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CA 2628486 A1 2007/05/10

(21) 2 628 486

(12) DEMANDE DE BREVET CANADIEN
CANADIAN PATENT APPLICATION

(13) A1

(86) Date de dépôt PCT/PCT Filing Date: 2006/11/03
(87) Date publication PCT/PCT Publication Date: 2007/05/10
(85) Entrée phase nationale/National Entry: 2008/05/02
(86) N° demande PCT/PCT Application No.: EP 2006/068088
(87) N° publication PCT/PCT Publication No.: 2007/051846
(30) Priorités/Priorities: 2005/11/03 (GB0522456.3); 2006/02/16 (GB0603132.2)

(51) Cl.Int./Int.Cl. *C07D 405/12* (2006.01), *A61K 31/422* (2006.01), *A61K 31/427* (2006.01), *A61K 31/4433* (2006.01), *A61K 31/497* (2006.01), *A61K 31/501* (2006.01), *A61K 31/505* (2006.01), *A61P 3/10* (2006.01), *C07D 309/06* (2006.01), *C07D 413/12* (2006.01), *C07D 417/12* (2006.01)

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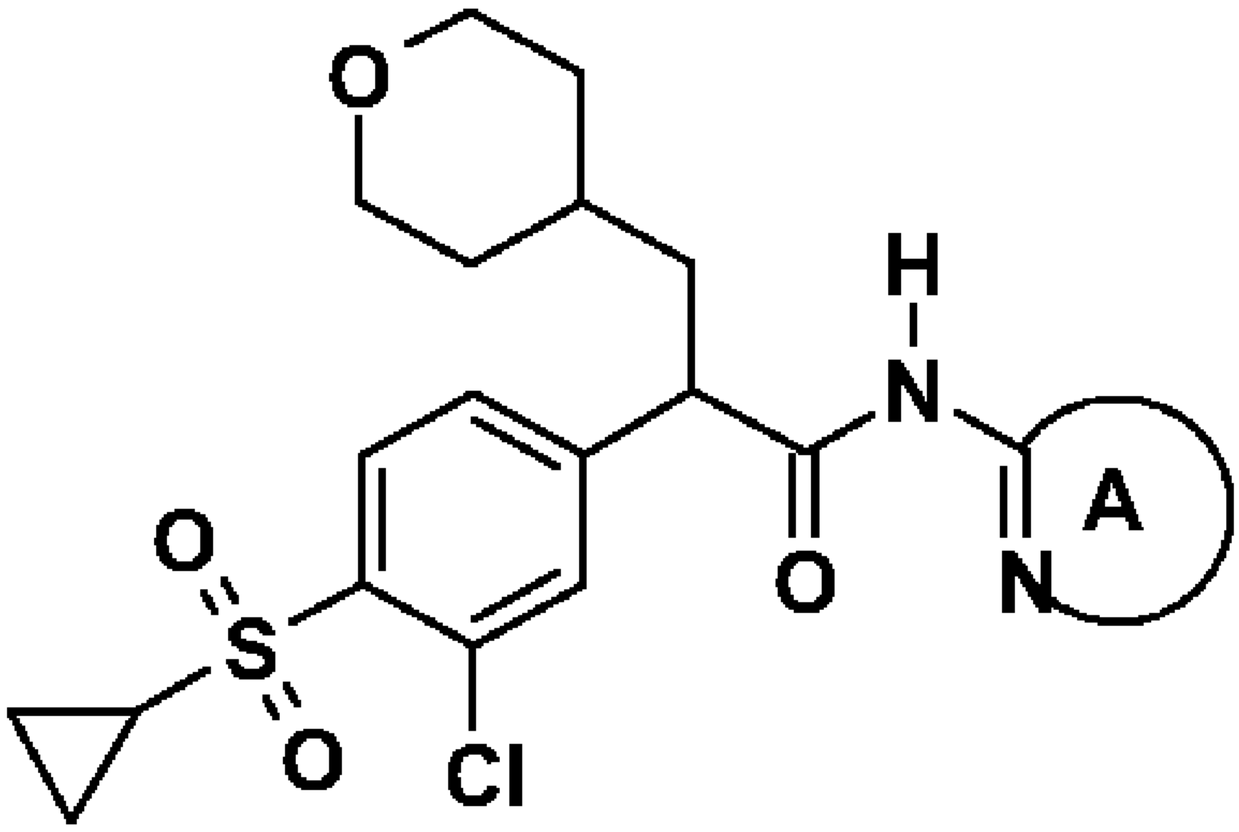
(54) Titre : AMIDES A SUBSTITUTION TRICYCLO
(54) Title: TRICYCLO SUBSTITUTED AMIDES



(I)

(57) Abrégé/Abstract:
Compounds of Formula (I): (formula) or pharmaceutically acceptable salts thereof, are useful in the prophylactic and therapeutic treatment of hyperglycemia and diabetes.

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
10 May 2007 (10.05.2007)

PCT

(10) International Publication Number
WO 2007/051846 A1

(51) International Patent Classification:
C07D 405/12 (2006.01) *A61K 31/501* (2006.01)
C07D 413/12 (2006.01) *A61K 31/505* (2006.01)
C07D 417/12 (2006.01) *A61K 31/422* (2006.01)
C07D 309/06 (2006.01) *A61K 31/427* (2006.01)
A61K 31/497 (2006.01) *A61P 3/10* (2006.01)
A61K 31/4433 (2006.01)

(21) International Application Number:
PCT/EP2006/068088

(22) International Filing Date:
3 November 2006 (03.11.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

0522456.3	3 November 2005 (03.11.2005)	GB
0603132.2	16 February 2006 (16.02.2006)	GB

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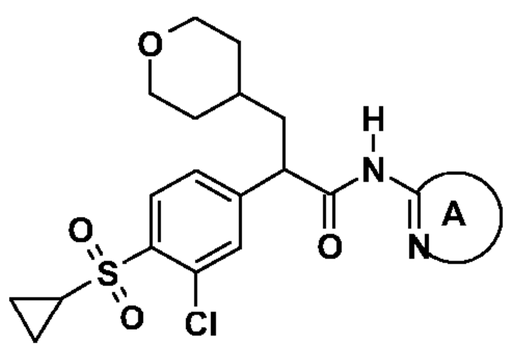
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: TRICYCLO SUBSTITUTED AMIDES



(I)

(57) Abstract: Compounds of Formula (I): (formula) or pharmaceutically acceptable salts thereof, are useful in the prophylactic and therapeutic treatment of hyperglycemia and diabetes.

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TRICYCLO SUBSTITUTED AMIDES

BACKGROUND OF THE INVENTION

The present invention is directed to tri(cyclo) substituted amide compounds. In particular, the present invention is directed to amide compounds substituted i) at the carbonyl carbon with an ethyl attached to a phenyl ring and a heterocyclic ring, and ii) at the amino with a nitrogen bearing heteroaryl ring, which are modulators of glucokinase and are useful in the prophylactic or therapeutic treatment of hyperglycemia and diabetes, particularly type II diabetes.

Glucokinase ("GK") is believed to be important in the body's regulation of its plasma glucose level. GK, found principally in the liver and pancreas, is one of four hexokinases that catalyze the initial metabolism of glucose. The GK pathway is saturated at higher glucose levels than the other hexokinase pathways (see R.L. Printz et al., *Annu. Rev. Nutr.*, 13:463-496 (1993)). GK is critical to maintaining the glucose balance in mammals. Animals that do not express GK die soon after birth with diabetes, while animals that overexpress GK have improved glucose tolerance. Activation of GK can lead to hyperinsulinemic hypoglycemia (see, for example, H.B.T. Christesen et al., *Diabetes*, 51:1240-1246 (2002)). Additionally, type II maturity-onset diabetes of the young is caused by the loss of function mutations in the GK gene, suggesting that GK operates as a glucose sensor in humans (Y. Liang et al., *Biochem. J.*, 309:167-173 (1995)). Thus, compounds that activate GK increase the sensitivity of the GK sensory system and would be useful in the treatment of hyperglycemia, particularly the hyperglycemia associated with type II diabetes. It is therefore desirable to provide novel compounds that activate GK to treat diabetes, in particular compounds which demonstrate improved properties desirable for pharmaceutical products compared to known GK activators.

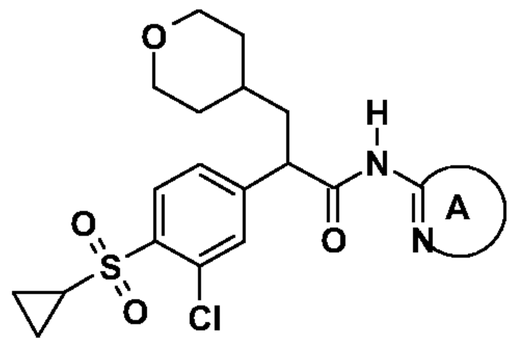
International Patent Publication No. WO2001/044216 and U.S. Patent No. 6,353,111 describe (*E*)-2,3-disubstituted-*N*-heteroarylacrylamides as GK activators. International Patent Publication No. WO2002/014312 and U.S. Patent Nos. 6,369,232, 6,388,088, and 6,441,180 describe tetrazolylphenylacetamide GK activators. International Patent Publication No. WO2000/058293, European Patent Application No. EP 1169312 and U.S. Patent No. 6,320,050 describe arylcycloalkylpropionamide GK activators. International Patent Publication No. WO2002/008209 and U.S. Patent No. 6,486,184 describe alpha-acyl and alpha-heteroatom-substituted benzene acetamide GK activators as anti-diabetic agents. International Patent Publication No. WO2001/083478 describes hydantoin-containing GK activators. International Patent Publication No. WO2001/083465 and U.S. Patent No. 6,388,071 describe alkynylphenyl heteroaromatic GK activators. International Patent Publication No. WO2001/085707 and U.S. Patent No. 6,489,485 describe para-amine substituted phenylamide GK activators. International Patent Publication No. WO2002/046173 and U.S. Patent Nos. 6,433,188, 6,441,184, and 6,448,399 describe fused heteroaromatic GK activators. International Patent Publication No. WO2002/048106 and U.S. Patent No. 6,482,951 describe isoindolin-1-one GK activators. International Patent Publication No. WO2001/085706 describes substituted phenylacetamide GK activators for treating type II diabetes. U.S. Patent No. 6,384,220 describes para-aryl or heteroaryl substituted phenyl GK activators. French Patent No. 2,834,295 describes methods for the purification and crystal structure of human GK. International Patent Publication No.

