiological glucose concentration range (the other three mammalian hexokinases have \( S_{0.5} \) values less than 0.5 mM), the lack of product inhibition by G6P, and its tissue distribution in cell types that are thought to be responsive to changing plasma glucose levels.

Given the role of GK as a molecular glucose sensor, it is not surprising that GK mutations have a profound influence on glucose homeostasis. About 2000 GK mutations that have been identified in humans result in impaired glucose-mediated insulin secretion and maturity-onset diabetes of the young type 2 (MODY-2). Some of these mutations result in decreased accumulation of hepatic glycogen, while others decrease GK activity by reducing the stability of the enzyme or by decreasing its \( V_{\text{max}} \). Mutations that result in activation of GK are implicated in the onset of persistent hyperinsulinemic hypoglycemia of infancy (PHHI). Single point mutations (e.g. V62M, D158A, Y214A, V455M, and F456V) in regions distinct from the substrate binding site of the enzyme lead to modulation of GK activity (Glaser, B. et al (1998) N. Engl. J. Med. 338: 226-230; Gloyn, A. L. (2003) Hum. Mutat. 22: 353-362; Gloyn, A. L. et al (2003) Diabetes 52: 2433-2440). These observations highlight that GK activity can be regulated through allosteric modulation.


The present disclosure provides a novel class of acamamide compounds characterized as glucokinase activators or modulators, and their potential use as medicament for the prophylactic or therapeutic treatment of hyperglycemia, diabetes, obesity, dyslipidemia, metabolic syndrome and like.

Summary of the invention

The present disclosure relates to a series of acamamide derivatives described by formula (I), their stereoisomers, tautomers, prodrugs, pharmaceutically acceptable salts, polymorphs, solvates and formulations thereof as glucokinase activators (GKAs);

![Chemical Structure](image)

wherein

ring A is an optionally substituted 4-12 membered mono or polycyclic cycloalkyl ring;
ring-B is an optionally substituted 4-12 membered mono or polycyclic ring containing 1-4 hetero atoms selected from N, O or S with at least one nitrogen in the ring;
ring C is a mono or a polycyclic ring selected from aryl, heteroaryl or heterocyclyl;
D is -SO₂⁻;
E is selected from the group consisting of cycloalkyl, heterocyclyl, and -N(G)R₈⁻;
G is selected from alkyl, cycloalkyl, aryl, heterocyclyl or heteroaryl, wherein said alkyl, cycloalkyl, aryl, heterocyclyl or heteroaryl are optionally substituted with 1 to 4 substituents independently selected from halogen, monohaloalkyl, dihaloalkyl or perhaloalkyl, monohaloalkoxy, dihaloalkoxy or perhaloalkoxy, cyano, nitro, alkyl, alkenyl, alkynyl, methylenedioxy, amidino -NR₄⁻R₅⁻, -OR₄⁻, -S(0)₅⁻R₄⁻, -S(0)₅⁻NR₄⁻R₅⁻, -NR₄⁻S(0)₅⁻R₄⁻, -NR₄⁻C(0)₅⁻R₅⁻, -OS(0)₅⁻R₄⁻, -NR₄⁻C(0)₅⁻OR₄⁻, -NR₄⁻C(0)₅⁻NR₄⁻R₅⁻, (CR₄⁻R₇⁻)₅⁻C(0)₅⁻OR₄⁻, (CR₄⁻R₇⁻)₅⁻C(0)₅⁻NR₄⁻R₅⁻, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkenyl, aryloxy, or heteroaryloxy groups;
X represents -O(CR₄⁻R₇⁻)₅⁻, -N(R₄⁻)(CR₄⁻R₇⁻)₅⁻, -S(0)₅⁻(CR₄⁻R₇⁻)₅⁻; wherein the heteroaom is connected through carbon that is alpha to the carbonyl group;
R¹ is selected from the group consisting of hydrogen, alkyl and perfluoroalkyl;
R² and R³ are independently selected from the group consisting of hydrogen, halogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, mono, di or tri substituted haloalkyl, nitrile, nitro, oxo, -NR₄R⁵, -OR⁴, -S(0)ₜR⁴, -S(0)ₜNR₄R⁵, -NR₄S(0)ₜR⁵, -NR₄C(0)R⁵, -OS(0)ₜR⁵, -NR₄C(0)OR₅, -(CR₆R₇)ₜC(0)OR₄, -(CR₆R₇)ₜ(CO)NR₄R⁵, -(CR₆R₇)ₜS(0)ₜNR₄R⁵, -(CR₆R₇)ₜN(R₄)C(0)R⁴, -(CR₆R₇)ₜOR₄, -(C(R₆R₇)ₜNR₄R₅, -(C(R₆R₇)ₜCO(R₄) and -S(0)ₜC(R₆R₇)ₜC(0)OR₄; wherein R² and R³ is each optionally substituted with one or more substituents selected from halo, straight chain or branched chain alkyl, alkyldiol, hydroxyalkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocycle, alkylsulfonyl, oxo, nitro, cyano, -(CR₆R₇)ₜC(0)OR₄, -(CR₆R₇)ₜ(CO)NR₄R⁵, -OR₄, -SR₄ or -NR₄R⁵;

in addition to R² and R³, ring-B is further optionally substituted with one or more substituents selected from halo, straight chain or branched chain alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, alkylsulfonyl, oxo, nitro, cyano, -COOR₄, -(C(0)NR₄R⁵, -OR₄, -SR₄ or -NR₄R⁵;

R⁴ and R⁵ are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl and heterocyclylalkyl; or

R⁴ and R⁵ taken together form a monocyclic or a bicyclic ring system which is saturated or partially unsaturated and optionally have additional heteroatoms selected from O, N or S, said ring system is further optionally substituted with 1 to 4 substituents independently selected from halo, alkyl, alkenyl, alkynyl, nitro, cyano, -OR₄, -SR₄, -NR₄R⁵, oxo, alkylsulfonyl, -COOR₄, -(C(0)NR₄R⁵, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl or heteroarylalkyl;

R⁶ and R⁷ are independently selected from the group consisting of hydrogen, fluorine, OR₄, alkyl, cycloalkyl and perfluoroalkyl; or

R⁶ and R⁷ taken together may form a monocyclic or a bicyclic ring system which is saturated or partially unsaturated and optionally have additional heteroatoms selected from O, N or S, said ring system is further optionally substituted with 1 to 4 substituents independently selected from halo, alkyl, alkenyl, alkynyl, nitro, cyano, oxo, -OR₄, -SR₄, -NR₄R⁵, alkylsulfonyl, -COOR₄, -(C(0)NR₄R⁵, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl or heteroarylalkyl;

wherein R⁴ and R⁵ are as described above;

R⁸ is selected from hydrogen, halogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl;
rings A, C and E are each optionally substituted with 1 to 4 substituents independently selected from alkyl, alkenyl, alkynyl, methylenedioxy, halogen, mono, di or perhaloalkyl, monohaloalkoxy, dihaloalkoxy or perhaloalkoxy, nitrile, nitro, oxo, amidino, -NR\(^4\)R\(^5\), -OR\(^4\), -S(0)\(_p\)R\(^4\), -S(0)\(_p\)NR\(^4\)R\(^5\), -NR\(^4\)S(0)\(_p\)R\(^5\), -NR\(^4\)C(0)R\(^5\), -OS(0)\(_p\)R\(^5\), -NR\(^4\)C(0)OR\(^5\), -NR\(^4\)C(0)NR\(^4\)R\(^5\), -(CR\(^6\)R\(^7\))\(_p\)C(0)OR\(^4\), -(CR\(^6\)R\(^7\))\(_p\)C(0)NR\(^4\)R\(^5\), -(CR\(^6\)R\(^7\))\(_p\)C(0)R\(^4\), cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkenyl, aryloxy or heteroaryloxy groups; wherein \(p = 0-2\) and \(n = 0-4\).

The disclosure also relates to the process of preparation of acetamide derivatives of formula-I.

These GKAs are beneficial for the prophylaxis, management, treatment, control of progression, or adjunct treatment of diseases and/or medical conditions such as Type-I and Type-II diabetes, obesity, dyslipidemia, metabolic syndrome and/or diabetes-related complications including retinopathy, nephropathy, neuropathy, ischemic heart disease, arteriosclerosis, \(\beta\)-cell dysfunction, and as therapeutic and/or prophylactic agents for obesity where the activation of glucokinase would be beneficial.

The present disclosure also relates to the compounds of formula (I) that are liver selective GK activators. Such liver selective GK activators may be useful for the treatment of hyperglycemia, diabetes, obesity, dyslipidemia, metabolic syndrome and the like, in mammals and have minimum hypoglycemic potential.

Surprisingly, compounds of the present invention were found to have superior glucokinase activating properties over the compounds disclosed in co-pending applications 409/CHE/2007 and 2266/CHE/2007.

These and other features, aspects, and advantages of the present subject matter will become better understood with reference to the following description and appended claims. This Summary is provided to introduce a selection of concepts in a simplified form. This Summary is not intended to identify key features or essential features of the claimed subject matter, nor is it intended to be used to limit the scope of the claimed subject matter.

**Detailed description of the invention**

**Definitions**

In the structural formulae given herein and throughout the present disclosure, the following terms have the indicated meaning:
The term "optionally substituted" as used herein means that the group in question is either unsubstituted or substituted with one or more of the substituents specified. When the group in question is substituted with more than one substituent, the substituents may be same or different.

The term "mono or bicyclic ring" refers to a carbocycle, an aryl, a heterocycle or a heteroaryl which can be aromatic or non-aromatic, saturated or unsaturated, 3 to 18 ring atoms system including 0 to 5 heteroatoms independently selected from S, N, O; the said rings can be optionally substituted.

The term "aryl", alone or in combination with any other term, refers to a monocyclic or a polycyclic aromatic ring system containing carbon-ring atoms, such as phenyl, biphenyl, naphthyl or anthryl which optionally carries one or more substituents, preferably one to four, each independently selected from halogen, mono, di or perhaloalkyl, mono, di or perhaloalkoxy, cyano, nitro, alky, alkenyl, alkynyl, methylenedioxy, amido, -NR^6R^7, -OR^6, -S(O) R^6, -S(O) pR^7, -NR^6S(0) pR^7, -NR^6C(0)OR^7, -NR^6C(0)R^7, -NR^6C(0)NR^6R^7, -(CR^8R^9) R^6, -(CR^8R^9) C(0)R^6, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkenyl, aryloxy, heteroaryloxy and the like.

"Heteroaryl", alone or in combination with any other term, refers to a monocyclic aromatic ring structure containing 5 or 6 ring atoms, or a bicyclic aromatic group having 8 to 12 atoms, containing one or more heteroatoms independently selected from O, S, and N, and optionally substituted with 1 to 4 groups or substituents each independently selected from halogen, mono, di or perhaloalkyl, mono, di or perhaloalkoxy, cyano, nitro, alky, alkenyl, alkynyl, methylenedioxy, amido, -NR^6R^7, -OR^6, -S(O) pR^6, -S(O) pNR^6R^7, -NR^6S(0) pR^7, -NR^6C(0)R^7, -OS(0) pR^7, -NR^6C(0)OR^7, -NR^6C(0)NR^6R^7, -(CR^8R^9) R^6, -(CR^8R^9) C(0)R^6, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkenyl, aryloxy, heteroaryloxy or the like. "Heteroaryl" is also intended to include oxidized S or N, such as sulfinyl, sulfonyl and N-oxide of tertiary ring nitrogen. A carbon or hetero-atom is the point of attachment of the heteroaryl ring structure such that a stable aromatic ring is retained. Examples of heteroaryl groups are azepinyl, benzimidazolyl, benisoaxazolyl, benzofurazanyl, benzopyranyl, benzothiazolyl, benzothienyl, benzoazoxyl, cinnolinyl, pyridinyl, pyridazinyl, pyrazinyl, quinoxolinyl, purinyl, indolyl, quinolinyl, pyrimidinyl, pyrrolyl, oxazolyl, oxadiazolyl, thiazolyl, thienyl, isoxazolyl, oxadiazolyl, isothiazolyl, tetrazolyl, imidazolyl, triazinyl, furanyl, benzofuryl, naphthyridinyl, thiadiazolyl, triazolyl, oxazolopyridinyl,
imidazopyridinyl, thiazolopyridinyl, thiazolotraizinyl, thiazolopyrazinyl, quinoxalinyl and the like. A substituted heteroaryl contains a substituent attached to an available carbon or heteroatom to produce a stable compound. "Heteroaryl" is also intended to encompass compounds where a heteroaryl is attached to another non-aromatic cycyl or heterocyclyl rings. Non-limiting examples include chromanyl, dihydrobenzofuranyl, indaliny, dihydrobenzothienyl, benzodioxoyl dihydrobenzothieryl, dihydrobenzothiopyranyl, isochromanyl, dihydrobenzothioypyryl sulfone, 1,3-dioxolanyl, benzofuryl, and the like.

As used herein, "heterocycle" or "heterocyclyl" refers to a stable 4 to 7-membered monocyclic or stable 8 to 12 membered bicyclic heterocyclic non-aromatic ring which is either saturated or unsaturated, and which consists of carbon atoms and from one to five heteroatoms selected from the group consisting of N, O, and S and may be optionally substituted with 1 to 4 groups or substituents each independently selected from halogen, mono, di or perhaloalkyl, mono, di or perhaloalkoxy, oxo, cyano, nitro, alkyl, alkenyl, alkynyl, methylenedioxy, amidino - NR^7R^7, -OR^7, -S(O)_pR^6, -S(O)_pNR^8R^7, -NR^8S(O)_pR^7, -NR^8C(0)R^7, -OS(O)_pR^7, -NR^8C(0)OR^7, -NR^8C(0)NR^6R^7, -(CR^8R^8)_pC(0)OR^6, -(CR^8R^8)_pC(0)NR^6R^7, -(CR^8R^8)_pC(0)R^6, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroaerylalkyl, aryloxy, heteroaryloxy, or the like. "Heterocyclyl" is also intended to include oxidized S or N, such as sulfiny, sulfonyl and N-oxide of tertiary ring nitrogen. A substituted heterocycle contains a substituent attached to an available carbon or heteroatom to produce a stable compound. The heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation of a stable structure. Non-limiting examples include imidazolidinyl, imidazolinyl, indolinyl, isoindolinyl, isoquinolinyl, isothiazolidinyl, isothiazolinyl, morpholinyl, 2-oxopiperazinyl, 2-oxopiperdinyln, 2-oxopyrrolidinyl, piperidyl, piperazinyl, pyrazolidinyl, pyrrolidinyl, quinoxalinyl, dihydroimidazole-one, tetrahydrofuryl, tetrahydroisoquinolinyl, tetrahydroquinozalinyl, tetrahydroquinocxalinyl, thiamorpholinyl sulfoxide, thiazolinyl, thiazolidine, benzoxazinone, benzothiazinone, isoxazoline, oxazolidin, dihydropyrazinyl, dihydrobenzazinyl, dihydrobenzothiazinyl, benzodioxonyl, dihydrobenzodioxonyl, dihydropropyridyl and dihydrobenzodiazepinone.

"Alkyl" refers to straight or branched chain having 1 to 10 carbon atoms which is/are further substituted. Examples of alkyl groups include, but are not limited to methyl, ethyl, propyl, isopropyl, butyl, t-butyl and the like.

"Cycloalkyl" refers to a monocyclic, bicyclic or polycyclic alkyl group containing 3 to 15 carbon atoms which are further substituted. Wherein bicyclic or polycyclic means a saturated ring fused with saturated, or unsaturated or partially unsaturated fused, spiro or bridged ring
assembly. Examples of cycloalkyl groups include, but are not limited to cyclopropyl indane, tetralin, 1,2,3,4-tetrahydrophenanthrene, spiro[4.4]nonane, spiro[4.5]decane, spiro[5.5]undecane, bicyclo[1.1.1]pentane, norbornane, bicyclo[2.2.2]octane, norpinane, 2,3,4-Tetrahydro-phenanthrene, 1,2,3,4,5,6,7,8-Octahydro-phenanthrene, tetradecahydro-anthracene, tetradecahydro-phenanthrene, bicyclo[3.2.1]octane, bicyclo[3.3.1]nonane, bicyclo[3.3.2]decan, bicyclo[3.3.3]undecane, bicyclo[4.1.1]octane, bicyclo[4.2.1]nonane, bicyclo[4.3.2]undecane, bicyclo[4.3.3]dodecane 1,4-cyclobutyl, cyclopentyl, bicyclo[4.4.0]decane, adamantanyl, bicycle[2.2.1]heptene and the like.

"Alkenyl", alone or in combination refers to a straight, branched, mono cyclic or polycyclic unsaturated hydrocarbon preferably containing 3 to 10 carbon atoms, and having 1 to 4 double bonds and preferably 1 double bond. Examples of alkenyl groups include, but are not limited to propenyl, isopropenyl, butenyl, bicycle[2.2.1]heptene and the like.

"Alkynyl", alone or in combination with any other term means a straight or branched hydrocarbon containing 3 to 10 carbon atoms containing 1 to 3 triple bonds and at least one triple bond. Examples of alkynyl groups include but are not limited to propynyl, butynyl and the like.

Alkyl, alkenyl, alkynyl, cycloalkyl defined above may optionally be substituted with 1 to 5 substituents, independently selected from the group consisting of alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkenyl, cycloalkyloxy, acyl, acylamino, acyloxy, amino, aminocarboxyl, alkoxy carbamylamino, azido, cyano, halogen, hydroxy, keto, thiocarboxyl, carboxy, carboxyalkyl, arylthio, heteroarylmethyl, heterocycloalkyl, thiol, alkylthio, aryl, aryloxy, heteroaryl, aminosulfonyl, aminocarboxyamino, heteroarylthio, heterocycloalkyl, heterocycloxy, nitro, -SO-alkyl, -SO-aryl, -SO-heteroaryl, -SCValkyl, SCVaryl and -SCVheteroaryl.

"Halo" or "Halogen", alone or in combination with any other term means halogens such as chloro (Cl), fluoro (F), bromo (Br) and iodo (I).

"Carboxylic acid isostere" refers to moiety selected from the group mentioned below

In functional terms, carboxylic acid isosteres mimic carboxylic acid by virtue of similar physical properties, including but not limited to molecular size, charge distribution or molecular shape. 3-or 5-hydroxy isoxazole or 3- or 5-hydroxy isothiazole may be optionally substituted with lower
alkyl or lower alkyl substituted with 1,2 or 3 substituents selected from group consisting of fluoro, aryl and heteroaryl, wherein aryl or heteroaryl may further be optionally substituted with 1,2 or 3 substituents selected from group consisting halogen, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio and fluoro substituted lower alkylthio. The nitrogen of sulfonamide may be optionally substituted with substituents selected from the group consisting of halogen, lower alkyl, fluoro substituted lower alkyl, acetyl, aryl, and heteroaryl wherein aryl and heteroaryl may be further substituted with 1,2 or 3 substituents selected from halogen, lower alkyl, fluoro substituted lower alkyl, lower alkoxy, fluoro substituted lower alkoxy, lower alkylthio and fluoro substituted lower alkylthio.

The compounds of the present disclosure may have the ability to crystallize in more than one form, a characteristic known as polymorphism, and all such polymorphic forms ("polymorphs") are encompassed within the scope of the disclosure. Polymorphism generally can occur as a response to changes in temperature or pressure or both, and can also result from variations in the crystallization process. Polymorphs can be distinguished by various physical characteristics, and typically the x-ray diffraction patterns, solubility behavior, and melting point of the compound are used to distinguish polymorphs.

The compounds described herein may contain one or more chiral centers and/or double bonds and therefore, may exist as stereoisomers, such as geometric isomers, enantiomers or diastereomers. Accordingly, the chemical structures depicted herein encompass all possible enantiomers and stereoisomers of the illustrated or identified compounds including the stereoisomerically pure form (e.g., geometrically pure, enantiomerically pure or diastereomerically pure) and enantiomeric and stereoisomeric mixtures. Enantiomeric and stereoisomeric mixtures can be resolved into their component enantiomers or stereoisomers using separation techniques or chiral synthesis techniques well known to the person skilled in the art. The compounds may also exist in several tautomeric forms including the enol form, the keto form and mixtures thereof. Accordingly, the chemical structures depicted herein encompass all possible tautomeric forms of the illustrated or identified compounds.

Compounds may exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, compounds may be hydrated, solvated or N-oxides. Certain compounds may exist in multiple crystalline or amorphous forms. Also contemplated within the scope of the disclosure are congeners, analogs, hydrolysis products, metabolites and precursor or prodrugs of the compound. In general, unless otherwise indicated, all physical forms are equivalent for the uses contemplated herein and are intended to be within the scope of the present disclosure.
"Prodrug" refers to a derivative of a drug molecule as, for example, esters, carbonates, carbamates, ureas, amides or phosphates that requires a transformation within the body to release the active drug. Prodrugs are frequently, although not necessarily, pharmacologically inactive until converted to the parent drug. Prodrugs may be obtained by bonding a promoiety (defined herein) typically via a functional group, to a drug.

"Promoiety" refers to a group bonded to a drug, typically to a functional group of the drug, via bond(s) that are cleavable under specified conditions of use. The bond(s) between the drug and promoiety may be cleaved by enzymatic or non-enzymatic means. Under the conditions of use, for example following administration to a patient, the bond(s) between the drug and promoiety may be cleaved to release the parent drug. The cleavage of the promoiety may proceed spontaneously, such as via a hydrolysis reaction, or it may be catalyzed or induced by another agent, such as by an enzyme, by light, by acid, or by a change of or exposure to a physical or environmental parameter, such as a change of temperature, pH, etc. The agent may be endogenous to the conditions of use, such as an enzyme present in the systemic circulation to which the prodrug is administered or the acidic conditions of the stomach or the agent may be supplied exogenously.

