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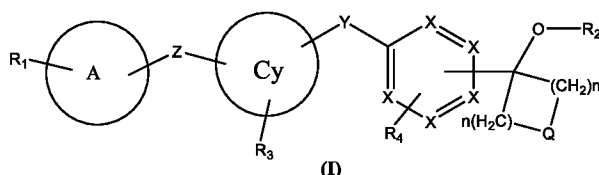
(57) Abstract: Present invention relates to compounds of general formula (I), their tautomeric forms, stereoisomers, pharmaceutically acceptable salts and pharmaceutical composition containing them. Invention also relates to process for the preparation of compounds of general formula (I) and intermediates thereof. Compounds of present invention can be useful in treating diseases such as hyperlipidemia and other disorders related to hyperlipidemia. Compounds of present invention also have a beneficial effect on lowering cholesterol.

NOVEL COMPOUNDS SUITABLE FOR THE TREATMENT OF DYSLIPIDEMIA

FIELD OF INVENTION

5 The present invention relates to compounds of the general formula (I), their tautomeric forms, their stereoisomers, their pharmaceutically acceptable salts, pharmaceutical compositions containing them, methods for their preparation, use of these compounds in medicine and the intermediates involved in their preparation.

10 The present invention is directed towards compounds which can be used to treat diseases such as hyperlipidemia and also have a beneficial effect on cholesterol.



15 The compounds of the general formula (I) lower blood glucose, lower or modulate triglyceride levels and/or cholesterol levels and/or low-density lipoproteins (LDL) and raises the high-density lipoproteins (HDL) plasma levels and hence are useful in combating different medical conditions, where such lowering of LDL (and/or raising of HDL) is beneficial. Thus, it can be used in the treatment and/or prophylaxis of obesity, hyperlipidemia, hypercholesteremia, hypertension, atherosclerotic disease events, vascular restenosis, diabetes and many other related conditions.

20 The compounds of general formula (I) are useful to prevent or reduce the risk of developing atherosclerosis, which leads to diseases and conditions such as arteriosclerotic cardiovascular diseases, stroke, coronary heart diseases, cerebrovascular diseases, peripheral vessel diseases and related disorders.

25 These compounds of general formula (I) are useful for the treatment and/or prophylaxis of metabolic disorders loosely defined as Syndrome X. The characteristic features of Syndrome X include initial insulin resistance followed by hyperinsulinemia, dyslipidemia and impaired glucose tolerance. The glucose intolerance can lead to non-insulin dependent diabetes mellitus (NIDDM, Type 2 diabetes), which is characterized by hyperglycemia, which if not controlled may lead to diabetic complications or metabolic disorders caused by insulin resistance. Diabetes is no longer considered to be associated

only with glucose metabolism, but it affects anatomical and physiological parameters, the intensity of which vary depending upon stages/duration and severity of the diabetic state. The compounds of this invention are also useful in prevention, halting or slowing progression or reducing the risk of the above mentioned disorders along with the resulting secondary diseases such as cardiovascular diseases, like arteriosclerosis, atherosclerosis; diabetic retinopathy, diabetic neuropathy and renal disease including diabetic nephropathy, glomerulonephritis, glomerular sclerosis, nephrotic syndrome, hypertensive nephrosclerosis and end stage renal diseases, like microalbuminuria and albuminuria, which may be result of hyperglycemia or hyperinsulinemia.

The compounds of the present invention can be useful as aldose reductase inhibitors; for improving cognitive functions in dementia, and in the treatment and/or prophylaxis of disorders such as psoriasis, polycystic ovarian syndrome (PCOS), cancer, osteoporosis, leptin resistance, inflammation and inflammatory bowel diseases, wound healing, xanthoma, pancreatitis, myotonic dystrophy, endothelial cell dysfunction and hyperlipidemia.

BACKGROUND OF THE INVENTION

Higher LDL cholesterol levels in the plasma increase cardiovascular risk and reduction in the levels of LDL would decrease CVD risk by a comparable percentage (PNAS, 2009, 106, 9546-9547). Clearance of LDL cholesterol from plasma is through the action of LDL receptors in the liver and LDL receptors are cell surface glycoproteins that bind to apolipoprotein B100 (apoB100) on LDL particles with high affinity and mediate their endocytic uptake (Journal of Biological Chemistry, 2009, 284, 10561-10570). Defect in hepatic cholesterol clearance and elevated levels of plasma LDL cholesterol that result from the mutations cause familial hypercholesterolemia. Such mutations are identified in the human LDL receptor and later in apolipoprotein-B (Nature Structural and Molecular Biology, 2007, 14, 413-419). Recently, mutations within certain subtypes of the pro-protein convertase subtilisin/ gene such as the subtype nine (hereinafter "the gene") were found to represent a third class of mutations associated with autosomal dominant hypercholesterolemia (ADH). The discovery, etiology and functions of this subtype gene is discussed in details in Nature Genetics, 2003, 34, 154-156, Trends in Biochemical Sciences, 2008, 33, 426-434 etc.. Several missense mutations (S127R, D129G, F216L, D374H, D374Y) are associated with hypercholesterolemia and premature atherosclerosis

(J Lipid Res. 2008, 49, 1333-1343). Loss-of-function mutations (R46L, L253F, A433T) lead to elevated receptor abundance, enhancing clearance of LDL cholesterol from the circulation and reducing cardiovascular risk (Nature Structural and Molecular Biology, 2007, 14, 413-419).

5 Detailed molecular mechanisms explaining the association of LDLR and the particular subtype gene and LDLR degradation is not very clear (Drug News Perspectives, 2008, 21, 323-330). Because of inhibition of LDLR recycling, number of LDL receptors on the cell surface are decreased and this increases plasma LDL levels (PNAS, 2009, 106, 9546-9547).

10 Various approaches for inhibiting this particular subtype gene are reported, including gene silencing by siRNA or antisense oligonucleotides, mAb disrupting protein-protein interactions or by peptides; all the above-mentioned strategies have shown lowering of LDL cholesterol which may be effective therapy for treating hypercholesterolemia (Biochemical Journal, 2009, 419, 577-584; PNAS, 2008, 105, 11915-11920; Journal of
15 Lipid Research, 2007, 48, 763-767; PNAS, 2009, 106, 9820-9825). However, very little success has been reported in trying to inhibit this subtype gene by using small molecules. Such small molecule inhibitors have their obvious clinical and therapeutic benefits over the other known approaches as discussed above. We herein disclose novel small molecules which have shown to inhibit this particular gene in *in-vitro* studies and therefore provide
20 an alternate beneficial approach for treating patients in need of such therapy.

We have disclosed earlier compounds which inhibits this particular gene in patent applications no. WO2015107541, WO2014192023, WO2012090220, WO2014002105 and WO2021130723. Inhibitors of this gene have been disclosed by few companies in application no WO2014150395, WO2014150326, WO2016021706, WO2016055901,
25 WO2017222953, WO2017034990, WO2017034997, WO2017034994, WO2018165718, WO2018053517, WO2018057409.

As compounds of present invention are related to PCSK9 protein, we have carried out PCSK9 protein and gene expression of Example 1 of WO2021130723. We have found that PCSK9 protein fold change has been found -2.12 and -4.82 at 10 μ M and 30 μ M
30 respectively.

Further pharmacokinetic study of same compound (3mg/Kg oral dose) has been carried out in Rat and Dog where $AUC_{(0-t)}$ has been found 4834 ± 1855 and 1117.41 ± 458.60 ng.h/mL respectively.

5 **PREFERRED EMBODIMENTS OF THE INVENTION**

The main objective of the present invention is to provide novel substituted heterocyclic derivatives represented by the general formula (I), their tautomeric forms, their stereoisomers, their pharmaceutically acceptable salts, and pharmaceutical compositions containing them or their mixtures thereof.

10 In an embodiment of the present invention is provided a process for the preparation of novel substituted heterocyclic derivatives represented by the general formula (I), their intermediates, their tautomeric forms, their stereoisomers, their pharmaceutically acceptable salts.

15 In a further embodiment of the present invention is provided pharmaceutical compositions containing compounds of the general formula (I), their tautomeric forms, their stereoisomers, their pharmaceutically acceptable salts, or their mixtures in combination with suitable carriers, solvents, diluents and other media normally employed in preparing such compositions.

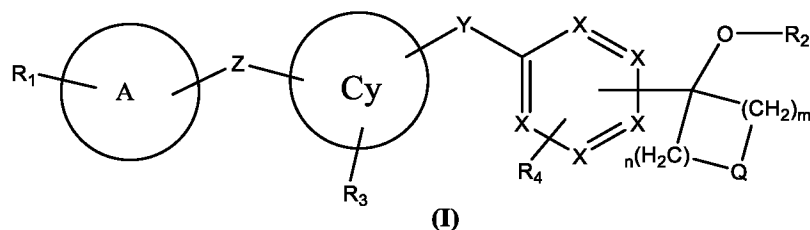
20 In an embodiment of the present invention is provided a pharmaceutical compositions in combination with additional therapeutic agents.

In a further embodiment of the present invention is provided a method of treatment of diseases such as dyslipidemia, hyperlipidemia etc. by providing therapeutically effective amount of the compounds of formula (I) or their pharmaceutically acceptable salts or their suitable pharmaceutical compositions.

25 The above and other embodiments are described in details hereinafter.

DETAILED DESCRIPTION OF THE INVENTION

Accordingly, the present invention relates to compounds of the general formula (I),



their tautomeric forms, their stereoisomers, their pharmaceutically acceptable salts, and pharmaceutical compositions containing them wherein

‘A’ represents an optionally substituted single or fused group selected from aryl or heteroaryl groups;

‘Y’ represents either a bond, or may be selected from (C₁-C₃)alkyl, -S(O)_o-, -C(O)-, -C(O)N(R₅)-, N(R₅)C(O)-, -N(R₅)-, -N(R₅)S(O)₂N(R₅)-, -N(R₅)C(O)N(R₅)-, -S(O)₂N(R₅), -N(R₅)S(O)₂-;

‘Z’ represents -O-, -S(O)_o-, -C(O)-, -N(R₅)-, -(C(R₅)₂)_p-, -O(C(R₅)₂)_p-, -(C(R₅)₂)_pO-, -O(C(R₅)₂)_pO-, -S(O)_o(C(R₅)₂)_p-, -(C(R₅)₂)_pS(O)_o-, -S(O)_o(C(R₅)₂)_pS(O)_o-, -N(R₅)(C(R₅)₂)_p-, -(C(R₅)₂)_pN(R₅)-, -N(R₅)(C(R₅)₂)_pN(R₅)-, -NHC(O)-, -C(O)NH-, -NHC(O)NH-, -NHS(O)₂NH-, -NHS(O)₂-, -S(O)₂NH- or ;

‘Q’ represents O, C(R₅)₂, NR₆ or S(O)_o; wherein R₆ represents H, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, -C(O)OR₅, -C(O)R₅, -C(O)NH₂;

‘o’ represents integers from 0-2;

‘m, n and p’ independently represent an integers from 0-4;

‘Cy’ represents saturated or partially unsaturated or unsaturated, monocyclic, bicyclic or spirocyclic groups containing 0-4 heteroatoms selected from O, N or S.

‘X’ at each occurrence independently represents either C or N;

R₁ at each occurrence independently represents halo, cyano, hydroxy or substituted or unsubstituted groups selected from alkyl, haloalkyl, perhaloalkyl, alkoxy, haloalkoxy, perhaloalkoxy, cycloalkyl, alkoxy, cycloalkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyl, heterocyclalkyl, heterocycloxy, heterocyclalkoxy, heterocyclalkoxyacyl, carboxylic acid and its derivatives such as esters and amides, carbonylamino, hydroxyalkyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthio, thioalkyl, alkylsulfonyl, haloalkylsulfonyl, perhaloalkylsulfonyl, hydroxyl, sulfonic acid and its derivatives.

R₂ represents hydrogen, or substituted or unsubstituted groups selected from alkyl, haloalkyl, perhaloalkyl, cycloalkyl, aryl, aralkyl, heterocyl, heterocyclalkyl,

heterocyclalkoxyacyl, Acyl, carbonylamino, hydroxyalkyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylsulfonyl.

Each of R₃ and R₄ at each occurrence independently represents hydrogen, halo, cyano, hydroxy or substituted or unsubstituted groups selected from alkyl, haloalkyl, perhaloalkyl, alkoxy, haloalkoxy, perhaloalkoxy, cycloalkyl, alkoxy, cycloalkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyl, heterocyclalkyl, heterocycloxy, heterocyclalkoxy, heterocyclalkoxyacyl, carboxylic acid and its derivatives such as esters and amides, carbonylamino, hydroxyalkyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthio, thioalkyl, alkylsulfonyl, hydroxyl, sulfonic acid and its derivatives.

R₅ at each occurrence independently represents H, (C₁-C₆)alkyl or (C₃-C₆)cycloalkyl;

When either of Cy or A are substituted with one or more groups, the substituents at each occurrence may be independently selected from hydroxyl, oxo, halo, thiol, nitro, amino, cyano, formyl, or substituted or unsubstituted groups selected from amidino, alkyl, haloalkyl, perhaloalkyl, alkoxy, haloalkoxy, perhaloalkoxy, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, bicycloalkyl, bicycloalkenyl, alkoxy, alkenoxy, cycloalkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyl, heterocyclalkyl, heterocycloxy, heterocyclalkoxy, heterocyclalkoxyacyl, acyl, acyloxy, acylamino, monosubstituted or disubstituted amino, arylamino, aralkylamino, carboxylic acid and its derivatives such as esters and amides, carbonylamino, hydroxyalkyl, aminoalkyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthio, thioalkyl, cycloalkylthio, arylthio, heterocyclthio, alkylsulfinyl, cycloalkylsulfinyl, arylsulfinyl, heterocyclsulfinyl, alkylsulfonyl, cycloalkylsulfonyl, arylsulfonyl, heterocyclsulfonyl, alkylsulfonylamino, cycloalkylsulfonylamino, arylsulfonylamino, heterocyclsulfonylamino, alkylsulfonyloxy, cycloalkylsulfonyloxy, arylsulfonyloxy, heterocyclsulfonyloxy, alkoxycarbonylamino, aryloxycarbonylamino, aralkyloxycarbonylamino, aminocarbonylamino, alkylaminocarbonylamino, alkoxyamino, hydroxyl amino, sulfinyl derivatives, sulfonyl derivatives, sulfonic acid and its derivatives.

When one or more of R₁, R₃ or R₄ are substituted, the substituents at each occurrence may be independently selected from hydroxyl, oxo, halo, thiol, nitro, amino, cyano, formyl, or substituted or unsubstituted groups selected from amidino, alkyl, haloalkyl, perhaloalkyl, alkoxy, haloalkoxy, perhaloalkoxy, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, bicycloalkyl, bicycloalkenyl, alkoxy, alkenoxy, cycloalkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyl, heterocyclalkyl, heterocycloxy, heterocyclalkoxy,

heterocyclalkoxyacyl, acyl, acyloxy, acylamino, monosubstituted or disubstituted amino, arylamino, aralkylamino, carboxylic acid and its derivatives such as esters and amides, carbonylamino, hydroxyalkyl, aminoalkyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthio, thioalkyl, cycloalkylthio, arylthio, heterocyclthio, alkylsulfinyl, cycloalkylsulfinyl, arylsulfinyl, heterocyclsulfinyl, alkylsulfonyl, cycloalkylsulfonyl, arylsulfonyl, heterocyclsulfonyl, alkylsulfonylamino, cycloalkylsulfonylamino, arylsulfonylamino, heterocyclsulfonylamino, alkylsulfonyloxy, cycloalkylsulfonyloxy, arylsulfonyloxy, heterocyclsulfonyloxy, alkoxycarbonylamino, aryloxycarbonylamino, aralkyloxycarbonylamino, aminocarbonylamino, alkylaminocarbonylamino, alkoxyamino, hydroxyl amino, sulfinyl derivatives, sulfonyl derivatives, sulfonic acid and its derivatives.

When the substituents on any of A, Cy, R₁, R₃ or R₄ are further substituted, the substituents may be selected from one or more groups described above.

In one of the preferred embodiment A is selected from optionally substituted phenyl, pyridine, thiophene, pyrimidine, benzo[d]thiazole and quinolone groups. In a more preferred embodiment A is optionally substituted phenyl and benzo[d]thiazole group.

In another preferred embodiment of present invention 'Y' is selected from -C(O)-, -S(O)_o-, -(C₁-C₃)alkyl-, -C(O)N(R₅)-, -N(R₅)-, -C(O)CH(R₅)₂-. In more preferred embodiment Y is -C(O)- and -C(O)N(R₅)₂-; R₅ is as defined earlier

In another preferred embodiment of present invention 'Z' is selected from -O-, -S(O)_o-, -C(O)-, -N(R₅)-, -(C(R₅)₂)_p-, -O(C(R₅)₂)_p-, -O(C(R₅)₂)_pO-, S(O)_o(C(R₅)₂)_p-, -S(O)_o(C(R₅)₂)_pS(O)_o-; -N(R₅)(C(R₅)₂)_p-, -NHC(O)-, -NHC(O)NH-, or ; R₅ is as defined earlier;

In a more preferred embodiment 'Z' is selected from -O-, -S(O)_o-, -N(R₅)-, -(C(R₅)₂)_p-, -O(C(R₅)₂)_p-, or .

In another preferred embodiment of present invention 'X' independently represent a carbon atom.

In yet another preferred embodiment 'Q' represents oxygen atom and integers of m and n are independently 1 to form an oxetane ring. The various groups, radicals and substituents used anywhere in the specification are described in the following paragraphs.

In a further preferred embodiment the groups, radicals described above may be selected from:

- the “alkyl” group used either alone or in combination with other radicals, denotes a linear or branched radical containing one to six carbons, selected from methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *tert*-butyl, amyl, *t*-amyl, *n*-pentyl, *n*-hexyl, and the like;
- 5 - the “alkenyl” group used either alone or in combination with other radicals, is selected from a radical containing from two to six carbons, more preferably groups selected from vinyl, allyl, 2-butenyl, 3-butenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl and the like; the “alkenyl” group includes dienes and trienes of straight and branched chains;
- 10 - the “cycloalkyl”, or “alicyclic” group used either alone or in combination with other radicals, is selected from a cyclic radical containing three to eight carbons, more preferably cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and the like;
- the “cycloalkenyl” group used either alone or in combination with other radicals, are preferably selected from cyclopropenyl, 1-cyclobutenyl, 2-cyclobutenyl, 1-cyclopentenyl, 2-cyclopentenyl, 3-cyclopentenyl, 1-cyclohexenyl, 2-cyclohexenyl, 3-cyclohexenyl and the like; The terms “bicycloalkenyl” means more than one cycloalkenyl groups fused together;
- 15 - the “alkoxy” group used either alone or in combination with other radicals, is selected from groups containing an alkyl radical, as defined above, attached directly to an oxygen atom, more preferably groups selected from methoxy, ethoxy, *n*-propoxy, *iso*-propoxy, *n*-butoxy, *t*-butoxy, *iso*-butoxy, pentyloxy, hexyloxy, and the like;
- 20 - the “cycloalkoxy” group used either alone or in combination with other radicals, is selected from a cyclic radical containing three to seven carbons, more preferably cyclopropyloxy, cyclobutylxoy, cyclopentyloxy, cyclohexyloxy and the like; The terms “bicycloalkyloxy” means more than one cycloalkyl groups fused together;
- 25 - the “alkenoxy” group used either alone or in combination with other radicals, is selected from groups containing an alkenyl radical, as defined above, attached to an oxygen atom, more preferably selected from vinyloxy, allyloxy, butenoxy, pentenoxy, hexenoxy, and the like;
- 30 - the “haloalkyl” group is selected from an alkyl radical, as defined above, suitably substituted with one or more halogens; such as perhaloalkyl, more preferably, perfluoro(C₁-C₆)alkyl such as fluoromethyl, difluoromethyl, trifluoromethyl,

fluoroethyl, difluoroethyl, trifluoroethyl, mono or polyhalo substituted methyl, ethyl, propyl, butyl, pentyl or hexyl groups;

- the “haloalkoxy” group is selected from suitable haloalkyl, as defined above, directly attached to an oxygen atom, more preferably groups selected from fluoromethoxy, chloromethoxy, fluoroethoxy, chloroethoxy and the like;
- the “aryl” or “aromatic” group used either alone or in combination with other radicals, is selected from a suitable aromatic system containing one, two or three rings wherein such rings may be attached together in a pendant manner or may be fused, more preferably the groups are selected from phenyl, naphthyl, tetrahydronaphthyl, indane, biphenyl, and the like;
- the “aryloxy” group used either alone or in combination with other radicals, is selected from groups containing an aryl radical, as defined above, attached directly to an oxygen atom, more preferably groups selected from phenoxy, naphthyloxy, tetrahydronaphthyloxy, biphenyloxy, and the like; the “heterocyclyl” or “heterocyclic” group used either alone or in combination with other radicals, is selected from suitable aromatic or non-aromatic radicals containing one or more hetero atoms selected from O, N or S. The non-aromatic radicals may be saturated, partially saturated or unsaturated mono, bi, tri or spirocyclic radicals, containing one or more heteroatoms selected from nitrogen, sulfur and oxygen, more preferably selected from aziridinyl, azetidiny, pyrrolidinyl, imidazolidinyl, piperidinyl, piperazinyl, 2-oxopiperidinyl, 4-oxopiperidinyl, 2-oxopiperazinyl, 3-oxopiperazinyl, morpholinyl, thiomorpholinyl, 2-oxomorpholinyl, azepinyl, diazepinyl, oxapinyl, thiazepinyl, oxazolidinyl, thiazolidinyl, dihydrothiophene, dihydropyran, dihydrofuran, dihydrothiazole, benzopyranyl, benzopyranonyl, benzodihydrofuranyl, benzodihydrothienyl, pyrazolopyrimidonyl, azaquinazolinoyl, thienopyrimidonyl, quinazolinoyl, pyrimidonyl, benzoxazinyl, benzoxazinonyl, benzothiazinyl, benzothiazinonyl, thienopiperidinyl, hexahydro-1H-furo[3,4-c]pyrrolyl, azaspiro[3.5]nonanyl, azaspiro[3.3]heptanyl, hexahydrocyclopenta[c]pyrrolyl, tetrahydrocyclopenta[c]pyrrolyl, azepanyl, azabicyclo[3.2.1]octanyl, hexahydropyrrolo[3,4-c]pyrrolyl, tetrahydropyrrolo[3,4-c]pyrrolyl, dihydropyrrolo[3,4-c]pyrrolyl, dihydropyrrolo[3,4-c]pyrazolyl, dihydroquinolinyl, tetrahydroquinolinyl, dihydroisoquinolinyl, tetrahydroisoquinolinyl, dihydropyrrolo[3,4-c]pyrazolyl and the like; the aromatic radicals, may be selected

- from suitable single or fused mono, bi or tricyclic aromatic heterocyclic radicals containing one or more hetero atoms selected from O, N or S, more preferably the groups are selected from pyridyl, thienyl, furyl, pyrrolyl, oxazolyl, thiazolyl, isothiazolyl, imidazolyl, isoxazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, benzofuranyl, benzothienyl, indolinyl, indolyl, azaindolyl, azaindolyl, pyrazolopyrimidinyl, azaquinazolinyl, pyridofuranyl, pyridothienyl, thienopyrimidinyl, quinolinyl, pyrimidinyl, pyrazolyl, quinazolinyl, pyrazinyl, pyridazinyl, triazinyl, benzimidazolyl, benzotriazolyl, phthalazynil, naphthylidinyl, purinyl, carbazolyl, phenothiazinyl, phenoxazinyl, benzoxazolyl, benzothiazolyl and the like;
- 5 benzofuranyl, benzothienyl, indolinyl, indolyl, azaindolyl, azaindolyl, pyrazolopyrimidinyl, azaquinazolinyl, pyridofuranyl, pyridothienyl, thienopyrimidinyl, quinolinyl, pyrimidinyl, pyrazolyl, quinazolinyl, pyrazinyl, pyridazinyl, triazinyl, benzimidazolyl, benzotriazolyl, phthalazynil, naphthylidinyl, purinyl, carbazolyl, phenothiazinyl, phenoxazinyl, benzoxazolyl, benzothiazolyl and the like;
- 10 - the groups “heterocycloxy”, “heterocylylalkoxy” are selected from suitable heterocyclyl, heterocylylalkyl groups respectively, as defined above, attached to an oxygen atom;
- 15 - the “acyl” group used either alone or in combination with other radicals, is selected from a radical containing one to eight carbons, more preferably selected from formyl, acetyl, propanoyl, butanoyl, *iso*-butanoyl, pentanoyl, hexanoyl, heptanoyl, benzoyl and the like, which may be substituted;
- 20 - the “acyloxy” group used either alone or in combination with other radicals, is selected from a suitable acyl group, as defined above, directly attached to an oxygen atom, more preferably such groups are selected from acetyloxy, propionyloxy, butanoyloxy, *iso*-butanoyloxy, benzoyloxy and the like;
- 25 - the “acylamino” group used either alone or in combination with other radicals, is selected from a suitable acyl group as defined earlier, attached to an amino radical, more preferably such groups are selected from CH₃CONH, C₂H₅CONH, C₃H₇CONH, C₄H₉CONH, C₆H₅CONH and the like, which may be substituted;
- 30 - the “mono-substituted amino” group used either alone or in combination with other radicals, represents an amino group substituted with one group selected from (C₁-C₆)alkyl, substituted alkyl, aryl, substituted aryl or arylalkyl groups as defined earlier, more preferably such groups are selected from methylamine, ethylamine, *n*-propylamine, *n*-butylamine, *n*-pentylamine and the like;
- 30 - the “disubstituted amino” group used either alone or in combination with other radicals, represents an amino group, substituted with two radicals that may be same or different selected from (C₁-C₆)alkyl, substituted alkyl, aryl, substituted aryl, or arylalkyl groups,

- as defined above, more preferably the groups are selected from dimethylamino, methylethylamino, diethylamino, phenylmethyl amino and the like;
- the “arylamino” used either alone or in combination with other radicals, represents an aryl group, as defined above, linked through amino having a free valence bond from the nitrogen atom, more preferably the groups are selected from phenylamino, naphthylamino, N-methyl anilino and the like;
 - the “oxo” or “carbonyl” group used either alone ($-C=O-$) or in combination with other radicals such as alkyl described above, for e.g. “alkylcarbonyl”, denotes a carbonyl radical ($-C=O-$) substituted with an alkyl radical described above such as acyl or alkanoyl;
 - the “carboxylic acid” group, used alone or in combination with other radicals, denotes a $-COOH$ group, and includes derivatives of carboxylic acid such as esters and amides;
 - the “ester” group used alone or in combination with other radicals, denotes $-COO-$ group, and includes carboxylic acid derivatives, more preferably the ester moieties are selected from alkoxycarbonyl, such as methoxycarbonyl, ethoxycarbonyl, and the like, which may optionally be substituted; aryloxycarbonyl group such as phenoxycarbonyl, naphthyloxycarbonyl, and the like, which may optionally be substituted; aralkoxycarbonyl group such as benzyloxycarbonyl, phenethyloxycarbonyl, naphthylmethoxycarbonyl, and the like, which may optionally be substituted; heteroaryloxycarbonyl, heteroaralkoxycarbonyl, wherein the heteroaryl group, is as defined above, which may optionally be substituted; heterocyclyloxycarbonyl, where the heterocyclic group, as defined earlier, which may optionally be substituted;
 - the “amide” group used alone or in combination with other radicals, represents an aminocarbonyl radical ($H_2N-C=O$), wherein the amino group is mono- or di-substituted or unsubstituted, more preferably the groups are selected from methyl amide, dimethyl amide, ethyl amide, diethyl amide, and the like;
 - the “aminocarbonyl” group used either alone or in combination with other radicals, may be selected from ‘aminocarbonyl’, ‘aminocarbonylalkyl’, “n-alkylaminocarbonyl”, “N-arylamino carbonyl”, “N,N-dialkylaminocarbonyl”, “N-alkyl-N-arylamino carbonyl”, “N-alkyl-N-hydroxyaminocarbonyl”, and “N-alkyl-N-hydroxyaminocarbonylalkyl”, each of them being optionally substituted. The terms “N-alkylaminocarbonyl” and “N,N-dialkylaminocarbonyl” denotes aminocarbonyl radicals, as defined above, which have been substituted with one alkyl radical and with

- two alkyl radicals, respectively. Preferred are “lower alkylaminocarbonyl” having lower alkyl radicals as described above attached to aminocarbonyl radical. The terms “N-arylaminocarbonyl” and “N-alkyl-N-arylaminocarbonyl” denote aminocarbonyl radicals substituted, respectively, with one aryl radical, or one alkyl, and one aryl radical. The term “aminocarbonylalkyl” includes alkyl radicals substituted with aminocarbonyl radicals;
- the “hydroxyalkyl” group used either alone or in combination with other radicals, is selected from an alkyl group, as defined above, substituted with one or more hydroxy radicals, more preferably the groups are selected from hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, hydroxypentyl, hydroxyhexyl and the like;
 - the “aminoalkyl” group used alone or in combination with other radicals, denotes an amino ($-NH_2$) moiety attached to an alkyl radical, as defined above, which may be substituted, such as mono- and di-substituted aminoalkyl. The term “alkylamino” used herein, alone or in combination with other radicals, denotes an alkyl radical, as defined above, attached to an amino group, which may be substituted, such as mono- and di-substituted alkylamino;
 - the “alkoxyalkyl” group used alone or in combination with other radicals, denotes an alkoxy group, as defined above, attached to an alkyl group as defined above, more preferably the groups may be selected from methoxymethyl, ethoxymethyl, methoxyethyl, ethoxyethyl and the like;
 - the “alkylthio” group used either alone or in combination with other radicals, denotes a straight or branched or cyclic monovalent substituent comprising an alkyl group as defined above, linked through a divalent sulfur atom having a free valence bond from the sulfur atom, more preferably the groups may be selected from methylthio, ethylthio, propylthio,
 - the “thioalkyl” group used either alone or in combination with other radicals, denotes an alkyl group, as defined above, attached to a group of formula $-SR'$, where R' represents hydrogen, alkyl or aryl group, e.g. thiomethyl, methylthiomethyl, phenylthiomethyl and the like, which may be optionally substituted.
 - the “alkoxycarbonylamino” group used alone or in combination with other radicals, is selected from a suitable alkoxycarbonyl group, as defined above, attached to an amino group, more preferably methoxycarbonylamino, ethoxycarbonylamino, and the like;