WO2003/095438 describes *N*-heteroaryl phenylacetamides and related compounds as GK activators for the treatment of type II diabetes. U.S. Patent No. 6,610,846 describes the preparation of cycloalkylheteroaryl propionamides as GK activators. International Patent Publication No. WO2003/000262 describes vinyl phenyl GK activators. International Patent Publication No. WO2003/000267 describes aminonicotinate derivatives as GK modulators. International Patent Publication No. WO2003/015774 describes compounds as GK modulators. International Patent Publication No. WO2003047626 describes the use of a GK activator in combination with a glucagon antagonist for treating type II diabetes. International Patent Publication No. WO2003/055482 describes amide derivatives as GK activators. International Patent Publication No. WO2003/080585 describes aminobenzamide derivatives with GK activity for the treatment of diabetes and obesity. International Patent Publication No. WO2003/097824 describes human liver GK crystals and their used for structure-based drug design. International Patent Publication No. WO2004/002481 discloses arylcarbonyl derivatives as GK activators. International Patent Publication Nos. WO2004/072031 and WO2004/072066 disclose tri(cyclo) substituted amide compounds as GK activators. International Patent Application PCT/GB2005/050129 (published after the priority date of the present application) discloses amide compounds substituted i) at the carbonyl carbon with an ethyl/ethenyl attached to a phenyl ring and a carbocyclic ring, and ii) at the amino with a nitrogen bearing heteroaryl or unsaturated heterocyclyl ring, which are modulators of glucokinase and are useful in the prophylactic or therapeutic treatment of hyperglycemia and diabetes, particularly type II diabetes.

The present invention provides novel GK activators which may demonstrate improved properties desirable for pharmaceutical products compared to known GK activators, such as increased potency.

SUMMARY OF THE INVENTION

Compounds represented by Formula (I):

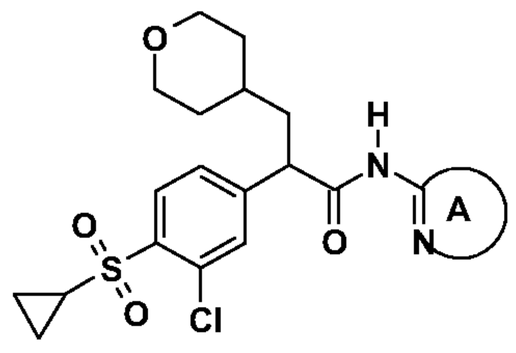


(I)

or pharmaceutically acceptable salts thereof, are useful in the prophylactic or therapeutic treatment of hyperglycemia and diabetes, particularly type II diabetes.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to compounds of Formula (I):



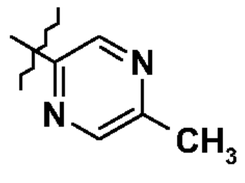
(I)

wherein A is a nitrogen containing heteroaryl ring selected from 5-methylpyrazin-2-yl, 5-methylpyrid-2-yl, 5-chloropyrid-2-yl, pyrid-2-yl, 5-methylisoxazol-3-yl, isoxazol-3-yl, 5-methylthiazol-2-yl, 6-methylpyridazin-3-yl, 1-methylpyrazol-3-yl, pyrazin-2-yl and pyrimidin-4-yl;

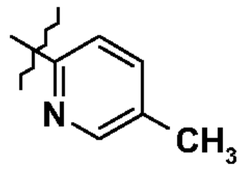
and pharmaceutically acceptable salts thereof.

A is preferably 5-methylpyrazin-2-yl or pyrazin-2-yl.

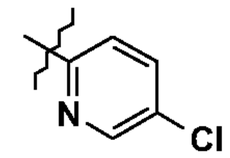
In one embodiment of the present invention A represents 5-methylpyrazin-2-yl:



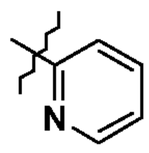
In a second embodiment of the present invention A represents 5-methylpyrid-2-yl:



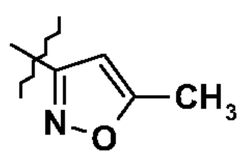
In a third embodiment of the present invention A represents 5-chloropyrid-2-yl:



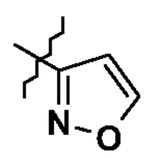
In a fourth embodiment of the present invention A represents pyrid-2-yl:



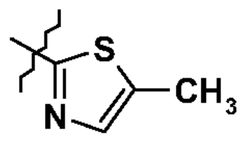
In a fifth embodiment of the present invention A represents 5-methylisoxazol-3-yl:



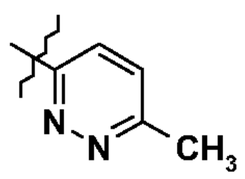
In a sixth embodiment of the present invention A represents isoxazol-3-yl:



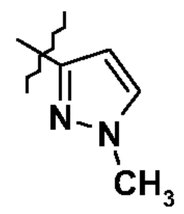
In a seventh embodiment of the present invention A represents 5-methylthiazol-2-yl:



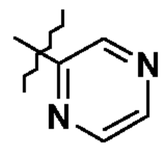
In an eighth embodiment of the present invention A represents 6-methylpyridazin-3-yl:



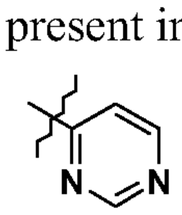
In a ninth embodiment of the present invention A represents 1-methylpyrazol-3-yl:



In a tenth embodiment of the present invention A represents pyrazin-2-yl:



In an eleventh embodiment of the present invention A represents pyrimidin-4-yl:



The carbon atom linking the phenyl ring and the tetrahydropyran containing sidechain to the amide carbonyl carbon is a chiral centre. Accordingly, at this centre, the compound may be present either as a racemate or as a single enantiomer in the (*R*)- or (*S*)-configuration. The (*R*)-enantiomers are preferred.

The term "pharmaceutically acceptable salts" includes salts prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include, for example, acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid and the like. Particularly preferred are citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric, methanesulfonic, and tartaric acids.

When the compound of the above formulae and pharmaceutically acceptable salts thereof exist in the form of solvates or polymorphic forms, the present invention includes any possible solvates and polymorphic forms. The type of solvent that forms the solvate is not particularly limited so long as the solvent is pharmacologically acceptable. For example, water, ethanol, propanol, acetone or the like can be used.

Since the compounds of Formula (I) are intended for pharmaceutical use they are preferably provided in substantially pure form, for example at least 60% pure, more suitably at least 75% pure, at least 95% pure and especially at least 98% pure (% are on a weight for weight basis).

The invention also encompasses a pharmaceutical composition that is comprised of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in combination with a pharmaceutically acceptable carrier.

Preferably the composition is comprised of a pharmaceutically acceptable carrier and a non-toxic therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

Moreover, within this embodiment, the invention encompasses a pharmaceutical composition for the prophylaxis or treatment of hyperglycemia and diabetes, particularly type II diabetes, by the activation of GK, comprising a pharmaceutically acceptable carrier and a non-toxic therapeutically effective amount of compound of Formula (I), or a pharmaceutically acceptable salt thereof.

The invention also provides the use of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, as a pharmaceutical.

The compounds and compositions of the present invention are effective for treating hyperglycemia and diabetes, particularly type II diabetes, in mammals such as, for example, humans.

The invention also provides a method of prophylactic or therapeutic treatment of a condition where activation of GK is desirable comprising a step of administering an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

The invention also provides 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), or a pharmaceutically acceptable salt thereof.

The invention also provides 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), or a pharmaceutically acceptable salt thereof.

The invention also provides the use of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, as a GK activator.

The invention also provides the use of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, for the prophylactic or therapeutic treatment of hyperglycemia or diabetes, particularly type II diabetes.

The invention also provides the use of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, for the prevention of diabetes, particularly type II diabetes, in a human demonstrating pre-diabetic hyperglycemia or impaired glucose tolerance.

The invention also provides the use of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the activation of GK.

The invention also provides the use of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the prophylactic or therapeutic treatment of hyperglycemia or diabetes, particularly type II diabetes.

The invention also provides the use of a compound of Formula (I), or a pharmaceutically acceptable salt 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 compounds and compositions of the present invention may be optionally employed in combination with one or more other anti-diabetic agents or anti-hyperglycemic agents, which include, for example, sulfonylureas (e.g. glyburide, glimepiride, glipyride, glipizide, chlorpropamide, gliclazide, glisoxepid, acetohexamide, glibornuride, tolbutamide, tolazamide, carbutamide, gliquidone, glyhexamide, phenbutamide, tolcyclamide, etc.), biguanides (e.g. metformin, phenformin, buformin, etc.), glucagon antagonists (e.g. a peptide or non-peptide glucagon antagonist), glucosidase inhibitors (e.g. acarbose, miglitol, etc.), insulin secetagogues, insulin sensitizers (e.g. troglitazone, rosiglitazone, pioglitazone, etc.) and the like; or anti-obesity agents (e.g. sibutramine, orlistat, etc.) and the like. The

compounds and compositions of the present invention and the other anti-diabetic agents or anti-hyperglycemic agents may be administered simultaneously, sequentially or separately.

The pharmaceutical compositions of the present invention comprise a compound of Formula (I), or a pharmaceutically acceptable salt thereof, as an active ingredient, a pharmaceutically acceptable carrier and optionally other therapeutic ingredients or adjuvants. The compositions include compositions suitable for oral, rectal, topical, and parenteral (including subcutaneous, intramuscular, and intravenous) administration, as well as administration through inhaling, although the most suitable route in any given case will depend on the particular host, and nature and severity of the conditions for which the active ingredient is being administered. The pharmaceutical compositions may be conveniently presented in unit dosage form and prepared by any of the methods well known in the art of pharmacy.

The pharmaceutical compositions according to the invention are preferably adapted for oral administration.

In practice, the compounds of Formula (I), or pharmaceutically acceptable salts thereof, can be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g. oral or parenteral (including intravenous). Thus, the pharmaceutical compositions of the present invention can be presented as discrete units suitable for oral administration such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient. Further, the compositions can be presented as a powder, as granules, as a solution, as a suspension in an aqueous liquid, as a non-aqueous liquid, as an oil-in-water emulsion, or as a water-in-oil liquid emulsion. In addition to the common dosage forms set out above, the compounds of Formula (I), or a pharmaceutically acceptable salt thereof, may also be administered by controlled release means and/or delivery devices. The compositions may be prepared by any of the methods of pharmacy. In general, such methods include a step of bringing into association the active ingredient with the carrier that constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both. The product can then be conveniently shaped into the desired presentation.