The present disclosure relates to a series of acetamide derivatives described in formula (I), their stereoisomers, tautomers, prodrugs, pharmaceutically acceptable salts, polymorphs, solvates and formulations thereof as glucokinase activators

![Image](image_url)

wherein

- ring A is an optionally substituted 4-12 membered mono or polycyclic cycloalkyl ring;
- ring-B is an optionally substituted 4-12 membered mono or polycyclic ring containing 1 - 4 hetero atoms selected from N, O or S, with at least one nitrogen in the ring;
- ring C is a mono or a polycyclic ring selected from aryl, heteroaryl or heterocyclyl;
- D is $\text{--SO}_2$-;
- E is selected from the group consisting of cycloalkyl, heterocyclyl, and $\text{--N(G)R}^8$;
- G is selected from alkyl, cycloalkyl, aryl, heterocyclyl or heteroaryl; wherein said alkyl, cycloalkyl, aryl, heterocyclyl or heteroaryl are optionally substituted with 1 to 4 substituents independently selected from halogen, monohaloalkyl, dihaloalkyl or perhaloalkyl, monohaloalkoxy, dihaloalkoxy or perhaloalkoxy, cyano, nitro, alkyl,
alkenyl, alkynyl, methylenedioxy, amidino -NR^4 R^5, -OR^4, -S(O)\_p R^4, -S(O)\_p NR^4 R^5, -NR^4 S(O)\_p R^5, -NR^4 C(O)R^5, -OS(O)\_p R^5, -NR^4 C(O)OR^5, -NR^4 C(O)NR^4 R^5, -(CR^6 R^7)_n C(O)OR^4, -(CR^6 R^7)_n C(O)NR^4 R^5, -(CR^6 R^7)_n C(O)R^4, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkenyl, aryloxy or heteroaryloxy groups;

X represents -(OR)^6(CR^6 R^7)_n-, -N(R^4)(CR^6 R^7)_n-, -S(O)\_p(CR^6 R^7)_n-, wherein the heteroaom is connected through carbon that is alpha to the carbonyl group;

R^1 is selected from the group consisting of hydrogen, alkyl and perfluoroalkyl;

R^2 and R^3 are independently selected from the group consisting of hydrogen, halogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, mono, di or tri substituted haloalkyl, nitrile, nitro, oxo, -NR^4 R^5, -OR^4, -S(O)\_p R^4, -S(O)\_p NR^4 R^5, -NR^4 S(O)\_p R^5, -NR^4 C(O)R^5, -OS(O)\_p R^5, -NR^4 C(O)OR^5, -CR^6 R^7 C(O)OR^4, -(CR^6 R^7)_n (CO)NR^4 R^5, -(CR^6 R^7)_n S(O)\_p NR^4 R^5, -(CR^6 R^7)_n N(R^4)C(O)R^4, -(CR^6 R^7)_n OR^4, -C(R^6 R^7)_n NR^4 R^5, -(CR^6 R^7)_n CO(R^4) and -S(O)\_p C(R^6 R^7)_n C(O)OR^4, wherein R^2 and R^3 is each optionally substituted with one or more substituents selected from halo, straight chain or branched chain alkyl, alkylidio, hydroxyalkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocycle, alkylsulfonyl, oxo, nitro, cyano, -(CR^6 R^7)_n C(O)OR^4, -(CR^6 R^7)_n (CO)NR^4 R^5, -(CR^6 R^7)_n OR^4, -SR^4 or -NR^4 R^5;

in addition to R^2 and R^3, ring-B is further optionally substituted with one or more substituents selected from halo, straight chain or branched chain alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclcyl, alkylsulfonyl, oxo, nitro, cyano, -COOR^4, -(C(O)NR^4 R^5, -OR^4, -SR^4 or -NR^4 R^5;

R^4 and R^5 are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl and heterocyclylalkyl; or

R^4 and R^5 taken together form a monocyclic or a bicyclic ring system which is saturated or partially unsaturated and optionally have additional heteroatoms selected from O, N or S, said ring system is further optionally substituted with 1 to 4 substituents independently selected from halo, alkyl, alkenyl, alkynyl, nitro, cyano, -OR^4, -SR^4, -NR^4 R^5, oxo, alkylsulfonyl, -COOR^4, -(C(O)NR^4 R^5, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl or heteroaryalkyl;

R^6 and R^7 are independently selected from the group consisting of hydrogen, fluorine, OR^4, alkyl, cycloalkyl and perfluoroalkyl; or

R^6 and R^7 taken together form a monocyclic or a bicyclic ring system which is saturated or partially unsaturated and optionally have additional heteroatoms selected from O, N or S,
said ring system is further optionally substituted with 1 to 4 substituents independently selected from halo, alkyl, alkenyl, alkynyl, nitro, cyano, o xo, -OR\(^4\), -SR\(^4\), -NR\(^4\)R\(^5\), alkylsulfonyl, -COOR\(^4\), -C(0)NR\(^4\)R\(^5\), cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroaryalkyl;

wherein R\(^4\) and R\(^5\) are as described above;

R\(^8\) is selected from hydrogen, halogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, arylalkyl, heteroaryl or heteroaryalkyl;

rings A, C and E are each optionally substituted with 1 to 4 substituents independently selected from alkyl, alkenyl, alkynyl, methylenedioxy, halogen, mono, di or perhaloalkyl, monohaloalkoxy, dihaloalkoxy or perhaloalkoxy, nitrile, nitro, o xo, amidino, -NR\(^4\)R\(^5\), -OR\(^4\), -S(0)\(_p\)R\(^4\), -S(0)\(_p\)NR\(^4\)R\(^5\), -NR\(^4\)S(0)\(_p\)R\(^5\), -NR\(^4\)C(0)R\(^5\), -OS(0)\(_p\)R\(^5\), -NR\(^4\)C(0)OR\(^5\), -NR\(^4\)C(0)NR\(^4\)R\(^5\), -(CR\(^6\)R\(^7\))\(_n\)C(0)OR\(^4\), -(CR\(^6\)R\(^7\))\(_n\)C(0)NR\(^4\)R\(^5\), -(CR\(^6\)R\(^7\))\(_n\)C(0)R\(^4\), cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroaryalkyl, cycloalkenyl, aryloxy or heteroaryloxy groups;

wherein p = 0-2 and n = 0-4.

According to an embodiment, the present disclosure relates to compounds of formula (I) wherein ring A is selected from

According to another embodiment, the present disclosure relates to compounds of formula (I) wherein ring B is selected from:
According to another embodiment, the present disclosure relates to compounds of formula (I) wherein ring C is selected from

![Ring C structures]

In another embodiment, the present disclosure relates to compounds of formula (I) wherein E is a cycloalkyl or a heterocyclyl and is selected from

![Ring E structures]

In another embodiment, the present disclosure related to compounds of formula (I) or their stereoisomers, tautomers, prodrugs, pharmaceutically acceptable salts, polymorphs, solvates and formulations thereof,

wherein ring A is selected from
E is a cycloalkyl or a heterocyclyl and is selected from

\[
\begin{align*}
\text{ring B is selected from:} & \\
\text{or}
\end{align*}
\]

\[
\begin{align*}
\text{ring C is selected from} & \\
\text{or}
\end{align*}
\]

E is a cycloalkyl or a heterocyclyl and is selected from
In another embodiment, the present disclosure relates to compounds of formula (I)
wherein E is -N(G)R₈ wherein G is selected from

According to another embodiment, the present disclosure relates to compounds of
formula (I), or its stereoisomers, tautomers, prodrugs, pharmaceutically acceptable salts,
polymorphs, solvates and formulations thereof

wherein ring-A is selected from

ring-B is selected from
ring-C is selected from

E is selected from

rings A, C and E are each optionally substituted with 1 to 4 substituents independently selected from alkyl, halogen, mono, di or tri substituted haloalkyl, nitrile, oxo, -NR^4R^5, -OR^4, -S(0)_p^R^4, -S(0)_p^NR^4R^5, -NR^4C(0)NR^5, -(CR^6R^7)_n^C(0)OR^4, -(CR^6R^7)_n^C(0)NR^4R^5, -(CR^6R^7)_n^C(0)R^5 or cycloalkyl; wherein p = 0-2; n = 0-4;

X is O;

R^1 is selected from the group consisting of hydrogen and alkyl;

R^2 and R^3 are independently selected from the group consisting of hydrogen, halogen, alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, mono, di or tri substituted haloalkyl, nitrile, oxo, -NR^4R^5, -OR^4, -S(0)_p^R^4, -S(0)_p^NR^4R^5, -NR^4C(0)R^5, -OS(0)_p^R^5, -NR^4C(0)OR^4, -(CR^6R^7)_n^C(0)OR^4, -(CR^6R^7)_n^C(0)S(0)_p^NR^4R^5, -(CR^6R^7)_n^C(0)NR^4R^5, -(CR^6R^7)_n^C(0)NR^4C(0)R^4 and -S(0)_p^C(R^6R^7)_n^C(0)OR^4, wherein R^2 and R^3 is each optionally substituted with one or more substituents selected from halo, straight chain or branched chain alkyl, alkydiol, hydroxyalkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocycle, alkylsulfonyl, oxo, nitro, cyano, -(CR^6R^7)_n^C(0)OR^4, -(CR^6R^7)_n^C(0)NR^4R^5, -OR^4, -SR^4 or -NR^4R^5; wherein n = 0-4.
According to another embodiment, the present disclosure relates to compounds of formula (I), or its stereoisomers, tautomers, prodrugs, pharmaceutically acceptable salts, polymorphs, solvates and formulations thereof;

wherein ring-A is selected from

```
  or
```

ring-B is selected from

```
N  N
```

ring-C is selected from

```
  or
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E is selected from