- the “arylthio” group used either alone or in combination with other radicals, denotes an aryl group as defined above, linked through a divalent sulfur atom having a free valence bond from the sulfur atom, more preferably the groups may be selected from phenylthio, naphthylthio, tetrahydronaphthylthio, indanethio, biphenylthio, and the like;
- the “heterocyclthio” group used either alone or in combination with other radicals, denotes an heterocycl group as defined above, linked through a divalent sulfur atom having a free valence bond from the sulfur atom, more preferably the groups may be selected from aziridinylthio, azetidinythio, pyrrolidinylthio, imidazolidinylthio, piperidinylthio, piperazinylthio, 2-oxopiperidinylthio, 4-oxopiperidinylthio, 2-oxopiperazinylthio, 3-oxopiperazinylthio, morpholinylthio, thiomorpholinylthio, 2-oxomorpholinylthio, azepinylthio, diazepinylthio, oxapinylthio, thiazepinylthio, oxazolidinylthio, thiazolidinylthio, dihydrothiophenethio, dihydropyranthio, dihydrofuranthio, dihydrothiazoethio, benzopyranthio, benzopyranonylthio, benzodihydrofuranthio, benzodihydrothienylthio, pyrazolopyrimidinylthio, azaquinazolinylthio, thienopyrimidinylthio, quinazolonylthio, pyrimidinylthio, benzoxazinylthio, benzoxazinonylthio, benzothiazinylthio, benzothiazinonylthio, thieno piperidinylthio, pyridylthio, thienylthio, furylthio, pyrrolylthio, oxazolylthio, thiazolylthio, isothiazolylthio, imidazolylthio, isoxazolylthio, oxadiazolylthio, thiadiazolylthio, triazolylthio, tetrazolylthio, benzofuranthio, benzothienylthio, indolinylthio, indolylthio, azaindolylthio, azaindolinythio, pyrazolopyrimidinylthio, azaquinazolinylthio, pyridofuranthio, pyridothienylthio, thienopyrimidinylthio, quinolinylthio, pyrimidinylthio, pyrazolylthio, quinazolinythio, pyridazinylthio, triazinylthio, benzimidazolylthio, benzotriazolylthio, phthalazynilthio, naphthylidinylthio, purinylthio, carbazolylthio, phenothiazinylthio, phenoxazinylthio, benzoxazolylthio, benzothiazolylthio and the like;
- the “alkoxycarbonylamino” group used alone or in combination with other radicals, is selected from a suitable alkoxycarbonyl group, as defined above, attached to an amino group, more preferably methoxycarbonylamino, ethoxycarbonylamino, and the like;
- the “aminocarbonylamino”, “alkylaminocarbonylamino”, “dialkylaminocarbonylamino” groups used alone or in combination with other radicals, is a carbonylamino ($-\text{CONH}_2$) group, attached to amino(NH_2), alkylamino group or dialkylamino group respectively, where alkyl group is as defined above;

- the “amidino” group used either alone or in combination with other radicals, represents a $-C(=NH)-NH_2$ radical; the “alkylamidino” group represents an alkyl radical, as described above, attached to an amidino group;
- the “alkoxyamino” group used either alone or in combination with other radicals, represents a suitable alkoxy group as defined above, attached to an amino group;
- the “hydroxyamino” group used either alone or in combination with other radicals, represents a $-NHOH$ moiety, and may be optionally substituted with suitable groups selected from those described above;
- the “sulfenyl” group or “sulfenyl derivatives” used alone or in combination with other radicals, represents a bivalent group, $-SO-$ or R_xSO , where R_x is an optionally substituted alkyl, aryl, heteroaryl, heterocyclyl, group selected from those described above;
- the “sulfonyl” group or “sulfones derivatives” used either alone or in combination with other radicals, with other terms such as alkylsulfonyl, represents a divalent radical $-SO_2-$, or R_xSO_2- , where R_x is as defined above. More preferably, the groups may be selected from “alkylsulfonyl” wherein suitable alkyl radicals, selected from those defined above, is attached to a sulfonyl radical, such as methylsulfonyl, ethylsulfonyl, propylsulfonyl and the like, “arylsulfonyl” wherein an aryl radical, as defined above, is attached to a sulfonyl radical, such as phenylsulfonyl and the like.
- The term “combination therapy” means the administration of two or more therapeutic agents to treat a therapeutic condition or disorder described in the present disclosure. Such administration encompasses co-administration of these therapeutic agents in a substantially simultaneous manner, such as in a single capsule having a fixed ratio of active ingredients or in multiple, separate capsules for each active ingredient. In addition, such administration also encompasses use of each type of therapeutic agent in a sequential manner. In either case, the treatment regimen will provide beneficial effects of the drug combination in treating the conditions or disorders described herein.
- The phrase “therapeutically effective” is intended to qualify the amount of active ingredients used in the treatment of a disease or disorder. This amount will achieve the goal of reducing or eliminating the said disease or disorder.
- The term “therapeutically acceptable” refers to those compounds (or salts, prodrugs, tautomers, zwitterionic forms, etc.) which are suitable for use in contact with the tissues

of patients without undue toxicity, irritation, and allergic response, are commensurate with a reasonable benefit/risk ratio, and are effective for their intended use.

- As used herein, reference to "treatment" of a patient is intended to include prophylaxis. The term "patient" means all mammals including humans. Examples of patients include humans, cows, dogs, cats, goats, sheep, pigs, and rabbits. Preferably, the patient is a human.

Suitable groups and substituents on the groups may be selected from those described anywhere in the specification.

Particularly useful compounds of formula (I) may be selected from-

- 10 (4-(3-hydroxyoxetan-3-yl)phenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;
- (4-(3-methoxyoxetan-3-yl)phenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;
- 3-(4-((4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methyl)phenyl)oxetan-3-ol;
- 15 (4-(3-hydroxyoxetan-3-yl)phenyl)(4-(4-((trifluoromethyl)sulfonyl)phenoxy)piperidin-1-yl)methanone;
- 4-((1-(4-(3-hydroxyoxetan-3-yl)benzoyl)piperidin-4-yl)oxy)benzoic acid;
- N-cyclopropyl-4-((1-(4-(3-hydroxyoxetan-3-yl)benzoyl)piperidin-4-yl)oxy)benzamide;
- 20 (4-(3-methoxypyrrolidin-3-yl)phenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;
- (4-(3-hydroxypyrrolidin-3-yl)phenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;
- (4-(3-hydroxy-1,1-dioxidothietan-3-yl)phenyl)(4-((5-(trifluoromethyl)pyridin-2-yl)oxy)piperidin-1-yl)methanone;
- 25 (4-(3-hydroxy-1,1-dioxidothietan-3-yl)phenyl)(4-(4-(trifluoromethyl)benzyl)piperidin-1-yl)methanone;
- 3-(4-((1-((4-(trifluoromethyl)phenyl)sulfonyl)piperidin-4-yl)amino)phenyl)oxetan-3-ol;
- 30 3-(4-((4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)sulfonyl)phenyl)oxetan-3-ol;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((5-(trifluoromethyl)pyridin-2-yl)sulfonyl)piperidin-1-yl)methanone;

- (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((5-(trifluoromethyl)pyridin-2-yl)sulfinyl)piperidin-1-yl)methanone;
- (3-(3-hydroxyoxetan-3-yl)phenyl)(4-((4-(trifluoromethyl)phenyl)sulfonyl)piperidin-1-yl)methanone;
- 5 1-(4-(3-hydroxyoxetan-3-yl)benzoyl)-4-(4-(trifluoromethyl)benzyl)piperidine-4-carboxylic acid;
- N-(3-(3-hydroxyoxetan-3-yl)-5-morpholinophenyl)-4-(4-(trifluoromethyl)phenoxy)piperidine-1-carboxamide;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((4-(trifluoromethyl)phenyl)amino)piperidin-1-yl)methanone;
- 10 (4-(3-methoxyoxetan-3-yl)phenyl)(4-((4-(trifluoromethyl)phenyl)amino)piperidin-1-yl)methanone;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(4-(methyl(4-(trifluoromethyl)phenyl)amino)piperidin-1-yl)methanone;
- 15 (3-(3-hydroxyoxetan-3-yl)phenyl)(3-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(3-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;
- (4-(3-methoxyoxetan-3-yl)phenyl)(3-(4-(trifluoromethyl)phenoxy)pyrrolidin-1-yl)methanone;
- 20 (4-(3-hydroxyoxetan-3-yl)phenyl)(3-(4-(trifluoromethyl)phenoxy)pyrrolidin-1-yl)methanone;
- (3-(3-methoxyoxetan-3-yl)phenyl)(3-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;
- 25 (4-([1,1'-biphenyl]-4-yloxy)piperidin-1-yl)(4-(3-hydroxyoxetan-3-yl)phenyl)methanone;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((2'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)oxy)piperidin-1-yl)methanone;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((3'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)oxy)piperidin-1-yl)methanone;
- 30 (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((4'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)oxy)piperidin-1-yl)methanone;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(4-(4-isopropylphenoxy)piperidin-1-yl)methanone;

- (4-(2-chloro-5-(trifluoromethyl)phenoxy)piperidin-1-yl)(4-(3-hydroxyoxetan-3-yl)phenyl)methanone;
(4-(4-(1H-imidazol-1-yl)phenoxy)piperidin-1-yl)(4-(3-hydroxyoxetan-3-yl)phenyl)methanone;
5 (4-((1-(4-(3-hydroxyoxetan-3-yl)benzoyl)piperidin-4-yl)oxy)phenyl)(morpholino)methanone;
4-((1-(4-(3-hydroxyoxetan-3-yl)benzoyl)piperidin-4-yl)oxy)benzonitrile;
(4-(3-hydroxyoxetan-3-yl)phenyl)(4-(4-(2-phenylpropan-2-yl)phenoxy)piperidin-1-yl)methanone;
10 (4-(3-hydroxyoxetan-3-yl)phenyl)(4-(4-phenoxyphenoxy)piperidin-1-yl)methanone;
(4-(3-chloro-4-(trifluoromethyl)phenoxy)piperidin-1-yl)(4-(3-hydroxyoxetan-3-yl)phenyl)methanone;
(4-(3-hydroxyoxetan-3-yl)phenyl)(4-(2-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;
15 (4-(3-hydroxyoxetan-3-yl)phenyl)(4-(3-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;
(4-(3-hydroxyoxetan-3-yl)phenyl)(4-(4-methoxyphenoxy)piperidin-1-yl)methanone;
(4-(4-(2H-tetrazol-5-yl)phenoxy)piperidin-1-yl)(4-(3-hydroxyoxetan-3-yl)phenyl)methanone;
20 (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((4-(trifluoromethyl)phenoxy)methyl)piperidin-1-yl)methanone;
(4-(3-hydroxyoxetan-3-yl)phenyl)(4-(2-(4-(trifluoromethyl)phenoxy)ethyl)piperazin-1-yl)methanone;
(4-(3-hydroxyoxetan-3-yl)phenyl)(4-(4-((trifluoromethyl)thio)phenoxy)piperidin-1-yl)methanone;
25 (4-(3-methoxyoxetan-3-yl)phenyl)(4-(4-((trifluoromethyl)thio)phenoxy)piperidin-1-yl)methanone;
(4-(3-(methoxy-d3)oxetan-3-yl)phenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;
30 (4-(3-((tetrahydro-2H-pyran-4-yl)methoxy)oxetan-3-yl)phenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;
(4-(3-hydroxyoxetan-3-yl)phenyl)(4-((5-(methylthio)pyrimidin-2-yl)oxy)piperidin-1-yl)methanone;

- (4-(3-isobutoxyoxetan-3-yl)phenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;
- (4-(4-(3-hydroxyoxetan-3-yl)benzoyl)piperazin-1-yl)(4-(trifluoromethyl)phenyl)methanone;
- 5 (1-(4-(3-hydroxyoxetan-3-yl)benzoyl)piperidin-4-yl)(4-(trifluoromethyl)phenyl)methanone;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(2-(4-(trifluoromethyl)phenoxy)-7-azaspiro[3.5]nonan-7-yl)methanone;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(6-(4-(trifluoromethyl)phenoxy)-2-azaspiro[3.3]heptan-2-yl)methanone;
- 10 (4-(3-methoxyoxetan-3-yl)phenyl)(6-(4-(trifluoromethyl)phenoxy)-2-azaspiro[3.3]heptan-2-yl)methanone;
- (4-(4-hydroxypiperidin-4-yl)phenyl)(5-(4-(trifluoromethyl)phenoxy)hexahydrocyclopenta[c]pyrrol-2(1H)-yl)methanone
- 15 hydrochloride;
- (4-(4-methoxypiperidin-4-yl)phenyl)(5-(4-(trifluoromethyl)phenoxy)hexahydrocyclopenta[c]pyrrol-2(1H)-yl)methanone
- hydrochloride;
- tert*-butyl 4-hydroxy-4-(4-(5-(4-(trifluoromethyl)phenoxy)octahydrocyclopenta[c]pyrrole-2-carbonyl)phenyl)piperidine-1-carboxylate;
- 20 (4-(4-(3-methoxyoxetan-3-yl)benzoyl)piperazin-1-yl)(4-(trifluoromethyl)phenyl)methanone;
- (4-(3-methoxyoxetan-3-yl)phenyl)(2-(4-(trifluoromethyl)phenoxy)-7-azaspiro[3.5]nonan-7-yl)methanone;
- 25 (4-(3-methoxyoxetan-3-yl)phenyl)(4-((5-(trifluoromethyl)thiophen-3-yl)oxy)piperidin-1-yl)methanone;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((5-(methylthio)pyrimidin-2-yl)amino)piperidin-1-yl)methanone;
- 30 N-(1-(4-(3-hydroxyoxetan-3-yl)benzoyl)piperidin-4-yl)-4-(trifluoromethyl)benzenesulfonamide;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((5-(trifluoromethyl)thiophen-3-yl)oxy)piperidin-1-yl)methanone;

- (3-(3-hydroxyoxetan-3-yl)phenyl)(4-(3-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((6-(trifluoromethyl)pyridin-3-yl)amino)piperidin-1-yl)methanone;
- 5 (4-(4-hydroxytetrahydro-2H-pyran-4-yl)phenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;
- (4-(3-hydroxyoxetan-3-yl)-3,5-dimethoxyphenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((5-(trifluoromethyl)pyridin-2-yl)amino)piperidin-1-yl)methanone;
- 10 (3-(3-hydroxyoxetan-3-yl)phenyl)(4-((4-(trifluoromethyl)phenyl)amino)piperidin-1-yl)methanone;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((3-(trifluoromethyl)phenyl)amino)piperidin-1-yl)methanone;
- 15 (3-(3-hydroxyoxetan-3-yl)phenyl)(4-((3-(trifluoromethyl)phenyl)amino)piperidin-1-yl)methanone;
- (2-fluoro-4-(3-hydroxyoxetan-3-yl)phenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((4-(trifluoromethyl)pyrimidin-2-yl)oxy)piperidin-1-yl)methanone;
- 20 (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((4-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)methanone;
- (4-(4-(difluoromethyl)phenoxy)piperidin-1-yl)(4-(3-hydroxyoxetan-3-yl)phenyl)methanone;
- 25 (4-(3-hydroxyoxetan-3-yl)phenyl)(4-(4-(trifluoromethyl)phenoxy)azepan-1-yl)methanone;
- (4-(3-hydroxyoxetan-3-yl)-2-methoxyphenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(4-(4-thiomorpholinophenoxy)piperidin-1-yl)methanone;
- 30 (4-(3-hydroxytetrahydrofuran-3-yl)phenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;

- (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)methanone;
(5-(3-hydroxyoxetan-3-yl)pyridin-3-yl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;
- 5 (5-(3-hydroxyoxetan-3-yl)pyridin-3-yl)(5-(4-(trifluoromethyl)phenoxy)hexahydrocyclopenta[c]pyrrol-2(1H)-yl)methanone;
(4-(3-hydroxyoxetan-3-yl)phenyl)(3-(4-(trifluoromethyl)phenoxy)azetidin-1-yl)methanone;
- 10 (4-(3-methoxyoxetan-3-yl)phenyl)(3-(4-(trifluoromethyl)phenoxy)azetidin-1-yl)methanone;
(3-(3-hydroxyoxetan-3-yl)phenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;
(4-(3-hydroxyoxetan-3-yl)phenyl)(3-(4-(trifluoromethyl)phenoxy)-8-azabicyclo[3.2.1]octan-8-yl)methanone;
- 15 (3-(3-hydroxyoxetan-3-yl)phenyl)(3-(4-(trifluoromethyl)phenoxy)-8-azabicyclo[3.2.1]octan-8-yl)methanone;
(4-(3-hydroxyoxetan-3-yl)phenyl)(5-(4-(trifluoromethyl)benzyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methanone;
4-(3-hydroxyoxetan-3-yl)-N-(1-(4-(trifluoromethyl)benzyl)pyrrolidin-3-yl)benzamide;
- 20 4-(3-hydroxyoxetan-3-yl)-N-(1-(3-(trifluoromethyl)benzyl)pyrrolidin-3-yl)benzamide;
4-(3-hydroxyoxetan-3-yl)-N-(1-(2-(trifluoromethyl)benzyl)pyrrolidin-3-yl)benzamide;
- 25 (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((4-(trifluoromethyl)benzyl)amino)piperidin-1-yl)methanone;
(4-(3-hydroxyoxetan-3-yl)phenyl)(4-(methyl(4-(trifluoromethyl)benzyl)amino)piperidin-1-yl)methanone;
- 30 2-(4-(3-hydroxyoxetan-3-yl)phenyl)-2-methyl-1-(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)propan-1-one;
2-(4-(3-methoxyoxetan-3-yl)phenyl)-2-methyl-1-(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)propan-1-one;

- (3-fluoro-4-(3-hydroxyoxetan-3-yl)phenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;
- (4-(3-hydroxyoxetan-3-yl)-3-methylphenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;
- 5 (3-(3-methoxyoxetan-3-yl)phenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;
- (3-fluoro-4-(3-methoxyoxetan-3-yl)phenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;
- (4-(3-methoxyoxetan-3-yl)-3-methylphenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;
- 10 *tert*-butyl 3-hydroxy-3-(4-(4-(4-(trifluoromethyl)phenoxy)piperidine-1-carbonyl)phenyl)pyrrolidine-1-carboxylate;
- (4-(3-hydroxyoxetan-3-yl)-2-methylphenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;
- 15 (4-(3-methoxyoxetan-3-yl)-2-methylphenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((5-(trifluoromethyl)pyridin-2-yl)oxy)piperidin-1-yl)methanone;
- (4-(3-methoxyoxetan-3-yl)phenyl)(4-((5-(trifluoromethyl)pyridin-2-yl)oxy)piperidin-1-yl)methanone;
- 20 (4-(3-hydroxyoxetan-3-yl)-3-methoxyphenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;
- (4-(3-hydroxyoxetan-3-yl)-2,6-dimethylphenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;
- 25 (3-methoxy-4-(3-methoxyoxetan-3-yl)phenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;
- (4-(3-methoxyoxetan-3-yl)-2,6-dimethylphenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;
- tert*-butyl 4-hydroxy-4-(4-(4-(4-(trifluoromethyl)phenoxy)piperidine-1-carbonyl)phenyl)piperidine-1-carboxylate;
- 30 (4-(4-hydroxypiperidin-4-yl)phenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone hydrochloride;

- 3-(4-(4-(4-(trifluoromethyl)phenoxy)piperidine-1-carbonyl)phenyl)oxetan-3-yl acetate;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((6-(trifluoromethyl)pyridin-3-yl)oxy)piperidin-1-yl)methanone;
- 5 (3-(3-hydroxyoxetan-3-yl)phenyl)(4-((6-(trifluoromethyl)pyridin-3-yl)oxy)piperidin-1-yl)methanone;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((4-(trifluoromethyl)phenyl)thio)piperidin-1-yl)methanone;
- (3-(3-hydroxyoxetan-3-yl)phenyl)(4-((4-(trifluoromethyl)phenyl)thio)piperidin-1-yl)methanone;
- 10 (4-(3-hydroxyoxetan-3-yl)phenyl)(5-(4-(trifluoromethyl)phenoxy)hexahydrocyclopenta[c]pyrrol-2(1H)-yl)methanone;
- (3-(3-hydroxyoxetan-3-yl)phenyl)(5-(4-(trifluoromethyl)phenoxy)hexahydrocyclopenta[c]pyrrol-2(1H)-yl)methanone;
- 15 (4-(3-hydroxyoxetan-3-yl)phenyl)(4-(4-(trifluoromethyl)benzylidene)piperidin-1-yl)methanone;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(4-(4-(trifluoromethyl)benzyl)piperidin-1-yl)methanone;
- (3-(3-hydroxyoxetan-3-yl)phenyl)(4-(4-(trifluoromethyl)benzyl)piperidin-1-yl)methanone;
- 20 (4-(3-methoxyoxetan-3-yl)phenyl)(4-(4-(trifluoromethyl)benzyl)piperidin-1-yl)methanone;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((4-(trifluoromethyl)phenyl)sulfonyl)piperazin-1-yl)methanone;
- 25 (3-(3-methoxyoxetan-3-yl)phenyl)(4-(4-(trifluoromethyl)benzyl)piperidin-1-yl)methanone;
- (4-(3-methoxyoxetan-3-yl)phenyl)(4-((4-(trifluoromethyl)phenyl)sulfonyl)piperazin-1-yl)methanone;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(4-(4-(trifluoromethyl)benzyl)piperazin-1-yl)methanone;
- 30 (4-(3-hydroxyoxetan-3-yl)phenyl)(5-(4-(trifluoromethyl)benzyl)hexahydrocyclopenta[c]pyrrol-2(1H)-yl)methanone;

- (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((6-(trifluoromethyl)benzo[d]thiazol-2-yl)oxy)piperidin-1-yl)methanone;
- (4-(3-methoxyoxetan-3-yl)phenyl)(4-((6-(trifluoromethyl)benzo[d]thiazol-2-yl)oxy)piperidin-1-yl)methanone;
- 5 (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((6-(trifluoromethyl)benzo[d]thiazol-2-yl)amino)piperidin-1-yl)methanone;
- (4-(3-methoxyoxetan-3-yl)phenyl)(4-(4-(trifluoromethoxy)phenoxy)piperidin-1-yl)methanone;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(4-(4-(trifluoromethoxy)phenoxy)piperidin-1-yl)methanone;
- 10 (4-(3-hydroxythietan-3-yl)phenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;
- (4-(3-hydroxy-1,1-dioxidothietan-3-yl)phenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;
- 15 (4-(3-hydroxythietan-3-yl)phenyl)(4-(4-(trifluoromethyl)benzyl)piperidin-1-yl)methanone;
- (4-(3-hydroxythietan-3-yl)phenyl)(4-((5-(trifluoromethyl)pyridin-2-yl)oxy)piperidin-1-yl)methanone;
- (4-(3-hydroxytetrahydrothiophen-3-yl)phenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;
- 20 (4-(4-hydroxytetrahydro-2H-thiopyran-4-yl)phenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;
- (4-(4-hydroxy-1,1-dioxidotetrahydro-2H-thiopyran-4-yl)phenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;
- 25 (4-(3-methoxyoxetan-3-yl)phenyl)(4-(3-(4-(trifluoromethyl)phenoxy)propoxy)piperidin-1-yl)methanone;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(4-(3-(4-(trifluoromethyl)phenoxy)propoxy)piperidin-1-yl)methanone;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(4-(2-(4-(trifluoromethyl)phenoxy)ethoxy)piperidin-1-yl)methanone;
- 30 (4-(3-methoxyoxetan-3-yl)phenyl)(4-(2-(4-(trifluoromethyl)phenoxy)ethoxy)piperidin-1-yl)methanone;

- (4-(3-methoxyoxetan-3-yl)phenyl)(4-(2-(4-(trifluoromethyl)phenoxy)ethyl)piperidin-1-yl)methanone;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(4-(2-(4-(trifluoromethyl)phenoxy)ethyl)piperidin-1-yl)methanone;
- 5 (4-(3-hydroxyoxetan-3-yl)phenyl)(4-(2-((5-(trifluoromethyl)pyridin-2-yl)oxy)ethyl)piperidin-1-yl)methanone;
- (4-(3-methoxyoxetan-3-yl)phenyl)(4-(2-((5-(trifluoromethyl)pyridin-2-yl)oxy)ethyl)piperidin-1-yl)methanone;
- 10 N-(4-(3-hydroxyoxetan-3-yl)phenyl)-4-((6-(trifluoromethyl)pyridin-3-yl)oxy)piperidine-1-carboxamide;
- N-(3-(3-hydroxyoxetan-3-yl)phenyl)-4-(4-(trifluoromethyl)phenoxy)piperidine-1-carboxamide;
- N-(4-(3-hydroxyoxetan-3-yl)phenyl)-3-(4-(trifluoromethyl)phenoxy)-8-azabicyclo[3.2.1]octane-8-carboxamide;
- 15 N-(4-(3-hydroxyoxetan-3-yl)phenyl)-4-(4-(trifluoromethyl)phenoxy)piperidine-1-carboxamide;
- 4-(2-chloro-4-(trifluoromethyl)phenoxy)-N-(4-(3-hydroxyoxetan-3-yl)phenyl)piperidine-1-carboxamide;
- N-(4-(3-hydroxyoxetan-3-yl)phenyl)-5-(4-
- 20 (trifluoromethyl)phenoxy)hexahydrocyclopenta[c]pyrrole-2(1H)-carboxamide;
- N-(4-(3-hydroxyoxetan-3-yl)phenyl)-4-((6-(trifluoromethyl)benzo[d]thiazol-2-yl)amino)piperidine-1-carboxamide;
- N-(4-(3-methoxyoxetan-3-yl)phenyl)-4-((6-(trifluoromethyl)benzo[d]thiazol-2-yl)amino)piperidine-1-carboxamide;
- 25 1-(4-(3-hydroxyoxetan-3-yl)benzoyl)-N-(4-(trifluoromethyl)phenyl)piperidine-4-carboxamide;
- N-(4-(3-hydroxyoxetan-3-yl)phenyl)-1-(4-(trifluoromethyl)benzyl)piperidine-4-carboxamide;
- 4-(3-hydroxyoxetan-3-yl)-N-(6-(3-(trifluoromethyl)phenoxy)pyridin-3-yl)benzamide;
- 30 N-(4-(3-methoxyoxetan-3-yl)phenyl)-6-(3-(trifluoromethyl)phenoxy)nicotinamide;
- 3-(4-(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)phenyl)oxetan-3-ol;
- 3-(3-morpholino-5-(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)phenyl)oxetan-3-ol;

- (4-(3-hydroxyoxetan-3-yl)-2-morpholinophenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;
tert-butyl 4-(3-(3-hydroxyoxetan-3-yl)-5-(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)phenyl)piperazine-1-carboxylate;
- 5 (4-(3-hydroxyoxetan-3-yl)-2-(piperazin-1-yl)phenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;
(4-(3-hydroxyoxetan-3-yl)-2-(piperazin-1-yl)phenyl)(5-(4-(trifluoromethyl)phenoxy)hexahydrocyclopenta[c]pyrrol-2(1H)-yl)methanone;
(4-(1-hydroxycyclobutyl)phenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-
- 10 yl)methanone;
(4-(3-hydroxyoxetan-3-yl)phenyl)(4-((5-(trifluoromethyl)pyrimidin-2-yl)oxy)piperidin-1-yl)methanone;
(4-(3-hydroxyoxetan-3-yl)phenyl)(4-(methyl(5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)methanone;
- 15 (4-(3-hydroxyoxetan-3-yl)phenyl)(4-(2-((5-(trifluoromethyl)pyrimidin-2-yl)amino)ethyl)piperidin-1-yl)methanone;
(4-(3-hydroxyoxetan-3-yl)phenyl)(4-(2-((5-(trifluoromethyl)pyrimidin-2-yl)amino)ethoxy)piperidin-1-yl)methanone;
(4-(3-hydroxyoxetan-3-yl)phenyl)(4-(2-((5-(trifluoromethyl)pyrimidin-2-
- 20 yl)amino)ethyl)piperazin-1-yl)methanone;
(4-(3-hydroxyoxetan-3-yl)phenyl)(4-((4-methoxy-5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)methanone;
(4-(3-hydroxyoxetan-3-yl)phenyl)(4-((4-methoxy-5-(trifluoromethyl)pyrimidin-2-yl)oxy)piperidin-1-yl)methanone;
- 25 (4-((4-chloro-5-(trifluoromethyl)pyrimidin-2-yl)oxy)piperidin-1-yl)(4-(3-hydroxyoxetan-3-yl)phenyl)methanone;
(4-((4-chloro-5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)(4-(3-hydroxyoxetan-3-yl)phenyl)methanone;
2-((1-(4-(3-hydroxyoxetan-3-yl)benzoyl)piperidin-4-yl)amino)-5-
- 30 (trifluoromethyl)pyrimidine-4-carbonitrile;
2-((1-(4-(3-hydroxyoxetan-3-yl)benzoyl)piperidin-4-yl)oxy)-5-(trifluoromethyl)pyrimidine-4-carbonitrile;