Thus, the pharmaceutical compositions of this invention may include a pharmaceutically acceptable carrier and a compound of Formula (I), or a pharmaceutically acceptable salt thereof. The compounds of Formula (I), or pharmaceutically acceptable salts thereof, can also be included in pharmaceutical compositions in combination with one or more other therapeutically active compounds.

The pharmaceutical compositions of this invention include pharmaceutically acceptable liposomal formulations containing a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

The pharmaceutical carrier employed can be, for example, a solid, liquid, or gas. Examples of solid carriers include lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, and stearic acid. Examples of liquid carriers are sugar syrup, peanut oil, olive oil, and water. Examples of gaseous carriers include carbon dioxide and nitrogen.

In preparing the compositions for oral dosage form, any convenient pharmaceutical media may be employed. For example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents, and the like may be used to form oral liquid preparations such as suspensions, elixirs and solutions; while carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents, and the like may be used to form oral solid preparations such as powders, capsules, and tablets. Because of their ease of administration, tablets and capsules are the preferred oral dosage units whereby solid pharmaceutical carriers are employed. Optionally, tablets may be coated by standard aqueous or nonaqueous techniques.

A tablet containing the composition of this invention may be prepared by compression or molding, optionally with one or more accessory ingredients or adjuvants. Compressed tablets may be prepared by compressing, in a suitable machine, the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent or other such excipient. These excipients may be, for example, inert diluents such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example, starch, gelatin, or acacia; and lubricating agents, for example, magnesium stearate, stearic acid, or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer time. For example, a time delay material such as glyceryl monostearate, or glyceryl distearate may be used.

In hard gelatin capsules, the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate, or kaolin. In soft gelatin capsules, the active ingredient is mixed with water or an oil medium, for example, peanut oil, liquid paraffin, or olive oil. Molded tablets may be made by molding in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent. Each tablet preferably contains from about 0.05mg to about 5g of the active ingredient and each cachet or capsule preferably contains from about 0.05mg to about 5g of the active ingredient.

For example, a formulation intended for the oral administration to humans may contain from about 0.5mg to about 5g of active agent, compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95% of the total composition. Unit dosage forms will generally contain between from about 1mg to about 2g of the active ingredient, typically 25mg, 50mg, 100mg, 200mg, 300mg, 400mg, 500mg, 600mg, 800mg, or 1000mg.

Pharmaceutical compositions of the present invention suitable for parenteral administration may be prepared as solutions or suspensions of the active compounds in water. A suitable surfactant can be included such as, for example, hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof in oils. Further, a preservative can be included to prevent the detrimental growth of microorganisms.

Pharmaceutical compositions of the present invention suitable for injectable use include sterile aqueous solutions or dispersions. Furthermore, the compositions can be in the form of sterile powders for the extemporaneous preparation of such sterile injectable solutions

or dispersions. In all cases, the final injectable form must be sterile and must be effectively fluid for easy syringability. The pharmaceutical compositions must be stable under the conditions of manufacture and storage and thus, preferably should be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g. glycerol, propylene glycol, and liquid polyethylene glycol), vegetable oils, and suitable mixtures thereof.

Pharmaceutical compositions of the present invention can be in a form suitable for topical use such as, for example, an aerosol, cream, ointment, lotion, dusting powder, or the like. Further, the compositions can be in a form suitable for use in transdermal devices. These formulations may be prepared, utilizing a compound of Formula (I), or a pharmaceutically acceptable salt thereof, via conventional processing methods. As an example, a cream or ointment is prepared by admixing hydrophilic material and water, together with about 5wt% to about 10wt% of the compound of Formula (I), to produce a cream or ointment having a desired consistency.

Pharmaceutical compositions of this invention can be in a form suitable for rectal administration wherein the carrier is a solid. It is preferable that the mixture forms unit dose suppositories. Suitable carriers include cocoa butter and other materials commonly used in the art. The suppositories may be conveniently formed by first admixing the composition with the softened or melted carrier(s) followed by chilling and shaping in molds.

Pharmaceutical compositions of this invention can be in a form suitable for inhaled administration. Such administration can be in forms and utilizing carriers described in, for example, 1) Particulate Interactions in Dry Powder Formulations for Inhalation, Xian Zeng et al, 2000, Taylor and Francis, 2) Pharmaceutical Inhalation Aerosol Technology, Anthony Hickey, 1992, Marcel Dekker, 3) Respiratory Drug Delivery, 1990, Editor: P.R. Byron, CRC Press.

In addition to the aforementioned carrier ingredients, the pharmaceutical compositions described above may include, as appropriate, one or more additional carrier ingredients such as diluents, buffers, flavoring agents, binders, surface-active agents, thickeners, lubricants, preservatives (including anti-oxidants) and the like. Furthermore, other adjuvants can be included to render the formulation isotonic with the blood of the intended recipient. Compositions containing a compound of Formula (I), or a pharmaceutically acceptable salt thereof, may also be prepared in powder or liquid concentrate form.

Generally, dosage levels of the order of from about 0.01mg/kg to about 150mg/kg of body weight per day are useful in the treatment of the above-indicated conditions, or alternatively about 0.5mg to about 10g per patient per day. For example, type II diabetes may be effectively treated by the administration of from about 0.01 to 100mg of the compound per kilogram of body weight per day, or alternatively about 0.5mg to about 7g per patient per day.

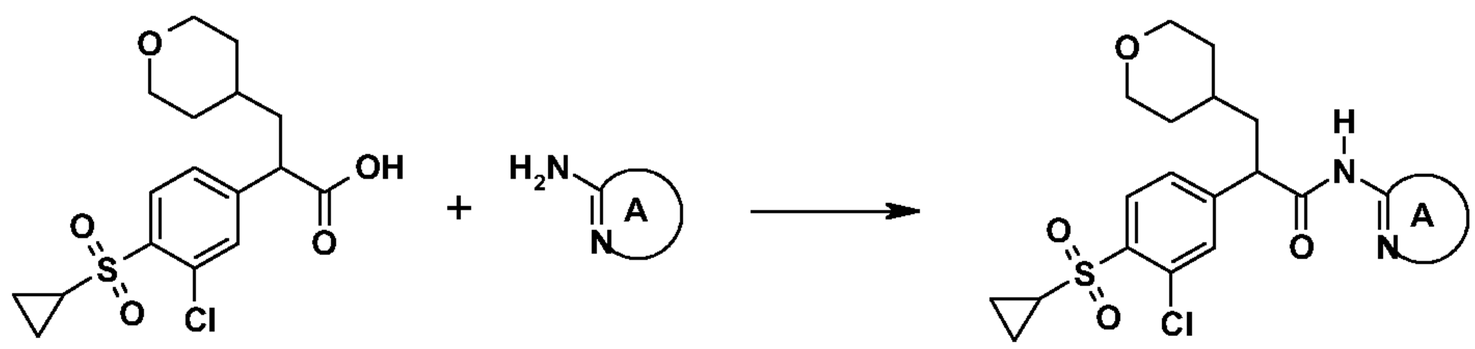
It is understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the disease in the particular diabetic patient undergoing therapy. Further, it is understood that the compounds and salts thereof of this invention can be administered at subtherapeutic levels prophylactically in anticipation of a hyperglycemic condition.

The compounds of Formula (I) may exhibit advantageous properties compared to known glucokinase activators, such properties may be illustrated in the assays described herein or in other assays known to those skilled in the art. In particular, compounds of the invention may exhibit improved values for K_m, V_{max}, EC_{50}, maximum activation (glucose concentration = 5mM), maximum blood glucose reduction on basal blood glucose levels and/or reduction of postprandial glucose peak in an oral glucose tolerance test (OGTT), or other advantageous pharmacological properties such as enhanced aqueous solubility, reduced plasma protein binding and/or enhanced metabolic stability, compared to known GK activators. The compounds of the invention may also demonstrate one or more of the following properties compared to known compounds: reduced neurotoxicity, longer duration of action (e.g. improved half-life/higher plasma protein binding), improved bioavailability, and /or increased potency (e.g. *in vitro* or *in vivo*).

EXPERIMENTAL

In accordance with this invention, the compounds of Formula (I) can be prepared following the protocol illustrated in **Scheme 1** below:

SCHEME 1



II III I

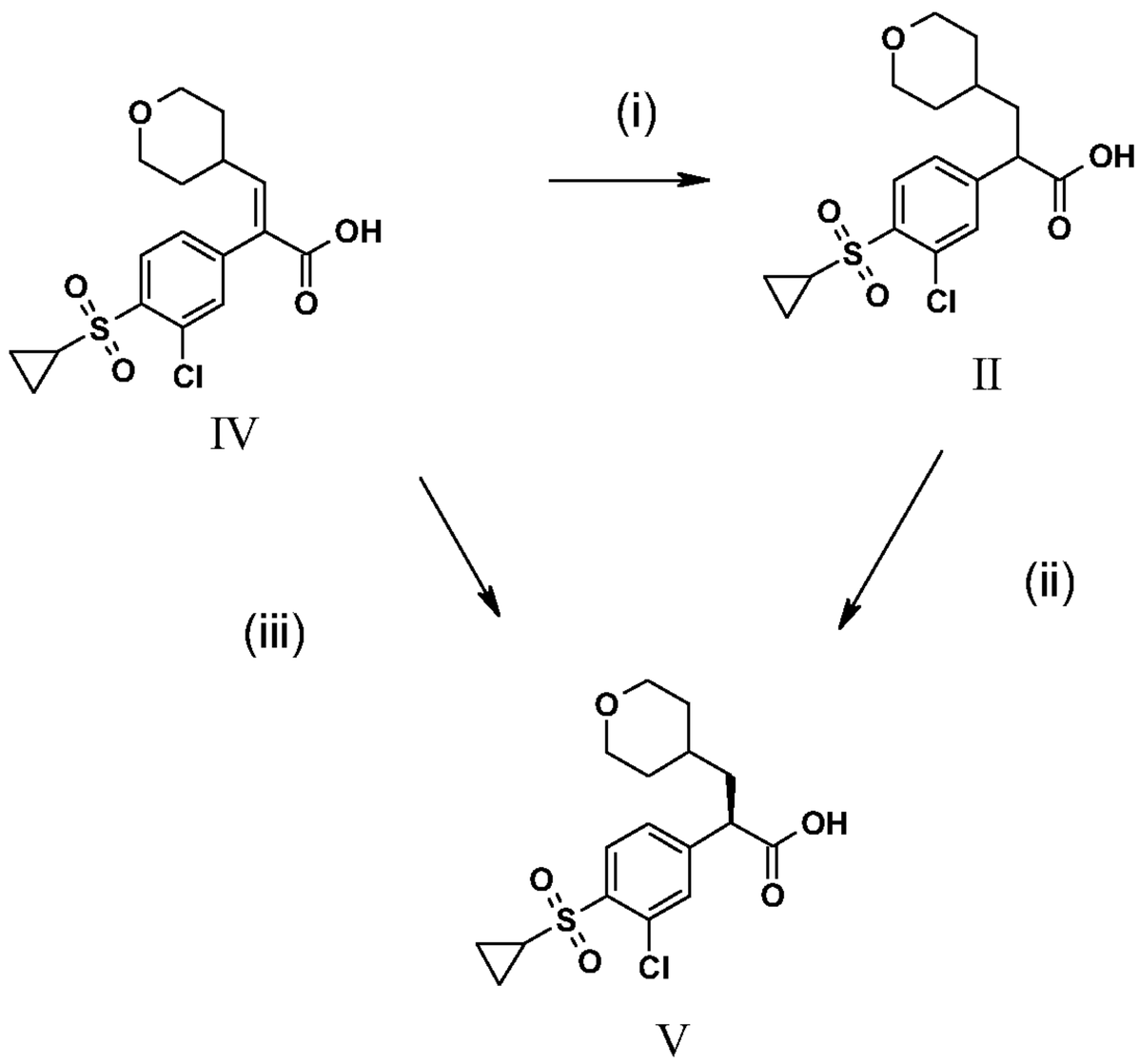
The carboxylic acid **II**, or an activated derivative thereof, may be condensed with the amine **III**, or a salt thereof e.g. the hydrochloride salt, using a variety of coupling conditions known to those skilled in the art. For example, it is possible to condense the enantiopure carboxylic acid **II** with amine **III**, or a salt thereof, using a reagent that causes negligible racemisation, e.g. benzotriazol-1-yloxytris(pyrrolidino)phosphonium hexafluorophosphate (J. Coste et al., *Tetrahedron Lett.*, **1990**, *31*, 205–208), to furnish enantiopure amides of Formula (I). Alternatively the carboxylic acid carboxylic acid **II** may be treated with $(COCl)_2$ and DMF in dichloromethane e.g. at -45°C, followed by the addition of the amine **III** and pyridine.

