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Patil et al.

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- (54) **GPR119 AGONIST COMPOUNDS**
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- (*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

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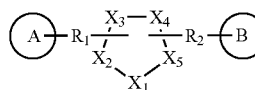
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(57) **ABSTRACT**

The present invention relates to novel compounds of formula (I), process for preparation of the same and composition comprising these compounds.

Formula (I)



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5 Claims, No Drawings

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GPR119 AGONIST COMPOUNDS

This application is a continuation of U.S. patent application Ser. No. 15/478,930, filed Apr. 4, 2017 under 35 U.S.C. § 120, and claims priority under 35 U.S.C. § 119(b) to Indian Provisional Application Number 201611012426, filed on Apr. 8, 2016, which is hereby incorporated by reference in its entirety.

FIELD OF INVENTION

The present invention relates to novel compounds that are useful in the treatment and prevention of metabolic disorders, including diabetes mellitus (type I and type II), and related disorders and also includes methods for making, pharmaceutical compositions containing, and therapeutic uses for such compounds.

BACKGROUND OF THE INVENTION

Diabetes is a life-style related disease derived from multiple causative factors. It is characterized by elevated levels of plasma glucose (hyperglycemia) in the fasting state or after administration of glucose during an oral glucose tolerance test. There are two generally recognized forms of diabetes: type 1 and type 2 diabetes mellitus. In type 1 diabetes, or insulin-dependent diabetes mellitus (IDDM), patients produce little or no insulin, the hormone which regulates glucose utilization. In type 2 diabetes, or noninsulin-dependent diabetes mellitus (T2DM), insulin is still produced in the body, and patients demonstrate resistance to the effects of insulin in stimulating glucose and lipid metabolism in the main insulin-sensitive tissues, namely, muscle, liver and adipose tissue. These patients often have normal levels of insulin, and may have hyperinsulinemia (elevated plasma insulin levels), as they compensate for the reduced effectiveness of insulin by secreting increased amounts of insulin.

The treatment of T2DM generally begins weight loss, healthy diet and exercise program. Although these factors are important especially to dissolve the increased risk of cardiovascular disorders related to diabetes mellitus, they are not effective generally for the control of diabetes mellitus itself. There are many drugs useful for the treatment of diabetes mellitus, including insulin, metformin, sulfonylureas, acarbose, thiazolidinedione, GLP-1 analogue and DPP IV inhibitor. There are, however deficiencies associated with currently available treatment, including hypoglycemic episodes, weight gain, loss in responsiveness to therapy over time, gastrointestinal problems, and edema.

Although a number of receptor classes exist in humans, by far the most abundant and therapeutically relevant is represented by the G protein-coupled receptor (GPCR) class, it is estimated that approximately 4% of the protein-coding genome encodes GPCRs. GPCRs are also known as seven-transmembrane domain receptors as they share a common structural motif, having seven sequences of between 22 to 24 hydrophobic amino acids that form seven alpha helices, each of which spans the membrane. Further, there has been renewed focus on pancreatic islet-based insulin secretion that is controlled by glucose-dependent insulin secretion (GDIS). In this regard, several orphan G-protein coupled receptors (GPCR's) have recently been identified that are preferentially expressed in the β -cell and are implicated in GDIS.

GPR119 is a cell-surface GPCR that is highly expressed in human (and rodent) islets as well as in insulin-secreting

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cell lines. Activation of GPR119 has been demonstrated to stimulate intracellular cAMP and lead to glucose dependent GLP-1 and insulin secretion (T. Soga et al Biochem. Biophys. Res. Commun. 2005, 326). Synthetic GPR119 agonists augment the release of insulin from isolated static mouse islets only under conditions of elevated glucose, and improve glucose tolerance in diabetic mice and diet-induced obese (DIO) C57/B6 mice without causing hypoglycemia.

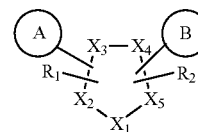
There still remains a need for alternative novel synthetic compounds which acts as GPR119 agonists and are useful in the treatment and prevention of metabolic disorders, including diabetes mellitus (type I and type II), and related disorders.

OBJECT OF THE INVENTION

An object of the present invention is to provide novel compounds which acts as GPR119 agonist, composition containing such compounds and process for the preparation thereof.

SUMMARY OF THE INVENTION

In one aspect, the present invention provides compounds of formula (I):



(I)

wherein,

X_1 , X_2 , X_3 , X_4 and X_5 are each independently N, O, S or CH; and

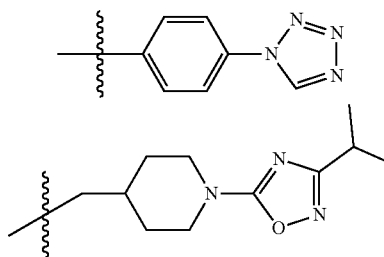
X_4 and X_5 may optionally combine to form a five membered ring comprising one or more of heteroatoms each independently selected from N, O and S and the additional five membered ring may be further optionally substituted with one or more of group selected from F, Cl, Br, I, CF_3 and C_{1-6} alkyl;

R_1 and R_2 is independently selected from the group comprising $-H$, $-O$, C_{1-6} alkyl, C_{1-6} alkoxy, $-(CH_2)_n$, amino, $-CO$, $-CONH$, $-NH(Alkyl)$, $-N(Alkyl)_2$, $-NH-aralkyl$, $-CH_2O$, $-OCH(CH_3)$, halogen $COOR_3$, $-CONR_3R_4$, NR_3COR_4 ;

R_3 and R_4 is independently selected from the group comprising hydrogen, or C_{1-6} straight chain or branched chain alkyl which may be further substituted with halogen or C_{1-6} alkyl;

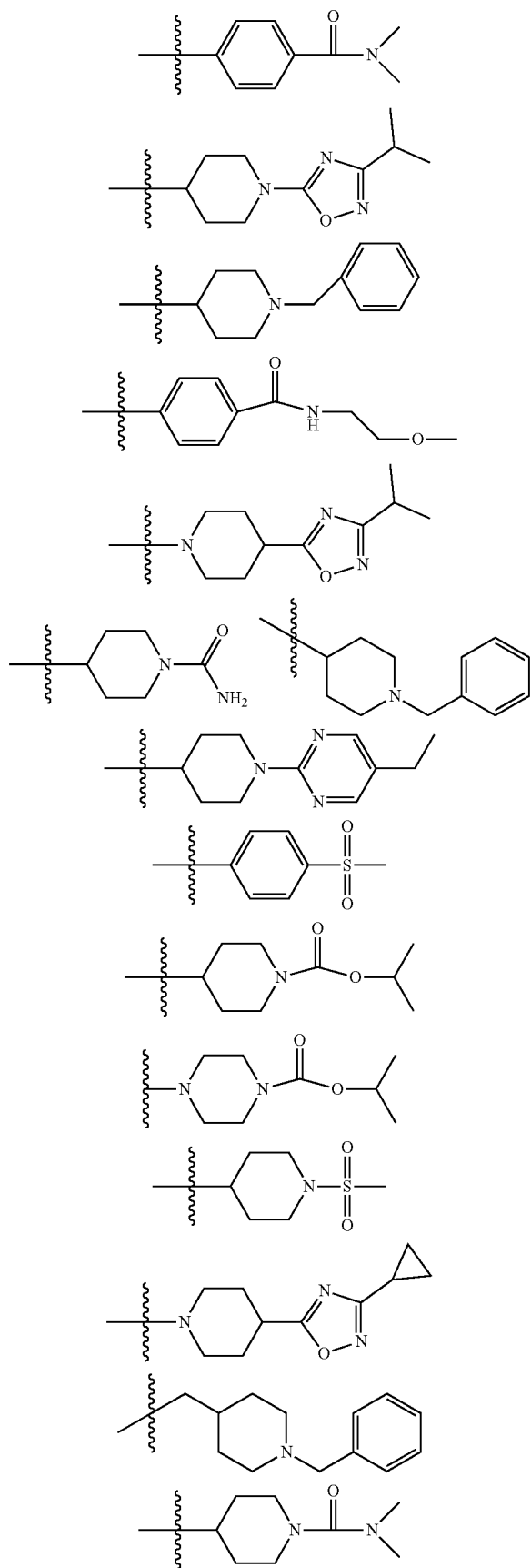
n is 0, 1, 2 or 3.

A is selected from

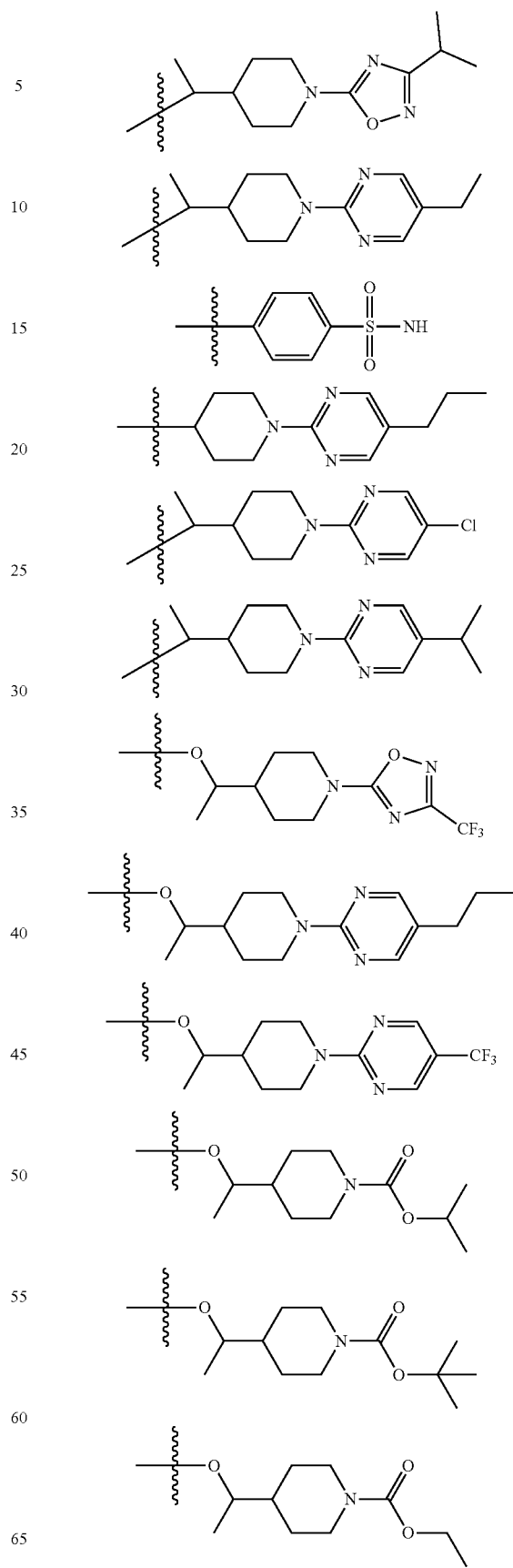


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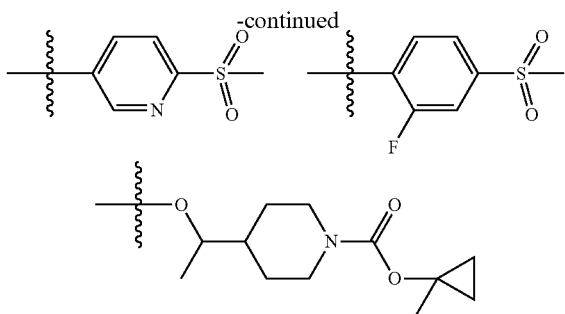
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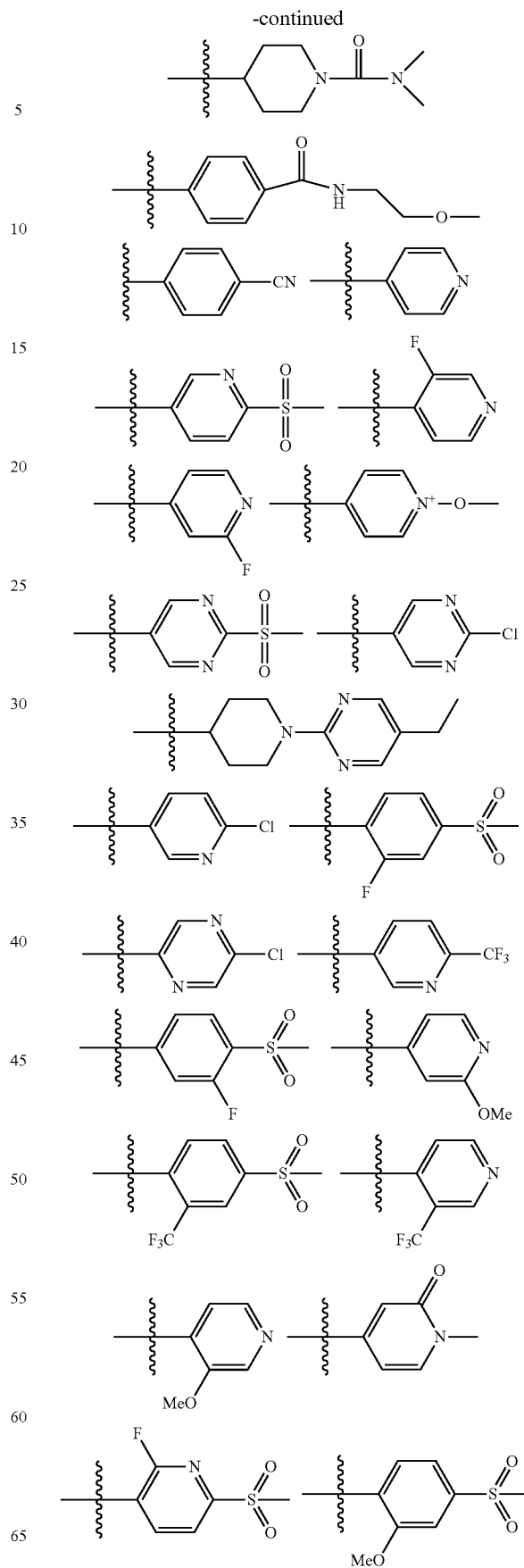
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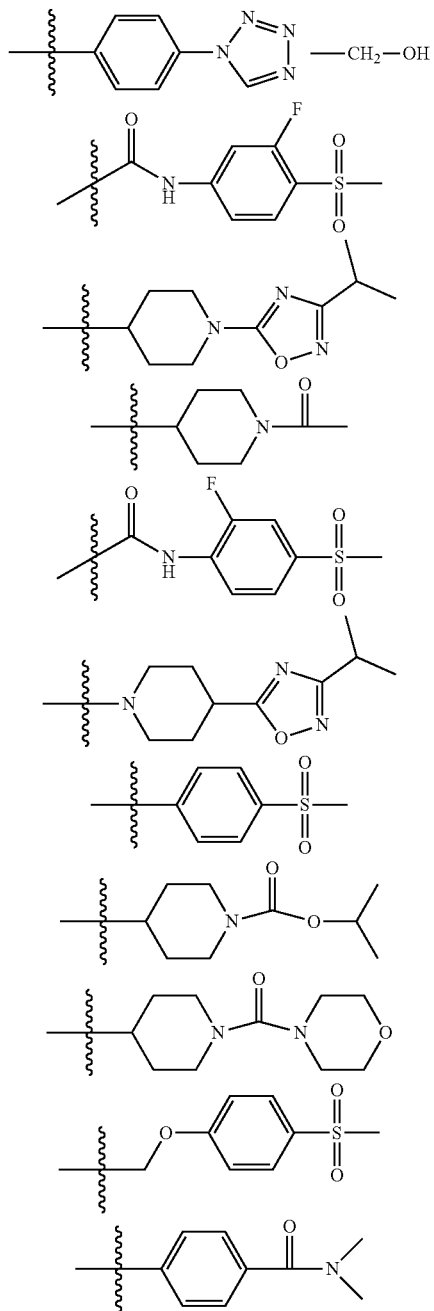
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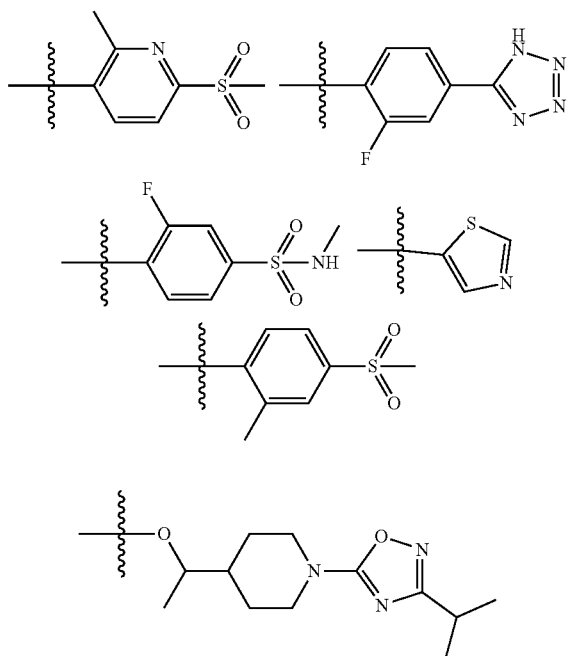


B is be selected from



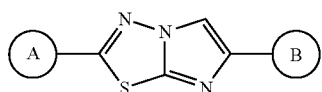
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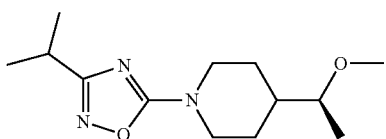


and pharmaceutically acceptable salts, hydrates and stereoisomers thereof.

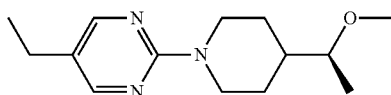
In one embodiment, there are provided compounds having the formula (II):



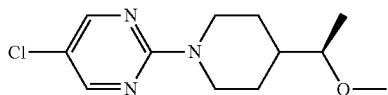
Individually contemplated are compounds wherein A is



Individually contemplated are compounds wherein A is

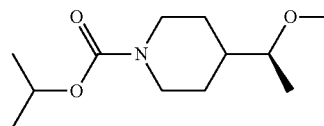


Individually contemplated are compounds wherein A is



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Also individually contemplated are compounds wherein A is



In a variant, the invention provides compounds having significant dose dependent glucose reduction at both 3 mpk and 10 mpk in oral glucose tolerance test in rat model.

In another variant, the invention provides compounds showing significant dose dependent glucose reduction at both 3 mpk and 10 mpk in oral glucose tolerance test in mice.

In another variant, the invention provides compounds showing active GLP-1 secretion greater than ~1 fold with respect to the vehicle.

In another aspect, the invention provides a method of treating diabetes comprising administering compounds of all embodiments and variants of the invention.

DETAILED DESCRIPTION OF THE INVENTION

A. Compounds of the Present Invention

The term “alkyl” refers to a linear or branched saturated monovalent hydrocarbon, wherein the alkylene may optionally be substituted as described herein. The term “alkyl” also encompasses both linear and branched alkyl, unless otherwise specified. In certain embodiments, the alkyl is a linear saturated monovalent hydrocarbon that has the specified number of carbon atoms, or branched saturated monovalent hydrocarbon of specified number of carbon atoms. As used herein, linear C1-C6 and branched C3-C6 alkyl groups are also referred as “lower alkyl.” Examples of alkyl groups include, but are not limited to, methyl, ethyl, propyl (including all isomeric forms), n-propyl, isopropyl, butyl (including all isomeric forms), n-butyl, isobutyl, sec-butyl, t-butyl, pentyl (including all isomeric forms), and hexyl (including all isomeric forms). For example, C1-C6 alkyl refers to a linear saturated monovalent hydrocarbon of 1 to 6 carbon atoms or a branched saturated monovalent hydrocarbon of 3 to 6 carbon atoms.

The term “alkoxy” refers to the group R'O— wherein R' is alkyl. The term “lower alkoxy” refers to alkoxy groups having from 1 to 3 carbon atoms; examples include methoxy, ethoxy, isopropoxy, and the like.

The term “aralkyl” or “aryl-alkyl” refers to a monovalent alkyl group substituted with aryl. In certain embodiments, the alkyl and aryl moieties are optionally substituted as described herein.

The term “halogen”, “halide” or “halo” refers to fluorine, chlorine, bromine, and iodine.

The term “heteroatom” as used herein means an atom of any element other than carbon or hydrogen. Preferred heteroatoms are nitrogen, oxygen, sulfur, phosphorus and selenium.

The term “optionally substituted” is intended to mean that a group, such as an alkyl, alkylene, alkenyl, alkenylene, alkynyl, alkynylene, alkoxy, alkylamino, dialkylamino, carbonylamino, cycloalkyl, cycloalkylene, aryl, aryleno, heteroaryl, heteroarylene, heterocyclyl, or heterocyclylene, may be substituted with one or more substituents independently selected from, e.g., (a) C1-C6 alkyl, C2-C6 alkenyl,

C2-C6 alkynyl, C3-C7 cycloalkyl, C6-C14 aryl, C7-C15 aralkyl, heteroaryl, and heterocyclyl, each optionally substituted with one or more substituents; and (b) halo, cyano ($-\text{CN}$), nitro ($-\text{NO}_2$), $-\text{C}(\text{O})\text{R}_3$, $-\text{C}(\text{O})\text{OR}_3$, $-\text{C}(\text{O})\text{NRbRC}$, $-\text{C}(\text{NR}_3)\text{NRcRC}$, $-\text{OR}_3$, $-\text{OC}(\text{O})\text{R}_3$, $-\text{OC}(\text{O})\text{OR}_3$, $-\text{OC}(\text{O})\text{NRbRC}$, $-\text{OC}(\text{O})\text{NRcRC}$, $-\text{OS}(\text{O})\text{R}_3$, $-\text{OS}(\text{O})\text{OR}_3$, $-\text{OS}(\text{O})\text{NRbRC}$, $-\text{OS}(\text{O})\text{NRcRC}$, $-\text{NRbRc}$, $-\text{NRcRd}$, $-\text{NR}_3\text{C}(\text{O})\text{Rd}$, $-\text{NR}_3\text{C}(\text{O})\text{ORd}$, $-\text{NR}_3\text{C}(\text{O})\text{NRbRC}$, $-\text{NR}_3\text{C}(\text{O})\text{NRcRC}$, $-\text{NR}_3\text{S}(\text{O})\text{Rd}$, $-\text{NR}_3\text{S}(\text{O})\text{ORd}$, $-\text{NR}_3\text{S}(\text{O})\text{NRbRC}$, $-\text{NR}_3\text{S}(\text{O})\text{NRcRC}$, $-\text{SR}_3$, $-\text{S}(\text{O})\text{R}_3$, $-\text{S}(\text{O})\text{OR}_3$, $-\text{S}(\text{O})\text{NRbRC}$, and $-\text{S}(\text{O})\text{NRcRC}$, wherein each R3, Rb, Rc, and Rd is independently (i) hydrogen; (ii) C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, C3-C7 cycloalkyl, C6-C14 aryl, C7-C15 aralkyl, heteroaryl, or heterocyclyl, each optionally substituted with one or more substituents; or (iii) Rb and Rc together with the N atom to which they are attached form heteroaryl or heterocyclyl, optionally substituted with one or more, in one embodiment, one, two, three, or four, substituents. As used herein, all groups that may be substituted are "optionally substituted," unless otherwise specified.

The use of terms "a" and "an" and "the" and similar references in the context of describing the invention (especially in the context of the following claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contraindicated by context.

The term "salt(s)", as employed herein, denotes acidic and/or basic salts formed with inorganic and/or organic acids and bases.

The term "pharmaceutically acceptable salts" refers to the acid addition salt compound formed with a suitable acid selected from an inorganic acid such as hydrochloric acid, hydrobromic acid; or an organic acid such as benzene sulfonic acid, maleic acid, oxalic acid, fumaric acid, succinic acid, p-toluenesulfonic acid and malic acid.

The term "hydrate" as used herein designates a crystalline molecular compound in which water molecules are incorporated into the crystal lattice. Generally speaking, a hydrate thus designates a crystalline form of a molecular compound, whereby the only further molecules incorporated into the crystal lattice are water molecules.

The term "stereoisomer's" refers to at least two compounds having the same molecular formula and connectivity of atoms, but having a different arrangement of atoms in a three-dimensional space. In view of the present disclosure, a stereoisomer can be, for example, an enantiomer, a diastereomer, or a meso compound.

The term "GPR119" as used herein refers to the G protein-coupled receptor that in humans is encoded by the GPR119 gene.

The present invention provides compound represented by formula (1) that act as GPR119 agonist and is used in the treatment of diabetes, preferably type 2 diabetes mellitus.

The compounds of the present invention may be illustrated but not limited to the examples as provided at Table 1.

TABLE 1

Illustrative compounds of present invention		
Compound No.	IUPAC name	Structure
1001	3,4-bis(4-(1H-tetrazol-1-yl)phenoxy)-1,2,5-thiadiazole	
1002	3,4-bis((1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)oxy)-1,2,5-thiadiazole	
1003	5-(1-(4-(4-(1H-tetrazol-1-yl)phenoxy)-1,2,5-thiadiazol-3-yl)piperidin-4-yl)-3-isopropyl-1,2,4-oxadiazole	

TABLE 1-continued

Illustrative compounds of present invention		
Compound No.	IUPAC name	Structure
1004	3-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yl)-4-(4-(methylsulfonyl)phenyl)-1,2,5-thiadiazole	
1005	3-(4-(1H-tetrazol-1-yl)phenoxy)-4-(1-(5-ethylpyrimidin-2-yl)-1,2,3,6-tetrahydropyridin-4-yl)-1,2,5-thiadiazole	
1006	5-(1-(4-(2-fluoro-4-(methylsulfonyl)phenoxy)methyl)-1,2,5-thiadiazol-3-yl)piperidin-4-yl)-3-isopropyl-1,2,4-oxadiazole	
1007	3-isopropyl-5-(1-(4-(4-(methylsulfonyl)phenyl)-1,2,5-thiadiazol-3-yl)piperidin-4-yl)-1,2,4-oxadiazole	

TABLE 1-continued

Illustrative compounds of present invention		
Compound No.	IUPAC name	Structure
1008	(4-(1-(5-ethylpyrimidin-2-yl)-1,2,3,6-tetrahydropyridin-4-yl)-1,2,5-thiadiazol-3-yl)methanol	
1009	5-(1-(4-((4-(1H-tetrazol-1-yl)phenoxy)methyl)-1,2,5-thiadiazol-3-yl)piperidin-4-yl)-3-isopropyl-1,2,4-oxadiazole	
1010	isopropyl 4-(4-(4-(1H-tetrazol-1-yl)phenoxy)-1,2,5-thiadiazol-3-yl)piperazine-1-carboxylate	
1011	3,4-bis((1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)methoxy)-1,2,5-thiadiazole	
1012	N-(2-fluoro-4-(methylsulfonyl)phenyl)-4-(4-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-1,2,5-thiadiazole-3-carboxamide	

TABLE 1-continued

Illustrative compounds of present invention

Compound No.	IUPAC name	Structure
1013	N-(3-fluoro-4-(methylsulfonyl)phenyl)-4-(4-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-1,2,5-thiadiazole-3-carboxamide	
1014	4-(1-(5-ethylpyrimidin-2-yl)-1,2,3,6-tetrahydropyridin-4-yl)-N-(2-fluoro-4-(methylsulfonyl)phenyl)-1,2,5-thiadiazole-3-carboxamide	
1015	4-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yl)-N-(2-fluoro-4-(methylsulfonyl)phenyl)-1,2,5-thiadiazole-3-carboxamide	
1016	3-isopropyl-5-(1-(6-(4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazol-2-yl)piperidin-4-yl)-1,2,4-oxadiazole	
1017	3-isopropyl-5-(4-(((6-(4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazol-2-yl)oxy)methyl)piperidin-1-yl)-1,2,4-oxadiazole	
1018	3-isopropyl-5-(4-(((6-(4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazol-2-yl)oxy)piperidin-1-yl)-1,2,4-oxadiazole	

TABLE 1-continued

Illustrative compounds of present invention		
Compound No.	IUPAC name	Structure
1019	2-(1-benzylpiperidin-4-yl)-6-(4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazole	
1020	isopropyl 4-(6-(4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazol-2-yl)piperazine-1-carboxylate	
1021	isopropyl 4-((6-(4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazol-2-yl)amino)piperidine-1-carboxylate	
1022	isopropyl 4-(methyl(6-(4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazol-2-yl)amino)piperidine-1-carboxylate	
1023	N-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yl)-6-(4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazol-2-amine	
1024	isopropyl 4-(6-(4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazol-2-yl)piperidine-1-carboxylate	
1025	4-(methyl(6-(4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazol-2-yl)amino)piperidine-1-carboxamide	
1026	4-(6-(4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazol-2-yl)piperidine-1-carboxamide	
1027	3-isopropyl-5-(4-(6-(4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazol-2-yl)piperidin-1-yl)-1,2,4-oxadiazole	

TABLE 1-continued

Illustrative compounds of present invention		
Compound No.	IUPAC name	Structure
1028	1-(4-(2-(4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazol-6-yl)piperidin-1-yl)ethanone	
1029	N-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)-N-methyl-6-(4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazol-2-amine	
1030	isopropyl 4-(2-(4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazol-6-yl)piperidine-1-carboxylate	
1031	6-(4-(methylsulfonyl)phenyl)-2-(1-(methylsulfonyl)piperidin-4-yl)imidazo[2,1-b][1,3,4]thiadiazole	
1032	3-isopropyl-5-(4-(2-(4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazol-6-yl)piperidin-1-yl)-1,2,4-oxadiazole	
1033	N,N-dimethyl-4-(6-(4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazol-2-yl)piperidine-1-carboxamide	
1034	isopropyl 4-(2-(4-(dimethylcarbamoyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazol-6-yl)piperidine-1-carboxylate	
1035	isopropyl 4-(2-(4-((2-methoxyethyl)carbamoyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazol-6-yl)piperidine-1-carboxylate	
1036	4-(2-(4-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-1-yl)imidazo[2,1-b][1,3,4]thiadiazol-6-yl)-N,N-dimethylbenzamide	

TABLE 1-continued

Illustrative compounds of present invention		
Compound No.	IUPAC name	Structure
1037	4-(2-(4-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-1-yl)imidazo[2,1-b][1,3,4]thiadiazol-6-yl)phenyl(morpholino) methanone	
1038	2-(1-benzylpiperidin-4-yl)-6-((4-(methylsulfonyl)phenoxy)methyl)imidazo[2,1-b][1,3,4]thiadiazole	
1039	4-(2-(4-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-1-yl)imidazo[2,1-b][1,3,4]thiadiazol-6-yl)-N-(2-methoxyethyl)benzamide	
1040	3-isopropyl-5-(1-(6-((4-(methylsulfonyl)phenoxy)methyl)imidazo[2,1-b][1,3,4]thiadiazol-2-yl)piperidin-4-yl)-1,2,4-oxadiazole	
1041	isopropyl 4-(6-((4-(methylsulfonyl)phenoxy)methyl)imidazo[2,1-b][1,3,4]thiadiazol-2-yl)piperidine-1-carboxylate	
1042	3-isopropyl-5-(4-(6-((4-(methylsulfonyl)phenoxy)methyl)imidazo[2,1-b][1,3,4]thiadiazol-2-yl)oxy)piperidin-1-yl)-1,2,4-oxadiazole	
1043	4-(2-(4-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-1-yl)imidazo[2,1-b][1,3,4]thiadiazol-6-yl)methoxy)-N,N-dimethylbenzamide	
1044	5-(1-(5-chloro-6-(4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazol-2-yl)piperidin-4-yl)-3-isopropyl-1,2,4-oxadiazole	

TABLE 1-continued

Illustrative compounds of present invention		
Compound No.	IUPAC name	Structure
1045	3-cyclopropyl-5-(1-(6-(4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazol-2-yl)piperidin-4-yl)-1,2,4-oxadiazole	
1046	4-(2-(4-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-1-yl)imidazo[2,1-b][1,3,4]thiadiazol-6-yl)benzotrile	
1047	4-(2-(1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)imidazo[2,1-b][1,3,4]thiadiazol-6-yl)benzotrile	
1048	4-(2-(1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)imidazo[2,1-b][1,3,4]thiadiazol-6-yl)-N,N-dimethylbenzamide	
1049	N,N-dimethyl-4-(2-(1-(1-(5-propylpyrimidin-2-yl)piperidin-4-yl)ethoxy)imidazo[2,1-b][1,3,4]thiadiazol-6-yl)benzamide	
1050	3-isopropyl-5-(4-(1-((6-(pyridin-4-yl)imidazo[2,1-b][1,3,4]thiadiazol-2-yl)oxy)ethyl)piperidin-1-yl)-1,2,4-oxadiazole	
1051	3-isopropyl-5-(1-(6-(pyridin-4-yl)imidazo[2,1-b][1,3,4]thiadiazol-2-yl)piperidin-4-yl)-1,2,4-oxadiazole	
1052	5-(1-(5-chloro-6-(pyridin-4-yl)imidazo[2,1-b][1,3,4]thiadiazol-2-yl)piperidin-4-yl)-3-isopropyl-1,2,4-oxadiazole	
1053	4-(2-((1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)methoxy)imidazo[2,1-b][1,3,4]thiadiazol-6-yl)benzotrile	

TABLE 1-continued

Illustrative compounds of present invention		
Compound No.	IUPAC name	Structure
1054	3-isopropyl-5-(4-(((6-(pyridin-4-yl)imidazo[2,1-b][1,3,4]thiadiazol-2-yl)oxy)methyl)piperidin-1-yl)-1,2,4-oxadiazole	
1055	3-isopropyl-5-(4-(1-((6-(methylsulfonyl)pyridin-3-yl)imidazo[2,1-b][1,3,4]thiadiazol-2-yl)oxy)ethyl)piperidin-1-yl)-1,2,4-oxadiazole	
1056	2-(1-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yl)ethoxy)-6-(pyridin-4-yl)imidazo[2,1-b][1,3,4]thiadiazole	
1057	3-isopropyl-5-(4-(1-((6-(4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazol-2-yl)oxy)ethyl)piperidin-1-yl)-1,2,4-oxadiazole	
1058	(R)-3-isopropyl-5-(4-(1-((6-(methylsulfonyl)pyridin-3-yl)imidazo[2,1-b][1,3,4]thiadiazol-2-yl)oxy)ethyl)piperidin-1-yl)-1,2,4-oxadiazole	
1059	(R)-3-isopropyl-5-(4-(1-((6-(pyridin-4-yl)imidazo[2,1-b][1,3,4]thiadiazol-2-yl)oxy)ethyl)piperidin-1-yl)-1,2,4-oxadiazole	
1060	(R)-3-isopropyl-5-(4-(1-((6-(4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazol-2-yl)oxy)ethyl)piperidin-1-yl)-1,2,4-oxadiazole	
1061	5-(4-(1-((5-fluoro-6-(4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazol-2-yl)oxy)ethyl)piperidin-1-yl)-3-isopropyl-1,2,4-oxadiazole	

TABLE 1-continued

Illustrative compounds of present invention		
Compound No.	IUPAC name	Structure
1062	(R)-2-(1-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yl)ethoxy)-6-(4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazole	
1063	5-(4-(1-((5-chloro-6-(4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazol-2-yl)oxy)ethyl)piperidin-1-yl)-3-isopropyl-1,2,4-oxadiazole	
1064	(S)-5-(4-(1-((6-(3-fluoropyridin-4-yl)imidazo[2,1-b][1,3,4]thiadiazol-2-yl)oxy)ethyl)piperidin-1-yl)-3-isopropyl-1,2,4-oxadiazole	
1065	(R)-5-(4-(1-((6-(2-fluoropyridin-4-yl)imidazo[2,1-b][1,3,4]thiadiazol-2-yl)oxy)ethyl)piperidin-1-yl)-3-isopropyl-1,2,4-oxadiazole	
1066	(R)-5-(4-(1-((5-fluoro-6-(4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazol-2-yl)oxy)ethyl)piperidin-1-yl)-3-isopropyl-1,2,4-oxadiazole	
1067	(S)-6-(4-(methylsulfonyl)phenyl)-2-(1-(1-(5-propylpyrimidin-2-yl)piperidin-4-yl)ethoxy)imidazo[2,1-b][1,3,4]thiadiazole	
1068	(S)-4-(2-(1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)imidazo[2,1-b][1,3,4]thiadiazol-6-yl)pyridine 1-oxide	
1069	2-(1-(1-(5-chloropyrimidin-2-yl)piperidin-4-yl)ethoxy)-6-(4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazole	

TABLE 1-continued

Illustrative compounds of present invention		
Compound No.	IUPAC name	Structure
1070	2-(1-(1-(5-isopropylpyrimidin-2-yl)piperidin-4-yl)ethoxy)-6-(4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazole	
1071	(S)-5-(4-(1-((6-(2-chloropyrimidin-5-yl)imidazo[2,1-b][1,3,4]thiadiazol-2-yl)oxy)ethyl)piperidin-1-yl)-3-isopropyl-1,2,4-oxadiazole	
1072	(S)-3-isopropyl-5-(4-(1-((6-(2-(methylsulfonyl)pyrimidin-5-yl)imidazo[2,1-b][1,3,4]thiadiazol-2-yl)oxy)ethyl)piperidin-1-yl)-1,2,4-oxadiazole	
1073	2-(1-(1-(3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)-6-(4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazole	
1074	2-(1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)-6-(2-(methylsulfonyl)pyrimidin-5-yl)imidazo[2,1-b][1,3,4]thiadiazole	
1075	2-(1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)-6-(6-chloropyridin-3-yl)imidazo[2,1-b][1,3,4]thiadiazole	
1076	2-((R)-1-(1-(3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)-6-(4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazole	
1077	2-((S)-1-(1-(3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)-6-(4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazole	
1078	2-((S)-1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)-6-(3-fluoro-4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazole	
1079	2-(1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)-6-(5-chloropyrazin-2-yl)imidazo[2,1-b][1,3,4]thiadiazole	

TABLE 1-continued

Illustrative compounds of present invention		
Compound No.	IUPAC name	Structure
1080	2-((R)-1-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yl)ethoxy)-6-(pyridin-4-yl)imidazo[2,1-b][1,3,4]thiadiazole	
1081	2-((R)-1-(1-(5-propylpyrimidin-2-yl)piperidin-4-yl)ethoxy)-6-(6-(methylsulfonyl)pyridin-3-yl)imidazo[2,1-b][1,3,4]thiadiazole	
1082	2-((S)-1-(1-(5-propylpyrimidin-2-yl)piperidin-4-yl)ethoxy)-6-(3-fluoropyridin-4-yl)imidazo[2,1-b][1,3,4]thiadiazole	
1083	2-((S)-1-(1-(5-chloropyrimidin-2-yl)piperidin-4-yl)ethoxy)-6-(4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazole	
1084	2-((R)-1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)-6-(6-(trifluoromethyl)pyridin-3-yl)imidazo[2,1-b][1,3,4]thiadiazole	
1085	2-((S)-1-(1-(5-propylpyrimidin-2-yl)piperidin-4-yl)ethoxy)-6-(2-fluoro-4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazole	
1086	2-((S)-1-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yl)ethoxy)-6-(2-fluoro-4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazole	
1087	2-((R)-1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)-6-(5-chloropyrazin-2-yl)imidazo[2,1-b][1,3,4]thiadiazole	

TABLE 1-continued

Illustrative compounds of present invention		
Compound No.	IUPAC name	Structure
1088	2-((R)-1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)-6-(2-fluoro-4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazole	
1089	2-((S)-1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)-6-(2-methoxy-pyridin-4-yl)imidazo[2,1-b][1,3,4]thiadiazole	
1090	2-((R)-1-(1-(5-chloropyrimidin-2-yl)piperidin-4-yl)ethoxy)-6-(2-fluoro-4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazole	
1091	2-(1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)-6-(2-(trifluoromethyl)-4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazole	
1092	2-(1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)-6-(3-(trifluoromethyl)pyridin-4-yl)imidazo[2,1-b][1,3,4]thiadiazole	
1093	2-((S)-1-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yl)ethoxy)-6-(2-methoxy-pyridin-4-yl)imidazo[2,1-b][1,3,4]thiadiazole	
1094	2-((S)-1-(1-(5-propylpyrimidin-2-yl)piperidin-4-yl)ethoxy)-6-(2-methoxy-pyridin-4-yl)imidazo[2,1-b][1,3,4]thiadiazole	
1095	2-(1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)-6-(3-methoxy-pyridin-4-yl)imidazo[2,1-b][1,3,4]thiadiazole	

TABLE 1-continued

Illustrative compounds of present invention		
Compound No.	IUPAC name	Structure
1096	4-(2-((S)-1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)imidazo[2,1-b][1,3,4]thiadiazol-6-yl)-1-methylpyridin-2(1H)-one	
1097	2-((S)-1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)-6-(3-fluoropyridin-4-yl)imidazo[2,1-b][1,3,4]thiadiazole hydrochloride	
1098	2-((S)-1-(1-(5-(trifluoromethyl)pyrimidin-2-yl)piperidin-4-yl)ethoxy)-6-(2-fluoro-4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazole	
1099	4-(2-((R)-1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)imidazo[2,1-b][1,3,4]thiadiazol-6-yl)-3-fluorobenzonitrile	
1100	2-((R)-1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)-6-(2-fluoro-6-(methylsulfonyl)pyridin-3-yl)imidazo[2,1-b][1,3,4]thiadiazole	
1101	isopropyl 4-(1-(6-(2-fluoro-4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazol-2-yloxy)ethyl)piperidine-1-carboxylate	
1102	2-((R)-1-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yl)ethoxy)-6-(2-fluoro-6-(methylsulfonyl)pyridin-3-yl)imidazo[2,1-b][1,3,4]thiadiazole	
1103	2-((S)-1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)-6-(2-methoxy-4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazole	

TABLE 1-continued

Illustrative compounds of present invention		
Compound No.	IUPAC name	Structure
1104	2-((S)-1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)-6-(2-methyl-6-(methylsulfonyl)pyridin-3-yl)imidazo[2,1-b][1,3,4]thiadiazole	
1105	2-((R)-1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)-6-(2-fluoro-4-(1H-tetrazol-5-yl)phenyl)imidazo[2,1-b][1,3,4]thiadiazole hydrochloride	
1106	tert-butyl 4-(1-(6-(6-fluoro-4-(methylsulfonyl)cyclohexa-1,5-dienyl)imidazo[2,1-b][1,3,4]thiadiazol-2-yloxy)ethyl)piperidine-1-carboxylate	
1107	ethyl 4-(1-(6-(2-fluoro-4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazol-2-yloxy)ethyl)piperidine-1-carboxylate	
1108	isopropyl 4-((S)-1-(6-(2-fluoro-4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazol-2-yloxy)ethyl)piperidine-1-carboxylate	
1109	3-fluoro-4-(2-(1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)imidazo[2,1-b][1,3,4]thiadiazol-6-yl)-N-methylbenzenesulfonamide	
1110	1-methylcyclopropyl 4-(1-(6-(2-fluoro-4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazol-2-yloxy)ethyl)piperidine-1-carboxylate	

TABLE 1-continued

Illustrative compounds of present invention		
Compound No.	IUPAC name	Structure
1111	2-(1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)-6-(thiazol-5-yl)imidazo[2,1-b][1,3,4]thiadiazole	
1112	2-((S)-1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)-6-(2-methyl-4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazole	
1113	ethyl 4-((S)-1-(6-(2-fluoro-4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazol-2-yloxy)ethyl)piperidine-1-carboxylate	
1114	4-(3-isopropyl-1,2,4-oxadiazol-5-yl)-1-(3-(4-(methylsulfonyl)phenyl)-1,2,4-thiadiazol-5-yl)piperidine	
1115	4-(1-(3-(4-(methylsulfonyl)phenyl)-1,2,4-thiadiazol-5-yloxy)ethyl)-1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidine	
1116	4-(3-(4-(methylsulfonyl)phenyl)-1,2,4-thiadiazol-5-yloxy)-1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidine	