```
,  ,  ,  ,  or
```

rings A, C and E are each optionally substituted with 1 to 4 substituents independently selected from alkyl, halogen, mono, di or perhaloalkyl, nitrile, oxo, -NR₄R₅, -OR₄, -S(0)ₚR₄, -S(0)ₚNR₄R₅, -NR₄C(0)R₅, -(CR₈R₇)ₚC(0)OR₄, -(CR₈R₇)ₚC(0)NR₄R₅, -(CR₈R₇)ₚC(0)R₄ or cycloalkyl; wherein p = 0-2; n= 0-4;

X is O;

R¹ is selected from the group consisting of hydrogen and alkyl;

one of R² and R³ is -OR₄ and the other is selected from the group consisting of hydrogen, halogen, alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, mono, di or tri substituted haloalkyl, nitrile, oxo, -NR₄R₅, -S(0)ₚR₄, -S(0)ₚNR₄R₅, -NR₄S(0)ₚR₅, -NR₄C(0)R₅, -OS(0)ₚR₅, -NR₄C(0)OR₅, -(CR₈R₇)ₚC(0)OR₄, -(CR₈R₇)ₚC(0)NR₄R₅, -(CR₈R₇)ₚS(0)ₚNR₄R₅, -(CR₈R₇)ₚN(R₄)C(0)R₄, -(CR₈R₇)ₚOR₄, -C(R₈R₇)ₚNR₄R₅, -C(R₈R₇)ₚCO(R₄) and -S(0)ₚC(R₈R₇)ₚC(0)OR₄;

R⁴ is selected from aryl or heteroaryl and is further substituted with one or more substituents selected from halo, straight chain or branched chain alkyl, alkyldiyl, hydroxyalkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocycle, alkylsulfonyl, oxo, nitro, cyano, -(CR₈R₇)ₚC(0)OR₄, -(CR₈R₇)ₚC(0)NR₄R₅, -OR₄, -SR₄ or -NR₄R₅.
According to another embodiment, the present disclosure relates to compounds of formula (I), or its stereoisomers, tautomers, prodrugs, pharmaceutically acceptable salts, polymorphs, solvates and formulations thereof;

wherein ring-A is selected from

- \[
\begin{align*}
\text{or } & \quad \text{or }
\end{align*}
\]

ring-B is selected from

- \[
\begin{align*}
\text{or } & \quad \text{or }
\end{align*}
\]

ring-C is selected from

- \[
\begin{align*}
\text{or } & \quad \text{or }
\end{align*}
\]

E is selected from

- \[
\begin{align*}
\text{or } & \quad \text{or }
\end{align*}
\]

rings A, C and E are each optionally substituted with 1 to 4 substituents independently selected from alkyl, halogen, mono, di or perhaloalkyl, nitrile, oxo, -NR\(_4\)R\(_5\), -OR\(_4\), -S(0)\(_p\)R\(_4\), -S(0)\(_p\)NR\(_4\)R\(_5\), -NR\(_4\)C(0)R\(_5\), -(CR\(_6\)R\(_7\)\(_n\))C(0)OR\(_4\), -(CR\(_6\)R\(_7\)\(_n\))C(0)NR\(_4\)R\(_5\), -(CR\(_6\)R\(_7\)\(_n\))C(0)R\(_4\) or cycloalkyl; wherein \(p = 0-2; n = 0-4;\)

X is O;

R\(_1\) is selected from the group consisting of hydrogen and alkyl;

one of R\(_2\) and R\(_3\) is -(CR\(_6\)R\(_7\)\(_n\))C(0)OR\(_4\), -(CR\(_6\)R\(_7\)\(_n\))C(0)NR\(_4\)R\(_5\), and the other is selected from the group consisting of hydrogen, halogen, alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, mono, di or tri substituted haloalkyl, nitrile, oxo, -OR\(_4\), -NR\(_4\)R\(_5\), -S(0)\(_p\)R\(_4\), -S(0)\(_p\)NR\(_4\)R\(_5\), -NR\(_4\)C(0)R\(_5\), -OS(0)\(_p\)R\(_5\), -NR\(_4\)C(0)OR\(_5\), -(CR\(_6\)R\(_7\)\(_n\))S(0)\(_p\)NR\(_4\)R\(_5\), -(CR\(_6\)R\(_7\)\(_n\))N(R\(_4\))C(0)R\(_4\), -(CR\(_6\)R\(_7\)\(_n\))OR\(_4\), -(CR\(_6\)R\(_7\)\(_n\))NR\(_4\)R\(_5\), -C(R\(_6\)R\(_7\)\(_n\))CO(R\(_4\)) and -S(0)\(_p\)C(R\(_6\)R\(_7\)\(_n\))C(0)OR\(_4\);

R\(_4\) and R\(_5\) are independently selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl, cycloalkyl and heterocyclyl; or

R\(_4\) and R\(_5\) taken together form a monocyclic which is saturated or partially unsaturated and optionally have additional heteroatoms selected from O, N or S, said ring system is
further optionally substituted with 1 to 4 substituents independently selected from halo, alkyl, cyano, -OR₄, -SR₄, oxo, alkylsulfonyl, -COOR₄, cycloalkyl or heterocyclyl; R⁶ and R⁷ are independently selected from the group consisting of hydrogen, fluorine, OR₄, alkyl, cycloalkyl and perfluoroalkyl; or R⁶ and R⁷ taken together form a monocyclic which is saturated or partially unsaturated and optionally have additional heteroatoms selected from O, N or S, said ring system further optionally substituted with 1 to 4 substituents independently selected from halo, alkyl, cyano, oxo, -OR₄, -SR₄, -COOR₄ or -C(O)NR₄R⁵.

According to an embodiment, the present disclosure relates to a process for the preparation of a compound of formula (I), their stereoisomers, tautomers, prodrugs, pharmaceutically acceptable salts, polymorphs, solvates, said process comprising:

reacting an acid of formula (II)

![Diagram](image)

wherein R is hydrogen, alkyl or arylalkyl, with a compound of formula (III)

![Diagram](image)

in presence of a suitable amide coupling reagent; optionally hydrolyzing; and optionally further coupling with an amine of formula NHR₆R⁷ to obtain compound of formula (I).

Compounds of formula I may be prepared as shown in the following reaction schemes and the description thereof, as well as relevant literature procedures that may be used by one skilled in the art. Exemplary reagents and procedures for these reactions appear hereinafter and in the working examples. Protection and deprotection in the schemes below may be carried out by procedures generally known in the art (see, for example, Greene, T. W. and Wuts, P.G.M., Protecting Groups in Organic Synthesis, 3rd Edition, 1999 [Wiley]).

The compounds of formula (I) may be prepared following independent general synthetic routes as outlined in the Schemes 1-5:

**Scheme 1**: General route for the synthesis of compounds of formula (I).
Compounds of formula (II) wherein R is hydrogen, alkyl or arylalkyl, may be reacted with compounds of formula (III) following amide coupling reaction conditions to obtain compounds of formula (I), as shown herein below.

Scheme 2: General route for the synthesis of compounds of formula (Ia) wherein either of R² or R³ of formula (I) is -(CR⁶R⁷)ₙ(CO)OH, from compounds of formula (lb) wherein either of R² or R³ is -(CR⁶R⁷)ₙ(CO)OR wherein R is a suitable alkyl group, following conditions for ester hydrolysis.

Scheme 3: General route for the synthesis of compounds of formula (Ic) wherein either of R² or R³ of formula (I) is -(CR⁶R⁷)ₙ(C(0)NR⁴R⁵), from compounds of formula (la) wherein either of R² or R³ is -(CR⁶R⁷)ₙ(CO)OH following conditions for amide coupling.

The compounds of formula (II), used in Scheme 1, may be prepared following independent synthetic routes as outlined in Schemes 5-6.

Scheme 4: General route for synthesis of compounds of formula (Id) wherein either of R² or R³ is OR⁴ and R⁴ is aryl, heteroaryl described as ring F in the following scheme. Compounds of formula (II) wherein R is hydrogen, alkyl or arylalkyl, may be reacted with compounds of formula (Ilia) wherein R' is alkyl following amide coupling reaction conditions to obtain
compounds of formula (Id). Compounds of formula (Id) may further be hydrolysed to obtain the corresponding carboxylic acid which may further be derivatised.

Scheme 5: General route for synthesis of compounds of formula (Ie) wherein either of R² or R³ is a heterocycle as described in the following scheme. Compounds of formula (II) wherein R is hydrogen, alkyl or arylalkyl, may be reacted with compounds of formula (Illb) wherein R' is alkyl following amide coupling reaction conditions to obtain compounds of formula (Ie). Compounds of formula (Ie) may further be hydrolysed to obtain the corresponding carboxylic acid which may further be derivatised.

The compounds of formula (II), may be prepared following independent synthetic routes as outlined in Schemes 6 -9.

Scheme 6: General route for the synthesis of (Ila):

Compounds of formula (IV) wherein R is alkyl may be condensed with tosyl hydrazine to obtain compounds of formula (V) which may be oxidized in the presence of a base like TEA, DBU to provide compounds of formula (VI). Alternatively, compounds of formula (VI) may also be obtained by reacting compounds of formula (VII) with tosylazide in presence of base. The compounds of formula (VI) may be reacted with compounds of formula (VIII) in the presence of a Rhodium catalyst to provide compounds of formula (lib) (following procedure as described in WO2002008209), which may be hydrolyzed to obtain intermediates of formula (Ila).
The compounds of formula (VII) may be prepared following independent synthetic routes as outlined in Schemes 10 -11.

Scheme 7: General route for the synthesis of compounds of formula (lid) wherein X is nitrogen and sulfur: Compounds of formula (IV), wherein R is hydrogen may be reduced to compounds of formula (Vila) followed by esterification to obtain compounds of formula (VII), which may be halogenated to obtain compounds of formula (IX). Compounds of formula (IX) may be reacted with compounds of formula (VIII) under nucleophilic substitution conditions to obtain the compounds of formula (lie) wherein R is alkyl or arylalkyl, which may be hydrolysed to obtain intermediates of formula (lid).

Scheme 8: General route for synthesis of compounds of formula (He) wherein E is heterocycle forming sulfonamide linkage or E is N(G)R₈: Compounds of formula (X) on oxidative chlorination provide compounds of formula (XI) (following procedure described in J. Org. Chem. 2007, 72(15), 5847-5850). Compound of formula XI may be subjected to coupling
reaction with an heterocyclyl amine to form sulfonamide linkage, in presence of organic or inorganic bases to obtain compounds of formula (XII). The compound of formula (XII) may be converted to compounds of formula (He) following the route as described in scheme 6.

Scheme 9: General route for synthesis of compounds of formula (IIf) wherein X is sulfur or nitrogen and E is heterocycle forming sulfonamide linkage of E is N(G)R^8: Compounds of formula (XI) may be halogenated to obtain compounds of formula (XIII), which may then be subjected to coupling reaction with an heterocyclyl amine to form sulfonamide linkage, in presence of organic or inorganic bases to obtain compounds of formula (XIV). The compound of formula (XIV) may be converted to compounds of formula (IIf) following the route as described in scheme 7.

Scheme 10: General route for the synthesis of compounds of formula (VII): Compounds of formula (X), which are available commercially, may be reacted with R^aLG, where LG is a suitable leaving group, using reaction conditions for nucleophilic substitution to obtain S-alkylated compounds of formula (XV). The compounds of formula (XIII) can be oxidized (sulfur to sulfone) to obtain compounds of formula (VII).

Scheme 11: General route for the synthesis of compounds of formula (VII) wherein E is cycloalkanon-3-yl: Compounds of formula (X) may be treated with cycloalk-2-enone such as
cyclohex-2-enone or cyclopent-2-enone, under Michael addition conditions to provide compounds of formula (XVib) which are then oxidized to obtain compounds of formula (VII).

**Coupling Conditions:** **Condition-I:** When \( R = H \), the amide coupling may be carried out using any suitable amide coupling regents such as oxalyl chloride, thionyl chloride, BOP-C1, DCC, HOBr, HOAt, HATU, EDCI, alkylchloroformate and the like in the presence of organic non-nucleophilic bases such as triethyl amine, di-isopropylethyl amine, pyridine, N-methyl pyrrolidine, N,N-dimethylaminopyridine, DBU, DABCO, other hindered amines and pyridines. The amide coupling reaction may be carried out in the presence of solvents such as dichloromethane, dichloroethane, DMF, dimethylacetamide, THF, acetonitrile or mixture of them may be used at a temperature ranging from -5 to 150 °C. The reaction may be carried out optionally in presence of catalytic amount of DMF. **Condition-II:** When \( R \) is not H, the amide coupling may be carried out by heating ester and amine either in the absence of solvent or in presence of high boiling solvent like toluene, xylene, DMSO. Amide coupling may be carried out in presence of trialkyl aluminium (Chem. Commun., 2008, 1100-1102).

**Halogenation Conditions:** Halogenation reaction may be carried out using reagents such as N-halosuccinimide, dihalogens and the like, in presence of radical generating reagents like peroxides such as benzoylperoxide. Solvents used for this reaction include, but are not limited to, carbon tetrachloride and ethers or mixtures thereof. The reaction may be carried out at a temperature ranging from -5 to 80 °C.

**Conditions for Nucleophilic Substitution:** Nucleophilic substitution reaction, may be carried out using any suitable organic or inorganic bases. Organic bases may be selected from a group consisting of mono, di or trialkyl amines particularly methylamine, ethylamine, dimethylamine, diethylamine or triethylamine. Inorganic bases may be selected from a group consisting of alkali and alkaline earth metal hydrides, hyroxides, carbonates and bicarbonates or mixtures thereof. Solvents used for this reaction may be selected from a group consisting of lower alcohols, acetone, acetonitrile, DMSO, DMF, dimethylacetamide, THF and toluene, or mixtures thereof. The reaction may be carried out at a temperature in the range of 0 to 150 °C.

**Conditions for Ester Hydrolysis:** Ester hydrolysis of carboxylic acids may be carried out using general saponification conditions employing inorganic bases such as alkali and alkaline earth metal hyroxides, carbonates and bicarbonates, for example lithium hydroxide,
sodium hydride, sodium carbonate, potassium carbonate, cesium carbonate and the like; in the presence of solvents such as water, methanol, ethanol, THF and diethyl ether or mixtures thereof. These reactions may be done at 0°C to refluxing temperature.

**Conditions for Esterification:** Ester formation, from the above mentioned carboxylic acids, may be carried out using general esterification conditions employing appropriate alcohol like methanol, ethanol and a suitable inorganic acid selected from HCl, H₂SO₄, or thionyl chloride, or base catalysed ester formation using alkyl halide and suitable base like sodium hydride, sodium hydroxide, sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate, cesium carbonate and the like in presence of solvents such as acetone, acetonitrile, DMF, DMSO, THF and diethyl ether or mixtures thereof.

**Conditions for Oxidation:** Oxidation of sulfanils to sulfonyls, may be carried out using appropriate oxidizing reagent such as H₂O₂, perbenzoic acid, mCPBA, Oxone, dioxirane and the like in the presence of a solvent such as DCM, DCE, DMF, DMSO, THF and diethyl ether or mixtures thereof. Reagents like OsO₄, KMnO₄, PCC can also be used for such oxidation process.

**Conditions for Reduction:** Reduction may be carried out using specific conditions known for transformation of acrylic carbonyl group to corresponding arylationy functionality. Such reductions may be done using known Wolf Kishner (KOH, NH₂-NH₂) or Clemmensen (Zn/HCl) reduction conditions.

**Sulfonamide Coupling Condition:** Sulfonamide may be prepared by reacting any appropriate amine with sulfonylhalide in the presence of base such as pyridine, triethylamine & diisopropylethylamine. The reaction may be carried out in suitable solvent like pyridine, dichloromethane or tetrahydrofuran.

**Oxidative Chlorination:** Thiols can be converted to sulfonyl chlorides under mild condition of oxidative chlorination. Here thiols are treated with combination of oxidant and chlorinating agent such as KNO₃-TMSCI, H₂O₂-SOCI₂, Oxone-SOCI₂ in appropriate solvent such as DCM, acetonitrile, DMF or combination of acetonitrile-AcOH. The reaction may be carried out at a temperature in the range of 5 to 100°C.

**Chlorosulfonation:** Aryl or heteroaryl sulfonyl chloride synthesis may be carried out by elecrophilic substitution reaction using reagent like chlorosulfonic acid, SO₂Cl₂ in appropriate solvent which are not limited to halogenated like DCM, DCE, CHCl₃, CCl₄, but also nonpolar solvents like Benzene, Tolune, Dioxane or mixture thereof. The reaction may be carried out at a temperature in the range of 0°C to 60°C.
Above mentioned conditions, for the respective functional group transformations, are only to illustrated the type of synthesis. More specific conditions for above transformations are well documented and referred in the literature (R. C. Larock in Comprehensive Organic Transformations, Wiley-VCH Publication; B. M. Trost and I. Fleming Ed. Comprehensive Organic Synthesis, Elsevier Publication).

Wherever desired or necessary, in any of the above mentioned processes, any of the compounds of formula (I) may be converted into a pharmaceutically acceptable salt or vice versa or converting one salt form into another pharmaceutically acceptable salt form.

According to an embodiment, the present disclosure relates to compounds of formula (I) their stereoisomers, tautomers, prodrugs, pharmaceutically acceptable salts, polymorphs, solvates and formulations thereof, which are glucokinase activators, and are beneficial for the prophylaxis, management, treatment, control of progression, or adjunct treatment of diseases and/or medical conditions where the activation of glucokinase would be beneficial, such as diabetes, dyslipidemia, metabolic syndrome, and/or diabetes-related complications including retinopathy, nephropathy, neuropathy, ischemic heart disease, arteriosclerosis, β-cell dysfunction, and as therapeutic and/or prophylactic agents for obesity.

According to yet another embodiment, the present disclosure relates to compounds of formula (I) their stereoisomers, tautomers, prodrugs, pharmaceutically acceptable salts, polymorphs, solvates and formulations thereof, which are liver selective Glucokinase activators, useful for the treatment of hyperglycemia, diabetes, obesity, dyslipidemia, metabolic syndrome and like, in mammals and have minimum hypoglycemic potential.

A further embodiment of the disclosure includes a method of treatment of glucokinase activator mediated disease by administering a therapeutically effective amount of a compound of formula (I) to a mammal in need of such treatment.

By "pharmaceutically acceptable salts" as used herein, it covers salts of compounds of formula (I) prepared from pharmaceutically acceptable non-toxic bases or acids including inorganic or organic bases and inorganic or organic acids. Inorganic bases salts include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N'-dibenzylethylene-diamine, diethyamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine,
N-ethyl-morpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, and the like. Salts in the solid form may exist in more than one crystal structure, and may also be in the form of hydrates. When the compound of the present disclosure is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids, such as acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, mandelic, methanesulfonic, mucic, nitrilic, pamoic, pantothentic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid, and the like. Particularly preferred are hydrochloric, maleic, phosphoric, citric, hydrobromic, sulfuric, fumaric, and tartaric acids.

By "therapeutically effective amount" in this disclosure, it means an amount of compound of formula (I), its polymorphs, stereoisomers, pharmaceutically acceptable salt, solvate or pro-drug thereof, that is sufficient for effective treatment of obesity and/or type II diabetes. The therapeutically effective amount or dosage of a compound according to this disclosure can vary within wide limits. The dosage will depend on individual requirements in each particular case including the specific compound(s) being administered, the manner of administration, the severity of condition being treated, as well as the patient being treated, which is readily determinable by a person skilled in the art.