Alternatively, a racemic mixture of amides can be prepared from racemic carboxylic acid **II** and then separated by means of chiral high performance liquid chromatography employing a chiral stationary phase (which can be purchased from, for example, Daicel Chemical Industries, Ltd, Tokyo, Japan) to provide the desired compound of Formula (I).

The amines **III** are commercially available or are readily prepared using known techniques.

The carboxylic acid **II** can be prepared following the protocol illustrated in **Scheme 2** below:

SCHEME 2



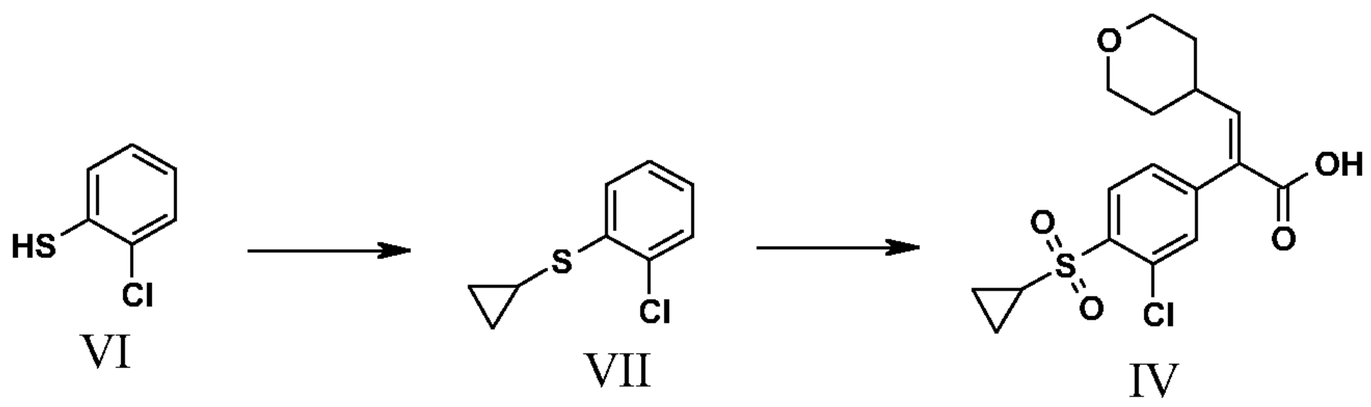
The compound of formula **IV** will typically be converted to the enantiomerically pure carboxylic acid **V** (illustrated as the (R)-isomer) by catalytic hydrogenation (i), followed by the reaction with an enantiomerically pure chiral agent, separation of diasteriomers using conventional techniques, and finally the removal of the chiral resolving agent (ii).

Catalytic hydrogenation will typically utilize a palladium catalyst. Racemic compounds **V** can be condensed, for example, with a chiral oxazolidinone derivative (see, for instance, F. T. Bizzarro et al. WO 00/58293) to generate a mixture of diastereoisomeric imides that are separable by any conventional method, e.g. column chromatography. Hydrolysis of the pure imides affords the stereopure (R)- and (S)-carboxylic acids that can then be condensed with heteroaryl amines **III**.

Alternatively, the compound of formula **IV** can be converted to the enantiomerically pure carboxylic acid **II** directly by means of an asymmetric reduction (iii).

The synthesis of compound **IV** can be prepared following the protocol illustrated in **Scheme 3** below:

SCHEME 3

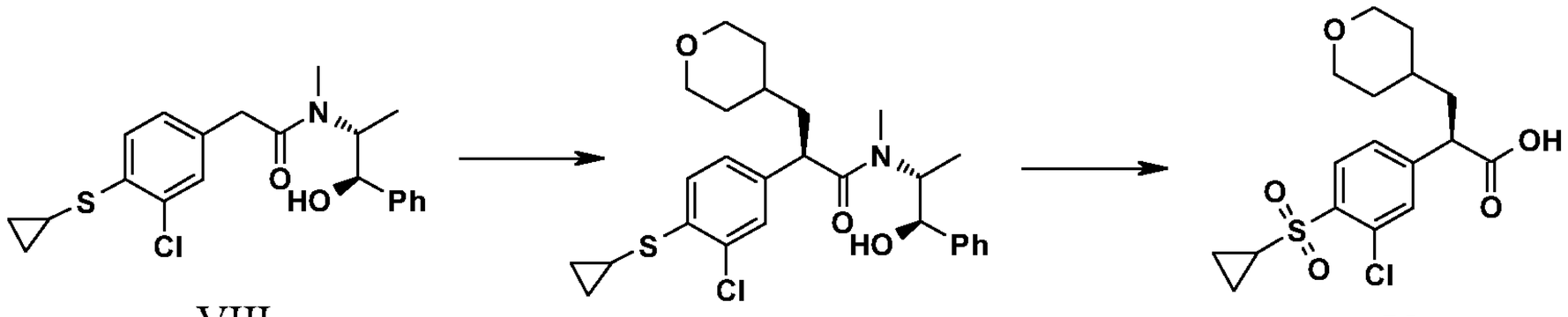


Cyclopropylation of compound **VI** may be performed by means such as those described in *J. Am. Chem. Soc.*1977 99:3080-3087 to provide the compound **VII**. Briefly, this involves treatment with $Br(CH_2)_3Cl$ in the presence of potassium hydroxide, followed by treatment with KNH_2 in the presence of $FeNO_3$.

Subsequently compound **VII** may be converted into the acid of formula **IV** by a four step (Friedel-Crafts, oxidation, Wittig, saponification) process. The initial Friedel-Crafts step may be carried out in an analogous manner to that described in WO03/95438, namely compound **VII** may be treated with ethyl chlorooxoacetate in the presence of $AlCl_3$ in a solvent such as chloroform to yield (3-chloro-4-cyclopropylsulfanyl-phenyl)oxoacetic acid ethyl ester. The subsequent steps may be performed by analogous means to those described in WO2004/072031 for the preparation of the non-chlorinated equivalent of compound **IV** (Preparations 22 and 23 therein).

Alternatively the compound of formula **V** may be prepared as shown in **Scheme 4**:

SCHEME 4



VIII IX V

(3-Chloro-4-cyclopropylsulfanylphenyl)oxoacetic acid ethyl ester mentioned above is saponified to give the corresponding carboxylic acid. The oxo group of this compound is converted into a methylene through the Wolff–Kishner protocol. The resultant phenylacetic acid is coupled with (1R,2R)-(-)-pseudo-ephedrine to give **VIII**. Asymmetric alkylation of this compound with 4-iodomethyltetrahydropyran furnishes amide **IX**, which is then hydrolysed with aqueous acid to yield an enantiopure thioether acid that is then oxidised to the enantiopure acid **V**.

Further details for the preparation of the compounds of Formula (I) are found in the examples.

During the synthesis of the compounds of Formula (I), labile functional groups in the intermediate compounds, e.g. hydroxy, oxo, carboxy and amino groups, may be protected. The protecting groups may be removed at any stage in the synthesis of the compounds of Formula (I) or may be present on the final compound of Formula (I). A comprehensive discussion of the ways in which various labile functional groups may be protected and methods for cleaving the resulting protected derivatives is given in, for example, Protective Groups in Organic Chemistry, T.W. Greene and P.G.M. Wuts, (1991) Wiley-Interscience, New York, 2nd edition.

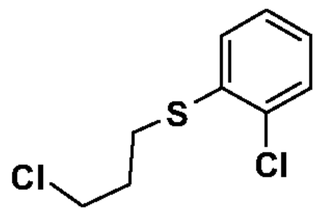
Any novel intermediates described above are also included in the present invention. Thus the invention also provides the novel intermediate of formula (II) and protected or activated derivatives thereof and the use of such compound in the synthesis of novel GK activators. In particular the invention provides the compound (2*R*)-2-(3-chloro-4-cyclopropanesulfonylphenyl)-3-(tetrahydropyran-4-yl)propionic acid and protected or activated derivatives thereof.

All publications, including, but not limited to, patents and patent application cited in this specification, are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as fully set forth.