TABLE 1-continued

Illustrative compounds of present invention		
Compound No.	IUPAC name	Structure
1117	4-(3-(4-(methylsulfonyl)phenyl)-1,2,4-thiazol-5-yloxy)methyl-1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidine	
1118	5-(3-(1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)-1,2,4-thiazol-5-yl)-2-(methylsulfonyl)pyridine	
1119	5-(3-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yloxy)-1,2,4-thiazol-5-yl)-2-(methylsulfonyl)pyridine	
1120	5-(3-((1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)methoxy)-1,2,4-thiazol-5-yl)-2-(methylsulfonyl)pyridine	
1121	5-(5-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yloxy)-1,2,4-thiazol-3-yl)-2-(methylsulfonyl)pyridine	

TABLE 1-continued

Illustrative compounds of present invention		
Compound No.	IUPAC name	Structure
1122	2-(4-(3-(6-(methylsulfonyl)pyridin-3-yl)-1,2,4-thiazol-5-yloxy)piperidin-1-yl)-5-ethylpyrimidine	
1123	2-(4-(3-(6-(methylsulfonyl)pyridin-3-yl)-1,2,4-thiazol-5-yloxy)piperidin-1-yl)-5-propylpyrimidine	
1124	N-(5-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yloxy)-1,2,4-thiazol-3-yl)-N-methyl-6-(methylsulfonyl)pyridin-3-amine	
1125	2-(4-(3-(2-fluoro-4-(methylsulfonyl)phenyl)-1,2,4-thiazol-5-yloxy)piperidin-1-yl)-5-ethylpyrimidine	
1126	1-(3-isopropyl-1,2,4-oxadiazol-5-yl)-N-(3-(6-(methylsulfonyl)pyridin-3-yl)-1,2,4-thiazol-5-yl)piperidin-4-amine	
1127	1-(3-isopropyl-1,2,4-oxadiazol-5-yl)-N-methyl-N-(3-(6-(methylsulfonyl)pyridin-3-yl)-1,2,4-thiazol-5-yl)piperidin-4-amine	

The present invention also provides for compounds of formula (1) as below:

- i. 3,4-bis(4-(1H-tetrazol-1-yl)phenoxy)-1,2,5-thiadiazole
- ii. 3,4-bis((1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)oxy)-1,2,5-thiadiazole
- iii. 5-(1-(4-(4-(1H-tetrazol-1-yl)phenoxy)-1,2,5-thiadiazol-3-yl)piperidin-4-yl)-3-isopropyl-1,2,4-oxadiazole
- iv. 3-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yl)-4-(4-(methylsulfonyl)phenyl)-1,2,5-thiadiazole
- v. 3-(4-(1H-tetrazol-1-yl)phenoxy)-4-(1-(5-ethylpyrimidin-2-yl)-1,2,3,6-tetrahydropyridin-4-yl)-1,2,5-thiadiazole
- vi. 5-(1-(4-(2-fluoro-4-(methylsulfonyl)phenoxy)methyl)-1,2,5-thiadiazol-3-yl)piperidin-4-yl)-3-isopropyl-1,2,4-oxadiazole
- vii. 3-isopropyl-5-(1-(4-(4-(methylsulfonyl)phenyl)-1,2,5-thiadiazol-3-yl)piperidin-4-yl)-1,2,4-oxadiazole
- viii. (4-(1-(5-ethylpyrimidin-2-yl)-1,2,3,6-tetrahydropyridin-4-yl)-1,2,5-thiadiazol-3-yl)methanol
- ix. 5-(1-(4-(4-(1H-tetrazol-1-yl)phenoxy)methyl)-1,2,5-thiadiazol-3-yl)piperidin-4-yl)-3-isopropyl-1,2,4-oxadiazole
- x. isopropyl 4-(4-(4-(1H-tetrazol-1-yl)phenoxy)-1,2,5-thiadiazol-3-yl)piperazine-1-carboxylate
- xi. 3,4-bis((1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)methoxy)-1,2,5-thiadiazole
- xii. N-(2-fluoro-4-(methylsulfonyl)phenyl)-4-(4-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-1,2,5-thiadiazole-3-carboxamide
- xiii. N-(3-fluoro-4-(methylsulfonyl)phenyl)-4-(4-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-1,2,5-thiadiazole-3-carboxamide
- xiv. 4-(1-(5-ethylpyrimidin-2-yl)-1,2,3,6-tetrahydropyridin-4-yl)-N-(2-fluoro-4-(methylsulfonyl)phenyl)-1,2,5-thiadiazole-3-carboxamide
- xv. 4-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yl)-N-(2-fluoro-4-(methylsulfonyl)phenyl)-1,2,5-thiadiazole-3-carboxamide
- xvi. 3-isopropyl-5-(1-(6-(4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazol-2-yl)piperidin-4-yl)-1,2,4-oxadiazole
- xvii. 3-isopropyl-5-(4-(((6-(4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazol-2-yl)oxy)methyl)piperidin-1-yl)-1,2,4-oxadiazole
- xviii. 3-isopropyl-5-(4-(((6-(4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazol-2-yl)oxy)piperidin-1-yl)-1,2,4-oxadiazole
- xix. 2-(1-benzylpiperidin-4-yl)-6-(4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazole
- xx. isopropyl-4-(6-(4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazol-2-yl)piperazine-1-carboxylate
- xxi. isopropyl-4-(((6-(4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazol-2-yl)amino)piperidine-1-carboxylate
- xxii. isopropyl 4-(methyl(6-(4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazol-2-yl)amino)piperidine-1-carboxylate
- xxiii. N-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yl)-6-(4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazol-2-amine
- xxiv. isopropyl-4-(6-(4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazol-2-yl)piperidine-1-carboxylate
- xxv. 4-(methyl(6-(4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazol-2-yl)amino)piperidine-1-carboxamide
- xxvi. 4-(6-(4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazol-2-yl)piperidine-1-carboxamide

- xxvii. 3-isopropyl-5-(4-(6-(4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazol-2-yl)piperidin-1-yl)-1,2,4-oxadiazole
- xxviii. 1-(4-(2-(4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazol-6-yl)piperidin-1-yl)ethanone
- xxix. N-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)-N-methyl-6-(4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazol-2-amine
- xxx. isopropyl-4-(2-(4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazol-6-yl)piperidine-1-carboxylate
- xxxi. 6-(4-(methylsulfonyl)phenyl)-2-(1-(methylsulfonyl)piperidin-4-yl)imidazo[2,1-b][1,3,4]thiadiazole
- xxxii. 3-isopropyl-5-(4-(2-(4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazol-6-yl)piperidin-1-yl)-1,2,4-oxadiazole
- xxxiii. N,N-dimethyl-4-(6-(4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazol-2-yl)piperidine-1-carboxamide
- xxxiv. isopropyl-4-(2-(4-(dimethylcarbamoyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazol-6-yl)piperidine-1-carboxylate
- xxxv. isopropyl-4-(2-(4-((2-methoxyethyl)carbamoyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazol-6-yl)piperidine-1-carboxylate
- xxxvi. 4-(2-(4-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-1-yl)imidazo[2,1-b][1,3,4]thiadiazol-6-yl)-N,N-dimethylbenzamide
- xxxvii. (4-(2-(4-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-1-yl)imidazo[2,1-b][1,3,4]thiadiazol-6-yl)phenyl)(morpholino)methanone
- xxxviii. 2-(1-benzylpiperidin-4-yl)-6-(4-(methylsulfonyl)phenoxy)methyl)imidazo[2,1-b][1,3,4]thiadiazole
- xxxix. 4-(2-(4-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-1-yl)imidazo[2,1-b][1,3,4]thiadiazol-6-yl)-N-(2-methoxyethyl)benzamide
- xl. 3-isopropyl-5-(1-(6-(((4-(methylsulfonyl)phenoxy)methyl)imidazo[2,1-b][1,3,4]thiadiazol-2-yl)piperidin-4-yl)-1,2,4-oxadiazole
- xli. isopropyl-4-(6-(((4-(methylsulfonyl)phenoxy)methyl)imidazo[2,1-b][1,3,4]thiadiazol-2-yl)piperidine-1-carboxylate
- xlii. 3-isopropyl-5-(4-(((6-(((4-(methylsulfonyl)phenoxy)methyl)imidazo[2,1-b][1,3,4]thiadiazol-2-yl)oxy)piperidin-1-yl)-1,2,4-oxadiazole
- xliii. 4-(((2-(4-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-1-yl)imidazo[2,1-b][1,3,4]thiadiazol-6-yl)methoxy)-N,N-dimethylbenzamide
- xliv. 5-(1-(5-chloro-6-(4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazol-2-yl)piperidin-4-yl)-3-isopropyl-1,2,4-oxadiazole
- xlv. 3-cyclopropyl-5-(1-(6-(4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazol-2-yl)piperidin-4-yl)-1,2,4-oxadiazole
- xlvi. 4-(2-(4-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-1-yl)imidazo[2,1-b][1,3,4]thiadiazol-6-yl)benzotrile
- xlvii. 4-(2-(1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)imidazo[2,1-b][1,3,4]thiadiazol-6-yl)benzotrile
- xlviii. 4-(2-(1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)imidazo[2,1-b][1,3,4]thiadiazol-6-yl)-N,N-dimethylbenzamide
- xliv. N,N-dimethyl-4-(2-(1-(1-(5-propylpyrimidin-2-yl)piperidin-4-yl)ethoxy)imidazo[2,1-b][1,3,4]thiadiazol-6-yl)benzamide
- l. 3-isopropyl-5-(4-(1-(((6-(pyridin-4-yl)imidazo[2,1-b][1,3,4]thiadiazol-2-yl)oxy)ethyl)piperidin-1-yl)-1,2,4-oxadiazole

- li. 3-isopropyl-5-(1-(6-(pyridin-4-yl)imidazo[2,1-b][1,3,4]thiadiazol-2-yl)piperidin-4-yl)-1,2,4-oxadiazole
- lii. 5-(1-(5-chloro-6-(pyridin-4-yl)imidazo[2,1-b][1,3,4]thiadiazol-2-yl)piperidin-4-yl)-3-isopropyl-1,2,4-oxadiazole
- liii. 4-(2-((1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)methoxy)imidazo[2,1-b][1,3,4]thiadiazol-6-yl)benzotriazole
- liv. 3-isopropyl-5-(4-(((6-(pyridin-4-yl)imidazo[2,1-b][1,3,4]thiadiazol-2-yl)oxy)methyl)piperidin-1-yl)-1,2,4-oxadiazole
- lv. 3-isopropyl-5-(4-(1-((6-(6-(methylsulfonyl)pyridin-3-yl)imidazo[2,1-b][1,3,4]thiadiazol-2-yl)oxy)ethyl)piperidin-1-yl)-1,2,4-oxadiazole
- lvi. 2-(1-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yl)ethoxy)-6-(pyridin-4-yl)imidazo[2,1-b][1,3,4]thiadiazole
- lvii. 3-isopropyl-5-(4-(1-((6-(4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazol-2-yl)oxy)ethyl)piperidin-1-yl)-1,2,4-oxadiazole
- lviii. (R)-3-isopropyl-5-(4-(1-((6-(6-(methylsulfonyl)pyridin-3-yl)imidazo[2,1-b][1,3,4]thiadiazol-2-yl)oxy)ethyl)piperidin-1-yl)-1,2,4-oxadiazole
- lix. (R)-3-isopropyl-5-(4-(1-((6-(pyridin-4-yl)imidazo[2,1-b][1,3,4]thiadiazol-2-yl)oxy)ethyl)piperidin-1-yl)-1,2,4-oxadiazole
- lx. (R)-3-isopropyl-5-(4-(1-((6-(4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazol-2-yl)oxy)ethyl)piperidin-1-yl)-1,2,4-oxadiazole
- lxi. 5-(4-(1-((5-fluoro-6-(4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazol-2-yl)oxy)ethyl)piperidin-1-yl)-3-isopropyl-1,2,4-oxadiazole
- lxii. (R)-2-(1-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yl)ethoxy)-6-(4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazole
- lxiii. 5-(4-(1-((5-chloro-6-(4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazol-2-yl)oxy)ethyl)piperidin-1-yl)-3-isopropyl-1,2,4-oxadiazole
- lxiv. (S)-5-(4-(1-((6-(3-fluoropyridin-4-yl)imidazo[2,1-b][1,3,4]thiadiazol-2-yl)oxy)ethyl)piperidin-1-yl)-3-isopropyl-1,2,4-oxadiazole
- lxv. (R)-5-(4-(1-((6-(2-fluoropyridin-4-yl)imidazo[2,1-b][1,3,4]thiadiazol-2-yl)oxy)ethyl)piperidin-1-yl)-3-isopropyl-1,2,4-oxadiazole
- lxvi. (R)-5-(4-(1-((5-fluoro-6-(4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazol-2-yl)oxy)ethyl)piperidin-1-yl)-3-isopropyl-1,2,4-oxadiazole
- lxvii. (S)-6-(4-(methylsulfonyl)phenyl)-2-(1-(1-(5-propylpyrimidin-2-yl)piperidin-4-yl)ethoxy)imidazo[2,1-b][1,3,4]thiadiazole
- lxviii. (S)-4-(2-(1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)imidazo[2,1-b][1,3,4]thiadiazol-6-yl)pyridine 1-oxide
- lxix. 2-(1-(1-(5-chloropyrimidin-2-yl)piperidin-4-yl)ethoxy)-6-(4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazole
- lxx. 2-(1-(1-(5-isopropylpyrimidin-2-yl)piperidin-4-yl)ethoxy)-6-(4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazole
- lxxi. (S)-5-(4-(1-((6-(2-chloropyrimidin-5-yl)imidazo[2,1-b][1,3,4]thiadiazol-2-yl)oxy)ethyl)piperidin-1-yl)-3-isopropyl-1,2,4-oxadiazole
- lxxii. (S)-3-isopropyl-5-(4-(1-((6-(2-(methylsulfonyl)pyrimidin-5-yl)imidazo[2,1-b][1,3,4]thiadiazol-2-yl)oxy)ethyl)piperidin-1-yl)-1,2,4-oxadiazole
- lxxiii. 2-((R)-1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)-6-(pyridin-4-yl)imidazo[2,1-b][1,3,4]thiadiazole

- lxxiv. 2-(1-(1-(3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)-6-(4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazole
- lxxv. 2-(1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)-6-(2-(methylsulfonyl)pyrimidin-5-yl)imidazo[2,1-b][1,3,4]thiadiazole
- lxxvi. 2-(1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)-6-(6-chloropyridin-3-yl)imidazo[2,1-b][1,3,4]thiadiazole
- lxxvii. 2-((R)-1-(1-(3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)-6-(4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazole
- lxxviii. 2-((S)-1-(1-(3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)-6-(4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazole
- lxxix. 2-((S)-1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)-6-(3-fluoro-4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazole
- lxxx. 2-(1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)-6-(5-chloropyrazin-2-yl)imidazo[2,1-b][1,3,4]thiadiazole
- lxxxi. 2-((R)-1-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yl)ethoxy)-6-(pyridin-4-yl)imidazo[2,1-b][1,3,4]thiadiazole
- lxxxii. 2-((R)-1-(1-(5-propylpyrimidin-2-yl)piperidin-4-yl)ethoxy)-6-(6-(methylsulfonyl)pyridin-3-yl)imidazo[2,1-b][1,3,4]thiadiazole
- lxxxiii. 2-((S)-1-(1-(5-propylpyrimidin-2-yl)piperidin-4-yl)ethoxy)-6-(3-fluoropyridin-4-yl)imidazo[2,1-b][1,3,4]thiadiazole
- lxxxiv. 2-((S)-1-(1-(5-chloropyrimidin-2-yl)piperidin-4-yl)ethoxy)-6-(4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazole
- lxxxv. 2-((R)-1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)-6-(6-(trifluoromethyl)pyridin-3-yl)imidazo[2,1-b][1,3,4]thiadiazole
- lxxxvi. 2-((S)-1-(1-(5-propylpyrimidin-2-yl)piperidin-4-yl)ethoxy)-6-(2-fluoro-4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazole
- lxxxvii. 2-((S)-1-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yl)ethoxy)-6-(2-fluoro-4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazole
- lxxxviii. 2-((R)-1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)-6-(5-chloropyrazin-2-yl)imidazo[2,1-b][1,3,4]thiadiazole
- lxxxix. 2-((R)-1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)-6-(2-fluoro-4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazole
- xc. 2-((S)-1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)-6-(2-methoxy-pyridin-4-yl)imidazo[2,1-b][1,3,4]thiadiazole
- xc. 2-((R)-1-(1-(5-chloropyrimidin-2-yl)piperidin-4-yl)ethoxy)-6-(2-fluoro-4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazole
- xcii. 2-(1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)-6-(2-(trifluoromethyl)-4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazole
- xciii. 2-(1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)-6-(3-(trifluoromethyl)pyridin-4-yl)imidazo[2,1-b][1,3,4]thiadiazole
- xciv. 2-((S)-1-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yl)ethoxy)-6-(2-methoxy-pyridin-4-yl)imidazo[2,1-b][1,3,4]thiadiazole
- xcv. 2-((S)-1-(1-(5-propylpyrimidin-2-yl)piperidin-4-yl)ethoxy)-6-(2-methoxy-pyridin-4-yl)imidazo[2,1-b][1,3,4]thiadiazole

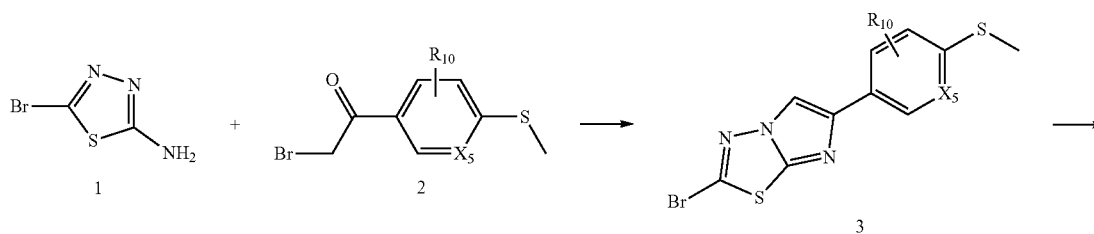
- xcvi. 2-(1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)-6-(3-methoxypyridin-4-yl)imidazo[2,1-b][1,3,4]thiadiazole
- xcvii. 4-(2-((S)-1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)imidazo[2,1-b][1,3,4]thiadiazol-6-yl)-1-methylpyridin-2(1H)-one
- xcviii. 2-((S)-1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)-6-(3-fluoropyridin-4-yl)imidazo[2,1-b][1,3,4]thiadiazole hydrochloride
- xcix. 2-((S)-1-(1-(5-(trifluoromethyl)pyrimidin-2-yl)piperidin-4-yl)ethoxy)-6-(2-fluoro-4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazole
- c. 4-(2-((R)-1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)imidazo[2,1-b][1,3,4]thiadiazol-6-yl)-3-fluorobenzonitrile
- ci. 2-((R)-1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)-6-(2-fluoro-6-(methyl sulfonyl)pyridin-3-yl)imidazo[2,1-b][1,3,4]thiadiazole
- cii. isopropyl 4-(1-(6-(2-fluoro-4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazol-2-yloxy)ethyl)piperidine-1-carboxylate
- ciii. 2-((R)-1-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yl)ethoxy)-6-(2-fluoro-6-(methyl sulfonyl)pyridin-3-yl)imidazo[2,1-b][1,3,4]thiadiazole
- civ. 2-((S)-1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)-6-(2-methoxy-4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazole
- cv. 2-((S)-1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)-6-(2-methyl-6-(methyl sulfonyl)pyridin-3-yl)imidazo[2,1-b][1,3,4]thiadiazole
- cvi. 2-((R)-1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)-6-(2-fluoro-4-(1H-tetrazol-5-yl)phenyl)imidazo[2,1-b][1,3,4]thiadiazole hydrochloride
- cvii. tert-butyl 4-(1-(6-(6-fluoro-4-(methylsulfonyl)cyclohexa-1,5-dienyl)imidazo[2,1-b][1,3,4]thiadiazol-2-yloxy)ethyl)piperidine-1-carboxylate
- cviii. ethyl 4-(1-(6-(2-fluoro-4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazol-2-yloxy)ethyl)piperidine-1-carboxylate
- cix. isopropyl 4-((S)-1-(6-(2-fluoro-4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazol-2-yloxy)ethyl)piperidine-1-carboxylate
- cx. 1-methylcyclopropyl 4-(1-(6-(2-fluoro-4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazol-2-yloxy)ethyl)piperidine-1-carboxylate
- cx. 2-(1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)-6-(thiazol-5-yl)imidazo[2,1-b][1,3,4]thiadiazole

- cxii. 2-((S)-1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)-6-(2-methyl-4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazole
- cxiii. ethyl 4-((S)-1-(6-(2-fluoro-4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazol-2-yloxy)ethyl)piperidine-1-carboxylate
- cxiv. 4-(3-isopropyl-1,2,4-oxadiazol-5-yl)-1-(3-(4-(methylsulfonyl)phenyl)-1,2,4-thiadiazol-5-yl)piperidine
- cxv. 4-(1-(3-(4-(methylsulfonyl)phenyl)-1,2,4-thiadiazol-5-yloxy)ethyl)-1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidine
- cxvi. 4-(3-(4-(methylsulfonyl)phenyl)-1,2,4-thiadiazol-5-yloxy)-1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidine
- cxvii. 4-((3-(4-(methylsulfonyl)phenyl)-1,2,4-thiadiazol-5-yloxy)methyl)-1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidine
- cxviii. 5-(3-(1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)-1,2,4-thiadiazol-5-yl)-2-(methylsulfonyl)pyridine
- cxix. 5-(3-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yloxy)-1,2,4-thiadiazol-5-yl)-2-(methyl sulfonyl)pyridine
- cxx. 5-(3-((1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)methoxy)-1,2,4-thiadiazol-5-yl)-2-(methylsulfonyl)pyridine
- cxxi. 5-(5-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yloxy)-1,2,4-thiadiazol-3-yl)-2-(methyl sulfonyl)pyridine
- cxxii. 2-(4-(3-(6-(methylsulfonyl)pyridin-3-yl)-1,2,4-thiadiazol-5-yloxy)piperidin-1-yl)-5-ethylpyrimidine
- cxxiii. 2-(4-(3-(6-(methylsulfonyl)pyridin-3-yl)-1,2,4-thiadiazol-5-yloxy)piperidin-1-yl)-5-propylpyrimidine
- cxxiv. N-(5-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yloxy)-1,2,4-thiadiazol-3-yl)-N-methyl-6-(methyl sulfonyl)pyridin-3-amine
- cxxv. 2-(4-(3-(2-fluoro-4-(methyl sulfonyl)phenyl)-1,2,4-thiadiazol-5-yloxy)piperidin-1-yl)-5-ethylpyrimidine
- cxxvi. 1-(3-isopropyl-1,2,4-oxadiazol-5-yl)-N-(3-(6-(methylsulfonyl)pyridin-3-yl)-1,2,4-thiadiazol-5-yl)piperidin-4-amine
- cxxvii. 1-(3-isopropyl-1,2,4-oxadiazol-5-yl)-N-methyl-N-(3-(6-(methylsulfonyl)pyridin-3-yl)-1,2,4-thiadiazol-5-yl)piperidin-4-amine

B. Synthesis of Compounds of the Present Invention

The present invention also relates to a process of preparing the compounds of formula (I). The compounds of present invention may be prepared by the schemes as here below:

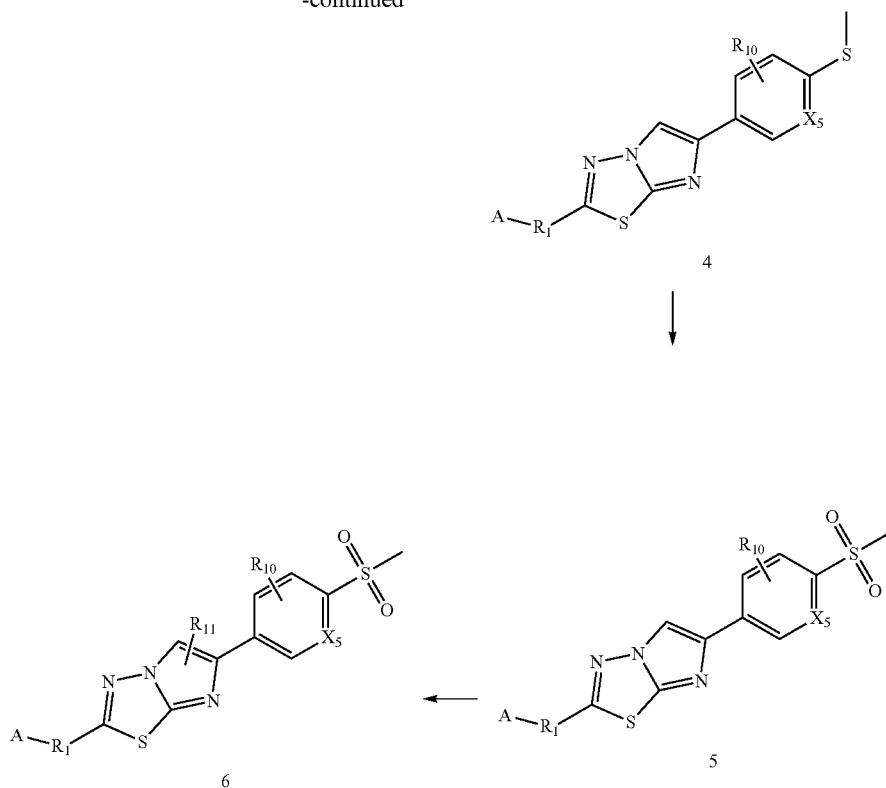
Synthetic Scheme 1:



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-continued



Wherein,

R₁ and A is as defined above;

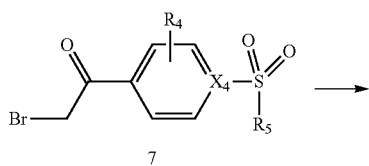
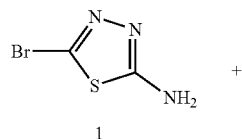
X₅ is CH, N, O, S;

R₁₀ is H, OH, halogen, C₁₋₆ alkyl, C₁₋₆alkoxy, -(CH₂)_n, amino, -CO, -CONH, -NH(Alkyl), -N(Alkyl)₂, -NH-aralkyl, -OCH(CH₃);

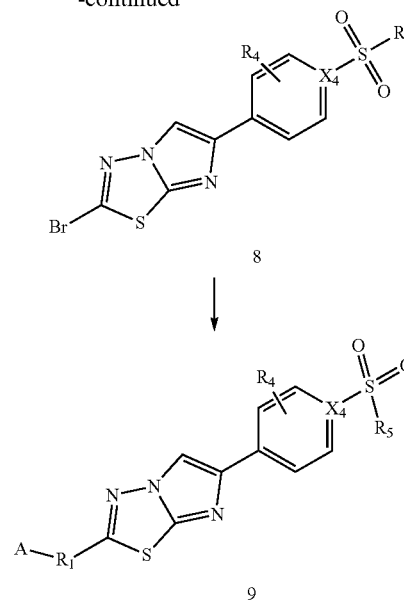
n is 0, 1, 2 or 3;

R₁₁ is halogen, H

Synthetic Scheme 2:



-continued



Wherein,

R₁ and A is as defined above;

X₄ is CH, N, O, S;

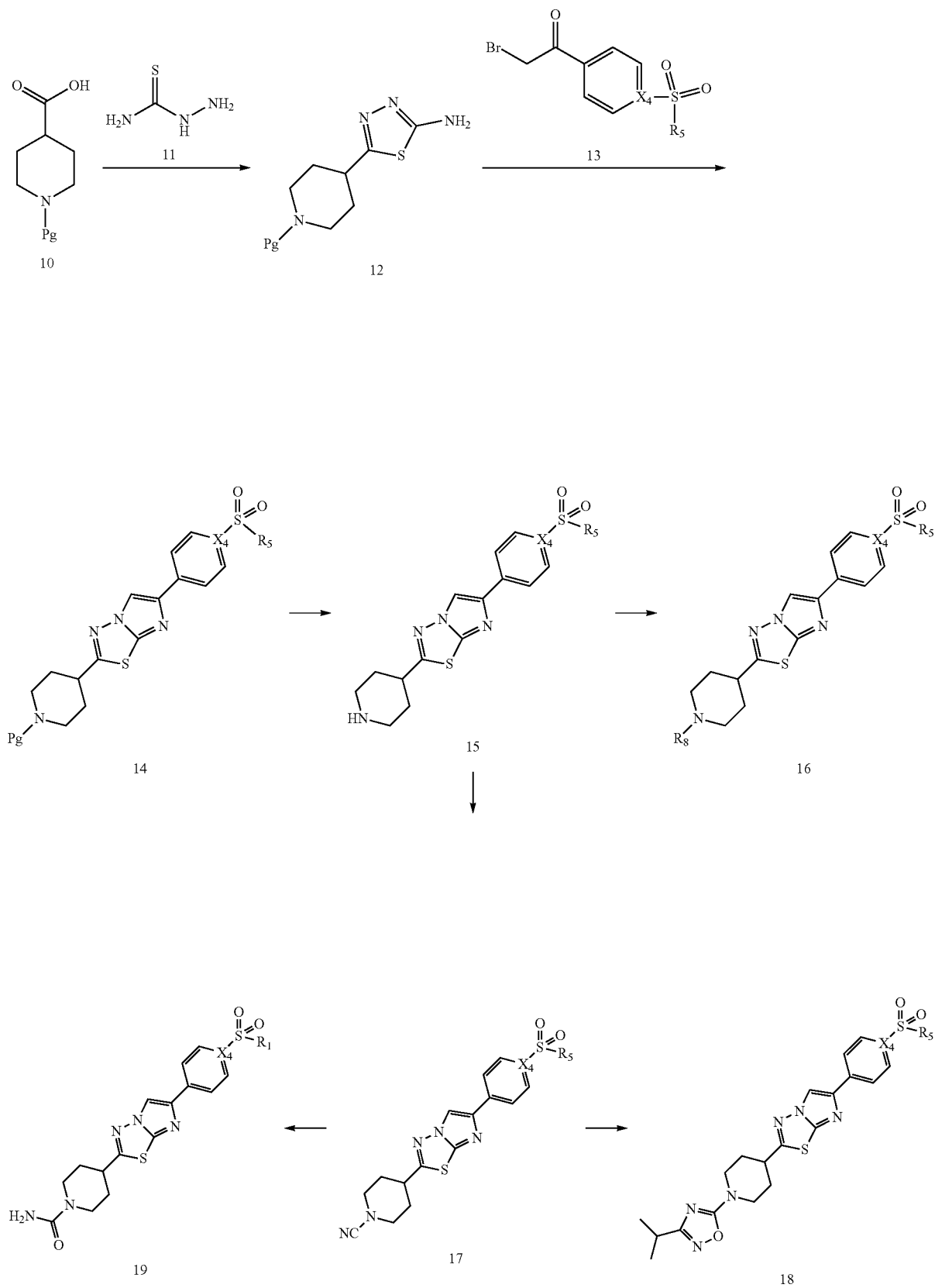
R₄ is H, OH, halogen, C₁₋₆ alkyl, C₁₋₆alkoxy, -(CH₂)_n, amino, -CO, -CONH, -NH(Alkyl), -N(Alkyl)₂, -NH-aralkyl, -OCH(CH₃);

n is 0, 1, 2 or 3;

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Synthetic Scheme 3:

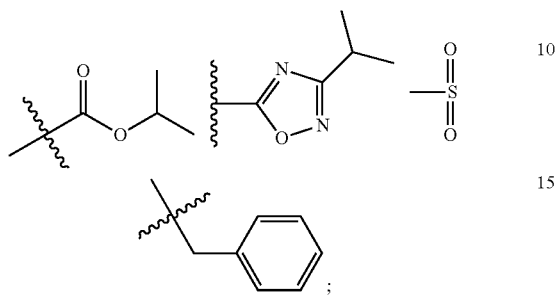


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Wherein,
 X_4 is CH, N, O, S;
 R_5 is H, OH, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, $-(CH_2)_n$,
 amino, $-CO$, $-CONH$, $-NH(Alkyl)$, $-N(Alkyl)_2$,
 $-NH-aralkyl$, $-OCH(CH_3)$;
 R_8 is

5



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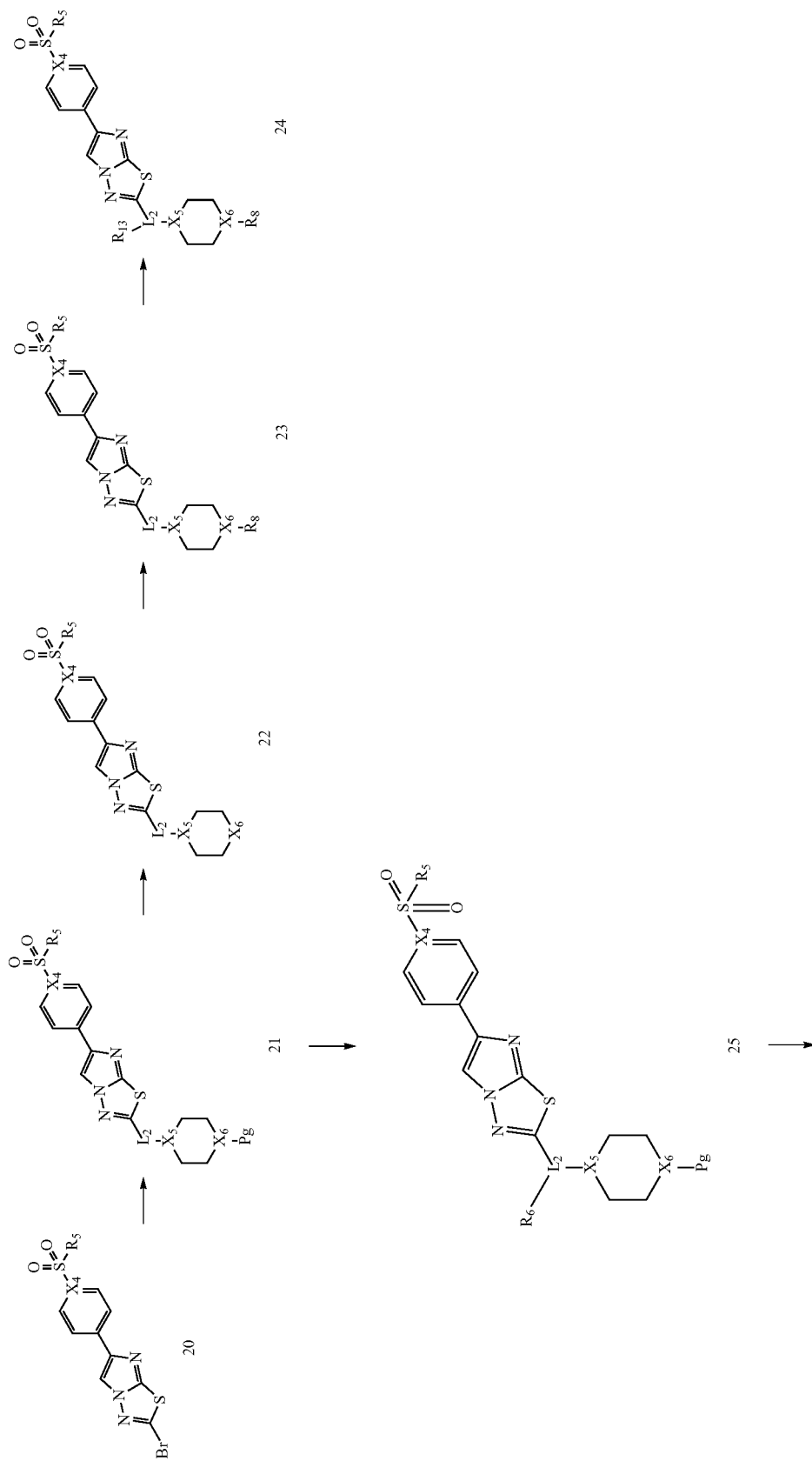
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n is 0, 1, 2 or 3;

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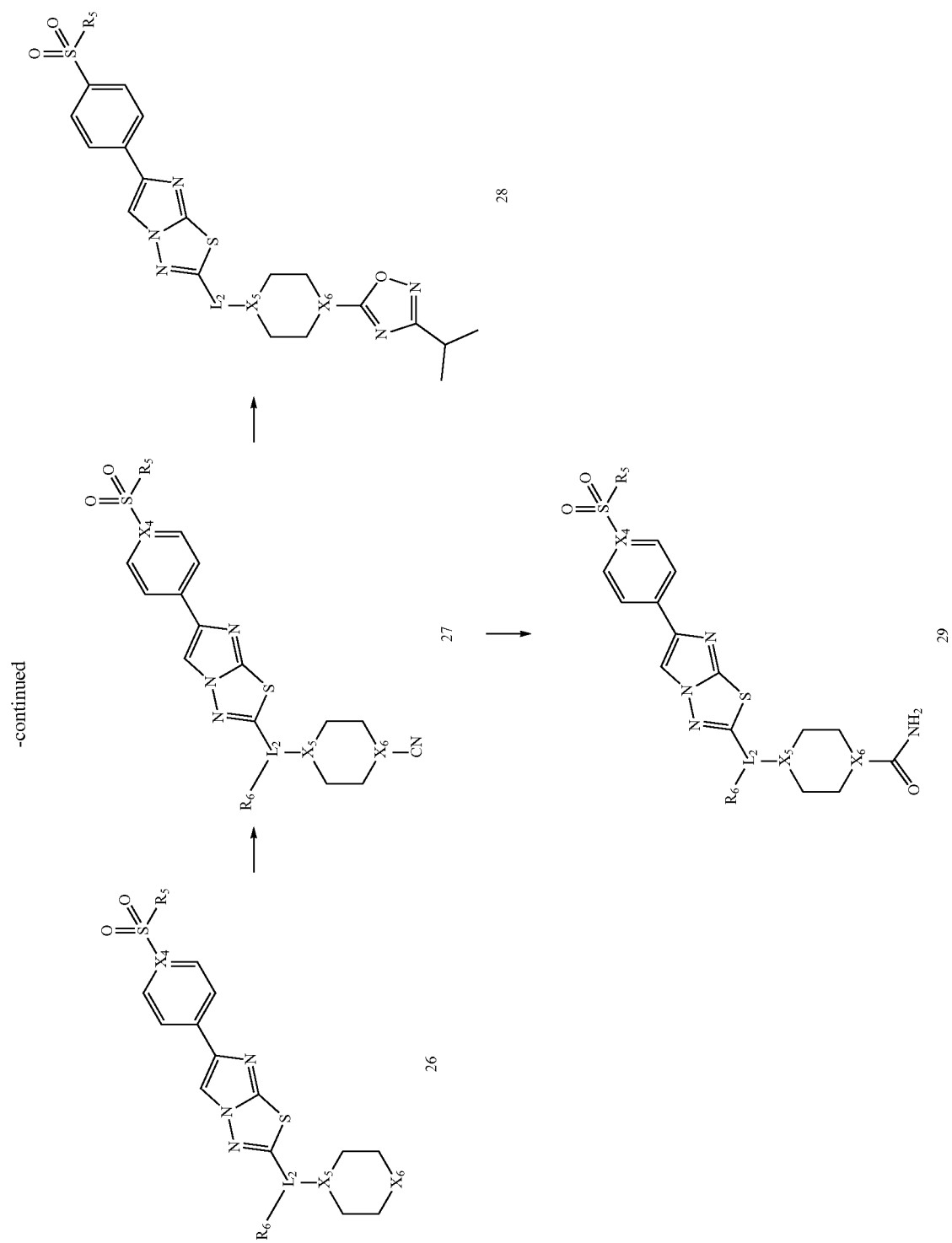
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Synthetic Scheme 4:



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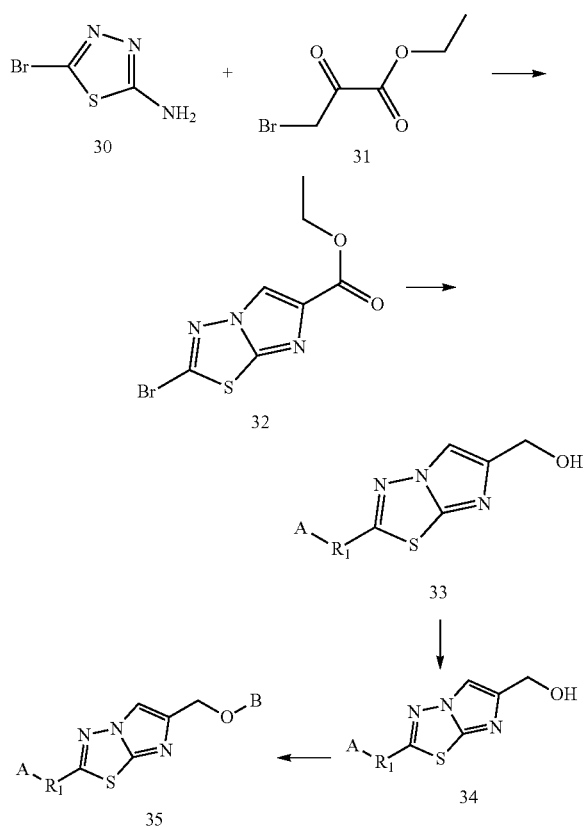
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Wherein,
 X_4, X_5, X_6 and L_2 is CH, N, O, S;
 R_5 and R_6 are H, OH, halogen, C_{1-6} alkyl, C_{1-6} alkoxy,
 $-(CH_2)_n$, amino, $-CO$, $-CONH$, $-NH(Alkyl)$,
 $-N(Alkyl)_2$, $-NH-aralkyl$, $-OCH(CH_3)$;
 n is 0, 1, 2 or 3;

Synthetic Scheme 5:



Wherein,
 R_1 , A and B is as defined above;
 X_4, X_5, X_6 and L_2 is CH, N, O, S;
 R_5 and R_6 are H, OH, halogen, C_{1-6} alkyl, C_{1-6} alkoxy,
 $-(CH_2)_n$, amino, $-CO$, $-CONH$, $-NH(Alkyl)$,
 $-N(Alkyl)_2$, $-NH-aralkyl$, $-OCH(CH_3)$;
 n is 0, 1, 2 or 3;

C. Salts and Isomers

The present invention includes within its scope the salts and isomers. Compounds of the present invention after being novel may in some cases form salts which are also within the scope of this invention. The term "salt(s)", as employed herein, denotes acidic and/or basic salts formed with inorganic and/or organic acids and bases. Pharmaceutically acceptable (i.e., non-toxic, physiologically acceptable) salts are preferred.

All stereoisomer's of the present compounds, such as those which may exist due to asymmetric carbons on the R substituents of the compound, including enantiomeric and diastereomeric forms, are contemplated within the scope of this invention.

The Compounds of the present invention may be present in their enantiomeric pure forms or their mixtures.

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D. Methods of Use and Pharmaceutical Composition Containing the Novel Entities of the Invention

The invention thus provides the use of the novel compounds as defined herein for use in human or veterinary medicine. The compounds of the present invention may be used in the treatment of diabetes. Particularly, the compounds of the present invention are effective in the treatment of type 2 diabetes mellitus. The compounds of present invention activates the GPR119 which increases the intracellular accumulation of cAMP, leading to enhanced glucose-dependent insulin secretion from pancreatic β -cells and increased release of the gut peptides GLP-1 (glucagon like peptide 1), GIP (glucose-dependent insulinotropic peptide) and PYY (polypeptide YY) and thus acts as GPR119 agonists.