- (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((5-(trifluoromethyl)pyrazin-2-yl)oxy)piperidin-1-yl)methanone;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((5-(trifluoromethyl)pyrazin-2-yl)amino)piperidin-1-yl)methanone;
- 5 (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((6-(trifluoromethyl)pyridazin-3-yl)amino)piperidin-1-yl)methanone;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((6-(trifluoromethyl)pyridazin-3-yl)oxy)piperidin-1-yl)methanone;
- 10 (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((6-(4-(trifluoromethyl)phenyl)pyridazin-3-yl)oxy)piperidin-1-yl)methanone;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((6-(4-(trifluoromethyl)phenyl)pyridazin-3-yl)amino)piperidin-1-yl)methanone;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((5-(4-(trifluoromethyl)phenyl)pyrimidin-2-yl)oxy)piperidin-1-yl)methanone;
- 15 (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((5-(4-(trifluoromethyl)phenyl)pyridin-2-yl)oxy)piperidin-1-yl)methanone;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((8-(trifluoromethyl)quinolin-4-yl)oxy)piperidin-1-yl)methanone;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((7-(trifluoromethyl)quinolin-4-yl)oxy)piperidin-1-yl)methanone;
- 20 (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((3-(trifluoromethyl)quinolin-7-yl)oxy)piperidin-1-yl)methanone;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((4-(trifluoromethyl)naphthalen-1-yl)oxy)piperidin-1-yl)methanone;
- 25 (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((4-(trifluoromethyl)-5,6,7,8-tetrahydronaphthalen-1-yl)oxy)piperidin-1-yl)methanone;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((6-(trifluoromethyl)naphthalen-2-yl)oxy)piperidin-1-yl)methanone;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((5-(4-(trifluoromethyl)phenyl)pyrimidin-2-yl)amino)piperidin-1-yl)methanone;
- 30 (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((4-(4-(trifluoromethyl)phenoxy)phenyl)amino)piperidin-1-yl)methanone;

- (4-(3-hydroxyoxetan-3-yl)phenyl)(3-methyl-4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;
 (4-(3-hydroxyoxetan-3-yl)phenyl)(2-methyl-4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;
 5 (3-fluoro-4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)(4-(3-hydroxyoxetan-3-yl)phenyl)methanone; 1-(4-(3-hydroxyoxetan-3-yl)benzoyl)-4-(4-(trifluoromethyl)phenoxy)piperidine-3-carboxylic acid;
 (4-(3-hydroxyoxetan-3-yl)phenyl)(3-methoxy-4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;
 10 1-(4-(3-hydroxyoxetan-3-yl)benzoyl)-4-(4-(trifluoromethyl)phenoxy)piperidine-3-carbonitrile;
 (3,3-difluoro-4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)(4-(3-hydroxyoxetan-3-yl)phenyl)methanone;
 (3-chloro-4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)(4-(3-hydroxyoxetan-3-yl)phenyl)methanone;
 15 (4-(3-hydroxyazetidin-3-yl)phenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;
 (4-(3-hydroxyoxetan-3-yl)phenyl)(4-(4-morpholinophenoxy)piperidin-1-yl)methanone;
 20 (4-(4-((2S,6R)-2,6-dimethylmorpholino)phenoxy)piperidin-1-yl)(4-(3-hydroxyoxetan-3-yl)phenyl)methanone;
 (4-(3-hydroxyoxetan-3-yl)phenyl)(4-(4-(tetrahydro-1H-furo[3,4-c]pyrrol-5(3H)-yl)phenoxy)piperidin-1-yl)methanone;
 N-(4-(3-hydroxyoxetan-3-yl)phenyl)-1-((4-(trifluoromethyl)phenyl)sulfonyl)piperidine-4-sulfonamide;
 25 N-(4-(3-hydroxyoxetan-3-yl)phenyl)-1-(4-(trifluoromethyl)benzoyl)piperidine-4-sulfonamide;
 4-(3-hydroxyoxetan-3-yl)-N-(1-(4-(trifluoromethyl)benzoyl)piperidin-4-yl)benzenesulfonamide;
 30 4-(3-hydroxyoxetan-3-yl)-N-(1-((4-(trifluoromethyl)phenyl)sulfonyl)piperidin-4-yl)benzenesulfonamide;
 (4-((4-(3-hydroxyoxetan-3-yl)phenyl)amino)piperidin-1-yl)(4-(trifluoromethyl)phenyl)methanone;

- (2,6-difluoro-4-(3-hydroxyoxetan-3-yl)phenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;
(4-(3-hydroxyoxetan-3-yl)-3,5-dimethylphenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;
5 (4-(3-methoxy-1,1-dioxidothietan-3-yl)phenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;
(4-(3-hydroxy-1,1-dioxidothietan-3-yl)phenyl)(4-(3-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;
(4-(3-hydroxy-1,1-dioxidothietan-3-yl)phenyl)(4-((6-(trifluoromethyl)pyridin-3-yl)oxy)piperidin-1-yl)methanone;
10 (4-(3-hydroxy-1,1-dioxidothietan-3-yl)phenyl)(4-((5-(trifluoromethyl)pyrimidin-2-yl)oxy)piperidin-1-yl)methanone;
(4-(3-hydroxy-1,1-dioxidothietan-3-yl)phenyl)(4-(4-(trifluoromethyl)benzyl)piperazin-1-yl)methanone;
15 (4-(3-hydroxy-1,1-dioxidothietan-3-yl)phenyl)(4-(3-(trifluoromethyl)benzyl)piperidin-1-yl)methanone;
(4-(3-hydroxyoxetan-3-yl)phenyl)(4-(3-(trifluoromethyl)benzyl)piperidin-1-yl)methanone;
(3-(3-hydroxyoxetan-3-yl)phenyl)(4-(3-(trifluoromethyl)benzyl)piperidin-1-yl)methanone;
20 (3-(3-hydroxyoxetan-3-yl)phenyl)(4-(3-(trifluoromethyl)benzyl)piperazin-1-yl)methanone;
(4-(3-hydroxyoxetan-3-yl)phenyl)(4-(3-(trifluoromethyl)benzyl)piperazin-1-yl)methanone;
25 (3-(3-hydroxyoxetan-3-yl)phenyl)(4-((6-(trifluoromethyl)pyridin-3-yl)methyl)piperidin-1-yl)methanone;
(4-(3-hydroxyoxetan-3-yl)phenyl)(4-((6-(trifluoromethyl)pyridin-3-yl)methyl)piperidin-1-yl)methanone;
(4-(3-hydroxyoxetan-3-yl)phenyl)(4-((6-(trifluoromethyl)pyridin-3-yl)methyl)piperazin-1-yl)methanone;
30 (4-(3-hydroxyoxetan-3-yl)phenyl)(6-(4-(trifluoromethyl)phenoxy)-3,4-dihydroquinolin-1(2H)-yl)methanone;

- (4-(3-hydroxyoxetan-3-yl)phenyl)(2-((4-(trifluoromethyl)phenyl)sulfonyl)-2,6-dihydropyrrolo[3,4-c]pyrazol-5(4H)-yl)methanone;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(2-(4-(trifluoromethyl)phenoxy)-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methanone;
- 5 (4-(3-hydroxyoxetan-3-yl)phenyl)(5-(4-(trifluoromethyl)phenoxy)indolin-1-yl)methanone;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(5-(4-(trifluoromethyl)phenoxy)-1H-indol-1-yl)methanone;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(6-(4-(trifluoromethyl)phenoxy)-3,4-
- 10 dihydroisoquinolin-2(1H)-yl)methanone;
- N-(4-(3-hydroxyoxetan-3-yl)phenyl)-2-(4-(trifluoromethyl)phenoxy)pyrimidine-5-carboxamide;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((6-(trifluoromethyl)benzo[d]thiazol-2-yl)methyl)piperidin-1-yl)methanone;
- 15 (3-(3-hydroxyoxetan-3-yl)phenyl)(4-((6-(trifluoromethyl)benzo[d]thiazol-2-yl)methyl)piperidin-1-yl)methanone;
- N-(4-(3-hydroxyoxetan-3-yl)phenyl)-4-((6-(trifluoromethyl)benzo[d]thiazol-2-yl)methyl)piperidine-1-carboxamide;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((6-(trifluoromethyl)benzo[d]thiazol-2-
- 20 yl)methyl)piperazin-1-yl)methanone;
- N-(4-(3-hydroxyoxetan-3-yl)phenyl)-4-((6-(trifluoromethyl)benzo[d]thiazol-2-yl)methyl)piperazine-1-carboxamide;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((6-(trifluoromethyl)benzo[d]oxazol-2-yl)oxy)piperidin-1-yl)methanone;
- 25 N-(4-(3-hydroxyoxetan-3-yl)phenyl)-4-((6-(trifluoromethyl)benzo[d]oxazol-2-yl)oxy)piperidine-1-carboxamide;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((6-(trifluoromethyl)-1H-benzo[d]imidazol-2-yl)oxy)piperidin-1-yl)methanone;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((6-(trifluoromethyl)-1H-benzo[d]imidazol-2-
- 30 yl)amino)piperidin-1-yl)methanone;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((6-(trifluoromethyl)benzofuran-2-yl)oxy)piperidin-1-yl)methanone;

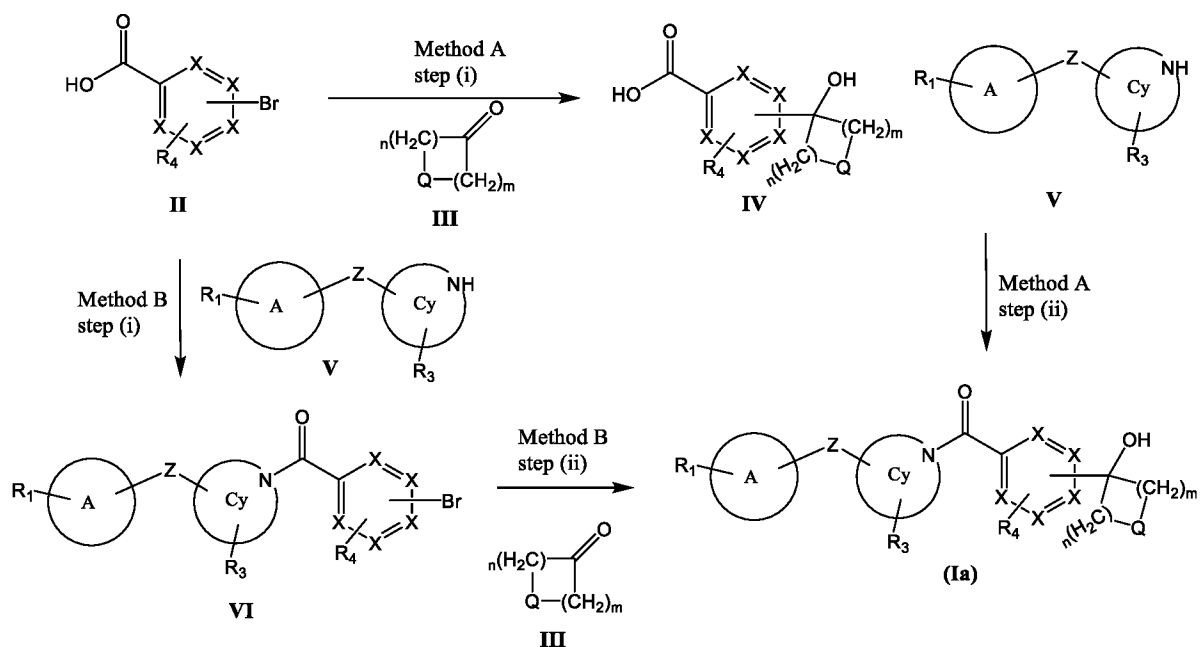
- (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((6-(trifluoromethyl)benzofuran-2-yl)amino)piperidin-1-yl)methanone;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((6-(trifluoromethyl)benzo[b]thiophen-2-yl)oxy)piperidin-1-yl)methanone;
- 5 (4-fluoro-4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)(4-(3-hydroxyoxetan-3-yl)phenyl)methanone;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(4-methyl-4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(4-methyl-4-((6-(trifluoromethyl)benzo[d]thiazol-2-yl)oxy)piperidin-1-yl)methanone;
- 10 (4-(3-hydroxyoxetan-3-yl)phenyl)(4-(4-(trifluoromethyl)phenoxy)-4-(4-(trifluoromethyl)phenyl)piperidin-1-yl)methanone;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((6-(trifluoromethyl)-1H-benzo[d]imidazol-2-yl)amino)piperidin-1-yl)methanone
- 15 (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((6-(trifluoromethyl)benzo[d]thiazol-2-yl)oxy)-4-(4-(trifluoromethyl)phenyl)piperidin-1-yl)methanone;
- N-(4-(3-hydroxyoxetan-3-yl)phenyl)-4-(4-(trifluoromethyl)phenoxy)piperidine-1-sulfonamide;
- 1-(1-(4-(3-hydroxyoxetan-3-yl)benzoyl)piperidin-4-yl)-3-(4-(trifluoromethyl)phenyl)urea;
- 20 1-(1-(4-(3-hydroxyoxetan-3-yl)benzoyl)piperidin-4-yl)-3-(4-(trifluoromethyl)phenyl)sulfonylurea;
- 1-(4-(3-hydroxyoxetan-3-yl)phenyl)-3-(1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)urea;
- 25 1-(4-(3-hydroxyoxetan-3-yl)phenyl)-3-(1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)sulfonylurea;
- 4-(4-(3-hydroxyoxetan-3-yl)benzoyl)-N-(4-(trifluoromethyl)phenyl)piperazine-1-carboxamide;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(4-(3-(2-methoxyethoxy)-4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;
- 30 (4-(3-hydroxyoxetan-3-yl)-3-(2-methoxyethoxy)phenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;

- (4-(3-(2-(methylsulfonyl)ethoxy)oxetan-3-yl)phenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;
 (4-(difluoro(4-(trifluoromethyl)phenyl)methyl)piperidin-1-yl)(4-(3-hydroxyoxetan-3-yl)phenyl)methanone;
- 5 (4-(3,3-difluoro-1-hydroxycyclobutyl)phenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;
 3-(3-(morpholinosulfonyl)-5-(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)phenyl)oxetan-3-ol;
 (4-(3-hydroxyoxetan-3-yl)phenyl)(5-((4-(trifluoromethyl)phenyl)sulfonyl)-3,5-
- 10 dihydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methanone;
 (4-(3-hydroxyoxetan-3-yl)phenyl)(5-((4-(trifluoromethyl)phenyl)sulfonyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methanone;
 (4-(3-hydroxyoxetan-3-yl)phenyl)(5-((4-(trifluoromethyl)phenyl)sulfonyl)-3,4,5,6-
- 15 tetrahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methanone;
 (4-(3-hydroxyoxetan-3-yl)phenyl)(5-(4-(trifluoromethyl)phenoxy)-3,4,5,6-tetrahydrocyclopenta[c]pyrrol-2(1H)-yl)methanone;
 (4-(3-hydroxyoxetan-3-yl)phenyl)(4-(pyrimidin-2-ylamino)piperidin-1-yl)methanone;
- 20 N-(1-benzylpyrrolidin-3-yl)-4-(3-hydroxyoxetan-3-yl)benzamide;
 (4-(3-hydroxyoxetan-3-yl)phenyl)(4-(pyridin-4-yloxy)piperidin-1-yl)methanone;
 (4-(3-hydroxyoxetan-3-yl)phenyl)(4-(quinolin-4-yloxy)piperidin-1-yl)methanone;
 (4-(3-methoxyoxetan-3-yl)phenyl)(4-(quinolin-4-yloxy)piperidin-1-yl)methanone;
 (4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)(4-(1,2,3-trihydroxypropan-2-yl)phenyl)methanone;
- 25 *tert*-butyl 3-hydroxy-3-(4-(4-(4-(trifluoromethyl)phenoxy)piperidine-1-carbonyl)phenyl)azetidine-1-carboxylate;
tert-butyl 3-methoxy-3-(4-(4-(4-(trifluoromethyl)phenoxy)piperidine-1-carbonyl)phenyl)azetidine-1-carboxylate;
- 30 (4-(3-methoxyazetidin-3-yl)phenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone hydrochloride;
 (4-(3-hydroxythietan-3-yl)phenyl)(4-(3-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;

- (3-(3-hydroxyoxetan-3-yl)phenyl)(4-(4-(trifluoromethyl)benzyl)piperazin-1-yl)methanone;
 N-(4-(3-methoxyoxetan-3-yl)phenyl)-4-(3-(trifluoromethyl)benzyl)piperidine-1-carboxamide;
 5 (4-(3-methoxyoxetan-3-yl)phenyl)(4-(3-(trifluoromethyl)benzyl)piperazin-1-yl)methanone;
 4-(3-hydroxyoxetan-3-yl)-N-((1*r*,4*r*)-4-(4-(trifluoromethyl)phenoxy)cyclohexyl)benzamide and
 (4-(4-hydroxypiperidin-4-yl)phenyl)(4-((4-(trifluoromethyl)phenyl)amino)piperidin-1-yl)methanone hydrochloride.

The novel compounds of this invention may be prepared using the reactions and techniques as shown in scheme below and described in this section. The reactions are performed in solvents appropriate to the reagents and materials employed and are suitable for the transformations being affected. It is understood by those skilled in the art that the nature and order of the synthetic steps presented may be varied for the purpose of optimizing the formation of the compounds of the present invention. It will also be well appreciated that one or more of the reactants may be protected and deprotected for facile synthesis by techniques known to persons skilled in the art. It will also be appreciated that one or more of the compounds of the present invention may exist in stereoisomeric and/or diastereomeric forms. Such stereoisomers and/or diastereoisomers as well as their optical antipodes are to be construed to be within the scope of the present invention. It will also be well appreciated that one or more of these compounds may be converted to their salts and other derivatives based on the specific groups present on the compounds, which can be well comprehended by persons skilled in the art. Such salts and/or other derivatives, as the case may be should also be construed to be within the scope of the present invention. The compounds of general formula (**Ia**) wherein 'Y' represents C=O and all other symbols are as defined earlier, may be prepared by reactions outlined in **Scheme 1** below which comprises:

30 **Scheme:1**



Compounds of formula (Ia) can be synthesized by two methods differentiated by sequence of addition of reactants. However reaction conditions remains same.

Method A

- 5 i. Reacting the compounds of general formula **II** and **III** wherein all the symbols are defined as earlier using suitable metal alkyls such as *n*-butyllithium, *s*-butyllithium and the like to prepare corresponding compounds of general formula **IV**. The reaction may be carried out in presence of suitable solvent(s) such as tetrahydrofuran, diethylether and the like or suitable mixtures thereof. The reaction may be carried out
- 10 at a temperature in the range of -78 °C to 28 °C and the reaction time may range from 1 to 48 hours;
- ii. The compounds of formula **IV** further reacted with compounds of general formula **V** wherein all symbols are defined as earlier for form compounds of formula (Ia). suitable conditions in presence of reagents(s) such as N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (EDC) & 1-Hydroxybenzotriazole (HOBT), 1-
- 15 [Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate (HATU), N,N,N',N'-Tetramethyl-O-(1H-benzotriazol-1-yl)uronium hexafluorophosphate (HBTU) and the like. The reaction may be carried
- 20 in presence of suitable organic bases such as N-ethylmorpholine, triethylamine, diisopropylethylamine, pyridine and the like. The reaction may be carried out in presence of suitable solvent(s) such as N,N-dimethylformamide, N,N-dimethylacetamide, dichloromethane and the like or suitable mixtures thereof. The

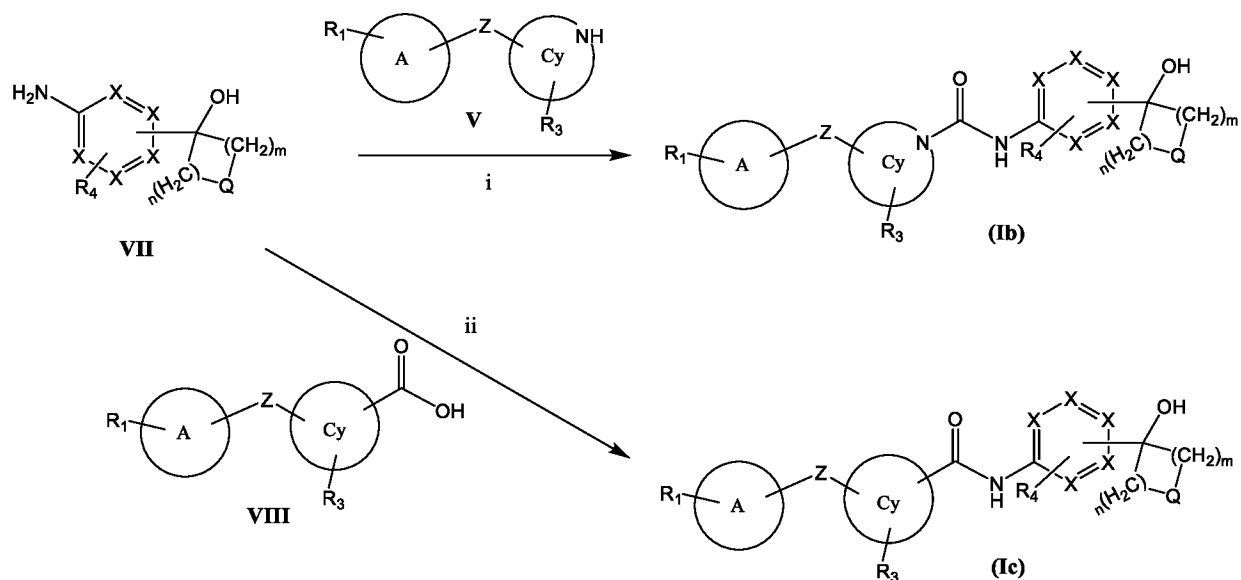
reaction may be carried out at a temperature in the range 0 °C to reflux temperature of the solvent(s) used and the reaction time may range from 1 to 48 hours.

Method B

- i. Reacting compounds of general formula **II** with compounds of general formula **V** wherein all the symbols are as defined earlier using suitable reaction conditions as provided in step ii of method A to obtain compounds of general formula **VI**.
- ii. Further in step ii, reacting compounds of general formula **VI** with compounds of formula **III** wherein wherein all the symbols are as defined earlier, using suitable metal alkyls such as n-butyllithium, s-butyllithium and the like. The reaction may be carried out in presence of suitable solvent(s) such as tetrahydrofuran, diethylether and the like or suitable mixtures thereof. The reaction may be carried out at a temperature in the range of -78 °C to 28 °C and the reaction time may range from 1 to 48 hours to obtain compounds of general formula (**Ia**) wherein all the symbols are as defined earlier.

The compounds of general formula **(Ib)** and **(Ic)** wherein ‘Y’ represents $-\text{C}(\text{O})\text{NH}-$ and all other symbols are as defined earlier, may be prepared by reactions outlined in **Scheme 2** below which comprises:

Scheme:2

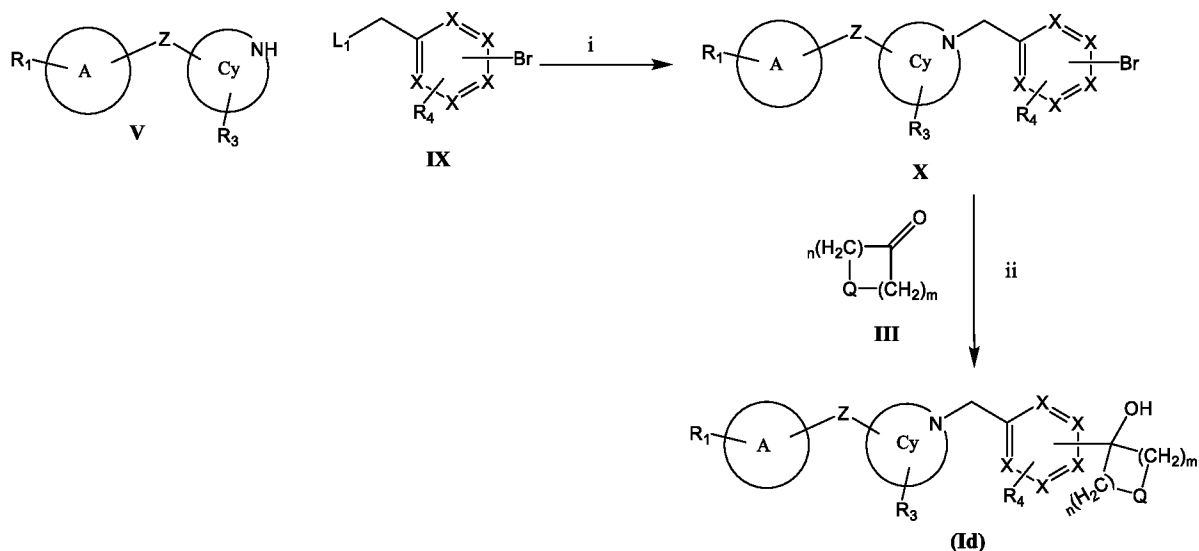


- 20 i. The compounds of formula **(Ib)** wherein all the symbols are as defined earlier may be prepared by reacting aryl amines of general formula **VII** wherein all the symbols are as defined earlier and corresponding cyclic amines of general formula **V** wherein all

- the symbols are as defined earlier under suitable conditions in presence of reagents(s) such as phosgene, triphosgene, Carbonyldiimidazole and the like. The reaction may be carried in presence of organic base(s) such as trimethylamine, diisopropylamine, pyridine and the like using suitable solvent(s) such as N,N-dimethyl formamide, tetrahydrofuran, dichloromethane, acetonitrile and the like or mixtures thereof. The reaction may be carried out at a temperature in the range 0 °C to reflux temperature of the solvent(s) used and the reaction time may range from 1 to 48 hours;
- ii. The compounds of formula (**Ic**) wherein all the symbols are as defined earlier may be prepared by coupling reaction of acids of general formula **VIII** wherein all the symbols are as defined earlier and amines of general formula **VII** wherein all the symbols are as defined earlier under suitable conditions in presence of reagents(s) such as N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (EDC) & 1-Hydroxybenzotriazole (HOBT), 1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate (HATU), N,N,N',N'-Tetramethyl-O-(1H-benzotriazol-1-yl)uronium hexafluorophosphate (HBTU) and the like. The reaction may be carried in presence of suitable organic bases such as triethyl amine, diisopropylethyl amine, pyridine and the like. The reaction may be carried out in presence of suitable solvent(s) such as N,N-dimethylformamide, N,N-dimethylacetamide, dichloromethane and the like or suitable mixtures thereof. The reaction may be carried out at a temperature in the range 0 °C to reflux temperature of the solvent(s) used and the reaction time may range from 1 to 48 hours.