In using a compound of formula (I), its polymorphs, stereoisomers, pharmaceutically acceptable salt, solvate or pro-drug thereof, for therapeutic or prophylactic purposes it will generally be administered so that a daily dose in the range, for example, about 0.01 mg to 100 mg per kg body weight is received, given if required in divided doses. In general lower doses will be administered when a parenteral route is employed. Thus, for example, for intravenous administration, a dose in the range, for example, about 0.01 mg to 30 mg per kg body weight will generally be used. Similarly, for administration by inhalation, a dose in the range, for example, about 0.01 mg to 30 mg per kg body weight will be used.

The disclosure also relates to compound of formula (I), or its polymorph, stereoisomer, prodrug, solvate or a pharmaceutically acceptable salt thereof, for treating a disease through Glucokinase activation.

The disclosure also relates to compounds of formula (I), or its polymorph, stereoisomer, prodrug, solvate or a pharmaceutically acceptable salt thereof, for treating a disease through Glucokinase modulation or regulation.
The disclosure also relates to compounds of formula (I), or its polymorph, stereoisomer, prodrug, solvate or a pharmaceutically acceptable salt thereof, for treating a disease through Glucokinase deinhibition.

The disclosure also relates to compounds of formula (I), or its polymorph, stereoisomer, prodrug, solvate or a pharmaceutically acceptable salt thereof, for prophylactic or therapeutic treatment of hyperglycemia or diabetes, particularly type II diabetes.

The disclosure also relates to compounds of formula (I), or its polymorph, stereoisomer, prodrug, solvate or a pharmaceutically acceptable salt thereof, for preventing diabetes, particularly type II diabetes, in a human demonstrating pre-diabetic hyperglycemia or impaired glucose tolerance.

The disclosure also relates to compounds of formula (I), or its polymorph, stereoisomer, prodrug, solvate or a pharmaceutically acceptable salt thereof, for combined treatment or preventing diabetes and obesity.

The disclosure also relates to compounds of formula (I), or its polymorph, stereoisomer, prodrug, solvate or a pharmaceutically acceptable salt thereof, for treating or preventing obesity.

The disclosure also relates to compounds of formula (I), or its polymorph, stereoisomer, prodrug, solvate or a pharmaceutically acceptable salt thereof, for enhancing the secretion of enteroinsulins, like GLP-1 and GIP, thereby managing diseases or disorders associated with modulation of secretions of enteroinsulins, such as hyperglycemia, insulin resistance, impaired glucose tolerance, obesity, gastric emptying, gastroparesis, satiety, leptin resistance, dyslipidemia, wound healing, diabetic complications, such as nephropathy, retinopathy, neuropathy and cataracts.

The disclosure also relates to the use of compounds of formula (I), or its polymorphs, stereoisomers, pharmaceutically acceptable salt, solvate or pro-drug thereof, in the prophylactic or therapeutic treatment of dyslipidemia.

The disclosure also relates to compound of formula (I), or its stereoisomers, tautomers, prodrugs, pharmaceutically acceptable salts, polymorphs, solvates and formulations thereof, for treating hyperglycemia, IGT, Syndrome X, type 2 diabetes, type 1 diabetes, dyslipidemia or hyperlipidemia, hypertension, for the treatment or prophylaxis of obesity, for lowering of food intake, for appetite regulation, for regulating feeding behaviour.

The disclosure also relates to identifying the compounds of formula (I), its polymorphs, stereoisomers, pharmaceutically acceptable salt, solvate or pro-drug thereof, which are beneficial for the prophylaxis, management, treatment, control of progression, or adjunct
treatment of diseases and/or medical conditions where the activation of glucokinase would be beneficial, such as diabetes (both Type-I and Type-II), obesity, dyslipidemia, metabolic syndrome X, and/or diabetes-related complications and as therapeutic and/or prophylactic agents for obesity, metabolic syndrome X includes Type-II diabetes, obesity, dyslipidemia, hypertension, and atherosclerosis and like.

The disclosure further relates to compounds of formula (I), its polymorphs, stereoisomers, pharmaceutically acceptable salt, solvate or pro-drug thereof, for use in the manufacture of medicament for the treatment of diabetes, obesity, metabolic syndrome X, insulin resistance, impaired glucose tolerance and dyslipidemia.

The disclosure also relates to the use of a compounds of formula (I), its polymorphs, stereoisomers, pharmaceutically acceptable salt, solvate or pro-drug thereof, in the manufacture of a medicament for the activation of Glucokinase.

The disclosure also relates to the use of a compounds of formula (I), its polymorphs, stereoisomers, pharmaceutically acceptable salt, solvate or pro-drug thereof, in the manufacture of a medicament for the prevention of diabetes, particularly type II diabetes, in a human demonstrating pre-diabetic hyperglycemia or impaired glucose tolerance.

The disclosure also relates to a method of prophylactic or therapeutic treatment of hyperglycemia or diabetes, particularly type II diabetes, comprising a step of administering an effective amount of a compound of formula (I), its polymorphs, stereoisomers, pharmaceutically acceptable salt, solvate or pro-drug thereof.

The disclosure also relates to a method for the prevention of diabetes, particularly type II diabetes, in a human demonstrating pre-diabetic hyperglycemia or impaired glucose tolerance comprising a step of administering an effective prophylactic amount of a compound of formula (I), its polymorphs, stereoisomers, pharmaceutically acceptable salt, solvate or pro-drug thereof.

The disclosure also relates to a method of combined treatment of diabetes and obesity by administering an effective amount of a compound of formula (I), its polymorph, stereoisomer, prodrug, solvate or a pharmaceutically acceptable salt thereof, to a mammal in need of such treatment.

The disclosure also relates to the use of a compound of formula (I), its polymorphs, stereoisomers, pharmaceutically acceptable salt, solvate or pro-drug thereof, for the prevention of diabetes, particularly type II diabetes, in a human demonstrating pre-diabetic hyperglycemia or impaired glucose tolerance.
The disclosure also relates to the use of a compound of formula (I), its polymorphs, stereoisomers, pharmaceutically acceptable salt, solvate or pro-drug thereof, for use as medicament, for the prophylactic or therapeutic treatment of hyperglycemia or diabetes, particularly type II diabetes.

The disclosure also relates to the use of a compound of formula (I), its polymorphs, stereoisomers, pharmaceutically acceptable salt, solvate or pro-drug thereof, in the manufacture of a medicament for the prophylactic or therapeutic treatment of hyperglycemia or diabetes, particularly type II diabetes.

The disclosure also relates to the use of a compound of formula (I), their stereoisomers, tautomers, prodrugs, pharmaceutically acceptable salts, polymorphs, and solvates, in the manufacture of a medicament for use in combined treatment or prevention of diabetes and obesity.

The disclosure also relates to the use of a compound of formula (I), their stereoisomers, tautomers, prodrugs, pharmaceutically acceptable salts, polymorphs, solvates and formulations thereof for prophylactic or therapeutic treatment of a disease selected from a group consisting of a disease needing Glucokinase activation, a disease needing Glucokinase deinhibition, hyperglycemia, IGT, Syndrome X, type 2 diabetes, type 1 diabetes, dyslipidemia, hyperlipidemia, hypertension, insulin resistance, impaired glucose tolerance, obesity, gastric emptying, gastroparesis, satiety, leptin resistance, dyslipidemia, wound healing, nephropathy, retinopathy, neuropathy and cataracts.

The disclosure also relates to the use of a compound of formula (I), their stereoisomers, tautomers, prodrugs, pharmaceutically acceptable salts, polymorphs, solvates and formulations thereof for lowering of food intake, for appetite regulation, for regulating feeding behaviour, for enhancing the secretion of enteroinsulins like GLP-1 and GIP.

The disclosure also relates to the use of a compound of formula (I), their stereoisomers, tautomers, prodrugs, pharmaceutically acceptable salts, polymorphs, solvates and formulations thereof for preventing diabetes, particularly type II diabetes, in a human demonstrating prediabetic hyperglycemia or impaired glucose tolerance, preventing obesity and preventing dyslipidemia.

The disclosure also relates to the use of a compound of formula (I), their stereoisomers, tautomers, prodrugs, pharmaceutically acceptable salts, polymorphs, solvates and formulations thereof for combined treatment or prevention of diabetes and obesity.
The disclosure also relates to pharmaceutical composition comprising, as an active ingredient, at least one compound of formula (I), or its stereoisomers, tautomers, prodrugs, pharmaceutically acceptable salts, polymorphs, and solvates thereof, together with one or more pharmaceutically acceptable carriers or excipients.

The compounds and compositions of the present disclosure may be optionally employed in combination with one or more, from current or future therapy, other anti-diabetic agents or anti-hyperglycemic agents, which include, for example, (a) insulin secretagogues such as sulfonylureas (e.g. Amaryl, glyburide, glimepiride, glipizide, etc.); (b) Insulinotropic sulfonyl urea receptor ligands such as meglitinides (e.g. nateglinide, repaglinide); (c) biguanides (e.g. metformin, phenformin, buformin, etc.); (d) glucagon antagonists (e.g. a peptide or non-peptide glucagon antagonist); (e) glucosidase inhibitors (e.g. acarbose, miglitol, etc.); (f) glucose sensitive insulinotropic agents (e.g. GLP-1, GLP-1 mimetics e.g. Exendin-4); (g) insulin sensitizers (e.g. troglitazone, rosiglitazone, pioglitazone, etc.); (h) Dipeptidyl peptidase-IV inhibitors (e.g. sitagliptin, vildagliptin); and the like. The said additional therapeutic agent is added in a dose range of about 0.01 mg to 100 mg per kg body weight.

The compounds and compositions of the present disclosure may also be optionally employed in combination with one or more, from current or future therapy, anti-obesity agents (e.g. sibutramine, orlistat, rimonabant etc.) and the like.

The compounds and compositions of the present disclosure may also be optionally employed in combination with one or more, from current or future therapy, dyslipidemic agents which include, for example: (a) fibrates (e.g. gemfibrozil, fenofibrate); (b) Niacin; (c) Statins (e.g. rosuvatatin, atorvastatin, simvastatin); (d) cholesterol absorption inhibitors (e.g. Ezetimibe); (e) bile acid sequestrants (e.g. cholestyramine) and the likes.

The compounds and compositions of the present disclosure may also be optionally employed in combination with one or more, from current or future therapy, antihypertensive agents such as: (a) diuretics (e.g hydrochlorothiazides, mannitol, indapamide, furosemide); (b) angiotensin converting enzyme (ACE) inhibitors (e.g. captopril, enalapril); (c) Angiotensin-II receptor type-I blockers (ARB) (e.g. losartan, irbesartan); (d) rennin inhibitors (e.g aliskerin); (e) -adrenergic receptor blockers (e.g. atenolol, metoprolol); (f) calcium channel blockers (e.g. amlodipine, nifedipine); (g) aldosterone receptor antagonist (e.g. spironolactone); (h) aldosterone synthase inhibitors (e.g. FAD286). The said additional therapeutic agent is added in a dose range of about 0.01 mg to 100 mg per kg body weight.
The compounds and compositions of the present disclosure and the other therapeutic agents such as described above may be administered simultaneously, sequentially or separately.

The pharmaceutical compositions of the present disclosure comprise a compound of formula (I), polymorphs, stereoisomers, pharmaceutically acceptable salt, solvate or pro-drug thereof, as an active ingredient, a pharmaceutically acceptable carrier and optionally other therapeutic active agent in any suitable ratios.

The disclosure also relates to pharmaceutical composition comprising, as an active ingredient, at least one compound of formula (I), or its stereoisomers, tautomers, prodrugs, pharmaceutically acceptable salts, polymorphs, and solvates thereof, wherein the pharmaceutically acceptable therapeutically active agent is selected from anti-diabetic agents, anti-hyperglycemic agents, anti-obesity agents, anti-hypertensive agents or anti-dyslipidemic agents.

The pharmaceutical compositions of the present disclosure comprising compounds of formula (I), polymorphs, stereoisomers, pharmaceutically acceptable salt, solvate or prodrugs thereof, may be manufactured in a manner that is known in the art, e.g. by means of conventional mixing, encapsulating, dissolving, granulating, emulsifying, entrapping, dragee making, or lyophilizing processes. These pharmaceutical preparations can be formulated with therapeutically inert, inorganic or organic carriers such as lactose, corn starch or derivatives thereof, talc, steric acid or its salts as carriers for tablets, coated tablets, drages and hard gelatin capsules. For soft gelatin capsules suitable carriers include vegetable oils, waxes and fats. Suitable carriers for the manufacture of solutions and syrups are water, polyols, saccharose, invert sugar and glucose. Suitable carriers for injection are water, alcohols, polyols, glycerine, vegetable oils, phospholipids and surfactants. Suitable carriers for suppositories are natural or hardened oils, waxes, fats and semiliquid polyols.

The pharmaceutical preparations can also contain preserving agents, solubilizing agents, stabilizing agents, wetting agents, emulsifying agents, sweetening agents, coloring agents, flavoring agents, salts for varying the osmotic pressure, buffers, coating agents or antioxidants. They can also contain other therapeutically valuable substances, including additional active ingredients other than those of formula (I), its polymorphs, stereoisomers, pharmaceutically acceptable salt, solvate or prodrugs thereof.

The pharmaceutical compositions containing the active ingredient of compound of formula (I), its polymorphs, stereoisomers, pharmaceutically acceptable salt, solvate or prodrugs thereof, maybe in a form suitable for oral use, for example, as tablets, troches, lozenges,
aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs; sterile injectable aqueous or oleaginous suspension; suppositories; topical use, for example creams, ointments, jellies, solutions or suspension etc including mouth washes and gargles. These compositions can be manufactured by any method known in the art with the active ingredient combined with non-toxic pharmaceutically acceptable excipients.

While the disclosure has been described and illustrated with reference to certain preferred embodiments thereof, those skilled in the art will appreciate that various changes, modifications and substitutions can be made therein without departing from the spirit and scope of the present disclosure. For example, the specific pharmacological responses observed may vary according to and depending on the particular active compound selected or whether there are present pharmaceutical carriers, as well as the type of formulation and mode of administration employed, and such expected variations or differences in the results are contemplated in accordance with the objects and practices of the present disclosure.

Abbreviations

The following abbreviations are employed in the examples and elsewhere herein:

DMF: Dimethyl formamide
DMSO: Dimethyl sulfoxide
DCM: Dichloromethane
dCE: Dichloroethane
THF: Tetrahydrofuran
TEA: Triethyl amine
mCPBA: meta chloro perbenzoic acid
BOP-C1: Bis(2-oxo-3-oxazolidinyl)phosphinic chloride
DABCO: 1,4-Diazabicyclo[2.2.2]octane
DBU: 1,8-Diazabicyclo[5.4.0]undec-7-ene
DMAP: \(\text{N}, \text{N}\)-dimethyl aminopyridine
DCC: \(\text{N}, \text{N}\)-Dicyclohexyl carbodiimide
EDCI: 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
HOBT: 1-Hydroxybenzotriazole
HOAT: 1-Hydroxy-7-azabenzotriazole
HBTU: 0-(benzotriazol-1-yl)-tetramethyluronium hexafluorophosphate
HATU: 0-(7-azabenzotriazol-1-yl)-tetramethyluronium hexafluorophosphate
TPP: triphenylphosphine
DEAD: diethyl azodicarboxylate
DIAD: diisopropyl azodicarboxylate
Examples

The disclosure is further illustrated by the following examples which in no way should be construed as being further limiting. One skilled in the art will readily appreciate that the specific methods and results described are merely illustrative. All stereoisomers of the compounds of the instant disclosure are contemplated, either in admixture or in pure or substantially pure form. The compounds of the present disclosure can have asymmetric centers at any of the carbon atoms, consequently, compounds of formula (I) can exist in enantiomeric, or diasteromeric forms, or in mixtures thereof. The processes for preparation can utilize racemates, enantiomers, or diastereomers as starting materials. When diastereomeric or enantiomeric products are obtained as mixtures, they can be separated by conventional methods for example, chromatographic separation or fractional crystallization or through diasteromeric salt formation. When intended, a desired enantiomer or diastereomer can also be obtained by following appropriate enantioselective or diastereoselective reactions.

Structures of the intermediates as well as the final compounds were confirmed by nuclear magnetic resonance spectra for proton (1H NMR) and LCMS.

Preparation 1: (4-Cyclopropanesulfanyl-phenyl)-[(tetrahydro-furan-3-yloxy)]-acetic acid

Step I: (4-Cyclopropylsulfanyl-phenyl)-oxo-acetic acid ethyl ester:

\[
\text{AICl}_3 (7.98 \text{ g, } 48.42 \text{ mmole}) \text{ was suspended in DCM (50 mL) and cooled to 0 } ^\circ\text{C under argon atmosphere. To this suspension was added chlorooxoy ethylacetate (4.5 mL, } 39.98 \text{ mmol) at 0 } ^\circ\text{C and stirred for 45 min. followed by addition of a solution of cyclopropylsulfanyl-benzene (5 g, } 33.28 \text{ mmol) in DCM (10 mL) and stirred at 25 } ^\circ\text{C for 2 hr. Reaction mixture} \\
\text{was slowly poured over crushed ice, organic layer was separated and aqueous layer was extracted with DCM (3 X 50 mL), combined organic layer was washed with brine solution, dried over}
\]
anhydrous sodium sulfate, filtered and concentrated under reduced pressure to obtain (4-cyclopropylsulfonyl-phenyl)-oxo-acetic acid ethyl ester (3.1 g) as an oily product.

1H NMR (400 MHz, CDCl3): δ 0.72-0.73 (m, 2H), 1.15-1.17 (m, 2H), 1.40 (t, J = 6.6 Hz, 3H), 2.18-2.21 (m, 1H), 4.41 (q, J = 6.8 Hz, 2H), 7.43 (d, J = 8.0 Hz, 2H), 7.90 (d, J = 8.0 Hz, 2H); MS (EI) m/z: 250.9 (M+).

Step II: (4-Cyclopropanesulfonyl-phenyl) oxo acetic acid ethyl ester:
(4-Cyclopropylsulfonyl-phenyl)-oxo-acetic acid ethyl ester (3.1 g, 12.53 mmole) in DCM (50 mL) was cooled to 0-5 °C followed by addition of mCPBA (9.8 g, 31.33 mmol) in portion wise at 0 °C. After stirring at 25 °C for 4 hr, the reaction mixture was filtered; filtrate was washed with saturated aq. Na2S2O3 and satd. aq. sodium bicarbonate solution followed by brine solution, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give (4-cyclopropanesulfonyl-phenyl) oxo acetic acid ethyl ester (3 g).

1H NMR (400 MHz, CDCl3): δ 1.05-1.10 (m, 2H), 1.36-1.39 (m, 2H), 1.40 (t, J = 6.8 Hz, 3H), 2.45-2.50 (m, 1H), 4.42 (q, J = 7.2 Hz, 2H), 8.01 (d, J = 8.4 Hz, 2H), 8.20 (d, J = 8.4 Hz, 2H); MS (EI) m/z: 297.1 (M+NH4).