EXAMPLES

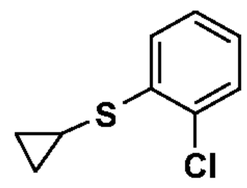
Abbreviations and acronyms: Ac: Acetyl; tBME: tert-Butylmethylether; ATP: Adenosine 5′-triphosphate; DMF: Dimethylformamide; Et: Ethyl; GK: Glucokinase; Glc: Glucose; G6P: Glucose-6-phosphate; G6PDH: Glucose-6-phosphate dehydrogenase; GST-GK: Glutathione *S*-transferase–Glucokinase fusion protein; NADP(H): β-Nicotinamide adenine dinucleotide phosphate (reduced); rt: Room temperature; THF: Tetrahydrofuran.

Preparation 1: 1-Chloro-2-(3-chloropropylsulfanyl)benzene



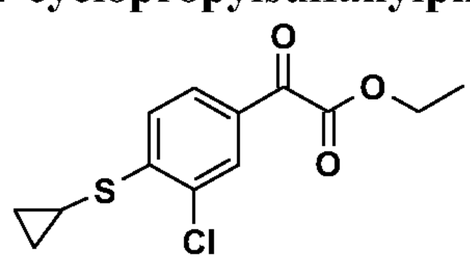
Tetrabutylammoniumchloride (1g, 0.0035mol, 0.002eq) was added to a mixture of 2-bromo-3-chloropropane (262g, 1.660mol, 1.2eq), KOH (508g, 3.680mol, 2.66eq) and tBME (3.0L). A solution of 2-chlorothiophenol (200g, 1.383mol, 1eq.) in tBME (0.2L) was added at rt followed by a first portion of H_2O (0.003L) which afforded gas evolution and an increase of the reaction temperature. A further amount of H_2O (0.027L) was carefully added keeping the temperature below 30°C. The reaction mixture was stirred overnight and the suspension filtered off over a frit. The filtrate was concentrated under vacuum to yield the title compound. δ_H ($CDCl_3$): 2.10–2.20 (m, 2H), 3.13 (t, 2H), 3.74 (t, 2H), 7.17 (t, 1H), 7.22 (t, 1H), 7.35 (d, 1H), 7.41 (d, 1H).

Preparation 2: 1-Chloro-2-cyclopropylsulfanylbenzene



Prepared from Preparation 1 according to the method of W.E. Truce *et al*, *J. Org. Chem.*, 1968, 33(1) 43. δ_H ($CDCl_3$): 0.70–0.80 (m, 2H), 1.12–1.20 (m, 2H), 2.12–2.21 (m, 1H), 7.07 (t, 1H), 7.23–7.36 (m, 2H), 7.58 (d, 1H).

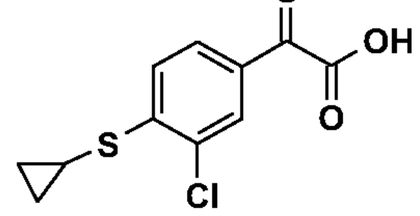
Preparation 3: Ethyl (3-chloro-4-cyclopropylsulfanylphenyl)oxoacetate



A suspension of $AlCl_3$ (70g, 0.525mol, 1.5 eq) in dichloroethane (0.8L) was cooled to 5°C. Oxalylesterchloride (71.7g, 0.525mol, 1.5 eq) was added to afford a solution. A solution of Preparation 2 (48.5g, 0.262mol, 1 eq) in dichloroethane (0.1L) was added over a 10min period keeping the temperature below 5°C. The cooling bath was removed and the reaction stirred at rt for 1.5h. The reaction was quenched with ice and acidified with aqueous

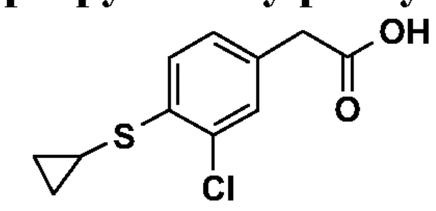
HCl solution (1M) and the layers separated. The organic phase was washed with H_2O (2 x 100mL) dried ($MgSO_4$) and concentrated under vacuum. The crude product was purified by column chromatography (SiO_2, 650g) and concentrated under vacuum to afford the title compound. δ_H ($CDCl_3$): 0.77–0.83 (m, 2H), 1.21–1.29 (m, 2H), 1.48 (t, 3H), 2.13–2.22 (m, 1H), 4.44 (q, 2H), 7.68 (d, 1H), 7.94 (d, 1H), 7.99 (s, 1H).

Preparation 4: (3-Chloro-4-cyclopropylsulfanylphenyl)oxoacetic acid



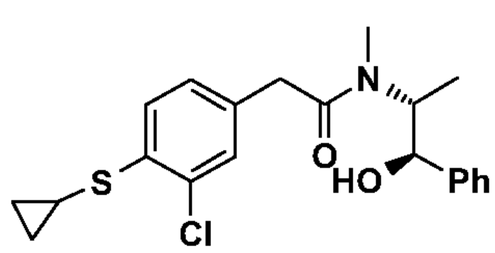
Aqueous NaOH (0.358L, 2M, 2eq) was added to Preparation 3 (102g, 0.358mol, 1eq) in ethanol (0.5L) and the reaction mixture stirred at rt for 1h. The ethanol was then distilled off and ice cold H_2O (80.5mL) added. The suspension was washed with isopropyl acetate (3 x 100mL) and the aqueous phase acidified with aqueous HCl. The product was extracted with isopropylacetate (3 x 200mL), the organic fraction collected and washed with H_2O (0.05L) and brine (0.05L) dried ($MgSO_4$) and concentrated under vacuum. Addition of a minimum of tBME followed by heptane and seeding gave a crystalline suspension which was cooled to 0°C. The crystalline material was filtered and dried at rt overnight to yield the title compound. The mother liquor was concentrated under slight vacuum affording the precipitation of a second crop of the title compound. δ_H ($CDCl_3$): 0.78–0.84 (m, 2H), 1.22–1.30 (m, 2H), 2.15–2.23 (m, 1H), 7.73 (d, 1H), 8.38–8.41 (m, 2H).

Preparation 5: (3-Chloro-4-cyclopropylsulfanylphenyl)acetic acid



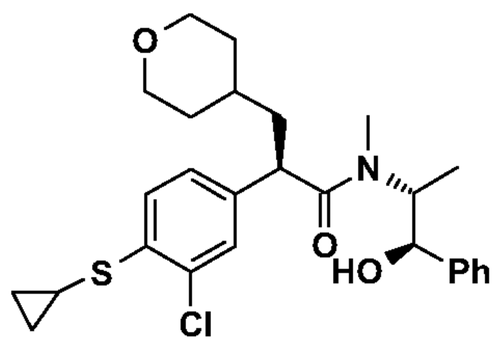
Preparation 4 (19.3g, 0.075mol, 1eq) and hydrazine hydrate (18.8g, 0.376mol, 5eq) were heated to 80°C. To the suspension was added KOH (3.37g, 0.051mol, 0.68eq) and the mixture stirred at 80°C. At 20min intervals 3 portions of KOH (each 3.37g, 0.051mol, 0.68eq) were added and the temperature increased to 110°C. After stirring overnight the reaction mixture was acidified with cold portions of concentrated aqueous HCl. The product was extracted with tBME (2 x 100mL), the combined organic fractions washed with H_2O (2 x 50mL) and brine (25mL) and concentrated under vacuum. This afforded spontaneous crystallisation of the desired product which was filtered over a frit to yield the title compound. δ_H ($CDCl_3$): 0.75–0.80 (m, 2H), 1.15–1.20 (m, 2H), 2.10–2.20 (m, 1H), 3.60 (s, 2H), 7.20 (d, 1H), 7.25 (s, 1H), 7.56 (d, 1H).

Preparation 6: 3-Chloro-*N*-[(1*R*,2*R*)-2-hydroxy-1-methyl-2-phenylethyl]-*N*-methyl-4-(cyclopropylthio)benzeneacetamide



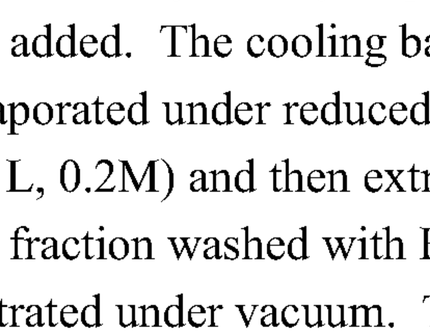
1,1'-Carbonydiimidazol (50.4g, 0.311mol, 1.2eq) was added to Preparation 5 (63.1g, 0.260mol, 1eq) and THF (0.5L) and the reaction stirred at rt for 2h before the addition of (1R,2R)-(-)-pseudo-ephedrine (42.9g, 0.260mol, 1eq) and the reaction mixture stirred overnight. The THF was then evaporated under vacuum. The crude product was dissolved in EtOAc (0.4L) and washed with an aqueous solution of citric acid (1M, 0.3L), H_2O (2 x 100mL), aqueous $NaHCO_3$ (100mL), H_2O (50mL) and brine (50mL). The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure to yield a foam. The crude product was used in the following step without further purification. δ_H ($CDCl_3$): 0.70–0.80 (m, 2H), 0.82 (d, 1H), 1.00–1.10 (m, 4H), 2.00–2.10 (m, 1H), 2.76 (s, 2.25H), 2.84 (s, 0.75H), 3.54 (s, 1.5H), 3.67 (s, 0.5H), 3.92–4.02 (m, 0.5H), 4.38–4.60 (m, 1.5H), 6.96–7.36 (m, 7H), 7.40 (d, 1H).

Preparation 7: (*αR*)-3-Chloro-*α*-(tetrahydropyran-4-ylmethyl)-*N*-[(1*R*,2*R*)-2-hydroxy-1-methyl-2-phenylethyl]-*N*-methyl-4-(cyclopropylthio)benzeneacetamide



Preparation 6 (52.0g, 0.133mol, 1eq) and THF (0.5L) were cooled to -50°C and a solution of lithium diisopropylamide (200mL, 2M, 0.400mol, 3eq) added. The reaction was stirred at -40°C and a solution of 4-iodomethyltetrahydropyran (WO2004/072031, 30.2g, 0.133mol, 1eq) in THF (0.15L) was added. The cooling bath was removed and the reaction stirred overnight. The THF was evaporated under reduced pressure and the crude product triturated with aqueous citric acid (1L, 0.2M) and then extracted with tBME (0.5L). The layers are separated and the organic fraction washed with H_2O (2 x 100mL) and brine (50mL), dried ($MgSO_4$) and concentrated under vacuum. The product was purified by column chromatography (1kg SiO_2, CH_2Cl_2/EtOAc 1:1) to give the title compound. *m/z* (ES^+) = 488, 490 $[M+H]^+$.