The compounds of general formula (**Id**) wherein 'Y' represents -CH₂- and all other symbols are as defined earlier, may be prepared by reactions outlined in **Scheme 3** below which comprises:

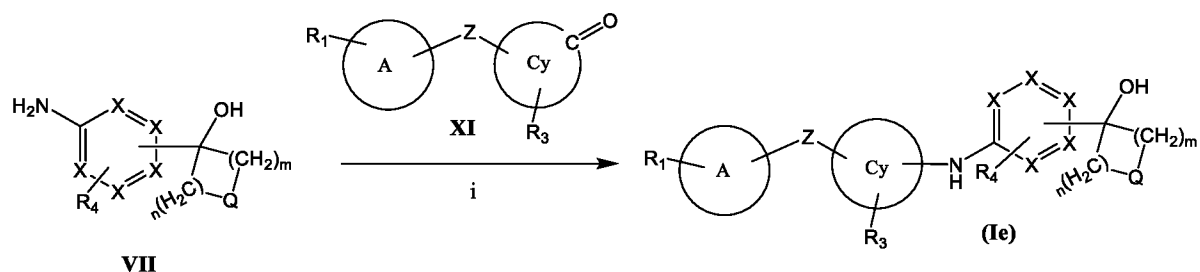
Scheme:3



- i. Reacting the compounds of general formula **V** wherein all the symbols are as defined earlier and the compounds of general formula **IX** wherein 'L₁' represents suitable leaving group and all other symbols are as defined earlier, using suitable inorganic base(s) such as K₂CO₃, Cs₂CO₃, NaOH, KOH, NaH, KH and the like or organic base(s) such as pyridine, triethyl amine, diisopropyl ethylamine and the like to prepare compounds of general formula **X** wherein the symbols are as defined earlier. The reaction may be carried out neat or in presence of suitable aprotic solvent(s) such as dimethyl formamide, tetrahydrofuran, dichloromethane and the like or suitable mixtures thereof. The reaction may be carried out at a temperature in the range of 0 °C to reflux temperature of the solvent(s) used and the reaction time may range from 1 to 48 hours;
- ii. Reacting Compounds of general formula **X** wherein all the symbols are as defined earlier and cyclic ketones of general formula **III**, using suitable metal alkyls such as *n*-butyllithium, *s*-butyllithium and the like to prepare corresponding compounds of general formula **(Id)** wherein the symbols are as defined earlier. The reaction may be carried out in presence of suitable solvent(s) such as tetrahydrofuran, diethylether and the like or suitable mixtures thereof. The reaction may be carried out at a temperature in the range of -78 °C to 28 °C and the reaction time may range from 1 to 48 hours;

The compounds of general formula **(Ie)** wherein 'Y' represents -NH- and all other symbols are as defined earlier, may be prepared by reactions outlined in **Scheme 4** below which comprises:

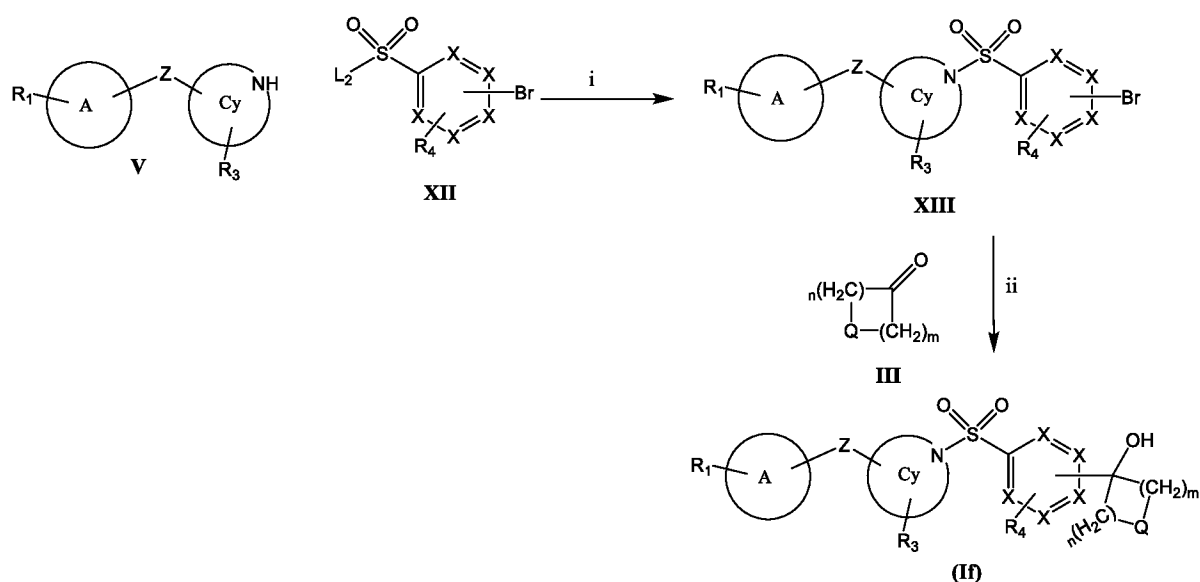
Scheme: 4



- i. Reacting the compounds of general formula **VII** wherein all the symbols are as defined earlier and the cyclic ketones of general formula **XI** wherein all the symbols are as defined earlier, using suitable methods available in the literature for the reductive amination to prepare compounds of general formula **(Ie)** wherein the symbols are as defined earlier. The reaction may be carried out using reducing agents such as sodium tritoxoborohydride, sodium cyanoborohydride, sodium borohydride and the like. The reaction may be carried out in presence of solvent(s) such as dichloromethane, 1,2-dichloroethane, toluene, methanol, ethanol, isopropanol, *n*-butanol and the like or suitable mixtures thereof. The reaction may be carried out at a temperature in the range of 0 °C to reflux temperature of the solvent(s) used and the reaction time may range from 1 to 48 hours;

The compounds of general formula **(If)** wherein 'Y' represents $-\text{SO}_2-$ and all other symbols are as defined earlier, may be prepared by reactions outlined in **Scheme 5** below which comprises:

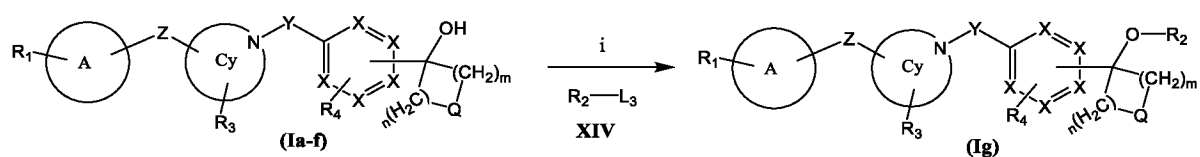
Scheme:5



- i. Reacting the compounds of general formula **V** wherein all the symbols are as defined earlier and the compounds of general formula **XII** wherein 'L₂' represents suitable leaving group such as Cl, Br and the like and all other symbols are as defined earlier, using suitable inorganic base(s) such as K₂CO₃, Cs₂CO₃, NaOH, KOH, NaH, KH and the like or organic base(s) such as pyridine, 4-(N,N-dimethylamino)pyridine, triethyl amine, diisopropyl ethylamine and the like to prepare compounds of general formula **XIII** wherein the symbols are as defined earlier. The reaction may be carried out neat or in presence of suitable aprotic solvent(s) such as N,N-dimethyl formamide, tetrahydrofuran, dichloromethane and the like or suitable mixtures thereof. The reaction may be carried out at a temperature in the range of 0 °C to reflux temperature of the solvent(s) used and the reaction time may range from 1 to 48 hours;
- ii. Reacting Compounds of general formula **XIII** wherein all the symbols are as defined earlier and cyclic ketones of general formula **III**, using suitable metal alkyls such as *n*-butyllithium, *s*-butyllithium and the like to prepare corresponding compounds of general formula (**If**) wherein the symbols are as defined earlier. The reaction may be carried out in presence of suitable solvent(s) such as tetrahydrofuran, diethylether and the like or suitable mixtures thereof. The reaction may be carried out at a temperature in the range of -78 °C to 28 °C and the reaction time may range from 1 to 48 hours;

The compounds of general formula (**Ig**) wherein all the symbols are as defined earlier, may be prepared by reactions outlined in **Scheme 6** below which comprises:

Scheme:6

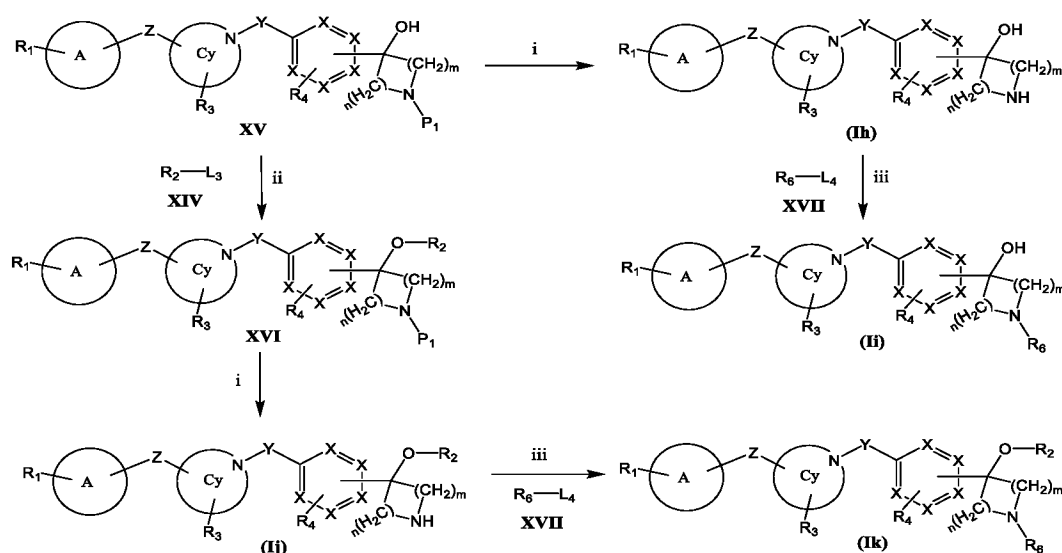


- i. Reacting the compounds of general formula (**Ia-f**) wherein all the symbols are as defined earlier and the compounds of general formula **XIV** wherein 'L₃' represents suitable leaving group such as and all other symbols are as defined earlier, using suitable inorganic base(s) such as K₂CO₃, Cs₂CO₃, NaOH, KOH, NaH, KH and the like to prepare compounds of general formula (**Ig**) wherein the symbols are as defined earlier. The reaction may be carried out neat or in presence of suitable solvent(s) such as N,N-dimethyl formamide, N,N-dimethylacetamide,

tetrahydrofuran, dichloromethane, toluene and the like or suitable mixtures thereof. The reaction may be carried out at a temperature in the range of 0 °C to reflux temperature of the solvent(s) used and the reaction time may range from 1 to 48 hours;

- 5 The compounds of general formula **(Ih)**, **(Ii)**, **(Ij)** & **(Ik)** wherein 'Q' represents –NH and NR₆ and all other symbols are as defined earlier, may be prepared by reactions outlined in **Scheme 7** below which comprises:

Scheme:7



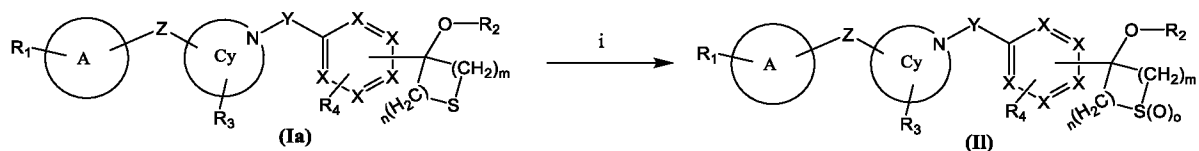
- 10 i. Compounds of general formula **(Ih)** and **(Ij)** wherein all the symbols are as defined earlier may be prepared from corresponding compounds of general formula **XV** and **XVI** wherein P_1 represents suitable protecting groups such as *tert*-butoxycarbonyl, Fmoc, benzyl and the like and all other symbols are as defined earlier using the suitable methods available in the literature for deprotection of
- 15 secondary amines.
- ii. Reacting the compounds of general formula **XV** wherein all the symbols are as defined earlier and the compounds of general formula **XIV** wherein all the symbols are as defined earlier, using suitable inorganic base(s) such as K_2CO_3 , Cs_2CO_3 , $NaOH$, KOH , NaH , KH and the like to prepare compounds of general formula **XVI**
- 20 wherein all the symbols are as defined earlier. The reaction may be carried out neat or in presence of suitable solvent(s) such as *N,N*-dimethyl formamide, tetrahydrofuran, dichloromethane, toluene and the like or suitable mixtures thereof. The reaction may be carried out at a temperature in the range of 0 °C to reflux

temperature of the solvent(s) used and the reaction time may range from 1 to 48 hours;

iii. Reacting the compounds of general formula **(Ih)** and **(Ij)** wherein all the symbols are as defined earlier and the compounds of general formula **XVII** wherein 'L₄' represents suitable leaving group such as and all other symbols are as defined earlier, using suitable inorganic base(s) such as K₂CO₃, Cs₂CO₃, NaOH, KOH, NaH, KH and the like or organic base(s) such as pyridine, triethyl amine, diisopropyl ethylamine and the like to prepare compounds of general formula **(II)** and **(Ik)** respectively, wherein the symbols are as defined earlier. The reaction may be carried out neat or in presence of suitable aprotic solvent(s) such as N,N-dimethyl formamide, tetrahydrofuran, dichloromethane, dimethyl sulfoxide, toluene and the like or suitable mixtures thereof. The reaction may be carried out at a temperature in the range of 0 °C to reflux temperature of the solvent(s) used and the reaction time may range from 1 to 48 hours;

15 The compounds of general formula **(II)** wherein ‘Q’ represents –S(O)_o– wherein ‘o’ represents integers 1 & 2 and all other symbols are as defined earlier, may be prepared by reactions outlined in **Scheme 8** below which comprises:

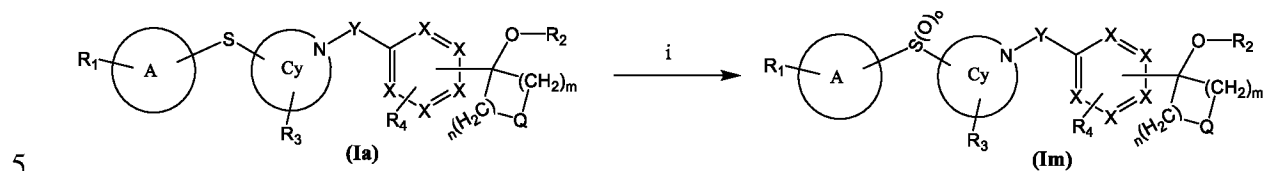
Scheme:8



20 i. The compounds of general formula (II) wherein all the symbols are as defined earlier may be prepared by the oxidation of the compounds of general formula (Ia) wherein 'Q' represents 'S' and all other symbols are as defined earlier using
25 suitable oxidizing agents such as H₂O₂, *m*-chloroperbenzoic acid, sodium periodate, potassium peroxymonosulfate and the like. The reaction may be carried in presence of suitable solvent(s) such as chloroform, dichloromethane, acetone, water, tetrahydrofuran, methanol, ethanol and the like or suitable mixtures thereof. The reaction may be carried out at a temperature in the range of -40 °C to reflux temperature of the solvent(s) used and the reaction time may range from 1 to 48 hours;

The compounds of general formula **(Im)** wherein 'Z' represents $-S(O)_o-$ wherein 'o' represents integers 1 & 2 and all other symbols are as defined earlier, may be prepared by reactions outlined in **Scheme 9** below which comprises:

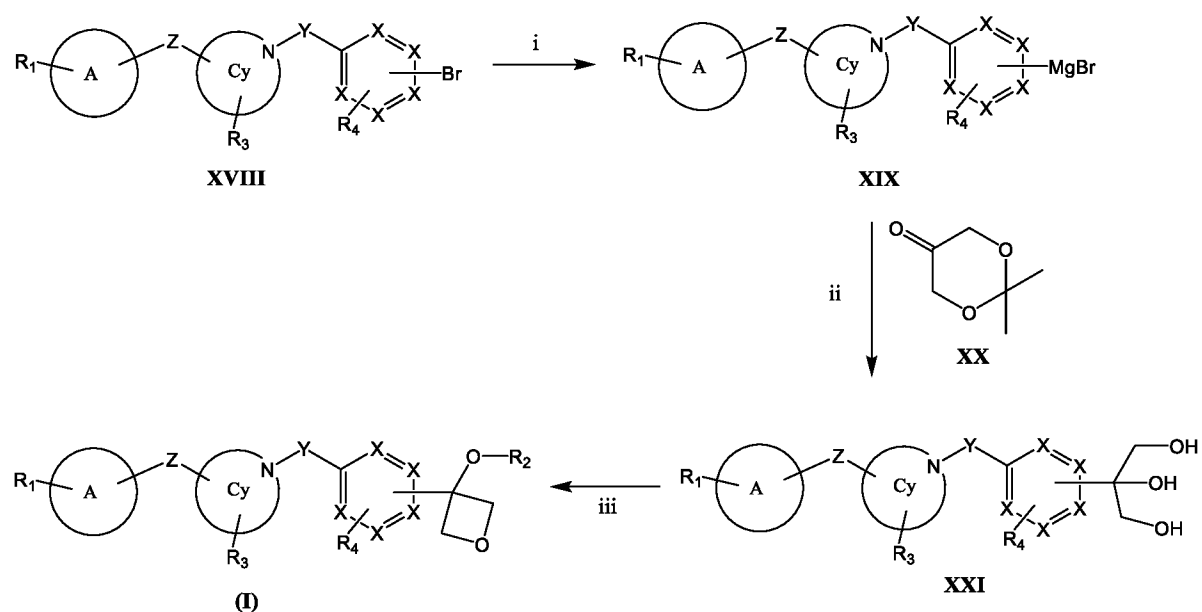
Scheme: 9



10 The compounds of general formula **(Im)** wherein all the symbols are as defined earlier may be prepared by the oxidation of the compounds of general formula **(Ia)** wherein 'Z' represents 'S' and all other symbols are as defined earlier using suitable oxidizing agents such as H_2O_2 , *m*-chloroperbenzoic acid, sodium periodate, potassium peroxymonosulfate and the like. The reaction may be carried in presence of suitable solvent(s) such as chloroform, dichloromethane, acetone, water, tetrahydrofuran, methanol, ethanol and the like or suitable mixtures thereof. The reaction may be carried out at a temperature in the range of $-40\text{ }^\circ\text{C}$ to reflux temperature of the solvent(s) used and the reaction time may range from 1 to 48 hours.

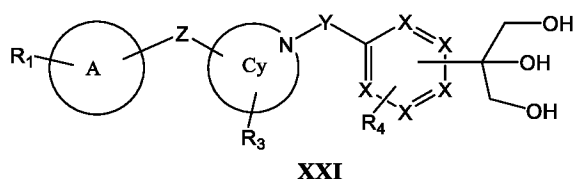
15 In one of the embodiment the compounds of general formula **(I)** wherein 'Q' represents 'O', 'm' and 'n' represents integer 1 and all other symbols are as defined earlier, may also be prepared by reactions outlined in **Scheme 10** below which comprises:

Scheme:10



- i. Reacting the compounds of general formula **XVIII** wherein all the symbols are as defined earlier and magnesium metal, using suitable methods available in the literature for the preparation of Grignard reagents to prepare compounds of general formula **XIX** wherein all the symbols are as defined earlier. The reaction may be carried out in presence of suitable solvent(s) such as tetrahydrofuran, diethylether and the like or suitable mixtures thereof. The reaction may be carried out at a temperature in the range of -78 °C to 28 °C and the reaction time may range from 1 to 48 hours;
- ii. Reacting the compounds of general formula **XIX** wherein all the symbols are as defined earlier and 2,2-dimethyl-1,3-dioxan-5-one to prepare compounds of general formula **XXI** wherein the symbols are as defined earlier. The reaction may be carried out in presence of suitable solvent(s) such as tetrahydrofuran, diethylether and the like or suitable mixtures thereof. The reaction may be carried out at a temperature in the range of -78 °C to 28 °C and the reaction time may range from 1 to 48 hours;
- iii. The compounds of formula (I) wherein all the symbols are as defined earlier may be prepared from compounds of general formula **XXI** wherein all the symbols are as defined earlier using the procedure given in literature (Angewandte Chemie, International Edition (2007), 46(15), 2616-2618; US6255540 and Journal of Medicinal Chemistry (1992), 35(14), 2600-2609) with appropriate modifications in the reaction conditions.

In an embodiment an intermediate of compound of formula **XXI** is



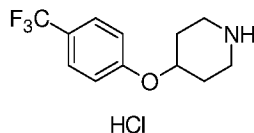
Wherein symbols are as defined earlier.

In a preferred embodiment of the present invention, wherein compound of formula **XXI** is (4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)(4-(1,2,3-trihydroxypropan-2-yl)phenyl)methanone. The said compound is an intermediate for the process for the preparation of compounds of formula (I).

The invention is explained in greater detail by the examples given below, which are provided by way of illustration only and therefore should not be construed to limit the scope of the invention. ¹H NMR spectral data given in the examples (vide infra) are

recorded using a 400 MHz spectrometer (Bruker AVANCE-400) and reported in δ scale. ESI-MS data is recorded using mass spectrometer (waters Xevo G2 QToF).

Intermediate - 1: 4-(4-(trifluoromethyl)phenoxy)piperidine hydrochloride



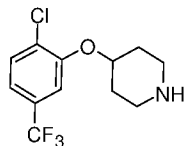
Step 1: Preparation of *tert*-butyl 4-(4-(trifluoromethyl)phenoxy)piperidine-1-carboxylate

To a stirred solution of *tert*-butyl 4-hydroxypiperidine-1-carboxylate (92 g, 457 mmol) in dimethylacetamide (750 ml), potassium *tert*-butoxide (103 g, 914 mmol) was added and stirred at 30 °C for 30 minute. To this 1-fluoro-4-(trifluoromethyl)benzene (58.0 ml, 457 mmol) was added maintaining the temperature of the reaction mixture below 40 °C and stirring was continued for 24 hours. The reaction mixture was poured into water (500 ml) and extracted with *tert*-butyl methyl ether (2 x 300 ml). The combined organic layer was washed with water (2 x 350 ml) & brine (350 ml), dried over sodium sulfate and evaporated on rotavapor under vacuum to yield crude product as thick liquid. The crude product was triturated with ice-cold hexane (250 ml), resulting solid was filtered, rinsed with ice cold hexane, and dried to yield *tert*-butyl 4-(4-(trifluoromethyl)phenoxy)piperidine-1-carboxylate (106 g, 67.2% yield) as a white solid. ¹H NMR (CDCl₃) δ : 1.63 (s, 9H), 1.75-1.82 (m, 2H), 1.92-1.98 (m, 2H), 3.35-3.42 (m, 2H), 3.68-3.74 (m, 2H), 4.54-4.58 (m, 1H), 6.98 (d, *J* = 8.4 Hz, 2H), 7.55 (d, *J* = 8.0 Hz, 2H).

Step 2: 4-(4-(trifluoromethyl)phenoxy)piperidine hydrochloride.

To a solution of *tert*-butyl 4-(4-(trifluoromethyl)phenoxy)piperidine-1-carboxylate (2 g, 5.79 mmol) in dichloromethane (10 ml), another solution of dioxane saturated with HCl (25 ml) was added and the reaction mixture was stirred for 5 hours at 30 °C. Solvent was evaporated under reduced pressure and the residue was stirred in diisopropyl ether (50 ml). The solid was filtered, washed with diisopropyl ether (10 ml) and dried to yield 4-(4-(trifluoromethyl)phenoxy)piperidine hydrochloride (1.307 g, 80% yield) as a white solid.

¹H NMR (DMSO-*d*₆) δ : 1.85-1.92 (m, 2H), 2.10-2.17 (m, 2H), 3.04-3.09 (m, 2H), 3.19-3.23 (m, 2H), 4.77-4.83 (m, 1H), 7.20 (d, *J* = 8.4 Hz, 2H), 7.66 (d, *J* = 8.4 Hz, 2H); ESI-MS: *m/z*: 246.11 (M+H)⁺, 100%.

Intermediate-2: 4-(2-chloro-5-(trifluoromethyl)phenoxy)piperidine**Step 1: *tert*-butyl 4-((methylsulfonyl)oxy)piperidine-1-carboxylate.**

To a stirred solution of *tert*-butyl 4-hydroxypiperidine-1-carboxylate (7 g, 34.8 mmol) in dichloromethane (50 mL), triethylamine (9.70 mL, 69.6 mmol) was added followed by the addition of methane sulfonyl chloride (2.98 mL, 38.3 mmol) dropwise at 5 °C over the period of 10 minutes under nitrogen atmosphere and the reaction mixture was stirred for 1 hour at ambient temperature. The reaction mixture was poured into with water (40 ml) and extracted with dichloromethane (3 x 30 ml). Organic layer was washed with diluted hydrochloric acid (10%, 50 ml), water (3 x 50 ml) & brine (50 ml), dried over sodium sulphate and evaporated under vacuum. The crude product was purified by column chromatography using 100-200 mesh silica gel column and 10% ethyl acetate in hexane as an eluent to yield *tert*-butyl 4-((methylsulfonyl)oxy)piperidine-1-carboxylate (9.5 gm, 98% yield) as yellowish solid.

¹H NMR (DMSO-*d*₆) δ : 1.47 (s, 9H), 1.80-1.85 (m, 2H), 1.95-1.98 (m, 2H), 3.05 (s, 3H), 3.28-3.34 (m, 2H), 3.69-3.75 (m, 2H), 4.88-4.90 (m, 1H); ESI-MS: *m/z* 280.07 (M+H), 70%.

Step 2: Preparation of *tert*-butyl 4-(2-chloro-5-(trifluoromethyl)phenoxy)piperidine-1-carboxylate

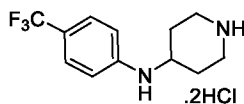
To a stirred solution of 2-chloro-5-(trifluoromethyl)phenol (0.500 g, 2.544 mmol) and *tert*-butyl 4-((methylsulfonyl)oxy)piperidine-1-carboxylate (0.782 g, 2.798 mmol) in N,N-dimethylformamide (5.0 ml), cesium carbonate (1.658 g, 5.088 mmol) was added at ambient temperature and the reaction mixture was stirred at 80 °C for 48 hours. The reaction mixture was poured into water (20 ml) and extracted with ethyl acetate (3 x 15 ml). The combined organic layer was washed with 1M NaOH (1 x 10 ml), water (25 ml) & brine (25 ml), dried over sodium sulfate and evaporated on rotavapor under vacuum to yield *tert*-butyl 4-(2-chloro-5-(trifluoromethyl)phenoxy)piperidine-1-carboxylate (0.7 g, 72% yield) as yellow liquid.

¹H NMR (CDCl₃) δ : 1.49 (s, 9H), 1.84-1.96 (m, 4H), 3.50-3.54 (m, 2H), 3.63-3.69 (m, 2H), 4.61-4.64 (m, 1H), 7.17 (d, *J* = 6.4 Hz, 1H), 7.20 (d, *J* = 1.2 Hz, 1H), 7.50 (d, *J* = 8.4 Hz, 1H).

Step 3: Preparation of 4-(2-chloro-5-(trifluoromethyl)phenoxy)piperidine

To a stirred solution of *tert*-butyl 4-(2-chloro-5-(trifluoromethyl)phenoxy)piperidine-1-carboxylate (700 mg, 1.843 mmol) in dichloromethane (50 ml), trifluoroacetic acid (1.420 ml, 18.43 mmol) was added and the reaction mixture was stirred at 30 °C for 24 hours. The reaction mixture was poured into saturated sodium bicarbonate solution (20 ml) and extracted with dichloromethane (2 x 20 ml). The combined organic layer was washed with water (20 ml) and dried over sodium sulfate and evaporated on rotavapor under vacuum to yield 4-(2-chloro-5-(trifluoromethyl)phenoxy)piperidine (400 mg, 71.0% yield) as brown liquid.

¹H NMR (DMSO-*d*₆) δ : 1.50-1.56 (m, 2H), 1.84-1.91 (m, 2H), 2.57-2.68 (m, 2H), 2.92-2.97 (m, 2H), 4.70-4.76 (m, 1H), 7.29 (dd, *J* = 8.0 & 1.6 Hz, 1H), 5.16 (d, *J* = 1.2 Hz, 1H), 7.67 (d, *J* = 8.4 & 0.4 Hz, 1H); ESI-MS: *m/z*: 280.10 (M+H)⁺, 100%.

Intermediate-3: N-(piperidin-4-yl)-6-(trifluoromethyl)pyridin-3-amine**15 dihydrochloride**

Step 1: Preparation of *tert*-butyl 4-((4-(trifluoromethyl)phenyl)amino)piperidine-1-carboxylate.

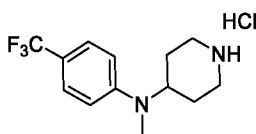
To a stirred solution of 4-(trifluoromethyl) aniline (3.90ml, 31.0 mmol) and *tert*-butyl 4-oxopiperidine-1-carboxylate (12.37 g, 62.1 mmol) in acetic acid (50 ml) sodium sulfate (44.1g, 310mmol) was added and the reaction mixture was stirred at 30 °C for 3.0 hours. To this sodium triacetoxyborohydride (19.73 g, 93 mmol) was added and stirring was continued for 20 hours. The reaction mixture was poured into water (50 ml). White solid separated was collected by filtration and washed with water (50 ml) and dried over phosphorous pentoxide to yield *tert*-butyl 4-((4-(trifluoromethyl)phenyl)amino)piperidine-1-carboxylate. (5.0g, 46.8% yield) as an off white solid. ¹H NMR (CDCl₃) δ : 1.30-1.40 (m, 2H), 1.47 (s, 9H), 2.02-2.06 (m, 2H), 2.92-2.97 (m, 2H), 3.45-3.50 (m, 1H), 3.97 (br s, 1H), 4.06-4.10 (m, 2H), 6.59 (d, *J* = 8.0 Hz, 2H), 7.38 (d, *J* = 8.0 Hz, 2H).

Step 2: Preparation of N-(piperidin-4-yl)-6-(trifluoromethyl)pyridin-3-amine dihydrochloride.

The title product (400 mg, 98% yield) was prepared from *tert*-butyl 4-((6-(trifluoromethyl)pyridin-3-yl)amino)piperidine-1-carboxylate (500 mg, 1.452 mmol) according to the procedure given in step-2 of **Intermediate-1** as a white solid.

¹H NMR (DMSO-*d*₆) δ : 1.58-1.62 (m, 2H), 2.03-2.06 (m, 2H), 3.01-3.06 (m, 2H), 3.18-3.20 (m, 2H), 3.78-3.88(m, 1H), 6.51 (d, *J* = 8.0 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 8.62 (s, 1H), 8.78 (s, 1H); ESI-MS: *m/z*: 245.13 (M+H)⁺, 100%.

Intermediate-4 : N-methyl-N-(4-(trifluoromethyl)phenyl)piperidin-4-amine hydrochloride



10

Step 1: Preparation of *tert*-butyl 4-(methyl(4-(trifluoromethyl)phenyl)amino)piperidine-1-carboxylate.