Step III: p-Toluene sulfonyl hydrazone (4-cyclopropyl sulfonyl) phenyl acetic acid ethyl ester:
A mixture of (4-cyclopropanesulfonyl-phenyl) oxo acetic acid ethyl ester (0.5 g, 1.77 mmole) and p-toluene sulfonyl hydrazide (0.48 g, 2.3 mmol) in toluene (15 mL) was refluxed for 16 hr using a Dean-Stark apparatus. Reaction mixture was concentrated to give the crude product which was purified by column chromatography over silica gel using 20-25% ethyl acetate in hexane as eluent to provide p-toluene sulfonyl hydrazone (4-cyclopropyl sulfonyl) phenyl acetic acid ethyl ester (0.5 g).

MS (EI) m/z: 451.0 (M+).

Step IV: (4-Cyclopropanesulfonfonyl-phenyl) diazo acetic acid ethyl ester:
To a solution of p-toluene sulfonyl hydrazone (4-cyclopropyl sulfonyl) phenyl acetic acid ethyl ester (0.5 g, 1.23 mmol) in dry DCM (6 mL), was added triethylamine (0.17 mL, 1.35 mmol) and stirred at 25 °C for 1 hr. Reaction mixture was concentrated to provide (4-cyclopropanesulfonfonyl-phenyl) diazo acetic acid ethyl ester (0.5 g) which was used in next reaction without any purification.

MS (EI) m/z: 295.1 (M+).

Step V: Cyclopentyloxy-(4-cyclopropanesulfonfonyl-phenyl)-acetic acid ethyl ester:
(4-Cyclopropanesulfonfonyl-phenyl) diazo acetic acid ethyl ester (1 g, 3.37 mmol) was dissolved in DCM (16 mL) under argon atmosphere. To this solution, cyclopentanol (0.77 mL, 8.44 mmol) was added followed by rhodium(II)acetate dimer (0.062 g, 0.14 mmol). Mixture was stirred at
25 °C for 12 hr. Reaction mixture was diluted with DCM (25 mL), organic layer was washed with water followed by brine solution, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a crude product which was purified by column chromatography using 25-35% ethyl acetate in hexane as eluent to provide cyclohexyloxy-(4-cyclopropanesulfonyl-phenyl)-acetic acid ethyl ester (0.45 g).

\[ \text{Step VI: Cyclohexyloxy-(4-cyclopropanesulfonyl-phenyl)-acetic acid:} \]

To cyclohexyloxy-(4-cyclopropanesulfonyl-phenyl)-acetic acid ethyl ester (0.35 g, 0.99 mmol) was added a solution of lithium hydroxide (0.208 g, 4.97 mmol) in water (4 mL) followed by THF (2 mL) and methanol (1 drop) and stirred for 12 hours at 25 °C. Organic solvents were evaporated from the reaction mixture and aqueous layer was acidified 1N HCl, extracted with ethyl acetate (3 X 10 mL), organic layer was washed with brine solution, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to provide cyclohexyloxy-(4-cyclopropanesulfonyl-phenyl)-acetic acid (0.210 g).

\[ \text{Step 1: Cyclohexyloxy-(4-cyclopropanesulfonyl-phenyl)-acetic acid ethyl ester:} \]

(4-Cyclopropanesulfonyl-phenyl) diazo acetic acid ethyl ester, obtained similarly as described in preparation 1, (1 g, 3.37 mmol) was dissolved in DCM (16 mL) under argon atmosphere. To this solution, cyclohexanol (0.87 mL, 8.43 mmol) was added followed by rhodium(II)acetate dimer (0.062 g, 0.14 mmol). Mixture was stirred at 25 °C for 3 hr. Reaction mixture was diluted with DCM (20 mL), organic layer was washed with water followed by brine solution, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a crude product which was purified by column chromatography using 20-30% ethyl acetate in hexane as eluent to provide cyclohexyloxy-(4-cyclopropanesulfonyl-phenyl)-acetic acid ethyl ester (0.45 g).
$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 1.02-1.06 (m, 2H), 1.19-1.30 (m, 7H), 1.33-1.39 (m, 2H), 1.53-1.59 (m, 2H), 1.73-1.75 (m, 2H), 1.88-1.90 (m, 2H), 2.40-2.50 (m, 1H), 3.35-3.45 (m, 1H), 4.17-4.20 (m, 2H), 5.10 (s, 1H), 7.68 (d, $J = 8.4$ Hz, 2H), 7.88 (d, $J = 8.4$ Hz, 2H); MS (EI) $m/z$: 384.0 (M+).

**Step II: Cyclohexyloxy-(4-cyclopropanesulfonyl-phenyl)-acetic acid:**

To cyclohexyloxy-(4-cyclopropanesulfonyl-phenyl)-acetic acid ethyl ester (0.45 g, 1.22 mmol) was added a solution of lithium hydroxide (0.257 g, 6.13 mmol) in water (4 mL) followed by THF (2 mL) and methanol (ldrop) and stirred for 12 hours at 25 °C. Organic solvents were evaporated from the reaction mixture and aqueous layer was acidified 1N HCl, extracted with ethyl acetate (3 X 20 mL), organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to provide cyclohexyloxy-(4-cyclopropanesulfonyl-phenyl)-acetic acid (0.35 g)

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 1.02-1.08 (m, 2H), 1.17-1.30 (m, 4H), 1.33-1.37 (m, 2H), 1.53-1.55 (m, 2H), 1.71-2.05 (m, 4H), 2.42-2.47 (m, 1H), 3.43-3.48 (m, 1H), 5.12 (s, 1H), 7.67 (d, $J = 8.4$ Hz, 2H), 7.90 (d, $J = 8.4$ Hz, 2H).

**Preparations 3 to 8 were prepared in analogous manner of preparation 2.**

<table>
<thead>
<tr>
<th>Preparation No.</th>
<th>IUPAC Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>2-(4-cyclopropylsulfonylphenyl)-2-(4-oxocyclohexoxy)acetic acid</td>
</tr>
<tr>
<td>4</td>
<td>2-(4-cyclopropylsulfonylphenyl)-2-oxindan-1-ylxyoxy-acetic acid</td>
</tr>
<tr>
<td>5</td>
<td>2-(4-cyclopropylsulfonylphenyl)-2-oxindan-2-yloxy-acetic acid</td>
</tr>
<tr>
<td>6</td>
<td>2-(4-cyclopropylsulfonylphenyl)-2-(9-methylspiro[5.5]undecan-9-yloxy)-acetic acid</td>
</tr>
<tr>
<td>7</td>
<td>2-(1-adamantylmethoxy)-2-(4-cyclopropylsulfonylphenyl)acetic acid</td>
</tr>
<tr>
<td>8</td>
<td>2-(2-adamantyloxy)-2-(4-cyclopropylsulfonylphenyl)acetic acid</td>
</tr>
</tbody>
</table>

**Preparation 9: Cyclohexyloxy-[4-(tetrahydro-pyran-4-sulfonyl)-phenyl]-acetic acid**

**Step-I:** (4-Mercapto-phenyl)-acetic acid methyl ester:

4-Mercato-phenyl acetic acid (15 g, 89.16 mmol) was dissolved in methanol (450 mL). To this solution, sulfuric acid (8.7 g, 89.16 mmol) was added and mixture was refluxed for 3 hr. Solvent was removed under reduced pressure. The resulting residue was dissolved in ethyl acetate (300
mL), and was washed with water, sodium bicarbonate solution and brine (150 mL each), dried over anhydrous sodium sulfate, and filtered. The organic solvent was removed under reduced pressure to give crude product which was purified by column chromatography using 10-15% ethyl acetate in hexane as eluent to provide (4-mercapto-phenyl)-acetic acid methyl ester (12.6 g).

*HNMR (CDCl₃, 400 MHz): δ 3.43 (s, 1H), 3.57 (s, 2H), 3.68 (s, 3H), 7.15 (d, J = 7.6 Hz, 2H), 7.23 (d, J = 8.0 Hz, 2H); MS (EI) m/z: 183.1 (M+1), 200.1 (M+18).

Step-II: [4-(Tetrahydro-pyran-4-sulfonyl)-phenyl]-acetic acid methyl ester:

(4-Mercapto-phenyl)-acetic acid methyl ester (3.8 g, 20.85 mmol) was dissolved in DMF (40 mL) at 0°C. Triethylamine (3.16 g, 31.27 mmol) was added and stirred for 15 minutes followed by addition of 4-iodo-tetrahydropyan (6.63 g, 31.27 mmol). The reaction mixture was stirred overnight at room temperature. Solvent was removed under reduced pressure, the resulting residue was taken into water and extracted with ethyl acetate (2 x 100 mL) washed with water and brine (100 mL each) dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to obtain a crude product which was purified by column chromatography over silica gel using 15% ethyl acetate in hexanes as eluent to provide [4-(Tetrahydro-pyran-4-sulfonyl)-phenyl]-acetic acid methyl ester (2.4 g).

*HNMR (CDCl₃, 400 MHz): δ 1.62-1.72 (m, 2H), 1.85-1.92 (m, 2H), 3.21-3.29 (m, 1H), 3.38-3.46 (m, 2H) 3.60 (s, 2H), 3.70 (s, 3 H), 3.94-4.00 (m, 2 H), 7.22 (d, J = 7.6 Hz, 2H), 7.38 (d, J = 8.0 Hz, 2H); MS (EI) m/z: 267.20 (M+1).

Step-III: [4-(Tetrahydro-pyran-4-sulfonyl)-phenyl]-acetic acid methyl ester:

[4-(Tetrahydro-pyran-4-sulfonyl)-phenyl]-acetic acid methyl ester (2.4 g, 9.02 mmol) was taken in dichloromethane (100 mL) at 0°C. mCPBA (9.33 g, 54.12 mmol) was added portion wise and stirred for 5 hrs at room temperature. Reaction mixture was diluted with dichloromethane (115 mL), solid was filtered, filtrate was washed with saturated solution of sodium thiosulphate (170 mL), saturated solution of sodium bicarbonate, water, brine (115 mL each) and dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to obtain crude product. Crude compound was purified by column chromatography over silica gel using 35% ethyl acetate in hexane as eluent to provide pure [4-(tetrahydro-pyran-4-sulfonyl)-phenyl]-acetic acid methyl ester (1.32 g).

*HNMR (CDCl₃, 400 MHz): δ 1.73-1.84 (m, 2H), 1.88-1.94 (m, 2H), 3.09-3.18 (m, 1H), 3.29-3.36 (m, 2H), 3.73 (s, 5H), 4.02 - 4.08 (m, 2H),), 7.50 (d, J = 8.4 Hz, 2H), 7.83 (d, J = 8.4 Hz, 2H); MS (EI) m/z: 299.10 (M+1), 316.2 (M+18).

Step IV: Diazo-[4-(Tetrahydro-pyran-4-sulfonyl)-phenyl]-acetic acid methyl ester:
[4-(Tetrahydro-pyran-4-sulfonyl)-phenyl]-acetic acid methyl ester (1.2g, 4.02 mmol) was dissolved in dry acetonitrile (10 mL) under argon atmosphere. To the above solution, para toluene sulfonyl azide (0.79g, 4.02 mmol) was added, followed by solution of DBU (0.90 mL, 6.03 mmol) in anhydrous acetonitrile (7mL) dropwise manner, and stirred for 30 min. Reaction mixture was poured in ice cold water (100mL), solid precipitated out, filtered and dried under vacum to afford Diazo-[4-(Tetrahydro-pyran-4-sulfonyl)-phenyl]-acetic acid methyl ester (1.05 g).

1H NMR (400 MHz, CDC13): δ 1.71-1.83 (m, 2H), 1.87-1.92 (m, 2H), 3.08-3.16 (m, 1H), 3.28-3.34 (m, 2H), 3.90 (s, 3H), 4.01-4.07 (m, 2H) 7.69 (d, J = 8.8 Hz, 2H), 7.84 (d, J = 8.8 Hz, 2H); MS (EI) m/z: 325.1 (M +1).

Step V: Cyclohexyloxy-[4-(tetrahydro-pyran-4-sulfonyl)-phenyl]-acetic acid methyl ester
Diazo-[4-(Tetrahydro-pyran-4-sulfonyl)-phenyl]-acetic acid methyl ester (0.6 g, 1.85 mmol) was dissolved in DCM (10 mL) under argon atmosphere. To this solution, cyclohexanol (0.23 mL, 2.22 mmol) was added followed by rhodium (II) acetate dimer (16 mg, 0.037 mmol). Mixture was stirred at 25 °C for 30 min. Reaction mixture was diluted with DCM (15 mL), organic layer was washed with water followed by brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a crude product. Crude product was purified by column chromatography over silica gel using 35 % ethyl acetate hexane as eluent to provide pure Cyclohexyloxy-[4-(tetrahydro-pyran-4-sulfonyl)-phenyl]-acetic acid methyl ester (0.55 g).

1H NMR (400 MHz, CDC13): δ 1.19-1.32 (m, 4H), 1.34-1.66 (m, 3H), 1.72-2.01 (m, 7H), 3.09-3.18 (m, 1H), 3.29-3.42 (m, 3H), 3.74 (s, 3H), 4.03-4.07 (m, 2H), 5.14 (s, 1H), 7.70 (d, J = 8.4 Hz, 2H), 7.85 (d, J = 8.4 Hz, 2H); MS (EI) m/z: 414.3 (M + 18).

Step VI: Cyclohexyloxy-[4-(tetrahydro-pyran-4-sulfonyl)-phenyl]-acetic acid:
To Cyclohexyloxy-[4-(tetrahydro-pyran-4-sulfonyl)-phenyl]-acetic acid methyl ester (0.5 g, 1.26 mmol) was added a solution of lithium hydroxide (0.264 g, 6.31 mmol) in water (5 mL) followed by THF (4 mL) and methanol (0.2 mL) and stirred for 2 hours at 25 °C. Organic solvents were evaporated from the reaction mixture and aqueous layer was acidified by using 1N HCl, extracted with ethyl acetate (3 X 50 mL), organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to provide Cyclopentyloxy-[4-(pyrrolidine-1-sulfonyl)-phenyl]-acetic acid (0.42 g).

1H NMR (400 MHz, CDC13): δ 1.19-1.30 (m, 4H), 1.34-1.58 (m, 3H), 1.70-2.01 (m, 7H), 3.09-3.18 (m, 1H), 3.29-3.48 (m, 3H), 4.03-4.08 (m, 2H), 5.14 (s, 1H), 7.71 (d, J = 8.0 Hz, 2H), 7.87 (d, J = 8.4 Hz, 2H); MS (EI) m/z: 383.2 (M + 1), 400.3 (M + 18)

Preparation 10: Cyclopentyloxy-[4-(tetrahydro-pyran-4-sulfonyl)-phenyl]-acetic acid:
Prepared in analogous manner of preparation 9.
Preparation 11: Cyclopentyl-oxy-[4-(pyrrolidine-1-sulfonyl)-phenyl]-acetic acid

Step I: (4-Chlorosulfonyl-phenyl)-acetic acid methyl ester:
(4-Mercapto-phenyl)-acetic acid methyl ester (obtained similarly as described in preparation 3, step I) (1.86 g, 10.2 mmol) was taken in a seal tube. To it DCM (30 mL) was added followed by KN0₃ (2.42 g, 22.4 mmol) and TMSCl (2.79 mL, 22.4 mmole). Mixture was heated at 50 °C for 24 hr, cooled to room temperature and filtered to remove solids, residue was washed with DCM (2 X 50 mL), combined filtrate was washed with water followed by brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to provide (4-chlorosulfonyl-phenyl)-acetic acid methyl ester (1.6 g).

\[ ^1H \text{NMR (400 MHz, CDCl}_3\text{):} \delta 3.70 (s, 3H), 3.75 (s, 2H), 7.53 (d, J = 8.8 Hz, 2H), 7.98 (d, J = 8.8 Hz, 2H). \]

Step II: [4-(Pyrrolidine-1-sulfonyl)-phenyl]-acetic acid methyl ester:
(4-Chlorosulfonyl-phenyl)-acetic acid methyl ester (1.4 g, 5.62 mmol) was taken in dry DCM (50 mL) under argon atmosphere and cooled to 0-5 °C, pyrrolidine (0.50 mL, 6.19 mmol) followed by triethylamine (0.81 mL, 6.19 mmol) was added dropwise to the mixture. Reaction mixture was then brought to room temperature and stirred for additional 2 hr. Reaction mixture was diluted with DCM (50 mL) and washed with water followed by brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure to give the crude product, which was purified by column chromatography using 20-30% ethyl acetate in hexane as eluent to give [4-(Pyrrolidine-1-sulfonyl)-phenyl]-acetic acid methyl ester (1.10 g).

\[ ^1H \text{NMR (400 MHz, CDCl}_3\text{):} \delta 1.58-1.77 (m, 4H), 3.22-3.26 (m, 4H), 3.71 (s, 2H), 3.73 (s, 3H), 7.44 (d, J = 8.4 Hz, 2H), 7.79 (d, J = 8.4 Hz, 2H); MS (EI) m/z: 284.1 (M + 1). \]

Step III: Diazo-[4-(pyrrolidine-1-sulfonyl)-phenyl]-acetic acid methyl ester:
[4-(Pyrrolidine-1-sulfonyl)-phenyl]-acetic acid methyl ester (1.4g, 4.93 mmol) was dissolved in dry acetonitrile (25 mL) under argon atmosphere. To the above solution para toluene sulfonyl azide (1.07g, 5.43 mmol) was added, followed by DBU (1.10 mL, 7.40 mmol) in dropwise manner, and stirred for 30 min. Reaction mixture was poured in ice cold water (100 mL), formed precipitate was filtered and dried under vaccum to afford Diazo-[4-(pyrrolidine-1-sulfonyl)-phenyl]-acetic acid methyl ester (1.10 g).
\[ ^1H \text{ NMR} (400 MHz, CDCl}_3): \delta 1.58-1.77 (m, 4H), 3.22-3.26 (m, 4H), 3.90 (s, 3H), 7.65 (d, J = 8.4 Hz, 2H), 7.82 (d, J = 8.4 Hz, 2H); MS (El) m/z: 310.1 (M + 1). \]

**Step IV: Cyclopentyloxy-[4-(pyrrolidine-1-sulfonyl)-phenyl]-acetic acid methyl ester:**

Diazo-[4-(pyrrolidine-1-sulfonyl)-phenyl]-acetic acid methyl ester (1.12 g, 3.62 mmol) was dissolved in DCM (18 mL) under argon atmosphere. To this solution, cyclopentanol (0.4 mL, 4.34 mmol) was added followed by rhodium (II) acetate dimer (0.033 g, 0.021 mmol). Mixture was stirred at 25 °C for 30 min. Reaction mixture was diluted with DCM (20 mL), organic layer was washed with water followed by brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a crude cyclopentyloxy-[4-(pyrrolidine-1-sulfonyl)-phenyl]-acetic acid methyl ester (1.2 g).

MS (El) m/z: 368.3 (M + 1).

**Step V: Cyclopentyloxy-[4-(pyrrolidine-1-sulfonyl)-phenyl]-acetic acid:**

To Cyclopentyloxy-[4-(pyrrolidine-1-sulfonyl)-phenyl]-acetic acid methyl ester (1.2 g, 3.26 mmol) was added a solution of lithium hydroxide (0.685 g, 16.32 mmol) in water (10 mL) followed by THF (8 mL) and methanol (0.2 mL) and stirred for 2 hours at 25 °C. Organic solvents were evaporated from the reaction mixture and aqueous layer was acidified by using 1N HCl, extracted with ethyl acetate (3 x 50 mL), organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to provide cyclopentyloxy-[4-(pyrrolidine-1-sulfonyl)-phenyl]-acetic acid (0.6 g).

\[ ^1H \text{ NMR} (400 MHz, DMSO-d}_6): \delta 1.57-1.59 (m, 2H), 1.72-1.79 (m, 10H), 3.23-3.26 (m, 4H), 4.08 (m, 1H), 5.01 (s, 1H), 7.62 (d, J = 8.0 Hz, 2H), 7.83 (d, J = 8.0 Hz, 2H); MS (El) m/z: 354.2 (M + 1). \]

**Intermediates-12a-12d** were either obtained from commercial source or prepared as per literature method.

**Preparation 13: 5-Morpholin-4-yl-thiazol-2-ylamine:**

![Chemical Structure](image-url)
To a mixture of 2-amino-5-bromothiazole monohydrobromide (2 g, 7.69 mmol) and powdered potassium carbonate (2.1 g, 15.38 mmol) in DMF (20 mL) was added morpholine (1.34 mL, 15.38 mmol) under argon atmosphere and heated at 60 °C for 3 hr. Reaction mixture was cooled to rt and poured over ice cold water (100 mL), extracted with ethylacetate (3 X 100 mL), washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. To the residue, diisopropyl ether (50 mL) was added, after stirring for 30 minutes product precipitated out, which was filtered and dried under vacuum to provide 5-morpholin-4-yl-thiazol-2-ylamine (0.95 g).

1H NMR (400 MHz, DMSO-d6): δ 7.05 (s, 1H), 7.08 (s, 1H), 7.17 (s, 1H), 7.62 (br.s, 2H), 8.15 (d, J = 2 Hz, 1H); MS (EI) m/z: 167 (M + 1).

Preparation 14: 5-Pyrazol-1-yl-thiazol-2-ylamine:

Preparation 14 was prepared in analogous manner of preparation 13.

1H NMR (400 MHz, DMSO-4): δ 7.05 (s, 1H), 7.08 (s, 1H), 7.17 (s, 1H), 7.62 (br.s, 2H), 8.15 (d, J = 2 Hz, 1H); MS (EI) m/z: 167 (M + 1).

Preparation 15: 5-Ethoxy-thiazolo[5,4-b]pyridin-2-ylamine

Step-I: 2-Amino-thiazolo[5,4-b]pyridin-5-ol
Synthesized as described in WO 2007/007886

Step-II: 5-Ethoxy-thiazolo[5,4-b]pyridin-2-ylamine
To a solution of 2-amino-thiazolo[5,4-b]pyridin-5-ol (4.7 g, 28.1 mmol) in Dimethylformamide (50 mL) was added cesium fluoride (12.8 g, 84.4 mmol) under argon atmosphere. Ethyl iodide (2.7 mL, 33.7 mmol) was added in drop wise manner at room temperature and stirred overnight. Completion of reaction was confirmed by TLC, reaction mixture was diluted with water (100 mL) and extracted with ethyl acetate (3 X 100 mL). Combined organic extracts were washed with water, brine (100 mL each) and dried over Na2SO4, filtered and concentrated under vacuum to afford ethoxy-thiazolo[5,4-b]pyridin-2-ylamine (2.1 g).

1H NMR (400 MHz, DMSO-d6): δ 1.30 (t, J = 7.2 Hz, 3H), 4.23 (q, J = 7.2, Hz, 2H), 6.65 (d, J = 8.8 Hz, 1H), 7.42 (bs, 2H), 7.59 (d, 7 = 8.8 Hz, 1H); MS (EI) m/z: 195.90 (M + 1).

Preparation 16: Methyl 5-(2-aminothiazol-5-yl)oxy-2-methyl-benzoate:
To a solution of 5-Bromothiazole-2-amine (3.23 g, 18 mmol) in acetone (30 mL) was added methyl 5-hydroxy-2-methyl-benzoate (2.5 g, 15 mmol) and cesium carbonate (9.81 g, 30.1 mmol) under argon atmosphere and refluxed for 5 hrs. The reaction mixture was cooled to room temperature and filtered; the filtrate was concentrated under reduced pressure. The residue was partitioned in between ethyl acetate and water. The layers were separated, the organic layer was washed with cold 2 N NaOH (5 mL), brine and dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to provide methyl 5-(2-aminothiazol-5-yl)oxy-2-methyl-benzoate (0.78 g).

\[ \text{HNMR (400 MHz, CDCl}_3\text{): } \delta 2.54 (s, 3H), 3.88 (s, 3H), 5.09 (bs, 2H), 6.75 (s, 1H), 7.13 (dd, J = 2.7 Hz, 7 = 8.3 Hz 1H), 7.19 (d, J = 8.3 Hz, 1H), 7.60 (d, J = 2.7 Hz, 1H); MS (EI) m/z: 265.1 (M+l). \]

Preparations 17 was prepared in analogous manner of preparation 16.

Preparation No. 17

IUPAC Name
4-(2-aminothiazol-5-yl)oxy-2-methyl-benzenecarboperoxoic acid

Preparation 18: tert-butyl 6-aminopyridine-3-carboxylate:

A reaction flask maintained under nitrogen atmosphere was charged with 6-Amino nicotinic acid (5 g, 3.6 mmol) and thionyl chloride (10 mL). The reaction mixture was refluxed for 12 hrs. Excess thionyl chloride was removed under reduced pressure. The obtained residue was redissolved in DCM (100 mL) under nitrogen atmosphere. To this mixture was added the solution of tri-ethylamine (30 mL) in tert-butanol (50 mL) very slowly foiled by DMAP (0.5 g) The reaction mixture was refluxed overnight and brought to room temperature. The solvent was removed under reduced pressure and diluted with DCM (100 mL). The organic layer was washed with brine, dried over sodium sulfate and concentrated under reduced pressure to obtain crude product. Purification of crude product was done using silica gel column chromatography using 50% ethyl acetate in hexane to obtain 1.5 g of tert-butyl 6-aminopyridine-3-carboxylate.