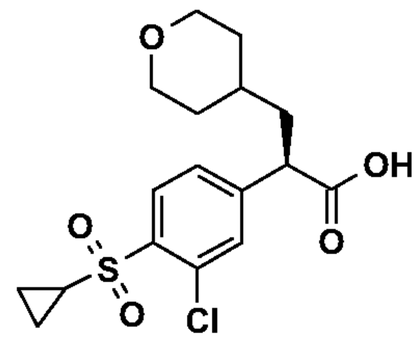
Preparation 8: (*R*)-2-(3-Chloro-4-cyclopropylsulfanylphenyl)-3-(tetrahydropyran-4-yl)propionic acid



Preparation 7 (12.6g, 0.0242mol) in dioxane (65mL) and concentrated aqueous HCl (65mL, 12M) was heated for 3h at 100°C. The reaction mixture was cooled to rt and diluted by addition of H_2O (200mL). The mixture was extracted with EtOAc, the layers separated and the organic phase washed with H_2O (50mL) and brine (25mL), dried ($MgSO_4$) and concentrated under reduced pressure to afford the title compound. δ_H ($CDCl_3$): 0.70–0.78 (m,

2H), 1.12–1.80 (m, 9H), 1.99–2.09 (m, 1H), 3.29–3.39 (m, 2H), 3.75–3.80 (m, 1H), 3.90–4.00 (m, 2H), 7.20 (d, 1H), 7.28 (s, 1H), 7.54 (d, 1H).

Preparation 9: (*R*)-2-(3-Chloro-4-cyclopropanesulfonylphenyl)-3-(tetrahydropyran-4-yl)propionic acid

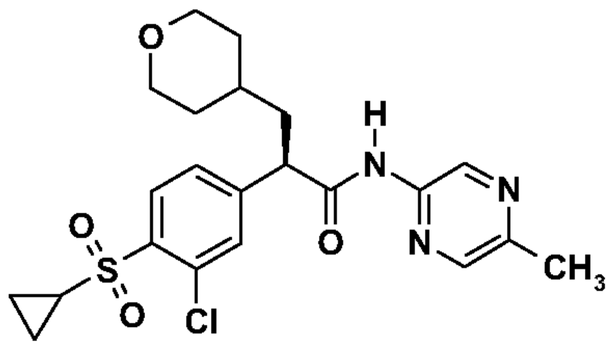
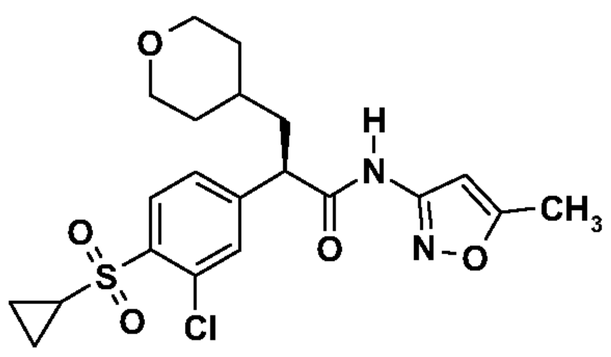
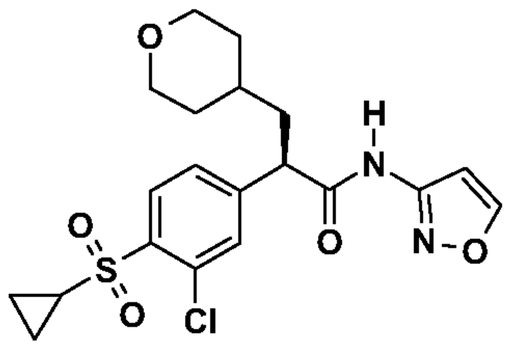
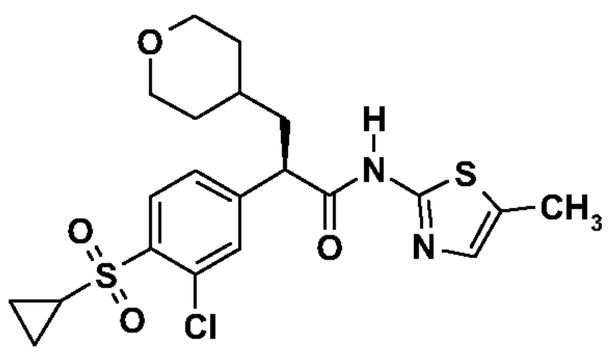
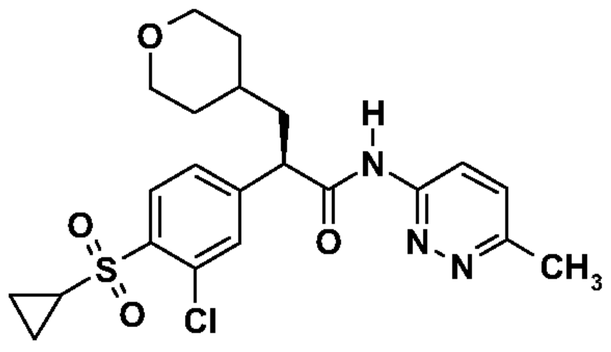


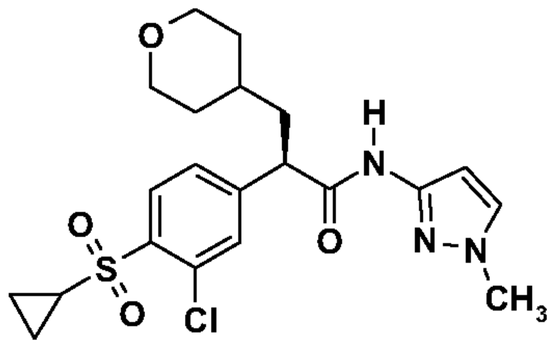
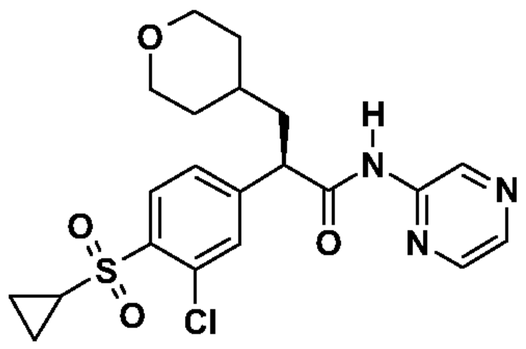
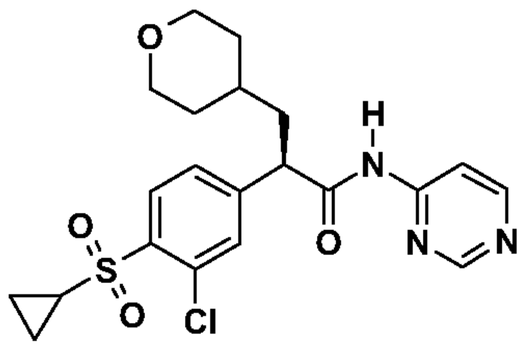
To a stirred solution of Preparation 8 (9.2g, 0.0216mol) in acetic acid (95mL) was added magnesium monoperphthalate (16.7g, 27mmol) in one portion. Stirring was continued at ambient temperature for 20h. Water (100mL) was added, followed by addition of aqueous saturated sodium sulfite solution until no more peroxide was detectable in the reaction mixture. Water (500mL) was added and the mixture extracted with EtOAc (3 x 500mL). The combined organic layers were washed with water (3 x 100mL) and brine (1 x 100mL), dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (EtOAc / acetic acid = 50 / 1) followed by crystallisation from the partially evaporated product containing fractions to yield the title compound. δ_H ($CDCl_3$): 0.95–1.05 (m, 2H), 1.20–1.45 (m, 5H), 1.50–1.60 (m, 2H), 1.61–1.69 (m, 1H), 1.95–2.05 (m, 1H), 2.90–3.00 (m, 1H), 3.20–3.30 (m, 2H), 3.75–3.80 (m, 1H), 3.85–3.95 (m, 2H), 7.31 (d, 1H), 7.46 (s, 1H), 7.91 (d, 1H); $[\alpha]_D^{20}$ – 49.4 (c = 0.91, DMSO).

Examples

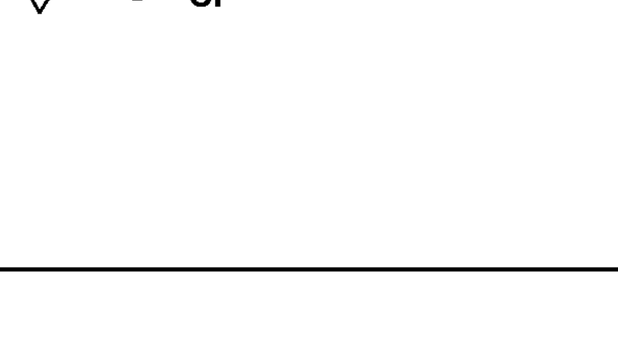
(2*R*)-2-(3-Chloro-4-cyclopropanesulfonylphenyl)-3-(tetrahydropyran-4-yl)propionic acid (Preparation 9) was coupled with amines selected from 2-amino-5-methylpyrazine, 3-amino-5-methylisoxazole, 3-aminoisoxazole, 2-amino-5-methylthiazole, 3-amino-6-methylpyridazine, 1-methyl-3-aminopyrazole, 2-aminopyrazine and 4-aminopyrimidine using the following procedure to provide Examples 1-8.