To a suspension of sodium hydride (87 mg, 2.178 mmol) in tetrahydrofuran (10 ml) *tert*-butyl 4-((4-(trifluoromethyl)phenyl)amino)piperidine-1-carboxylate (500 mg, 1.452 mmol) in tetrahydrofuran (3 ml) was added followed by addition of iodomethane (309 mg, 2.178 mmol) at 0 °C and stirring was continued at 30 °C for 3 hours under nitrogen atmosphere. The reaction mixture was poured into ice cold water (25 ml) and extracted with ethyl acetate (3 x 25 ml). The combined organic extract was washed with water (2 x 20 ml) & brine (25 ml), dried over sodium sulfate and evaporated under reduced pressure. Crude product was purified by column chromatography using 100-200 mesh silica gel column and 15% ethyl acetate in *n*-hexane as an eluent to yield *tert*-butyl 4-(methyl(4-(trifluoromethyl)phenyl)amino)piperidine-1-carboxylate (300 mg, 57.7% yield) as a white solid. ¹H NMR (CDCl₃) δ : 1.5 (s, 9H), 1.6-1.76 (m, 5H), 2.76-2.81 (m, 2H), 2.83 (s, 3H), 4.28-4.30 (m, 2H), 6.78 (d, *J* = 8.0 Hz, 2H), 7.46 (d, *J* = 8.0 Hz, 2H); ESI-MS: *m/z* 359.5 (M+H)⁺, 100%.

25

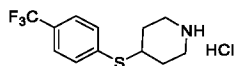
Step 2: Preparation of N-methyl-N-(4-(trifluoromethyl)phenyl)piperidin-4-amine hydrochloride

The title product (400 mg 98% yield) was prepared from *tert*-butyl 4-(methyl(4-(trifluoromethyl)phenyl)amino)piperidine-1-carboxylate (500 mg, 1.452 mmol) according to the procedure given in step-2 of **Intermediate-1** as white solid. ¹H NMR (DMSO-*d*₆) δ : 1.73-1.76 (m, 2H), 1.99-2.09 (m, 2H), 2.79 (s, 3H), 2.99-3.08 (m, 2H), 3.31-3.39(m, 2H),

30

4.11-4.17 (m, 1H), 6.96 (d, $J = 8.0$ Hz, 2H), 7.47 (d, $J = 8.0$ Hz, 2H), 9.0 (s, 2H); ESI-MS: m/z : 259.16 (M+H)⁺, 100%.

Intermediate-5: 4-((4-(trifluoromethyl)phenyl)thio)piperidine hydrochloride



5

Step 1: *tert*-butyl 4-((4-(trifluoromethyl)phenyl)thio)piperidine-1-carboxylate.

To a stirred solution of *tert*-butyl 4-((methylsulfonyl)oxy)piperidine-1-carboxylate (678 mg, 3.37 mmol) in N,N-dimethylformamide (5 ml), potassium carbonate (776 mg, 5.61 mmol) was added followed by the addition of 4-(trifluoromethyl)benzenethiol (500 mg, 2.81 mmol) at ambient temperature and stirring was continued for further 16 hours. The reaction mixture was poured into water (15 ml) and extracted with ethyl acetate (2 x 15 ml). The combined organic layer was washed with water (2 x 30 ml) & brine (30 ml), dried over sodium sulphate and evaporated on rotavapor under vacuum. The crude product was purified by column chromatography using 100-200 mesh silica gel column and 15% ethyl acetate in *n*-hexane as eluent to yield pure *tert*-butyl 4-((4-(trifluoromethyl)phenyl)thio)piperidine-1-carboxylate (315 mg, 0.872 mmol, 31.1% yield) as off-white solid.

¹H NMR (DMSO-*d*₆) δ : 1.34-1.44 (m, 11H), 1.91-1.95 (m, 2H), 2.98 (m, 2H), 3.63-3.70 (m, 1H), 3.81-3.85 (m, 2H), 7.57 (d, $J = 8.4$ Hz, 2H), 7.67 (d, $J = 8.4$ Hz, 2H).

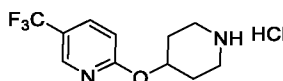
20 **Step 2:** 4-((4-(trifluoromethyl)phenyl)thio)piperidine hydrochloride.

The title product (235 mg, 93% yield) was prepared from *tert*-butyl 4-((4-(trifluoromethyl)phenyl)thio)piperidine-1-carboxylate (300 mg, 0.830 mmol) according to the procedure described in step-2 of **Intermediate-1** as white solid.

¹H NMR (DMSO-*d*₆) δ : 1.68-1.77 (m, 2H), 2.09-2.12 (m, 2H), 2.97-3.02 (m, 2H), 3.25-3.28 (m, 2H), 3.72-3.77 (m, 1H), 7.60 (d, $J = 8.4$ Hz, 2H), 7.69 (d, $J = 8.0$ Hz, 2H), 8.82 (br s, 2H);

ESI-MS: m/z 262.06 (M+H), 100%.

Intermediate-6: 2-(piperidin-4-yloxy)-5-(trifluoromethyl)pyridine hydrochloride



30

Step 1: *tert*-butyl 4-((5-(trifluoromethyl)pyridin-2-yl)oxy)piperidine-1-carboxylate.

To a stirred solution of *tert*-butyl 4-hydroxypiperidine-1-carboxylate (1.95 g, 9.73 mmol) in N-Methyl-2-pyrrolidone (10 ml), 50% sodium hydride (0.849 g, 17.70 mmol) was added at 0-5 °C followed by addition of 2-bromo-5-(trifluoromethyl)pyridine (2 g, 8.85 mmol) and stirring was continued for further 1.5 hours at ambient temperature.

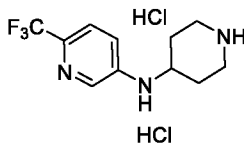
5 Reaction mixture was quenched with water (10 ml) and extracted with ethyl acetate (2 x 20 ml). The combined organic layer was washed with water (2 x 30 ml) & brine (30 ml), dried over sodium sulfate and evaporated on rotavapor under vacuum. The crude product was purified by column chromatography using 100-200 mesh silica gel column and 5% ethyl acetate in *n*-hexane as eluent to yield *tert*-butyl 4-((5-(trifluoromethyl)pyridin-2-yl)oxy)piperidine-1-carboxylate. (1.97 g, 64.3% Yield) as a thick liquid. ¹H NMR (CDCl₃) δ: 1.49 (s, 9H), 1.71-1.29 (m, 2H), 1.98-2.03 (m, 2H), 3.28-3.34 (m, 2H), 3.77-3.82 (m, 2H), 5.77-5.33 (m, 1H), 6.81 (d, *J* = 8.4 Hz, 1H), 7.78 (dd, *J* = 8.4 Hz, & *J* = 2.4 Hz, 1H), 8.42 (d, *J* = 2.4 Hz, 1H); ESI-MS: *m/z* 247.14 (M+H)⁺, 100%.

Step 2: 2-(piperidin-4-yloxy)-5-(trifluoromethyl)pyridine hydrochloride.

15 The title product (1.36 g, 88.0% yield) was prepared from *tert*-butyl 4-((5-(trifluoromethyl)pyridin-2-yl)oxy)piperidine-1-carboxylate (1.90 g, 5.49 mmol) according to the procedure given in step-2 of **Intermediate-1** as an off white solid.

¹H NMR (DMSO-*d*₆) δ: 1.90-1.98 (m, 2H), 2.14-2.19 (m, 2H), 3.07-3.13 (m, 2H), 3.20-3.33 (m, 2H), 5.30-5.36 (m, 1H), 7.05 (d, *J* = 8.4 Hz, 1H), 8.10 (dd, *J* = 8.4 Hz, & *J* = 2.4 Hz, 1H), 8.58 (d, *J* = 2.4 Hz, 1H), 9.14 (brs, 2H); ESI-MS: *m/z* 247.14 (M+H)⁺, 100%.

Intermediate-7: N-(piperidin-4-yl)-6-(trifluoromethyl)pyridin-3-amine dihydrochloride



25 **Step 1:** Preparation of *tert*-butyl 4-((6-(trifluoromethyl)pyridin-3-yl)amino)piperidine-1-carboxylate.

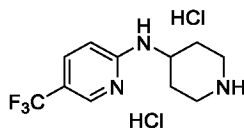
To a stirred solution of 6-(trifluoromethyl)pyridin-3-amine (0.500 g, 3.08 mmol) and *tert*-butyl 4-oxopiperidine-1-carboxylate (0.737 g, 3.70 mmol) in 1,2-dichloroethane (20 ml), acetic acid (0.177 ml, 3.08 mmol) was added and stirring was continued at ambient temperature for 3.0 hours. To this sodium triacetoxyborohydride (0.981 g, 4.63 mmol) was added and stirred at 60 °C for 48 hours. The reaction mixture was poured into water (50

ml). Separated solid was collected by filtration, washed with water (20 ml) and dried over P_2O_5 to yield crude product as an off white solid. The crude product was purified by column chromatography using 230-400 mesh silica gel column and 10% ethyl acetate in *n*-hexane as eluent to yield pure *tert*-butyl 4-((6-(trifluoromethyl)pyridin-3-yl)amino)piperidine-1-carboxylate (175 mg, 16.43% yield) as a white solid. 1H NMR ($DMSO-d_6$) δ : 1.21-1.30 (m, 2H), 1.41 (s, 9H), 1.86-1.90 (m, 2H), 2.93 (m, 2H), 3.53-3.55 (m, 1H), 3.85-3.89 (m, 2H), 6.58 (d, J = 8.0 Hz, 1H), 7.05 (d, J = 8.4 & 1.6 Hz, 1H), 7.51 (d, J = 8.4 Hz, 1H), 8.07 (d, J = 2.4 Hz, 1H).

Step 2: Preparation of N-(piperidin-4-yl)-6-(trifluoromethyl)pyridin-3-amine dihydrochloride.

The title product (138 mg, 100% yield) was prepared from *tert*-butyl 4-((6-(trifluoromethyl)pyridin-3-yl)amino)piperidine-1-carboxylate (150 mg, 0.434 mmol) according to the procedure described in step-2 of **Intermediate-1** as white solid.

Intermediate-8: N-(piperidin-4-yl)-5-(trifluoromethyl)pyridin-2-amine dihydrochloride



Step 1: Preparation of *tert*-butyl 4-((5-(trifluoromethyl)pyridin-2-yl)amino)piperidine-1-carboxylate.

To a stirred solution of 2-bromo-5-(trifluoromethyl)pyridine (400 mg, 1.770 mmol) in *N,N*-dimethylformamide (20 ml), cesium carbonate (807 mg, 2.478 mmol) was added followed by addition of *tert*-butyl 4-aminopiperidine-1-carboxylate (390 mg, 1.947 mmol) under nitrogen atmosphere at ambient temperature and stirred at 80 °C for 24 hours. Reaction mixture was poured to water (20 ml) and extracted with ethyl acetate (2 x 20 ml). Combined organic layer was washed with water (2 x 30 ml) & brine (30 ml), dried over sodium sulfate and concentrated under vacuum. Crude product was purified by column chromatography using 230-400 mesh silica gel column and 15% ethyl acetate in *n*-hexane as eluent to yield *tert*-butyl 4-((5-(trifluoromethyl)pyridin-2-yl)amino)piperidine-1-carboxylate (600 mg, 99.0% yield) as a white solid. 1H NMR ($CDCl_3$) δ : 1.35-1.46 (m, 2H), 1.49 (s, 9H), 2.04-2.08 (m, 2H), 2.94-2.99 (m, 2H), 3.89-3.92 (m, 1H), 4.08 (m, 2H),

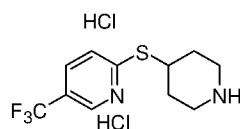
4.71 (d, $J = 7.6$ Hz, -NH), 6.40 (d, $J = 8.8$ Hz, 1H), 7.58 (dd, $J = 8.8$ & 2.4 Hz, 1H), 8.34 (s, 1H); ESI-MS: m/z : 344.25 (M-H)⁺, 75%.

Step 2: Preparation of N-(piperidin-4-yl)-5-(trifluoromethyl)pyridin-2-amine dihydrochloride

5 The title product (737 mg, 100% yield) was prepared from *tert*-butyl 4-((5-(trifluoromethyl)pyridin-2-yl)amino)piperidine-1-carboxylate (800 mg, 2.316 mmol) according to the procedure described in step-2 of **Intermediate-1** as white solid.

¹H NMR (DMSO-*d*₆) δ : 1.71-1.80 (m, 2H), 2.05-2.09 (m, 2H), 2.95-3.00 (m, 2H), 3.30-3.33 (m, 2H), 4.11-4.13 (m, 1H), 6.91 (d, $J = 9.2$ Hz, 1H), 7.83-7.85 (m, 1H), 8.28 (s, 1H),
10 8.60 (br s, -NH), 9.09 (br s, 2HCl); ESI-MS: m/z : 246.13 (M+H)⁺, 100%.

Intermediate-9: 2-(piperidin-4-ylthio)-5-(trifluoromethyl)pyridine dihydrochloride



Step 1: Preparation of *tert*-butyl 4-((5-(trifluoromethyl)pyridin-2-yl)thio)piperidine-1-carboxylate.
15

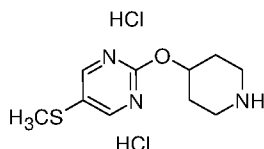
To a stirred suspension of sodium hydride (268 mg, 5.58 mmol) in 1,2-dimethoxyethane (2.0 ml), a solution of 5-(trifluoromethyl)pyridine-2-thiol (500 mg, 2.79 mmol) in 1,2-dimethoxyethane (5.0 ml) was added at 0 °C and stirring was continued for 30 minutes. To this another solution of *tert*-butyl 4-((methylsulfonyl)oxy)piperidine-1-carboxylate (936 mg, 3.35 mmol) in 1,2-dimethoxyethane (2.0 ml) was added and stirred
20 at 85 °C for 48 hours. The reaction mixture was poured into water (20 ml) and extracted with ethyl acetate (3 x 20 ml). The combined organic layer was washed with water (25 ml) & brine (15 ml), dried over sodium sulfate and evaporated under vacuum to yield crude product as a yellow liquid. The crude product was purified by column chromatography
25 using 230-400 mesh silica gel and 5% ethyl acetate in *n*-hexane as eluent to yield *tert*-butyl 4-((5-(trifluoromethyl)pyridin-2-yl)thio)piperidine-1-carboxylate (550 mg, 54.4% yield) as a thick liquid.

¹H NMR (CDCl₃) δ : 1.48 (s, 9H), 1.63-1.68 (m, 2H), 2.07-2.11 (m, 2H), 3.09-3.14 (m, 2H), 3.95-3.98 (m, 2H), 4.07-4.13 (m, 1H), 7.24-7.28 (m, 1H), 7.67 (dd, $J = 8.4$ & 2.0
30 Hz, 1H), 8.67 (s, 1H); ESI-MS: m/z : 363.08 (M+H)⁺, 100%.

Step 2: Preparation of 2-(piperidin-4-ylthio)-5-(trifluoromethyl)pyridine dihydrochloride

The title product (458 mg, 99% yield) was prepared from of *tert*-butyl 4-((5-(trifluoromethyl)pyridin-2-yl)thio)piperidine-1-carboxylate (500 mg, 1.380 mmol) according to the procedure given in step-2 of **Intermediate-1** as white solid.

5 **Intermediate-10: 5-(methylthio)-2-(piperidin-4-yloxy)pyrimidine dihydrochloride**



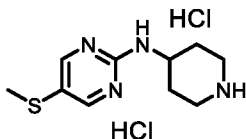
Step 1: Preparation of *tert*-butyl 4-((5-(methylthio)pyrimidin-2-yl)oxy)piperidine-1-carboxylate.

10 To a stirred suspension of sodium hydride (90 mg, 1.868 mmol) in N,N-dimethylacetamide (2.0 ml), a solution of *tert*-butyl 4-hydroxypiperidine-1-carboxylate (251 mg, 1.245 mmol) in N,N-dimethylacetamide (0.5 ml) was added at 0 °C and stirring was continued for 15 minutes. To this another solution of 2-chloro-5-(methylthio)pyrimidine (200 mg, 1.245 mmol) in N,N-dimethylacetamide (1.0 ml) was
15 added and stirred at 30 °C for 20 hours. The reaction mixture was poured into water (25 ml), separated solid was collected by filtration, washed with water and dried over P₂O₅ under vacuum to yield *tert*-butyl 4-((5-(methylthio)pyrimidin-2-yl)oxy)piperidine-1-carboxylate (144 mg, 35.5% yield) as white solid.

Step 2: Preparation of 5-(methylthio)-2-(piperidin-4-yloxy)pyrimidine dihydrochloride

20 The title product (132 mg, 100% yield) was prepared from of *tert*-butyl 4-((5-(methylthio)pyrimidin-2-yl)oxy)piperidine-1-carboxylate (144 mg, 0.442 mmol) according to the procedure given in step-2 of **Intermediate-1** as a white solid.

25 **Intermediate-11: 5-(methylthio)-N-(piperidin-4-yl)pyrimidin-2-amine dihydrochloride**



Step 1: Preparation of *tert*-butyl 4-((5-(methylthio)pyrimidin-2-yl)amino)piperidine-1-carboxylate.

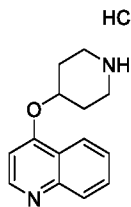
To a stirred solution of *tert*-butyl 4-aminopiperidine-1-carboxylate (343 mg, 1.712 mmol) in N,N-dimethylformamide (20 ml), cesium carbonate (710 mg, 2.179 mmol) was added followed by addition of 2-chloro-5-(methylthio)pyrimidine (250 mg, 1.556 mmol) under nitrogen atmosphere at ambient temperature and the reaction mixture was stirred at 80 °C for 16 hours. The reaction mixture was poured into water (20 ml) and extracted with ethyl acetate (2 x 20 ml). The combined organic layers were washed with water (2 x 15 ml) & brine (15 ml), dried over sodium sulfate and evaporated on rotavapor under vacuum to yield crude product as brown thick liquid. The crude product was purified by column chromatography using 230-400 mesh silica gel column and 44% ethyl acetate in *n*-hexane as eluent to yield *tert*-butyl 4-((5-(methylthio)pyrimidin-2-yl)amino)piperidine-1-carboxylate (325 mg, 64% yield) as a thick liquid. ¹H NMR (CDCl₃) δ : 1.36-1.48 (m, 2H), 1.50 (s, 9H), 2.02-2.06 (m, 2H), 2.38 (s, 3H), 2.93-2.99 (m, 2H), 3.94-4.07 (m, 3H), 5.09 (d, *J* = 7.6 Hz, -NH), 8.36 (s, 2H); ESI-MS: *m/z*: 325.15 (M+H)⁺, 20%.

Step 2: Preparation of 5-(methylthio)-N-(piperidin-4-yl)pyrimidin-2-amine dihydrochloride.

The title product (260 mg, 72.9% yield) was prepared from *tert*-butyl 4-((5-(methylthio)pyrimidin-2-yl)amino)piperidine-1-carboxylate (325 mg, 1.002 mmol) according to the procedure given in step-2 of **Intermediate-1** as white solid.

¹H NMR (DMSO-*d*₆) δ : 1.66-1.75 (m, 2H), 1.99-2.03 (m, 2H), 2.37 (s, 3H), 2.93-3.01 (m, 2H), 3.25-3.39 (m, 2H), 3.92-3.99 (m, 1H), 7.27 (m NH), 8.38 (s, 2H), 8.79 (br s, HCl), 9.00 (br s, HCl); ESI-MS: *m/z*: 225.11 (M+H)⁺, 100%.

Intermediate-12: 4-(piperidin-4-yloxy)quinoline hydrochloride



Step 1: Preparation of *tert*-butyl 4-(quinolin-4-yloxy)piperidine-1-carboxylate.

To a stirred solution of *tert*-butyl 4-hydroxypiperidine-1-carboxylate (0.693 g, 3.44 mmol) and quinolin-4-ol (0.5 g, 3.44 mmol) in tetrahydrofuran (10 ml) triphenyl phosphine (2.2g, 8.61mmol) was added followed by the addition of diisopropyl azodicarboxylate (1.67ml, 8.61mmol) at ambient temperature and stirring was continued

for 24 hours. The reaction mixture was poured into ice cold water (50 ml) and extracted with ethyl acetate (3 x 75 ml). The combined organic extract was washed with water (2 x 50 ml) & brine (75 ml), dried over sodium sulfate and concentrated on rotavapor under vacuum to yield *tert*-butyl 4-(quinolin-4-yloxy)piperidine-1-carboxylate (400 mg, 35% yield) as a thick liquid.

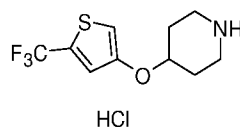
¹H NMR (CDCl₃) δ : 1.50 (s, 9H), 2.08-2.10 (m, 2H), 1.89-1.93 (m, 2H), 3.40-3.48 (m, 2H), 3.80-3.85 (m, 2H), 5.0-5.10 (m, 1H), 7.28-7.30 (m, 1H), 7.57-7.61 (m, 2H), 7.84-7.88 (m, 1H), 8.17-8.19 (m, 1H), 8.80 (s, 1H); ESI-MS: *m/z*: 329.18 (M+H)⁺, 100%.

Step 2: Preparation of 4-(piperidin-4-yloxy)quinoline hydrochloride.

The title product (300 mg 93% yield) was prepared from *tert*-butyl 4-(2-(4-(trifluoromethyl)phenoxy)ethyl)piperidine-1-carboxylate. (400 mg, 1.28 mmol) according to the procedure described in step-2 of **Intermediate-1** as white solid.

¹H NMR (DMSO-*d*₆) δ : 2.13-2.15 (m, 2H), 2.26-2.31 (m, 2H), 3.19-3.22 (m, 2H), 3.38-3.40 (m, 2H), 5.73-5.76 (m, 1H), 7.80-7.83 (m, 1H), 8.12-8.14 (m, 3H), 8.33-8.35 (m, 1H), 8.38-8.35 (m, 1H), 9.52 (s, 1H), 9.74 (s, 1H); ESI-MS: *m/z*: 229.17 (M+H)⁺, 100%.

Intermediate-13: 4-((5-(trifluoromethyl)thiophen-3-yl)oxy)piperidine hydrochloride



Step 1: Preparation of *tert*-butyl 4-((5-(trifluoromethyl)thiophen-3-yl)oxy)piperidine-1-carboxylate.

To a stirred solution of 5-(trifluoromethyl)thiophen-3-ol (340 mg, 2.022 mmol) and *tert*-butyl 4-((methylsulfonyl)oxy)piperidine-1-carboxylate (621 mg, 2.224 mmol) in N,N-dimethylformamide (5.0 ml), cesium carbonate (1.318 gm, 4.04 mmol) was added at ambient temperature and stirred at 100 °C for 3.0 hours. The reaction mixture was poured into water (20 ml) and extracted with ethyl acetate (3 x 15 ml). The combined organic layers were washed with 1M NaOH (10 ml), water (25 ml) & brine (20 ml), dried over sodium sulfate and evaporated on rotavapor under vacuum. The crude product was purified by column chromatography using 230-400 mesh silica gel column and 7% ethyl acetate in *n*-hexane as eluent to yield pure *tert*-butyl 4-((5-(trifluoromethyl)thiophen-3-yl)oxy)piperidine-1-carboxylate (450 mg, 63.3% yield) as a brown liquid.

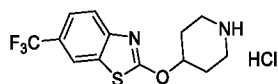
^1H NMR (CDCl_3) δ : 1.48 (s, 9H), 1.72-1.78 (m, 2H), 1.90-2.02 (m, 2H), 3.35-3.38 (m, 2H), 3.66-3.68 (m, 2H), 4.25-4.33 (m, 1H), 6.47 (s, 1H), 7.11 (d, $J=1.6$ Hz, 1H).

Step 2: Preparation of 4-((5-(trifluoromethyl)thiophen-3-yl)oxy)piperidine hydrochloride.

The title product (300 mg, 79% yield) was prepared from *tert*-butyl 4-((5-(trifluoromethyl)thiophen-3-yl)oxy)piperidine-1-carboxylate (440 mg, 1.252 mmol) according to the procedure given in step-2 of **Intermediate-1** as white solid.

^1H NMR ($\text{DMSO}-d_6$) δ : 1.83-1.90 (m, 2H), 2.10-2.15 (m, 2H), 3.01-3.06 (m, 2H), 3.20-3.23 (m, 2H), 4.53-4.59 (m, 1H), 7.19 (s, 1H), 7.52 (d, $J=1.6$ Hz, 1H); ESI-MS: m/z : 252.07 ($\text{M}+\text{H}$) $^+$, 100%.

Intermediate-14: 2-(piperidin-4-yloxy)-6-(trifluoromethyl)benzo[d]thiazole hydrochloride



Step 1: 6-(trifluoromethyl)benzo[d]thiazol-2-amine.

To a stirred solution of 4-(trifluoromethyl)aniline (1.0 gm, 6.21 mmol) and ammonium thiocyanate (0.945 gm, 12.41 mmol) in acetic acid (20ml), another solution of bromine (0.416 ml, 8.07 mmol) in acetic acid (3ml) was added under nitrogen atmosphere at 10 °C. The reaction mixture was warmed to ambient temperature and stirring was continued for next 12 hours. The reaction mixture was poured into ice-cold water (50 ml), basified with aqueous solution of ammonium hydroxide (25%, pH = 9) and extracted with ethyl acetate (3 x 30 ml). The organic layer was washed with water (2 x 30 ml) & brine (25 ml), dried over sodium sulphate and evaporated on rotavapor under vacuum. The crude product was purified by column chromatography using 100-200 mesh silica gel column and 30% ethyl acetate in *n*-hexane as an eluent to yield pure 6-(trifluoromethyl)benzo[d]thiazol-2-amine (430 mg, 31.8% yield) as pale yellow solid. ^1H NMR (CDCl_3) δ : 7.46 (d, $J=8.4$ Hz, 1H), 7.52 (d, $J=8.4$ Hz, 1H), 7.96 (br s, 2H), 8.13 (d, $J=9.6$ Hz, 1H); ESI-MS: m/z 218.90 ($\text{M}+\text{H}$) $^+$, 100%.

Step 2: 2-chloro-6-(trifluoromethyl)benzo[d]thiazole.

To a stirred suspension of copper(II) chloride (1.479 g, 11.00 mmol) in acetonitrile (20 ml), *tert*-butyl nitrite (1.418 gm, 13.75 mmol) was added followed by the addition of 6-(trifluoromethyl)benzo[d]thiazol-2-amine (2.0 gm, 9.17 mmol) under nitrogen atmosphere at ambient temperature and the reaction mixture was stirred at 65 °C for 30

minutes. The reaction mixture was cooled to ambient temperature, poured into 1N hydrochloric acid (50 ml) and extracted with ethyl acetate (3 x 50 ml). The organic layer was washed with water (2 x 50 ml) & brine (50 ml), dried over sodium sulphate and evaporated on rotavapor under vacuum. The crude product was purified by column chromatography using 100-200 mesh silica gel column and 5% ethyl acetate in *n*-hexane to yield pure 2-chloro-6-(trifluoromethyl)benzo[d]thiazole (9.6 gm, 73.5% yield) as yellow solid.

¹H NMR (CDCl₃) δ: 7.76 (d, *J* = 8.4 Hz, 1H), 8.08 (d, *J* = 8.4 Hz, 1H), 8.12 (s, 1H).

Step 3: *tert*-butyl 4-((6-(trifluoromethyl)benzo[d]thiazol-2-yl)oxy)piperidine-1-carboxylate.

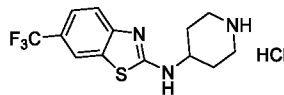
To a stirred solution of 2-chloro-6-(trifluoromethyl)benzo[d]thiazole (600 mg, 2.52 mmol) in *N,N*-dimethyl acetamide (6 ml), *tert*-butyl 4-hydroxypiperidine-1-carboxylate (457 mg, 2.272 mmol) was added followed by the addition of potassium *tert*-butoxide (567 mg, 5.05 mmol) under nitrogen atmosphere at ambient temperature and stirring was continued for 12 hours at 80 °C. The reaction mixture was cooled to ambient temperature, poured into water (50 ml) and extracted with ethyl acetate (2 x 25 ml). The organic layer was washed with water (2 x 50 ml) & brine (25 ml), dried over sodium sulphate and evaporated on rotavapor under vacuum. The crude product was purified by column chromatography using 100-200 mesh silica gel column and 10% ethyl acetate in *n*-hexane as an eluent to yield pure *tert*-butyl 4-((6-(trifluoromethyl)benzo[d]thiazol-2-yl)oxy)piperidine-1-carboxylate (600 mg, 59% yield) as a thick liquid. ¹H NMR (CDCl₃) δ: 1.50 (s, 9H), 1.88-1.94 (m, 2H), 2.09-2.14 (m, 2H), 3.35-3.42 (m, 2H), 3.75-3.80 (m, 2H), 5.39-5.43 (m, 1H), 7.62 (d, *J* = 8.8 Hz, 1H), 7.75 (d, *J* = 8.4 Hz, 1H), 7.95 (s, 1H).

Step 4: 2-(piperidin-4-yloxy)-6-(trifluoromethyl)benzo[d]thiazole hydrochloride.

The title product (350 mg, 69% yield) was prepared from *tert*-butyl 4-((6-(trifluoromethyl)benzo[d]thiazol-2-yl)oxy)piperidine-1-carboxylate (0.6 gm, 1.491 mmol) according to the procedure described in step-2 of **Intermediate-1** as an off-white solid.

¹H NMR (DMSO-*d*₆) δ: 2.04-2.12 (m, 2H), 2.21-2.33 (m, 2H), 3.16 (m, 2H), 3.25 (m, 2H), 5.44-5.48 (m, 1H), 7.73 (d, *J* = 8.4 Hz, 1H), 7.85 (d, *J* = 8.4 Hz, 1H), 8.44 (s, 1H), 9.05 (br s, 2H); ESI-MS: *m/z* 303.07 (M+H)⁺, 70%.