\[ \text{HNMR (400 MHz, DMSO- } d_6\text{): } \delta 1.50 (s, 9H), 6.42 (d, J = 8.8 Hz, 1H), 6.75 (br. s, 2H), 7.77 (dd, 7 = 2.4, 8.8 Hz, 1H), 8.44 (d, J = 2.4 Hz, 1H); MS (EI) m/z: 195.1 (M+l). \]
Example Al: 4-{2-[2-Cyclopentyloxy-2-(4-cyclopropanesulfonyl-phenyl)-acetylamino]-thiazol-5-yloxy}-benzoic acid methyl ester:

![Chemical Structure](image)

To a mixture of cyclopentyloxy-(4-cyclopropanesulfonyl-phenyl)-acetic acid (Preparation 1) (0.1 g, 0.30 mmol), 4-(2-Amino-thiazol-5-yloxy)-benzoic acid methyl ester (0.085 g, 0.33 mmol), HOBt (0.045 g, 0.33 mmol), and EDCI (0.063 g, 0.33 mmol) in DCM (5 mL), was added N-methyl morpholine (0.033 g, 0.30 mmol). The resulting mixture was stirred at room temperature overnight followed by dilution with methylene chloride (20 mL). The reaction mixture was poured into water; organic layer was washed with water, brine, dried over sodium sulfate, and the organic solvent evaporated to get a residue which was purified by preparative TLC to provide the title compound (0.145 g).

$^1$H NMR (400 MHz, CDC13): $\delta$ 1.03-1.05 (m, 2H), 1.34-1.38 (m, 2H), 1.58-1.65 (m, 2H), 1.76-1.81 (m, 6H), 2.42-2.45 (m, 1H), 3.89 (s, 3H), 4.05-4.15 (m, 1H), 5.08 (s, 1H), 7.07 (d, $J = 8.8$ Hz, 2H), 7.15 (s, 1H), 7.68 (d, $J = 8.4$ Hz, 2H), 7.92 (d, $J = 8.4$ Hz, 2H), 7.99 (d, $J = 8.8$ Hz, 2H), 9.72 (s, 1H); MS (EI) m/z: 556.9 (M + 1).

Example A2: 2-Cyclohexyloxy-2-(4-cyclopropanesulfonyl-phenyl)-N-thiazolo [5,4-b]pyridin-2-yl-acetamide:

![Chemical Structure](image)

The compound of example A2 was obtained by similar method described in example A1 using Cyclohexyloxy-(4-cyclopropanesulfonyl-phenyl)-acetic acid (Preparation 2) (0.050 g, 0.14 mmol), thiazolo[5,4-b]pyridin-2-ylamine (0.024 g, 0.16 mmol), HOBt (0.024 g, 0.17 mmol), and EDCI (0.033 g, 0.17 mmol), N-methyl morpholine (0.037 g, 0.36 mmol) in DCM (3 mL) and DMF (2 mL) to provide the title compound (0.018 g).

$^1$H NMR (400 MHz, DMSO- $d_6$): $\delta$ 1.02-1.23 (m, 8H), 1.34-1.47 (m, 2H), 1.62-2.0 (m, 4H), 2.82-2.87 (m, 7H), 3.44-3.48 (m, 1H), 5.52 (s, 1H), 7.49-7.52 (m, 1H), 7.80 (d, $J = 8.4$ Hz, 2H), 7.94 (d, $J = 8.4$ Hz, 2H), 8.14 (d, $J = 8.0$ Hz, 1H), 8.47-8.49 (m, 1H), 9.21 (br. s, 1H); MS (EI) m/z: 472.0 (M + 1).
Example A3: 2-(cyclohexoxy)-N-(5-ethoxythiazolo[5,4-b]pyridin-2-yl)-2-(4-tetrahydropyran-4-ylsulfonylphenyl)acetamide:

The compound of example A3 was obtained by similar method described in example A1 using cyclohexyloxy-[4-(tetrahydro-pyran-4-sulfonyl)-phenyl]-acetic acid (preparation 9) (0.2 g, 0.523 mmol), 5-ethoxy-thiazolo[5,4-b]pyridin-2-ylamine (0.153 g, 0.785 mmol), HOBt (0.10 g, 0.785 mmol), and EDCI (0.15 g, 0.785 mmol), N-methyl morpholine (0.17 mL, 1.57 mmol) in DCM (10 mL) to provide the title compound (0.178 g).

1H NMR (400 MHz, CDCl3): δ 1.22-1.30 (m, 4H), 1.39-1.50 (m, 5H), 1.75-2.09 (m, 8H), 3.09-3.18 (m, 1H), 3.26-3.36 (m, 2H), 3.44-3.52 (m, 1H), 4.02-4.07 (m, 2H), 4.41 (q, J = 7.2 Hz, 2H), 5.23 (s, 1H), 6.81 (d, J = 8.8 Hz, 1H), 7.75 (d, J = 8.4 Hz, 2H), 7.88-7.92 (m, 3H), 9.91 (s, 1H).

MS (EI) m/z: 560.2 (M + 1).

Example A4: 2-Cyclopentyloxy-N-(5-fluoro-thiazol-2-yl)-2-[4-(pyrrolidine-1-sulfonyl)-phenyl]-acetamide:

The compound of example A4 was obtained by similar method described in example A1 using cyclopentyloxy-[4-(pyrrolidine-1-sulfonyl)-phenyl]-acetic acid (preparation 10) (0.1 g, 0.28 mmol), 5-Fluoro-thiazol-2-ylamine hydrochloride (0.053 g, 0.34 mmol), HOBt (0.046 g, 0.34 mmol), and EDCI (0.065 mg, 0.34 mmol), N-methyl morpholine (0.1 mL, 0.71 mmol) in DCM (5 mL) to provide the title compound (0.78 g).

1H NMR (400 MHz, CDCl3): δ 1.59-1.62 (m, 4H), 1.74-1.80 (m, 5H), 2.22-2.32 (m, 2H), 3.26-3.36 (m, 2H), 3.44-3.52 (m, 1H), 4.02-4.07 (m, 2H), 4.41 (q, J = 7.2 Hz, 2H), 5.23 (s, 1H), 6.81 (d, J = 8.8 Hz, 1H), 7.75 (d, J = 8.4 Hz, 2H), 7.88-7.92 (m, 3H), 9.91 (s, 1H).

MS (EI) m/z: 454.1 (M + 1).

Example A5: tert-Butyl 6-[[2-(4-cyclopropylsulfonylphenyl)-2-indan-2-yloxy-acetyl]amino]pyridine-3-carboxylate:
The compound of example A5 was obtained by similar method described in example A1 using 2-(4-cyclopropylsulfonlfylophenyl)-2-indan-2-yloxy-acetic acid (preparation 5) (0.54 g, 1.46 mmol), tert-butyl 6-aminopyridine-3-carboxylate (0.19 g, 0.97 mmol), HOBt (0.33 g, 2.44 mmol), and EDCI (0.46 g, 2.44 mmol), N-methyl morpholine (0.32 mL, 2.93 mmol) in DCM (20 mL) to provide the title compound (0.12 g).

\[ ^1H \text{ NMR (400 MHz, CDC13):} \delta 1.01-1.06 (m, 2H), 1.32-1.37 (m, 2H), 1.59 (s, 9H), 2.40-2.48 (m, 1H), 3.05-3.30 (m, 4H), 4.50-4.58 (m, 1H), 5.14 (s, 1H), 7.16-7.24 (m, 4H), 7.71 (d, \( J = 8.3 \) Hz, 2H), 7.91 (d, \( J = 8.4 \) Hz, 2H), 8.18-8.22 (m, 2H), 8.83 (s, 1H), 9.25 (br. s, 1H); MS (El) m/z: 549.2 (M + 1). \]

**Example A6**: tert-butyl 6-[[2-(4-cyclopropylsulfonylophenyl)-2-(9-methylspiro[5.5]undecan-9-yl)oxy-acetyl]amino]pyridine-3-carboxylate:

The compound of example A6 was obtained by similar method described in example A1 using 2-(4-cyclopropylsulfonylophenyl)-2-(9-methylspiro[5.5]undecan-9-yl)oxy-acetic acid (0.251 g, 0.61 mmol, preparation 6), tert-butyl 6-aminopyridine-3-carboxylate (0.100 g, 0.51 mmol), HOBt (0.173 g, 1.28 mmol), and EDCI (0.245 g, 1.28 mmol), N-methyl morpholine (0.14 mL, 1.28 mmol) in DCM (5 mL) to provide the title compound (0.106 g).

\[ ^1H \text{ NMR (400 MHz, CDC13):} \delta 1.03-1.12 (m, 5H), 1.20-1.30 (m, 4H), 1.31-1.46 (m, 13H), 1.55-1.75 (m, 7H), 1.82-1.93 (m, 2H), 2.41-2.47 (m, 1H), 3.43-3.48 (m, 1H), 5.11 (s, 1H), 7.73 (d, \( J = 8.3 \) Hz, 2H), 7.91 (d, \( J = 8.5 \) Hz, 2H), 8.21 (d, \( J = 2.5 \) Hz, 1H), 8.88 (d, \( J = 1.7 \) Hz, 1H), 9.36 (s, 1H); MS (El) m/z: 582.7 (M + 1). \]

**Examples A7 to A26** were prepared in analogues manner of examples A1-A6 from the appropriate intermediate that are available commercially or synthesized as above.

<table>
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<tr>
<th>Example No.</th>
<th>MS (El)m/z:</th>
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<td>A7</td>
<td>4-[2-[2-Cyclohexyloxy-2-(4-cyclopropanesulfonyl-phenyl)-acetylamino]-thiazol-5-yloxy]-benzoic acid methyl ester</td>
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<td>All</td>
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<td>A14</td>
<td>{5-Chloro-2-[2-cyclohexylxoy-2-(4-cyclopropanesulfonyl-phenyl)-acetylamino]-thiazol-4-ylyl} acetic acid ethyl ester</td>
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</tr>
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<td>A17</td>
<td>2-Cyclopentylxoy-2-[4-(tetrahydro-pyran-4-sulfonyl)-phenyl]-N-thiazolo[5,4-b]pyridin-2-yl-acetamide</td>
<td>501.6</td>
</tr>
<tr>
<td>A18</td>
<td>2-Cyclopentylxoy-N-(5-fluoro-thiazol-2-yl)-2-[4-(tetrahydro-pyran-4-sulfonyl)-phenyl]-acetamide</td>
<td>482.6</td>
</tr>
<tr>
<td>A19</td>
<td>methyl 5-[2-[2-(4-cyclopropanesulfonylphenyl)-2-(4-oxocyclohexoxy)acetyl]amino]thiazol-5-yl]oxy-2-methylbenzoate</td>
<td>599.3</td>
</tr>
<tr>
<td>A20</td>
<td>methyl 4-[2-[2-(4-cyclopropanesulfonylphenyl)-2-indan-1-yloxy-acetyl]amino]thiazol-5-yl]oxy-2-methylbenzoate</td>
<td>619.2</td>
</tr>
<tr>
<td>A22</td>
<td>ethyl 2-[5-chloro-2-[2-(4-cyclopropanesulfonylphenyl)-2-indan-1-yloxy-acetyl]amino]thiazol-4-yl] acetate</td>
<td>575.2</td>
</tr>
<tr>
<td>A23</td>
<td>ethyl 2-[5-chloro-2-[2-(4-cyclopropanesulfonylphenyl)-2-indan-2-yloxy-acetyl]amino]thiazol-4-yl] acetate</td>
<td>575.2</td>
</tr>
<tr>
<td>A24</td>
<td>tert-butyl 6-[2-(cyclohexoxy)-2-(4-cyclopropanesulfonylphenyl)acetyl]amino]pyridine-3-carboxylate</td>
<td>514.7</td>
</tr>
<tr>
<td>A25</td>
<td>tert-butyl 6-[2-(1-adamantylmethoxy)-2-(4-cyclopropanesulfonylphenyl)acetyl]amino]pyridine-3-carboxylate</td>
<td>581.0</td>
</tr>
<tr>
<td>A26</td>
<td>tert-butyl 6-[2-(2-adamantylxy)-2-(4-cyclopropanesulfonylphenyl)acetyl]amino]pyridine-3-carboxylate</td>
<td>567.3</td>
</tr>
</tbody>
</table>

Example B1: 4-[2-[2-Cyclopentyloxy-2-(4-cyclopropanesulfonyl-phenyl)-acetylamino]-thiazol-5-yloxy]-benzoic acid:
4-{2-[2-Cyclopentyloxy-2-(4-cyclopropanesulfonyl-phenyl)-acetylamino]-thiazol-5-yloxy}-
benzoic acid methyl ester (0.145 g, 0.26 mmol, obtained in example Al) was taken in H₂O : THF
(1:2, 6 mL) to it was added MeOH (1 drop) followed by LiOH (0.054 g, 1.30 mmol) and stirred
for 12 hr. After completion of the reaction, organic solvent was removed under reduced
pressure. The aqueous layer was washed with diisopropyl ether then acidified with 1 N HCl to
pH 4. The solid formed was filtered, washed with water, diisopropyl ether & dried under
vacuum to get the title compound (0.12 g).

I H NMR- (400 MHz DMSO-d₆):- χ 1.01-1.05 (m, 2H), 1.09-1.13 (m, 2H), 1.22-1.49 (m, 2H),
1.59-1.73 (m, 6H), 2.82-2.86 (m, IH), 3.99-4.01 (m, IH), 5.31 (s, IH), 7.16 (d, J = 8.4 Hz, 2H),
7.37 (s, IH), 7.74 (d, J = 8.4 Hz, 2H), 7.91 (m, 4H), 12.55 (br. s, IH), 12.90 (br.s, IH); MS (EI)

Example B2: 6-[[2-(4-cyclopropylsulfonylphenyl)-2-indan-2-yloxy-acetyl]amino]pyridine-3-carboxylic acid:

To a solution of tert-butyl 6-[[2-(4-cyclopropylsulfonylphenyl)-2-indan-2-yloxy-acetyl]amino]pyridine-3-carboxylate (120 mg, 0.219 mmole, obtained in example A5) in DCM
(3 mL) was added TFA (3 mL) at 0 °C. Reaction mixture was stirred at rt for 1 hr. TFA was
removed under reduced pressure. The residue was neutralised using sat.NaHCC₃ solution,
extracted with ethyl acetate (3 X 10 mL) washed with brine, dried over anhydrous sodium
sulfate and concentrated under reduced pressure. The obtained crude product was purified using
preparative TLC to provide the title compound (0.050 g).

I H NMR- (400 MHz DMSO-d₆):- χ 0.98-1.05 (m, 2H), 1.06-1.14 (m, 2H), 2.80-2.88 (m, IH),
2.92-3.22 (m, 4H), 4.40-4.45 (m, IH), 5.54 (s, IH), 7.10-7.18 (m, 2H), 7.20-7.28 (m, 2H), 7.79
(d, J = 7.8 Hz, 2H), 7.91 (d, J = 8.1 Hz, 2H), 8.08 (d, J = 8.6 Hz, IH), 8.24 (d, J = 8.8 Hz, IH),
8.82 (s, IH), 10.89 (br. s, IH); MS (EI) m/z: 493.1 (M+1)

Example B3: 6-[[2-(4-cyclopropylsulfonylphenyl)-2-(9-methylspiro[5.5]undecan-9-yloxy-
acetyl]amino]pyridine-3-carboxylic acid:
To a solution of tert-butyl 6-[[2-(4-cyclopropylsulfonylphenyl)-2-indan-2-yloxy-
acetyl]amino]pyridine-3-carboxylate (106 mg, 0.18 mmole, obtained in example A6) in DCM (1 mL) was added TFA (2.0 mL) at 0 °C. Reaction mixture was stirred at rt for 15 hrs. TFA was removed under reduced pressure. The residue was neutralised using sat.NaHCO₃ solution, extracted with ethyl acetate (3 X 10 mL) washed with brine ,dried over anhydrous sodium sulfate and concentrated under reduced pressure. The obtained crude product was purified using preparative TLC to provide the title compound (0.044 g).  

$^1$H NMR (400 MHz, DMSO-d₆): δ 0.99-1.13 (m, 6H), 1.19 (m, 2H), 1.35 (m, 8H), 1.42-1.59 (m, 4H), 1.68-1.79 (m, 2H), 2.81-2.88 (m, IH), 3.41-3.46 (m, IH), 5.4 (s, IH), 7.77 (d, 8.3 Hz, 2H), 7.91 (d, $J = 8.4$ Hz, 2H), 8.11 (d, $J = 8.9$ Hz, IH), 8.25 ($dd, J = 2.2, 8.5$ Hz, IH), 8.84 (d, $J = 1.7$ Hz, IH), 10.74 (br. s, IH), 13.30 (br. s, IH). MS (EI) m/z: 527.2 (M + 1).

Examples B4 to B14 were prepared in analogues manner of example B1 and B3 from the appropriate intermediate that are available commercially or synthesized as above.

<table>
<thead>
<tr>
<th>Example No.</th>
<th>Mass</th>
<th>IUPAC Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>B4</td>
<td>556.9</td>
<td>4-[[2-Cyclohexyloxy-2-(4-cyclopropanesulfonylethyl)acetyl]amino]-thiazol-5-yloxy-2-methylbenzoic acid</td>
</tr>
<tr>
<td>B5</td>
<td>512.9</td>
<td>[5-Chloro-2-[2-cyclohexyloxy-2-(4-cyclopropanesulfonyl)phenyl]acetylamino]-thiazol-4-yl ]-acetic acid</td>
</tr>
<tr>
<td>B6</td>
<td>498.9</td>
<td>[5-Chloro-2-[2-cyclopentyloxy-2-(4-cyclopropanesulfonyl)phenyl]acetylamino]-thiazol-4-yl ]-acetic acid</td>
</tr>
<tr>
<td>B7</td>
<td>559.2</td>
<td>5-[[2-(4-cyclopropanesulfonylethyl)-2-(4-oxocyclohexoxy)acetyl]amino]thiazol-5-yloxy-2-methylbenzoic acid</td>
</tr>
<tr>
<td>B8</td>
<td>605.2</td>
<td>4-[2-[[2-(4-cyclopropanesulfonylethyl)-2-indan-1-yloxy-2-acetyl]amino]thiazol-5-yl] oxy-2-methylbenzoic acid</td>
</tr>
<tr>
<td>B10</td>
<td>547.1</td>
<td>2-[5-chloro-2-[[2-(4-cyclopropanesulfonylethyl)-2-indan-1-yloxy-acetyl]amino]thiazol-4-yl] acetic acid</td>
</tr>
<tr>
<td>B11</td>
<td>547.2</td>
<td>2-[5-chloro-2-[[2-(4-cyclopropanesulfonylethyl)-2-indan-2-yloxy-acetyl]amino]thiazol-4-yl] acetic acid</td>
</tr>
<tr>
<td>B12</td>
<td>458.6</td>
<td>6-[2-(4-cyclohexyloxy)-2-(4-cyclopropanesulfonylethyl)acetylamino]pyridine-3-carboxylic acid</td>
</tr>
<tr>
<td>B13</td>
<td>525.2</td>
<td>6-[2-(1-adamantylmethoxy)-2-(4-cyclopropanesulfonylethyl)acetylamino]pyridine-3-carboxylic acid</td>
</tr>
</tbody>
</table>
Example CI: N-{5-[4-(Azetidine-1-carbonyl)-phenoxy]-thiazol-2-yl}-2-cyclohexyloxy-2-(4-cyclopropanesulfonyl-phenyl)-acetamide:

To a solution of 4-2-[2-Cyclohexyloxy-2-(4-cyclopropanesulfonyl-phenyl)-acetylamino]-thiazol-5-yloxy]-benzoic acid (0.050 g, 0.089 mmol) in DMF (3 mL) was added azetidine hydrochloride (0.011 g, 0.11 mmol), HoAt (0.5M in DMF) (0.23 mL, 0.115 mmol), EDCI (0.021 g, 0.111 mmol) and diisopropylethylamine (0.03 mL, 0.231 mmol) and mixture was stirred for 12 hours at 25 °C under argon atmosphere. Reaction mixture was diluted with water (15 mL) and extracted with ethylacetate (3 X 15 mL). Combined organic layer was washed with brine solution, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was triturated with diisopropylether to get the title compound (0.032 g).

$^1$H NMR (400 MHz, DMSO-d$_6$): δ 1.03-1.04 (m, 2H), 1.11-1.15 (m, 2H), 1.16-1.20 (m, 2H), 1.60-1.67 (m, 4H), 1.83-1.89 (m, 4H), 2.20-2.27 (m, 2H), 2.28-2.89 (m, 1H), 3.39-3.41 (m, 1H), 4.00-4.01 (m, 2H), 4.26-4.27 (m, 2H), 5.44 (s, 1H), 7.13 (d, J = 8.8 Hz, 2H), 7.35 (s, 1H), 7.63 (d, J = 8.4 Hz, 2H), 7.76 (d, J = 8.4 Hz, 2H), 7.92 (2H, J = 8.0 Hz, 2H); MS (EI) m/z: 595.9 (M+1).

Example C2: 4-2-[2-Cyclohexyloxy-2-(4-cyclopropanesulfonyl-phenyl)-acetylamino]-thiazol-5-yloxy]-benzamide:
To a solution of 4- \{2-\text{(2-Cyclohexyloxy-2-(4-cyclopropanesulfonyl-phenyl)-acetylamino)-thiazol-5-yloxy}\}-benzoic acid (0.050 g, 0.089 mmol) in DCM (5 mL) was added triethyl amine (0.025 mL, 0.186 mmol) at 0 °C followed by ethyl chloroformate (0.02 mL, 0.186 mmol) and reaction mixture was stirred at 0 °C to 5 °C for 1 hr. Aq. ammonia solution (24%, 10 mL) was taken in 100 mL round bottom flask, cooled to 0 °C, to it above reaction mixture was added slowly with vigorous stirring. After complete addition reaction mixture was stirred for another 1 hr. After completion of the reaction, organic solvent was removed under reduced pressure to get a residue which was purified by preparative TLC to provide the title compound (0.032 g).

\[
^1\text{H NMR (400 MHz, DMSO-}d_6\text{)}: \delta 1.03-1.05 \text{(m, 2H), 1.15-1.30 \text{(m, 4H), 1.33-1.37 \text{(m, 2H), 1.40-2.05 \text{(m, 6H), 2.42-2.45 \text{(m, 1H), 3.40-3.50 \text{(m, 1H), 5.19 \text{(s, 1H), 7.10 \text{(d, J = 6.8 Hz, 2H), 7.15 \text{(s, 1H), 7.69 \text{(d, J = 8.4 Hz, 2H), 7.88 \text{(d, J = 6.8 Hz, 2H), 7.91 \text{(d, J = 8.4 Hz, 2H), 9.89 \text{(br.s, 1H); MS (EI) m/z; 556.3 (M+).}}}
\]

**Examples C3 and C4 were prepared in analogous manner of example CI**

<table>
<thead>
<tr>
<th>Example No.</th>
<th>Mass</th>
<th>IUPAC Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>C3</td>
<td>581.9</td>
<td>N-[5-[4-(Azetidine-1-carbonyl)-phenoxy]-thiazol-2-yl]-2-cyclopentyl-oxo-2-(4-cyclopropanesulfonyl-phenyl)-acetamide</td>
</tr>
<tr>
<td>C4</td>
<td>541.8</td>
<td>4-[2-(4-Cyclopentyl-oxo-2-(4-cyclopropanesulfonyl-phenyl)-acetylamino)-thiazol-5-yloxy]-benzamide</td>
</tr>
</tbody>
</table>

The below list of examples, but not to be limited to these, can also be synthesized following the general synthesis described above:

2-(cyclobutoxy)-2-(4-cyclopropylsulfonylphenyl)-N-[3-(1,2-dihydroxyethyl)-l,2,4-thiadiazol-5-yl]acetamide,
2-[5-chloro-2-[2-(cyclobutoxy)-2-(4-cyclopropylsulfonylphenyl)acetyl] amino]thiazol-4-yl]-2-hydroxy-acetic acid,
N-[4-(1-acetyl-4-piperidyl)thiazol-2-yl]-2-(cyclobutoxy)-2-(4-cyclopropylsulfonylphenyl) acetamide,
2-(cyclobutoxy)-2-(4-cyclopropylsulfonylphenyl)-N-[5-[4-(1,2-dihydroxyethyl)phenoxy] thiazol-2-yl] acetamide,
2-(cyclopentoxy)-2-(4-cyclopentylsulfonylphenyl)-N-(4,5,6,7-tetrahydro-l,3-benzothiazol-2-yl)acetamide,
2-(cyclopentoxy)-2-(4-cyclopentylsulfonylphenyl)-N-thiazolo[5,4-d]pyrimidin-2-yl-acetamide,
2-(cyclopentoxy)-2-(4-cyclopentylsulfonylphenyl)-N-[5-[4-(hydroxymethyl)phenoxy] thiazol-2-yl]acetamide,
2-(cyclopentoxy)-2-(4-cyclopentylsulfonlfyln phenyl)-N-(5-methyl-6,7-dihydro-4H-thiazolo[4,5-c]pyridin-2-yl)acetamide,
2-(cyclohexoxy)-2-(4-cyclopentylsulfonlfyln phenyl)-N-[4-(1,2-dihydroxyethyl)thiazol-2-yl]acetamide,
2-(cyclohexoxy)-2-(4-cyclopentylsulfonlfyln phenyl)-N-[4-(1,2-dihydroxyethyl)-5-fluoro-thiazol-2-yl]acetamide,
2-(cyclohexoxy)-2-(4-cyclohexylsulfonlfyln phenyl)-N-[5-(1,2-dihydroxyethyl)thiazol-2-yl]acetamide,
6-[[2-(cyclohexoxy)-2-(4-tetrahydropyran-4-ylsulfonlfyln phenyl)acetyl]amino]pyridine-3-carboxylic acid,
2-(cyclohexoxy)-2-(4-cyclohexylsulfonlfyln phenyl)-N-[5-(hydroxymethyl)-2-pyridyl]acetamide,
N-[5-chloro-4-(2-hydroxyethyl)thiazol-2-yl]-2-(4-tetrahydropyran-4-ylsulfonlfyln phenyl)acetamide,
2-(cyclohexoxy)-2-(4-cyclohexylsulfonlfyln phenyl)-N-[4-(hydroxymethyl)-5-methyl-thiazol-2-yl]acetamide,
2-[3-[[2-(cyclopentoxy)-2-(4-cyclopropylsulfonlfyln phenyl)acetyl]amino]pyrazol-1-yl]-2-methylpropanoic acid,
2-[2-[[2-(4-cyclohexylsulfonlfyln phenyl)acetyl]amino]thiazolo[5,4-b]pyridin-5-yl]oxyacetic acid,
2-[2-(cyclopentoxy)-2-(4-cyclopropylsulfonlfyln phenyl)acetyl]amino]-1,3-benzothiazole-6-carboxylic acid,
2-(cycloheptoyxy)-2-(4-cyclohexylsulfonlfyln phenyl)-N-[5-(1,2-dihydroxyethyl)thiazolo[5,4-b]pyridin-2-yl]acetamide,
1-[[2-[2-(cycloheptoyxy)-2-(4-tetrahydropyran-4-ylsulfonlfyln phenyl)acetyl]amino]thiazol-5-yl]piperidine-4-carboxylic acid,
2-[2-(cyclobutoxy)-2-(4-tetrahydropyran-4-ylsulfonlfyln phenyl)acetyl]amino]-5-(4-fluorophenoxy)thiazole-4-carboxylic acid,
2-[2-(cyclobutoxy)-2-(4-cyclohexylsulfonlfyln phenyl)acetyl]amino]-5-(4-fluorophenoxy)thiazole-4-carboxylic acid,
4-[[6-[[2-(cyclopentoxy)-2-(4-tetrahydropyran-4-ylsulfonlfyln phenyl)acetyl]amino]-3-pyridyl]oxy]benzoic acid,
4-[[2-(4-cyclohexylsulfonlfyln phenyl)acetyl]amino]thiazol-5-yl]benzoic acid,
N-(5-chlorothiazol-2-yl)-2-cyclopentylsulfonyl-2-(4-cyclopropylsulfonlfyln phenyl) acetamide,
2-(cyclopentylamino)-2-(4-cyclohexylsulfonlfyln phenyl)-N-(6-fluoro-1,3-benzothiazol-2-yl)acetamide,
4-[2-[2-cyclohexylsulfanyl-2-(4-cyclopentylsulfonylphenyl)acetyl]hydrazino]thiazol-5-yl]oxybenzoic acid,
4-[2-([2-(cyclohexylamino)-2-(4-cyclopentylsulfonylphenyl)acetyl]amino]thiazol-5-yl]oxybenzoic acid,
N-[4-(1-acetyl-4-piperidyl)thiazol-2-yl]-2-(cyclobutoxy)-2-(4-pyrrolidin-1-ylsulfonl phenyl) acetamide,
2-[5-chloro-2-[[2-(cyclobutoxy)-2-(4-morpholinosulfonylphenyl)acetyl]amino]thiazol-4-yl]-2-hydroxy-acetic acid; formic acid,
2-(cyclopentoxy)-2-(4-morpholinosulfonylphenyl)-N-(4,5,6,7-tetrahydro-1,3-benzothiazol-2-yl)acetamide,
2-cyclopentylsulfanyl-2-(4-pyrrolidin-1-ylsulfonlphenyl)-N-thiazolo[5,4-d]pyrimidin-2-ylacetamide,
2-[2-[[2-(cyclohexoy)-2-(4-oxocyclopentyl)sulfonylphenyl)acetyl]amino]thiazol-5-yl]sulfanylacetic acid,
2-[3-[[2-(cyclohexoxy)-2-(4-oxocyclopentyl)sulfonylphenyl]acetyl]amino]pyrazol-1-yl]acetic acid,
4-[[2-(cyclohexylamino)-2-(4-pyrrolidin-1-ylsulfonlphenyl)acetyl]amino]thiazol-5-yl]oxybenzoic acid,