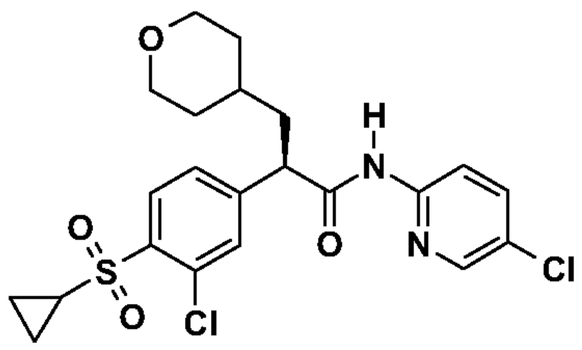
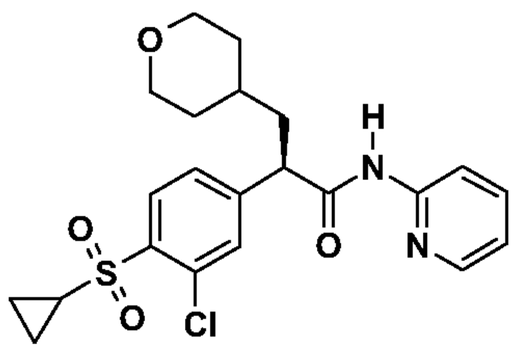
CH_2Cl_2 (60mL) and DMF (0.08mL, 1.064mmol, 1.2 eq) were cooled to -10°C and oxalylchloride slowly added (0.09mL, 0.465mol, 1.2 eq). After stirring for 15 min the reaction mixture was cooled to -30°C and (2*R*)-2-(4-cyclopropanesulfonylphenyl)-3-(tetrahydropyran-4-yl)propionic acid (Preparation 8, 0.300g, 0.886mmol, 1.0 eq) was added. The reaction was stirred at -30°C for 45min then pyridine (1.395mol, 0.31mL in 1mL CH_2Cl_2, 4.5eq) and the amine (4.43mmol, 5.0eq) were slowly added in parallel at -40°C. The reaction mixture was stirred for 15min then the ice bath removed. The reaction mixture was stirred for 2h until it reached rt. The solvent was removed under partial vacuum and the crude mixture dissolved in EtOAc (10mL) and aqueous HCl (1.5mL). The layers were separated and the aqueous phase extracted with EtOAc (5mL). The organic fractions were combined and washed with H_2O (10mL), saturated aqueous $NaHCO_3$ (2 x 10mL), water (5mL) and brine (5mL) and dried ($MgSO_4$). Purification was by flash chromatography (EtOAc:heptane, 2:1) and/or recrystallisation.

Eg	Structure	Name	^{1}H-NMR δ_H ($CDCl_3$) *m/z* (ES)
1		(*R*)-2-(3-Chloro-4-cyclopropanesulfon-ylphenyl)-*N*-(5-methylpyrazin-2-yl)-3-(tetrahydropyran-4-yl)propionamide	0.95–1.05 (m, 2H), 1.18–1.50 (m, 5H), 1.52–1.62 (br m, 2H), 1.70–1.80 (m, 1H), 2.10–2.20 (m, 1H), 2.47 (s, 3H), 2.91–3.00 (m, 1H), 3.20–3.30 (m, 2H), 3.65–3.75 (m, 1H), 3.83–3.90 (m, 2H), 7.37 (d, 1H), 7.54 (s, 1H), 7.95 (d, 1H), 8.00–8.08 (m, 2H), 9.34 (s, 1H) *m/z* (ES^-) = 462 [*M* – H]$^-$
2		(*R*)-2-(3-Chloro-4-cyclopropanesulfon-ylphenyl)-*N*-(5-methylisoxazol-3-yl)-3-(tetrahydropyran-4-yl)propionamide	0.93–1.03 (m, 2H), 1.20–1.50 (m, 5H), 1.55–1.65 (m, 2H), 1.70–1.80 (m, 1H), 2.10–2.20 (m, 1H), 2.40 (s, 3H), 2.90–3.00 (m, 1H), 3.20–3.30 (m, 2H), 3.75–3.90 (m, 3H), 6.74 (s, 1H), 7.39 (d, 1H), 7.57 (s, 1H), 7.88 (d, 1H), 10.35 (s, 1H) *m/z* (ES^-) = 451 [*M* – H]$^-$
3		(*R*)-2-(3-Chloro-4-cyclopropanesulfon-ylphenyl)-*N*-(isoxazol-3-yl)-3-(tetrahydropyran-4-yl)propionamide	0.93–1.03 (m, 2H), 1.18–1.50 (m, 5H), 1.51–1.62 (m, 2H), 1.70–1.80 (m, 1H), 2.10–2.20 (m, 1H), 2.88–2.98 (m, 1H), 3.20–3.30 (m, 2H), 3.80–3.90 (m, 2H), 4.00–4.10 (br, 1H), 7.10 (d, 1H), 7.41 (dd, 1H), 7.58 (d, 1H), 7.88 (d, 1H), 8.31 (d, 1H), 10.43 (s, 1H) *m/z* (ES^-) = 437 [*M* – H]$^-$
4		(*R*)-2-(3-Chloro-4-cyclopropanesulfon-ylphenyl)-*N*-(5-methylthiazol-2-yl)-3-(tetrahydropyran-4-yl)propionamide	0.97–1.08 (m, 2H), 1.18–1.50 (m, 5H), 1.52–1.62 (m, 2H), 1.70–1.80 (m, 1H), 2.12–2.23 (m, 1H), 2.37 (s, 3H), 2.90–2.96 (m, 1H), 3.20–3.30 (m, 2H), 3.80–3.90 (m, 3H), 7.02 (d, 1H), 7.33 (dd, 1H), 7.50 (d, 1H), 7.87 (d, 1H) *m/z* (ES^+) = 510 [*M* + H + MeCN]$^+$
5		(*R*)-2-(3-Chloro-4-cyclopropanesulfon-ylphenyl)-*N*-(6-methylpyridazin-3-yl)-3-(tetrahydropyran-4-yl)propionamide	0.90–1.00 (m, 2H), 1.15–1.50 (m, 5H), 1.55–1.82 (m, 3H), 2.05–2.15 (m, 1H), 2.65 (s, 3H), 2.85–2.95 (m, 1H), 3.17–3.27 (m, 2H), 3.77–3.87 (m, 2H), 4.73–4.78 (m, 1H), 7.46 (d, 1H), 7.56 (d, 1H), 7.78 (s, 1H), 7.84 (d, 1H), 8.56 (d, 1H), 11.90 (br s, 1H) *m/z* (ES^-) = 462 [*M* – H]$^-$

6		(*R*)-2-(3-Chloro-4-cyclopropanesulfon-ylphenyl)-*N*-(1-methylpyrazol-3-yl)-3-(tetrahydropyran-4-yl)propionamide	0.98–1.08 (m, 2H), 1.20–1.50 (m, 5H), 1.51–1.60 (m, 2H), 1.63–1.73 (m, 1H), 2.08–2.20 (m, 1H), 2.90–3.00 (m, 1H), 3.20–3.30 (m, 2H), 3.58–3.64 (m, 1H), 3.71 (s, 3H), 3.80–3.90 (m, 2H), 6.59 (d, 1H), 7.19 (s, 1H), 7.34 (dd, 1H), 7.51 (d, 1H), 7.89 (d, 1H), 8.14 (br s, 1H) *m/z* (ES^-) = 496 $[M + HCO_2]^-$
7		(*R*)-2-(3-Chloro-4-cyclopropanesulfon-ylphenyl)-*N*-(pyrazin-2-yl)-3-(tetrahydropyran-4-yl)propionamide	0.95–1.05 (m, 2H), 1.15–1.50 (m, 5H), 1.52–1.62 (m, 2H), 1.70–1.80 (m, 1H), 2.10–2.22 (m, 1H), 2.90–3.00 (m, 1H), 3.20–3.30 (m, 2H), 3.68–3.78 (m, 1H), 3.80–3.90 (m, 2H), 7.38 (dd, 1H), 7.54 (d, 1H), 7.93 (d, 1H), 8.10–8.18 (m, 2H), 8.30 (d, 1H), 9.47 (s, 1H) *m/z* (ES^+) = 491 $[M + H + MeCN]^+$
8		(*R*)-2-(3-Chloro-4-cyclopropanesulfon-ylphenyl)-*N*-(pyrimidin-2-yl)-3-(tetrahydropyran-4-yl)propionamide	1.00–1.10 (m, 2H), 1.20–1.50 (m, 5H), 1.51–1.61 (br, 2H), 1.70–1.80 (m, 1H), 2.10–2.20 (m, 1H), 2.90–3.00 (m, 1H), 3.20–3.30 (m, 2H), 3.64–3.73 (m, 1H), 3.80–3.90 (m, 2H), 7.38 (dd, 1H), 7.52(d, 1H), 7.92–8.00 (m, 2H), 8.19 (s, 1H), 8.31 (d, 1H) 9.46 (s, 1H) *m/z* (ES^-) = 897 $[2M - H]^-$.

(2*R*)-2-(3-Chloro-4-cyclopropanesulfonylphenyl)-3-(tetrahydropyran-4-yl)propionic acid (Preparation 9) may also be coupled with amines selected from 2-amino-5-methylpyridine, 2-amino-5-chloropyridine and 2-aminopyridine using the procedure described above to provide Examples 9-11.

Eg	Structure	Name
9		(*R*)-2-(3-Chloro-4-cyclopropanesulfonylphenyl)-*N*-(5-methylpyridin-2-yl)-3-(tetrahydropyran-4-yl)propionamide

10		(*R*)-2-(3-Chloro-4-cyclopropanesulfonylphenyl)-*N*-(5-chloropyridin-2-yl)-3-(tetrahydropyran-4-yl)propionamide
11		(*R*)-2-(3-Chloro-4-cyclopropanesulfonylphenyl)-*N*-(pyridin-2-yl)-3-(tetrahydropyran-4-yl)propionamide

ASSAYS

In vitro GK activity

Using a protocol similar to that described in WO2000/58293, GK activity may be measured by coupling the production of G6P by GST-GK to the generation of NADH with G6PDH as the coupling enzyme.

The assay is performed at room temperature (23°C) in clear flat bottom 96-well plates in a total volume of 100 µl consisting of 25 mM Hepes (pH 7.4), 25 mM KCl, 5 mM D-glucose, 1 mM ATP, 1 mM NADP, 2 mM $MgCl_2$, 1 mM dithiothreitol, 0.2 µg purified GST-GK derived from human liver GK and a range of activator concentrations in a final concentration of 5 % DMSO. The incubation time is 15 minutes at which time the reaction has been shown to be linear. The generation of NADH, as an indirect determination of GK activity, is measured at OD_{340} in a SpectraMAX 190 microplate spectrophotometer (Molecular Devices Corp).

Typically compounds are tested over a range of 10 dilutions from 100 µM to 0.004 µM in a final DMSO concentration of 5%. The degree of activation is calculated as a ratio over a control reaction with 5% DMSO only. Values quoted represent the concentration of compound required to produce a 2-fold activation of GK derived from a dose response curve constructed using a 4-parameter logistic model. Additionally, maximum fold activation and an EC_{50} (concentration required to produce half the maximum fold activation) can be calculated from the same dose response curve.