Intermediate-15: N-(piperidin-4-yl)-6-(trifluoromethyl)benzo[d]thiazol-2-amine hydrochloride



Step 1: *tert*-butyl 4-((6-(trifluoromethyl) benzo[d]thiazol-2-yl) amino) piperidine-1-carboxylate.

To a stirred solution of 2-chloro-6-(trifluoromethyl)benzo[d]thiazole (200 mg, 0.842 mmol) in N,N-dimethylformamide (3 ml), *tert*-butyl 4-aminopiperidine-1-carboxylate (202 mg, 1.010 mmol) was added followed by the addition of diisopropylethyl amine (0.176 ml, 1.010 mmol) under nitrogen atmosphere at ambient temperature and stirring was continued for 12 hours. The reaction mixture was poured into water (50 ml) and extracted with ethyl acetate (2 x 25 ml). Organic layer was washed with water (2 x 25 ml) & brine (25 ml), dried over sodium sulphate and evaporated on rotavapor under vacuum. The crude product was purified by column chromatography using 100-200 mesh silica gel column and 20% ethyl acetate in *n*-hexane as an eluent to yield pure *tert*-butyl 4-((6-(trifluoromethyl)benzo[d]thiazol-2-yl)amino)piperidine-1-carboxylate (250 mg, 74% yield) as a thick liquid.

¹H NMR (DMSO-*d*₆) δ : 1.38 (s, 9H), 1.88-1.94 (m, 2H), 2.09-2.14 (m, 2H), 3.35-3.42 (m, 2H), 3.75-3.80 (m, 2H), 7.62 (d, *J* = 8.8 Hz, 1H), 7.75 (d, *J* = 8.4 Hz, 1H), 7.95 (s, 1H), 9.20 (br s, 1H); ESI-MS: *m/z* 402.14 (M+H)⁺.

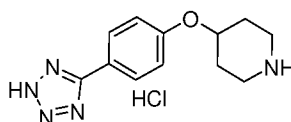
Step 2: N-(piperidin-4-yl)-6-(trifluoromethyl)benzo[d]thiazol-2-amine hydrochloride.

The title product (150 mg, 71% yield) was prepared from *tert*-butyl 4-((6-(trifluoromethyl)benzo[d]thiazol-2-yl)amino)piperidine-1-carboxylate (0.25 gm, 0.623 mmol) according to the procedure described in step-2 of **Intermediate-1** as an off-white solid.

¹H NMR (DMSO-*d*₆) δ : 1.74-1.77 (m, 2H), 2.14-2.17 (m, 2H), 3.18-3.21 (m, 2H), 3.29-3.37 (m, 2H), 3.57 (s, 1H), 4.10-4.17 (m, 1H), 7.52 (d, *J* = 8.4 Hz, 2H), 8.20 (s, 1H), 9.02 (br s, 2H);

ESI-MS: *m/z* 302.09 (M+H)⁺, 100%.

Intermediate-16: 4-(4-(2H-tetrazol-5-yl)phenoxy)piperidine hydrochloride



Step 1: Preparation of *tert*-butyl 4-(4-(2H-tetrazol-5-yl)phenoxy)piperidine-1-carboxylate

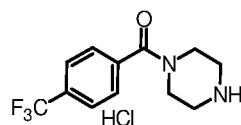
To a stirred solution of *tert*-butyl 4-(4-cyanophenoxy)piperidine-1-carboxylate (750 mg, 2.480 mmol) in N,N-dimethylformamide (5.0 ml), sodium azide (806 mg, 12.40 mmol) was added followed by addition of ammonium chloride (663 mg, 12.40 mmol) under nitrogen atmosphere at ambient temperature and stirred at 140 °C for 8.0 hours. The reaction mixture was cooled, poured into water (25 ml) and neutralized using aqueous hydrochloric acid. Separated solid was collected by filtration, washed with water and dried over P₂O₅ under vacuum to yield *tert*-butyl 4-(4-(2H-tetrazol-5-yl)phenoxy)piperidine-1-carboxylate (0.650 g, 76% yield) as a white solid. ¹H NMR (CDCl₃) δ: 1.50 (s, 9H), 1.76-1.84 (m, 2H), 1.94-1.99 (m, 2H), 3.37-3.43 (m, 2H), 3.68-3.74 (m, 2H), 4.57-4.59 (m, 1H), 7.03 (d, *J* = 8.8 Hz, 2H), 8.06 (d, *J* = 8.8 Hz, 2H).

Step 2: Preparation of 4-(4-(2H-tetrazol-5-yl)phenoxy)piperidine hydrochloride

The title product (255 mg, 99% yield) was prepared from *tert*-butyl 4-(4-(2H-tetrazol-5-yl)phenoxy)piperidine-1-carboxylate (300 mg, 0.869 mmol) according to the procedure described in step-2 of **Intermediate-1** as white solid.

¹H NMR (DMSO-*d*₆) δ: 1.84-1.93 (m, 2H), 2.13-2.18 (m, 2H), 3.07-3.09 (m, 2H), 3.23-3.39 (m, 2H), 4.78-4.81 (m, 1H), 7.23 (d, *J* = 9.2 Hz, 2H), 8.04 (d, *J* = 8.8 Hz, 2H), 9.11 (br s, -2HCl); ESI-MS: *m/z*: 246.13 (M+H)⁺, 100%.

Intermediate-17: piperazin-1-yl(4-(trifluoromethyl)phenyl)methanone hydrochloride



Step 1: Preparation of *tert*-butyl 4-(4-(trifluoromethyl)benzoyl)piperazine-1-carboxylate

To a stirred solution of *tert*-butyl piperazine-4-carboxylate (0.98 g, 5.26 mmol), 4-(trifluoromethyl)benzoic acid (1.0 g, 5.26 mmol) and HBTU (2.99 g, 7.89 mmol) in N,N-dimethylformamide (5.0 ml), diisopropylethylamine (2.76 ml, 15.78 mmol) was added and stirred at 30 °C for 16 hours. The reaction mixture was poured into water (50 ml), separated solid was collected by filtration, washed with water and dried over P₂O₅ under vacuum to yield *tert*-butyl 4-(4-(trifluoromethyl)benzoyl)piperazine-1-carboxylate (1.7 g,

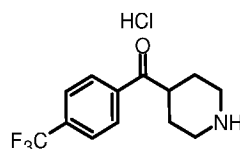
90% yield) as an off white solid. ^1H NMR (DMSO- d_6) δ : 1.41 (s, 9H), 3.26-3.43 (m, 6H), 3.61 (m, 2H), 7.64 (d, J = 8.0 Hz, 2H), 7.83 (d, J = 8.0 Hz, 2H).

Step 2: Preparation of piperazin-1-yl(4-(trifluoromethyl)phenyl)methanone hydrochloride

5 The title product (617 mg, 100% yield) was prepared from *tert*-butyl 4-(4-(trifluoromethyl)benzoyl)piperazine-1-carboxylate (750 mg, 2.093 mmol) according to the procedure described in step-2 of **Intermediate-1** as white solid.

^1H NMR (DMSO- d_6) δ : 3.11-3.17 (m, 4H), 3.57-3.69 (m, 2H), 3.86 (m, 2H), 7.70 (d, J = 8.0 Hz, 2H), 7.84 (d, J = 8.0 Hz, 2H), 9.50 (br s, 2HCl); ESI-MS: m/z : 259.10 (M+H) $^+$,
10 100%.

Intermediate-18: Piperidin-4-yl(4-(trifluoromethyl)phenyl)methanone hydrochloride



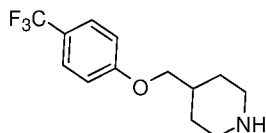
15 **Step 1:** Preparation of *tert*-butyl 4-(4-(trifluoromethyl)benzoyl)piperidine-1-carboxylate
To a stirred solution of 1-bromo-4-(trifluoromethyl)benzene (0.467 ml, 3.33 mmol) in dry tetrahydrofuran (50 ml), *n*-butyllithium (1.600 ml, 4.00 mmol) was added dropwise over a period of 15 minutes at -78°C and stirring was continued for 30 minutes at -78°C. To this another solution of *tert*-butyl 4-(methoxy(methyl)carbamoyl)piperidine-1-carboxylate (0.908 g, 3.33 mmol) in tetrahydrofuran (5.0 ml) was added and the reaction
20 mixture was allowed to warm to ambient temperature. The reaction mixture was poured into water (10 ml) and extracted with diethyl ether (2 x 50 ml). The combined organic layer was washed with water (25 ml) & brine (25 ml), dried over sodium sulfate and evaporated on rotavapour under vacuum. The crude product was purified by column chromatography
25 using 230-400 mesh silica gel column and 20% ethyl acetate as eluent in *n*-hexane to yield *tert*-butyl 4-(4-(trifluoromethyl)benzoyl)piperidine-1-carboxylate (245 mg, 20.57% yield) as a thick liquid.

^1H NMR (CDCl $_3$) δ : 1.49 (s, 9H), 1.70-1.77 (m, 2H), 1.85-1.89 (m, 2H), 2.90-2.96 (m, 2H), 3.39-3.44 (m, 1H), 4.17 (m, 2H), 7.73 (d, J = 8.4 Hz, 2H), 8.05 (d, J = 8.0 Hz, 2H).

30 **Step 2:** Preparation of piperidin-4-yl(4-(trifluoromethyl)phenyl)methanone hydrochloride.

The title product (205 mg, 100% yield) was prepared from *tert*-butyl 4-(4-(trifluoromethyl)benzoyl)piperidine-1-carboxylate (250 mg, 0.700 mmol) according to the procedure described in step-2 of **Intermediate-1** as white solid.

5 **Intermediate-19: 4-((4-(trifluoromethyl)phenoxy)methyl)piperidine**



Step 1: Preparation of *tert*-butyl 4-((4-(trifluoromethyl)phenoxy)methyl)piperidine-1-carboxylate

To a stirred solution of 1-bromo-4-(trifluoromethyl)benzene (400 mg, 1.778 mmol) and *tert*-butyl 4-(hydroxymethyl)piperidine-1-carboxylate (383 mg, 1.778 mmol) in dimethylacetamide (5.0 ml), potassium *tert*-butoxide (399 mg, 3.56 mmol) was added at ambient temperature and stirred at 90 °C for 6.0 hours. The reaction mixture was poured into water (20 ml) and extracted with ethyl acetate (3 x 20 ml). The combined organic layer was washed with water (25 ml) & brine (15 ml), dried over sodium sulfate and evaporated under vacuum. The crude product was purified by column chromatography using 230-400 mesh silica gel column and 10% ethyl acetate in *n*-hexane as eluent to yield pure *tert*-butyl 4-((4-(trifluoromethyl)phenoxy)methyl)piperidine-1-carboxylate (400 mg, 62.6% yield) as a white solid.

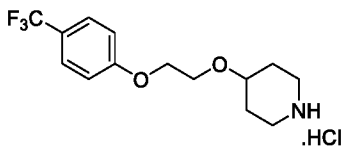
Step 2: Preparation of 4-((4-(trifluoromethyl)phenoxy)methyl)piperidine.

The title product (215 mg, 72.8% yield) was prepared from *tert*-butyl 4-((4-(trifluoromethyl)phenoxy)methyl)piperidine-1-carboxylate (400 mg, 1.113 mmol) according to the procedure described in step-2 of **Intermediate-2** as a yellow liquid.

¹H NMR (CDCl₃) δ : 1.15-1.34 (m, 2H), 1.67-1.70 (m, 2H), 1.76-1.86 (m, 1H), 2.45-2.51 (m, 2H), 2.94-2.97 (m, 2H), 7.11 (d, *J* = 8.4 Hz, 2H), 7.63 (d, *J* = 8.8 Hz, 2H);

ESI-MS: *m/z*: 260.10 (M+H)⁺, 100%.

Intermediate-20: 4-(2-(4-(trifluoromethyl)phenoxy)ethoxy)piperidine hydrochloride



Step 1: Preparation of *tert*-butyl 4-(2-ethoxy-2-oxoethoxy)piperidine-1-carboxylate.

To a stirred solution of *tert*-butyl 4-hydroxypiperidine-1-carboxylate (2 g, 9.94 mmol) in Tetrahydrofuran (20 ml), 50% sodium hydride (0.596 g, 24.84 mmol) was added at 0-5 °C under nitrogen atmosphere. After 30 minutes of stirring ethyl bromoacetate (2.213 ml, 19.87 mmol) was added and stirring was continued for 24 hours at ambient temperature.

- 5 Reaction mixture was poured in water (10 ml) and extracted with ethyl acetate (2 x 40 ml). The combined organic layer was washed with water (2 x 30 ml) & brine (30 ml), dried over sodium sulfate and evaporated on rotavapor under vacuum. The crude product was purified by column chromatography using 100-200 mesh silica gel column and 5% ethyl acetate in *n*-hexane as eluent to yield *tert*-butyl 4-(2-ethoxy-2-oxoethoxy)piperidine-1-carboxylate. (1.5 g, 52.5% Yield) as a thick liquid. ¹H NMR (CDCl₃) δ: 1.26 (t, *J* = 8.0 Hz, 3H), 1.47 (s, 9H), 1.57-1.61 (m, 2H), 1.80-1.83 (m, 2H), 3.09-3.15 (m, 2H), 3.47-3.49 (m, 1H), 3.56-3.60 (m, 2H), 4.10 (s, 2H), 4.23 (q, *J* = 8.0 Hz, 2H).

Step 2: Preparation of *tert*-butyl 4-(2-hydroxyethoxy)piperidine-1-carboxylate.

- To a stirred solution of *tert*-butyl 4-(2-ethoxy-2-oxoethoxy)piperidine-1-carboxylate. (1.5 g, 5.22 mmol) in tetrahydrofuran (15 ml), lithium aluminium hydride (0.218g, 5.74mmol) was added in portions at 0-5 °C under nitrogen atmosphere and stirring was continued for 2 hours. Excess LiAlH₄ was quenched by addition of saturated sodium sulfate solution until white solid separated out. The solid was filtered and washed with ethyl acetate (50 ml). The combined filtrate was dried over sodium sulfate and evaporated on rotavapor under vacuum. The crude product was purified by column chromatography using 100-200 mesh silica gel column and 5% ethyl acetate in *n*-hexane as eluent to yield *tert*-butyl 4-(2-hydroxyethoxy)piperidine-1-carboxylate. (1.0 g, 78% Yield) as a thick liquid. ¹H NMR (CDCl₃) δ: 1.50 (s, 9H), 1.51-1.57 (m, 2H), 1.84-1.87 (m, 4H), 2.10 (s, 1H), 3.30-3.12 (m, 3H), 3.48-3.51 (m, 1H), 3.57-3.59 (m, 1H), 3.73-3.75 (m, 2H).

- 25 **Step 3:** Preparation of *tert*-butyl 4-(2-(4-(trifluoromethyl)phenoxy)ethoxy)piperidine-1-carboxylate.

- To a solution of *tert*-butyl 4-(2-hydroxyethoxy) piperidine-1-carboxylate (1.45 g, 6.09 mmol) in dimethylacetamide (10 ml), potassium *tert*-butoxide (1.36 g, 12.19 mmol) was added and stirred at 30 °C for 30 minutes. To this 1-fluoro-4-(trifluoromethyl) benzene (1.0g, 6.09 mmol) was added maintaining the temperature of the reaction mixture below 40 °C. Then reaction mixture was stirred at 60 °C for 24 hours. Reaction mixture was cooled to ambient temperature, poured into water (50 ml) and extracted with ethyl acetate (2 x 100 ml). The combined organic layer was washed with water (2 x 50 ml) & brine (350

ml), dried over sodium sulfate and evaporated on rotavapor under vacuum. The crude product was purified by column chromatography using 100-200 mesh silica gel column and 5-20% ethyl acetate in *n*-hexane as eluent to yield *tert*-butyl 4-(2-(4-(trifluoromethyl)phenoxy)ethoxy)piperidine-1-carboxylate. (1.0 g, 42.0% Yield) as a thick liquid.

¹H NMR (CDCl₃) δ : 1.52 (s, 9H), 1.57-1.63 (m, 2H), 1.86-1.89 (m, 2H), 3.09-3.15 (m, 2H), 3.57-3.59 (m, 1H), 3.77-3.80 (m, 2H), 3.85 (t, *J* = 8.0 Hz, 2H), 4.17 (t, *J* = 8.0 Hz, 2H), 6.99 (d, *J* = 8.0 Hz, 2H), 7.54 (d, *J* = 8.0 Hz, 2H).

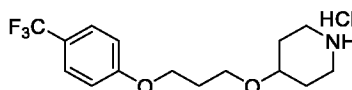
Step 4. Preparation of 4-(2-(4-(trifluoromethyl)phenoxy)ethoxy)piperidine hydrochloride.

The title product (600 mg 81% yield) was prepared from *tert*-butyl 4-(2-(4-(trifluoromethyl) phenoxy)ethoxy)piperidine-1-carboxylate. (890 mg, 2.28 mmol) according to the procedure described in step-2 of **Intermediate-1** as white solid.

¹H NMR (DMSO-*d*₆) δ : 1.92-1.99 (m, 4H), 2.83-2.92 (m, 2H), 2.93-2.96 (m, 2H), 3.33-3.35 (m, 3H), 4.17 (t, *J* = 8.0 Hz, 2H), 7.11 (d, *J* = 8.0 Hz, 2H), 7.64 (d, *J* = 8.0 Hz, 2H), 8.82 (s, 2H);

ESI-MS: *m/z*: 304 (M+H)⁺, 100%.

Intermediate-21: 4-(3-(4-(trifluoromethyl)phenoxy)propoxy)piperidine hydrochloride



Step 1: Preparation of *tert*-butyl 4-(3-ethoxy-3-oxopropoxy)piperidine-1-carboxylate.

To a stirred solution of *tert*-butyl 4-hydroxypiperidine-1-carboxylate (2.0 g, 9.94 mmol) in tetrahydrofuran (20 ml), ethyl acrylate (2.98 g, 29.84 mmol) was added at 0-5 °C under nitrogen atmosphere. After 30 minutes potassium hydroxide (0.056g, 0.994 mmol) was added and stirring was continued for 24 hours at ambient temperature. Reaction mixture was poured into water (10 ml) and extracted with ethyl acetate (2 x 40 ml). The combined organic layer was washed with water (2 x 30 ml) & brine (30 ml), dried over sodium sulfate and evaporated on rotavapor under vacuum. The crude product was purified by column chromatography using 100-200 mesh silica gel column and 5% ethyl acetate in *n*-hexane as eluent to yield *tert*-butyl 4-(2-ethoxy-2-oxoethoxy)piperidine-1-carboxylate. (1.0 g, 33.4% Yield) as a thick liquid.

^1H NMR (CDCl_3) δ : 1.26 (t, $J = 8.0$ Hz, 3H), 1.47 (s, 9H), 1.57-1.61 (m, 2H), 1.80-1.83 (m, 2H), 2.56 (t, $J = 8.0$ Hz, 2H), 3.09-3.15 (m, 2H), 3.47-3.49 (m, 1H), 3.71-3.76 (m, 4H), 4.15 (q, $J = 8.0$ Hz, 2H).

Step 2: Preparation of *tert*-butyl 4-(3-hydroxypropoxy)piperidine-1-carboxylate.

5 To a stirred solution of *tert*-butyl 4-(3-ethoxy-3-oxopropoxy) piperidine-1-carboxylate (1.0 g, 5.22 mmol) in tetrahydrofuran (15 ml), lithium aluminium hydride (0.139g, 3.65 mmol) was added in portions at 0-5 °C under nitrogen atmosphere and stirring was continued for 2 hours. Excess LiAlH_4 was quenched by addition of saturated sodium sulfate solution until white solid separated out. The solid was filtered and washed
10 with ethyl acetate (50 ml). The combined filtrate was dried over sodium sulfate and evaporated on rotavapor under vacuum. The crude product was purified by column chromatography using 100-200 mesh silica gel column and 5% ethyl acetate in *n*-hexane as eluent to yield *tert*-butyl 4-(2-hydroxyethoxy)piperidine-1-carboxylate. (0.7g, 71% Yield) as a thick liquid.

15 ^1H NMR (CDCl_3) δ : 1.43-1.45 (m, 1H), 1.45 (s, 9H), 1.49-1.54 (m, 2H), 1.81-1.87 (m, 3H), 2.50 (s, 1H), 3.07-3.14 (m, 2H), 3.46-3.48 (m, 1H), 3.65-3.67 (m, 2H), 3.72-3.78 (m, 4H).

Step 3: Preparation of *tert*-butyl 4-(2-(4-(trifluoromethyl)phenoxy)ethoxy)piperidine-1-carboxylate.

20 To a solution of *tert*-butyl 4-(3-(4-(trifluoromethyl)phenoxy)propoxy)piperidine-1-carboxylate (0.474 g, 1.82 mmol) in dimethylacetamide (8 ml), potassium *tert*-butoxide (0.4 g, 3.66 mmol) was added and stirred at 30 °C for 30 minutes. To this 1-fluoro-4-(trifluoromethyl) benzene (0.3 g, 1.828 mmol) was added keeping the temperature of the reaction mixture below 40 °C and stirring was continued at 60 °C for 24 hours. Reaction
25 mixture cooled to ambient temperature, poured into water (50 ml) and extracted with ethyl acetate (2 x 40 ml). The combined organic layer was washed with water (2 x 30 ml) & brine (30 ml), dried over sodium sulfate and evaporated on rotavapor under vacuum. The crude product was purified by column chromatography using 100-200 mesh silica gel column and 5-20% ethyl acetate in *n*-hexane as eluent to yield *tert*-butyl 4-(2-(4-
30 (trifluoromethyl)phenoxy)ethoxy)piperidine-1-carboxylate. (0.3 g, 40.7% Yield) as a thick liquid.

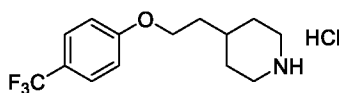
^1H NMR (CDCl_3) δ : 1.41-1.47 (m, 2H), 1.54 (s, 9H), 1.58-1.63 (m, 2H), 1.86-1.89 (m, 2H), 3.09-3.15 (m, 2H), 3.57-3.59 (m, 1H), 3.77-3.80 (m, 2H), 3.84-3.87 (m, 2H), 4.17 (t, $J = 8.0$ Hz, 2H), 6.99 (d, $J = 8.0$ Hz, 2H), 7.54 (d, $J = 8.0$ Hz, 2H).

Step 4: Preparation of 4-(3-(4-(trifluoromethyl)phenoxy)propoxy)piperidine hydrochloride.

The title product (400 mg 86% yield) was prepared from *tert*-butyl 4-(2-(4-(trifluoromethyl)phenoxy)ethoxy)piperidine-1-carboxylate. (550 mg, 1.363 mmol) according to the procedure described in step-2 of **Intermediate-1** as a white solid.

^1H NMR ($\text{DMSO}-d_6$) δ : 1.60-1.68 (m, 2H), 1.92-1.99 (m, 4H), 2.89-2.92 (m, 2H), 2.93-2.96 (m, 2H), 3.33-3.57 (m, 3H), 4.11 (t, $J = 8.0$ Hz, 2H), 7.11 (d, $J = 8.0$ Hz, 2H), 7.64 (d, $J = 8.0$ Hz, 2H), 8.82 (s, 2H); ESI-MS: m/z : 304 ($\text{M}+\text{H}$) $^+$, 100%.

Intermediate-22: 4-(2-(4-(trifluoromethyl)phenoxy)ethyl)piperidine hydrochloride



Step 1: Preparation of *tert*-butyl 4-(2-ethoxy-2-oxoethylidene)piperidine-1-carboxylate

To a stirred solution of propyl 2-(diethoxyphosphoryl) acetate (6.28 ml, 31.4 mmol) in tetrahydrofuran (50 ml), 50% sodium hydride (1.642 g, 37.64 mmol) was added at 0-5 °C under nitrogen atmosphere and stirred for 30 minutes. To this *tert*-butyl 4-oxopiperidine-1-carboxylate (5.0 g, 25.09 mmol) was added and stirring was continued for 24 hours at ambient temperature. Reaction mixture was poured into water (50 ml) and extracted with ethyl acetate (2 x 100 ml). The combined organic layer was washed with water (2 x 50 ml) & brine (50 ml), dried over sodium sulfate and evaporated on rotavapor under vacuum. The crude product was purified by column chromatography using 100-200 mesh silica gel column and 5-20% ethyl acetate in *n*-hexane as eluent to yield *tert*-butyl 4-(2-ethoxy-2-oxoethylidene)piperidine-1-carboxylate (6.0 g, 89% Yield) as a thick liquid.

^1H NMR (CDCl_3) δ : 1.24 (t, $J = 8.0$ Hz, 3H), 1.38 (s, 9H), 2.26 (t, $J = 6.0$ Hz, 2H), 2.91 (t, $J = 8.0$ Hz, 2H), 3.45-3.51 (m, 4H), 4.12 (q, $J = 8.0$ Hz, 2H), 5.70 (s, 1H).

Step 2: Preparation of *tert*-butyl 4-(2-ethoxy-2-oxoethyl) piperidine-1-carboxylate.

A solution of *tert*-butyl 4-(2-ethoxy-2-oxoethylidene)piperidine-1-carboxylate (6.0 g, 22.28 mmol) in methanol (50 ml) was added to a suspension of 10% Pd-C (1.0 g, 0.940 mmol) in methanol (35 ml) and stirred the reaction mixture for 2 hours under hydrogen atmosphere at ambient temperature. Reaction mixture was filtered through celite bed and

washed with methanol. Filtrate was concentrated on rotavapor under vacuum to yield *tert*-butyl 4-(2-ethoxy-2-oxoethyl)piperidine-1-carboxylate (6.0 g, 99% yield) as a thick liquid.

^1H NMR (CDCl_3) δ : 1.11-1.15 (m, 2H), 1.24-1.29 (m, 3H), 1.46 (s, 9H), 1.68-1.71 (m, 2H), 1.91-1.96 (m, 1H), 2.23-2.24 (m, 2H), 2.69-2.75 (m, 2H), 4.10-4.16 (m, 4H).

5 **Step 3:** Preparation of *tert*-butyl 4-(2-hydroxyethyl)piperidine-1-carboxylate.

The title product (3.0g 59.2% yield) was prepared from *tert*-butyl 4-(2-ethoxy-2-oxoethyl)piperidine-1-carboxylate. (6.0g, 22.11 mmol) according to the procedure described in step-2 of **Intermediate-20** as a thick liquid.

10 ^1H NMR (CDCl_3) δ : 1.04-1.10 (m, 2H), 1.48 (s, 9H), 1.49-1.55 (m, 3H), 1.60-1.66 (m, 2H), 2.27 (s, 1H), 2.64 (t, $J = 8.0$ Hz, 2H), 3.64 (t, $J = 8.0$ Hz, 2H), 4.03-4.08 (m, 2H).

Step 4: Preparation of *tert*-butyl 4-(2-(4-(trifluoromethyl)phenoxy)ethyl)piperidine-1-carboxylate.

15 The title product (1.0g 40.0% yield) was prepared from *tert*-butyl 4-(2-hydroxyethyl)piperidine-1-carboxylate (1.537g, 6.70 mmol) and 1-fluoro-4-(trifluoromethyl)benzene (1.1g, 6.70 mmol) according to the procedure described in step-1 of **Intermediate-1** as a thick liquid.

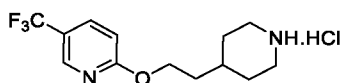
^1H NMR (CDCl_3) δ : 1.18-1.24 (m, 2H), 1.44 (s, 9H), 1.68-1.79 (m, 5H), 2.69-2.75 (m, 2H), 4.05-4.14 (m, 4H), 6.95 (d, $J = 8.4$ Hz, 2H), 7.54 (d, $J = 8.8$ Hz, 2H).

Step 5: Preparation of 4-(2-(4-(trifluoromethyl)phenoxy)ethyl)piperidine hydrochloride.

20 The title product (500 mg 100% yield) was prepared from *tert*-butyl 4-(2-(4-(trifluoromethyl)phenoxy)ethyl)piperidine-1-carboxylate. (600 mg, 1.607 mmol) according to the procedure described in step-2 of **Intermediate-1** as white solid.

25 ^1H NMR ($\text{DMSO}-d_6$) δ : 1.39-1.42 (m, 2H), 1.68-1.72 (m, 2H), 1.75-1.78 (m, 1H), 1.80-1.87 (m, 2H), 2.78-2.87 (m, 2H), 3.20-3.24 (m, 2H), 4.09 (t, $J = 6.8$ Hz, 2H), 7.10 (d, $J = 8.4$ Hz, 2H), 7.63 (d, $J = 8.8$ Hz, 2H), 8.80 (s, 1H), 9.04 (s, 1H); ESI-MS: m/z : 274.13 ($\text{M}+\text{H}$) $^+$, 100%.

Intermediate-23: 2-(2-(piperidin-4-yl)ethoxy)-5-(trifluoromethyl)pyridine hydrochloride

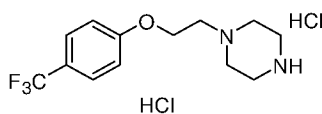


30 **Step 1:** Preparation of 2-(2-(piperidin-4-yl)ethoxy)-5-(trifluoromethyl)pyridine hydrochloride.

The title product (500 mg, 100% yield) was prepared from *tert*-butyl 4-(2-hydroxyethyl)piperidine-1-carboxylate (1.54 g, 6.64 mmol) and 2-bromo-5-(trifluoromethyl)pyridine (1.1g, 6.70 mmol) according to the procedures described in **Intermediate-22** as a white solid.