The compound for use as a pharmaceutical may be presented as a pharmaceutical composition. The invention therefore provides in a further aspect a pharmaceutical composition comprising the novel compounds of the invention along with pharmaceutically acceptable excipients/carriers thereof and optionally other therapeutic and/or prophylactic ingredients. The excipients/carriers must be "acceptable" in the sense of being compatible with the other ingredients of the composition and not deleterious to the recipient thereof. Suitably the pharmaceutical composition will be in an appropriate formulation.

The pharmaceutical formulations may be any formulation and include those suitable for oral, intranasal, or parenteral (including intramuscular and intravenous) administration. The formulations may, where appropriate, be conveniently presented in discrete dosage units and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing into association the active compound with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product into the desired formulation.

For these purposes the compounds of the present invention may be administered orally, topically, intranasally, parenterally, by inhalation spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques. In addition to the treatment of warm-blooded animals such as mice, rats, horses, dogs, cats, etc. The compounds of the present invention are effective in the treatment of humans.

In an aspect, compound of the present invention may be administered in a dose ranging from 0.1 to 100 mg/kg body weight per day. The compounds of the present invention are useful for the prevention and treatment of metabolic disorders, particularly for the treatment of type I and type II diabetes, obesity and related disorders.

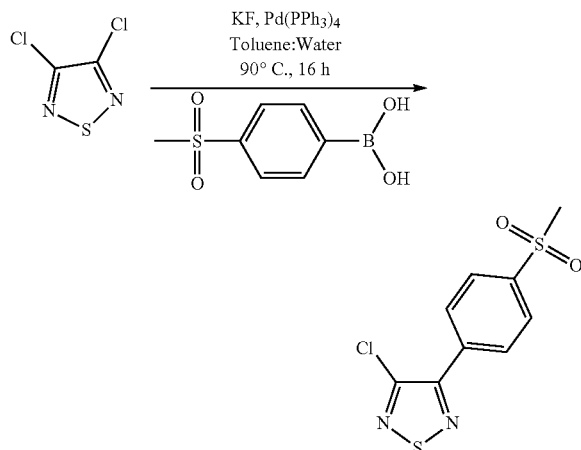
Without being limited by theory, it is submitted that the novel compounds of the present invention exhibit substantially different pharmacokinetic and pharmacodynamic profiles. The invention is described in detail herein below with respect to the following examples which are provided merely for illustration. However, these examples may not be construed to restrict the scope of the invention. Any embodiments that may be apparent to a person skilled in the art are deemed to fall within the scope of present invention.

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EXPERIMENTALS

Example 1: 3-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yl)-4-(4-(methylsulfonyl)phenyl)-1,2,5-thiadiazole [1004]

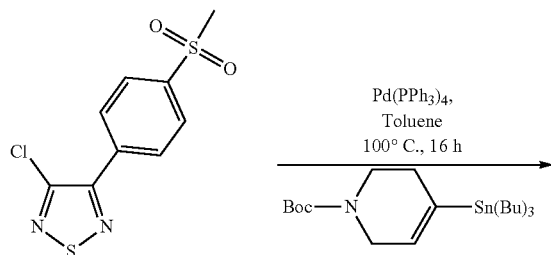
Step-1: Synthesis of 3-chloro-4-(4-(methylsulfonyl)phenyl)-1,2,5-thiadiazole



To a stirred solution of 3,4-dichloro-1,2,5-thiadiazole (0.2 g, 1.307 mmol) and 4-(methylsulfonyl)phenylboronic acid (0.259 g, 1.307 mmol) in toluene (5 mL) was added KF (0.226 g, 3.898 mmol) in water (5 mL), reaction mass was purged with nitrogen for 30 min. After 30 min Pd(PPh₃)₄ (0.0075 g, 0.0653 mmol) was added to reaction mixture, heated at 90° C. for 16 h. Reaction was monitored by TLC. On completion, reaction was quenched with water, extracted with ethyl acetate. Organic layer was washed with water, brine, dried over sodium sulphate, concentrated under reduced pressure obtained crude which was purified by Combiflash chromatography; eluent 15% EtOAc/Hexane to afford 3-chloro-4-(4-(methylsulfonyl)phenyl)-1,2,5-thiadiazole (0.075 g, 20.94%) as off white solid.

MS: 275.20 [M+1]

Step-2: Synthesis of t-butyl 5,6-dihydro-4-(4-(4-(methylsulfonyl)phenyl)-1,2,5-thiadiazol-3-yl)pyridine-1(2H)-carboxylate



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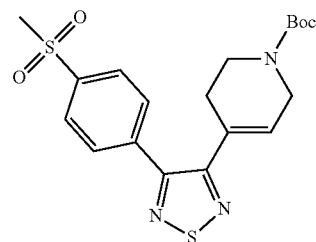
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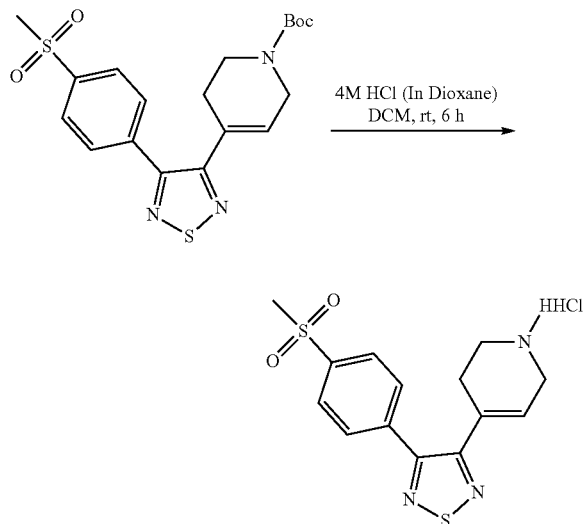
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To a stirred solution of 3-chloro-4-(4-(methylsulfonyl)phenyl)-1,2,5-thiadiazole (0.07 g, 0.255 mmol) and t-butyl 4-(tributyl stannyl)-5,6-dihydropyridine-1(2H)-carboxylate (0.145 g, 0.306 mmol) in toluene (10 mL), nitrogen was purged for 30 min. After 30 min Pd(PPh₃)₄ (0.029 g, 0.0255 mmol) was added to reaction mass and heated at 100° C. for 16 h. Reaction was monitored by TLC. On completion reaction was concentrated under reduced pressure obtained crude which was purified by Column chromatography (100-200 mesh); eluent 25% EtOAc/Hexane to afford t-butyl 5,6-dihydro-4-(4-(4-(methylsulfonyl)phenyl)-1,2,5-thiadiazol-3-yl)pyridine-1(2H)-carboxylate (0.065 g, 60.11%) as off white solid.

MS: 422.11[M⁺+1]

Step-3: Synthesis of 1,2,3,6-tetrahydro-4-(4-(4-(methylsulfonyl)phenyl)-1,2,5-thiadiazol-3-yl)pyridine hydrochloride

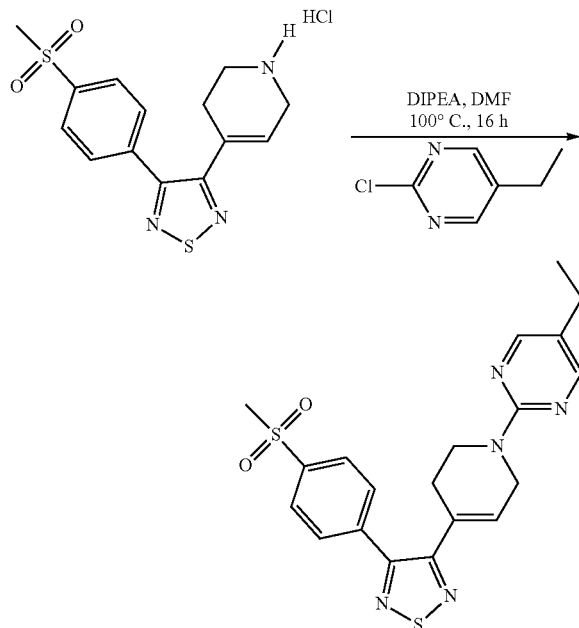


To t-butyl 5,6-dihydro-4-(4-(4-(methylsulfonyl)phenyl)-1,2,5-thiadiazol-3-yl)pyridine-1(2H)-carboxylate (0.06 g, 0.141 mmol) in DCM (5 mL) was added 4 M HCl in Dioxane (1 mL) and stirred at room temperature for 6 h. Reaction was monitored by TLC. On completion reaction mixture was concentrated under reduced pressure to afford 1,2,3,6-tetrahydro-4-(4-(4-(methyl sulfonyl)phenyl)-1,2,5-thiadiazol-3-yl)pyridine hydrochloride (0.04, g 80.0%) as white solid.

MS: 322.06[M⁺+1]

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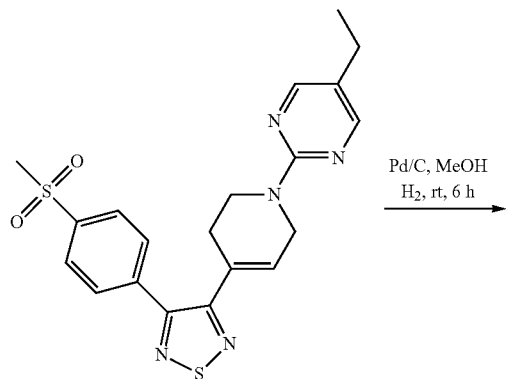
Step-4: Synthesis of 5-ethyl-2-(5,6-dihydro-4-(4-(4-(methylsulfonyl)phenyl)-1,2,5-thiadiazol-3-yl)pyridin-1(2H)-yl)pyrimidine



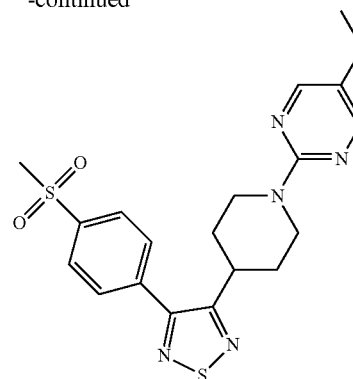
To a stirred solution of 1,2,3,6-tetrahydro-4-(4-(4-(methylsulfonyl)phenyl)-1,2,5-thiadiazol-3-yl)pyridine hydrochloride (0.04 g, 0.111 mmol) and 2-chloro-5-ethylpyrimidine (0.023 g, 0.166 mmol) in DMF (5 mL) was added DIPEA (0.45 mL, 0.555 mmol) and stirred at 100° C. for 16 h. Reaction was monitored by TLC. On completion reaction mass was quenched with water, extracted with ethyl acetate. The organic layer was washed with water, brine, dried over sodium sulphate evaporated under reduced pressure obtained crude which was purified by silica gel (100-200 Mesh) column chromatography, eluent 25% EtOAc/Hexane to afford 5-ethyl-2-(5,6-dihydro-4-(4-(4-(methylsulfonyl)phenyl)-1,2,5-thiadiazol-3-yl)pyridin-1(2H)-yl)pyrimidine (0.024 g, 51.06%) as off white solid.

MS: 428.11[M⁺+1]

Step-5: Synthesis of 5-ethyl-2-(4-(4-(4-(methylsulfonyl)phenyl)-1,2,5-thiadiazol-3-yl)piperidin-1-yl)pyrimidine

**66**

-continued

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To a stirred solution of 5-ethyl-2-(5,6-dihydro-4-(4-(4-(methylsulfonyl)phenyl)-1,2,5-thiadiazol-3-yl)pyridin-1(2H)-yl)pyrimidine (0.2 g, 0.0467 mmol) in MeOH (5 mL) was added 10% Pd/C (0.04 g) reaction mass was purged with hydrogen for 6 h, and monitored by TLC. On completion, reaction was filtered on celite, filtrate was concentrated under reduced pressure obtained crude which was purified by Column chromatography (100-200 mesh); eluent 25% EtOAc in Hexane obtained 5-ethyl-2-(4-(4-(4-(methylsulfonyl)phenyl)-1,2,5-thiadiazol-3-yl)piperidin-1-yl)pyrimidine (0.005 g 25%) as off white solid.

MS: 430.13[M⁺+1]

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Example 2: 3-(4-(1H-tetrazol-1-yl)phenoxy)-4-(1-(5-ethylpyrimidin-2-yl)-1,2,3,6-tetrahydropyridin-4-yl)-1,2,5-thiadiazole

Step 1: Synthesis of 1-(4-(4-chloro-1,2,5-thiadiazol-3-yloxy)phenyl)-1H-tetrazole

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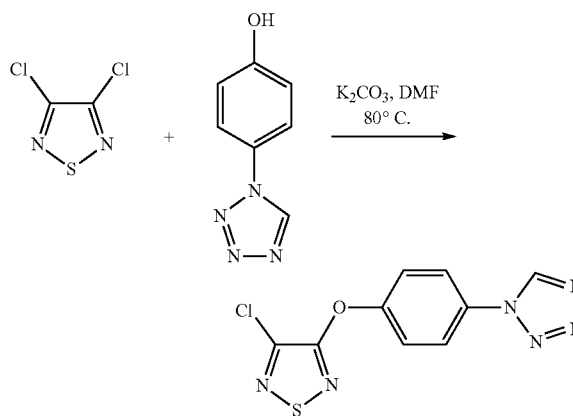
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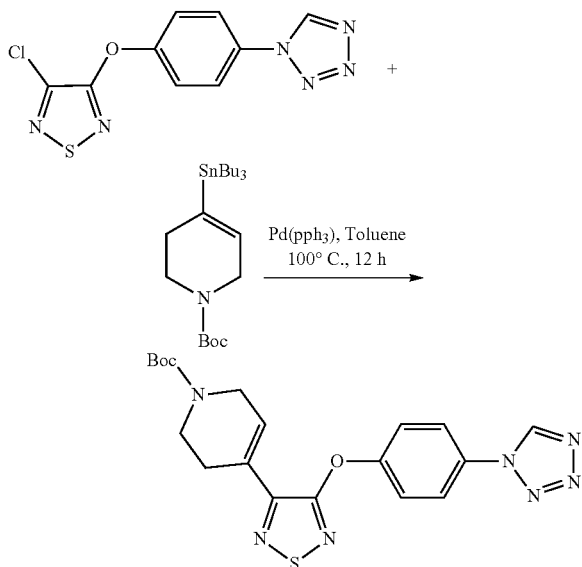


To a stirred solution of 3,4-dichloro-1,2,5-thiadiazole (0.3 g, 1.93 mmol) in DMF (10 mL) was added solution of 4-(1H-tetrazol-1-yl)phenol (0.313 g, 1.93 mmol) in DMF (2 mL) and heat reaction mass at 80° C. for 12 h. Reaction was monitored by TLC. On completion, reaction mass was diluted with water, extracted with EtOAc. Organic layer was washed with water, brine, dried over Na₂SO₄ and evaporated under reduced pressure to give crude product. Purification of the crude was done by silica gel (100-200 Mesh) column chromatography; eluent 25% EtOAc:hexane to obtain 1-(4-(4-chloro-1,2,5-thiadiazol-3-yloxy)phenyl)-1H-tetrazole (0.1 g, 18%) as white solid.

MS: 280.99[M⁺+1]

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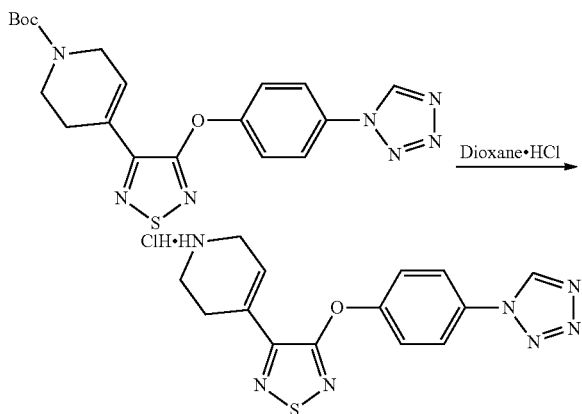
Step 2: Synthesis of t-butyl 4-(4-(4-(1H-tetrazol-1-yl)phenoxy)-1,2,5-thiadiazol-3-yl)-5,6-dihydropyridine-1 (2H)-carboxylate



To a stirred solution of 1-(4-(4-chloro-1,2,5-thiadiazol-3-yloxy)phenyl)-1H-tetrazole (0.1 g, 0.36 mmol) and the room temperature-butyl 4-(tributylstannyl)-5,6-dihydropyridine-1 (2H)-carboxylate (0.2 g, 0.43 mmol) in toluene (10 mL), N₂ was purged for 30 min. After 30 min, Pd(PPh₃)₄ (0.041 g, 0.035 mmol) was added to reaction mixture and heated at 100° C. for 12 h. Reaction was monitored by TLC. On completion, all volatiles were evaporated under reduced pressure to give crude which was purified by column chromatography (100-200 mesh); eluent 30% EtOAc/Hexane to obtain t-butyl 4-(4-(4-(1H-tetrazol-1-yl)phenoxy)-1,2,5-thiadiazol-3-yl)-5,6-dihydropyridine-1(2H)-carboxylate (0.05 g, 33%) as yellow sticky mass.

MS: 428.14[M⁺+1]

Step 3: Synthesis of 4-(4-(4-(1H-tetrazol-1-yl)phenoxy)-1,2,5-thiadiazol-3-yl)-1,2,3,6-tetrahydropyridine hydrochloride

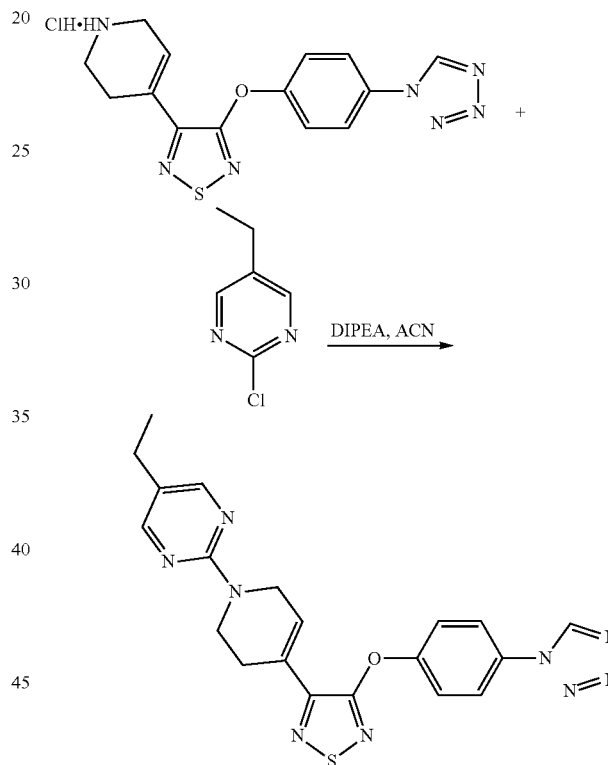


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To a stirred solution of the room temperature-butyl 4-(4-(4-(1H-tetrazol-1-yl)phenoxy)-1,2,5-thiadiazol-3-yl)-5,6-dihydro pyridine-1(2H)-carboxylate (0.05 g, 0.11 mmol) in DCM (10 mL) was added 4 M HCl in Dioxane (1 mL). Reaction mixture was allowed to stir at room temperature for 6 h. Reaction was monitored by TLC. On completion, reaction mixture was concentrated under reduced pressure to give of 4-(4-(4-(1H-tetrazol-1-yl)phenoxy)-1,2,5-thiadiazol-3-yl)-1,2,3,6-tetrahydropyridine hydrochloride (0.03 g, 78%) as off-white solid.

MS: 328.14[M⁺+1]

Step 4: Synthesis of 2-(4-(4-(4-(1H-tetrazol-1-yl)phenoxy)-1,2,5-thiadiazol-3-yl)-5,6-dihydropyridin-1(2H)-yl)-5-ethylpyrimidine



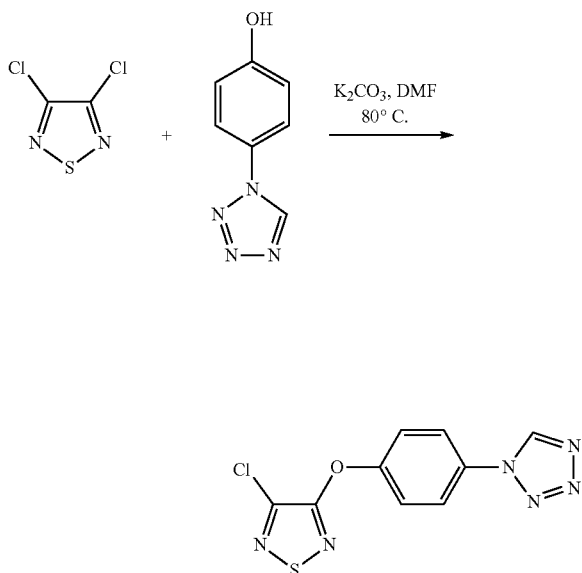
To a stirred solution of 4-(4-(4-(1H-tetrazol-1-yl)phenoxy)-1,2,5-thiadiazol-3-yl)-1,2,3,6-tetrahydro pyridine hydrochloride (0.03 g, 0.097 mmol) in ACN (7 mL.) was added DIPEA (0.09 mL, 0.48 mmol) followed by 2-chloro-5-ethylpyrimidine (0.028 g, 0.19 mmol) at room temperature. Reaction mixture was allowed to stir at room temperature for 12 h. Reaction was monitored by TLC. On completion, reaction mixture was diluted with water and extracted with EtOAc. Organic layer was washed with water, brine, dried over sodium sulphate and evaporated under reduced pressure to give crude product. Purification of the crude was done by silica gel (100-200 Mesh) column chromatography; eluent 2% MeOH in DCM to obtain 2-(4-(4-(4-(1H-tetrazol-1-yl)phenoxy)-1,2,5-thiadiazol-3-yl)-5,6-dihydropyridin-1 (2H)-yl)-5-ethylpyrimidine (0.01 g, 25%) as off-white solid.

MS: 434.14[M⁺+1]

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Example 3: Isopropyl 4-(4-(4-(1H-tetrazol-1-yl)phenoxy)-1,2,5-thiadiazol-3-yl)piperazine-1-carboxylate

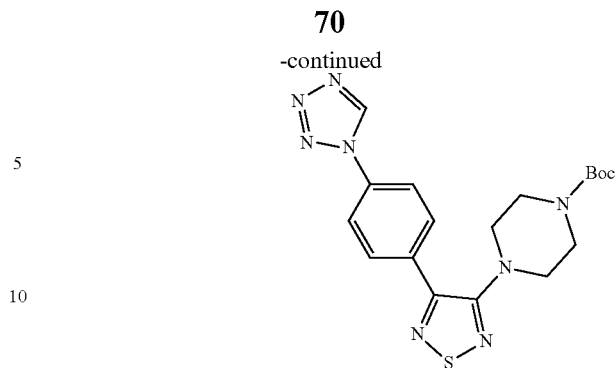
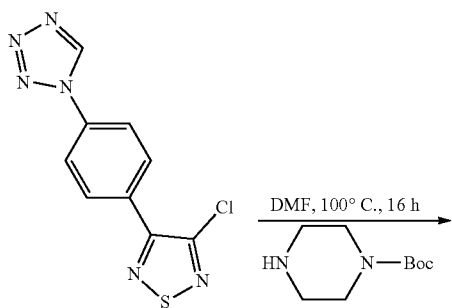
Step 1: Synthesis of 1-(4-(4-chloro-1,2,5-thiadiazol-3-yloxy)phenyl)-1H-tetrazole



To a stirred solution of 3,4-dichloro-1,2,5-thiadiazole (0.3 g, 1.93 mmol) in DMF (10 mL) was added solution of 4-(1H-tetrazol-1-yl)phenol (0.313 g, 1.93 mmol) in DMF (2 mL) and heat reaction mass at $80^\circ C$ for 12 h. Reaction was monitored by TLC. On completion, reaction mass was diluted with water, extracted with EtOAc. Organic layer was washed with water, brine, dried over Na_2SO_4 and evaporated under reduced pressure to give crude product. Purification of the crude was done by silica gel (100-200 Mesh) column chromatography; eluent 25% EtOAc:hexane to obtain 1-(4-(4-chloro-1,2,5-thiadiazol-3-yloxy)phenyl)-1H-tetrazole (0.1 g, 18%) as white solid.

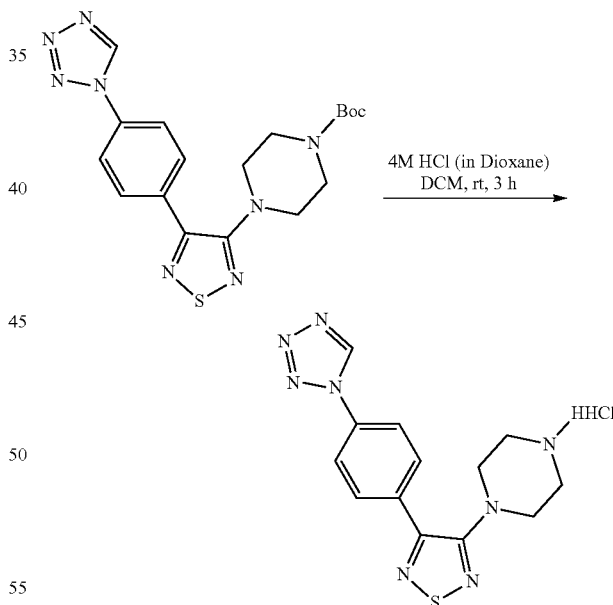
MS: 280.99[$M^+ + 1$]

Step-2: Synthesis of t-butyl 4-(4-(4-(1H-tetrazol-1-yl)phenyl)-1,2,5-thiadiazol-3-yl)piperazine-1-carboxylate



To a stirred solution of 1-(4-(4-chloro-1,2,5-thiadiazol-3-yl)phenyl)-1H-tetrazole (0.15 g, 0.534 mmol) and t-butyl piperazine-1-carboxylate (0.199 g, 1.068 mmol) in DMF (10 mL). Reaction was stirred at $100^\circ C$ for 16 h. Reaction was monitored by TLC. On completion reaction was quenched with water, extracted with ethyl acetate. The organic layer was washed with water, brine, dried over sodium sulphate, concentrated under reduced pressure obtained crude which was purified by silica gel (100-200 Mesh) column chromatography, eluent 30% EtOAc/Hexane obtained t-butyl 4-(4-(4-(1H-tetrazol-1-yl)phenyl)-1,2,5-thiadiazol-3-yl)piperazine-1-carboxylate (0.090 g, 39.13%) as off white solid. MS: 415.16[$M^+ + 1$]

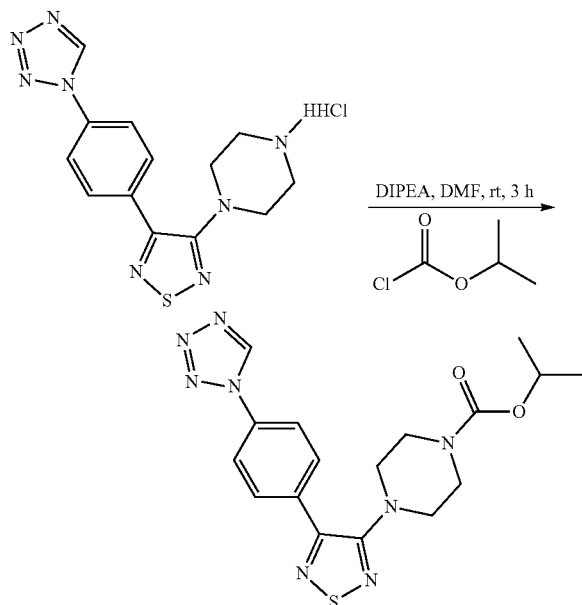
Step-3: Synthesis of 1-(4-(4-(1H-tetrazol-1-yl)phenyl)-1,2,5-thiadiazol-3-yl)piperazine hydrochloride



To a stirred solution of t-butyl 4-(4-(4-(1H-tetrazol-1-yl)phenyl)-1,2,5-thiadiazol-3-yl)piperazine-1-carboxylate (0.09 g, 0.208 mmol) in DCM (5 mL) was added 4 M HCl in Dioxane (0.2 mL, 1.042 mmol) and reaction allowed to stirred at room temperature for 3 h. Reaction was monitored by TLC. On completion reaction mixture was concentrated under reduced pressure obtained 1-(4-(4-(1H-tetrazol-1-yl)phenyl)-1,2,5-thiadiazol-3-yl)piperazine hydrochloride (0.07 g, 80.00%) as Yellow solid. MS: 314.13[$M^+ + 1$]

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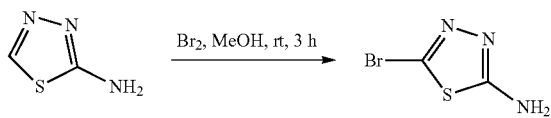
Step-4: Synthesis of isopropyl 4-(4-(4-(1H-tetrazol-1-yl)phenyl)-1,2,5-thiadiazol-3-yl)piperazine-1-carboxylate



To a stirred solution of 1-(4-(4-(1H-tetrazol-1-yl)phenyl)-1,2,5-thiadiazol-3-yl)piperazine hydrochloride (0.04 g, 0.109 mmol) in DMF (5 mL) was added DIPEA (0.097 mL, 0.546 mmol) and reaction allowed to stirred at room temperature for 30 min then added isopropylchloroformate (2M in toluene) (0.109 mL, 0.218 mmol) and stirred for 3 h. Reaction was monitored by TLC. Reaction was quenched with ice cold water, extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulphate, concentrated under reduced pressure obtained crude which was purified by silica gel (100-200 Mesh) column chromatography, eluent 20% EtOAc/Hexane to afford isopropyl 4-(4-(4-(1H-tetrazol-1-yl)phenyl)-1,2,5-thiadiazol-3-yl)piperazine-1-carboxylate (0.004 g, 8.88%) as off white solid. MS: 401.14[M⁺+1]

Example 4: 3-isopropyl-5-(1-(6-(4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazol-2-yl)piperidin-4-yl)-1,2,4-oxadiazole

Step-1: Synthesis of 5-bromo-1, 3, 4-thiadiazol-2-amine



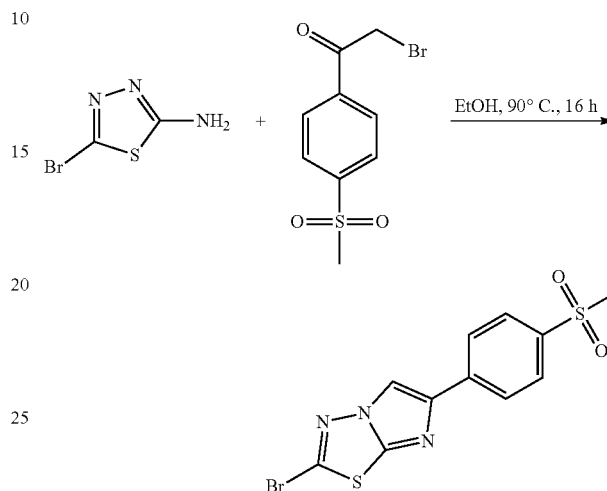
To a stirred solution of 1, 3, 4-thiadiazol-2-amine (5 g, 49.44 mmol) in MeOH (250 mL) was added bromine (23.70 g, 148.32 mmol) dropwise at room temperature and stirred for 3 h. Completion of reaction was monitored by TLC. Reaction mixture was evaporated under reduced pressure. After addition of water to reaction mass, solid precipitate out

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which was filtered off. Solid was washed with water, dried under vacuum to obtained 5-bromo-1, 3, 4-thiadiazol-2-amine (6.5 g, 72.95%) as yellow solid. MS: 178.96[M⁺+1]

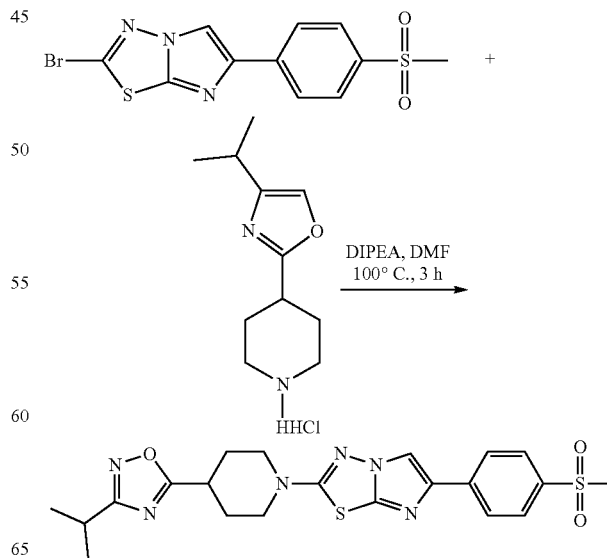
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Step 2: synthesis of 2-bromo-6-(4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazole



To a stirred solution of 5-amino-2-bromo-1,3,4-thiadiazole (1.0 g, 5.55 mmol) and 2-bromo-1-(4-(methylsulfonyl)phenyl) ethanone (1.53 g, 5.55 mmol) in ethanol (50 mL) was heated at 90° C. for 16 h. After cooled to room temperature, the precipitated solid was filtered off, washed with hot ethanol, dried under vacuum obtained 2-bromo-6-(4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazole (1.2 g, 60.60%) as off white solid. MS: 358.1 [M⁺+1]

Step-3: Synthesis of 2-(4-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-6-(4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazole



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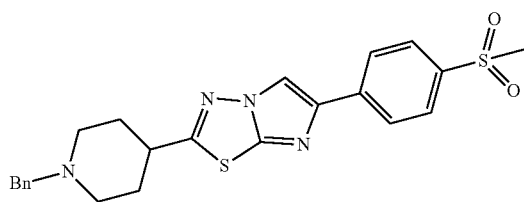
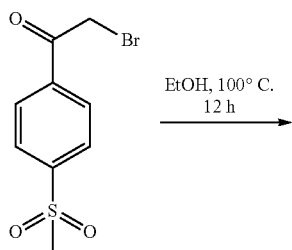
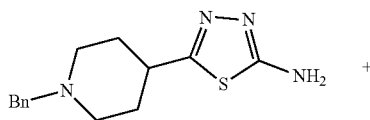
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To a stirred solution of 2-bromo-6-(4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazole (0.03 g, 0.083 mmol) and 4-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidine-HCl salt (0.03 g, 0.125 mmol) in DMF (10 mL) was added DIPEA (0.29 mL, 0.0167 mmol) and reaction heated at 100° C. for 6 h. Reaction was monitored by TLC. On completion, quenched with water, extracted with ethyl acetate. The organic layer was washed with water, brine, dried over sodium sulphate, concentrated under reduced pressure to obtain crude. Purification of the crude was done by silica gel (100-200 Mesh) column chromatography eluent 2% MeOH/DCM obtained 2-(4-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-6-(4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazole (0.014 g, 35.89%) as off white solid.

MS: 473.21[M⁺+1]

Example 5: 2-(1-benzylpiperidin-4-yl)-6-(4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazole

Step 1



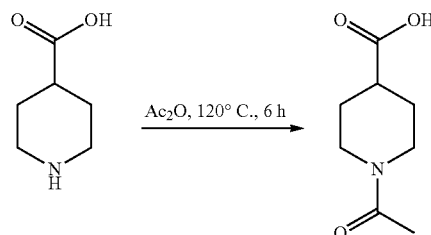
To a stirred solution of 5-(1-benzylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine (0.1 g, 0.36 mmol) and 2-bromo-1-(4-(methylsulfonyl)phenyl)ethanone (0.11 g, 0.40 mmol) in EtOH (30 mL) was heated at 100° C. for 12 h. Reaction was cooled to room temperature, Obtained precipitates were filtered off, washed with boiling EtOH (10 mL) and dried under vacuum to obtain 2-(1-benzylpiperidin-4-yl)-6-(4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazole (0.04 g, 24%) as light yellow solid.

MS: 453.13[M⁺+1]

74

Example 6: 1-(4-(2-(4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazol-6-yl)piperidin-1-yl)ethanone

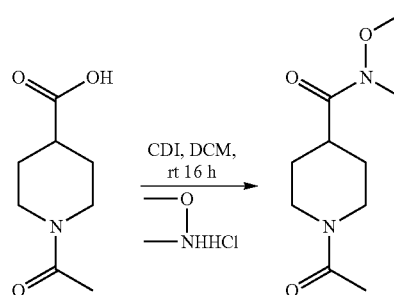
Step-1: Synthesis of 1-acetylpiperidine-4-carboxylic acid



To a solution of piperidine-4-carboxylic acid (5.0 g) in acetic anhydride (50 mL) was heated at 130° C. for 6 h, Completion of reaction was monitored by TLC. On completion all volatiles were evaporated under reduced pressure obtained crude which was triturated with petroleum ethers solid precipitated out which was filtered off, solid was dried under vacuum obtained 1-acetylpiperidine-4-carboxylic acid (5.20 g, 78.43%) as off white solid.

MS: 171.98[M⁺+1]

Step-2: Synthesis of 1-acetyl-N-methoxy-N-methylpiperidine-4-carboxamide

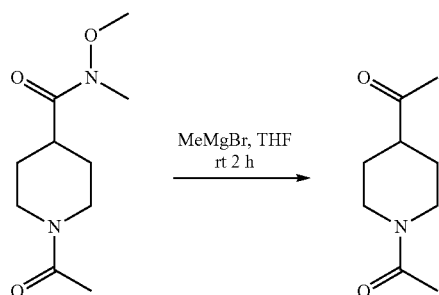


To a stirred solution of 1-acetylpiperidin-4-carboxylic acid (5.0 g, 29.207 mmol) in dichloromethane (100 mL) was added CDI (9.47 g, 58.414 mmol) and stirred for 0.5 h. After 0.5 h N-methoxymethanamine hydrochloride (4.27 g, 43.810 mmol) was added to reaction mass. The mixture was stirred at room temperature for 16 h. On completion, 4M HCl in Dioxane (20 mL) was added slowly. The slurry was agitated for 30 minutes and then filtered. Filtrate was washed twice with sodium bicarbonate solution, dried over sodium sulphate, concentrated under vacuum obtained 1-acetyl-N-methoxy-N-methylpiperidine-4-carboxamide (5.20 g, 83.20%) as yellow oil.

MS: 215.05[M⁺+1]

75

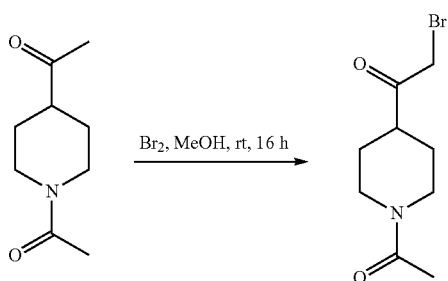
Step-3: Synthesis of N-acetyl-1-(piperidin-4-yl) ethanone



To a stirred solution of N-acetyl-N-methoxy-N-methylpiperidine-4-carboxamide (4.0 g, 18.668 mmol) in THF (100 mL) was added methyl magnesium bromide (2 M in THF) (28 mL, 56.006 mmol) at 0° C., after the addition the mixture was stirred at room temperature for 2 h. On completion, reaction mixture was quenched with NH₄Cl solution, extracted with EtOAc. The organic layer was washed with water, brine, dried over Na₂SO₄, evaporated under reduced pressure obtained N-acetyl-1-(piperidin-4-yl) ethanone (3.01 g, 95.55%) as yellow oil.

MS: 170.03[M⁺+1]

Step-4: Synthesis of 1-(1-acetylpiperidin-4-yl)-2-bromoethanone

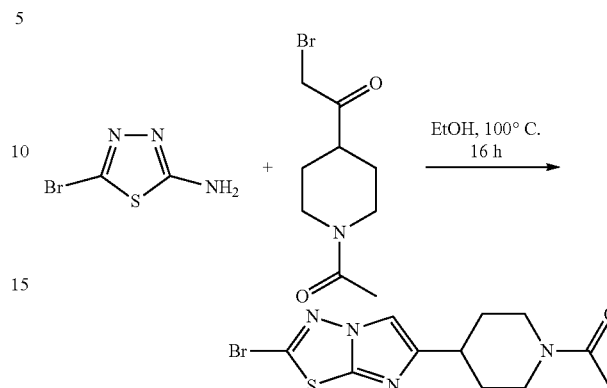


To a stirred solution of N-acetyl-1-(piperidin-4-yl) ethanone (2.0 g, 11.81 mmol) in MeOH (50 mL) was added bromine dropwise (1.88 g, 11.81 mmol) at room temperature, after the addition the mixture was stirred for 16 h. On completion, reaction mixture was quenched with water, extracted with EtOAc. The organic layer was washed with water, NaHCO₃ solution, dried over Na₂SO₄ and Concentrated under reduced pressure obtained 1-(1-acetylpiperidin-4-yl)-2-bromoethanone (1.60 g, 54.60%) as yellow oil.

MS: 247.91[M⁺+1]

76

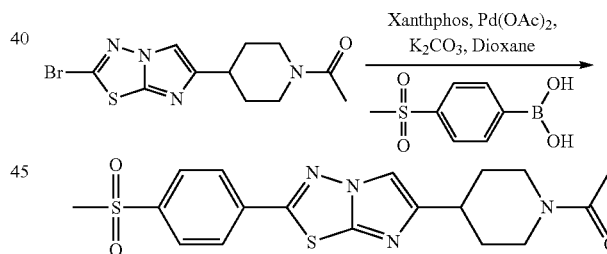
Step-5: Synthesis of 1-(4-(2-bromoimidazo[2,1-b][1,3,4]thiadiazol-6-yl)piperidin-1-yl)ethanone



To a stirred solution of 5-amino-2-bromo-1,3,4-thiadiazole (1.0 g, 5.553 mmol) and 1-(1-acetylpiperidin-4-yl)-2-bromoethanone (1.37 g, 5.553 mmol) in ethanol (50 mL) was heated at 120° C. for 16 h. On completion, all volatiles were evaporated under reduced pressure obtained yellow sticky mass which was purified by silica gel (100-200 Mesh) column chromatography eluent 3% MeOH/DCM obtained 1-(4-(2-bromoimidazo[2,1-b][1,3,4]thiadiazol-6-yl)piperidin-1-yl)ethanone (0.495 g, 27.5%) as off white solid.

MS: 328.94[M+1]

Step-6: Synthesis of 1-(4-(2-(4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazol-6-yl)piperidin-1-yl)ethanone



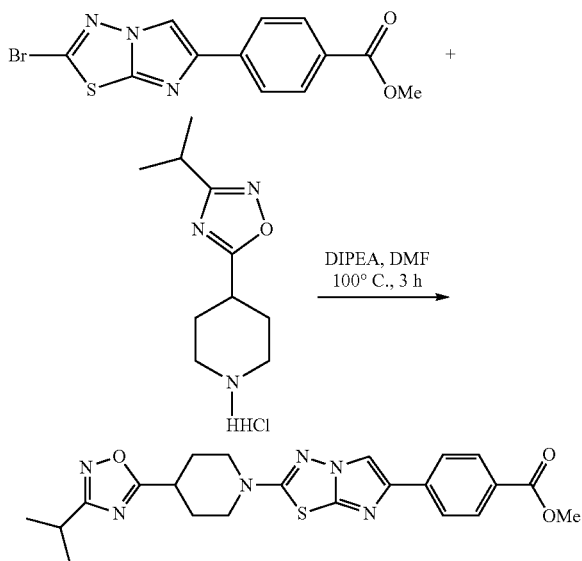
To a stirred solution of 1-(4-(2-bromoimidazo[2,1-b][1,3,4]thiadiazol-6-yl)piperidin-1-yl)ethanone (0.04 g, 0.121 mmol) and 4-(methylsulfonyl)phenylboronic acid (0.029 g, 0.145 mmol) in Dioxane (5 mL) were added K₂CO₃ (0.027 g, 0.19 mmol) and Xantphos (0.0036 g, 0.006 mmol) and nitrogen was purged for 30 min. After 30 min Pd(OAc)₂ (0.0013 g, 0.006 mmol) was added to reaction mass and heated at 100° C. for 6 h. Reaction was monitored by TLC. On completion, reaction was quenched with water, extracted with ethyl acetate. Organic layer was washed with water, brine dried over sodium sulphate, concentrated under reduced pressure obtained crude. Purification of the crude was done by silica gel (100-200 Mesh) column chromatography; eluent 2% MeOH/DCM to afford 1-(4-(2-(4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazol-6-yl)piperidin-1-yl)ethanone (0.011 g, 22.44%) as off white solid.