2-[[2-(cyclohexylamino)-2-[4-(1-piperidylsulfonyl)phenyl]acetyl]amino]thiazol-4-yl]-2-isopropoxy-acetic acid,
2-[[2-(cyclohexoxy)-2-(4-pyrrolidin-1-ylsulfonlphenyl)acetyl]amino]-5-fluoro-thiazol-4-yl]-2-methyl-propanoic acid,
2-(cyclopentoxy)-N-(6-fluoro-1,3-benzothiazol-2-yl)-2-[4-(1-piperidylsulfonyl)phenyl]acetamide,
2-cyclopentylsulfanyl-N-(6-fluoro-1,3-benzothiazol-2-yl)-2-[4-(1-piperidylsulfonyl)phenyl]acetamide,
2-[2-(cyclopentoxy)-2-[4-(1-piperidylsulfonyl)phenyl]acetyl]amino]-5-(4-fluorophenoxy)thiazole-4-carboxylic acid,
4-[[2-(cyclopentylamino)-2-(4-sulfamoylphenyl)acetyl]amino]thiazol-5-yl]oxybenzoic acid,
4-[[2-[4-(cyclopentylsulfoxamoyl)phenyl]-2-cyclopentylsulfanyl-acetyl]amino]thiazol-5-yl]oxybenzoic acid,
2-[[4-[1-(cyclopentoxy)-2-[3-(1,2-dihydroxyethyl)-1,2,4-thiadiazol-5-yl]amino]-2-oxoethyl]phenyl] sulfonyl-cyclopentyl-amino] acetic acid,
2-(cyclohexoxy)-2-[4-cyclopropylmethyl(4-pyridyl)sulfamoyl]phenyl]-N-[3-(1,2-dihydroxyethyl)-1,2,4-thiadiazol-5-yl]acetamide,
2-[2-[[4-[[acetyl(ethyl)sulfamoyl]phenyl]-2-(cyclohexoxy)acetyl]amino]-1,3-benzothiazole-6-carboxylic acid,
2-(cyclopentoxy)-2-(6-cyclopropylsulfonyl-3-pyridyl)-N-(1,2,4-thiadiazol-5-yl)acetamide,
2-(cyclohexoxy)-2-(6-cyclopropylsulfonyl-3-pyridyl)-N-(1,2,4-thiadiazol-5-yl)acetamide,
2-[5-chloro-2-[[2-(cyclopentoxy)-2-(6-cyclopropylsulfonyl-3-pyridyl)acetyl]amino][thiazol-4-yl]acetic acid,
2-[5-chloro-2-[[2-(cyclohexoxy)-2-(6-cyclopropylsulfonyl-3-pyridyl)acetyl]amino][thiazol-4-yl]acetic acid,
N-[4-(1-acetyl-4-piperidyl)thiazol-2-yl]-2-(cyclopentoxy)-2-(6-cyclopropylsulfonyl-3-pyridyl) acetamide,
N-[4-(1-acetyl-4-piperidyl)thiazol-2-yl]-2-(cyclohexoxy)-2-(6-cyclopropylsulfonyl-3-pyridyl) acetamide,
2-(cyclopentoxy)-2-(6-cyclopropylsulfonyl-3-pyridyl)-N-[5-[4-(1,2-dihydroxyethyl)phenoxy] thiazol-2-yl]acetamide,
2-(cyclohexoxy)-2-(6-cyclopropylsulfonyl-3-pyridyl)-N-[5-[4-(1,2-dihydroxyethyl)phenoxy] thiazol-2-yl]acetamide,
2-(cyclopentoxy)-2-(5-cyclopentylsulfonyl-2-pyridyl)-N-(4,5,6,7-tetrahydro-1,3-benzothiazol-2-yl)acetamide,
2-(cyclohexoxy)-2-(5-cyclopentylsulfonyl-2-pyridyl)-N-(4,5,6,7-tetrahydro-1,3-benzothiazol-2-yl)acetamide,
2-(cyclopentoxy)-2-(5-cyclopentylsulfonyl-2-pyridyl)-N-thiazolo[5,4-d]pyrimidin-2-ylacetamide,
2-(cyclohexoxy)-2-(5-cyclopentylsulfonyl-2-pyridyl)-N-thiazolo[5,4-d]pyrimidin-2-ylacetamide,
4-[2-[[2-(cyclopentoxy)-2-(5-pyrrolidin-1-ylsulfonyl-2-pyridyl)acetyl]amino][thiazol-5-yl]oxybenzoic acid,
4-[2-[[2-(cyclohexoxy)-2-(5-pyrrolidin-1-ylsulfonyl-2-pyridyl)acetyl]amino][thiazol-5-yl]oxybenzoic acid,
2-(cyclopentoxy)-2-(5-cyclopentylsulfonyl-2-pyridyl)-N-(5-methyl-6,7-dihydro-4H-thiazolo[4,5-c]pyridin-2-yl)acetamide,
2-(cyclopentoxy)-2-(5-cyclopropylsulfonyl-2-pyridyl)-N-(5-ethoxythiazolo[5,4-b]pyridin-2-yl)acetamide,
2-(cyclohexoxy)-2-(5-cyclopropylsulfonyl-2-pyridyl)-N-(5-ethoxythiazolo[5,4-b]pyridin-2-yl)acetamide
2-(4-cyclopropylsulfonylphenyl)-2-spiro [4,5]decan-3-yloxy-N-(1,2,4-thiadiazol-5-yl)acetamide,
2-[5-chloro-2-[(2-(4-cyclopropylsulfonylphenyl)-2-spiro [4,5]decan-8-yloxyacetamido]thiazol-4-yl]acetic acid,
N-[4-(1-acetyl-4-piperidyl)thiazol-2-yl]-2-(1-adamantyloxy)-2-(4-cyclopropylsulfonylphenyl)acetamide,
2-(4-cyclopropylsulfonylphenyl)-N-[5-[4-(1,2-dihydroxyethyl)phenoxy]thiazol-2-yl]-2-(spiro[4,5]decan-3-y lamino)acetamide; spiro[4,5]decan-8-amine,
2-[4-[1-(1-adamantylamino)-2-oxo-2-(thiazolo[5,4-d]pyrimidin-2-ylamino)ethyl]phenyl] sulfonyl-cyclopentyl-amino] acetic acid,
4-[2-[2-(4-pyrrolidin-1-ylsulfonylphenyl)-2-spiro[4,5]decan-8-yloxy-acetamido]thiazol-5-yl]oxybenzoic acid,
N-(5-methyl-6,7-dihydro-4H-thiazolo[4,5-c]pyridin-2-yl)-2-[4-(l-piperidylsulfonyl) phenyl] -2-spiro[4,5]decan-3-yloxy-acetamide,
2-[4-[acetyl(ethyl)sulfamoyl]phenyl]-N-(5-ethoxythiazolo[5,4-b]pyridin-2-yl)-2-spiro[4,5]decan-3-yloxy-acetamide,
4-[2-[2-(4-cyclopropylsulfonylphenyl)-2-(3-oxocyclopentoxy)acetamido]thiazol-5-yloxybenzoic acid,
2-[5-chloro-2-[2-(4-cyclopropylsulfonylphenyl)-2-(4-oxocyclohexoxy)acetyl] amino]thiazol-4-yl]acetic acid

Glucokinase Activity Assay:

The glucokinase (GK) assay is a coupled enzymatic assay. GK catalyzes the first step of glycolysis, the conversion of glucose to glucose-6-phosphate (G6P) in the presence of ATP. G6P in turn is converted by glucose-6-phosphate dehydrogenase (G6PD) to 6-phosphogluconate, a process that requires NAD, resulting in NADH formation. Since the GK-catalyzed step is the rate-limiting step of this coupled enzymatic process, the rate of accumulation of 6-phosphogluconate and NADH is directly proportional to the rate of glucose phosphorylation by GK. The rate of the GK-catalyzed reaction can therefore be measured by monitoring the increase in NADH absorbance at 340 nm.
The assay is carried out according to the protocol outlined in Hariharan et al (1997), Diabetes 46: 11-16. Briefly, the test compounds are incubated in a reaction mix containing 25 mM HEPES (pH 7.2), 10 mM MgCl₂, 100 mM KCl, 5 mM ATP, 2 mM DTT, 0.5 mM NAD, 1 U/mL *Leuconostoc mesenteroides* G6PD, 0.3 U/mL of purified human recombinant GK, and different concentrations of glucose. Enzymatic activity is calculated from the initial reaction velocity, measured from the change in NADH absorbance as a function of time.

Compounds described in formula (I), in concentration ranges from 1.0 nM to 500 μM, are tested in the purified human recombinant glucokinase assay described above.

A compound is considered to be a glucokinase activator if it, in its testable range of concentrations, yields a higher rate of glucose phosphorylation than in its absence at a particular glucose concentration, for example at 5 mM glucose.

**Characterization of glucokinase activators from the in vitro glucokinase assay:**

Compounds of general formula (I) are tested in the in vitro GK enzymatic assay to monitor dose-dependent effect on glucokinase activation (in kinetic mode), as described above, at various glucose concentrations. The S₀.₅ of glucokinase for glucose at different concentration of each compound of interest is calculated from the following modified version of the Michaelis-Menten equation, \( V = \frac{V_{max} \times [S]}{S_0^n + [S]} \), where [S] is the glucose concentration and \( n \) is the Hill coefficient (taken as 1.7 to account for the sigmoidal kinetics of glucokinase with respect to glucose). The S₀.₅ is plotted against the log of the compound concentration. The change in the S₀.₅ of glucokinase (AS₀.₅) for glucose is calculated by subtracting the S₀.₅ at each concentration of the compound from the S₀.₅ in the vehicle control. The AS₀.₅ is then normalized to a percent scale, where the S₀.₅ in the vehicle control is set to 0% and 0 mM glucose is set to 100%. The % AS₀.₅ is then plotted against the log of the compound concentration. The EC₅₀ and Eₙ₅₀ of % change in S₀.₅ is obtained from the sigmoidal fit of the data. Detailed protocol has been described in our copending application no. 409/CHE/2007 which is incorporated herein by reference. Characterization data of some representative glucokinase activators of the present disclosure, which are illustrative but not limiting, are given in table I.

**Table I: EC₅₀ and Eₙ₅₀ (with respect to % AS₀.₅) of GK activators**

<table>
<thead>
<tr>
<th>Example No.</th>
<th>EC₅₀ (nM)</th>
<th>% Eₙ₅₀</th>
</tr>
</thead>
<tbody>
<tr>
<td>A4</td>
<td>0.54</td>
<td>96</td>
</tr>
<tr>
<td>A15</td>
<td>0.73</td>
<td>86</td>
</tr>
<tr>
<td>B1</td>
<td>0.3</td>
<td>90</td>
</tr>
<tr>
<td>B4</td>
<td>1.6</td>
<td>90</td>
</tr>
</tbody>
</table>
Measurement of glycogen synthesis in primary rat hepatocytes:

Primary hepatocytes are collected from male Wistar rats, and tested for viability by trypan blue exclusion. Primary hepatocytes cultures with viability greater than 95% are selected for the glycogen synthesis assay. The cells are seeded in a 48-well plate at a density of 200,000 cells/well in 250 μl Minimal Essential Medium (MEM) containing 10% foetal calf serum (FCS) and 1.7 μM insulin, and incubated for 4 hours at 37°C to allow attachment. The medium is replaced with fresh MEM containing 10% FCS, 1.7 μM insulin and 10 mM dexamethasone, and the cells are incubated for 16 hours at 37°C. The medium is then replaced with fresh MEM (serum-free) containing 2 μCi/ml of D-[U-14C]-Glucose along with 10 μM of the compound in a final DMSO concentration of 0.1%. The final glucose concentration is brought to 10 mM by the addition of D-Glucose (MEM already contains 5 mM glucose). The cells are incubated for 3 hours at 37°C. The cells are washed twice with 150 mM NaCl, lysed with 0.1 N NaOH, and the lysate precipitated with 8% w/v trichloroacetic acid (TCA) and 1 mg/well unlabeled glycogen as carrier. Cell debris is pelleted by centrifugation, the supernatant is removed, and the glycogen is precipitated with 63% ethanol. After another round of centrifugation, the supernatant is removed, and the pellet containing the precipitated glycogen is dried overnight. De novo synthesized glycogen is estimated in a scintillation counter (MicroBeta Trilux, Perkin Elmer), and expressed as fold increase over DMSO control.


Compounds described in formula (I), in concentration ranges from 1.0 nM to 500 μM, are tested in glycogen synthesis assay described above.

A compound is considered to be a glucokinase activator in a cellular environment if it demonstrates significant increase of glycogen synthesis over DMSO control as described in the above mentioned glycogen synthesis assay.

The glycogen synthesis data of some representative compounds of the present invention, which are illustrative but not limiting, is given in the table 2 below.

Table 2: Glycogen synthesis data

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>C2</td>
<td>0.18</td>
<td>93</td>
</tr>
<tr>
<td>B9</td>
<td>0.3</td>
<td>92</td>
</tr>
<tr>
<td>Examples</td>
<td>Fold increase in glycogen synthesis at 10 µM</td>
<td></td>
</tr>
<tr>
<td>----------</td>
<td>------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>B1</td>
<td>7.4</td>
<td></td>
</tr>
<tr>
<td>B4</td>
<td>4.6</td>
<td></td>
</tr>
</tbody>
</table>

Although the subject matter has been described in considerable details with reference to certain preferred embodiments thereof, other embodiment are possible. As such, the spirit and scope of the appended claims should not be limited to the description of the preferred embodiments contained therein.
We claim:

1. A compound of formula (I),

or their stereoisomers, tautomers, prodrugs, pharmaceutically acceptable salts, polymorphs, solvates and formulations wherein,

ring A is an optionally substituted 4-12 membered mono or polycyclic cycloalkyl ring;

ring-B is an optionally substituted 4-12 membered mono or polycyclic ring containing 1 - 4 hetero atoms selected from N, O or S, with at least one nitrogen in the ring;

ring C is a mono or a polycyclic ring selected from aryl, heteroaryl or heterocyclyl;

D is -SO₂⁻;

E is selected from the group consisting of cycloalkyl, heterocyclyl, and -N(G)R⁸;

G is selected from alkyl, cycloalkyl, aryl, heterocyclyl or heteroaryl; wherein said alkyl, cycloalkyl, aryl, heterocyclyl or heteroaryl are optionally substituted with 1 to 4 substituents independently selected from halogen, monohaloalkyl, dihaloalkyl or perhaloalkyl, monohaloalkoxy, dihaloalkoxy or perhaloalkoxy, cyano, nitro, alkyl, alkenyl, alkynyl, methylenedioxy, amidino -NR⁴R⁵, -OR⁴, -S(0)⁸R⁴, -S(0)⁸NR⁴R⁵, -NR⁴S(0)⁸R⁵, -NR⁴C(0)R⁵, -OS(0)⁸R⁵, -NR⁴C(0)OR⁵, -NR⁴C(0)NR⁴R⁵, -CR⁴R⁵ₙC(0)OR, -(CR⁴R⁵ₙ)ₙC(0)NR⁴R⁵, -(CR⁴R⁵ₙ)ₙC(0)R, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkenyl, arylxy or heteroaralkoxy groups;

X represents -O(CR⁶R⁷)ₙ₋₁, -N(R)⁴(CR⁶R⁷)ₙ₋₁, -S(0)⁸p(CR⁶R⁷)ₙ₋₁; wherein the heteroaom is connected through carbon that is alpha to the carbonyl group;

R¹ is selected from the group consisting of hydrogen, alkyl and perfluoroalkyl;

R² and R³ are independently selected from the group consisting of hydrogen, halogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, arylalkyl, heteroaryl, heteroaryl alkyl, mono, di or tri substituted haloalkyl, nitro, nitro, oxo, -NR⁴R⁵, -OR⁴, -S(0)⁸R⁴, -S(0)⁸NR⁴R⁵, -NR⁴S(0)⁸R⁵, -NR⁴C(0)R⁵, -OS(0)⁸R⁵, -NR⁴C(0)OR⁵, -(CR⁴R⁵ₙ)ₙC(0)OR⁴, -CR⁴R⁵ₙ(CO)NR⁴R⁵, -(CR⁴R⁵ₙ)ₙS(0)⁸NR⁴R⁵, -CR⁴R⁵ₙN(R⁴C(0)R⁴, -(CR⁴R⁵ₙ)ₙOR⁴, -C(R⁶R⁷)ₙNR⁴R⁵, -C(R⁶R⁷)ₙCO(R⁴) and -S(0)⁸pC(R⁶R⁷)ₙC(0)OR⁴; wherein R² and R³ is each optionally substituted with one or more substituents selected from halo, straight chain or branched chain alkyl, alkylidiol,
hydroxyalkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocycle, alkylsulfonyl, oxo, nitro, cyano, -(CR R 7 )n C(0)R 4 0 OR 4 , -(CR R 7 )n (CO)NR 4 R 5 , -OR 4 , -SR 4 or -NR 4 R 5 ;
in addition to R 2 and R 3 , ring-B is further optionally substituted with one or more substituents selected from halo, straight chain or branched chain alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, alkylsulfonyl, oxo, nitro, cyano, -COOR 4 , -C(0)NR 4 R 5 , -OR 4 , -SR 4 or -NR 4 R 5 ,
R 4 and R 5 are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl and heterocyclylalkyl; or
R 4 and R 5 taken together form a monocyclic or a bicyclic ring system which is saturated or partially unsaturated and optionally have additional heteroatoms selected from O, N or S, said ring system is further optionally substituted with 1 to 4 substituents independently selected from halo, alkyl, alkenyl, alkynyl, nitro, cyano, -OR 4 , -SR 4 , -NR 4 R 5 , oxo, alkylsulfonyl, -COOR 4 , -C(0)NR 4 R 5 , cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl or heteroarylalkyl;
R 6 and R 7 are independently selected from the group consisting of hydrogen, fluorine, OR 4 , alkyl, cycloalkyl and perfluoroalkyl; or
R 6 and R 7 taken together form a monocyclic or a bicyclic ring system which is saturated or partially unsaturated and optionally have additional heteroatoms selected from O, N or S, said ring system is further optionally substituted with 1 to 4 substituents independently selected from halo, alkyl, alkenyl, alkynyl, nitro, cyano, oxo, -OR 4 , -SR 4 , -NR 4 R 5 , alkylsulfonyl, -COOR 4 , -C(0)NR 4 R 5 , cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroarylalkyl;
wherein R 4 and R 5 are as described above;
R 8 is selected from hydrogen, halogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl or heteroarylalkyl;
rings A, C and E are each optionally substituted with 1 to 4 substituents independently selected from alkyl, alkenyl, alkynyl, methylenedioxy, halogen, mono, di or perhaloalkyl, monohaloalkoxy, dihaloalkoxy or perhaloalkoxy, nitrile, nitro, oxo, amidino, -NR 4 R 5 , -OR 4 , -S(0)p R 4 , -S(0)p NR 4 R 5 , -NR 4 S(0)p R 5 , -NR 4 C(0)R 5 , -OS(0)0 R 5 , -NR 4 C(0)OR 5 , -NR 4 C(0)NR 4 R 5 , -(CR R 7 )n C(0)OR 4 , -(CR R 7 )n C(0)NR 4 R 5 , -(CR R 7 )n C(0)R 4 , cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkenyl, aryloxy or heteroaryloxy groups;
wherein p = 0-2 and n = 0-4.
2. The compound as claimed in claim 1, or their stereoisomers, tautomers, prodrugs, pharmaceutically acceptable salts, polymorphs, solvates and formulations thereof, wherein

ring A is selected from

\[ \text{structures} \]

ring B is selected from:

\[ \text{structures} \]

ring C is selected from

\[ \text{structures} \]

E is a cycloalkyl or a heterocyclyl and is selected from

\[ \text{structures} \]
rings A, C and E are each optionally substituted with 1 to 4 substituents independently selected from alkyl, halogen, mono, di or perhaloalkyl, nitrile, oxo, -NR\textsuperscript{4}R\textsuperscript{5}, -OR\textsuperscript{4}, -S(0)\textsubscript{p}R\textsuperscript{4}, -S(0)\textsubscript{p}NR\textsuperscript{4}R\textsuperscript{3}, -NR\textsuperscript{4}C(0)R\textsuperscript{5}, -(CR\textsuperscript{6}R\textsuperscript{7})\textsubscript{n}C(0)OR\textsuperscript{4}, -(CR\textsuperscript{6}R\textsuperscript{7})\textsubscript{n}C(0)NR\textsuperscript{4}R\textsuperscript{5}, -(CR\textsuperscript{6}R\textsuperscript{7})\textsubscript{n}C(0)R\textsuperscript{4} or cycloalkyl; wherein p = 0-2; n = 0-4;
X is O;
R\textsuperscript{1} is selected from the group consisting of hydrogen and alkyl;
R\textsuperscript{2} and R\textsuperscript{3} are independently selected from the group consisting of hydrogen, halogen, alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, mono, di or tri substituted haloalkyl, nitrile, oxo, -NR\textsuperscript{4}R\textsuperscript{5}, -OR\textsuperscript{4}, -S(0)\textsubscript{p}R\textsuperscript{4}, -S(0)\textsubscript{p}NR\textsuperscript{4}R\textsuperscript{5}, -NR\textsuperscript{4}C(0)R\textsuperscript{5}, -OS(0)\textsubscript{p}R\textsuperscript{5}, -NR\textsuperscript{4}C(0)OR\textsuperscript{5}, -(CR\textsuperscript{6}R\textsuperscript{7})\textsubscript{n}C(0)OR\textsuperscript{4}, -(CR\textsuperscript{6}R\textsuperscript{7})\textsubscript{n}(CO)NR\textsuperscript{4}R\textsuperscript{5}, -(CR\textsuperscript{6}R\textsuperscript{7})\textsubscript{n}S(0)\textsubscript{p}NR\textsuperscript{4}R\textsuperscript{5}, -(CR\textsuperscript{6}R\textsuperscript{7})\textsubscript{n}N(R\textsuperscript{4})C(0)R\textsuperscript{4}, -(CR\textsuperscript{6}R\textsuperscript{7})\textsubscript{n}OR\textsuperscript{4}, -C(R\textsuperscript{6}R\textsuperscript{7})\textsubscript{n}NR\textsuperscript{4}R\textsuperscript{5}, -C(R\textsuperscript{6}R\textsuperscript{7})\textsubscript{n}CO(R\textsuperscript{4}) and -S(0)\textsubscript{p}C(R\textsuperscript{6}R\textsuperscript{7})\textsubscript{n}C(0)OR\textsuperscript{4}; wherein R\textsuperscript{2} and R\textsuperscript{3} is each optionally substituted with one or more substituents selected from halo, straight chain or branched chain alkyl, alkyldiol, hydroxyalkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocycle, alkylsulfonyl, oxo, nitro, cyano, -(CR\textsuperscript{6}R\textsuperscript{7})\textsubscript{n}C(0)OR\textsuperscript{4}, -(CR\textsuperscript{6}R\textsuperscript{7})\textsubscript{n}(CO)NR\textsuperscript{4}R\textsuperscript{5}, -OR\textsuperscript{4}, -SR\textsuperscript{4} or -NR\textsuperscript{4}R\textsuperscript{5}; wherein n = 0-4.

3. The compound as claimed in claim 1, or their stereoisomers, tautomers, prodrugs, pharmaceutically acceptable salts, polymorphs, solvates and formulations thereof, wherein E is -N(G)R\textsuperscript{8} wherein G is selected from
4. A process for the preparation of a compound of formula (I), their stereoisomers, tautomers, prodrugs, pharmaceutically acceptable salts, polymorphs, solvates, wherein said process comprising of:

reacting an acid of formula (II)

\[
\begin{align*}
\text{E} & \quad \text{D} \\
\text{C} & \quad \text{O} \quad \text{X} \\
\text{A} & \quad \text{R}
\end{align*}
\]

wherein R is hydrogen, alkyl or arylalkyl, with a compound of formula (III)

\[
\begin{align*}
\text{B} & \quad \text{R}^1 \\
\text{R}^2 & \quad \text{R}^3 \\
\text{H} & \quad \text{N} \quad \text{X}
\end{align*}
\]

in presence of a suitable amide coupling reagent; optionally hydrolyzing; and optionally further coupling with an amine of formula NHR\(^6\)R\(^7\) to obtain compound of formula (I).

5. A compound as claimed in claim 1 which is

4. \{2-[2-Cyclopentyloxy-2-(4-cyclopropanesulfonyl-phenyl)-acetylamino]-thiazol-5-yloxy\} benzoic acid methyl ester,

2-Cyclohexyloxy-2-(4-cyclopropanesulfonyl-phenyl)-N-thiazolo[5,4-b]pyridin-2-yl-acetamide,

2-(cyclohexoxy)-N-(5-ethoxythiazolo[5,4-b]pyridin-2-yl)-2-(4-tetrahydropyran-4-ylsulfonlyphenyl)acetamide,
2-Cyclopentyloxy-N-(5-fluoro-thiazol-2-yl)-2-[4-(pyrrolidine-1-sulfonyl)-phenyl]-acetamide,
tert-Butyl 6-[[2-(cyclopropylsulfonylphenyl)-2-indan-2-yloxy-acetyl]amino] pyridine-3-carboxylate,