- 5 ¹H NMR (DMSO-*d*₆) δ : 1.02-1.10 (m, 2H), 1.32-1.37 (m, 3H), 1.43-1.46 (m, 2H), 2.80-2.86 (m, 2H), 3.12-3.22 (m, 2H), 4.32-4.38 (m, 2H), 6.98 (d, *J* = 8.8 Hz, 1H), 8.04 (d, *J* = 8.8 Hz, 1H), 8.57 (s, 1H), 8.91 (s, 1H), 9.11 (s, 1H); ESI-MS: *m/z*: 275.13 (M+H)⁺, 100%.

Intermediate-24: 1-(2-(4-(trifluoromethyl)phenoxy)ethyl)piperazine dihydrochloride



Step 1: Preparation of *tert*-butyl 4-(2-(4-(trifluoromethyl)phenoxy)ethyl)piperazine-1-carboxylate.

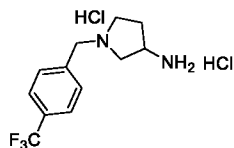
- To a stirred solution of 1-fluoro-4-(trifluoromethyl)benzene (500 mg, 3.05 mmol) and *tert*-butyl 4-(2-hydroxyethyl)piperazine-1-carboxylate (702 mg, 3.05 mmol) in dimethylacetamide (5.0 ml), potassium *tert*-butoxide (684 mg, 6.09 mmol) was added at ambient temperature and stirred at 60 °C for 24 hours. The reaction mixture was poured into water (20 ml) and extracted with ethyl acetate (2 x 20 ml). The combined organic layer was washed with water (2 x 15 ml) & brine (15 ml), dried over sodium sulfate and evaporated on rotavapor under vacuum. The crude product was purified by column chromatography using 230-400 mesh silica gel column and 20% ethyl acetate in *n*-hexane as eluent to yield pure *tert*-butyl 4-(2-(4-(trifluoromethyl)phenoxy)ethyl)piperazine-1-carboxylate (700 mg, 61.4% yield) as a thick liquid. ¹HNMR (CDCl₃) δ : 1.48 (s, 9H), 2.53.-2.56 (m, 4H), 2.85 (t, *J* = 5.6 Hz, 2H), 3.46-3.49 (m, 4H), 4.16 (t, *J* = 5.6 Hz, 2H), 6.98 (d, *J* = 8.4 Hz, 2H), 7.55 (d, *J* = 8.8 Hz, 2H).
- 15
- 20
- 25

Step 2: Preparation of 1-(2-(4-(trifluoromethyl)phenoxy)ethyl)piperazine dihydrochloride

The title product (617 mg 95% yield) was prepared from *tert*-butyl 4-(2-(4-(trifluoromethyl)phenoxy)ethyl)piperazine-1-carboxylate (700 mg, 1.870 mmol) according to the procedure described in step-2 of **Intermediate-1** as a white solid.

30

Intermediate-25: 1-(4-(trifluoromethyl)benzyl)pyrrolidin-3-amine dihydrochloride



Step 1: *tert*-butyl (1-(4-(trifluoromethyl)benzyl)pyrrolidin-3-yl)carbamate.

To a stirred solution of *tert*-butyl pyrrolidin-3-ylcarbamate (0.2 g, 1.074 mmol) in N,N-dimethylformamide (3 ml), cesium carbonate (1.050 g, 3.22 mmol) was added followed by the addition of 1-(bromomethyl)-4-(trifluoromethyl)benzene (0.257 g, 1.074 mmol) and stirring was continued further for 16 hours at ambient temperature. The reaction mixture was poured into water (15 ml) and extracted with ethyl acetate (2 x 15 ml). The combined organic layer was washed with water (2 x 30 ml) & brine (30 ml), dried over sodium sulfate and concentrated on rotavapor under vacuum. The crude product was purified by column chromatography using 100-200 mesh silica gel column and 50% ethyl acetate in *n*-hexane as eluent to yield *tert*-butyl (1-(4-(trifluoromethyl)benzyl)pyrrolidin-3-yl)carbamate (0.170 g, 46% Yield) as a thick liquid.

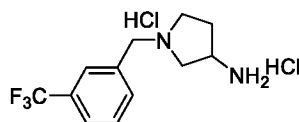
ESI-MS: *m/z* 345.17 (M+H)⁺, 100%.

Step 2: 1-(4-(trifluoromethyl)benzyl)pyrrolidin-3-amine dihydrochloride.

The title product (0.140 g, 86% yield) was prepared from *tert*-butyl (1-(4-(trifluoromethyl)benzyl)pyrrolidin-3-yl)carbamate (0.165 g, 0.479 mmol) according to the procedure described in step-2 of **Intermediate-1** as an off white solid.

¹H NMR (DMSO-*d*₆) δ: 2.04-2.08 (m, 1H), 2.18-2.27 (m, 1H), 3.19-3.22 (m, 1H), 3.40-3.73 (m, 3H), 3.82-4.07 (m, 1H), 4.56-4.63 (m, 2H), 7.86 (s, 4H), 8.45-8.61 (m, 3H), 11.55-11.87 (m, 1H); ESI-MS: *m/z* 245.12 (M+H)⁺, 100%.

Intermediate-26: 1-(4-(trifluoromethyl)benzyl)pyrrolidin-3-amine dihydrochloride



Step 1: *tert*-butyl (1-(3-(trifluoromethyl)benzyl)pyrrolidin-3-yl)carbamate.

To a stirred solution of *tert*-butyl pyrrolidin-3-ylcarbamate (0.5 g, 2.68 mmol) in 1, 2-dichloromethane (4 ml), 3-(trifluoromethyl)benzaldehyde (0.514 g, 2.95 mmol) was added at ambient temperature followed by addition of sodium triacetoxyborohydride (1.422 g, 6.71 mmol) and stirring was continued further for 24 hours. Reaction mixture was poured into water (15 ml) and extracted with 1, 2-dichloromethane (20 ml). The organic layer was

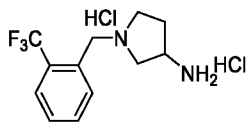
washed with water (2 x 20 ml) & brine (20 ml), dried over sodium sulfate and evaporated on rotavapor under vacuum to yield *tert*-butyl (1-(3-(trifluoromethyl)benzyl)pyrrolidin-3-yl)carbamate (0.314 g, 34% Yield) as a thick liquid. ESI-MS: m/z 345.18 (M+H)⁺, 100%.

Step 2: 1-(3-(trifluoromethyl)benzyl)pyrrolidin-3-amine dihydrochloride.

5 The title product (0.101 g, 40% yield) was prepared from *tert*-butyl (1-(3-(trifluoromethyl)benzyl)pyrrolidin-3-yl)carbamate (0.310 g, 0.900 mmol) according to the procedure described in step-2 of **Intermediate-1** as an off white solid.

¹H NMR (DMSO-*d*₆) δ : 2.04-2.08 (m, 1H), 2.25-2.33 (m, 1H), 3.20-3.24 (m, 1H), 3.52-3.57 (m, 3H), 3.92-4.08 (m, 1H), 4.56-4.64 (m, 2H), 7.17 (t, J = 7.6 Hz, 1H), 7.78 (m, 1H),
10 7.82-7.84 (m, 1H), 7.93-7.99 (m, 1H), 8.55-8.72 (m, 3H), 11.58-11.99 (m, 1H); ESI-MS: m/z 245.12 (M+H)⁺, 100%.

Intermediate-27: 1-(2-(trifluoromethyl)benzyl)pyrrolidin-3-amine dihydrochloride



15 **Step 1:** *tert*-butyl (1-(2-(trifluoromethyl)benzyl)pyrrolidin-3-yl)carbamate.

To a stirred solution of *tert*-butyl pyrrolidin-3-ylcarbamate (0.5 g, 2.68 mmol) in tetrahydrofuran (5 ml), 2-(trifluoromethyl)benzaldehyde (0.514 g, 2.95 mmol) was added at ambient temperature and the mixture was stirred at 45 °C for 4 hours. To this sodium triacetoxyborohydride (1.422 g, 6.71 mmol) was added at 0-5 °C and stirring was continued
20 for further 16 hours at ambient temperature. Reaction mixture was poured into water (15 ml) and extracted with ethyl acetate (2 x 15 ml). Combined organic layer was washed with water (2 x 20 ml) & brine (20 ml), dried over sodium sulfate and evaporated on rotavapor under vacuum. Crude product was purified by column chromatography using 100-200 mesh silica gel column and 30% ethyl acetate in *n*-hexane as eluent to yield *tert*-butyl (1-(2-(trifluoromethyl)benzyl)pyrrolidin-3-yl)carbamate (0.470 g, 51% Yield) as a thick
25 liquid.

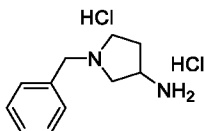
ESI-MS: m/z 345.18 (M+H)⁺, 100%.

Step 2: 1-(2-(trifluoromethyl)benzyl)pyrrolidin-3-amine dihydrochloride.

30 The title product (0.298 g, 78% yield) was prepared from *tert*-butyl (1-(2-(trifluoromethyl)benzyl)pyrrolidin-3-yl)carbamate (0.460 g, 1.336 mmol) according to the procedure described in step-2 of **Intermediate-1** as an off white solid.

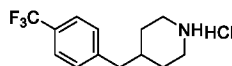
^1H NMR ($\text{DMSO-}d_6$) δ : 2.13-2.18 (m, 1H), 2.36-2.42 (m, 1H), 3.30-3.38 (m, 1H), 3.42-3.64 (m, 3H), 3.91-4.08 (m, 1H), 4.64-4.69 (m, 2H), 7.66 (t, $J = 7.6$ Hz, 1H), 7.79-7.91 (m, 3H), 8.72-8.80 (m, 3H), 11.47-12.05 (m, 1H); ESI-MS: m/z 245.12 ($\text{M}+\text{H}$) $^+$, 100%.

5 **Intermediate-28: *tert*-butyl (1-benzylpyrrolidin-3-yl)carbamate**



The title product (0.890 g, 99% yield) was prepared from *tert*-butyl (1-benzylpyrrolidin-3-yl)carbamate (1 g, 3.62 mmol) according to the procedure described in step-2 of **Intermediate-1** as an off white solid. ^1H NMR ($\text{DMSO-}d_6$) δ : 2.09-2.31 (m, 2H),
 10 3.18-3.25 (m, 1H), 3.50-3.68 (m, 3H), 3.80-3.91 (m, 1H), 4.44-4.51 (m, 2H), 7.45-7.64 (m, 5H), 11.34-11.87 (m, 1H).

Intermediate-29: 4-(4-(trifluoromethyl)benzyl)piperidine hydrochloride



15 **Step 1: Diethyl (4-(trifluoromethyl)benzyl)phosphonate.**

A mixture of 1-(bromomethyl)-4-(trifluoromethyl)benzene (2.0 gm, 8.37 mmol) and triethyl phosphate (2.195 ml, 12.55 mmol) was heated for 16 hours at 150 °C. The reaction mixture was cooled to ambient temperature, diluted with ethyl acetate (30 ml), washed with water (3 x 25 ml) & brine (25 ml), dried over sodium sulphate and concentrated on
 20 rotavapor under vacuum. The crude product was purified by column chromatography using 230-400 mesh silica gel column and 5% ethyl acetate in *n*-hexane as an eluent to yield pure diethyl (4-(trifluoromethyl)benzyl)phosphonite (1.5 gm, 64% yield) as a thick liquid.

^1H NMR (CDCl_3) δ : 1.27 (t, $J = 7.2$ Hz, 6H), 3.19 (s, 2H), 4.01-4.04 (m, 4H), 7.44 (d, $J = 6.4$ Hz, 2H), 7.59 (d, $J = 8.0$ Hz, 2H); ESI-MS: m/z 297.10 ($\text{M}+\text{H}$), 100%.

25 **Step 2: *tert*-butyl 4-(4-(trifluoromethyl)benzylidene)piperidine-1-carboxylate.**

To a stirred suspension of sodium hydride (50%, 292 mg, 6.04 mmol) in tetrahydrofuran (3 ml), a solution of diethyl (4-(trifluoromethyl)benzyl)phosphonate (1.2 gm, 4.05 mmol) in tetrahydrofuran (2 ml) was added dropwise over a period of 3 minutes under nitrogen atmosphere at ambient temperature. To this *tert*-butyl 4-oxopiperidine-1-
 30 carboxylate (686 mg, 3.44 mmol) was added followed by 18-crown-6 (86 mg, 0.324 mmol) and stirring was continued for 6 hours. The reaction mixture was poured into ice-cold water

(50 ml) and extracted with ethyl acetate (3 x 30 ml). The organic layer was washed with water (3 x 50 ml) & brine (50 ml), dried over sodium sulfate and concentrated on rotavapor under vacuum. The crude product was purified by column chromatography using 230-400 mesh silica gel column and 5% ethyl acetate in *n*-hexane as an eluent to yield pure *tert*-butyl 4-(4-(trifluoromethyl)benzylidene)piperidine-1-carboxylate (1.12 g, 81% yield) as thick liquid.

¹H NMR (CDCl₃) δ: 1.50 (s, 9H), 2.36-2.39 (m, 2H), 2.44-2.47 (m, 2H), 3.41-3.44 (m, 2H), 3.53-3.55 (m, 2H), 6.39 (s, 1H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.59 (d, *J* = 8.0 Hz, 2H).

Step 3: *tert*-butyl 4-(4-(trifluoromethyl)benzyl)piperidine-1-carboxylate.

A solution of *tert*-butyl 4-(4-(trifluoromethyl)benzyl)piperidine-1-carboxylate (1.0 gm, 2.93 mmol) in methanol (20 ml) was added to a suspension of 10% Pd-C (156 mg, 0.146 mmol) in methanol (5 ml) and the reaction mixture was stirred under hydrogen atmosphere at 50 psi pressure for 3 hours at ambient temperature. The reaction mixture was filtered through celite bed, washed with methanol and filtrate was concentrated on rotavapor under vacuum. The crude product was purified by column chromatography using 230-400 mesh silica gel column and 5% ethyl acetate in *n*-hexane as an eluent to yield pure *tert*-butyl 4-(4-(trifluoromethyl)benzyl)piperidine-1-carboxylate (1.0 gm, 99% yield) as a thick liquid.

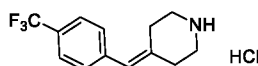
¹H NMR (CDCl₃) δ: 1.13-1.22 (m, 2H), 1.49 (s, 9H), 1.66-1.73 (m, 3H), 2.60-2.68 (m, 2H), 4.10 (br s, 2H), 7.26 (d, *J* = 8.0 Hz, 2H), 7.55 (d, *J* = 8.0 Hz, 2H).

Step 4: 4-(4-(trifluoromethyl)benzyl)piperidine hydrochloride.

The title product (750 mg, 92% yield) was prepared from *tert*-butyl 4-(4-(trifluoromethyl)benzyl)piperidine-1-carboxylate (1.0 gm, 2.91 mmol) according to the procedure described in step-2 of **Intermediate-1** as white solid.

¹H NMR (DMSO-*d*₆) δ: 1.29-1.40 (m, 2H), 1.67-1.72 (m, 2H), 1.81-1.86 (m, 1H), 2.63-2.68 (m, 2H), 2.75-2.82 (m, 2H), 3.20-3.23 (m, 2H), 7.43 (d, *J* = 8.0 Hz, 2H), 7.67 (d, *J* = 8.0 Hz, 2H), 8.65 (br s, 2H); ESI-MS: *m/z* 244.10 (M+H), 100%.

Intermediate-30: 4-(4-(trifluoromethyl)benzylidene)piperidine hydrochloride

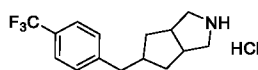


The title product (240 mg, 98% yield) was prepared from *tert*-butyl 4-(4-(trifluoromethyl)benzylidene)piperidine-1-carboxylate (0.3 gm, 0.879 mmol) according to the procedure described in step-2 of **Intermediate-1** as an off-white solid.

¹H NMR (DMSO-*d*₆) δ : 2.36-2.39 (m, 2H), 2.44-2.47 (m, 2H), 3.41-3.44 (m, 2H), 3.53-3.55 (m, 2H), 6.39 (s, 1H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.59 (d, *J* = 8.0 Hz, 2H), 8.93 (s, 1H), 9.02 (s, 1H); ESI-MS: *m/z* 242.11 (M+H)⁺, 100%.

Intermediate-31: 5-(4-(trifluoromethyl)benzyl)octahydrocyclopenta[c]pyrrole hydrochloride

10

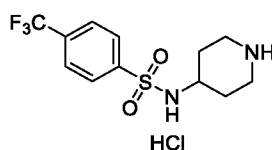


The title product (200 mg, 77% yield) was prepared from *tert*-butyl 5-(4-(trifluoromethyl)benzyl)hexahydrocyclopenta[c]pyrrole-2(1H)-carboxylate (0.25 gm, 0.667 mmol) according to the procedure described in step-2 of **Intermediate-1** as white solid.

¹H NMR (DMSO-*d*₆) δ : 0.95 (m, 1H), 1.09 (m, 1H), 1.83 (m, 1H), 1.94 (m, 1H), 2.11-2.15 (m, 1H), 2.56 (m, 2H), 2.73 (d, *J* = 6.8 Hz, 2H), 3.49-3.63 (m, 4H), 7.39 (d, *J* = 8.0 Hz, 2H), 7.49 (d, *J* = 8.4 Hz, 2H); ESI-MS: *m/z* 270.18 (M+H)⁺, 100%.

Intermediate-32: N-(piperidin-4-yl)-4-(trifluoromethyl)benzenesulfonamide hydrochloride

20



Step 1: Preparation of *tert*-butyl 4-((4-(trifluoromethyl)phenyl)sulfonamido)piperidine-1-carboxylate

To a stirred solution of *tert*-butyl 4-aminopiperidine-1-carboxylate (300 mg, 1.498 mmol) in dichloromethane (20 ml), triethylamine (0.626 ml, 4.49 mmol) was added followed by the addition of 4-(trifluoromethyl)benzenesulfonyl chloride (476 mg, 1.947 mmol) at 0 °C and stirring was continued for 30 minutes. The reaction mixture was poured into water (20 ml) and extracted with dichloromethane (3 x 20 ml). The combined organic layer was washed with water (2 x 20 ml) & brine (20 ml), dried over sodium sulfate and evaporated on rotavapor under vacuum. The solid product was triturated with diisopropyl

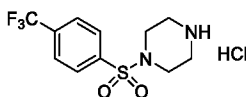
ether (20 ml), filtered through a Buchner Funnel, rinsed with diisopropyl ether (5.0 ml) and dried to yield *tert*-butyl 4-((4-(trifluoromethyl)phenyl)sulfonamido)piperidine-1-carboxylate (500 mg, 82% yield) as a white solid. ^1H NMR (CDCl_3) δ : 1.37-1.46 (m, 2H), 1.47 (s, 9H), 1.77-1.81 (m, 2H), 2.78-2.84 (m, 2H), 3.34-3.38 (m, 1H), 3.94-3.97 (m, 2H), 4.77 (d, $J = 7.6$ Hz, 1H), 7.81 (d, $J = 8.4$ Hz, 2H), 8.04 (d, $J = 8.4$ Hz, 2H); ESI-MS: m/z : 407.05 (M-H) $^+$, 100%.

Step 2: Preparation of N-(piperidin-4-yl)-4-(trifluoromethyl)benzenesulfonamide hydrochloride

The title product (384 mg, 91% yield) was prepared from *tert*-butyl 4-((4-(trifluoromethyl)phenyl)sulfonamido)piperidine-1-carboxylate (500 mg, 1.224 mmol) according to the procedure described in step-2 of **Intermediate-1** as white solid.

^1H NMR ($\text{DMSO}-d_6$) δ : 1.54-1.64 (m, 2H), 1.72-1.80 (m, 2H), 2.82-2.90 (m, 2H), 3.13-3.16 (m, 2H), 8.00 (d, $J = 8.4$ Hz, 2H), 8.05 (d, $J = 8.4$ Hz, 2H), 8.34 (d, $J = 6.8$ Hz, 1H), 8.80 (br s, HCl), 8.91 (br s, HCl); ESI-MS: m/z : 309.10 (M-H) $^+$, 100%.

Intermediate-33: 1-((4-(trifluoromethyl)phenyl)sulfonyl)piperazine hydrochloride



Step 1: *tert*-butyl 4-((4-(trifluoromethyl)phenyl)sulfonyl)piperazine-1-carboxylate.

To a stirred solution of 4-(trifluoromethyl)benzenesulfonyl chloride (0.4 gm, 1.635 mmol) in dichloromethane (5 ml), *tert*-butyl piperazine-1-carboxylate (0.3 gm, 1.635 mmol) was added followed by the addition of triethylamine (0.342 ml, 2.453 mmol) under nitrogen atmosphere at 0 °C and the reaction mixture was warmed to ambient temperature over a period of 1 hour. The reaction mixture was poured into ice-cold water (30 ml) and extracted with dichloromethane (2 x 25 ml). The organic layer was washed with water (2 x 30 ml) & brine (30 ml), dried over calcium chloride and concentrated under vacuum to yield *tert*-butyl 4-((4-(trifluoromethyl)phenyl)sulfonyl)piperazine-1-carboxylate (0.6 gm, 93% yield) as a thick liquid. ^1H NMR (CDCl_3) δ : 1.43 (s, 9H), 3.02-3.04 (m, 4H), 3.53-3.55 (m, 4H), 7.84 (d, $J = 8.4$ Hz, 2H), 7.90 (d, $J = 8.0$ Hz, 2H).

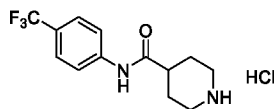
Step 2: 1-((4-(trifluoromethyl)phenyl)sulfonyl)piperazine hydrochloride.

The title product (750 mg, 100% yield) was prepared from *tert*-butyl 4-((4-(trifluoromethyl)phenyl)sulfonyl)piperazine-1-carboxylate (0.85 gm, 2.155 mmol) according to the procedure described in step-2 of **Intermediate-1** as a white solid.

^1H NMR (DMSO- d_6) δ : 3.19 (s, 4H), 3.34 (s, 4H), 8.02 (d, J = 8.4 Hz, 2H), 8.11 (d, J = 8.4 Hz, 2H), 9.10 (br s, 2H); ESI-MS: m/z 295.07 ($M+H$) $^+$, 100%.

Intermediate-34: N-(4-(trifluoromethyl)phenyl)piperidine-4-carboxamide

5 hydrochloride



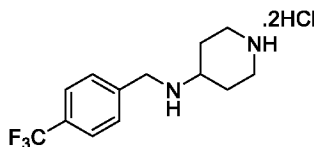
Step 1: *tert*-butyl 4-((4-(trifluoromethyl)phenyl)carbamoyl)piperidine-1-carboxylate.

To a stirred solution of 1-(*tert*-butoxycarbonyl)piperidine-4-carboxylic acid (0.5 gm, 2.181 mmol), 4-(trifluoromethyl)aniline (0.351 gm, 2.181 mmol), HATU (1.244 gm, 3.27 mmol) in *N,N*-dimethylformamide (5 ml), diisopropyl ethyl amine (1.143 ml, 6.54 mmol) was added under nitrogen atmosphere at ambient temperature and the reaction mixture was stirred for 16 hours at 70 °C. The reaction mixture was cooled to ambient temperature, poured into ice-cold water (50 ml) and extracted with ethyl acetate (3 x 30 ml). The organic layer was washed with water (2 x 30 ml) & brine (30 ml), dried over sodium sulfate and evaporated on rotavapor under vacuum to yield *tert*-butyl 4-((4-(trifluoromethyl)phenyl)carbamoyl)piperidine-1-carboxylate (550 mg, 68% yield) as a thick liquid.

Step 2: N-(4-(trifluoromethyl)phenyl)piperidine-4-carboxamide hydrochloride.

The title product (240 mg, 96% yield) was prepared from *tert*-butyl 4-((4-(trifluoromethyl)phenyl)carbamoyl)piperidine-1-carboxylate (0.3 gm, 0.806 mmol) according to the procedure described in step-2 of **Intermediate-1** as white solid.

Intermediate-35: N-(4-(trifluoromethyl)benzyl)piperidin-4-amine hydrochloride



Step 1: Preparation of *tert*-butyl 4-(benzylamino)piperidine-1-carboxylate.

To a stirred solution of *tert*-butyl 4-aminopiperidine-1-carboxylate (2.0 g, 9.99 mmol) and 4-(trifluoromethyl)benzaldehyde (1.74 g, 9.99 mmol) in acetic acid (10 ml), sodium sulfate (8.82g, 62.1mmol) was added and the reaction mixture was stirred at 30 °C for 3 hours. To this sodium triacetoxyborohydride (3.95 g, 18.62 mmol) was added and stirring

was continued for 20 hours. The reaction mixture was poured into water (50 ml). White solid separated was filtered through Buchner funnel, washed with water (50 ml) and dried over phosphorous pentoxide to yield *tert*-butyl 4-((4-(trifluoromethyl)phenyl)amino)piperidine-1-carboxylate. (2.0 g, 55.5% yield) as an off white solid.

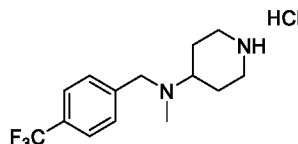
^1H NMR (CDCl_3) δ : 1.25-1.28 (m, 2H), 1.46 (s, 9H), 1.85-1.88 (m, 2H), 2.64-2.67 (m, 2H), 2.69-2.84 (m, 2H), 3.89-3.92 (m, 2H), 4.12-4.14 (m, 2H), 5.3 (s, 1H), 7.45 (d, $J = 8.0$ Hz, 2H), 7.57 (d, $J = 8.0$ Hz, 2H).

Step 2: Preparation of N-(4-(trifluoromethyl)benzyl)piperidin-4-amine hydrochloride.

The title product (350 mg 97% yield) was prepared from *tert*-butyl 4-(2-(4-(trifluoromethyl) phenoxy)ethyl)piperidine-1-carboxylate. (500 mg, 1.395 mmol) according to the procedure described in step-2 of **Intermediate-1** as white solid.

^1H NMR ($\text{DMSO}-d_6$) δ : 1.92-1.96 (m, 2H), 2.01-2.28 (m, 2H), 2.87-2.96 (m, 2H), 3.3-3.5 (m, 3H), 4.27-4.32 (m, 2H), 7.67 (d, $J = 8.4$ Hz, 2H), 7.87 (d, $J = 8.0$ Hz, 2H), 9.31 (s, 2H), 9.05 (s, 1H), 9.31 (s, 1H); ESI-MS: m/z : 259.17 ($\text{M}+\text{H}$) $^+$, 100%.

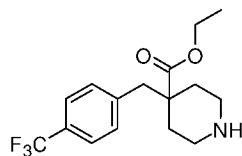
Intermediate-36: N-methyl-N-(4-(trifluoromethyl)benzyl)piperidin-4-amine hydrochloride



The title product (150 mg, 60.3% yield) was prepared from *tert*-butyl 4-((4-(trifluoromethyl)phenyl)amino)piperidine-1-carboxylate (0.5g, 1.45 mmol) according to the procedure described in **Intermediate-4** as a white solid.

^1H NMR ($\text{DMSO}-d_6$) δ : 1.09-1.11 (m, 2H), 2.04-2.09 (m, 2H), 2.50 (s, 3H), 2.89-2.96 (m, 2H), 3.36-3.41 (m, 2H), 3.54-3.57 (m, 1H), 4.52-4.54 (m, 1H), 7.83 (d, $J = 8.0$ Hz, 2H), 7.83 (d, $J = 8.0$ Hz, 2H), 9.06 (s, 1H), 9.21 (s, 1H), 11.52 (s, 1H); ESI-MS: m/z : 271.19 ($\text{M}+\text{H}$) $^+$, 100%.

Intermediate-37: 1-(*tert*-butyl) 4-ethyl 4-(4-(trifluoromethyl)benzyl)piperidine-1,4-dicarboxylate



Step 1: Preparation of 1-(*tert*-butyl) 4-ethyl 4-(4-(trifluoromethyl)benzyl)piperidine-1,4-dicarboxylate.

To a solution of diisopropylamine (1.994 ml, 13.99 mmol) in tetrahydrofuran (50 ml),
 5 *n*-butyl lithium (5.60 ml, 13.99 mmol) was added below 0 °C and stirred for 30 minutes at 0 °C. The reaction mixture was cooled to -78 °C and a solution of 1-(*tert*-butyl) 4-ethyl piperidine-1,4-dicarboxylate (1.8 g, 6.99 mmol) in tetrahydrofuran (5.0 ml) was added and continued to stir at -78 °C for 1 hour. To this another solution of 1-(bromomethyl)-4-(trifluoromethyl)benzene (1.839 g, 7.69 mmol) in tetrahydrofuran (5.0 ml) was added and
 10 continued to stir at -78 °C for further 1 hour and the reaction mixture was slowly warmed to room temperature over period of 2 hours. Reaction mixture was poured into saturated ammonium chloride solution (100 ml) and extracted with ethyl acetate (3 x 50 ml). The combined organic layer was washed with water (2 x 50 ml) & brine (50 ml), dried over sodium sulfate and evaporated on rotavapor. The crude product was purified by column
 15 chromatography using 230-400 mesh silica gel column and 7% ethyl acetate in *n*-hexane as eluent to yield pure 1-(*tert*-butyl) 4-ethyl 4-(4-(trifluoromethyl)benzyl)piperidine-1,4-dicarboxylate (2.1 g, 72.3% yield) as a thick liquid.