MS: 405.01[M+1]

77

Example 7: 4-(2-(4-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-1-yl)imidazo[2,1-b][1,3,4]thiadiazol-6-yl)-N,N-dimethylbenzamide

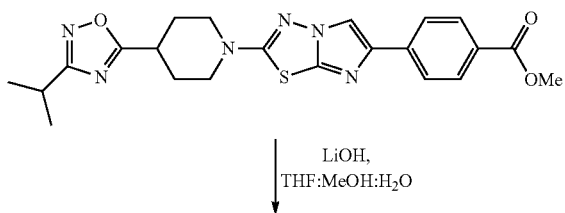
Step 1: Synthesis of methyl 4-(2-(4-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-1-yl)imidazo[2,1-b][1,3,4]thiadiazol-6-yl)benzoate



To a stirred solution of methyl 4-(2-bromoimidazo[2,1-b][1,3,4]thiadiazol-6-yl)benzoate (0.1 g, 0.29 mmol) and 4-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidine hydrochloride (0.07 g, 0.32 mmol) in DMF (10 ml) was added DIPEA (0.06 g, 0.44 mmol) and reaction was heated at 100° C. for 3 h. Reaction was monitored by TLC. On completion, reaction was quenched with water, extracted with ethyl acetate. The organic layer was washed with water, then brine, dried over Na₂SO₄ evaporated under reduced pressure to give crude. Purification of the compound was done by silica gel (100-200 Mesh) column chromatography, eluent 1% MeOH:DCM to obtain methyl 4-(2-(4-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-1-yl)imidazo[2,1-b][1,3,4]thiadiazol-6-yl)benzoate (0.1 g, 75%) as light yellow solid.

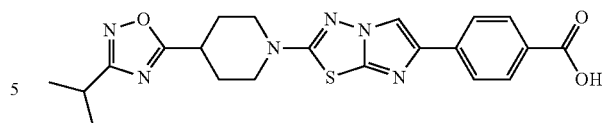
MS: 453.16[M⁺+1]

Step 2: synthesis of 4-(2-(4-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-1-yl)imidazo[2,1-b][1,3,4]thiadiazol-6-yl)benzoic acid



78

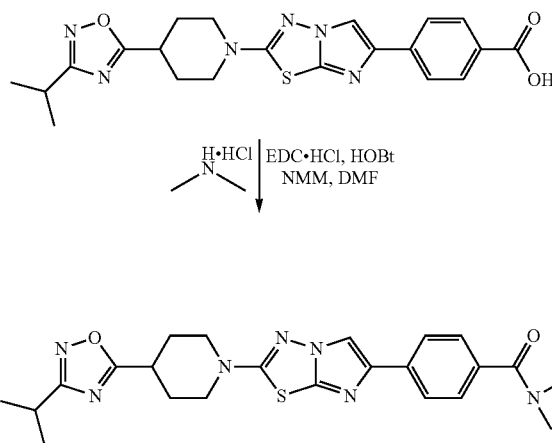
-continued



To a stirred solution of methyl 4-(2-(4-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-1-yl)imidazo[2,1-b][1,3,4]thiadiazol-6-yl)benzoate (0.1 g, 0.24 mmol) in mixture of THF: MeOH:H₂O (20 mL) was added LiOH (0.015 g, 0.33 mmol). After the addition, the mixture was stirred for 2 h at room temperature. On completion, all volatiles were evaporated under reduced pressure. Reaction mass diluted with water, acidify with 6N HCl and extracted with EtOAc. Organic poroomtemperatureions were combined, dried over Na₂SO₄, evaporated under reduced pressure to obtain 4-(2-(4-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-1-yl)imidazo[2,1-b][1,3,4]thiadiazol-6-yl)benzoic acid (0.07 g, 72%) as white solid.

MS: 439.15[M⁺+1]

Step 3: synthesis of 4-(2-(4-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-1-yl)imidazo[2,1-b][1,3,4]thiadiazol-6-yl)-N,N-dimethylbenzamide



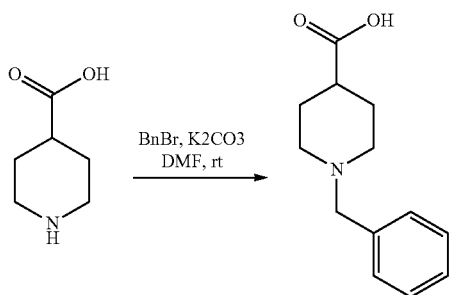
To a stirred solution of 4-(2-(4-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-1-yl)imidazo[2,1-b][1,3,4]thiadiazol-6-yl)benzoic acid (0.030 g, 0.068 mmol) and dimethyl amine hydrochloride (0.006 g, 0.068 mmol) in DMF (2 mL) were added EDC·HCl (0.02 g, 0.10 mmol), HOBT (0.014 g, 0.10 mmol) and NMM (0.014 g, 0.13 mmol). Reaction mixture was stirred at room temperature for 16 h. Reaction was monitored by TLC. On completion, reaction was quenched with water, extracted with ethyl acetate. Organic layer was washed with water, brine, dried over sodium sulphate and evaporated under reduced pressure to give crude product. Purification of the crude was done by silica gel (100-200 Mesh) column chromatography; eluent 3% MeOH:DCM to obtain 4-(2-(4-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-1-yl)imidazo[2,1-b][1,3,4]thiadiazol-6-yl)-N,N-dimethylbenzamide (0.012 g, 39%) as light yellow solid.

MS: 466.19[M⁺+1]

79

Example 8: 2-(1-benzylpiperidin-4-yl)-6-((4-(methylsulfonyl)phenoxy)methyl)imidazo[2,1-b][1,3,4]thiadiazole

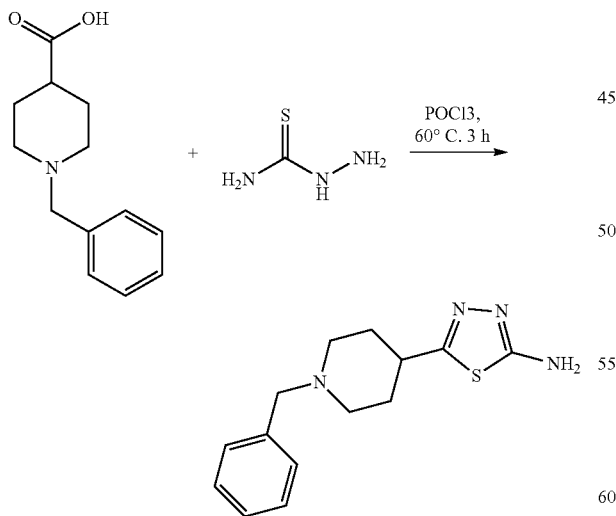
Step 1: Synthesis of 1-benzylpiperidine-4-carboxylic acid



To a stirred solution of piperidine-4-carboxylic acid (5.0 g, 38.7 mmol) in DMF (20 mL) was added K_2CO_3 (13.3 g, 96.8 mmol) followed by drop wise addition of benzyl bromide (9.2 mL, 77.5 mmol). Reaction was allowed to stir at room temperature for 12 h. Reaction was monitored by TLC. On completion, reaction mass was diluted with cold water (100 mL) and extracted with EtOAc. The organic layer was washed with water, brine, dried over Na_2SO_4 , evaporated under reduced pressure to give crude product. Purification of the compound was done by silica gel (100-200 Mesh) column chromatography eluent 20% EtOAc:hexane to obtain 1-benzylpiperidine-4-carboxylic acid (5.0 g, 59%) as light yellow oil.

MS: 220.14[M⁺+1]

Step 2: Synthesis of 5-(1-benzylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine



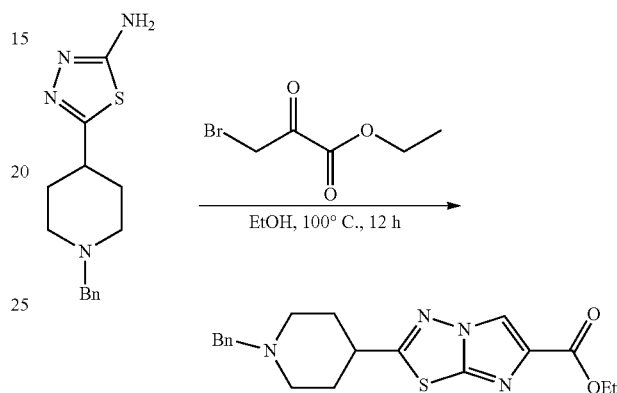
To a stirred solution of 1-benzylpiperidine-4-carboxylic acid (4.0 g, 18.2 mmol) in $POCl_3$ (20 mL) was added thiosemicarbazide (1.66 g, 18.2 mmol) and heated at 60° C. for 3 h. Reaction was monitored by TLC. On completion, reaction mass was quenched with saturated solution of

80

$NaHCO_3$ (500 mL), extracted with EtOAc. The organic layer was combined, dried over Na_2SO_4 , evaporated under reduced pressure to give crude product. Purification of the compound was done by silica gel (100-200 Mesh) column chromatography eluent 5% MeOH:DCM to obtain 5-(1-benzylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine (1.8 g, 36%) as yellow solid.

MS: 275.14[M⁺+1]

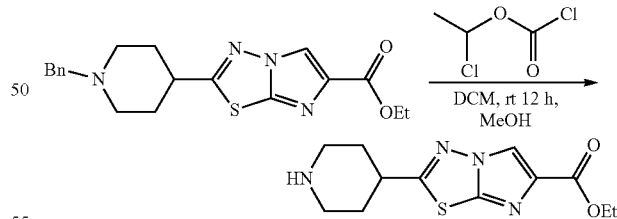
Step 3: Synthesis of ethyl 2-(1-benzylpiperidin-4-yl)imidazo[2,1-b][1,3,4]thiadiazole-6-carboxylate



To a stirred solution of 5-(1-benzylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine (0.6 g, 2.18 mmol) and ethyl 3-bromo-2-oxopropanoate (0.42 g, 2.18 mmol) in EtOH (50 mL) was heated at 100° C. for 12 h. Reaction was monitored by TLC. On completion, EtOH was evaporated to give crude product. Purification of the compound was done by silica gel (100-200 Mesh) column chromatography, eluent 4% MeOH:DCM to obtain ethyl 2-(1-benzylpiperidin-4-yl)imidazo[2,1-b][1,3,4]thiadiazole-6-carboxylate (0.3 g, 37%) as yellow sticky mass.

MS: 371.15[M⁺+1]

Step 4: Synthesis of ethyl 2-(piperidin-4-yl)imidazo[2,1-b][1,3,4]thiadiazole-6-carboxylate

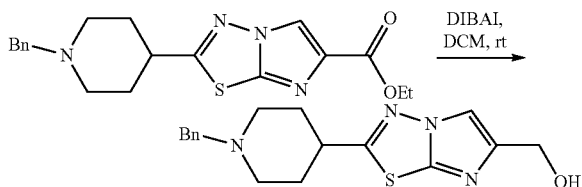


To a stirred solution of ethyl 2-(1-benzylpiperidin-4-yl)imidazo[2,1-b][1,3,4]thiadiazole-6-carboxylate (0.3 g, 0.81 mmol) in DCM (50 mL) was added 1-chloroethyl chloroformate (0.17 g, 1.21 mmol) and stir at room temperature for 12 h. Reaction was monitored by TLC. On completion, DCM was evaporated to give sticky mass which was dissolved in MeOH (10.0 mL) and heat at 50° C. for 1 h, then MeOH was evaporated under reduced pressure to obtain ethyl 2-(piperidin-4-yl)imidazo[2,1-b][1,3,4]thiadiazole-6-carboxylate (0.2 g, 26%) as yellow sticky mass.

MS: 281.1[M⁺+1]

81

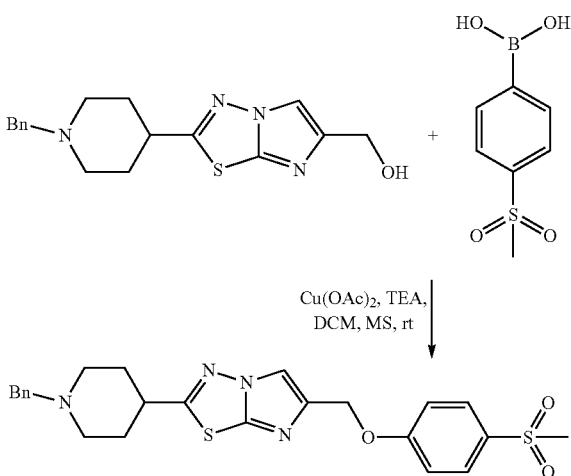
Step 5: Synthesis of (2-(1-benzylpiperidin-4-yl)imidazo[2,1-b][1,3,4]thiadiazol-6-yl)methanol



To a stirred solution of ethyl 2-(1-benzylpiperidin-4-yl)imidazo[2,1-b][1,3,4]thiadiazole-6-carboxylate (0.06 g, 0.16 mmol) in DCM (15 mL) was added DIBAL (1M in THF, 0.48 mL, 0.48 mmol) at 0° C. and reaction was allowed to stir at room temperature for 12 h. Reaction was monitored by TLC. On completion, reaction was quenched with addition of water, extracted with DCM. The organic layer was washed with water, dried over Na₂SO₄, evaporated under reduced pressure to obtain (2-(1-benzylpiperidin-4-yl)imidazo[2,1-b][1,3,4]thiadiazol-6-yl)methanol (0.040 g, 75%) as light yellow solid.

MS: 329.14[M⁺+1]

Step 6: Synthesis of 6-((4-(methylsulfonyl)phenoxy)methyl)-2-(1-benzylpiperidin-4-yl)imidazo[2,1-b][1,3,4]thiadiazole



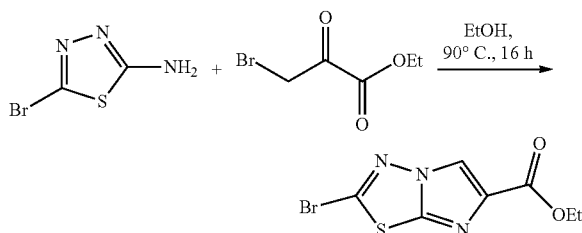
To a stirred solution of (2-(1-benzylpiperidin-4-yl)imidazo[2,1-b][1,3,4]thiadiazol-6-yl)methanol (0.04 g, 0.12 mmol) in DCM (20 mL) was added 4-(methylsulfonyl)phenylboronic acid (0.037 g, 0.18 mmol) followed by Cu(OAc)₂ (0.025 g, 0.12 mmol), TEA (0.1 mL, 0.60 mmol), and molecular sieves 4° (0.015 g) at room temperature. Reaction mass was allowed to stir at room temperature for 12 h. Reaction was monitored by TLC. On completion, reaction mass was filtered, washed with DCM (20 mL). Filtrate was evaporated under reduced pressure to obtain crude product. Purification of crude was done by silica gel (100-200 Mesh) column chromatography; eluent 4% MeOH:DCM to obtain 6-((4-(methylsulfonyl)phenoxy)

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methyl)-2-(1-benzylpiperidin-4-yl)imidazo[2,1-b][1,3,4]thiadiazole (0.02 g, 34%) as light yellow solid.
MS: 483.14[M⁺+1]

5 Example 9: 3-isopropyl-5-(1-(6-((4-(methylsulfonyl)phenoxy)methyl)imidazo[2,1-b][1,3,4]thiadiazol-2-yl)piperidin-4-yl)-1,2,4-oxadiazole

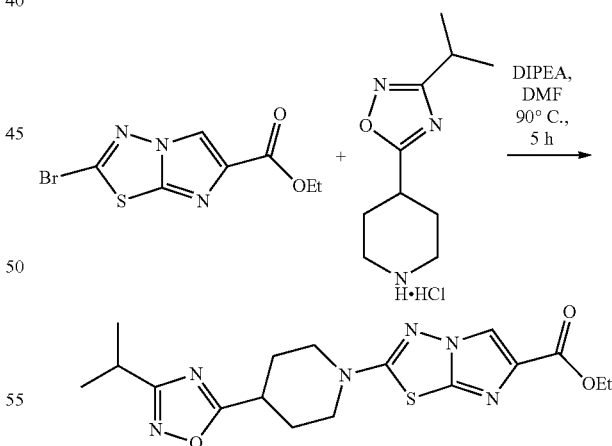
10 Step 1: Synthesis of ethyl 2-bromoimidazo[2,1-b][1,3,4]thiadiazole-6-carboxylate



To a stirred solution of 5-amino-2-bromo-1,3,4-thiadiazole (0.5 g, 2.80 mmol) and ethyl 3-bromo-2-oxopropanoate (0.6 g, 3.08 mmol) in EtOH (50 mL) was heated at 90° C. for 16 h. Reaction was cooled to room temperature, the solid precipitated out which was filtered off, washed with boiling EtOH (10 mL) and dried under vacuum to obtain ethyl 2-bromoimidazo[2,1-b][1,3,4]thiadiazole-6-carboxylate (0.2 g, 26%) as light yellow solid.

MS: 276.11[M⁺+1]

35 Step 2: Synthesis of ethyl 2-(4-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-1-yl)imidazo[2,1-b][1,3,4]thiadiazole-6-carboxylate



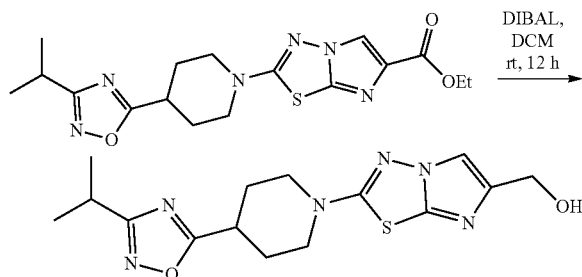
To a stirred solution of ethyl 2-bromoimidazo[2,1-b][1,3,4]thiadiazole-6-carboxylate (0.1 g, 3.62 mmol) and 4-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidine hydrochloride (0.1 g, 0.43 mmol) in DMF (10 mL) was added DIPEA (0.11 g, 0.90 mmol) and reaction was heated at 100° C. for 5 h. Reaction was monitored by TLC. On completion, reaction was quenched with water, extracted with ethyl acetate. The organic layer was washed with water, then brine, dried over Na₂SO₄ evaporated under reduced pressure to give crude.

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Purification of the compound was done by silica gel (100-200 Mesh) column chromatography eluent 20% EtOAc:hexane to obtain ethyl 2-(4-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-1-yl)imidazo[2,1-b][1,3,4]thiadiazole-6-carboxylate (0.08 g, 56%) as brown solid.

MS: 391.15[M⁺+1]

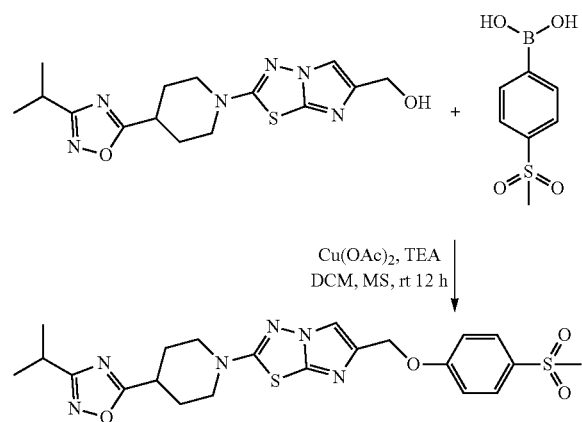
Step 3: Synthesis of (2-(4-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-1-yl)imidazo[2,1-b][1,3,4]thiadiazol-6-yl)methanol



To a stirred solution of ethyl 2-(4-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-1-yl)imidazo[2,1-b][1,3,4]thiadiazole-6-carboxylate (0.08 g, 0.20 mmol) in DCM (20 mL) was added DIBAL (0.6 mL, 0.61 mmol, 1M in THF) at 0° C. and reaction was allowed to stir at room temperature for 12 h. Reaction was monitored by TLC. On completion, reaction was quenched with water, extracted with DCM. The organic layer was washed with water, dried over Na₂SO₄, evaporated under reduced pressure to give (2-(4-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-1-yl)imidazo[2,1-b][1,3,4]thiadiazol-6-yl)methanol (0.06 g, 84%) as light yellow solid.

MS: 349.14[M⁺+1]

Step 4: Synthesis of 6-((4-(methylsulfonyl)phenoxy)methyl)-2-(4-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-1-yl)imidazo[2,1-b][1,3,4]thiadiazole



To a stirred solution of (2-(4-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-1-yl)imidazo[2,1-b][1,3,4]thiadiazol-6-yl)methanol (0.04 g, 0.11 mmol) in DCM (20 mL) was added 4-(methylsulfonyl)phenylboronic (0.035 g, 0.17 mmol) followed by Cu(OAc)₂ (0.023 g, 0.11 mmol), TEA

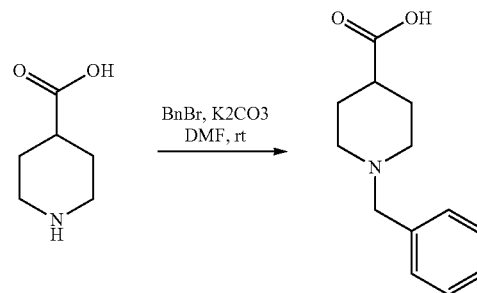
84

(0.08 mL, 0.57 mmol), and molecular sieves 4° (0.02 g). Reaction mixture was allowed to stir at room temperature for 12 h. Reaction was monitored by TLC. On completion, reaction mass was filtered, washed with DCM (20 mL), filtrate was evaporated under reduced pressure to obtain crude product. Purification of the compound was done by silica gel (100-200 Mesh) column chromatography eluent 2% MeOH:DCM to obtain 6-((4-(methyl sulfonyl)phenoxy)methyl)-2-(4-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-1-yl)imidazo[2,1-b][1,3,4]thiadiazole (0.02 g, 35%) as off-white solid.

MS: 503.15[M⁺+1]

Example 10: Isopropyl 4-(6-((4-(methylsulfonyl)phenoxy)methyl)imidazo[2,1-b][1,3,4]thiadiazol-2-yl)piperidine-1-carboxylate

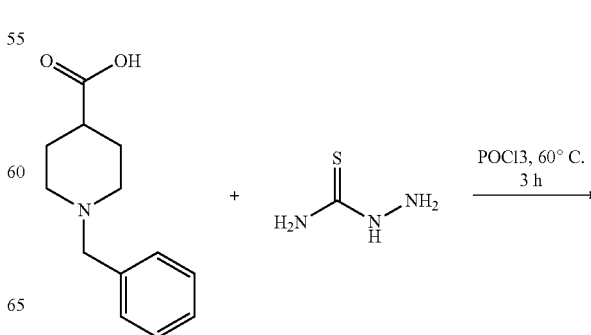
Step 1: Synthesis of 1-benzylpiperidine-4-carboxylic acid



To a stirred solution of piperidine-4-carboxylic acid (5.0 g, 38.7 mmol) in DMF (20 mL) was added K₂CO₃ (13.3 g, 96.8 mmol) followed by drop wise addition of benzyl bromide (9.2 mL, 77.5 mmol). Reaction was allowed to stir at room temperature for 12 h. Reaction was monitored by TLC. On completion, reaction mass was diluted with cold water (100 mL) and extracted with EtOAc. The organic layer was washed with water, brine, dried over Na₂SO₄, evaporated under reduced pressure to give crude product. Purification of the compound was done by silica gel (100-200 Mesh) column chromatography eluent 20% EtOAc:hexane to obtain 1-benzylpiperidine-4-carboxylic acid (5.0 g, 59%) as light yellow oil.

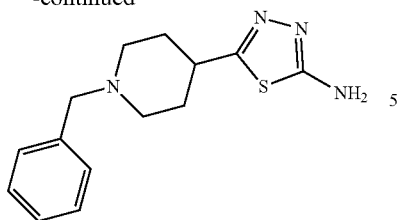
MS: 220.14[M⁺+1]

Step 2: Synthesis of 5-(1-benzylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine



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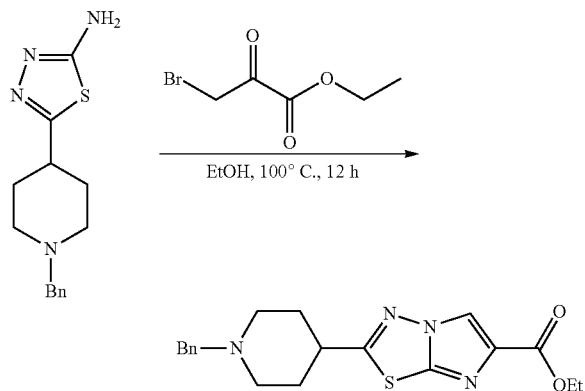
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To a stirred solution of 1-benzylpiperidine-4-carboxylic acid (4.0 g, 18.2 mmol) in POCl_3 (20 mL) was added thiosemicarbazide (1.66 g, 18.2 mmol) and heated at 60°C . for 3 h. Reaction was monitored by TLC. On completion, reaction mass was quenched with saturated solution of NaHCO_3 (500 mL), extracted with EtOAc. The organic layer was combined, dried over Na_2SO_4 , evaporated under reduced pressure to give crude product. Purification of the compound was done by silica gel (100-200 Mesh) column chromatography eluent 5% MeOH:DCM to obtain 5-(1-benzylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine (1.8 g, 36%) as yellow solid.

MS: 275.14 $[\text{M}^++1]$

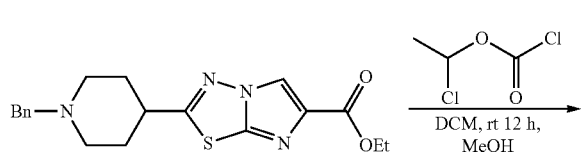
Step 3: Synthesis of ethyl 2-(1-benzylpiperidin-4-yl)imidazo[2,1-b][1,3,4]thiadiazole-6-carboxylate



To a stirred solution of 5-(1-benzylpiperidin-4-yl)-1,3,4-thiadiazol-2-amine (0.6 g, 2.18 mmol) and ethyl 3-bromo-2-oxopropanoate (0.42 g, 2.18 mmol) in EtOH (50 mL) was heated at 100°C . for 12 h. Reaction was monitored by TLC. On completion, EtOH was evaporated to give crude product. Purification of the compound was done by silica gel (100-200 Mesh) column chromatography, eluent 4% MeOH:DCM to obtain ethyl 2-(1-benzylpiperidin-4-yl)imidazo[2,1-b][1,3,4]thiadiazole-6-carboxylate (0.3 g, 37%) as yellow sticky mass.

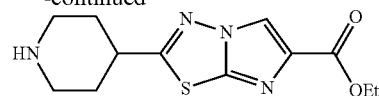
MS: 371.15 $[\text{M}^++1]$

Step 4: Synthesis of ethyl 2-(piperidin-4-yl)imidazo[2,1-b][1,3,4]thiadiazole-6-carboxylate



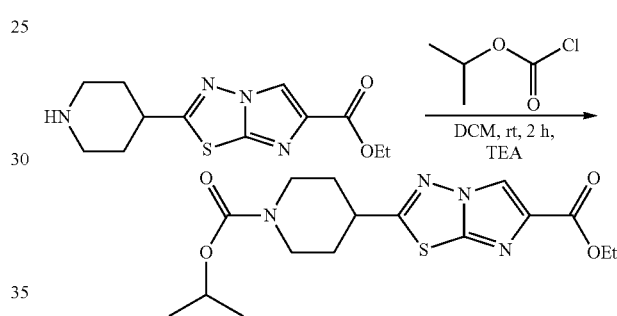
86

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To a stirred solution of ethyl 2-(1-benzylpiperidin-4-yl)imidazo[2,1-b][1,3,4]thiadiazole-6-carboxylate (0.3 g, 0.81 mmol) in DCM (50 mL) was added 1-chloroethyl chloroformate (0.17 g, 1.2 mmol) and stir at room temperature for 12 h. Reaction was monitored by TLC. On completion, DCM was evaporated to give sticky mass which was dissolved in MeOH (10.0 mL) and heat at 50°C . for 1 h, then MeOH was evaporated under reduced pressure to obtain ethyl 2-(piperidin-4-yl)imidazo[2,1-b][1,3,4]thiadiazole-6-carboxylate (0.2 g, 26%) as yellow sticky mass. MS: 281.1 $[\text{M}^++1]$

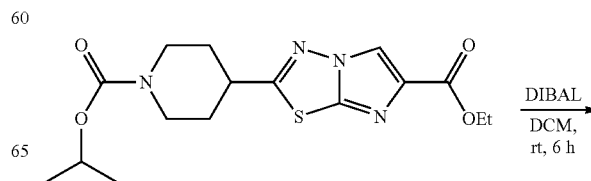
Step 5: Synthesis of ethyl 2-(1-(isopropoxycarbonyl)piperidin-4-yl)imidazo[2,1-b][1,3,4]thiadiazole-6-carboxylate



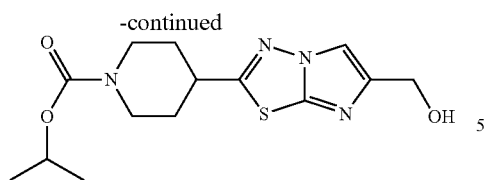
To a stirred solution of ethyl 2-(piperidin-4-yl)imidazo[2,1-b][1,3,4]thiadiazole-6-carboxylate (0.1 g, 0.35 mmol) in DCM (20 mL) was added TEA ((0.072 g, 0.71 mmol) followed by drop wise addition of isopropyl chloroformate (0.065 g, 0.53 mmol) and stir the reaction mass at room temperature for 2 h. Reaction was monitored by TLC. On completion, water was added to reaction mass, extracted with DCM. The organic layer were combined, dried over Na_2SO_4 , evaporated under reduced pressure to give crude product. Purification of the compound was done by silica gel (100-200 Mesh) column chromatography eluent 30% EtOAc:DCM to obtain ethyl 2-(1-(isopropoxycarbonyl)piperidin-4-yl)imidazo[2,1-b][1,3,4]thiadiazole-6-carboxylate (0.06 g, 46%) as light yellow sticky mass.

MS: 367.14 $[\text{M}^++1]$

Step 6: Synthesis of isopropyl 4-(6-(hydroxymethyl)imidazo[2,1-b][1,3,4]thiadiazol-2-yl)piperidine-1-carboxylate



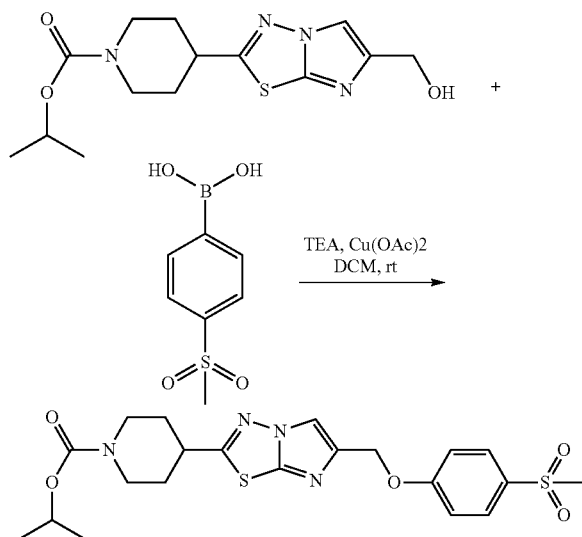
87



To a stirred solution of ethyl 2-(1-(isopropoxycarbonyl)piperidin-4-yl)imidazo[2,1-b][1,3,4]thiadiazole-6-carboxylate (0.06 g, 0.16 mmol) in DCM (15 mL) was added DIBAL (1M in THF) (0.5 mL, 0.49 mmol) in DCM (15 mL) at 0° C. and reaction was allowed to stir at room temperature for 6 h. Reaction was monitored by TLC. On completion, reaction was quenched with water, extracted with DCM. The organic layer was washed with water, dried over Na₂SO₄, evaporated under reduced pressure to obtain isopropyl 4-(6-(hydroxymethyl)imidazo[2,1-b][1,3,4]thiadiazol-2-yl)piperidine-1-carboxylate. (0.04 g, 75%) as light yellow solid.

MS: 325.13[M⁺+1]

Step 7: Synthesis of isopropyl 4-(6-((4-(methylsulfonyl)phenoxy)methyl)imidazo[2,1-b][1,3,4]thiadiazol-2-yl)piperidine-1-carboxylate



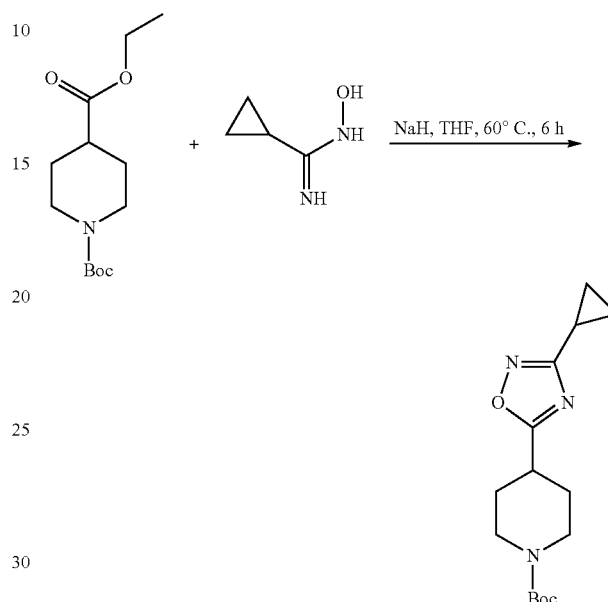
To a stirred solution of isopropyl 4-(6-(hydroxymethyl)imidazo[2,1-b][1,3,4]thiadiazol-2-yl)piperidine-1-carboxylate (0.05 g, 0.15 mmol) in DCM (20 mL) was added 4-(methylsulfonyl)phenylboronic acid (0.046 g, 0.23 mmol) followed by Cu(OAc)₂ (0.031 g, 0.15 mmol), TEA (0.1 mL, 0.77 mmol), and molecular sieves 4° (0.015 g) at room temperature. Allowed the reaction mass to stir at room temperature for 12 h. Reaction was monitored by TLC. On completion, reaction mass was filtered, washed with DCM (20 mL), filtrate was evaporated under reduced pressure to obtain crude product. Purification of the compound was done by silica gel (100-200 Mesh) column chromatography eluent 2% MeOH:DCM to obtain isopropyl 4-(6-((4-(methylsulfonyl)phenoxy)methyl)imidazo[2,1-b][1,3,4]thiadiazol-2-yl)piperidine-1-carboxylate (0.02 g, 27%) as off-white solid.

MS: 479.13[M⁺+1]

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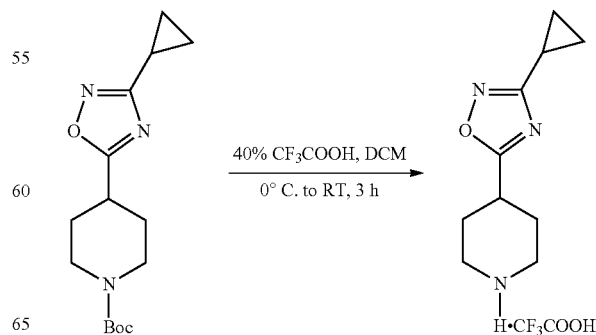
Example 11: 3-cyclopropyl-5-(1-(6-(4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazol-2-yl)piperidin-4-yl)-1,2,4-oxadiazole

Step 1: Synthesis of tert-butyl 4-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)piperidine-1-carboxylate



To a stirred solution of tert-butyl ethyl piperidine-1,4-dicarboxylate (0.5 g, 1.945 mmol) in THF (15 mL), was added NaH (60%) (0.31 g, 7.782 mmol) at 0° C. and stirred for 15 min. solution of N-hydroxycyclopropanecarboxamide (0.39 g, 3.891 mmol) in THF (5 mL) was then added to the reaction mixture and heated at 60° C. for 6 h. Progress of reaction was monitored by TLC. After reaction completion reaction mass was quenched with water and extracted with ethyl acetate. Organic layer was washed with brine, dried over sodium sulphate and concentrated under reduced pressure to give tert-butyl 4-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)piperidine-1-carboxylate (0.5 g, 87.6%) as yellow liquid. Mass: 294.3 [M⁺+1]

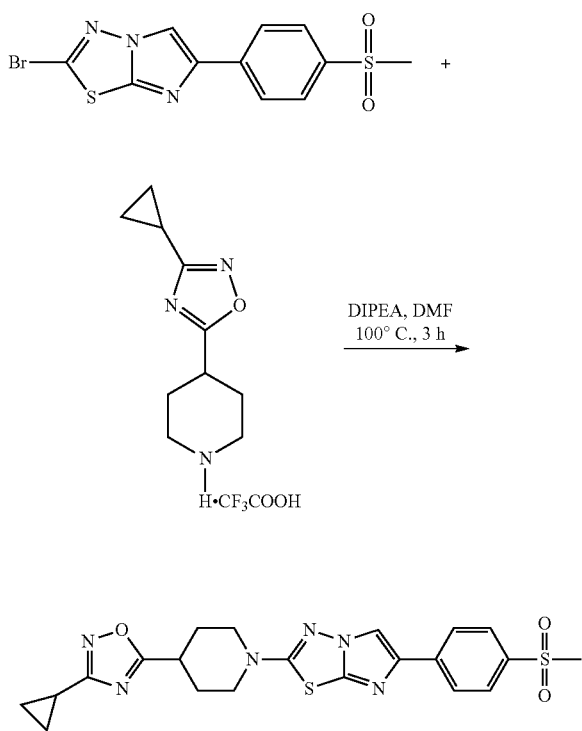
Step 2: Synthesis of 4-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)piperidine trifluoroacetate



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To a stirred solution of tert-butyl 4-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)piperidine-1-carboxylate (0.24 g, 0.819 mmol) in DCM (10 mL) was added 40% TFA (20 mL) at 0° C. and allowed the reaction to stir for 1 h at RT. Progress of reaction was monitored by TLC. After reaction completion reaction mass was concentrated under reduced pressure to give 4-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)piperidinetrifluoroacetate (0.2 g, 79%) as off white solid. Mass: 308.2

Step 3: synthesis of 2-(4-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-6-(4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazole



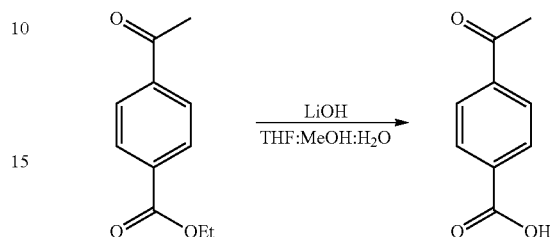
To a stirred solution of 2-bromo-6-(4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazole (0.025 g, 0.0698 mmol) and 4-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)piperidinetrifluoroacetate (0.0257 g, 0.0837 mmol) in DMF (10 mL) was added DIPEA (0.045 g, 0.349 mmol) and reaction was heated at 100° C. for 6 h. Reaction was monitored by TLC. On completion, reaction was quenched with water and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over sodium sulphate and concentrated under reduced pressure to give crude. Purification of the compound was done by silica gel (100-200 Mesh) column chromatography eluent 2% MeOH in DCM to give 2-(4-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)piperidin-1-yl)-6-(4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazole (0.02 g, 52.3%) as off white solid.

MS: 471.1[M⁺+1]

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Example 12: N,N-dimethyl-4-(2-(1-(1-(5-propylpyrimidin-2-yl)piperidin-4-yl)ethoxy)imidazo[2,1-b][1,3,4]thiadiazol-6-yl)benzamide

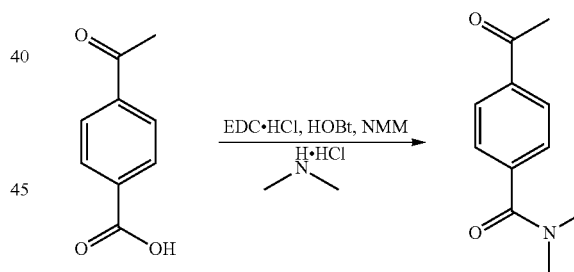
Step 1: Synthesis of 4-acetylbenzoic acid



To a stirred solution of ethyl 4-acetylbenzoate (0.5 g, 2.8 mmol) in mixture of THF:MeOH:H₂O (18 mL, 5:3:1) was added LiOH (0.23 g, 5.61 mmol). And allowed to stir for 2 h at room temperature. On completion, all volatiles were evaporated under reduced pressure. Reaction mass diluted with water, acidify with 6N HCl and extracted with EtOAc. Organic portions were combined, dried over Na₂SO₄, evaporated under reduced pressure to obtain 4-acetylbenzoic acid (0.3 g, 76%) as white solid.

MS: 165.05[M⁺+1]

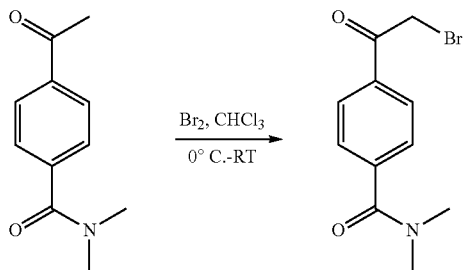
Step 2: Synthesis of 4-acetyl-N,N-dimethylbenzamide



To a stirred solution of 4-acetylbenzoic acid (0.35 g, 2.13 mmol) and dimethyl amine hydrochloride (0.25 g, 3.20 mmol) in DMF (2 mL) were added EDC.HCl (0.61 g, 3.20 mmol), HOBT (0.43 g, 3.20 mmol) and NMM (0.43 g, 4.26 mmol). Then reaction mixture was stirred at room temperature for 16 h. Reaction was monitored by TLC. On completion, reaction was quenched with water, extracted with ethyl acetate. Organic layer was washed with water, brine, dried over sodium sulphate and evaporated under reduced pressure to give crude product. Purification of the crude was done by silica gel (100-200 Mesh) column chromatography; eluent 3% MeOH in DCM to obtain 4-acetyl-N,N-dimethylbenzamide (0.3 g, 74%) as light yellow solid. MS: 192.09[M⁺+1]

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Step 3: Synthesis of
4-(2-bromoacetyl)-N,N-dimethylbenzamide

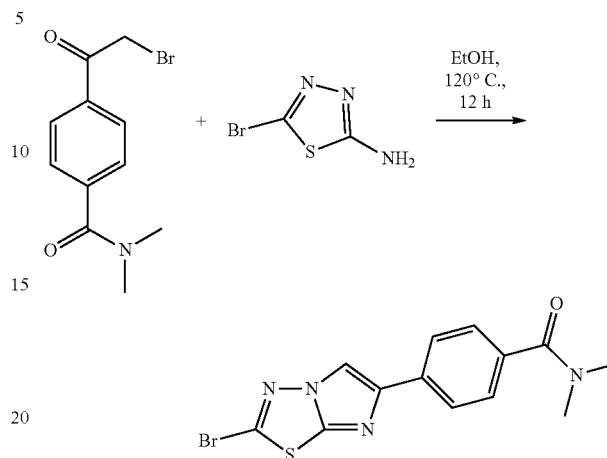


To a stirred solution of 4-acetyl-N,N-dimethylbenzamide (0.3 g, 1.57 mmol in CHCl₃ (30 mL)) was added bromine (0.081 mL, 1.57 mmol) drop wise at 0° C. and allowed to stir for 3 h at room temperature. Completion of reaction was monitored by TLC. Reaction mixture was evaporated under reduced pressure. Reaction mass was diluted with water, extracted with EtOAc. Organic layer was washed with water, brine, dried over sodium sulphate, evaporated under reduced pressure to obtain desired product 4-(2-bromoacetyl)-N,N-dimethylbenzamide (0.3 g, 71%) as dark yellow sticky mass.