tert-butyl 6-[[2-(cyclopropylsulfonylphenyl)-2-(9-methylspiro[5.5]undecan-9-yl)oxy-acetyl]amino]pyridine-3-carboxylate,
4-[[2-Cyclohexyloxy-2-(cyclopropanesulfonyl-phenyl)-acetylamino]-thiazol-5-yloxy]-benzoic acid methyl ester,
2-Cyclopentyloxy-2-(cyclopropanesulfonyl-phenyl)-N-thiazolo[5,4-b]pyridin-2-yl-acetamide,
2-Cyclopentyloxy-2-(cyclopropanesulfonyl-phenyl)-N-(5-pyrazol-1-yl-thiazol-2-yl)-acetamide,
2-Cyclopentyloxy-2-(cyclopropanesulfonyl-phenyl)-N-(5-morpholin-4-yl-thiazol-2-yl)-acetamide,
2-Cyclohexyloxy-N-(5-fluoro-thiazol-2-yl)-2-[4-(tetrahydro-pyran-4-sulfonyl)-phenyl]-acetamide,
methyl 5-[2-[[2-(cyclopropylsulfonylphenyl)-2-(oxocyclohexoxy)acetyl]amino] thiazol-5-yloxy-2-methyl-benzoate,
methyl 4-[[2-(cyclopropanesulfonylphenyl)-2-indan-1-yloxy-acetyl]amino] thiazol-5-yloxy-2-methyl-benzoate,
methyl 4-[2-[(4-cyclopropylsulfonylphenyl)-2-indan-2-yloxy-acetyl]amino][thiazol-5-yl]oxy-2-methyl-benzoate,
ethyl 2-[5-chloro-2-[(4-cyclopropylsulfonylphenyl)-2-indan-1-yloxy-acetyl]amino][thiazol-4-yl]acetate,
ethyl 2-[5-chloro-2-[(4-cyclopropylsulfonylphenyl)-2-indan-2-yloxy-acetyl]amino][thiazol-4-yl]acetate,
tert-butyl 6-[[2-(cyclohexoxy)-2-(4-cyclopropylsulfonylphenyl)acetyl]amino][pyridine-3-carboxylate],
tert-butyl 6-[[2-(1-adamantylmethoxy)-2-(4-cyclopropylsulfonylphenyl)acetyl]amino][pyridine-3-carboxylate],
4-[(2-Cyclohexyloxy-2-(4-cyclopropanesulfonyl-phenyl)-acetylamino]-thiazol-5-yloxy]-benzoic acid,
6-[[2-(4-cyclopropylsulfonylphenyl)-2-indan-2-yloxy-acetyl]amino][pyridine-3-carboxylic acid],
6-[[2-(4-cyclopropylsulfonylphenyl)-2-(9-methylspiro[5.5]undecan-9-yl)oxy-acetyl]amino][pyridine-3-carboxylic acid],
4-[(2-Cyclohexyloxy-2-(4-cyclopropanesulfonyl-phenyl)-acetylamino]-thiazol-5-yloxy]-benzoic acid,
{5-Chloro-2-[2-cyclohexyloxy-2-(4-cyclopropanesulfonyl-phenyl)-acetylamino]-thiazol-4-yl]-acetic acid,
{5-Chloro-2-[2-cyclopentyloxy-2-(4-cyclopropanesulfonyl-phenyl)-acetylamino]-thiazol-4-yl]-acetic acid,
5-[2-((4-cyclopropylsulfonylphenyl)-2-(4-xocyclohexoxy)acetyl]amino][thiazol-5-yl]oxy-2-methyl-benzoic acid,
4-[2-[[2-(4-cyclopropylsulfonylphenyl)-2-indan-1-yloxy-acetyl]amino][thiazol-5-yl]oxy-2-methyl-benzoic acid,
4-[2-[[2-(4-cyclopropylsulfonylphenyl)-2-indan-2-yloxy-acetyl]amino][thiazol-5-yl]oxy-2-methyl-benzoic acid,
2-[5-chloro-2-[[2-(4-cyclopropylsulfonylphenyl)-2-indan-1-yloxy-acetyl]amino][thiazol-4-yl]acetic acid,
2-[5-chloro-2-[[2-(4-cyclopropylsulfonylphenyl)-2-indan-2-yloxy-acetyl]amino][thiazol-4-yl]acetic acid,
6-[[2-(cyclohexoxy)-2-(4-cyclopropylsulfonylphenyl)acetyl]amino]pyridine-3-carboxylic acid,
6-[[2-(l-adamantylmethoxy)-2-(4-cyclopropylsulfonylphenyl)acetyl]amino]pyridine-3-carboxylic acid,
6-[[2-(l-adamantylmethoxy)-2-(4-cyclopropylsulfonylphenyl)acetyl]amino]pyridine-3-carboxylic acid,
6-[[2-(2-adamantyloxy)-2-(4-cyclopropylsulfonylphenyl)acetyl]amino]pyridine-3-carboxylic acid,
N-{{5-[4-(Azetidin-1-carbonyl)-phenoxy]-thiazol-2-yl}-2-cyclohexyloxy-2-(4-cyclopropanesulfonyl-phenyl)-acetamide,
4-{2-[2-Cyclohexyloxy-2-(4-cyclopropanesulfonyl-phenyl)-acetylamino]-thiazol-5-yloxy}-benzamide,
N-{{5-[4-(Azetidin-1-carbonyl)-phenoxy]-thiazol-2-yl}-2-cyclopentyloxy-2-(4-cyclopropanesulfonyl-phenyl)-acetamide,
4-{2-[2-Cyclopentyloxy-2-(4-cyclopropanesulfonyl-phenyl)-acetylamino]-thiazol-5-yloxy }-benzamide,
2-(cyclobutoxy)-2-(4-cyclopropylsulfonylphenyl)-N-[3-(1,2-dihydroxyethyl)-1,2,4-thiadiazol-5-yl]acetamide,
2-[5-chloro-2-[[2-(cyclobutoxy)-2-(4-cyclopropylsulfonylphenyl)acetyl] amino]thiazol-4-yl]-2-hydroxy-acetic acid,
N-[4-(1-acetyl-4-piperidyl)thiazol-2-yl]-2-(cyclobutoxy)-2-(4-cyclopropylsulfonylphenyl)acetamide,
2-(cyclobutoxy)-2-(4-cyclopropylsulfonylphenyl)-N-[5-[4-(1,2-dihydroxyethyl)phenoxy]thiazol-2-yl] acetamide,
2-(cyclopentoxy)-2-(4-cyclopropylsulfonylphenyl)-N-(4,5,6,7-tetrahydro-1,3-benzothiazol-2-yl)acetamide,
2-(cyclopentoxy)-2-(4-cyclopropylsulfonylphenyl)-N-thiazolo[5,4-d]pyrimidin-2-yl acetamide,
2-(cyclopentoxy)-2-(4-cyclopropylsulfonylphenyl)-N-[5-[4-(hydroxymethyl)phenoxy]thiazol-2-yl] acetamide,
2-(cyclopentoxy)-2-(4-cyclopropylsulfonylphenyl)-N-(5-methyl-6,7-dihydro-4H-thiazolo[4,5-c]pyridin-2-yl)acetamide,
2-(cyclohexoxy)-2-(4-cyclopropylsulfonylphenyl)-N-[4-(1,2-dihydroxyethyl)thiazol-2-yl]acetamide,
2-[(cyclohexyloxy)-2-(4-cyclopropylsulfonylphenyl)acetyl]amino]pyrazole-1-carboxylic acid,
2-[2-[(cyclohexyloxy)-2-(4-cyclopropylsulfonylphenyl)acetyl]amino]thiazole-5-yl]oxybenzoic acid,
4-[[6-[[2-(cyclopentoxy)-2-(4-tetrahydropyran-4-ylsulfonylphenyl)acetyl]amino]-3-pyridyloxy]benzoic acid,
4-[[2-[(cyclohexyloxy)-2-(4-cyclopropylsulfonylphenyl)acetyl]amino]thiazol-5-yl]benzoic acid,
N-[5-chlorothiazol-2-yl]-2-cyclopentylsulfanyl-2-(4-cyclopropylsulfonylphenyl)acetamide,
2-(cyclopentylamino)-2-(4-cyclopropylsulfonylphenyl)-N-(6-fluoro-1,3-benzothiazol-2-yl)acetamide,
4-[2-[2-(cyclohexylamino)-2-(4-cyclopentylsulfonylphenyl)acetyl]amino]thiazol-5-yl]oxybenzoic acid,
N-[4-(1-acetyl-4-piperidyl)thiazol-2-yl]-2-(cyclobutoxy)-2-(4-pyrrolidin-1-ylsulfonylphenyl)acetamide,
2-[5-chloro-2-[(2-cyclobutoxy)-2-(4-morpholinosulfonylethenyl)acetyl]amino]thiazol-4-yl]-2-hydroxy-acetic acid; formic acid,
2-(cyclopentoxy)-2-(4-morpholinosulfonylphenyl)N-(4,5,6,7-tetrahydro-1,3-benzothiazol-2-yl)acetamide,
2-cyclopentylsulfanyl-2-(4-pyrrolidin-1-ylsulfonylphenyl)-N-thiazolo[5,4-d]pyrimidin-2-ylacetamide,
2-[2-(cyclopentoxy)-2-[4-(3-oxocyclopentyl)sulfonylphenyl)acetyl]amino]thiazol-5-yl]sulfanylacetic acid,
2-[3-(2-(cyclohexoxy)-2-[4-(3-oxocyclopentyl)sulfonylphenyl]acetyl]amino]pyrazol-1-yl]acetic acid,
4-[2-[2-(cyclohexylamino)-2-(4-pyrrolidin-1-ylsulfonylphenyl)acetyl]amino]thiazol-5-yl]oxybenzoic acid,
2-[2-[2-(cyclohexylamino)-2-[4-(1-piperidylsulfonyl)phenyl]acetyl]amino]thiazol-4-yl]-2-isopropanoyl-acetic acid,
2-[2-[2-(cycloheptoxy)-2-(4-pyrrolidin-1-ylsulfonylphenyl)acetyl]amino]-5-fluoro-thiazol-4-yl]-2-methyl-propanoic acid,
2-(cyclopentoxy)-N-(6-fluoro-1,3-benzothiazol-2-yl)-2-[4-(1-piperidylsulfonyl)phenyl]acetamide,
2-cyclopentylsulfanyl-N-(6-fluoro-1,3-benzothiazol-2-yl)-2-[4-(1-piperidylsulfonyl)phenyl]acetamide,
2-[2-(cyclopentoxy)-2-[4-(1-piperidylsulfonyl)phenyl]acetyl]amino]-5-(4-fluorophenoxy)thiazole-4-carboxylic acid,
4-[2-[2-(cyclopentoxy)-2-(4-sulfamoylphenyl)acetyl]amino]thiazol-5-yl]oxybenzoic acid,
4-[2-[4-(cyclopentylsulfamoyl)phenyl]-2-cyclopentylsulfanyl-acetyl]amino] thiazol-5-yl]oxybenzoic acid,
2-[4-[1-(cyclopentoxy)-2-[3-(1,2-dihydroxyethyl)-1,2,4-thiadiazol-5-yl]amino]-2-oxo-ethyl]phenyl sulfonylethylacetate-mono acetic acid,
2-(cyclohexoxy)-2-[4-cyclopropylmethyl(4-pyridyl)sulfamoyl]phenyl]-N-[3-(1,2-dihydroxyethyl)]-1,2,4-thiadiazol-5-yl]acetamide,
2-[[2-[4-[acyethyl(ethyl)sulfamoyl]phenyl]-2-(cyclohexoxy)acetyl]amino]-1,3-benzothiazole-6-carboxylic acid,
2-[[2-(cyclohexoxy)-2-[4-[ethyl(methoxymethyl)sulfamoyl]phenyl]acetyl]amino] thiazol-5-yl)sulfanylacetic acid
2-(cyclopentoxy)-2-(6-cyclopropylsulfonyl-3-pyridyl)-N-(1,2,4-thiadiazol-5-yl)acetamide,
2-(cyclohexoxy)-2-(6-cyclopropylsulfonyl-3-pyridyl)-N-(1,2,4-thiadiazol-5-yl)acetamide,
2-[5-chloro-2-[2-(cyclopentoxy)-2-(6-cyclopropylsulfonyl-3-pyridyl)acetyl]amino]thiazol-4-yl] acetic acid,
2-[5-chloro-2-[2-(cyclohexoxy)-2-(6-cyclopropylsulfonyl-3-pyridyl)acetyl]amino]thiazol-4-yl acetic acid,
N-[4-(1-acetyl-4-piperidyl)thiazol-2-yl]-2-(cyclopentoxy)-2-(6-cyclopropylsulfonyl-3-pyridyl)acetamide,
N-[4-(1-acetyl-4-piperidyl)thiazol-2-yl]-2-(cyclohexoxy)-2-(6-cyclopropylsulfonyl-3-pyridyl)acetamide,
2-(cyclopentoxy)-2-(6-cyclopropylsulfonyl-3-pyridyl)-N-[5-[4-(1,2-dihydroxyethyl)phenoxy] thiazol-2-yl]acetamide,
2-(cyclohexoxy)-2-(6-cyclopropylsulfonyl-3-pyridyl)-N-[5-[4-(1,2-dihydroxyethyl)phenoxy] thiazol-2-yl]acetamide,
2-(cyclopentoxy)-2-(5-cyclopentylsulfonyl-2-pyridyl)-N-(4,5,6,7-tetrahydro-1,3-benzothiazol-2-yl) acetamide,
2-(cyclohexoxy)-2-(5-cyclopentylsulfonyl-2-pyridyl)-N-(4,5,6,7-tetrahydro-1,3-benzothiazol-2-yl) acetamide,
2-(cyclopentoxy)-2-(5-cyclopentylsulfonyl-2-pyridyl)-N-thiazolo[5,4-d]pyrimidin-2-yl]acetamide,
2-(cyclohexoxy)-2-(5-cyclopentylsulfonyl-2-pyridyl)-N-thiazolo[5,4-d]pyrimidin-2-yl]acetamide,
4-[2-[[2-(cyclopentoxy)-2-(5-pyrrolidin-1-ylsulfonyl-2-pyridyl)acetyl]amino]thiazol-5-yl]oxybenzoic acid,
4-[2-[[2-(cyclohexoxy)-2-(5-pyrrolidin-1-ylsulfonyl-2-pyridyl)acetyl]amino]thiazol-5-yl]oxybenzoic acid,
2-(cyclopentoxy)-2-(5-cyclopentylsulfonyl-2-pyridyl)-N-(5-methyl-6,7-dihydro-4H-thiazolo[4,5-c]pyridin-2-yl)acetamide,
2-(cyclohexoxy)-2-(5-cyclopentylsulfonyl-2-pyridyl)-N-(5-methyl-6,7-dihydro-4H-thiazolo[4,5-c]pyridin-2-yl)acetamide,
2-(cyclopentoxy)-2-(5-cyclopropylsulfonyl-2-pyridyl)-N-(5-ethoxythiazolo[5,4-b]pyridin-2-yl)acetamide,
2-(cyclohexoxy)-2-(5-cyclopropylsulfonyl-2-pyridyl)-N-(5-ethoxythiazolo[5,4-b]pyridin-2-yl)acetamide
2-(4-cyclopropylsulfonylphenyl)-2-spiro[4.5]decan-3-yloxy-N-(1,2,4-thiadiazol-5-yl)acetamide,
2-[5-chloro-2-[[2-(4-cyclopropylsulfonylphenyl)-2-spiro[4.5]decan-8-yl]amino]thiazol-4-yl] acetic acid,
N-[4-(1-acetyl-4-piperidyl)thiazol-2-yl]-2-(1-adamantyloxy)-2-(4-cyclopropylsulfonylphenyl)acetamide,
2-(4-cyclopropylsulfonylphenyl)-N-[5-[4-(1,2-dihydroxyethyl)phenoxy]thiazol-2-yl]-2-(1-adamantyloxy)-2-(4-cyclopropylsulfonylphenyl)acetamide,
2-amino-2-(4-cyclopentylsulfonylphenyl)-N-(4,5,6,7-tetrahydro-1,3-benzothiazol-2-yl)acetamide;
spiro[4.5]decan-8-amine,
2-[[4-[1-(1-adamantyloxy)-2-oxo-2-(thiazolo[5,4-d]pyrimidin-2-ylamino)ethyl]phenyl]sulfonyl-cyclopentyl-amino] acetic acid,
4-[2-[[2-(4-pyrrolidin-1-ylsulfonylphenyl)-2-spiro[4.5]decan-8-yloxy-acetyl]amino]thiazol-5-yl]oxybenzoic acid,
N-(5-methyl-6,7-dihydro-4H-thiazolo[4,5-c]pyridin-2-yl)-2-[4-(1-piperidylsulfonyl)phenyl]-2-spiro[4.5]decan-3-yloxy-acetamide,
2-[4-[acetyl(ethyl)sulfamoyl]phenyl]-N-(5-ethoxythiazolo[5,4-b]pyridin-2-yl)-2-spiro[4.5]decan-3-yloxy-acetamide,
4-[2-[2-(4-cyclopropylsulfonylphenyl)-2-(3-oxocyclopentoxy)acetyl]amino]thiazol-5-yl]oxybenzoic acid,
2-[5-chloro-2-[2-(4-cyclopropylsulfonylphenyl)-2-(4-oxocyclohexoxy)acetyl] amino]thiazol-4-yl] acetic acid

6. A compound of formula (I), as claimed in any one of the claims 1 to 5, or its stereoisomers, tautomers, prodrugs, pharmaceutically acceptable salts, polymorphs, solvates and formulations thereof, for treating a disease through Glucokinase activation.

7. A compound of formula (I), as claimed in any one of the claims 1 to 5, or its stereoisomers, tautomers, prodrugs, pharmaceutically acceptable salts, polymorphs, solvates and formulations thereof, for treating a disease through Glucokinase deinhibition.

8. A compound of formula (I), as claimed in any one of the claims 1 to 5, or its stereoisomers, tautomers, prodrugs, pharmaceutically acceptable salts, polymorphs, solvates and
formulations thereof, for prophylactic or therapeutic treatment of hyperglycemia or diabetes, particularly type II diabetes.

9. A compound of formula (I), as claimed in any one of the claims 1 to 5, or its stereoisomers, tautomers, prodrugs, pharmaceutically acceptable salts, polymorphs, solvates and formulations thereof, for preventing diabetes, particularly type II diabetes, in a human demonstrating pre-diabetic hyperglycemia or impaired glucose tolerance.

10. A compound of formula (I), as claimed in any one of the claims 1 to 5, or its stereoisomers, tautomers, prodrugs, pharmaceutically acceptable salts, polymorphs, solvates and formulations thereof, for combined treatment or prevention of diabetes and obesity.

11. A compound of formula (I), as claimed in any one of the claims 1 to 5, or its stereoisomers, tautomers, prodrugs, pharmaceutically acceptable salts, polymorphs, solvates and formulations thereof, for treating or preventing obesity.

12. A compound of formula (I), as claimed in any one of the claims 1 to 5, or its stereoisomers, tautomers, prodrugs, pharmaceutically acceptable salts, polymorphs, solvates and formulations thereof, for treatment or prevention of dyslipidemia.

13. A compound of formula (I), as claimed in any one of the claims 1 to 5, or its stereoisomers, tautomers, prodrugs, pharmaceutically acceptable salts, polymorphs, solvates and formulations thereof, for combined treatment or prevention of diabetes, obesity and dyslipidemia.

14. A compound of formula (I), as claimed in any one of the claims 1 to 5, or its stereoisomers, tautomers, prodrugs, pharmaceutically acceptable salts, polymorphs, solvates and formulations thereof, for treating hyperglycemia, IGT, Syndrome X, type 2 diabetes, type 1 diabetes, dyslipidemia or hyperlipidemia, hypertension, for the treatment or prophylaxis of obesity, for lowering of food intake, for appetite regulation, for regulating feeding behaviour.

15. A compound of formula (I), as claimed in any one of the claims 1 to 5, or its stereoisomers, tautomers, prodrugs, pharmaceutically acceptable salts, polymorphs, solvates and formulations thereof, for enhancing the secretion of enteroincretins, like GLP-1 and GIP, thereby managing diseases or disorders associated with modulation of secretions of enteroincretins, like hyperglycemia, insulin resistance, impaired glucose tolerance, obesity, gastric emptying, gastroparesis, satiety, leptin resistance, dyslipidemia, wound healing, diabetic complications, such as nephropathy, retinopathy, neuropathy and cataracts.

16. A pharmaceutical composition comprising, as an active ingredient, at least one compound of formula (I), as claimed in any one of the claims 1 to 5, or its stereoisomers, tautomers,
prodrugs, pharmaceutically acceptable salts, polymorphs, and solvates thereof, together with one or more pharmaceutically acceptable carriers or excipients.

17. A pharmaceutical composition comprising, as an active ingredient, at least one compound of formula (I), as claimed in any one of the claims 1 to 5, or its stereoisomers, tautomers, prodrugs, pharmaceutically acceptable salts, polymorphs, and solvates thereof, in combination with one or more pharmaceutically acceptable therapeutically active agents.

18. The pharmaceutical composition as claimed in claim 17 wherein, the pharmaceutically acceptable therapeutically active agent is selected from antidiabetic agents, anti-hyperglycemic agents, anti-obesity agents, anti-hypertensive agents or anti-dyslipidemic agents.

19. The pharmaceutical composition as claimed in claim 17 or 18 wherein the pharmaceutically acceptable therapeutically active agent is selected from insulin secretagogues like sulfonylureas selected from amlaryl, glyburide, glimepiride, glipiride, glipizide; insulinotropic sulfonyl urea receptor ligands like meglitinides selected from nateglinide, repaglinide; biguanides like metformin, phenformin, buformin; glucagon antagonists like a peptide or non-peptide glucagon antagonist; glucosidase inhibitors like acarbose, miglitol; glucose sensitive insulinoactive agents like GLP-1, GLP-1 mimetics like exendin-4; insulin sensitizers like troglitazone, rosiglitazone, pioglitazone; dipeptidyl peptidase-IV inhibitors like sitagliptin, vildagliptin; sibutramine, orlistat, rimonabant; fibrates like gemfibrozil, fenofibrate; niacin; statins like rosuvastatin, atorvastatin, simvastatin; cholesterol absorption inhibitors like ezetimibe; bile acid sequestrants like cholestyramine; diuretics like hydrochlorothiazides, mannitol, indapamide, furosemide; angiotensin converting enzyme (ACE) inhibitors like captopril, enalapril; angiotensin-II receptor type-I blockers (ARB) like losartan, irbesartan; rennin inhibitors like aliskerin; β-adrenergic receptor blockers like atenolol, metoprolol; calcium channel blockers like amlodipine, nifedipine; aldosterone receptor antagonist like spironolactone, aldosterone synthase inhibitors like FAD286.

20. A use of compound of formula (I) as claimed in any of the claims 1-5, its polymorphs, stereoisomers, pharmaceutically acceptable salt, solvate or pro-drug thereof, in the manufacture of a medicament for the activation of Glucokinase.

21. A method of treatment of glucokinase activator mediated disease by administering a therapeutically effective amount of a compound of formula (I) as claimed in any of the claims 1-5, its polymorphs, stereoisomers, pharmaceutically acceptable salt, solvate or pro-drug thereof to a mammal in need of such treatment.
22. A method of combined treatment or prevention of diabetes, obesity and dislipidemia by administering an effective amount of a compound of formula (I) as claimed in any of the claims 1-5, its polymorph, stereoisomer, prodrug, solvate or a pharmaceutically acceptable salt thereof, to a mammal in need of such treatment.

23. A method of combined treatment of diabetes and obesity by administering an effective amount of a compound of formula (I) as claimed in any of the claims 1-5, its polymorph, stereoisomer, prodrug, solvate or a pharmaceutically acceptable salt thereof, to a mammal in need of such treatment.
### A. CLASSIFICATION OF SUBJECT MATTER

**IPC(8) -** A01N 37/44; A61K 31/16; A61K 31/195 (2011.01)

**USPC -** 514/563, 514/613

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)
USPC: 514/563: 514/613

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 514/365-366 (see search terms below)

Electronic database consulted during the international search (name of database and, where practicable, search terms used)
WEST: PGPB, USPT, USOC, EPAB, JPAB

Google: Scholar/patents: acetamide glucokinase activation deinhibition diabetes obesity dyslipidemia antihypertensive cyclopropyl phenyl indane sulfonyl cyclicalkyl

### C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
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<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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<tbody>
<tr>
<td>X</td>
<td>WO 2009/047798 A2 (BHUNIYA et al.) 16 April 2009 (16.04.2009) pg 5, ln 11-25; pg 6, ln 8-34; pg 7, ln 1-21; pg 15, ln 16-21; pg 16, 1-32; pg 18, ln 3-13; pg 25, ln 19-27; pg 27, ln 1-31; pg 28, ln 1-10; pg 30, ln 27-31; pg 31, ln 1-10, ln 20-23; pg 32, ln 11-24</td>
<td>1-3, 5-18, 20-23</td>
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<td>Y</td>
<td>WO 2008/104994 A1 (MOOKHTIAR et al.) 04 September 2008 (04.09.2008) pg 6, ln 1-2; pg 7, ln 4-5; pg 11, ln 4-9; pg 13, ln 10-18; pg 14, ln 1-3</td>
<td>1-3, 5-18, 20-23</td>
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* 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
03 December 2011 (03.12.2011)

Date of mailing of the international search report
29 DEC 2011

Name and mailing address of the ISA/US
Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 2231 3-1450
Facsimile No. 571-272-3281

Authorized officer: Lee W. Young
PCT Helpdesk: 571-272-4300
PCT OSP: 571-272-7774
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<td>2. ☐ Claims Nos.: because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:</td>
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<td>3. ☒ Claims Nos. 19 because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).</td>
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<td>2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.</td>
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<td>3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:</td>
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<td>4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:</td>
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<th>The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.</th>
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Form PCT/ISA/210 (continuation of first sheet (2)) (July 2009)