In vivo GK activity (I)

Following a 4.5 h fasting period, C57BL/6 mice are dosed orally via gavage with GK activator at 10mg/kg body weight followed by a glucose load of 2 g/kg. Blood Glc determinations are made 3 times during the 2.5h post-dose study period.
Mice (n = 9) are weighed and fasted for 4.5h before oral treatment. GK activators are dissolved in Gelucire 44/14–water (1:9 v/v) at a concentration of 1mg/mL. Mice are dosed orally with 10mL formulation per kg of body weight to equal a 10mg/kg dose. Fifteen min prior to dosing, a pre-dose blood Glc reading is acquired by snipping off a small portion of the animals' tails (<1mm) and collecting 20µL blood for analysis. After GK activator treatment, further blood Glc readings are taken at 0.5, 1.0, and 2.5h post-dose from the same tail wound. Results are interpreted by comparing the mean blood Glc values of the vehicle

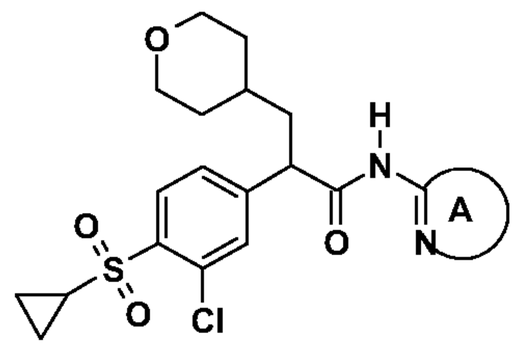
treated mice with the the GK activator treated mice over the study duration. Compounds are considered active when they exhibited a statistically significant decrease in blood Glc compared to vehicle for 2 consecutive assay time points following compound administration.

In vivo GK activity (II)

The antihyperglycaemic effects of examples of the GK activators of the invention may be evaluated in oral glucose tolerance tests in 7-8 week old male C57Bl/6 *ob/ob* mice. Briefly, mice (n = 6) are weighed and their basal blood glucose levels determined from 20µL of blood withdrawn from a tail cut (T – 27h). After 22h (T – 5h), food is removed and the mice are placed in fresh cages with access to water *ad libitum*. The blood glucose levels are determined at T – 0.75h from 20µL of blood withdrawn from the tail wound. The GK activators are dissolved in a Gelucire 44/14–water (1:9 v/v) mixture at a concentration of 1mg/mL, then, at T – 0.5h, the mice are dosed orally with 10mL formulation per kg of body weight to equal a 10mg/kg dose. At T = 0 h, the mice are bled (20µL) for analysis of blood glucose levels, then immediately dosed orally with glucose (2g/kg). Further blood samples (20µL) are taken from each animal at T = +0.5, +1.0, +1.5, +2.0, +3.0, and +4.0h for the analysis of glucose levels. GK activators typically reduce the area under the glucose curve by at least 20% in the 2h following administration of glucose.

WHAT IS CLAIMED IS:

1. A compound of Formula (I):



(I)

wherein A is a nitrogen containing heteroaryl ring selected from 5-methylpyrazin-2-yl, 5-methylpyrid-2-yl, 5-chloropyrid-2-yl, pyrid-2-yl, 5-methylisoxazol-3-yl, isoxazol-3-yl, 5-methylthiazol-2-yl, 6-methylpyridazin-3-yl, 1-methylpyrazol-3-yl, pyrazin-2-yl and pyrimidin-4-yl;

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein the carbon atom linking the phenyl ring and the tetrahydropyran containing sidechain to the amide carbonyl carbon is in the (*R*)-configuration.

3. A compound according to claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein A represents 5-methylpyrazin-2-yl.

4. A compound according to claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein A represents 5-methylpyrid-2-yl.

5. A compound according to claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein A represents 5-chloropyrid-2-yl.

6. A compound according to claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein A represents pyrid-2-yl.

7. A compound according to claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein A represents 5-methylisoxazol-3-yl.

8. A compound according to claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein A represents isoxazol-3-yl.

9. A compound according to claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein A represents 5-methylthiazol-2-yl.

10. A compound according to claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein represents 6-methylpyridazin-3-yl.

11. A compound according to claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein A represents 1-methylpyrazol-3-yl.

12. A compound according to claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein A represents pyrazin-2-yl.

13. A compound according to claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein A represents pyrimidin-4-yl.

14. A pharmaceutical composition comprising a compound according to any one of claims 1 to 13, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

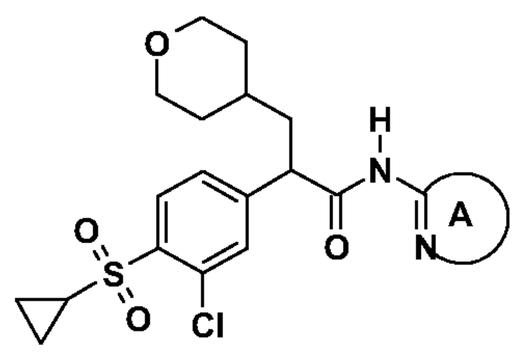
15. A method of prophylactic or therapeutic treatment of a condition where activation of GK is desirable comprising a step of administering an effective amount of a compound according to any one of claims 1 to 13, or a pharmaceutically acceptable salt thereof.

16. A method of prophylactic or therapeutic treatment of hyperglycemia or diabetes comprising a step of administering an effective amount of a compound according to any one of claims 1 to 13, or a pharmaceutically acceptable salt thereof.

17. The method according to claim 16 wherein the compound according to any one of claims 1 to 13, or a pharmaceutically acceptable salt thereof, is administered in combination with one or more other anti-hyperglycemic agents or anti-diabetic agents.

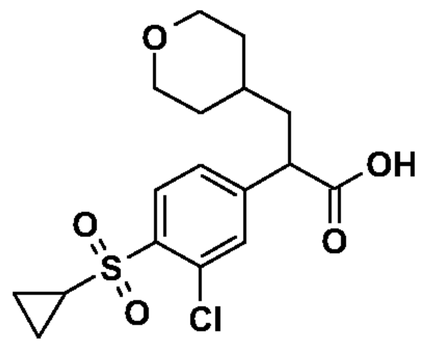
18. A method of prevention of diabetes in a human demonstrating pre-diabetic hyperglycemia or impaired glucose tolerance comprising a step of administering an effective prophylactic amount of a compound according to any one of claims 1 to 13, or a pharmaceutically acceptable salt thereof.

19. A process for the preparation of a compound of Formula (I):



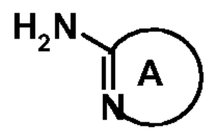
(I)

or a pharmaceutically acceptable salt thereof, said process comprising the condensation of a compound of Formula (II) or an activated derivative thereof:



(II)

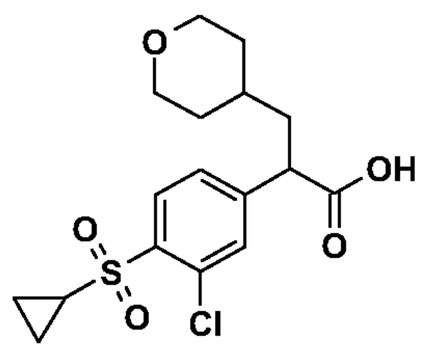
with a compound of Formula (III):



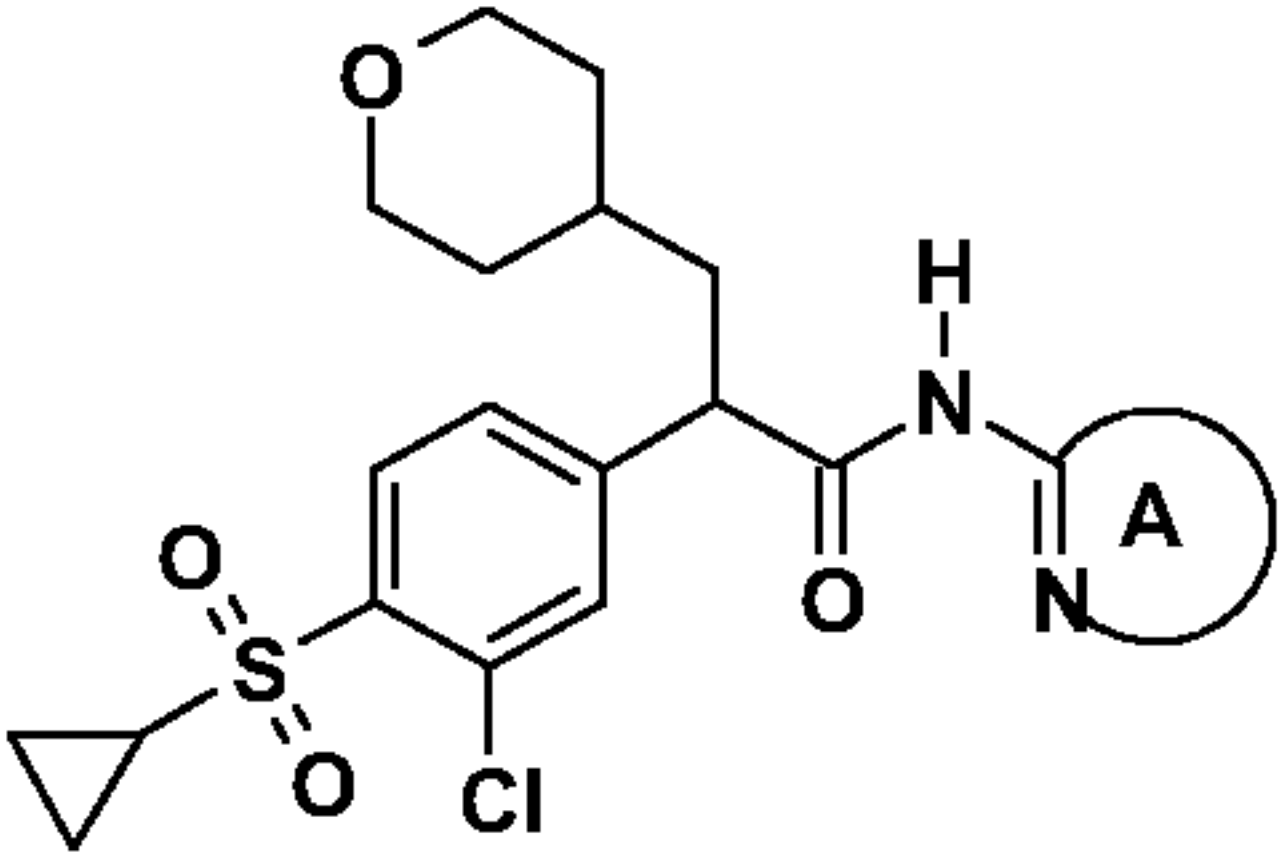
(III)

or a salt thereof, wherein A is as defined in claim 1.

20. A compound of formula (II), or a protected or activated derivative thereof:



(II)



(I)