MS: 270.01[M⁺+1]

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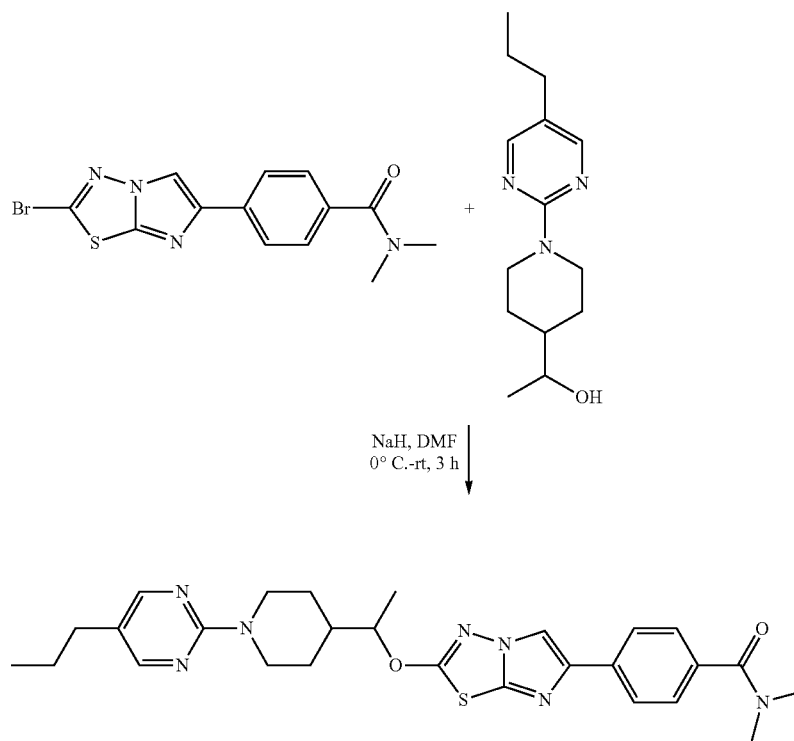
Step 4: Synthesis of 4-(2-bromoimidazo [2,1-b][1,3,4]thiadiazol-6-yl)-N,N-dimethylbenzamide



To a stirred solution of 5-amino-2-bromo-1,3,4-thiadiazole (0.4 g, 2.22 mmol) in EtOH (30 mL) was added 4-(2-bromoacetyl)-N,N-dimethylbenzamide (0.5 g, 2.22 mmol) and heated at 90° C. for 16 h. Reaction was cooled to room temperature, Precipitates were formed which was filtered off, washed with boiling EtOH (10 mL) and dried under vacuum to obtain pure product 4-(2-bromoimidazo [2,1-b][1,3,4]thiadiazol-6-yl)-N,N-dimethylbenzamid (0.2 g, 26%) as off white solid.

MS: [M+1] 351.22

Step 5: Synthesis of 4-(2-(1-(1-(5-propylpyrimidin-2-yl)piperidin-4-yl)ethoxy)imidazo[2,1-b][1,3,4]thiadiazol-6-yl)-N,N-dimethylbenzamide



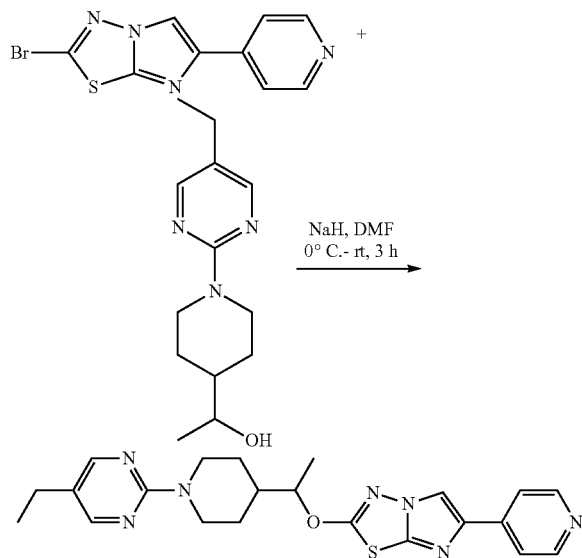
93

To a stirred solution of 1-(1-(5-propylpyrimidin-2-yl)piperidin-4-yl)ethanol (0.05 g, 0.20 mmol) in DMF (2 ml) was added sodium hydride (0.012 g, 0.30 mmol) at 0° C. and reaction allowed to stir at 0° C. for 30 min. After 30 min, 4-(2-bromoimidazo[2,1-b][1,3,4]thiadiazol-6-yl)-N,N-dimethylbenzamide (0.077 g, 0.22 mmol) in DMF (1 mL) was added to reaction mixture and stirred at room temperature for 3 h. Reaction was monitored by TLC. On completion reaction was quenched with ice cold water, extracted with ethyl acetate. The organic layer was washed with water, brine, dried over sodium sulphate and concentrated under reduced pressure to give crude desired product that was purified by silica gel (100 to 200 Mesh) chromatography, eluent 3% MeOH in DCM to obtain 4-(2-(1-(1-(5-propylpyrimidin-2-yl)piperidin-4-yl)ethoxy)imidazo[2,1-b][1,3,4]thiadiazol-6-yl)-N,N-dimethylbenzamide (0.02 g, 19%) as light yellow solid.

MS: 520.24[M⁺+1]

Example 13: 2-(1-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yl)ethoxy)-6-(pyridin-4-yl)imidazo[2,1-b][1,3,4]thiadiazole

Step 1: Synthesis of 2-(1-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yl)ethoxy)-6-(pyridin-4-yl)imidazo[2,1-b][1,3,4]thiadiazole



To a stirred solution of 1-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yl)ethanol (0.03 g, 0.12 mmol) in DMF (2 mL) was added sodium hydride (0.08 g, 0.19 mmol) at 0° C. and reaction allowed to stir at 0° C. for 30 min. To it, 2-bromo-6-(pyridin-4-yl)imidazo[2,1-b][1,3,4]thiadiazole (0.035 g, 0.12 mmol) in DMF (1 mL) was added to reaction mixture and allowed to stir at room temperature for 3 h. Reaction was monitored by TLC. On completion, reaction was quenched with ice cold water, extracted with ethyl acetate. The organic

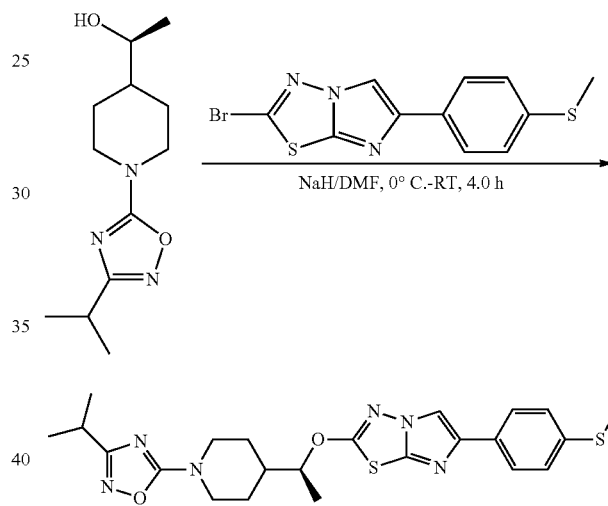
94

layer was washed with water, brine, dried over sodium sulphate and concentrated under reduced pressure to give crude desired product which was purified by silica gel (100 to 200 mesh) chromatography, eluent 2% MeOH in DCM to obtain 2-(1-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yl)ethoxy)-6-(pyridin-4-yl)imidazo[2,1-b][1,3,4]thiadiazole (0.012 g, 21%) as light yellow solid.

MS: 436.18[M⁺+1]

Example 14: (R)-3-isopropyl-5-(4-(1-((6-(4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazol-2-yl)oxy)ethyl)piperidin-1-yl)-1,2,4-oxadiazole

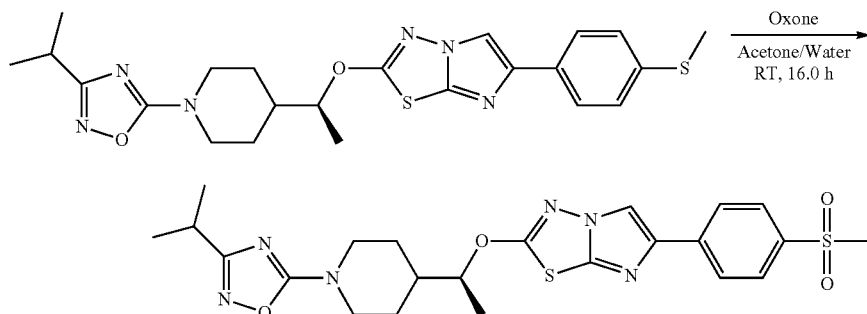
Step 1: Synthesis of 2-((S)-1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)-6-(4-(methylthio)phenyl)imidazo[2,1-b][1,3,4]thiadiazole



To a stirred solution of (S)-1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethanol (0.03 g, 0.13 mmol) in DMF (5.0 mL), sodium hydride (0.008 g, 0.19 mmol) was added at 0° C. and allowed to stir the reaction at 0° C. for 30 min. Then to it, 2-bromo-6-(4-(methylthio)phenyl)imidazo[2,1-b][1,3,4]thiadiazole (0.05 g, 0.14 mmol) was added to reaction mixture and stirred at room temperature for 3.5 h. Reaction was monitored by TLC. On completion, reaction mixture was quenched with ice cold water and compound was extracted with ethyl acetate. The organic layer was washed with water, brine, dried over sodium sulphate and concentrated under reduced pressure to give crude product. Purification of the compound was done by silica gel (100-200 mesh) column chromatography using 5% methanol in DCM to give 2-((S)-1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)-6-(4-(methylthio)phenyl)imidazo[2,1-b][1,3,4]thiadiazole (0.03 g, 49.34%) as yellow solid.

MS: 485.17[M⁺+1].

Step 2: Synthesis of 2-((S)-1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)-6-(4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazole

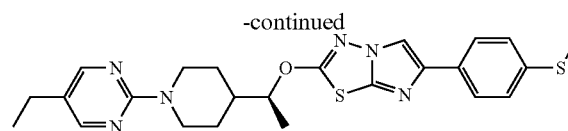
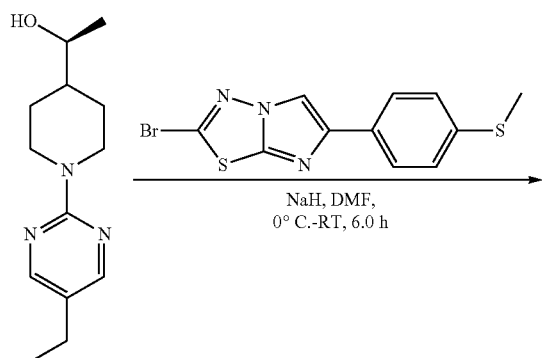


To a stirred solution of compound 2-((S)-1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)-6-(4-(methylthio)phenyl)imidazo[2,1-b][1,3,4]thiadiazole (0.03 g, 0.06 mmol) in Acetone (5.0 mL), Oxone (0.08 g, 0.25 mmol) in Water (1.0 mL) was added and reaction continued at room temperature for 16 h. Progress of reaction was monitored by TLC. On completion, acetone was evaporated. Residue was quenched with water and extracted with ethyl acetate. The organic layer was concentrated under reduced pressure to give crude compound. Purification of the compound was done by silica gel (100-200 mesh) column chromatography using 5% methanol in DCM to give 2-((S)-1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)-6-(4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazole (0.019 g, 59.41%) as yellow solid.

MS: 517.20[M⁺+1].

Example 15: (R)-2-(1-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yl)ethoxy)-6-(4-(methylthio)phenyl)imidazo[2,1-b][1,3,4]thiadiazole

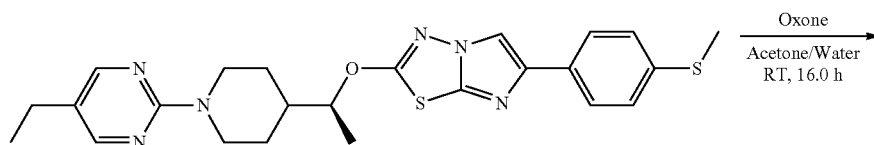
Step 1: Synthesis of 2-((S)-1-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yl)ethoxy)-6-(4-(methylthio)phenyl)imidazo[2,1-b][1,3,4]thiadiazole



To a stirred solution of (S)-1-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yl)ethanol (0.025 g, 0.11 mmol) in DMF (3.0 mL), sodium hydride (0.007 g, 0.16 mmol) was added at 0° C. and allowed the reaction to stir at 0° C. for 30 min. Then it, 2-bromo-6-(4-(methylthio)phenyl)imidazo[2,1-b][1,3,4]thiadiazole (0.04 g, 0.12 mmol) was added to reaction mixture and stirred at room temperature for 5.30 h. Reaction was monitored by TLC. On completion, reaction mixture was quenched with ice cold water and compound was extracted with ethyl acetate. The organic layer was washed with water, brine, dried over sodium sulphate and concentrated under reduced pressure to give crude. Purification of the compound was done by silica gel (100-200 mesh) column chromatography using 1% methanol in DCM to give 2-((S)-1-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yl)ethoxy)-6-(4-(methylthio)phenyl)imidazo[2,1-b][1,3,4]thiadiazole (0.022 g, 43.09%) as yellow semi solid.

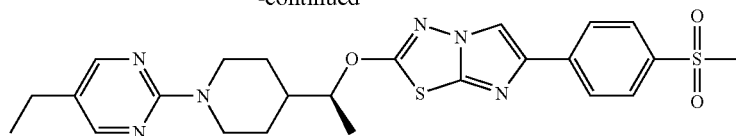
MS: 481.18[M⁺+1].

Step 2: Synthesis of 2-((S)-1-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yl)ethoxy)-6-(4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazole



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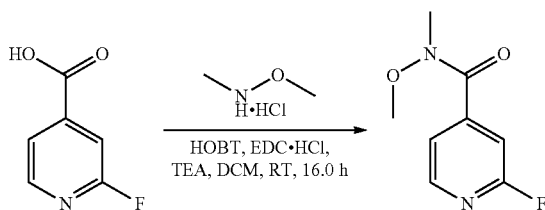


To a stirred solution of compound 2-((S)-1-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yl)ethoxy)-6-(4-(methylthio)phenyl)imidazo[2,1-b][1,3,4]thiadiazole (0.02 g, 0.04 mmol) in Acetone (3.0 mL), Oxone (0.05 g, 0.17 mmol) in Water (0.5 mL) was added and reaction continued at room temperature for 16 h. Progress of reaction was monitored by TLC. On completion, acetone was evaporated from reaction mixture. Residue was quenched with water and extracted with ethyl acetate. The organic layer was concentrated under reduced pressure to give crude. Purification of the compound was done by silica gel (100-200 mesh) column chromatography using 1% methanol in DCM to give 2-((S)-1-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yl)ethoxy)-6-(4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazole (0.009 g, 42.19%) as light brown solid.

MS: 513.30[M⁺+1].

Example 16: (R)-5-(4-(1-((6-(2-fluoropyridin-4-yl)imidazo[2,1-b][1,3,4]thiadiazol-2-yl)oxy)ethyl)piperidin-1-yl)-3-isopropyl-1,2,4-oxadiazole

Step 1: Synthesis of 2-fluoro-N-methoxy-N-methylpyridine-4-carboxamide

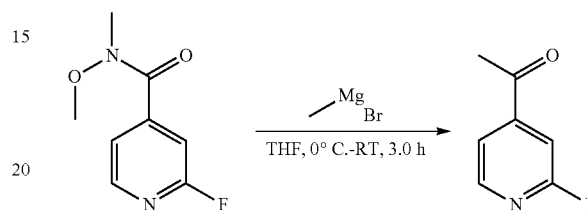


To a stirred solution of 2-fluoropyridine-4-carboxylic acid (1.0 g, 7.10 mmol) in DCM (20.0 mL), N-methoxymethanamine hydrochloride (1.03 g, 10.6 mmol), HOBT (1.19 g, 7.8 mmol), EDC.HCl (1.49 g, 7.8 mmol) and tri ethyl amine (3.94 mL, 28.4 mmol) was added at 25° C. and allowed to stir at room temperature for 16 h. Reaction was monitored by TLC. On completion, reaction mixture was quenched with ice cold water and compound was extracted with DCM. The organic layer was washed with water, brine, dried over sodium sulphate and concentrated under reduced pressure to give crude. Purification of the compound was done by silica gel (100-200 mesh) column chromatography using 20% ethyl acetate in hexane to give 2-fluoro-N-methoxy-N-methylpyridine-4-carboxamide (1.0 g, 76.92%) as yellow liquid.

MS: 185.04[M⁺+1].

98

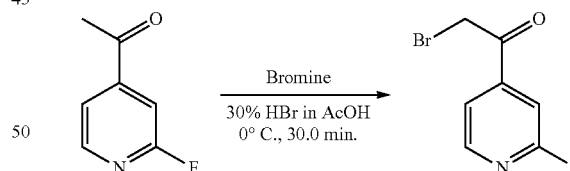
Step 2: Synthesis of 1-(2-fluoropyridin-4-yl)ethanone



To a stirred solution of 2-fluoro-N-methoxy-N-methylpyridine-4-carboxamide (1.0 g, 5.4 mmol) in dry THF (30.0 mL), methyl magnesium bromide (8.15 mL, 16.3 mmol) was added at 0° C. and reaction allowed to stir at room temperature for 3 h. Reaction was monitored by TLC. On completion, reaction mixture was quenched with ice cold aqueous ammonium chloride solution and extracted with ethyl acetate. The organic layer was washed with water, dried over sodium sulphate and concentrated under reduced pressure to give 1-(2-fluoropyridin-4-yl) ethanone (0.69 g, 91.27%) as yellow solid.

MS: 139.94[M⁺+1].

Step 3: Synthesis of 2-bromo-1-(2-fluoropyridin-4-yl)ethanone

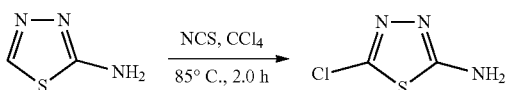


To a stirred solution of 1-(2-fluoropyridin-4-yl)ethanone (0.2 g, 1.44 mmol) in 30% HBr in Acetic acid (4.0 mL), Bromine (0.07 mL, 1.29 mmol) was added at 0° C. and allowed to stir at 0° C. for next 30 min. Reaction was monitored by TLC. On completion, reaction mixture was quenched with ice cold water and compound was extracted with di ethyl ether. The organic layer was washed with water, brine, dried over sodium sulphate and concentrated under reduced pressure to give 2-bromo-1-(2-fluoropyridin-4-yl)ethanone (0.32 g, Crude) as yellow liquid.

MS: 217.95[M⁺+1].

99

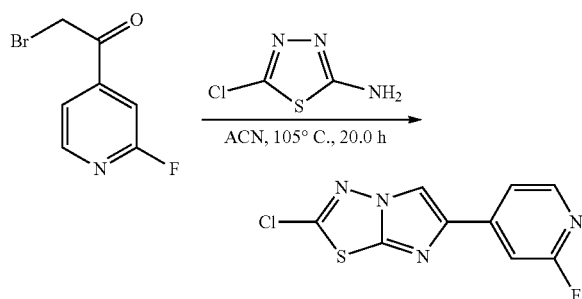
Step 4: Synthesis of
5-chloro-1,3,4-thiadiazol-2-amine



To a stirred solution of 1,3,4-thiadiazol-2-amine (0.5 g, 4.95 mmol) in CCl_4 (10.0 mL), N-Chlorosuccinimide (0.73 g, 5.45 mmol) was added at 25° C. and reaction allowed to stir at 85° C. for 2 h. Reaction was monitored by TLC. On completion, reaction mixture was quenched with ice cold water and compound was extracted with 10% methanol in DCM. The organic layer was washed with water, brine, dried over sodium sulphate and concentrated under reduced pressure to give crude. Purification of the compound was done by silica gel (100-200 mesh) column chromatography using 20% ethyl acetate in hexane to give 5-chloro-1,3,4-thiadiazol-2-amine (0.18 g, 26.94%) as light brown solid.

MS: 135.97[M⁺+1].

Step 5: Synthesis of 2-chloro-6-(2-fluoropyridin-4-yl)imidazo[2,1-b][1,3,4]thiadiazole

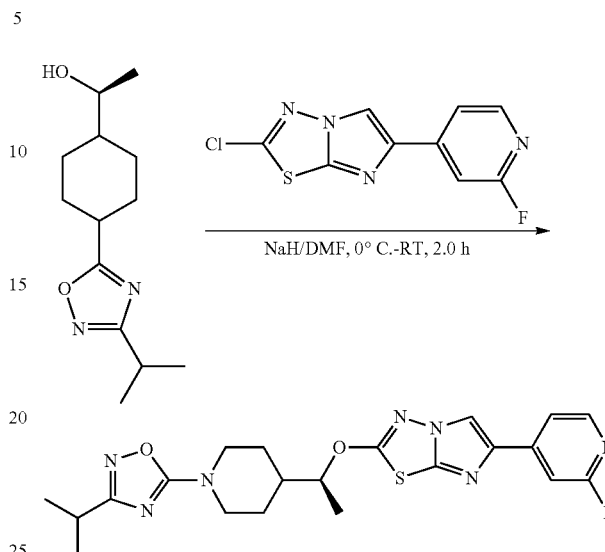


To a stirred solution of 2-bromo-1-(2-fluoropyridin-4-yl)ethanone (0.25 g, 1.15 mmol) in ACN (5.0 mL), 5-chloro-1,3,4-thiadiazol-2-amine (0.16 g, 1.15 mmol) was added at room temperature and allowed to stir at 105° C. for 20 h. Reaction was monitored by TLC. On completion reaction mixture was quenched with ice cold water and compound was extracted with ethyl acetate. The organic layer was washed with water, brine, dried over sodium sulphate and concentrated under reduced pressure to give crude product. Purification of the compound was done by silica gel (100-200 mesh) column chromatography using 15% ethyl acetate in hexane to give 2-chloro-6-(2-fluoropyridin-4-yl)imidazo[2,1-b][1,3,4]thiadiazole (0.055 g, 18.79%) as white solid.

MS: 254.83[M⁺+1].

100

Step 6: Synthesis of 2-((S)-1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)-6-(2-fluoropyridin-4-yl)imidazo[2,1-b][1,3,4]thiadiazole

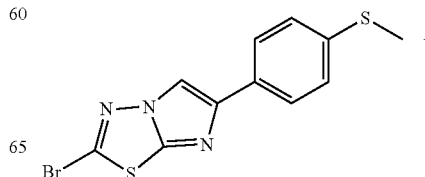


To a stirred solution of (S)-1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethanol (0.02 g, 0.08 mmol) in DMF (3.0 mL), sodium hydride (0.005 g, 0.13 mmol) was added at 0° C. and allowed to stir at 0° C. for 30 min. Then to it, 2-chloro-6-(2-fluoropyridin-4-yl)imidazo[2,1-b][1,3,4]thiadiazole (0.028 g, 0.11 mmol) was added to reaction mixture and stirred at room temperature for 2 h. Reaction was monitored by TLC. On completion, reaction mixture was quenched with ice cold water and extracted with ethyl acetate. The organic layer was washed with water, brine, dried over sodium sulphate and concentrated under reduced pressure to give crude. Purification of the compound was done by silica gel (100-200 mesh) column chromatography using 45% ethyl acetate in hexane to give crude which was purified using prep. TLC (Mobile phase 50% EtOAc in Hexane) to give 2-((S)-1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)-6-(2-fluoropyridin-4-yl)imidazo[2,1-b][1,3,4]thiadiazole (0.007 g, 18.31%) as white solid.

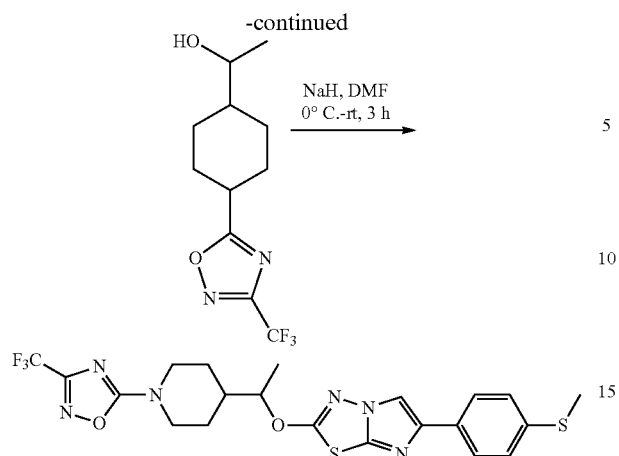
MS: 458.10[M⁺+1].

Example 17: 2-(1-(1-(3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)-6-(4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazole

Step 1: Synthesis of 2-(1-(1-(3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)-6-(4-(methylthio)phenyl)imidazo[2,1-b][1,3,4]thiadiazole



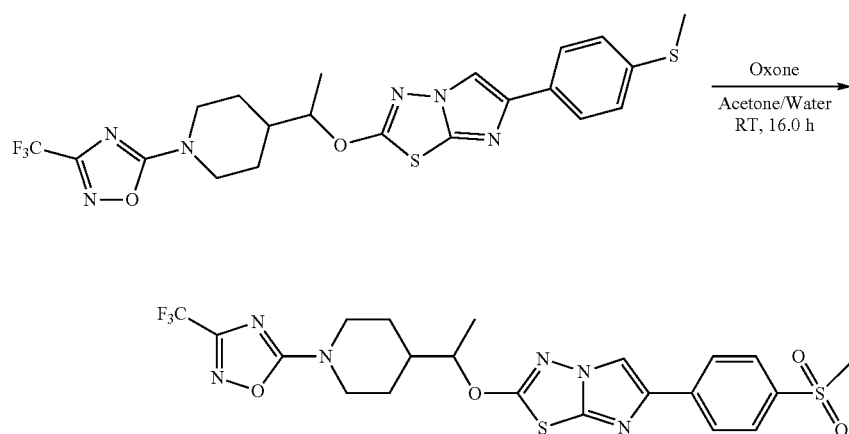
101



To compound 1-(1-(3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethanol (0.050 g, 0.20 mmol) in DMF (5 mL) was added sodium hydride (0.010 g, 0.33 mmol) at 0° C. and reaction allowed to run at 0° C. for 30 min. After 30 min 2-bromo-6-(4-(methylthio)phenyl)imidazo[2,1-b][1,3,4]thiadiazole (0.047 g, 0.23 mmol) dissolved in DMF was added to reaction mass, stirred at RT for 1 hr. Reaction was monitored by TLC. On completion reaction was quenched with ice cold water and reaction mixture extracted with ethyl acetate. The organic layer was washed with water, brine, dried over sodium sulphate, concentrated under reduced pressure to give crude desired product that was purified by silica gel (100 to 200# column) chromatography, eluent 2% MeOH/DCM to afford (0.025 g, 18%) 2-(1-(1-(3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)-6-(4-(methylthio)phenyl)imidazo[2,1-b][1,3,4]thiadiazole as off white solid.

MS: 511.63[M⁺+1]

Step 2: Synthesis 2-(1-(1-(3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)-6-(4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazole



To a stirred soln. of compound 2-(1-(1-(3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)-6-(4-(methylthio)phenyl)imidazo[2,1-b][1,3,4]thiadiazole (0.010 g, 0.020 mmol) in Acetone (5.0 mL), Oxone (0.012 g, 0.041 mmol) in Water (1.5 mL) was added and reaction continued at RT for 16.0 h. Progress of reaction was monitored by

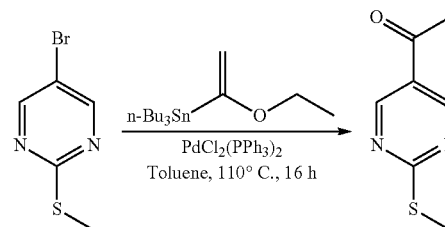
102

TLC. On completion acetone was evaporated from reaction mixture and residue was quenched with water, compound was extracted with ethyl acetate. The organic layer was concentrated under reduced pressure to give crude desired compound. Purification of the compound was done by silica gel (100-200 mesh) column chromatography using 1.5% methanol in DCM that was concentrated to get compound 2-(1-(1-(3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)-6-(4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazole (0.004 g, 40%) white solid.

MS: 543.65[M⁺+1].

Example 18: 2-(1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)-6-(2-(methylsulfonyl)pyrimidin-5-yl)imidazo[2,1-b][1,3,4]thiadiazole

Step 1: Synthesis of 1-(2-(methylthio)pyrimidin-5-yl)ethanone



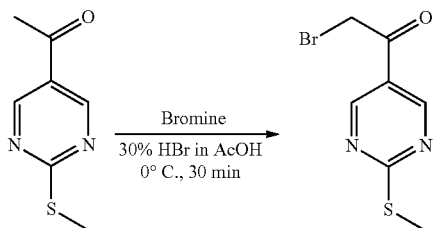
To a stirred solution of 5-bromo-2-(methylthio)pyrimidine (0.1 g, 0.48 mmol) and tributyl(1-ethoxyvinyl)stannane (0.193 g, 0.53 mmol) in toluene (10.0 ml), was degassed with N₂ for 15 minute, after that PdCl₂(PPh₃)₂ (0.017 g, 0.024 mmol) was added to reaction mass and stirred at 100° C. for 16 h. Reaction was monitored by TLC. On completion reaction mixture was quenched with water, extracted with ethyl acetate. The organic layer was dried over sodium sulphate, evaporated under reduced pressure to obtain crude

desired product. Purification of the compound was done by silica gel (100-200 mesh) column chromatography using 20% ethyl acetate in hexane as a eluent to afford 1-(2-(methylthio)pyrimidin-5-yl)ethanone (0.06 g, 74%) as a white solid.

MS: 169.1[M⁺+1].

103

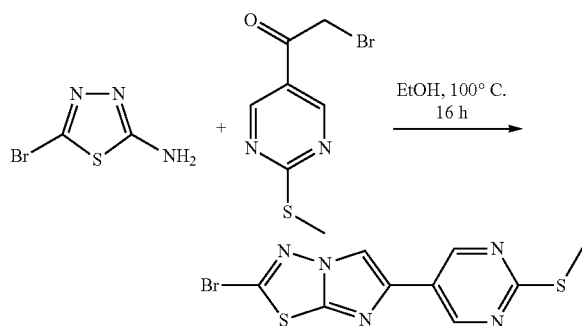
Step 2: Synthesis of
2-bromo-1-(2-(methylthio)pyrimidin-5-yl)ethanone



To a stirred solution of 1-(2-(methylthio)pyrimidin-5-yl)ethanone (0.150 g, 0.89 mmol) in 30% HBr in Acetic acid (5.0 mL), Bromine (0.04 mL, 0.8 mmol) was added at 0° C. and allowed to stir at 0° C. for next 30 min. Reaction was monitored by TLC. On completion, reaction mixture was quenched with ice cold water and extracted with EtOAc. The organic layer was washed with water, brine, dried over sodium sulphate and concentrated under reduced pressure to afford 2-bromo-1-(2-(methylthio)pyrimidin-5-yl)ethanone (0.15 g, 57%) as light yellow solid.

MS: 247.1[M⁺+1].

Step 3: Synthesis of 2-bromo-6-(2-(methylthio)pyrimidin-5-yl)imidazo[2,1-b][1,3,4]thiadiazole

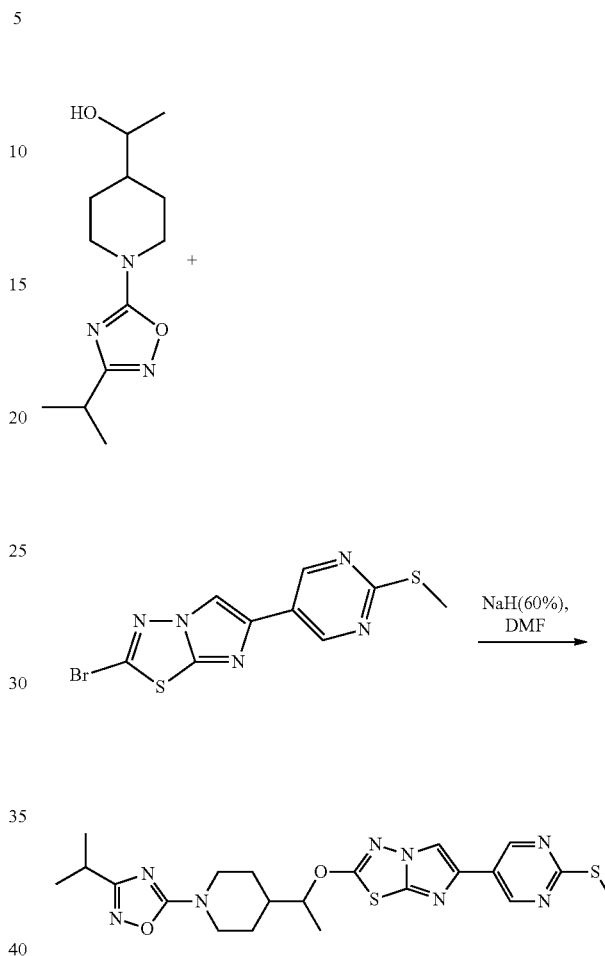


To a stirred solution of 5-amino-2-bromo-1,3,4-thiadiazole (0.250 g, 1.38 mmol) and 2-bromo-1-(2-(methylthio)pyrimidin-5-yl)ethanone (0.341 g, 1.38 mmol) in ethanol (20 mL) was heated at 120° C. for 16 h. On completion, all volatiles were evaporated under reduced pressure obtained yellow sticky mass which was purified by silica gel (100-200 Mesh) column chromatography eluent 2% MeOH/DCM obtained 2-bromo-6-(2-(methylthio)pyrimidin-5-yl)imidazo[2,1-b][1,3,4]thiadiazole (0.15 g, 33%) as light yellow solid.

MS: 328.1[M⁺+1]

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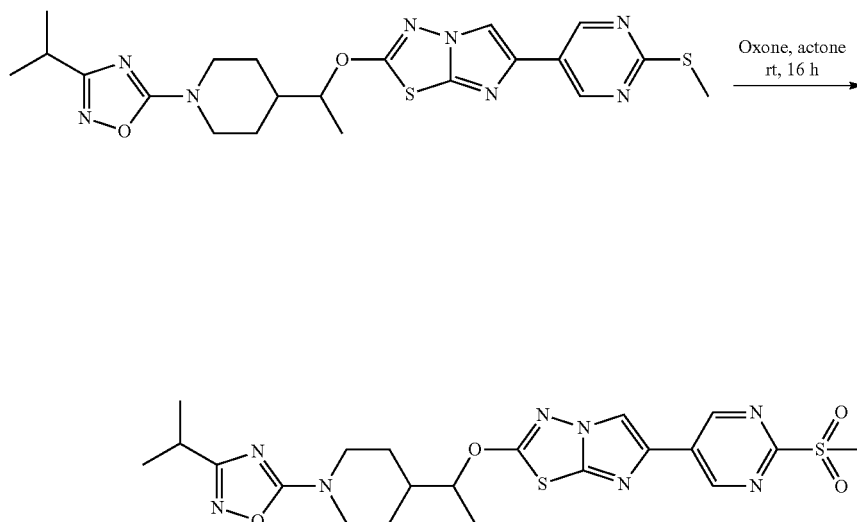
Step 4: Synthesis of 2-(1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)-6-(2-(methylthio)pyrimidin-5-yl)imidazo[2,1-b][1,3,4]thiadiazole



To 1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethanol (0.03 g, 0.12 mmol) in DMF (1 mL) was added sodium hydride (0.008 g, 0.18 mmol) at 0° C. and allowed the reaction to stir at 0° C. for 30 min. After 30 min, 2-bromo-6-(2-(methylthio)pyrimidin-5-yl)imidazo[2,1-b][1,3,4]thiadiazole (0.045 g, 0.13 mmol) in DMF (1 mL) was added to reaction mixture and stirred it at room temperature for 2 h. Reaction was monitored by TLC. On completion, reaction was quenched with ice cold water (2 mL) and extracted with EtOAc. The organic layer was washed with water, brine, dried over Na₂SO₄, evaporated under reduced pressure to give crude product that was purified by silica gel (100 to 200 mesh) chromatography, eluent 50% EtOAc/Hexane to obtain 2-(1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)-6-(2-(methylthio)pyrimidin-5-yl)imidazo[2,1-b][1,3,4]thiadiazole (0.015 g, 24%) as light yellow solid.

MS: 487.1 [M⁺+1]

Step 5: Synthesis of 2-(1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)-6-(2-(methylsulfonyl)pyrimidin-5-yl)imidazo[2,1-b][1,3,4]thiadiazole

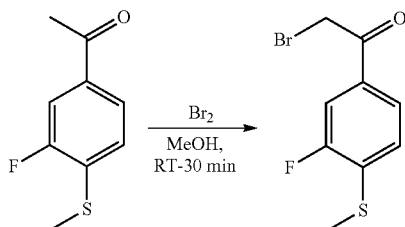


To a stirred solution of 2-(1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)-6-(2-(methylthio)pyrimidin-5-yl)imidazo[2,1-b][1,3,4]thiadiazole (0.02 g, 0.04 mmol) in acetone (5.0 mL), Oxone (0.025 g, 0.08 mmol) in water (2 mL) was added drop wise at room temperature. Allowed the reaction to stir for 16 h. Completion of reaction was monitored by TLC. Reaction mass was evaporated, diluted with water, extracted with EtOAc. Organic portions were combined, dried over Na_2SO_4 , evaporated under reduced pressure to obtain crude product as yellow solid which was purified by column chromatography using silica gel (100-200 mesh); eluent 2% MeOH in DCM to obtain 2-(1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)-6-(2-(methylsulfonyl)pyrimidin-5-yl)imidazo[2,1-b][1,3,4]thiadiazole (0.01 g, 47%) as off-white solid.

MS: 519.28[M⁺+1]

Example 19: 2-((S)-1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)-6-(3-fluoro-4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazole

Step 1: Synthesis of 2-bromo-1-(3-fluoro-4-(methylthio) phenyl) ethanone

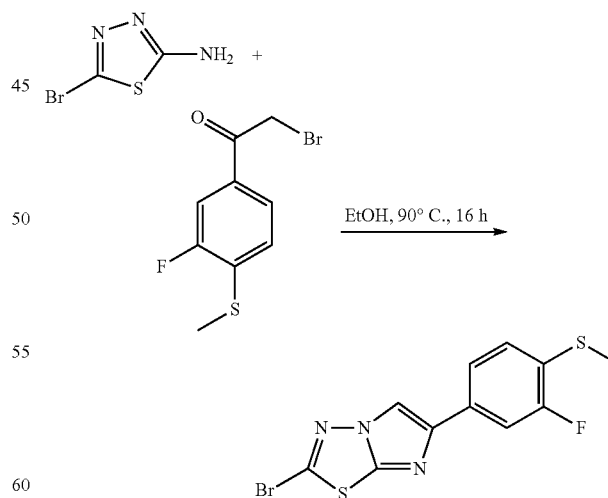


To a stirred solution of 1-(3-fluoro-4-(methylthio) phenyl) ethanone (0.500 g, 3.44 mmol) in MeOH (10 mL) was added

Br_2 (0.052 mL, 1.07 mmol) in MeOH (2 mL) drop wise at RT, stirred at room temperature for 0.5 hr. Completion of reaction was monitored by TLC. Diethyl ether was added to reaction mass, solid precipitate out which was filtered on Buchner funnel, solid was washed with diethyl ether, dried under vacuum to afford (0.200 gm., 25%) 2-bromo-1-(3-fluoro-4-(methylthio)phenyl)ethanone as off white solid.

MS: 263[M⁺+2]

Step 2: Synthesis 2-bromo-6-(3-fluoro-4-(methylthio) phenyl) imidazo [2,1-b][1,3,4] thiadiazole



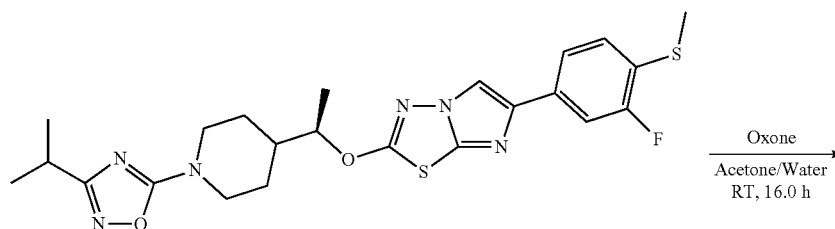
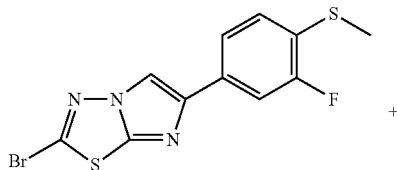
To a stirred solution of 5-amino-2-bromo-1,3,4-thiadiazole (0.174 gm, 0.982 mmol) and 2-bromo-1-(3-fluoro-4-(methylthio)phenyl)ethanone (0.200 gm, 0.982 mmol) in Ethanol (50 mL), Reaction mass was heated at 90° C. for 16 h. cooled to room temperature, the precipitated solid was

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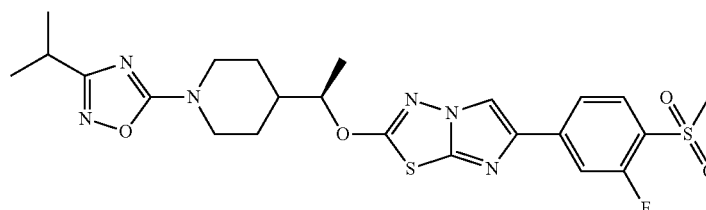
filtered off, washed with hot ethanol, dried under vacuum to afford 2-bromo-6-(3-fluoro-4-(methylthio)phenyl)imidazo[2,1-b][1,3,4]thiadiazole as off white solid.

MS: $[M^+ + 2]$ 345.92

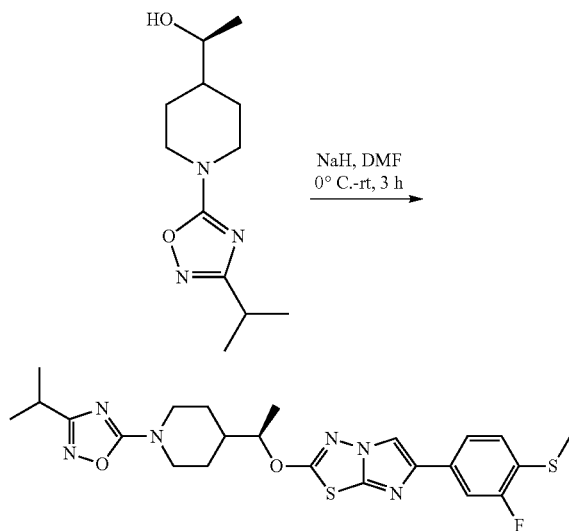
Step 3: Synthesis of 2-((R)-1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)-6-(3-fluoro-4-(methylthio)phenyl)imidazo[2,1-b][1,3,4]thiadiazole



Step 4: Synthesis of 2-((R)-1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)-6-(3-fluoro-4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazole



-continued



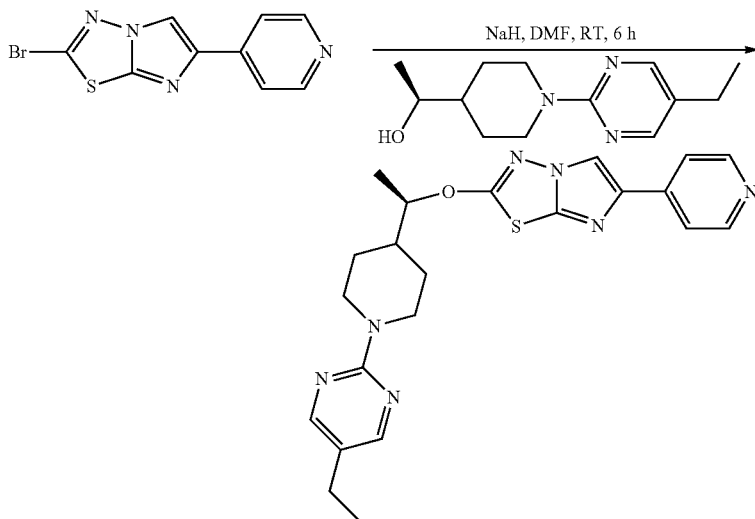
To a stirred soln. of compound 2-((R)-1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)-6-(3-fluoro-4-(methylthio)phenyl)imidazo[2,1-b][1,3,4]thiadiazole (0.010 g, 0.020 mmol) in Acetone (5.0 mL), Oxone (0.012 g, 0.041 mmol) in Water (1.5 mL) was added and reaction continued at RT for 16.0 h. Progress of reaction was monitored by TLC. On completion acetone was evaporated from reaction mixture and residue was quenched with water, compound was extracted with ethyl acetate. The organic layer was concentrated under reduced pressure to give crude desired compound. Purification of the compound was done by silica gel (100-200 mesh) column chromatography using 1.5% methanol in DCM that was concentrated to get compound 2-((R)-1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)-6-(3-fluoro-4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazole (0.004 g, 40%) white solid.

MS: 535.65 $[M^+ + 1]$.

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Example 20: 2-((S)-1-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yl)ethoxy)-6-(pyridin-4-yl)imidazo[2,1-b][1,3,4]thiadiazole

Step 1: Synthesis of 2-((S)-1-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yl)ethoxy)-6-(pyridin-4-yl)imidazo[2,1-b][1,3,4]thiadiazole



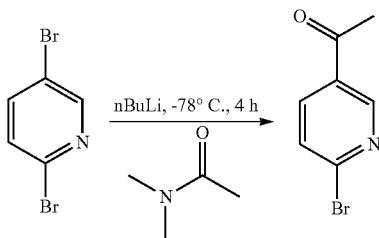
30

To a stirred solution of (S)-1-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yl)ethanol (0.03 g, 0.107 mmol) in DMF (3 mL) was added sodium hydride (0.0085 g, 0.214 mmol) at 0° C. and stirred for 30 min at room temperature. After 30 min solution of 2-bromo-6-(pyridin-4-yl)imidazo[2,1-b][1,3,4]thiadiazole (0.027 g, 0.117 mmol) in DMF (2 mL) was added to the reaction mixture and stirred for 6 h. Progress of reaction was monitored by TLC. After completion reaction mass was quenched with ice cold water and extracted with ethyl acetate. The organic layer was washed with water, brine, dried over sodium sulphate and concentrated under reduced pressure to give crude product. Crude was purified by neutral alumina column chromatography using 28% ethyl acetate in hexane as eluent to give 2-((S)-1-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yl)ethoxy)-6-(pyridin-4-yl)imidazo[2,1-b][1,3,4]thiadiazole (0.004 g, 8.58%) as white solid.

MS: 436.5 [M+1]

Example 21: 2-((S)-1-(1-(5-propylpyrimidin-2-yl)piperidin-4-yl)ethoxy)-6-(6-(methylsulfonyl)pyridin-3-yl)imidazo[2,1-b][1,3,4]thiadiazole

Step 1: Synthesis of 1-(6-bromopyridin-3-yl)ethanone



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To a stirred solution of 1-(6-bromopyridin-3-yl) ethanone (0.5 g, 2.5 mmol) in DMF (10 mL) was added sodium thiomethoxide soln (1.25 mL, 3.75 mmol) at room temperature and allowed to stir for 6 h at same temperature. Progress of reaction was monitored by TLC. After completion reaction mass was quenched with ice cold water and partitioned with EtOAc. The organic layer was washed with brine, dried over sodium sulphate and concentrated under reduced pressure to give 1-(6-(methylthio)pyridin-3-yl)ethanone (0.4 g, 95%) as yellow solid

MS: 168.1 [M⁺+1]

110

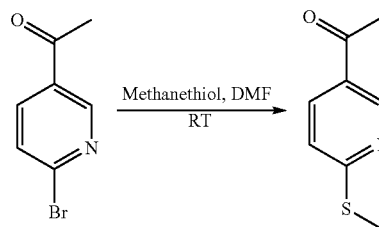
To a stirred solution of 2,5-dibromopyridine (1.0 g, 4.219 mmol) in diethyl ether (10 mL) at -78° C. was added n-Butyl lithium (2.0 mL, 5.0 mmol, 2.5M in hexane) under nitrogen and stirred for 1 h at the same temperature. Dimethyl acetamide (0.58 g, 6.3 mmol) was then added drop wise to the reaction mixture, stirred for 4 h at -78° C. Progress of reaction was monitored by TLC. After comple-

5

tion reaction mass was quenched with ice cold water and partitioned between saturated NH₄Cl solution and EtOAc. The organic layer was washed with brine, dried over sodium sulphate and concentrated under reduced pressure to give 1-(6-bromopyridin-3-yl) ethanone (0.4 g, 47%) as yellow solid

MS: 200.1 [M⁺+1]

Step 2: Synthesis of 1-(6-(methylthio)pyridin-3-yl)ethanone



50

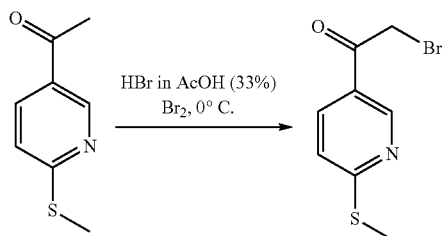
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111

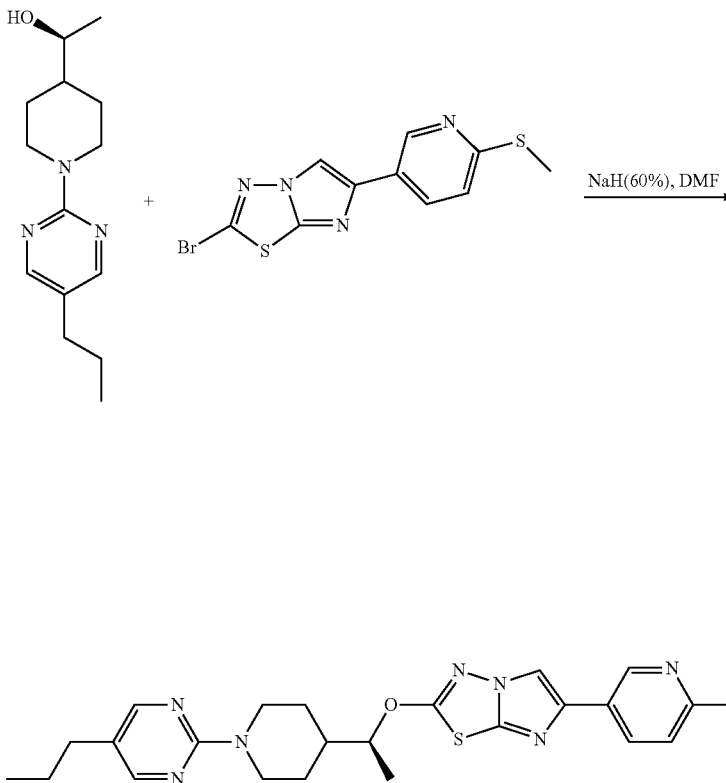
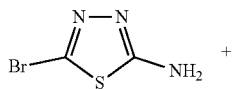
Step 3: Synthesis of
2-bromo-1-(6-(methylthio)pyridin-3-yl)ethanone



To a stirred solution of 1-(6-(methylthio)pyridin-3-yl)ethanone (0.4 g, 2.39 mmol) in 30% HBr in Acetic acid (5.0 mL), Bromine (0.344 g, 2.15 mmol) was added at 0° C. and allowed to stir at 0° C. for next 30 min. Reaction was monitored by TLC. On completion, diethyl ether was added to reaction mixture, solid precipitate out which was filtered off, washed with diethyl ether to afford 2-bromo-1-(6-(methylthio)pyridin-3-yl)ethanone (0.4 g, 68%) as light yellow solid.

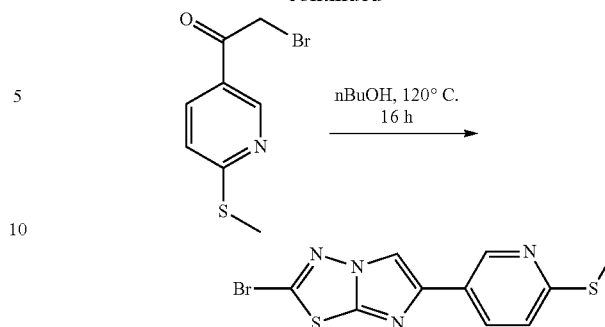
MS: 246.1[M⁺+1].

Step 4: Synthesis of 2-bromo-6-(6-(methylthio)pyridin-3-yl)imidazo[2,1-b][1,3,4]thiadiazole



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-continued



To a stirred solution of 5-amino-2-bromo-1,3,4-thiadiazole (0.440 g, 2.44 mmol) and 2-bromo-1-(6-(methylthio)pyridin-3-yl)ethanone (0.6 g, 2.44 mmol) in n-butanol (20 mL) was heated at 120° C. for 16 h. On completion, all volatiles were evaporated under reduced pressure obtained yellow sticky mass which was purified by silica gel (100-200 Mesh) column chromatography eluent 2% MeOH/DCM obtained 2-bromo-6-(6-(methylthio)pyridin-3-yl)imidazo[2,1-b][1,3,4]thiadiazole (0.25 g, 31%) as yellow solid.

MS: 327.1[M⁺+1]

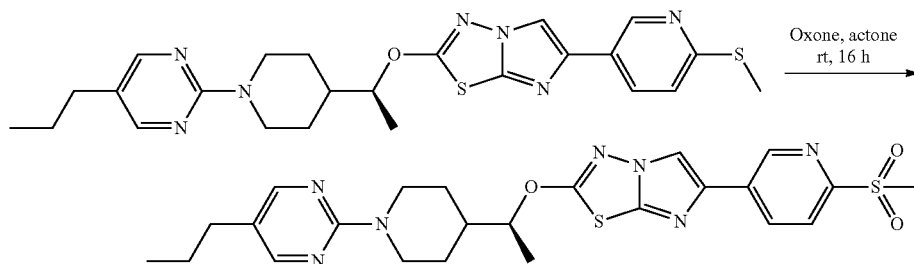
Step 5: Synthesis of 2-((S)-1-(1-(5-propylpyrimidin-2-yl)piperidin-4-yl)ethoxy)-6-(6-(methylthio)pyridin-3-yl)imidazo[2,1-b][1,3,4]thiadiazole

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To (S)-1-(1-(5-propylpyrimidin-2-yl)piperidin-4-yl)ethanol (0.04 g, 0.16 mmol) in DMF (1 mL) was added sodium hydride (0.009 g, 0.24 mmol) at 0° C. and allowed the reaction to stir at 0° C. for 30 min. After 30 min, 2-bromo-6-(6-(methylthio)pyridin-3-yl)imidazo[2,1-b][1,3,4]thiadiazole (0.062 g, 0.19 mmol) in DMF (1 mL) was added to reaction mixture and stirred it at room temperature for 6 h. Reaction was monitored by TLC. On completion, reaction was quenched with ice cold water (2 mL) and extracted with EtOAc. The organic layer was washed with water, brine, dried over Na₂SO₄, evaporated under reduced pressure to give crude product that was purified by silica gel (100 to 200 mesh) chromatography, eluent 2% MeOH/DCM to obtain 2-((S)-1-(1-(5-propylpyrimidin-2-yl)piperidin-4-yl)ethoxy)-6-(6-(methylthio)pyridin-3-yl)imidazo[2,1-b][1,3,4]thiadiazole (0.02 g, 25%) as off-white solid.

MS: 496.1 [M⁺+1]

Step 6: Synthesis of 2-((S)-1-(1-(5-propylpyrimidin-2-yl)piperidin-4-yl)ethoxy)-6-(6-(methylsulfonyl)pyridin-3-yl)imidazo[2,1-b][1,3,4]thiadiazole

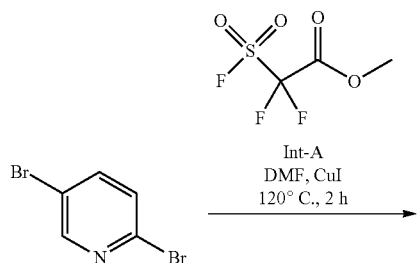


To a stirred solution of 2-((S)-1-(1-(5-propylpyrimidin-2-yl)piperidin-4-yl)ethoxy)-6-(6-(methylthio)pyridin-3-yl)imidazo[2,1-b][1,3,4]thiadiazole (0.02 g, 0.04 mmol) in acetone (5.0 mL), Oxone (0.025 g, 0.08 mmol) in water (2 mL) was added drop wise at room temperature. Allowed the reaction to stir for 16 h. Completion of reaction was monitored by TLC. Reaction mass was evaporated, diluted with water, extracted with EtOAc. Organic portions were combined, dried over Na₂SO₄, evaporated under reduced pressure to obtain crude product as yellow solid which was purified by column chromatography using silica gel (100-200 mesh); eluent 20% acetone in DCM to obtain 2-((S)-1-(1-(5-propylpyrimidin-2-yl)piperidin-4-yl)ethoxy)-6-(6-(methylsulfonyl)pyridin-3-yl)imidazo[2,1-b][1,3,4]thiadiazole (0.01 g, 47%) as off-white solid.

MS: 528.2 [M⁺+1]

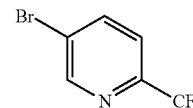
Example 22: 2-((S)-1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)-6-(6-(trifluoromethyl)pyridin-3-yl)imidazo[2,1-b][1,3,4]thiadiazole

Step-1: Synthesis of 5-bromo-2-(trifluoromethyl)pyridine



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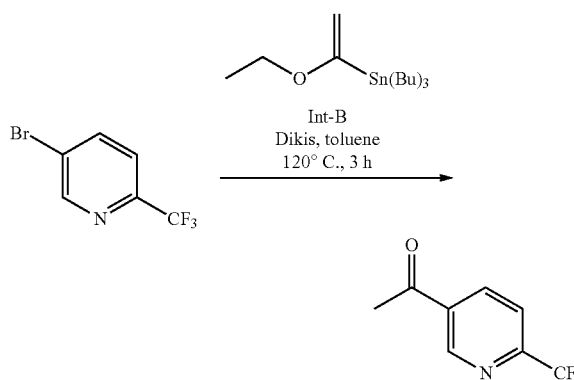
-continued



To a stirred solution of 2,5-dibromopyridine (0.3 g, 1.27 mmol) in DMF (10 mL), CuI (1.69 g, 8.8 mmol) was added and allow to stirred for 30 min. To resultant reaction mass Int-A (1.22 g, 6.3 mmol) was added and stirred for 2 h at RT. Completion of reaction was monitored by TLC. On completion, quenched with ice water, extracted with pentane. The organic layer was washed with water, brine, dried over sodium sulphate, concentrated under reduced pressure obtained crude. Purification of the crude was done via silica gel (100-200 Mesh) column chromatography eluent 15% MDC/n-Hexane to obtained 5-bromo-2-(trifluoromethyl)pyridine (0.07 g, 24.64%) as colourless oily mass.

Mass: 226.2 [M⁺+1]

Step-2: Synthesis of 1-(6-(trifluoromethyl)pyridin-3-yl)ethanone

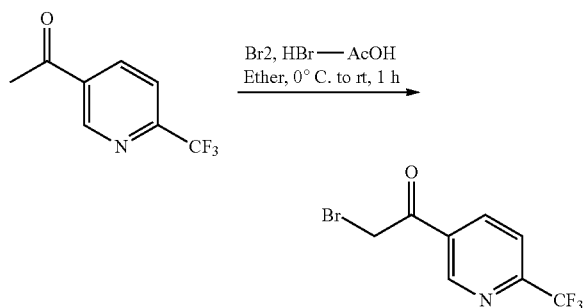


To a stirred solution of 5-bromo-2-(trifluoromethyl)pyridine (0.07 g, 0.31 mmol) in dry toluene (10 mL), Int-B (0.124 g, 0.34 mmol) was added. Purged reaction mass with nitrogen for 30 min. To resultant reaction mass Dikis (0.01 g, 0.015 mmol) was added and stirred at 120° C. for 3 h. Completion of reaction was monitored by TLC. On completion, quenched with ice water, extracted with ether. The organic layer was washed with water, brine, dried over sodium sulphate, concentrated under reduced pressure obtained crude. Purification of the crude was done via silica gel (100-200 Mesh) column chromatography and desired compound eluted at 15% ethyl acetate/n-Hexane to obtained 1-(6-(trifluoromethyl)pyridin-3-yl)ethanone (0.035 g, 59.25%) as off white solid.

Mass: 190.08 [M⁺+1]

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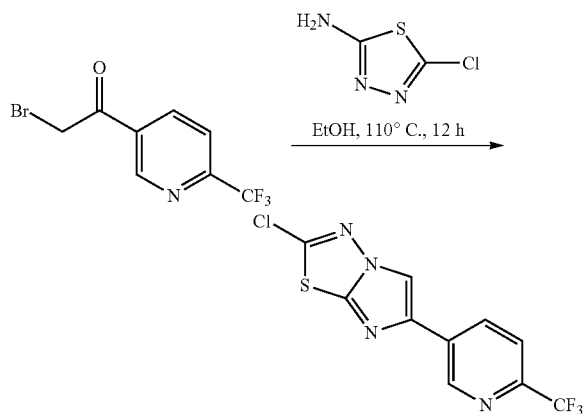
Step-3: Synthesis of 2-bromo-1-(6-(trifluoromethyl)pyridin-3-yl)ethanone



To a stirred solution of 1-(6-(trifluoromethyl)pyridin-3-yl)ethanone (0.035 g, 0.18 mmol) in ether (2 mL) was added HBr—AcOH (0.5 mL). To resultant reaction mass Br₂ (diluted in 0.5 mL HBr—AcOH) (0.027 g, 0.17 mmol) was added at 0° C. and stirred for 30 min. Allow temp to increase gradually to RT. Completion of reaction was monitored by TLC. On completion, quenched with ice water, extracted with ether. The organic layer was washed with aqueous-bicarbonate, brine, dried over sodium sulphate, concentrated under reduced pressure obtained 2-bromo-1-(6-(trifluoromethyl)pyridin-3-yl)ethanone (0.26 g, 86.66%) as semisolid brownish gummy mass.

Mass: 268.2 [M⁺+1]

Step-4: Synthesis of 2-chloro-6-(6-(trifluoromethyl)pyridin-3-yl)imidazo[2,1-b][1,3,4]thiadiazole

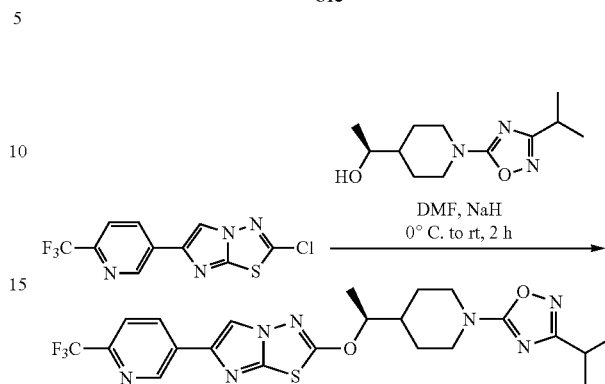


To a stirred solution of 5-amino-2-chloro-1,3,4-thiadiazole (0.179 g, 0.8 mmol) and 2-bromo-1-(6-(trifluoromethyl)pyridin-3-yl)ethanone (0.16 g, 0.84 mmol) in EtOH (5 mL) was heated at 110° C. for 16 h. After cooled to room temperature, concentrated under reduced pressure to obtain crude mass. Purification of the crude was done via silica gel (100-200 Mesh) column chromatography and desired compound eluted at 7% acetone/n-Hexane to obtain 2-chloro-6-(6-(trifluoromethyl)pyridin-3-yl)imidazo[2,1-b][1,3,4]thiadiazole (0.050 g, 32.0%) as off white solid.

MS: 351.0 [M+1]

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Step-5: Synthesis of 2-((S)-1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)-6-(6-(trifluoromethyl)pyridin-3-yl)imidazo[2,1-b][1,3,4]thiadiazole

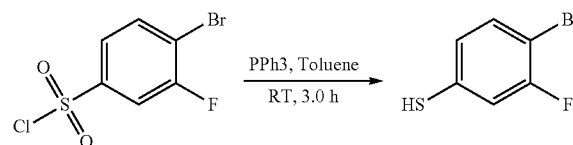


To a stirred solution of (S)-1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethanol (0.035 g, 0.13 mmol) in DMF (2.5 mL), NaH (0.010 mg, 0.30 mmol) was added at 0° C. and stirred for 1 h. To resultant reaction mass, 2-chloro-6-(6-(trifluoromethyl)pyridin-3-yl)imidazo[2,1-b][1,3,4]thiadiazole (0.045 g, 0.143 mmol) was added and stirred for 1 h at RT. Reaction was monitored by TLC. On completion, quenched with water, extracted with ethyl acetate. The organic layer was washed with water, brine, dried over sodium sulphate, concentrated under reduced pressure obtained crude. Purification of the crude was done by silica gel (100-200 Mesh) column chromatography and desired compound eluted at 12% acetone/n-Hexane to obtain 2-((S)-1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)-6-(6-(trifluoromethyl)pyridin-3-yl)imidazo[2,1-b][1,3,4]thiadiazole (0.005 g, 6.70%) as off white solid.

MS: 508.2 [M+1]

Example 23: 2-((S)-1-(1-(5-propylpyrimidin-2-yl)piperidin-4-yl)ethoxy)-6-(2-fluoro-4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazole

Step 1: Synthesis of 4-bromo-3-fluorobenzenethiol



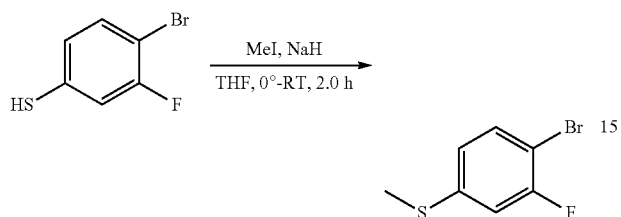
To a stirred soln. of Triphenylphosphine (1.4 gm, 5.48 mmol) in Toluene, compound 4-bromo-3-fluorobenzene-1-sulfonyl chloride (0.5 gm, 1.83 mmol) was added at room temperature and reaction allowed to run at same temperature for 3.0 h. Reaction was monitored by TLC. On completion reaction mixture was quenched by IN HCl and compound was extracted with DCM. The organic layer was dried over sodium sulphate and concentrated under reduced pressure to give crude desired product. Purification of the compound was done by silica gel (100-200 mesh) column chromatog-

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raphy using 1% ethyl acetate in hexane that was concentrated to get compound 4-bromo-3-fluorobenzenethiol (0.23 g, 61.09%) as yellow liquid.

MS: 205.0[M⁻-1].

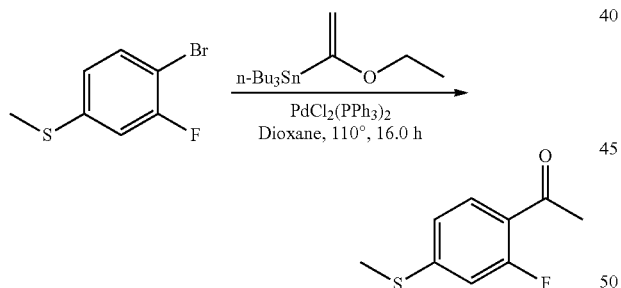
Step 2: Synthesis of
(4-bromo-3-fluorophenyl)(methyl)sulfane



To a stirred soln. of 4-bromo-3-fluorobenzenethiol (0.23 gm, 1.12 mmol) in Dry THF (4.0 ml), sodium hydride (0.05 gm, 1.34 mmol) at 0° C. and reaction allowed to run at 0° C. for 10.0 min. then methyl iodide (0.08 ml, 1.23 mmol) was added to reaction mixture and reaction continued at RT for next 1.5 h. Reaction was monitored by TLC. On completion reaction mixture was quenched with ice cold water and compound was extracted with ethyl acetate. The organic layer was washed with water, brine, dried over sodium sulphate and concentrated under reduced pressure to give desired product (4-bromo-3-fluorophenyl)(methyl)sulfane (0.24 g, 97.69%) as yellow liquid.

MS: 220.94[M⁺+1].

Step 3: Synthesis of
1-(2-fluoro-4-(methylthio)phenyl)ethanone

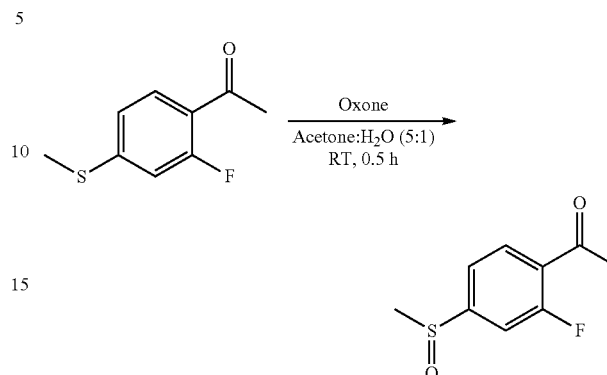


To a stirred soln. of compound (4-bromo-3-fluorophenyl)(methyl)sulfane (0.24 gm, 1.09 mmol) and tributyl(1-ethoxyvinyl)stannane (0.39 gm, 1.09 mmol) in Dioxane (5.0 ml), PdCl₂(PPh₃)₂ (0.04 gm, 0.05 mmol) was added under nitrogen degassing. Reaction allowed to run at 110° C. for 16.0 h. Reaction was monitored by TLC. On completion solvent was evaporated from reaction mixture. Residue was quenched with water, compound was extracted with ethyl acetate. The organic layer was concentrated under reduced pressure to get crude desired product. Purification of the compound was done by silica gel (100-200 mess) column chromatography using 3% ethyl acetate in hexane that was concentrated to get compound 1-(2-fluoro-4-(methylthio)phenyl)ethanone (0.12 g, 59.76%) as yellow solid.

MS: 185.1[M⁺+1].

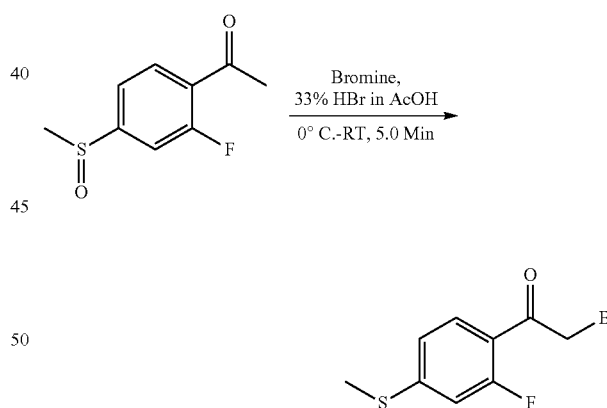
118

Step 4: Synthesis of
1-(2-fluoro-4-(methylsulfinyl)phenyl)ethanone



To a stirred soln. of compound 1-(2-fluoro-4-(methylthio)phenyl)ethanone (0.2 gm, 1.09 mmol) in Acetone (5.0 ml), Oxone (0.34 gm, 1.09 mmol) in Water (1.0 ml) was added and reaction continued at RT for 0.5 h. Progress of reaction was monitored by TLC. On completion acetone was evaporated from reaction mixture and residue was quenched with water, compound was extracted with ethyl acetate. The organic layer was concentrated under reduced pressure to get compound 1-(2-fluoro-4-(methylsulfinyl)phenyl)ethanone (0.2 g, 92.02%) white semi solid. MS: 201.1[M⁺+1].

Step 5: Synthesis of
2-bromo-1-(2-fluoro-4-(methylthio)phenyl)ethanone

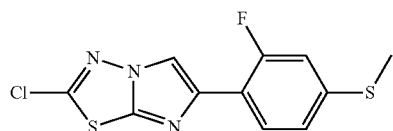
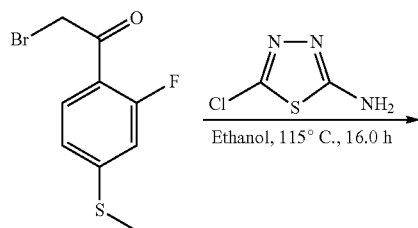


To a stirred soln. of 1-(2-fluoro-4-(methylsulfinyl)phenyl)ethanone (0.05 gm, 0.25 mmol) in 33% HBr in Acetic acid (0.5 ml), Bromine (0.04 gm, 0.22 mmol) in 0.2 ml HBr in AcOH was added at 0° C. and reaction allowed to run at RT for next 5.0 min. Reaction was monitored by TLC. On completion reaction mixture was quenched with ice cold water and compound was extracted with di ethyl ether. The organic layer was washed with water, brine, dried over sodium sulphate and concentrated under reduced pressure to get crude compound 2-bromo-1-(2-fluoro-4-(methylthio)phenyl)ethanone (0.05 g, Crude) as yellow semi solid.

MS: 262.95[M⁺+1].

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Step 6: Synthesis of 2-chloro-6-(2-fluoro-4-(methylthio)phenyl)imidazo[2,1-b][1,3,4]thiadiazole

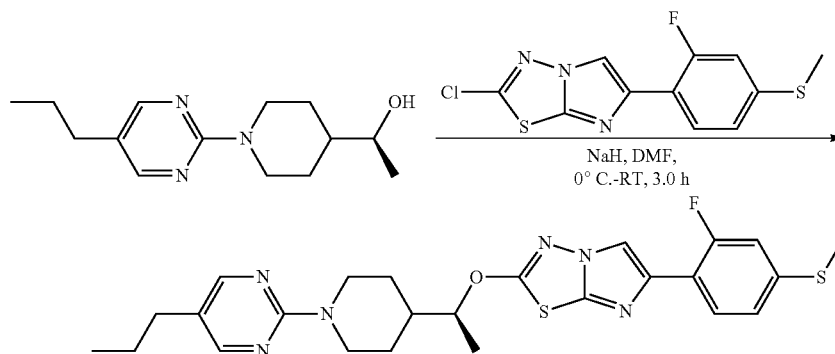


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To a stirred soln. of 2-bromo-1-(2-fluoro-4-(methylthio)phenyl)ethanone (0.3 gm, 1.15 mmol) in Ethanol (6.0 ml), 5-chloro-1,3,4-thiadiazol-2-amine (0.15 gm, 1.15 mmol) was added at RT and reaction allowed to run at 115° C. for 16.0 h. Reaction was monitored by TLC. On completion reaction mixture was concentrated under reduced pressure to get crude desired product. Purification of the compound was done by silica gel (100-200 mess) column chromatography using 15% ethyl acetate in hexane that was concentrated to get compound 2-chloro-6-(2-fluoro-4-(methylthio)phenyl)imidazo[2,1-b][1,3,4]thiadiazole (0.06 g, 17.52%) as yellow solid.

MS: 300.0[M⁺+1].

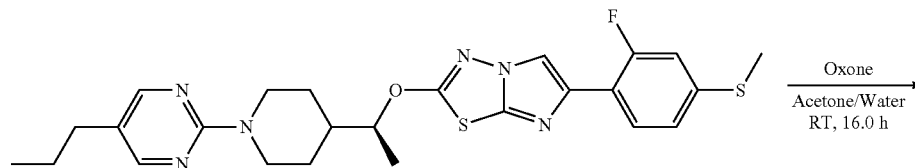
Step 7: Synthesis of 2-((S)-1-(1-(5-propylpyrimidin-2-yl)piperidin-4-yl)ethoxy)-6-(2-fluoro-4-(methylthio)phenyl)imidazo[2,1-b][1,3,4]thiadiazole



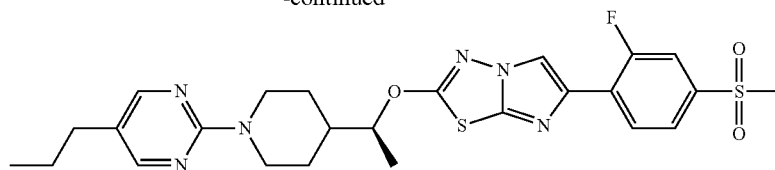
To a stirred soln. of (S)-1-(1-(5-propylpyrimidin-2-yl)piperidin-4-yl)ethanol (0.015 gm, 0.06 mmol) in DMF (3.0 ml), sodium hydride (0.004 gm, 0.09 mmol) at 0° C. and reaction allowed to run at 0° C. for 30.0 min. then 2-chloro-6-(2-fluoro-4-(methylthio)phenyl)imidazo[2,1-b][1,3,4]thiadiazole (0.02 gm, 0.07 mmol) was added to reaction mixture and reaction continued at RT for next 3.0 h. Reaction was monitored by TLC. On completion reaction mixture was quenched with ice cold water and compound was extracted with ethyl acetate. The organic layer was washed with water, brine, dried over sodium sulphate and concentrated under reduced pressure to give crude desired product. Purification of the compound was done by silica gel (100-200 mess) column chromatography using 20% Acetone in hexane that was concentrated to get compound 2-((S)-1-(1-(5-propylpyrimidin-2-yl)piperidin-4-yl)ethoxy)-6-(2-fluoro-4-(methylthio)phenyl)imidazo[2,1-b][1,3,4]thiadiazole (0.012 g, 38.92%) as white solid.

MS: 513.18[M⁺+1].

Step 8: Synthesis of 2-((S)-1-(1-(5-propylpyrimidin-2-yl)piperidin-4-yl)ethoxy)-6-(2-fluoro-4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazole



-continued

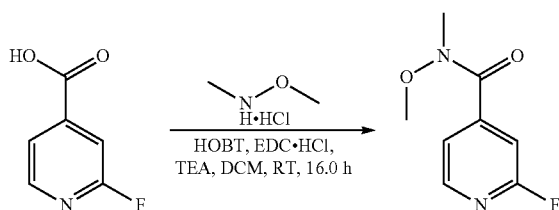


To a stirred soln. of compound 2-((S)-1-(1-(5-propylpyrimidin-2-yl)piperidin-4-yl)ethoxy)-6-(2-fluoro-4-(methylthio)phenyl)imidazo[2,1-b][1,3,4]thiadiazole (0.01 gm, 0.02 mmol) in Acetone (2.0 ml), Oxone (0.01 gm, 0.04 mmol) in Water (0.5 ml) was added and reaction continued at RT for 16.0 h. Progress of reaction was monitored by TLC. On completion acetone was evaporated from reaction mixture and residue was quenched with water, compound was extracted with ethyl acetate. The organic layer was concentrated under reduced pressure to give crude desired compound. Purification of the compound was done by silica gel (100-200 mesh) column chromatography using 20% Acetone in hexane that was concentrated to get compound 2-((S)-1-(1-(5-propylpyrimidin-2-yl)piperidin-4-yl)ethoxy)-6-(2-fluoro-4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazole (0.008 g, 75.33%) white solid.

MS: 545.17[M⁺+1].

Example 23: 2-((S)-1-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yl)ethoxy)-6-(2-methoxypyridin-4-yl)imidazo[2,1-b][1,3,4]thiadiazole

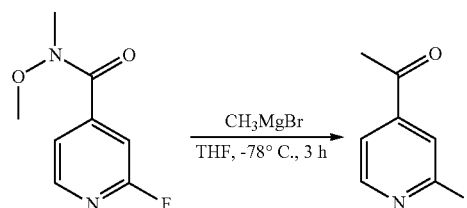
Step 1: Synthesis of 3-fluoro-N-methoxy-N-methylpyridine-4-carboxamide



To a stirred solution of 3-fluoropyridine-4-carboxylic acid (1 g, 7.09 mmol) and N-methoxymethanamine hydrochloride (1 g, 10.63 mmol) in DCM (20 mL) was added EDCI (1.3 g, 10.63 mmol), HOBT (1.4 g, 10.63 mmol) and DIPEA (3.6 mL, 21.01 mmol) then reaction mixture was stirred at rt for 16 hr. Reaction was monitored by TLC. On completion reaction was quenched with water and reaction mixture extracted with ethyl acetate. Organic layer was washed with water, brine dried over sodium sulphate and concentrated under reduced pressure to give crude. Purification of the crude was done by silica gel (100-200 Mesh) column chromatography; eluent 1% EA/HEX give (1.2 g) (99%) 3-fluoro-N-methoxy-N-methylpyridine-4-carboxamide of as reddish colour sticky solid.

MS: 186[M⁺+1]

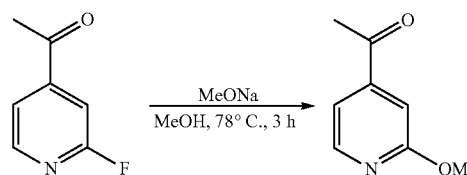
Step 2: Synthesis of 1-(2-fluoropyridin-4-yl)ethanone



To a stirred solution of 3-fluoro-N-methoxy-N-methylpyridine-4-carboxamide (1.2 g, 0.65 mmol) in THF (15 mL) was added methyl magnesium bromide (2 M in THF) (16 mL, 32.5 mmol) at 0° C., after the addition the mixture was stirred at rt for 2 h. On completion reaction mixture was quenched with NH₄Cl solution and reaction mixture was extracted with EtOAc. The organic layer was washed with water, brine, dried over Na₂SO₄ and evaporated under reduced pressure to give 0.650 gm. (92%) 1-(3-fluoropyridin-4-yl) ethanone as colourless oil

MS: 140.1[M⁺+1]

Step 3: Synthesis of 1-(2-methoxypyridin-4-yl) ethanone

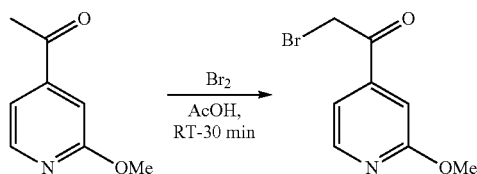


To a stirred solution of 1-(2-fluoropyridin-4-yl) ethanone (1.2 g, 0.65 mmol) in MeOH (15 mL) was added Sodium methoxide (1.6, 32.5 mmol) at 0° C., after the addition the mixture was stirred at 90° C. for 2 h. On completion reaction mixture was concentrated solution and reaction mixture was extracted with EtOAc. The organic layer was washed with water, brine, dried over Na₂SO₄ and evaporated under reduced pressure to give 0.650 gm. (92%) 1-(2-methoxypyridin-4-yl) ethanone as colourless oil

MS: 152.1[M⁺+1]

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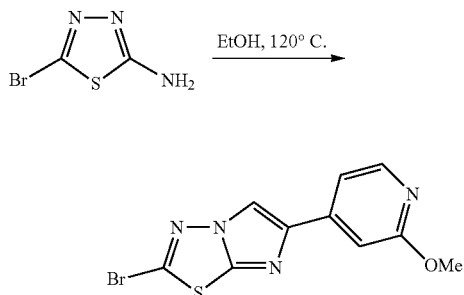
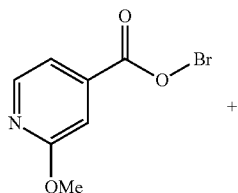
Step 4: Synthesis of
2-bromo-1-(2-methoxypyridin-4-yl) ethanone



To a stirred solution of 1-(2-methoxypyridin-4-yl) ethanone (0.15 g, 1.07 mmol) in HBr:AcOH (10:5 mL) was added Br₂ (0.052 mL, 1.07 mmol) in AcOH 1.0 mL drop wise at 0° C. and stirred for 1 hr. Completion of reaction was monitored by TLC. Diethyl ether was added to reaction mass, solid precipitate out which was filtered off through Buchner funnel, solid was washed with diethyl ether, dried under vacuum to obtained pure product (0.2 g, 90%) 2-bromo-1-(2-methoxypyridin-4-yl)ethanone as yellow solid.

MS: 230.96[M⁺+2]

Step 5: Synthesis of 2-bromo-6-(2-methoxypyridin-4-yl) imidazo [2,1-b][1,3,4]thiadiazole

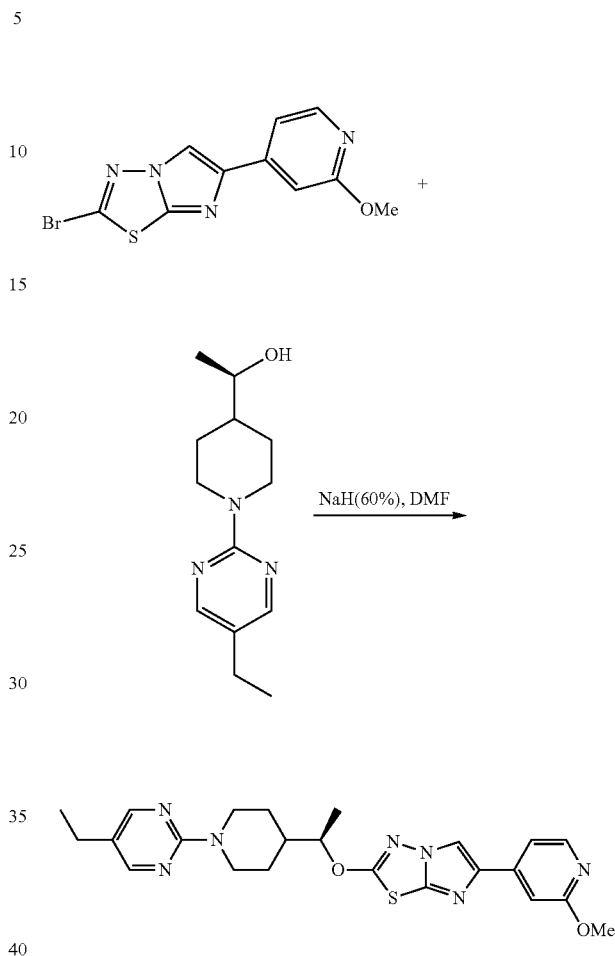


To a stirred solution of 2-bromo-1-(2-methoxypyridin-4-yl) ethanone (0.2 g, 0.92 mmol) in EtOH (10 mL) was added 5-bromo-1,3,4-thiadiazol-2-amine (0.2 g, 1.11 mmol) and heated at 120° C. for 12 hr. Completion of reaction was monitored by TLC. After 12 hr. of heating solid precipitate out at rt which was filtered off through Buchner funnel, solid product was washed with diethyl ether, dried under vacuum to obtained pure product 2-bromo-6-(2-methoxypyridin-4-yl)imidazo[2,1-b][1,3,4]thiadiazole (0.080 g, 28%) as light yellow solid.

MS: 311.95 [M⁺+2]

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Step 6: Synthesis of 2-((R)-1-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yl)ethoxy)-6-(2-methoxypyridin-4-yl)imidazo[2,1-b][1,3,4]thiadiazole

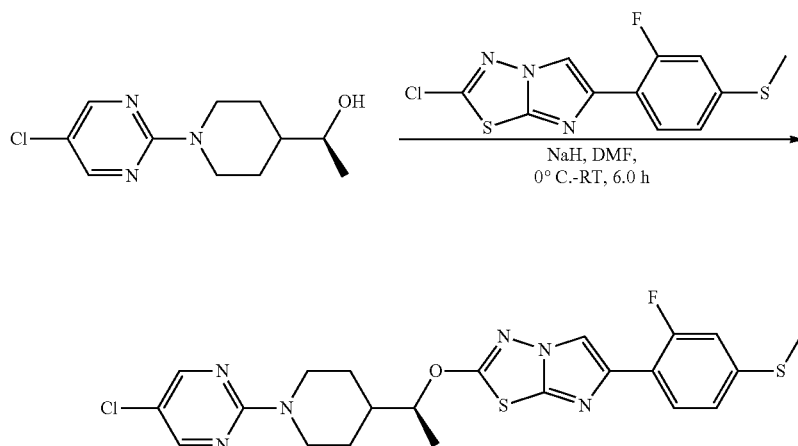


To (S)-1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethanol (0.020 g, 0.15 mmol) in DMF (1 ml) was added sodium hydride (0.009 g, 0.23 mmol) at 0° C. and reaction allowed to run at 0° C. for 30 min. After 30 min 2-bromo-6-(3-fluoropyridin-4-yl)imidazo[2,1-b][1,3,4]thiadiazole (0.036 g, 0.15 mmol) in DMF (1 mL) was added to reaction mixture and reaction stirred at RT for 2 hr. Reaction was monitored by TLC. On completion, reaction was quenched with ice cold water (2 mL) and reaction mixture extracted with EtOAc. The organic layer was washed with water, brine, dried over Na₂SO₄, evaporated under reduced pressure to give crude desired product that was purified by silica gel (100 to 200 mesh) chromatography, eluent 1% MeOH/DCM to obtained pure product 2-((R)-1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)-6-(3-fluoropyridin-4-yl)imidazo[2,1-b][1,3,4]thiadiazole (0.003 g, 27%) as off white solid.

MS: 466.23 [M⁺+1]

Example 24: 2-((S)-1-(1-(5-chloropyrimidin-2-yl)piperidin-4-yl)ethoxy)-6-(2-fluoro-4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazole

Step 1: Synthesis of 2-((S)-1-(1-(5-chloropyrimidin-2-yl)piperidin-4-yl)ethoxy)-6-(2-fluoro-4-(methylthio)phenyl)imidazo[2,1-b][1,3,4]thiadiazole



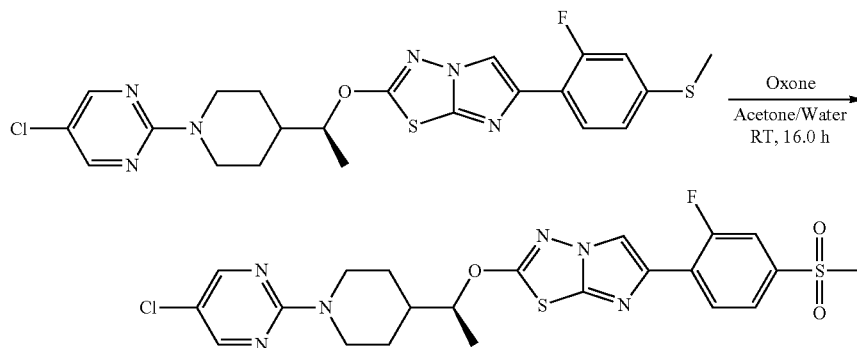
To a stirred soln. of (S)-1-(1-(5-chloropyrimidin-2-yl)piperidin-4-yl)ethanol (0.015 gm, 0.06 mmol) in DMF (2.0 ml), sodium hydride (0.004 gm, 0.09 mmol) at 0° C. and reaction allowed to run at 0° C. for 30.0 min. then 2-chloro-6-(2-fluoro-4-(methylthio)phenyl)imidazo[2,1-b][1,3,4]thiadiazole (0.023 gm, 0.07 mmol) was added to reaction mixture and reaction continued at RT for next 6.0 h. Reaction was monitored by TLC. On completion reaction mixture was quenched with ice cold water and compound was extracted with ethyl acetate. The organic layer was washed with water, brine, dried over sodium sulphate and concentrated under reduced pressure to give crude desired product. Purification of the compound was done by silica gel (100-200 mess) column chromatography using 15% Acetone in hexane that was concentrated to get compound 2-((S)-1-(1-(5-chloropyrimidin-2-yl)piperidin-4-yl)ethoxy)-6-(2-fluoro-4-(methylthio)phenyl)imidazo[2,1-b][1,3,4]thiadiazole (0.015 g, 47.83%) as light yellow semi solid.

MS: 505.10[M⁺+1].

Step 2: Synthesis of 2-((S)-1-(1-(5-chloropyrimidin-2-yl)piperidin-4-yl)ethoxy)-6-(2-fluoro-4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazole

To a stirred soln. of compound 2-((S)-1-(1-(5-chloropyrimidin-2-yl)piperidin-4-yl)ethoxy)-6-(2-fluoro-4-(methylthio)phenyl)imidazo[2,1-b][1,3,4]thiadiazole (0.015 g, 0.03 mmol) in Acetone (3.0 ml), Oxone (0.018 g, 0.06 mmol) in water (0.7 ml) was added and reaction continued at RT for 16.0 h. Progress of reaction was monitored by TLC. On completion acetone was evaporated from reaction mixture and residue was quenched with water, compound was extracted with ethyl acetate. The organic layer was concentrated under reduced pressure to give crude desired compound. Purification of the compound was done by silica gel (100-200 mess) column chromatography using 15% Acetone in hexane that was concentrated to get compound 2-((S)-1-(1-(5-chloropyrimidin-2-yl)piperidin-4-yl)ethoxy)-6-(2-fluoro-4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazole (0.006 g, 37.62%) white solid.

MS: 537.09[M⁺+1].

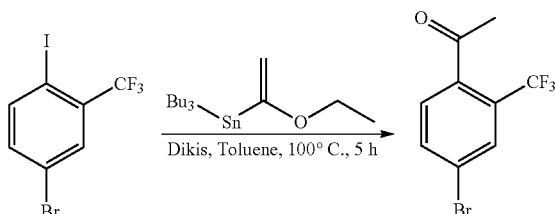


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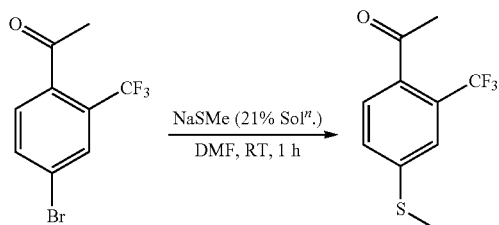
Example 25: 2-(1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)-6-(2-(trifluoromethyl)-4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazole

Step 1:

1-(4-bromo-2-(trifluoromethyl)phenyl)ethanone

MS: 266.9 [M⁺+1]

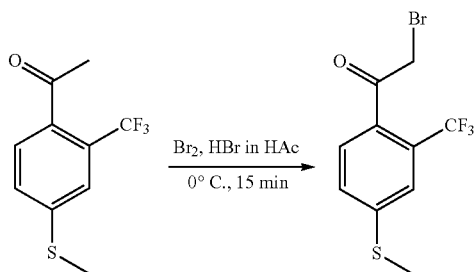
Step 2: 1-(2-(trifluoromethyl)-4-(methylthio)phenyl)ethanone



To a stirred solution of 1-(4-bromo-2-(trifluoromethyl)phenyl)ethanone (0.630 g, 2.359 mmol) in DMF (10 mL) was added 21% aq. solution of sodium thiomethoxide (0.215 mg, 3.06 mmol) at 0° C. and stirred for 1 h at room temperature. Progress of reaction was monitored by TLC. On completion, D.M. water was added to reaction mixture and extracted with EtOAc. Organic layers were combined, dried over sodium sulphate and concentrated under reduced pressure to give crude product. Crude product was purified by column chromatography using (silica gel, 100-200 mesh, 0-8% EtOAc in hexane as eluent) to give 1-(2-(trifluoromethyl)-4-(methylthio)phenyl)ethanone (0.4 g, 72.4%) as yellow oil.

MS: 235.03 [M⁺+1]

Step-3: 2-bromo-1-(2-(trifluoromethyl)-4-(methylthio)phenyl)ethanone



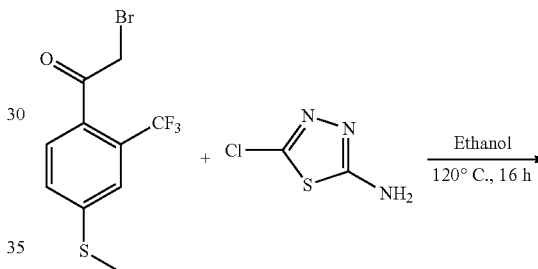
128

To a stirred solution of 1-(2-(trifluoromethyl)-4-(methylthio)phenyl)ethanone (0.250 g, 1.068 mmol) in acetic acid (5 mL) was added solution of bromine (0.154 g, 0.961 mmol) in 47% HBr in acetic acid (0.8 mL) at 0° C. and stirred for 15 min. Progress of reaction was monitored by TLC. On completion, cold D.M. water was added to reaction mixture and extracted with Diethyl ether. Organic layers were combined, dried over sodium sulphate and concentrated under reduced pressure to give 2-bromo-1-(2-(trifluoromethyl)-4-(methylthio)phenyl)ethanone (0.32 g, 95.69%) as Brown gum.

MS: 312.9 [M⁺+1]

Step-4: 2-chloro-6-(2-(trifluoromethyl)-4-(methylthio)phenyl)imidazo[2,1-b][1,3,4]thiadiazole

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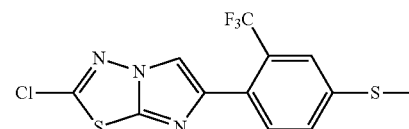


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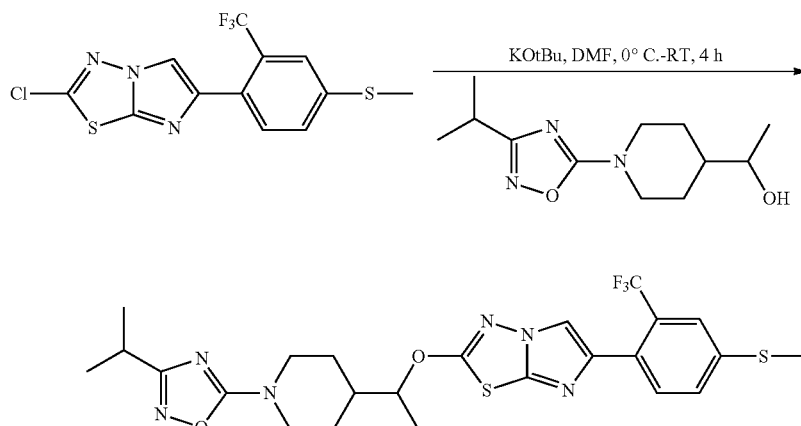
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Solution of 2-bromo-1-(2-(trifluoromethyl)-4-(methylthio)phenyl)ethanone (0.320 g, 1.022 mmol) and 5-chloro-1,3,4-thiadiazol-2-amine (0.138 g, 1.022 mmol) in ethanol (10 mL) was heated to 120° C. for 16 h in a sealed tube. Progress of reaction was monitored by TLC. After reaction completion reaction mixture was concentrated to dryness. D.M. water was added to reaction mixture and extracted with EtOAc. Organic layers were combined, washed with brine, dried over sodium sulphate and concentrated under reduced pressure to give crude product. Crude product was purified by column chromatography using (silica gel, 100-200 mesh, 0-2% MeOH in DCM as eluent) to give 2-chloro-6-(2-(trifluoromethyl)-4-(methylthio)phenyl)imidazo[2,1-b][1,3,4]thiadiazole (0.028 g, 7.94%) as brown solid.

MS: 349.9 [M⁺+1]

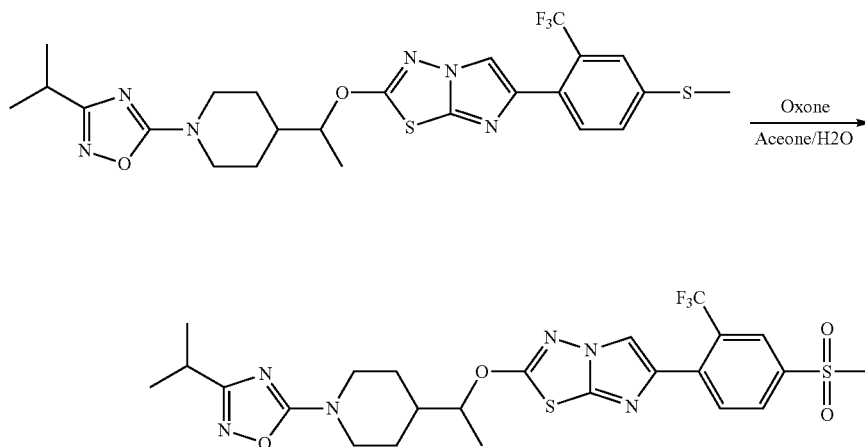
Step 5: 2-(1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)-6-(2-(trifluoromethyl)-4-(methylthio)phenyl)imidazo[2,1-b][1,3,4]thiadiazole



To a stirred solution of 1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethanol (0.015 g, 0.063 mmol) in DMF (3 mL) was added KOtBu (0.010 g, 0.094 mmol) at 0° C. and stirred for 45 min at 0° C. Then to it, solution of 2-chloro-6-(2-(trifluoromethyl)-4-(methylthio)phenyl)imidazo[2,1-b][1,3,4] thiadiazole (0.022 g, 0.063 mmol) in DMF (1 mL) was added to the reaction mixture and stirred for 4 h at room temperature. Progress of reaction was monitored by TLC. After completion of reaction mass was quenched with ice cold water and extracted with ethyl acetate. The organic layer was washed with water, dried over sodium sulphate and concentrated under reduced pressure to give crude product which was purified by column chromatography using (silica gel, 100-200 mesh, 0-2% MeOH in DCM as eluent) to give 2-(1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)-6-(2-(trifluoromethyl)-4-(methylthio)phenyl)imidazo[2,1-b][1,3,4]thiadiazole (0.012 g, 34.2%) as colourless gum.

MS: 513.16 [M⁺+1]

Step 6: 2-(1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)-6-(2-(trifluoromethyl)-4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazole



To a stirred solution of 2-(1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)-6-(2-(trifluoromethyl)-4-(methylthio)phenyl)imidazo[2,1-b][1,3,4]thiadiazole (0.012 g, 0.021 mmol) in acetone (8 mL) and water (2 mL) was added oxone (0.020 g, 0.065 mmol) and the mixture was stirred at room temperature for 16 h and then heated at 40° C. for 3 h. Progress of reaction was monitored by TLC. D.M. water was added to reaction mixture and extracted with EtOAc. Organic layers were combined, washed with brine, dried over sodium sulphate and concentrated under reduced pressure to give crude product. Crude product was purified by column chromatography using (silica gel, 100-200 mesh, 0-2% MeOH in DCM as eluent) followed by (Neutral alumina, 0-4% Acetone:DCM as eluent) to give 2-(1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)-6-(2-(trifluoromethyl)-4-(methylsulfonyl) phenyl)imidazo[2,1-b][1,3,4]thiadiazole (0.002 g, 14.97%) as off white sticky solid.

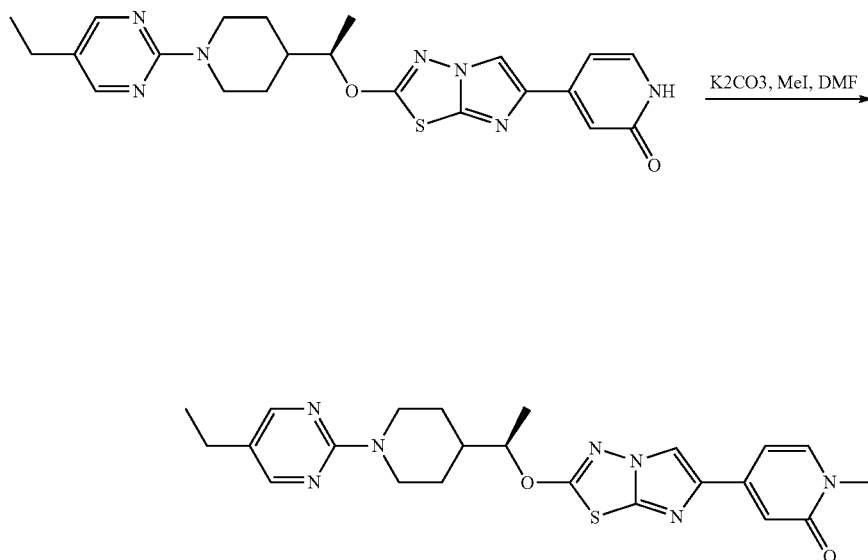
MS: 553.16 [M⁺+1]

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Example 26: 4-(2-((S)-1-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yl)ethoxy)imidazo[2,1-b][1,3,4]thiadiazol-6-yl)-1-methylpyridin-2(1H)-one

Step 1: Synthesis of 4-(2-((S)-1-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yl)ethoxy)imidazo[2,1-b][1,3,4]thiadiazol-6-yl)-1-methylpyridin-2(1H)-one

5



To a stirred soln. 4-(2-((S)-1-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yl)ethoxy)imidazo[2,1-b][1,3,4]thiadiazol-6-yl)pyridin-2(1H)-one (0.015 gm, 0.0655 mmol) in DMF (3.0 ml), potassium carbonate (0.006 gm, 0.15 mmol) at 0° C. and reaction allowed to run at 0° C. for 30.0 min. then MeI (0.021 gm, 0.720 mmol) followed by 18 crown 6 (catalytic) was added to reaction mixture and reaction continued at RT for next 5.0 h. Reaction was monitored by TLC. On completion reaction mixture was quenched with water and compound was extracted with ethyl acetate. The organic layer was washed with water, brine, dried over sodium sulphate and concentrated under reduced pressure to give crude desired product. Purification of the compound was done by silica gel (100-200 mess) column chromatography using

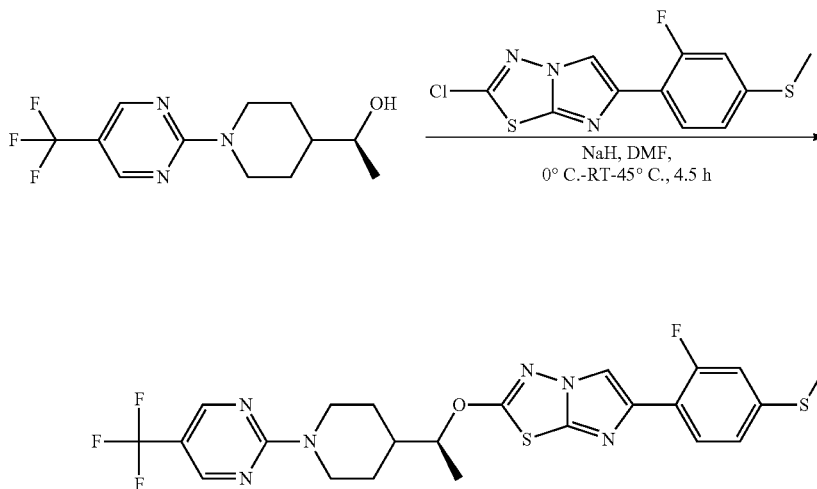
15% Acetone in hexane that was concentrated to get compound 4-(2-((S)-1-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yl)ethoxy)imidazo[2,1-b][1,3,4]thiadiazol-6-yl)-1-methylpyridin-2(1H)-one (0.015 gm, 32.50%) as Greenish colour solid. MS: 465.23 [M⁺+1]

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Example 27: 2-((S)-1-(1-(5-(trifluoromethyl)pyrimidin-2-yl)piperidin-4-yl)ethoxy)-6-(2-fluoro-4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazole

Step 1: Synthesis of 2-((S)-1-(1-(5-(trifluoromethyl)pyrimidin-2-yl)piperidin-4-yl)ethoxy)-6-(2-fluoro-4-(methylthio)phenyl)imidazo[2,1-b][1,3,4]thiadiazole

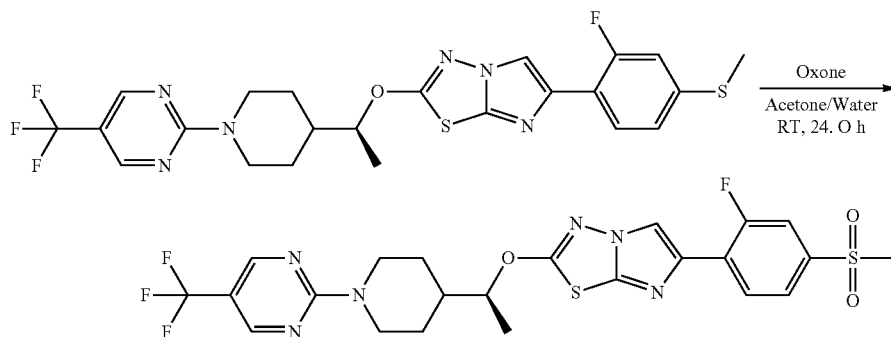


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To a stirred soln. of (S)-1-(1-(5-(trifluoromethyl)pyrimidin-2-yl)piperidin-4-yl)ethanol (0.015 gm, 0.05 mmol) in DMF (2.0 ml), sodium hydride (0.012 gm, 0.33 mmol) at 0° C. and reaction allowed to run at 0° C. for 30.0 min. then 2-chloro-6-(2-fluoro-4-(methylthio)phenyl)imidazo[2,1-b][1,3,4]thiadiazole (0.026 gm, 0.09 mmol) was added to reaction mixture and reaction continued at RT to 45° C. for next 4.0 h. Reaction was monitored by TLC. On completion reaction mixture was quenched with ice cold water and compound was extracted with ethyl acetate. The organic layer was washed with water, brine, dried over sodium sulphate and concentrated under reduced pressure to give crude desired product. Purification of the compound was done by silica gel (100-200 mess) column chromatography using 15% Acetone in hexane that was concentrated to get compound 2-((S)-1-(1-(5-(trifluoromethyl)pyrimidin-2-yl)piperidin-4-yl)ethoxy)-6-(2-fluoro-4(methylthio)phenyl)imidazo[2,1-b][1,3,4]thiadiazole (0.015 gm, 51.12%) as light yellow semi solid.

MS: 539.66 [M⁺+1].

Step 2: Synthesis of 2-((S)-1-(1-(5-(trifluoromethyl)pyrimidin-2-yl)piperidin-4-yl)ethoxy)-6-(2-fluoro-4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazole (MKP10275.01)



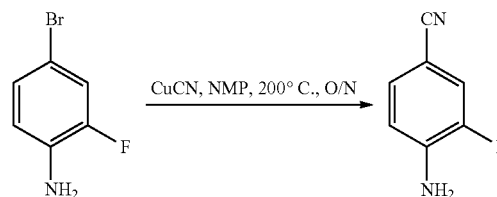
To a stirred soln. of compound 2-((S)-1-(1-(5-(trifluoromethyl)pyrimidin-2-yl)piperidin-4-yl)ethoxy)-6-(2-fluoro-4-(methylthio)phenyl)imidazo[2,1-b][1,3,4]thiadiazole (0.015 gm, 0.03 mmol) in Acetone (4.0 ml), Oxone (0.017 g, 0.06 mmol) in water (0.5 ml) was added and reaction continued at RT for 24.0 h. Progress of reaction was monitored by TLC. On completion acetone was evaporated from reaction mixture and residue was quenched with water, compound was extracted with ethyl acetate. The organic layer was concentrated under reduced pressure to give crude desired compound. Purification of the compound was done by silica gel (100-200 mess) column chromatography using 20% Acetone in hexane that was concentrated to get compound 2-((S)-1-(1-(5-(trifluoromethyl)pyrimidin-2-yl)piperidin-4-yl)ethoxy)-6-(2-fluoro-4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazole (0.01 gm, 62.93%) white solid.

MS: 571.73 [M⁺+1].

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Example 28: 4-(2-((S)-1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)imidazo[2,1-b][1,3,4]thiadiazol-6-yl)-3-fluorobenzonitrile

Step 1: Synthesis of 4-amino-3-fluorobenzonitrile

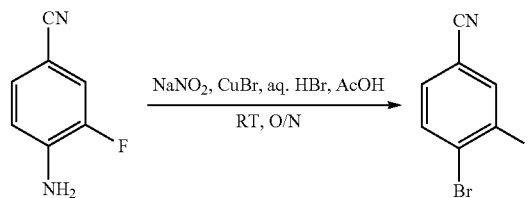


To a solution of 4-bromo-2-fluorobenzaniline (3 g, 15.789 mmol) in NMP (6 mL) was added copper cyanide (2.8 g, 31.578 mmol) and heated overnight at 200° C. in a sealed tube. Progress of reaction was monitored by TLC. After reaction completion, 2-diaminoethane (3 mL) and reaction mixture was poured into water. Product was extracted with ethyl acetate and washed with 10% 1,2-diaminoethane solution in water and then with water.

Organic layer was dried over sodium sulphate, concentrated under reduced pressure. Crude was purified by silica (100-200) column chromatography using 15% ethyl acetate in hexane as eluent to give 4-amino-3-fluorobenzonitrile (1.6 g, 74.76%) as white solid.

MS: 137.1 [M+1]

Step 2: Synthesis of 4-bromo-3-fluorobenzonitrile



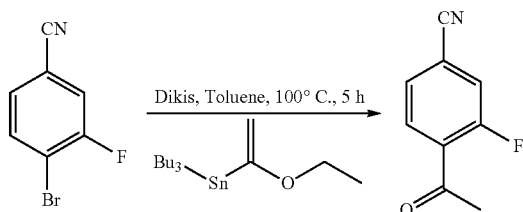
To conc. sulphuric acid (6 mL) was added sodium nitrite (0.97 g, 14.117 mmol) portion wise at 5° C. and stirred for 30 min at RT. Mixture was cooled to 0° C. and acetic acid (9.8 mL) was added dropwise, stirred for 5 min and then 4-amino-3-fluorobenzonitrile (1.6 g, 11.764 mmol) was added in small portions. Mixture was stirred for 1 h at RT.

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Solution of copper (I) bromide (2.5 g, 17.647 mmol) in aq. HBr (6 mL) was then added at 10° C. The resulting mixture was stirred overnight at RT. Progress of reaction was monitored by TLC. After reaction completion water was added and extracted with diethyl ether. The organic layer was dried over sodium sulphate and concentrated under reduced pressure. Crude was purified by silica (100-200) column chromatography using 2% ethyl acetate in hexane as eluent to give 4-bromo-3-fluorobenzonitrile (0.8 g, 34.7%) as white solid.

MS: 201.1 [M+1]

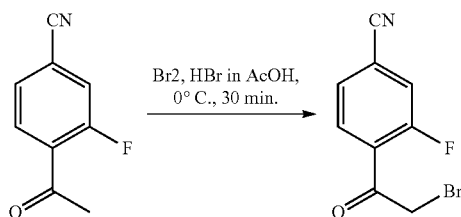
Step 3: Synthesis of 4-acetyl-3-fluorobenzonitrile



To a stirred solution of 4-bromo-3-fluorobenzonitrile (0.5 g, 2.512 mmol) in toluene (5 mL) was added tributyl(1-ethoxyvinyl)stannane (0.99 g, 2.763). Dikis (0.088 g, 0.125 mmol) was added after degassing the mixture for 30 min. with nitrogen. The resulting mixture was then heated to 110° C. for 4 h. Progress of reaction was monitored by TLC. After reaction completion water (5 mL) was added to the reaction mixture and the product extracted with ethyl acetate. The organic layer was dried over sodium sulphate, concentrated under reduced pressure. Crude was purified by silica (100-200) column chromatography using 2% ethyl acetate in hexane as eluent to give 4-acetyl-3-fluorobenzonitrile (0.3 g, 70.5%) as white solid.

MS: 164.1 [M+1]

Step 4: Synthesis of 4-(2-bromoacetyl)-3-fluorobenzonitrile

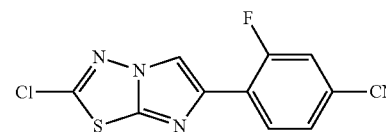
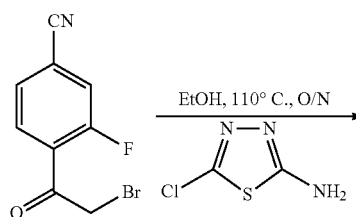


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To a stirred solution of 4-acetyl-3-fluorobenzonitrile (0.3 g, 1.84 mmol) in 47% HBr in acetic acid (3 mL) was added solution of bromine (0.26 g, 1.656 mmol) in 47% HBr in acetic acid (0.3 mL) at 0° C. and stirred for 15 min. Progress of reaction was monitored by TLC. After reaction completion added water and product extracted with ethyl acetate. Organic washed with saturated aq. solution of sodium bicarbonate, dried over sodium sulphate and concentrated to give 4-(2-bromoacetyl)-3-fluorobenzonitrile (0.3 g, 67.4%) as yellow solid.

MS: 243.08 [M+1]

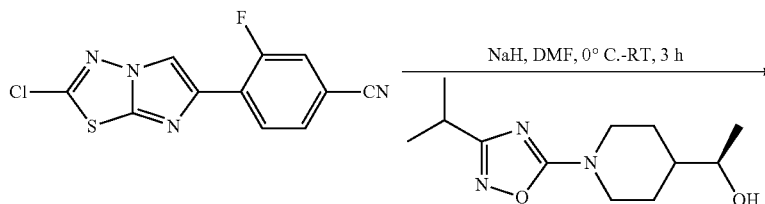
Step 5: Synthesis of 4-(2-chloroimidazo[2,1-b][1,3,4]thiadiazol-6-yl)-3-fluorobenzonitrile



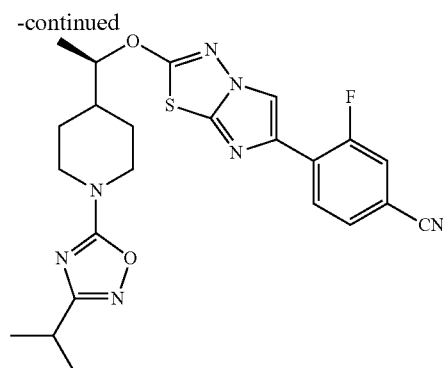
Solution of 4-(2-bromoacetyl)-3-fluorobenzonitrile (0.3 g, 1.239 mmol) and 5-chloro-1,3,4-thiadiazol-2-amine (0.13 g, 0.991 mmol) in ethanol (3 mL) was heated to 110° C. for 16 h in a sealed tube. Progress of reaction was monitored by TLC. After reaction completion reaction mixture was concentrated to dryness. Crude was purified by silica (100-200) column chromatography using 70% DCM/hexane to DCM as eluent to give 4-(2-chloroimidazo[2,1-b][1,3,4]thiadiazol-6-yl)-3-fluorobenzonitrile (0.15 g, 43.6%) as white solid.

MS: 279.6 [M+1]

Step 6: Synthesis of 4-(2-((S)-1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)imidazo[2,1-b][1,3,4]thiadiazol-6-yl)-3-fluorobenzonitrile



137

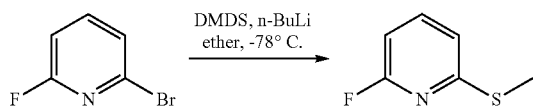


To a stirred solution of (R)-1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethanol (0.02 g, 0.089 mmol) in DMF (3 mL) was added sodium hydride (0.0072 g, 0.179 mmol) at 0° C. and stirred for 30 min at room temperature. After 30 min solution of 4-(2-chloroimidazo[2,1-b][1,3,4]thiadiazol-6-yl)-3-fluorobenzonitrile (0.025 g, 0.089 mmol) in DMF (2 mL) was added to the reaction mixture and stirred for 3 h. Progress of reaction was monitored by TLC. After completion reaction mass was quenched with ice cold water and extracted with ethyl acetate. The organic layer was washed with water, brine, dried over sodium sulphate and concentrated under reduced pressure to give crude product. Crude was purified by neutral alumina column chromatography using 10% acetone in hexane as eluent to give 4-(2-((R)-1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)imidazo[2,1-b][1,3,4]thiadiazol-6-yl)-3-fluorobenzonitrile (0.004 g, 9.23%) as white solid.

MS: 482.5 [M+1]

Example 29: 2-((S)-1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)-6-(2-fluoro-6-(methylsulfonyl)pyridin-3-yl)imidazo[2,1-b][1,3,4]thiadiazole

Step-1: Synthesis of 2-fluoro-6-(methylthio)pyridine

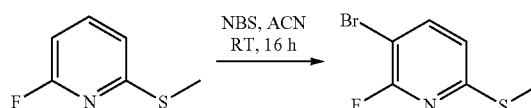


To a stirred solution of 2-bromo-6-fluoropyridine (0.1 g, 0.69 mmol) in ether (0.3 mL), n-BuLi (2.5 M) (0.29 mL, 0.74 mmol) was added dropwise at -78° C. and allow to stirred for 30 min. To resultant reaction mixture, DMDS (dimethyl disulphide) (0.129 g, 0.72 mmol) was added and stirred for 2 h at RT. Completion of reaction was monitored by TLC. On completion, quenched with ice water, extracted with ether. The organic layer was washed with water, brine, dried over sodium sulphate, concentrated under reduced pressure obtained crude reaction mass. Purification of the crude was done via silica gel (100-200 Mesh) column chromatography and desired compound eluted at 10% ether/n-Hexane to obtained 2-fluoro-6-(methylthio)pyridine (0.05 g, 60.97%) as colourless oily mass.

MS: 144.2 [M+1]

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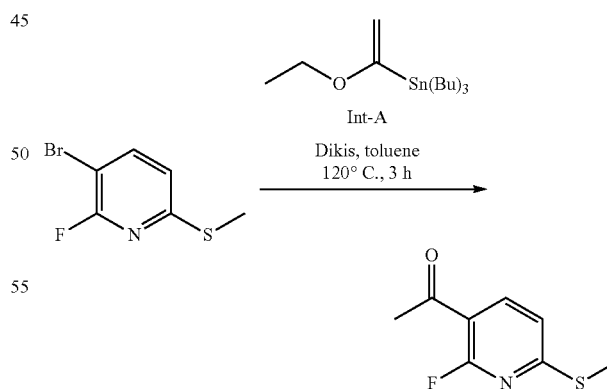
Step-2: Synthesis of 3-bromo-2-fluoro-6-(methylthio) pyridine



To a stirred solution of 2-fluoro-6-(methylthio)pyridine (0.05 g, 0.34 mmol) in ACN (2.5 mL), NBS (0.074 g, 0.41 mmol) was added portion-wise at -0° C. and allow to stirred for 30 min. Resultant reaction mass was then placed at RT and stirred for 16 h. Completion of reaction was monitored by TLC. On completion, concentrated under reduced pressure to obtained crude mass. Purification of the crude was done via silica gel (100-200 Mesh) column chromatography and desired compound eluted at 5% ether/n-Hexane to obtained 3-bromo-2-fluoro-6-(methylthio)pyridine (0.26 g, 33.76%) as colourless oily mass.

MS: 222.1 [M+1]

Step-3: Synthesis of 1-(2-fluoro-6-(methylthio)pyridin-3-yl)ethanone



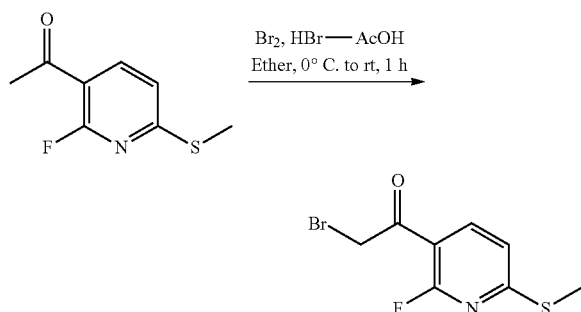
To a stirred solution of 3-bromo-2-fluoro-6-(methylthio)pyridine (0.10 g, 0.45 mmol) in dry toluene (10 mL), Int-A (0.21 g, 0.58 mmol) was added and purged with nitrogen for 30 min. To resultant reaction mixture Dikis (0.0015 g, 0.0062 mmol) was added and stirred at 120° C. for 3 h. Completion of reaction was monitored by TLC. On completion, quenched with ice water, extracted with ether. The

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organic layer was washed with water, brine, dried over sodium sulphate, concentrated under reduced pressure obtained crude. Purification of the crude was done via silica gel (100-200 Mesh) column chromatography and desired compound eluted at 1.5% ethyl acetate/n-Hexane to obtained 1-(2-fluoro-6-(methylthio)pyridin-3-yl)ethanone (0.040 g, 47.99%) as off white solid.

MS: 186.1 [M+1]

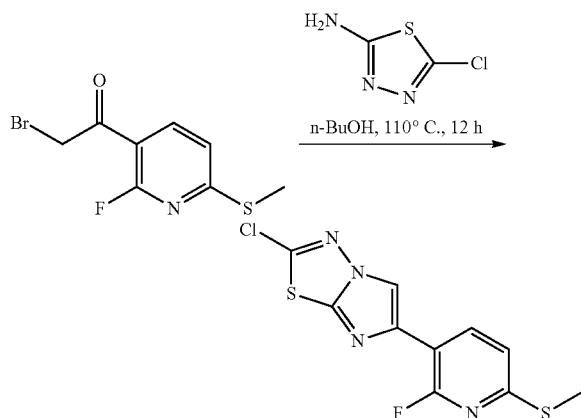
Step-4: Synthesis of 2-bromo-1-(2-fluoro-6-(methylthio)pyridin-3-yl)ethanone



To a stirred solution of 1-(2-fluoro-6-(methylthio)pyridin-3-yl)ethanone (0.020 g, 0.10 mmol) in ether (2 mL), HBr—AcOH (0.5 mL) was added. To resultant reaction mass Br₂ (diluted in 0.5 mL HBr—AcOH) (0.015 g, 0.097 mmol) was added at 0° C. and stirred for 30 min. Allow temp. to increase gradually to RT. Completion of reaction was monitored by TLC. On completion, quenched with ice water, extracted with ether. The organic layer was washed with aqueous-bicarbonate, brine, dried over sodium sulphate, concentrated under reduced pressure obtained 2-bromo-1-(2-fluoro-6-(methylthio)pyridin-3-yl)ethanone (0.004 g, 13.7%) as semisolid brownish gummy mass.

MS: 264.3 [M+1]

Step-5: Synthesis of 2-chloro-6-(2-fluoro-6-(methylthio)pyridin-3-yl)imidazo [2,1-b][1,3,4] thiadiazole

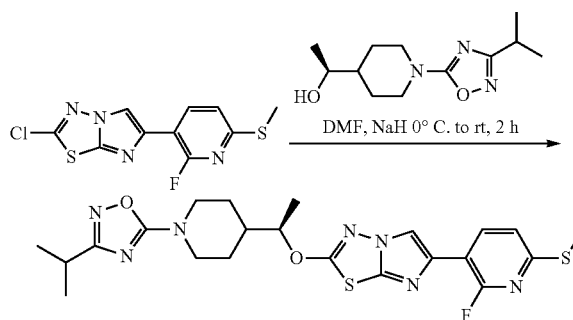


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To a stirred solution of 5-amino-2-chloro-1,3,4-thiadiazole (0.135 g, 0.60 mmol) and 2-bromo-1-(2-fluoro-6-(methylthio)pyridin-3-yl)ethanone (0.20 g, 0.75 mmol) in n-BuOH (3 mL), heated at 110° C. for 16 h. After cooled to room temperature, concentrated under reduced pressure to obtained crude mass. Purification of the crude was done via silica gel (100-200 Mesh) column chromatography and desired compound eluted at 3% ethyl acetate/n-Hexane to obtained 2-chloro-6-(2-fluoro-6-(methylthio)pyridin-3-yl)imidazo [2,1-b][1,3,4] thiadiazole (0.05 g, 22.0%) as off white solid (1.2 g, 60.60%) as off white solid.

MS: 300 [M+1]

Step-6: Synthesis of 2-((S)-1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)-6-(2-fluoro-6-(methylthio)pyridin-3-yl)imidazo[2,1-b][1,3,4]thiadiazole

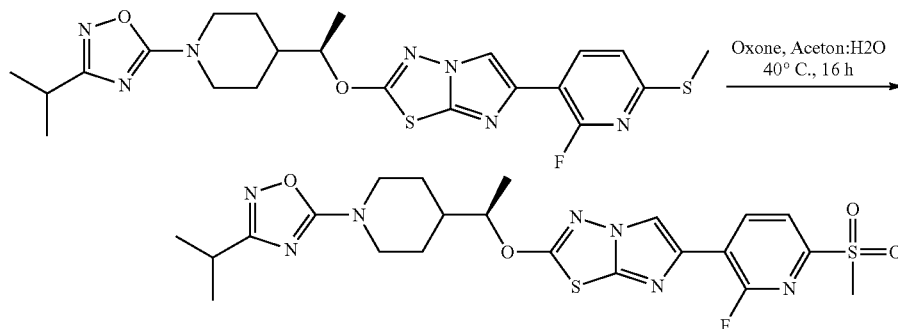


To a stirred solution of (S)-1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethanol (0.021 g, 0.09 mmol) in DMF (3 mL), NaH (0.010 g, 0.27 mmol) was added at 0° C. and stirred for 1 h. To resultant reaction mass, 2-chloro-6-(2-fluoro-6-(methylthio)pyridin-3-yl)imidazo [2,1-b][1,3,4] thiadiazole (0.03 g, 0.1 mmol) was added and stirred for 1 h at RT. Reaction was monitored by TLC. On completion, quenched with water, extracted with ethyl acetate. The organic layer was washed with water, brine, dried over sodium sulphate, concentrated under reduced pressure obtained crude. Purification of the crude was done via silica gel (100-200 Mesh) column chromatography and desired compound eluted at 12% acetone/n-Hexane to obtained 2-((S)-1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)-6-(2-fluoro-6-(methylthio)pyridin-3-yl)imidazo [2,1-b][1,3,4]thiadiazole (0.025 g, 49.51%) as off white solid.

MS: 504.75 [M⁺+1]

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Step-7: Synthesis of 2-((S)-1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)-6-(2-fluoro-6-(methylsulfonyl)pyridin-3-yl)imidazo[2,1-b][1,3,4]thiadiazole

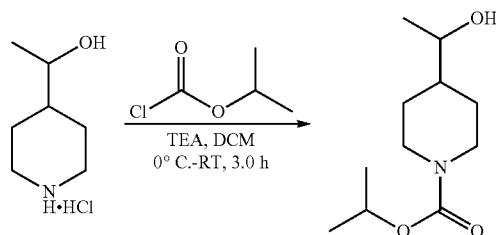


To a stirred solution of 2-((S)-1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)-6-(2-fluoro-6-(methylthio)pyridin-3-yl)-5,6-dihydroimidazo [2,1-b][1,3,4]thiadiazole (0.025 g, 0.04 mmol) in Acetone:H₂O (15:05 mL), oxone (0.045 g, 0.14 mmol) was added at rt and stirred for 30 min. After 30 min, place reaction mass at 40° C. and stirred for 16 h. Reaction was monitored by TLC. On completion, quenched with ice cold water, extracted with ethyl acetate. The organic layer was washed with water, brine, dried over sodium sulphate, concentrated under reduced pressure obtained crude desired product which was purified via silica gel (100 to 200 Mesh) column chromatography and desired compound eluted at 20% acetone/DCM obtained 2-((S)-1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)-6-(2-fluoro-6-(methylsulfonyl)pyridin-3-yl)imidazo[2,1-b][1,3,4]thiadiazole (0.007 g, 16.66%) as white solid.

MS: 535.9 [M⁺+1]

Example 30: Isopropyl 4-(1-(6-(2-fluoro-4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazol-2-yloxy)ethyl)piperidine-1-carboxylate

Step 1: Synthesis of isopropyl 4-(1-(hydroxyethyl)piperidine-1-carboxylate



To a stirred soln. of compound 1-(piperidin-4-yl)ethanol hydrochloride (0.2 gm, 1.55 mmol) in DCM (5.0 ml), Triethylamine (0.64 ml, 4.65 mmol) was added at 0° C. and reaction allowed to run at same temperature for 0.5 h, then followed by 2.0 M isopropyl chloroformate (0.77 ml, 1.55 mmol) and reaction further continued for next 3.0 h at RT. Reaction was monitored by TLC. On completion reaction mixture was quenched with ice cold water and compound

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was extracted with DCM. The organic layer was washed with water, brine, dried over sodium sulphate and concentrated under reduced pressure to give crude desired product. Purification of the compound was done by silica gel (100-

20

200 mess) column chromatography using 20% Acetone in hexane, that was concentrated to get compound isopropyl 4-(1-(hydroxyethyl)piperidine-1-carboxylate (0.12 gm, 36.01%) as light yellow semi solid.

MS: 216.1[M⁺+1].

Step 2: Synthesis of isopropyl 4-(1-(6-(2-fluoro-4-(methylthio)phenyl)imidazo[2,1-b][1,3,4]thiadiazol-2-yloxy)ethyl)piperidine-1-carboxylate

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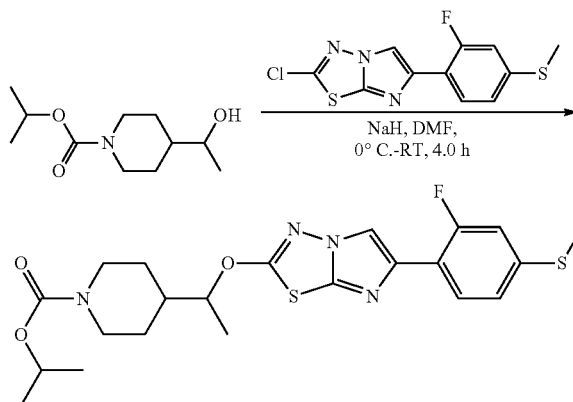
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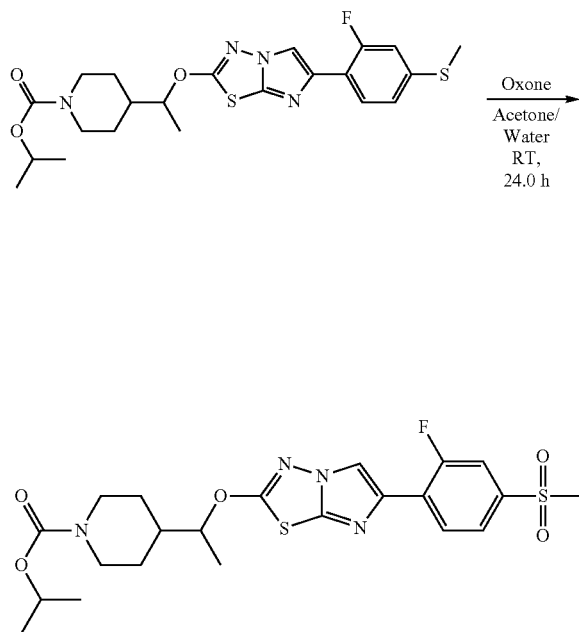


To a stirred soln. of isopropyl 4-(1-(hydroxyethyl)piperidine-1-carboxylate (0.025 g, 0.12 mmol) in DMF (3.0 ml), sodium hydride (0.007 g, 0.17 mmol) at 0° C. and reaction allowed to run at 0° C. for 30.0 min. then 2-chloro-6-(2-fluoro-4-(methylthio)phenyl)imidazo[2,1-b][1,3,4]thiadiazole (0.042 g, 0.14 mmol) was added to reaction mixture and reaction continued at RT for next 4.0 h. Reaction was monitored by TLC. On completion reaction mixture was quenched with ice cold water and compound was extracted with ethyl acetate. The organic layer was washed with water, brine, dried over sodium sulphate and concentrated under reduced pressure to give crude desired product. Purification of the compound was done by silica gel (100-200 mesh) column chromatography using 15% Acetone in hexane that was concentrated to get compound isopropyl 4-(1-(6-(2-fluoro-4-(methylthio)phenyl)imidazo[2,1-b][1,3,4]thiadiazol-2-yloxy)ethyl)piperidine-1-carboxylate (0.025 gm, 44.99%) as light yellow semi solid.

MS: 478.8[M⁺+1].

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Step 3: Synthesis of isopropyl 4-(1-(6-(2-fluoro-4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazol-2-yloxy)ethyl)piperidine-1-carboxylate



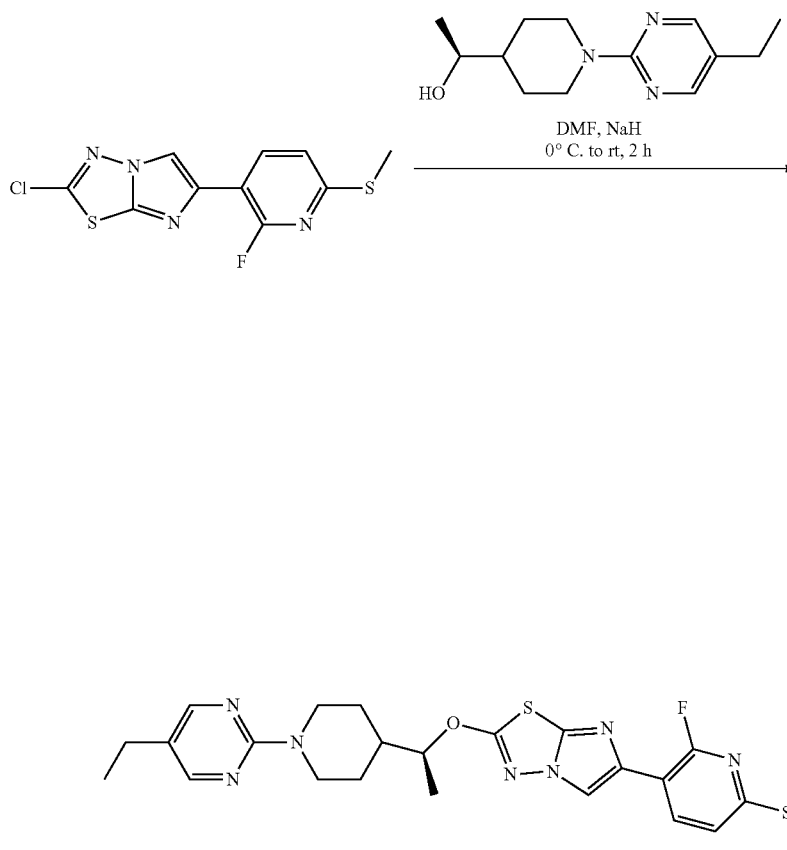
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To a stirred soln. of compound isopropyl 4-(1-(6-(2-fluoro-4-(methylthio)phenyl)imidazo[2,1-b][1,3,4]thiadiazol-2-yloxy)ethyl)piperidine-1-carboxylate (0.025 g, 0.05 mmol) in Acetone (4.0 ml), Oxone (0.03 g, 0.10 mmol) in water (0.8 ml) was added and reaction continued at RT for 24.0 h. Progress of reaction was monitored by TLC. On completion acetone was evaporated from reaction mixture and residue was quenched with water, compound was extracted with ethyl acetate. The organic layer was concentrated under reduced pressure to give crude desired compound. Purification of the compound was done by silica gel (100-200 mesh) column chromatography using 15% Acetone in hexane that was concentrated to get compound isopropyl 4-(1-(6-(2-fluoro-4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazol-2-yloxy)ethyl)piperidine-1-carboxylate (0.023 g, 86.24%) off white solid.

MS: 510.9[M⁺+1].

Example 31: 2-((S)-1-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yl)ethoxy)-6-(2-fluoro-6-(methylsulfonyl)pyridin-3-yl)imidazo[2,1-b][1,3,4]thiadiazole

Step-1: Synthesis of 2-((S)-1-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yl)ethoxy)-6-(2-fluoro-6-(methylthio)pyridin-3-yl)imidazo[2,1-b][1,3,4]thiadiazole

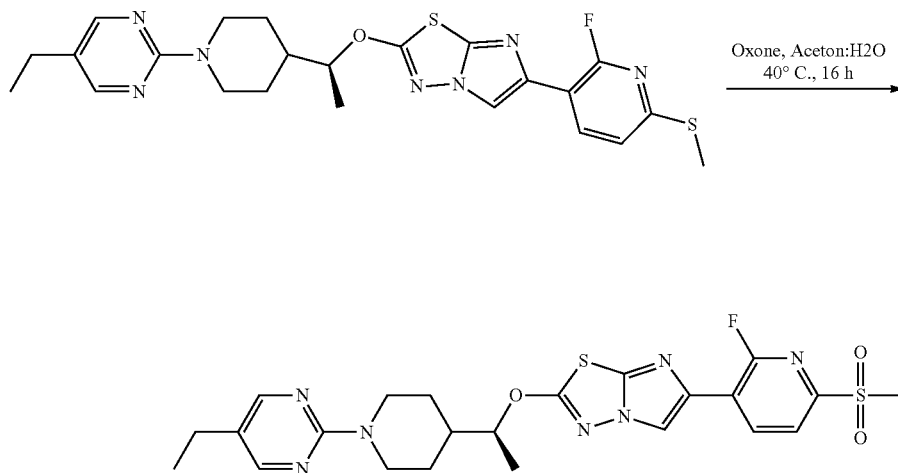


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To a stirred solution of (S)-1-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yl)ethanol (0.019 g, 0.074 mmol) in DMF (2 mL), NaH (0.004 mg, 0.0167 mmol) was added at 0° C. and stirred for 1 h. To resultant reaction mass, 2-chloro-6-(2-fluoro-6-(methylthio)pyridin-3-yl)imidazo [2,1-b][1,3,4] thiadiazole (0.025 g, 0.083 mmol) was added and stirred for 1 h at RT. Reaction was monitored by TLC. On completion, quenched with water, extracted with ethyl acetate. The organic layer was washed with water, brine, dried over sodium sulphate, concentrated under reduced pressure obtained crude. Purification of the crude was done via silica gel (100-200 Mesh) column chromatography and desired compound eluted at 18% acetone/n-Hexane to obtained 2-((S)-1-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yl)ethoxy)-6-(2-fluoro-6-(methylthio)pyridin-3-yl)imidazo[2,1-b][1,3,4]thiadiazole (0.014 g, 35.89%) as off white solid.

MS: 500.43[M⁺+1]

Step-2: Synthesis of 2-((S)-1-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yl)ethoxy)-6-(2-fluoro-6-(methylsulfonyl)pyridin-3-yl)imidazo[2,1-b][1,3,4]thiadiazole



To a stirred solution of 2-((S)-1-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yl)ethoxy)-6-(2-fluoro-6-(methylthio)pyridin-3-yl)imidazo[2,1-b][1,3,4]thiadiazole (0.024 g, 0.05 mmol) in Acetone:H₂O (10:03 mL), oxone (0.053 g, 0.17 mmol) was added at rt and stirred for 30 min. After 30 min, place reaction mass at 40° C. and stirred for 16 h. Reaction was monitored by TLC. On completion, quenched with ice cold water, extracted with ethyl acetate. The organic layer was washed with water, brine, dried over sodium sulphate, concentrated under reduced pressure to obtained crude which was purified via silica gel (100 to 200 Mesh) column chromatography, and desired compound eluted at 2% MeOH/DCM to obtained 2-((1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)methoxy)-6-(4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazole (0.010 g, 22.55%) as off white solid.

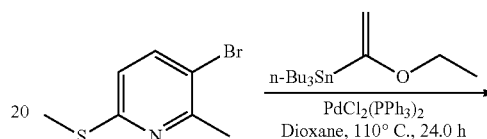
MS: 532[M⁺+1]

146

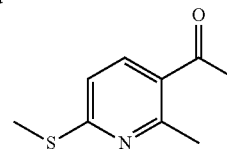
Example 32: 2-((S)-1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)-6-(2-methyl-6-(methylsulfonyl)pyridin-3-yl)imidazo[2,1-b][1,3,4]thiadiazole

Step 1: Synthesis of

1-(2-methyl-6-(methylthio)pyridin-3-yl)ethanone



-continued

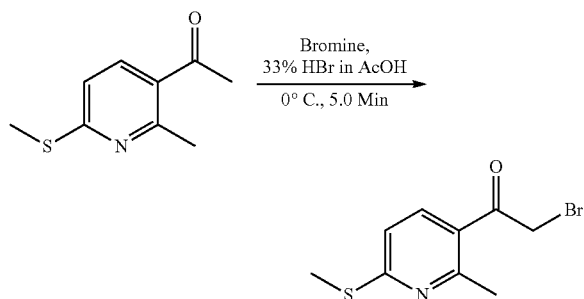


To a stirred soln. of compound 3-bromo-2-methyl-6-(methylthio)pyridine (0.35 g, 1.61 mmol) and tributyl(1-ethoxyvinyl)stannane (0.7 g, 1.94 mmol) in Dioxane (10.0 mL), PdCl₂(PPh₃)₂ (0.12 gm, 0.16 mmol) was added under nitrogen degassing. Reaction allowed to run at 110° C. for 24.0 h. Reaction was monitored by TLC. On completion solvent was evaporated from reaction mixture. Residue was quenched with water, compound was extracted with ethyl acetate. The organic layer was concentrated under reduced pressure to get crude desired product. Purification of the compound was done by silica gel (100-200 mesh) column chromatography using 5% ethyl acetate in hexane that was concentrated to get compound 1-(2-methyl-6-(methylthio)pyridin-3-yl)ethanone (0.14 g, 47.93%) as yellow liquid.

MS: 182.0[M⁺+1].

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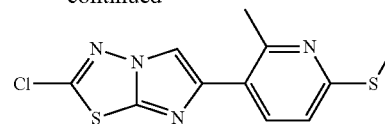
Step 2: Synthesis of 2-bromo-1-(2-methyl-6-(methylthio)pyridin-3-yl)ethanone



To a stirred soln. of 1-(2-methyl-6-(methylthio)pyridin-3-yl)ethanone (0.14 g, 0.77 mmol) in 33% HBr in Acetic acid (1.5 ml), Bromine (0.11 g, 0.69 mmol) in 0.5 ml HBr in AcOH was added at 0° C. and reaction allowed to run at same temp for next 5.0 min. Reaction was monitored by TLC. On completion reaction mixture was quenched with ice cold water and compound was extracted with di ethyl

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-continued



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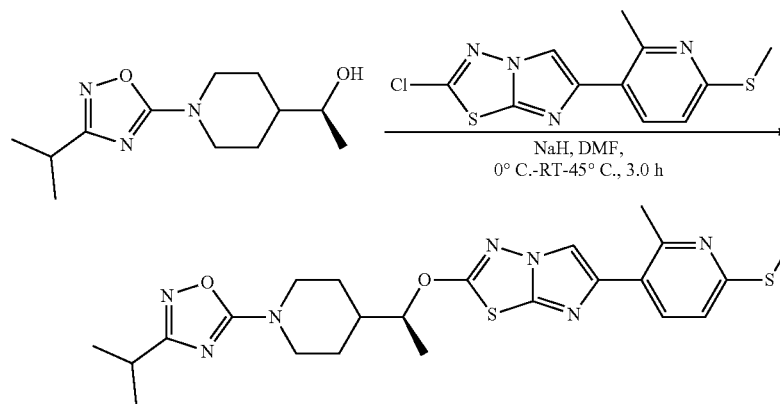
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To a stirred soln. of 2-bromo-1-(2-methyl-6-(methylthio)pyridin-3-yl)ethanone (0.14 g, 0.54 mmol) in Ethanol (4.0 ml), 5-chloro-1,3,4-thiadiazol-2-amine (0.07 g, 0.54 mmol) was added at RT and reaction allowed to run at 110° C. for 24.0 h. Reaction was monitored by TLC. On completion reaction mixture was concentrated under reduced pressure to get crude desired product. Purification of the compound was done by silica gel (100-200 mesh) column chromatography using 10% ethyl acetate in hexane that was concentrated to get compound 2-chloro-6-(2-methyl-6-(methylthio)pyridin-3-yl)imidazo[2,1-b][1,3,4]thiadiazole (0.06 gm, 37.49%) as light yellow semi solid.

MS: 296.9[M⁺+1].

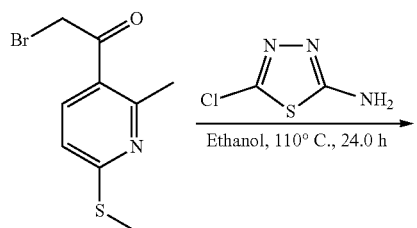
Step 4: Synthesis of 2-((S)-1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)-6-(2-methyl-6-(methylthio)pyridin-3-yl)imidazo[2,1-b][1,3,4]thiadiazole



ether. The organic layer was washed with water, bicarbonate, brine, dried over sodium sulphate and concentrated under reduced pressure to get crude compound 2-bromo-1-(2-methyl-6-(methylthio)pyridin-3-yl)ethanone (0.15 g, 74.91%) as yellow semi solid.

MS: 259.80[M⁺+1].

Step 3: Synthesis of 2-chloro-6-(2-methyl-6-(methylthio)pyridin-3-yl)imidazo[2,1-b][1,3,4]thiadiazole



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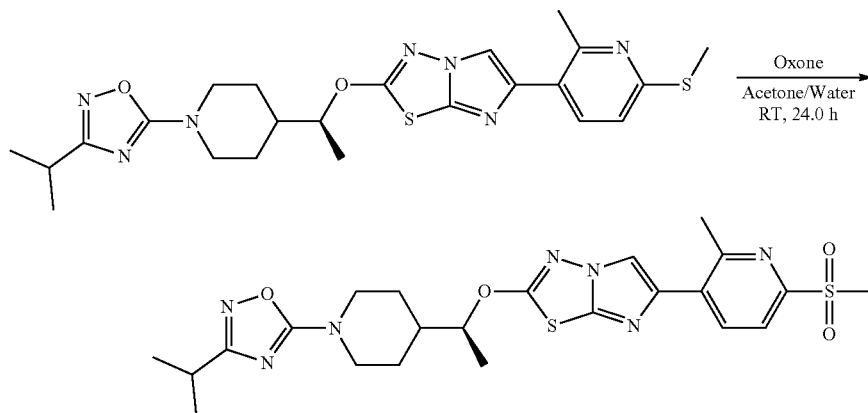
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To a stirred soln. of (S)-1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethanol (0.02 g, 0.08 mmol) in DMF (3.0 ml), sodium hydride (0.005 g, 0.13 mmol) at 0° C. and reaction allowed to run at 0° C. for 30.0 min. then 2-chloro-6-(2-methyl-6-(methylthio)pyridin-3-yl)imidazo[2,1-b][1,3,4]thiadiazole (0.03 g, 0.10 mmol) was added to reaction mixture and reaction continued at RT to 45° C. for next 3.0 h. Reaction was monitored by TLC. On completion reaction mixture was quenched with ice cold water and compound was extracted with ethyl acetate. The organic layer was washed with water, brine, dried over sodium sulphate and concentrated under reduced pressure to give crude desired product. Purification of the compound was done by silica gel (100-200 mess) column chromatography using 15% Acetone in hexane that was concentrated to get compound 2-((S)-1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)-6-(2-methyl-6-(methylthio)pyridin-3-yl)imidazo[2,1-b][1,3,4]thiadiazole (0.024 g, 57.49%) as light yellow semi solid.

MS: 499.90[M⁺+1].

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Step 5: Synthesis of 2-((S)-1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)-6-(2-methyl-6-(methylsulfonyl)pyridin-3-yl)imidazo[2,1-b][1,3,4]thiadiazole

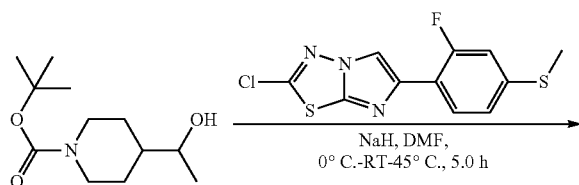


To a stirred soln. of compound 2-((S)-1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)-6-(2-methyl-6-(methylthio)pyridin-3-yl)imidazo[2,1-b][1,3,4]thiadiazole (0.022 g, 0.04 mmol) in Acetone (4.0 ml), Oxone (0.03 gm, 0.09 mmol) in Water (0.8 ml) was added and reaction continued at RT for 24.0 h. Progress of reaction was monitored by TLC. On completion acetone was evaporated from reaction mixture and residue was quenched with water, compound was extracted with ethyl acetate. The organic layer was concentrated under reduced pressure to give crude desired compound. Purification of the compound was done by silica gel (100-200 mess) column chromatography using 20% Acetone in hexane that was concentrated to get compound 2-((S)-1-(1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidin-4-yl)ethoxy)-6-(2-methyl-6-(methyl sulfonyl)pyridin-3-yl)imidazo[2,1-b][1,3,4]thiadiazole (0.015 g, 64.08%) light yellow solid.

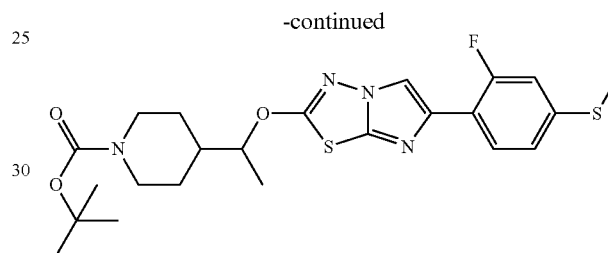
MS: 531.90[M⁺+1].

Example 33: tert-butyl 4-((S)-1-(6-(2-fluoro-4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazol-2-yloxy)ethyl)piperidine-1-carboxylate

Step 1: Synthesis of tert-butyl 4-(1-(6-(2-fluoro-4-(methylthio)phenyl)imidazo[2,1-b][1,3,4]thiadiazol-2-yloxy)ethyl)piperidine-1-carboxylate



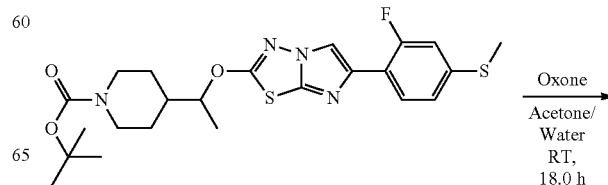
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To a stirred soln. of ethyl 4-(1-hydroxyethyl)piperidine-1-carboxylate (0.015 gm, 0.0655 mmol) in DMF (3.0 ml), sodium hydride (0.006 gm, 0.15 mmol) at 0° C. and reaction allowed to run at 0° C. for 30.0 min. then 2-chloro-6-(2-fluoro-4-(methylthio)phenyl)imidazo[2,1-b][1,3,4]thiadiazole (0.021 gm, 0.720 mmol) was added to reaction mixture and reaction continued at RT to 45° C. for next 5.0 h. Reaction was monitored by TLC. On completion reaction mixture was quenched with ice cold water and compound was extracted with ethyl acetate. The organic layer was washed with water, brine, dried over sodium sulphate and concentrated under reduced pressure to give crude desired product. Purification of the compound was done by silica gel (100-200 mess) column chromatography using 15% Acetone in hexane that was concentrated to get compound tert-butyl 4-(1-(6-(2-fluoro-4-(methylthio)phenyl)imidazo[2,1-b][1,3,4]thiadiazol-2-yloxy)ethyl)piperidine-1-carboxylate (0.015 g, 32.50%) as yellow semi solid.

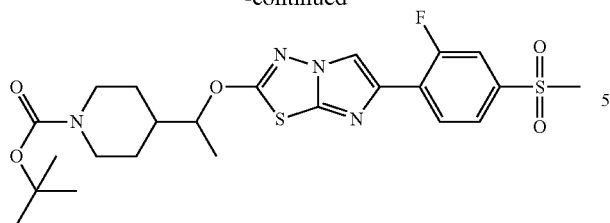
MS: 493.17[M⁺+1].

Step 2: Synthesis of tert-butyl 4-(1-(6-(2-fluoro-4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazol-2-yloxy)ethyl)piperidine-1-carboxylate



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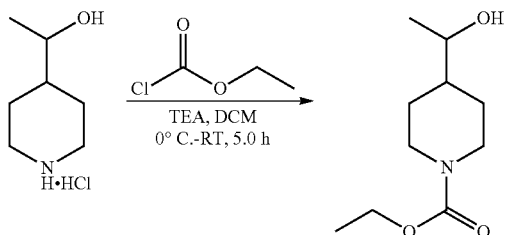
To a stirred soln. of compound ethyl 4-(1-(6-(2-fluoro-4-(methylthio)phenyl)imidazo[2,1-b][1,3,4]thiadiazol-2-yloxy)ethyl)piperidine-1-carboxylate (0.015 gm, 0.03 mmol) in Acetone (4.0 ml), Oxone (0.02 g, 0.06 mmol) in water (0.8 ml) was added and reaction continued at room temperature for 18 h. Progress of reaction was monitored by TLC. On completion acetone was evaporated from reaction mixture and residue was quenched with water, compound was extracted with ethyl acetate. The organic layer was concentrated under reduced pressure to give crude desired compound. Purification of the compound was done by silica gel (100-200 mess) column chromatography using 15% Acetone in hexane that was concentrated to get compound

tert-butyl 4-(1-(6-(2-fluoro-4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazol-2-yloxy)ethyl)piperidine-1-carboxylate (0.008 g, 49.90%) off white solid.

MS: 496.8[M⁺+1].

Example 34: Ethyl 4-(1-(6-(2-fluoro-4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazol-2-yloxy)ethyl)piperidine-1-carboxylate

Step 1: Synthesis of ethyl 4-(1-(hydroxyethyl)piperidine-1-carboxylate

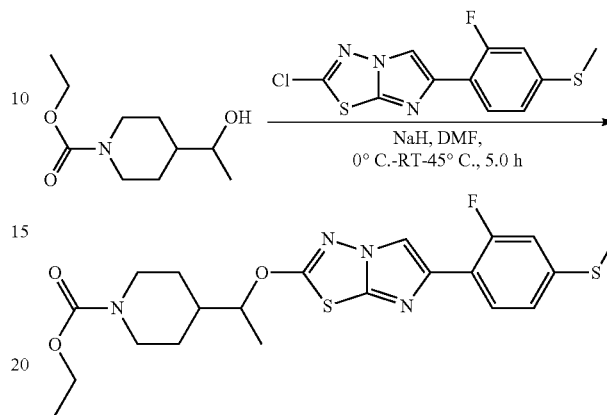


To a stirred soln. of compound 1-(piperidin-4-yl)ethanol hydrochloride (0.15 g, 1.16 mmol) in DCM (4.0 ml), Triethylamine (0.5 ml, 3.49 mmol) was added at 0° C. and reaction allowed to run at same temperature for 0.5 h, then followed by ethyl chloroformate (0.1 ml, 1.16 mmol) and reaction further continued for next 5.0 h at RT. Reaction was monitored by TLC. On completion reaction mixture was quenched with ice cold water and compound was extracted with DCM. The organic layer was washed with water, brine, dried over sodium sulphate and concentrated under reduced pressure to give crude desired product. Purification of the compound was done by silica gel (100-200 mess) column chromatography using 50% EtOAc in hexane, that was concentrated to get compound ethyl 4-(1-(hydroxyethyl)piperidine-1-carboxylate (0.09 g, 38.52%) as light yellow liquid.

MS: 202.1[M⁺+1].

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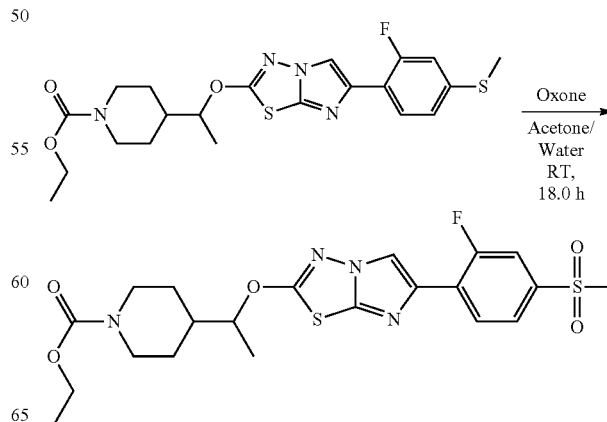
Step 2: Synthesis of ethyl 4-(1-(6-(2-fluoro-4-(methylthio)phenyl)imidazo[2,1-b][1,3,4]thiadiazol-2-yloxy)ethyl)piperidine-1-carboxylate



To a stirred soln. of ethyl 4-(1-(hydroxyethyl)piperidine-1-carboxylate (0.02 gm, 0.09 mmol) in DMF (3.0 ml), sodium hydride (0.006 g, 0.15 mmol) at 0° C. and reaction allowed to run at 0° C. for 30.0 min. then 2-chloro-6-(2-fluoro-4-(methylthio)phenyl)imidazo[2,1-b][1,3,4]thiadiazole (0.04 g, 0.12 mmol) was added to reaction mixture and reaction continued at RT to 45° C. for next 5.0 h. Reaction was monitored by TLC. On completion reaction mixture was quenched with ice cold water and compound was extracted with ethyl acetate. The organic layer was washed with water, brine, dried over sodium sulphate and concentrated under reduced pressure to give crude desired product. Purification of the compound was done by silica gel (100-200 mesh) column chromatography using 15% Acetone in hexane that was concentrated to get compound ethyl 4-(1-(6-(2-fluoro-4-(methylthio)phenyl)imidazo[2,1-b][1,3,4]thiadiazol-2-yloxy)ethyl)piperidine-1-carboxylate (0.015 g, 32.50%) as yellow semi solid.

MS: 464.9[M⁺+1].

Step 3: Synthesis of ethyl 4-(1-(6-(2-fluoro-4-(methyl sulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazol-2-yloxy)ethyl)piperidine-1-carboxylate



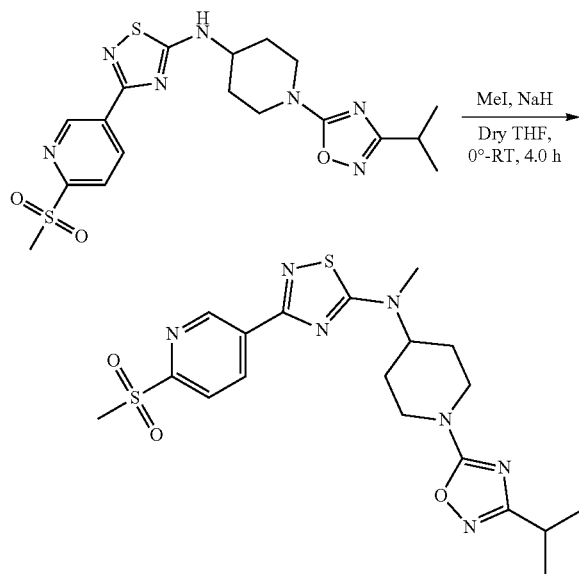
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To a stirred soln. of compound ethyl 4-(1-(6-(2-fluoro-4-(methylthio)phenyl)imidazo[2,1-b][1,3,4]thiadiazol-2-yloxy)ethyl)piperidine-1-carboxylate (0.015 g, 0.03 mmol) in Acetone (4.0 ml), Oxone (0.02 g, 0.06 mmol) in Water (0.8 ml) was added and reaction continued at RT for 18.0 h. Progress of reaction was monitored by TLC. On completion acetone was evaporated from reaction mixture and residue was quenched with water, compound was extracted with ethyl acetate. The organic layer was concentrated under reduced pressure to give crude desired compound. Purification of the compound was done by silica gel (100-200 mesh) column chromatography using 15% Acetone in hexane that was concentrated to get compound ethyl 4-(1-(6-(2-fluoro-4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazol-2-yloxy)ethyl)piperidine-1-carboxylate (0.008 g, 49.90%) off white solid.

MS: 496.8[M⁺+1].

Example 35: 1-(3-isopropyl-1,2,4-oxadiazol-5-yl)-N-methyl-N-(3-(6-(methylsulfonyl)pyridin-3-yl)-1,2,4-thiadiazol-5-yl)piperidin-4-amine

Step 1: Synthesis of 1-(3-isopropyl-1,2,4-oxadiazol-5-yl)-N-methyl-N-(3-(6-(methylsulfonyl)pyridin-3-yl)-1,2,4-thiadiazol-5-yl)piperidin-4-amine



To a stirred soln. of 1-(3-isopropyl-1,2,4-oxadiazol-5-yl)-N-(3-(6-(methylsulfonyl)pyridin-3-yl)-1,2,4-thiadiazol-5-yl)piperidin-4-amine (0.01 g, 0.02 mmol) in Dry THF (3.0 ml), sodium hydride (0.002 gm, 0.03 mmol) at 0° C. and reaction allowed to run at 0° C. for 10.0 min. then methyl iodide (0.004 gm, 0.02 mmol) was added to reaction mixture and reaction continued at RT for next 4.0 h. Reaction was monitored by TLC. On completion reaction mixture was quenched with ice cold water and compound was extracted with ethyl acetate. The organic layer was washed with water, brine, dried over sodium sulphate and concentrated under reduced pressure to give to give crude desired product. Purification of the compound was done by silica gel (100-200 mess) column chromatography using 35% EtOAc in hexane that was concentrated to get compound 1-(3-isopropyl-1,2,4-oxadiazol-5-yl)-N-methyl-N-(3-(6-(methylsulfo-

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nyl)pyridin-3-yl)-1,2,4-thiadiazol-5-yl)piperidin-4-amine (0.008 g, 77.59%) as off white sticky.

MS: 463.9 [M⁺+1].

Example 36: In Vitro Cyclic AMP Assay

cAMP measurements were done using Cisbio dynamic 2 HTRF kit according to the manufacturer's protocol. Briefly, CHO-hGPR119 cells were plated at a cell density of 5000 cells/well/5 μ l into a white small volume 384 well plate. The final concentrations of IBMX and DMSO used were 1 mM and 0.5% respectively. Cells were treated with various concentrations of the test compound for 60 min at room temperature. Cells were lysed by buffer containing Anti-cAMP antibody and d2-cAMP reagents and incubated for 1 hour at room temperature. HTRF was measured at 337 nm excitation and emission wavelengths of 665 nm and 620 nm on a microplate reader (Fluorstar, BMG Labtech). Graphpad prism software was utilized for EC50 determinations.

Results: The results of the compounds were represented in terms of % induction at 1 μ M and EC50 and the same is represented at Table 1 herein below.

Compound	Induction	EC50
1001	NA	
1002	NA	
1003	3	
1004	6	
1005	2	
1006	9	
1007	-8	
1008	NA	
1009	NA	
1010	2	
1011	2	
1012	22	
1013	NA	
1014	NA	
1015	3	
1016	54	
1017	39	
1018	20	
1019	11	
1020	1	
1021	NA	
1022	16	
1023	0	
1024	38	
1025	11	
1026	NA	
1027	41	
1028	NA	
1029	9	
1030	26	
1031	1	
1032	41	
1033	2	
1034	53	
1035	21	
1036	24	
1037	NA	
1038	6	
1039	11	
1040	4	
1041	NA	
1042	2	
1043	NA	
1044	71	
1045	22	
1046	26	
1047	51	
1048	56	
1049	55	
1050	68	

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-continued

Compound	Induction	EC50
1051	7	
1052	12	
1053	49	
1054	16	
1055	76	
1056	73	
1057	82	
1058	73	A+
1059	68	A++
1060	65	A+
1061	79	
1062	78	A+
1063	61	
1064	75	A++
1065	62	A
1066	72	A+
1067	55	A++
1068	59	B
1069	65	A+
1070	55	B
1071	75	A++
1072	72	A++
1073	33	
1074	44	
1075	64	
1076	15	
1077	33	
1078	54	
1079	87	
1080	74	
1081	66	A++
1082	80	A
1083	77	
1084	72	
1085	74	A++
1086	87	A++
1087	75	A
1088	73	A++
1089	72	A
1090	76	A++
1091	33	
1092	25	
1093	75	A
1094	68	
1095	8	
1096	32	
1097	NA	
1098	68	
1099	63	
1100	78	A++
1101	84	
1102	84	A+
1103	9	
1104	46	
1105	30	
1106	62	
1107	67	
1108	70	A++
1109	55	
1110	71	
1111	63	
1112	71	
1113	68	A+
1114	4	
1115	14	
1116	36	
1117	2	
1118	NA	
1119	7	
1120	15	
1121	NA	
1122	NA	
1123	18	
1124	6	
1125	NA	

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-continued

Compound	Induction	EC50
1126	7	
1127	4	

Example 37: Anti-Diabetic Effect of Compounds of the Invention in an In-Vitro Model of Pancreatic Beta Cells (HIT-T15)

Cell Culture:

HIT-T15 cells were grown in Ham's F12K medium with 2 mM l-glutamine containing 2.5% horse serum and 10% fetal bovine serum. Cells were grown in minimal glucose concentration for insulin secretion studies. Studies were performed with cell passage numbers between 65 to 72.

cAMP Assay:

HIT-T15 cells were plated at a cell density of 5000 cells/well/5 μ l into a white small volume 384 well plate. The final concentrations of IBMX and DMSO used were 1 mM and 0.5% respectively. Cells were treated with various concentrations of the test compound for 60 min at room temperature. Cells were lysed by buffer containing Anti-cAMP antibody and d2-cAMP reagents and incubated for 1 hour at room temperature. HTRF was measured at 337 nm excitation and emission wavelengths of 665 nm and 620 nm on a microplate reader (Fluorstar, BMG Labtech). GraphPad prism 6 software was utilized for EC50 determinations.

Representative compounds of the invention were found to increase cAMP at an EC50 of less than 10 μ M. Compounds showing an EC50 of less than 1 μ M in the cAMP assay may be preferred.

Insulin Secretion Assay:

HIT-T15 cells were utilised for assessment of potentiation of glucose stimulated insulin secretion (GSIS) by test compounds. Cells were seeded at a cell density of 50,000 cells per well in 96 well plate. After 48 hours, cells were washed with Krebs-Ringer Bicarbonate buffer (KRB) and incubated with buffer containing 0.2 mM glucose for 30 minutes. After incubating cells twice in KRB buffer containing 0.2 mM glucose, cells were exposed to 11 mM glucose and test compounds at 10 μ M and 1 μ M for 1 hour. Supernatants were collected for measurement of insulin secreted from the cells. Insulin was measured using Cisbio insulin test kit following manufacturer's instructions, with a standard curve of known insulin concentrations. For each well, insulin levels are corrected by subtraction of the basal secretion level from the preincubation in the absence of glucose. Data is analysed using GraphPad prism 6 software. Representative compounds of the invention were studied for their insulin potentiation capacity and showed increase in insulin secretion at an EC50 of less than 10 μ M, however the compounds showing increase in insulin secretion at an EC50 of less than 1 μ M may be preferred.

Example 38: Glucagon-Like Peptide-1 (GLP-1) Secretion

To study the effect of GPR119 agonists on secretion of GLP-1 in C57BL/6 mice, animals were grouped based on basal glucose levels and fasted for 16 hours. Animals were dosed orally with vehicle or test compound at 10 mpk (n=20). After 30 minutes of compound dosing, ten animals were sacrificed from each group and blood was collected by cardiac puncture method. To the remaining 10 animals in

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each group, glucose, 3 g/kg, was administered. After ten minutes of glucose administration, animals were sacrificed by CO₂ asphyxiation method and blood was collected by cardiac puncture method. To avoid degradation of active GLP-1 in blood, DPP-IV inhibitor was added to the blood collection tubes. Plasma active GLP-1 levels were measured by using Merck Millipore ELISA kit. Statistical comparisons of the data were performed by one-way analysis of variance (ANOVA), followed by Bonferroni's test.

Results:

Compounds of the present invention showed significant increase in active GLP-1 secretion. Compounds which showed active GLP-1 secretion greater than ~1 fold with respect to vehicle may be preferred.

Example 39: Oral Glucose Tolerance Test

Male C57BL/6 mice (8-10 weeks) were grouped based on basal glucose levels and animals were fasted for 16 hours. Glucose level of each animal was estimated in blood collected from tail vein before animals were dosed orally with 0.5% Tween 80 and 0.5% NaCMC (vehicle control) and compounds at 3 and 10 mpk (n=5). After 30 minutes of compound dosing, blood glucose was again estimated and 2 g/kg/10 ml (20%) of Glucose solution was administered orally to all the animals. Blood glucose was estimated at 15, 30, 60, 90 and 120 minutes time points after glucose administration. Accu-Check active blood glucose meter was utilised for estimation of blood from tail vein.

Results:

Glucose reduction observed in animals treated with compounds of present invention is represented in terms of % AUC reduction. A greater glucose reduction in oral glucose tolerance test indicates the compound's efficacy in this rodent species. The compounds 1059, 1067, 1071, 1072, 1081, 1086, 1087, 1088, 1090, 1100, 1101, 1108 and 1109 showed significant dose dependent glucose reduction at both 3 mpk and 10 mpk respectively.

Example 40: Oral Glucose Tolerance Test in Sprague-Dawley Rats

Male SD rats (8-10 weeks) were grouped based on basal glucose levels and animals were fasted for 16 hours. Glucose level of each animal was estimated in blood collected from tail vein before animals were dosed orally with 0.5% Tween 80 and 0.5% NaCMC (vehicle control) and compounds at 3 and 10 mpk (n=5). After 30 minutes of compound dosing, blood glucose was again estimated and 2 g/kg/10 ml (20%)

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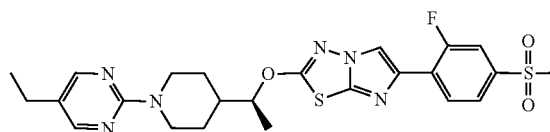
of Glucose solution was administered orally to all the animals. Blood glucose was estimated at 15, 30, 60, 90 and 120 minutes time points after glucose administration. Accu-Check active blood glucose meter was utilised for estimation of blood from tail vein.

Results:

Glucose reduction observed in animals treated with GPR119 agonists is represented in terms of % AUC reduction. A greater glucose reduction in oral glucose tolerance test indicates the compound's efficacy in this rodent species. The compounds 1059, 1067, 1071, 1072, 1086, 1087, 1090, 1091, 1101, 1108 and 1109 showed significant dose dependent glucose reduction at both 3 mpk and 10 mpk respectively.

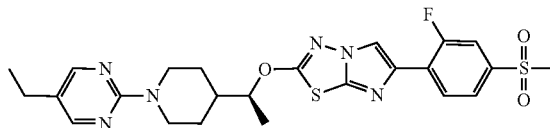
We claim:

1. A compound which is 2-((S)-1-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yl)ethoxy)-6-(2-fluoro-4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazole represented by the following structural formula:



or a physiologically acceptable salt thereof.

2. A method of treating diseases and conditions mediated through GPR119 to a patient in need thereof comprising administering the compound which is 2-((S)-1-(1-(5-ethylpyrimidin-2-yl)piperidin-4-yl)ethoxy)-6-(2-fluoro-4-(methylsulfonyl)phenyl)imidazo[2,1-b][1,3,4]thiadiazole represented by the following structural formula:



3. The method of claim 2, wherein said disease is metabolic disorder.

4. The method of claim 3, wherein said disease is diabetes.

5. The method of claim 4, wherein said disease is Type II diabetes.

* * * * *