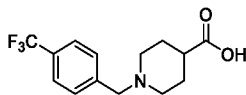
¹HNMR (CDCl₃) δ : 1.20 (t, *J* = 7.2 Hz, 3H), 1.46 - 1.47 (m, 11H), 2.09 – 2.12 (m, 2H), 2.82-2.89 (m, 4H), 3.85-.3.90 (m, 2H), 4.12 (q, *J* = 7.0 Hz, 2H), 7.18 (d, *J* = 8.0 Hz, 2H),
 20 7.53 (d, *J* = 8.0 Hz, 2H).

Step 2: Preparation of ethyl 4-(4-(trifluoromethyl)benzyl)piperidine-4-carboxylate.

The title product (380 mg, 100% yield) was prepared from 1-(*tert*-butyl) 4-ethyl 4-(4-(trifluoromethyl)benzyl)piperidine-1,4-dicarboxylate (500 mg, 1.204 mmol) according to the procedure described in step-2 of **Intermediate-2** as a yellow liquid.

¹HNMR (CDCl₃) δ : 1.19 (t, *J* = 6.8 Hz, 3H), 1.74-1.82 (m, 2H), 2.23.-2.26 (m, 2H), 2.76-2.88 (m, 2H), 2.93 (s, 2H), 3.23-3.26 (m, 2H), 4.14 (q, *J* = 7.0 Hz, 2H), 7.18 (d, *J* = 7.6 Hz, 2H), 7.54 (d, *J* = 8.0 Hz, 2H);
 25 ESI-MS: *m/z*: 316.14 (M+H)⁺, 100%.

30 **Intermediate-38: 1-(4-(trifluoromethyl)benzyl)piperidine-4-carboxylic acid**



Step 1: Ethyl 1-(4-(trifluoromethyl)benzyl)piperidine-4-carboxylate.

To a stirred solution of 1-(bromomethyl)-4-(trifluoromethyl)benzene (2.0 gm, 8.37 mmol) and ethyl piperidine-4-carboxylate (1.315 gm, 8.37 mmol) in acetonitrile (20 ml), diisopropyl ethyl amine (1.754 ml, 1.298 mmol) was added under nitrogen atmosphere at ambient temperature and the reaction mixture was refluxed over the period of 2 hours. The reaction mixture was cooled to ambient temperature, poured into water (50 ml) and extracted with ethyl acetate (2 x 30 ml). The organic layer was washed with water (2 x 30 ml) & brine (30 ml), dried over sodium sulfate and evaporated on rotavapor under vacuum to yield ethyl 1-(4-(trifluoromethyl)benzyl)piperidine-4-carboxylate (2.6 gm, 99% yield) as a thick liquid.

^1H NMR (CDCl_3) δ : 1.27 (t, $J = 7.2$ Hz, 3H), 1.74-1.82 (m, 2H), 1.88-1.92 (m, 2H), 2.04-2.10 (m, 2H), 2.27-2.37 (m, 1H), 2.83-2.85 (m, 2H), 3.55 (s, 2H), 4.16 (q, $J = 14.4$ Hz, 2H), 7.46 (d, $J = 8.0$ Hz, 2H), 7.58 (d, $J = 8.0$ Hz, 2H);

ESI-MS: m/z 316.15 ($\text{M}+\text{H}$) $^+$, 100%.

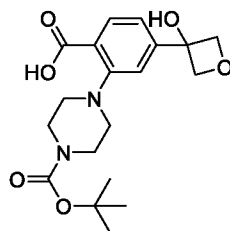
Step 2: 1-(4-(trifluoromethyl)benzyl)piperidine-4-carboxylic acid.

To a stirred solution of ethyl 1-(4-(trifluoromethyl)benzyl)piperidine-4-carboxylate (2.6 gm, 8.25 mmol) in ethanol (20 ml), another solution of sodium hydroxide (0.71 gm, 16.49 mmol) in water (10 ml) was added at ambient temperature and stirring was continued for 6 hours. Solvent was removed on rotavapor under vacuum, residue was added to water (50 ml) and acidified with concentrated hydrochloric acid ($\text{pH} = 2$). Off-white solid formed was collected by filtration and dried over Phosphorous pentoxide to yield 1-(4-(trifluoromethyl)benzyl)piperidine-4-carboxylic acid (2.0 gm, 84% yield) as a white solid.

^1H NMR ($\text{DMSO}-d_6$) δ : 1.50-1.60 (m, 2H), 1.77-1.80 (m, 2H), 1.98-2.04 (m, 2H), 2.16-2.28 (m, 1H), 2.60-2.74 (m, 2H), 3.53 (s, 2H), 7.52 (d, $J = 8.0$ Hz, 2H), 7.68 (d, $J = 8.0$ Hz, 2H), 12.12 (br s, 1H);

ESI-MS: m/z 288.12 ($\text{M}+\text{H}$) $^+$, 100%.

Intermediate-39: 2-(4-(tert-butoxycarbonyl)piperazin-1-yl)-4-(3-hydroxyoxetan-3-yl)benzoic acid



Step 1: Preparation of *tert*-butyl 4-(5-bromo-2-formylphenyl)piperazine-1-carboxylate.

To a stirred solution of 4-bromo-2-fluorobenzaldehyde (1.0g, 4.93 mmol) and *tert*-butyl piperazine-1-carboxylate (1.376 g, 7.39 mmol) in dimethyl formamide (10 ml) potassium carbonate (2.04 g, 14.78 mmol) was added at 30 °C and stirring was continued at 100 °C for 24 hours. Reaction mixture was cooled to ambient temperature, poured into ice cold water (50 ml) and extracted with ethyl acetate (3 x 75 ml). The combined organic extract was washed with water (2 x 50 ml) & brine (75 ml), dried over sodium sulfate and concentrated on rotavapor under vacuum to yield 4-bromo-2-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)benzoic acid (1.0 g, 55% yield) as a thick liquid.

¹H NMR (CDCl₃) δ : 1.48 (s, 9H), 3.04 (t, J = 4.8 Hz, 4H), 3.63 (t, J = 4.8 Hz, 4H), 7.25-7.31 (m, 2H), 7.68 (d, J = 8.0 Hz, 1H), 10.26 (s, 1H).

Step 2: Preparation of 4-bromo-2-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)benzoic acid.

To a stirred solution of *tert*-butyl 4-(5-bromo-2-formylphenyl)piperazine-1-carboxylate (2.0 g, 5.42 mmol) and sulphamic acid (4.31 g, 44.4 mmol) in water (10 ml) sodium chlorite (1.34 g, 11.92mmol) was added and stirring was continued at ambient temperature for 20 hours. The reaction mixture was poured into ice cold water (50 ml) and extracted with ethyl acetate (3 x 75 ml). The combined organic extract was washed with water (2 x 50 ml) & brine (75 ml), dried over sodium sulfate and concentrated on rotavapor under vacuum to yield 4-bromo-2-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)benzoic acid (1.8 g, 86% yield) as an off white solid.

¹H NMR (DMSO-*d*₆) δ : 1.43 (s, 9H), 3.01-3.06 (t, J = 4.8 Hz, 4H), 3.33-3.40 (t, J = 4.8 Hz, 4H), 7.39-7.42 (m, 1H), 7.6 (s, 1H), 7.73(d, J = 8.4 Hz, 1H), 14.63 (s, 1H).

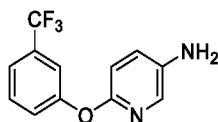
Step 3: Preparation of 2-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)-4-(3-hydroxyoxetan-3-yl)benzoic acid:

To a stirred solution of 4-bromo-2-(4-(isopropoxycarbonyl)piperazin-1-yl)benzoic acid (700mg, 1.817 mmol) in tetrahydrofuran (15 ml), *n*-butyllithium (25% in hexane) (1.2 ml, 4.54 mmol) was added dropwise under nitrogen atmosphere at -78 °C over a period of 10 minutes. To this another solution of oxetan-3-one (196 mg, 2.73 mmol) in

tetrahydrofuran (3.0 ml) was added dropwise at -78 °C. The reaction mixture was allowed to warm to room temperature over a period of 3 hours with vigorous stirring. The reaction mixture was poured into saturated ammonium chloride solution (10 mL), acidified with saturated solution of citric acid and extracted with ethyl acetate (3 x 25 ml). The combined
5 organic layer was washed with brine (30 ml), dried over sodium sulfate and evaporated on rotavapor under vacuum. The crude product was purified by triturating with diethyl ether to yield 2-(4-(tert-butoxycarbonyl)piperazin-1-yl)-4-(3-hydroxyoxetan-3-yl)benzoic acid. (350mg, 50.9% yield) as an off white solid.

¹H NMR (DMSO-*d*₆) δ : 1.44 (s, 9H), 3.01-3.06 (m, 4H), 3.33-3.40 (m, 4H), 4.7-4.78 (m,
10 4H), 6.56 (s, 1H), 7.57-7.60 (m, 1H), 7.72 (s, 1H), 7.98(d, *J* = 8.0 Hz, 1H), 16.0 (s, 1H).

Intermediate-40: 6-(3-(trifluoromethyl)phenoxy)pyridin-3-amine



Step 1: Preparation of 5-nitro-2-(3-(trifluoromethyl)phenoxy)pyridine

15 To a stirred solution of 3-(trifluoromethyl) phenol (1.0 g, 6.17 mmol) in N,N-dimethylformamide (10 ml), cesium carbonate (4.02 g, 12.34 mmol) was added followed by the addition of 2-chloro-5-nitropyridine (0.978 g, 6.17 mmol) under nitrogen atmosphere at ambient temperature and continued stirring for 24 hours. The reaction mixture was poured into water (30 ml) and extracted by ethyl acetate (2 x 50 ml). The
20 combined organic layers were washed with water (2 x 25 ml) & brine (50 ml), dried over sodium sulfate and evaporated on rotavapor under vacuum. The crude product was purified by column chromatography using 230-400 silica gel column and 5-25% ethyl acetate in *n*-hexane as an eluent to yield 5-nitro-2-(3-(trifluoromethyl)phenoxy)pyridine (700 mg, 40% yield) as a thick liquid.

25 ¹H NMR (CDCl₃) δ : 7.02 (d, *J* = 8.0 Hz, 1H), 7.28 (s, 1H), 7.33-7.36 (m, 1H), 7.57-7.59 (m, 2H), 8.53-8.56 (m, 1H), 9.04 (d, *J* = 2.8 Hz, 1H);

ESI-MS: *m/z*: 285.04 (M+H)⁺ 100%.

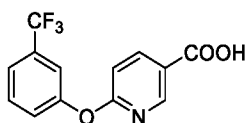
Step 2. Preparation of 6-(3-(trifluoromethyl)phenoxy)pyridin-3-amine

To a solution of 5-nitro-2-(3-(trifluoromethyl)phenoxy)pyridine (2.0 g, 7.04 mmol) in
30 ethanol (20 ml), stannous chloride (6.67g, 35.2 mmol) was added at 30 °C. and stirred at 50 °C for 3 hours. The reaction mixture was concentrated on rotavapor under vacuum and

the residue was diluted with ethylacetate (50 ml) and basified with aqueous ammonia to (pH =10). Solid was filtered and washed with ethyl acetate (3 x 50 ml). The combined filtrate was dried over sodium sulfate and concentrated on rotavapor under vacuum to yield 6-(3-(trifluoromethyl)phenoxy)pyridin-3-amine (1.0 g, 55.9% yield) as a thick liquid.

- 5 ¹H NMR (CDCl₃) δ : 6.82 (d, J = 8.0 Hz, 1H), 7.04-7.08 (m, 1H), 7.11-7.14 (m, 1H), 7.24-7.26 (m, 1H), 7.31-7.34 (m, 1H), 7.36-7.38 (m, 1H), 7.73 (d, J = 2.4 Hz, 1H); ESI-MS: m/z : 255.09 (M+H)⁺ 100%.

Intermediate-41: 6-(3-(trifluoromethyl)phenoxy)nicotinic acid



10

Step 1: Preparation of methyl 6-(3-(trifluoromethyl)phenoxy)nicotinate.

- To a stirred solution of 3-(trifluoromethyl)phenol (1.0 g, 6.17 mmol) in N,N-dimethylformamide (10 ml), cesium carbonate (4.02 g, 12.34 mmol) was added followed by the addition of methyl 6-chloronicotinate (1.058 g, 6.17 mmol) under nitrogen atmosphere at 30 °C and stirring was continued at 90 °C for 24 hours. The reaction mixture was poured into water (30 ml) and extracted with ethyl acetate (2 x 50 ml). The combined organic layer was washed with water (2 x 25 ml) & brine (50 ml), dried over sodium sulfate and evaporated on rotavapor under vacuum. The crude product was purified by column chromatography using 230-400 mesh silica gel column and 5-25% ethyl acetate in *n*-hexane as an eluent to yield 5-nitro-2-(3-(trifluoromethyl)phenoxy)pyridine (1.0 g, 54.5% yield) as a thick liquid.

- 15 ¹H NMR (CDCl₃) δ : 3.96 (s, 3H), 6.85-6.89 (m, 1H), 7.22-7.25 (m, 1H), 7.55-7.65 (m, 3H), 8.10-8.16 (m, 1H), 8.73 (s, 1H); ESI-MS: m/z : 398.04 (M+H)⁺ 100%.

Step 2: Preparation of 6-(3-(trifluoromethyl)phenoxy)nicotinic acid.

- 25 To a stirred solution of methyl 6-(3-(trifluoromethyl)phenoxy)nicotinate (2.0 g, 6.43 mmol) in a mixture of methanol (15 ml), water (15 ml) and tetrahydrofuran (30.0 ml), lithium hydroxide hydrate (0.38g, 12.85 mmol) was added and continued to stir at 30 °C for 24 hours. Reaction mixture was concentrated on rotavapor under vacuum. The residue was dissolved in water (50 ml) and washed with ethyl acetate (25 ml). The aqueous layer was neutralized with citric acid (pH = 7) and extracted with ethyl acetate (3 x 25 ml). Organic layer was washed with water (15 ml) & brine (15 ml), dried over sodium sulfate

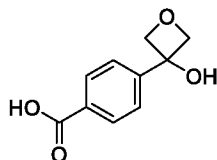
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and concentrated on rotavapor under vacuum to yield 6-(3-(trifluoromethyl)phenoxy)nicotinic acid. (1.0 g, 55% yield) as a white solid.

^1H NMR (DMSO- d_6) δ : 6.89-6.91 (m, 1H), 7.20-7.222 (m, 1H), 7.62-7.65 (m, 3H), 8.12-8.15 (m, 1H), 8.73 (s, 1H), 13.13 (s, 1H); ESI-MS: m/z : 284.07 ($M+H$) $^{+}$ 100%.

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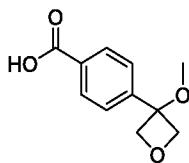
Intermediate-42: 4-(3-hydroxyoxetan-3-yl)benzoic acid



To a stirred solution of 4-bromobenzoic acid (40 g, 199 mmol) in tetrahydrofuran (900 ml), *n*-butyllithium (25% in hexane) (185 ml, 497 mmol) was added dropwise under nitrogen atmosphere at -78 °C over a period of 50 minutes. To this another solution of oxetan-3-one (17.21 g, 239 mmol) in tetrahydrofuran (30 ml) was added dropwise at -78 °C. The reaction mixture was allowed to warm to room temperature over a period of 3 hours with vigorous stirring. The reaction mixture was poured into saturated ammonium chloride solution (100 mL), acidified with dilute hydrochloric acid and extracted with ethyl acetate (3 x 500 ml). The combined organic layer was washed with brine (500 ml), dried over sodium sulfate and evaporated on rotavapor under vacuum. The crude product was purified by triturating with diethyl ether to yield 4-(3-hydroxyoxetan-3-yl)benzoic acid (13.8 g, 35% Yield) as an off white solid.

^1H NMR (DMSO- d_6) δ : 4.68 (d, J = 6.8 Hz, 2H), 4.80 (d, J = 6.8 Hz, 2H), 6.53 (s, 1H), 7.74 (d, J = 6.8 Hz, 2H), 7.98 (d, J = 6.8 Hz, 2H), 12.93 (br s, 1H); ESI-MS: m/z 193.04 ($M-1$), 100%.

Intermediate-43: 4-(3-methoxyoxetan-3-yl)benzoic acid



Step 1: benzyl 4-(3-hydroxyoxetan-3-yl) benzoate.

To a stirred solution of 4-(3-hydroxyoxetan-3-yl)benzoic acid (3.0 g, 15.45 mmol) in *N,N*-dimethylformamide (15 ml), cesium carbonate (5.03 g, 16.99 mmol) was added at ambient temperature followed by the addition of benzyl bromide (2.021 ml, 16.99 mmol)

and stirring was continued for 16 hours at 100 °C. The reaction mixture was cooled to ambient temperature, poured into water (50 ml) and extracted with ethyl acetate (2 x 50 ml). The combined organic layer was washed with water (2 x 50 ml) & brine (50 ml), dried over sodium sulfate and concentrated on rotavapor under vacuum. The crude product was purified by column chromatography using 100-200 mesh silica gel column and 50% ethyl acetate in *n*-hexane as eluent to yield benzyl 4-(3-hydroxyoxetan-3-yl)benzoate. (4.0 g, 91% Yield) as a thick liquid.

¹H NMR (CDCl₃) δ : 3.69 (s, 1H), 4.12 (d, *J* = 6.8 Hz, 2H), 4.95 (d, *J* = 7.2 Hz, 2H), 5.39 (s, 2H), 7.28-7.38 (m, 5H), 7.74 (d, *J* = 8.0 Hz, 2H), 8.12 (d, *J* = 8.0 Hz, 2H).

Step 2: benzyl 4-(3-methoxyoxetan-3-yl) benzoate.

To a suspension of sodium hydride (1.35 g, 28.1 mmol) in tetrahydrofuran (20 ml), a solution of benzyl 4-(3-hydroxyoxetan-3-yl)benzoate (4.0 g, 14.07 mmol) in tetrahydrofuran (10 ml) was added followed by the addition of iodomethane (1.759 ml, 28.1 mmol) at 0 °C and stirring was continued at ambient temperature for 3 hours under nitrogen atmosphere. The reaction mixture was poured into ice cold water (50 ml) and extracted with ethyl acetate (3 x 75 ml). The combined organic extract was washed with water (2 x 50 ml) & brine (75 ml), dried over sodium sulfate and concentrated on rotavapor under vacuum to yield benzyl 4-(3-methoxyoxetan-3-yl)benzoate (3.0g, 75% yield) as thick liquid.

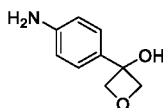
¹H NMR (CDCl₃) δ : 3.0 (s, 3H), 4.12 (d, *J* = 6.8 Hz, 2H), 4.95 (d, *J* = 7.2 Hz, 2H), 5.39 (s, 2H), 7.28-7.38 (m, 5H), 7.74 (d, *J* = 8.0 Hz, 2H), 8.12 (d, *J* = 8.0 Hz, 2H).

Step 3: 4-(3-methoxyoxetan-3-yl) benzoic acid.

The title product (1.5g 71.6% yield) was prepared from benzyl 4-(3-methoxyoxetan-3-yl)benzoate (3.0g, 75% yield) as thick liquid according to the procedure described in step-2 of **intermediate-22** as a yellow solid.

¹H NMR (DMSO-*d*₆) δ : 3.0 (s, 3H), 4.68 (d, *J* = 6.8 Hz, 2H), 4.80 (d, *J* = 6.8 Hz, 2H), 7.74 (d, *J* = 6.8 Hz, 2H), 7.98 (d, *J* = 6.8 Hz, 2H), 12.93 (br s, 1H); ESI-MS: *m/z*: 209.05 (M+H)⁺, 100%.

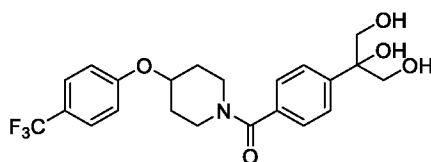
Intermediate-44: 3-(4-aminophenyl)oxetan-3-ol



To a stirred solution of 3-(4-bromophenyl)oxetan-3-ol (100 mg, 0.437 mmol) in ammonium hydroxide Solution (1 ml) in a microwave vial, copper(II) oxide (34.7 mg, 0.437 mmol) was added under nitrogen atmosphere at ambient temperature and the reaction mixture was microwave irradiated at 100 °C and 40 psi pressure for 1 hour in a CEM microwave *synthesizer*. The reaction mixture was cooled to ambient temperature, added to ethyl acetate (10 ml) and filtered through celite bed. The filtrate was dried over sodium sulfate and evaporated under vacuum to yield 3-(4-aminophenyl)oxetan-3-ol (70 mg, 97% yield) as a pale brown solid.

¹H NMR (DMSO-*d*₆) δ : 4.63 (d, *J* = 6.4 Hz, 2H), 4.68 (d, *J* = 6.4 Hz, 2H), 5.02 (s, 2H), 5.96 (s, 1H), 6.56 (d, *J* = 8.4 Hz, 2H), 7.20 (d, *J* = 8.4 Hz, 2H); ESI-MS: *m/z* 166.11 (M+H)⁺, 100%.

Intermediate-45: (4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)(4-(1,2,3-trihydroxypropan-2-yl)phenyl)methanone

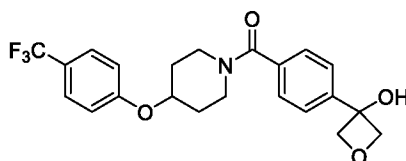


To a mixture of magnesium turning (60 mg, 2.45 mmol) in tetrahydrofuran (2 ml), was added catalytic amount of methyl iodide (1 drop) to activate magnesium and stirred vigorously till the solution became clear. After that a solution of (4-bromophenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone (1 g, 2.34 mmol) in tetrahydrofuran (10 ml) was added dropwise under nitrogen atmosphere over a period of 10 min at ambient temperature and stirred for 1 hour to obtained clear solution. Then the reaction mixture was cooled to 0 °C and a solution of 2,2-dimethyl-1,3-dioxan-5-one (304 mg, 2.34 mmol) in tetrahydrofuran (2 ml) was added dropwise over a period of 10 min. The reaction mixture was stirred at ambient temperature for 1 hour. The reaction mixture was poured into ice cold saturated aqueous ammonium chloride solution (100 ml) and extracted with ethyl acetate (3 x 50 ml). The combined organic layer was washed with water (2 x 100 ml) & brine (100 ml), dried over sodium sulfate and evaporated under vacuum. The crude product was purified by column chromatography using 100-200 mesh silica gel column and 2-3% methanol in chloroform as an eluent to yield (4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)(4-(1,2,3-trihydroxypropan-2-yl)phenyl)methanone (515 mg, 22% yield) as a white solid.

^1H NMR ($\text{DMSO}-d_6$) δ : 1.64-1.68 (m, 2H), 1.97-2.01 (m, 2H), 3.34-3.37 (m, 2H), 3.54-3.62 (m, 5H), 3.94-3.99 (m, 1H), 4.61 (t, $J = 5.6$ Hz, 2H), 4.79-4.82 (m, 1H), 4.83 (s, 1H), 7.18 (d, $J = 8.8$ Hz, 2H), 7.34 (d, $J = 8.4$ Hz, 2H), 7.54 (d, $J = 8.4$ Hz, 2H), 7.64 (d, $J = 8.8$ Hz, 2H);

5 ESI-MS: m/z 440.16 ($\text{M}+\text{H}$) $^+$, 100%.

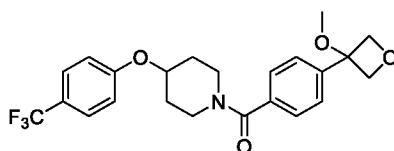
Example- 1 : (4-(3-hydroxyoxetan-3-yl)phenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone



10 To a stirred solution of 4-(4-(trifluoromethyl)phenoxy)piperidine hydrochloride (114 mg, 0.408 mmol), 4-(3-hydroxyoxetan-3-yl)benzoic acid (79 mg, 0.408 mmol) and HBTU (232 mg, 0.612 mmol) in N,N -dimethylformamide (3.0 ml), diisopropylethylamine (0.214 ml, 1.223 mmol) was added under nitrogen atmosphere at ambient temperature and stirred for 18 hours. The reaction mixture was poured into water (50 ml) and extracted with ethyl acetate (3 x 25 ml). The combined organic layer was washed with water (2 x 25 ml) & brine (25 ml), dried over sodium sulfate and evaporated under vacuum. The crude product was purified by column chromatography using 100-200 mesh silica gel column and 50% ethyl acetate in n -hexane as an eluent to yield (4-(3-hydroxyoxetan-3-yl)phenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone (100 mg, 55% yield) as a white solid.

20 ^1H NMR ($\text{DMSO}-d_6$) δ : 1.66 (m, 2H), 2.02 (m, 2H), 3.37-3.43 (m, 2H), 3.56-3.60 (m, 1H), 4.00 (br s, 1H), 4.69 (d, $J = 6.8$ Hz, 2H), 4.78-4.82 (m, 3H), 6.44 (s, 1H), 7.18 (d, $J = 8.4$ Hz, 2H), 7.46 (d, $J = 8.0$ Hz, 2H), 7.64-7.68 (m, 4H); ESI-MS: m/z 422 ($\text{M}+\text{H}$) $^+$, 100%.

Example- 2 : (4-(3-methoxyoxetan-3-yl)phenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone

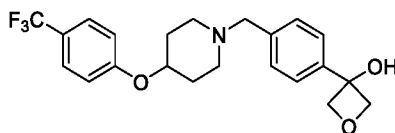


To a stirred suspension of sodium hydride (17.08 mg, 0.356 mmol) in tetrahydrofuran (1 ml), a solution of (4-(3-hydroxyoxetan-3-yl)phenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone (100 mg, 0.237 mmol) in

tetrahydrofuran (3 ml) was added followed by addition of iodomethane (0.018 ml, 0.285 mmol) at 0 °C and stirred at 30 °C for 3 hours. The reaction mixture was poured into ice cold water (25 ml) and extracted with ethyl acetate (3 x 25 ml). The combined organic extract was washed with water (2 x 20 ml) & brine (25 ml), dried over sodium sulfate and evaporated under reduced pressure to yield (4-(3-methoxyoxetan-3-yl)phenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone (60 mg, 56.9% yield) as pale yellow solid.

¹H NMR (DMSO-*d*₆) δ 1.67 (m, 2H), 1.99 (m, 2H), 3.05 (m, 3H), 3.38-3.43 (m, 3H), 4.00 (m, 1H), 4.75-4.83 (m, 5H), 7.18 (d, *J* = 8.4 Hz, 2H), 7.48-7.54 (m, 4H), 7.65 (d, *J* = 8.4 Hz, 2H); ESI-MS: *m/z* 436 (M+H)⁺, 100%.

Example- 3 : 3-(4-((4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methyl)phenyl)oxetan-3-ol



Step 1: 1-(4-bromobenzyl)-4-(4-(trifluoromethyl)phenoxy)piperidine

To a stirred solution of 1-bromo-4-(bromomethyl)benzene (0.359 g, 1.436 mmol) and 4-(4-(trifluoromethyl)phenoxy)piperidine hydrochloride (0.337 g, 1.197 mmol) in dimethylformamide (4 ml), cesium carbonate (1.170 g, 3.59 mmol) was added under nitrogen atmosphere at ambient temperature and stirred at 90 °C for 16 hours. The reaction mixture was poured into ice cold water (20 ml) and extracted with ethyl acetate (3 x 20 ml). The combined organic extract was washed with water (2 x 30 ml) & brine (30 ml), dried over sodium sulfate and evaporated under reduced pressure. The crude product was purified by column chromatography using 100-200 mesh silica gel column and 6% ethyl acetate in *n*-hexane as an eluent to yield 1-(4-bromobenzyl)-4-(4-(trifluoromethyl)phenoxy)piperidine (0.394 g, 79%) as a thick liquid.

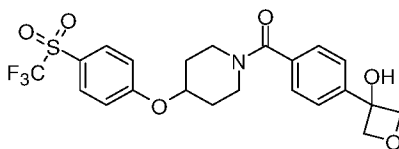
¹H NMR (CDCl₃) δ : 1.80-1.98 (m, 2H), 1.99-2.03 (m, 2H), 2.31-2.35 (m, 2H), 2.72-2.80 (m, 2H), 3.49 (s, 2H), 4.39-4.67 (m, 1H), 6.96 (d, *J* = 8.8 Hz, 2H), 7.23 (d, *J* = 8.4 Hz, 2H), 7.47 (d, *J* = 8.8 Hz, 2H), 7.54 (d, *J* = 8.4 Hz, 2H); ESI-MS: *m/z* 416.05 (M+H)⁺, 100%.

Step 2: 3-(4-((4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methyl)phenyl)oxetan-3-ol.

To a stirred solution of 1-(4-bromobenzyl)-4-(4-(trifluoromethyl)phenoxy)piperidine (0.390 g, 0.941 mmol) in tetrahydrofuran (5 ml), *n*-buthyllithium (2.5M in hexane) (0.565 ml, 1.412 mmol) was added dropwise over a period of 10 minute under nitrogen atmosphere at -78 °C and stirring was continued for 30 minute at -78 °C. To this another solution of oxetan-3-one (0.081 g, 1.130 mmol) in tetrahydrofuran (1 ml) was added dropwise at -78 °C and reaction mixture was allowed to warm to -30 °C over a period of 2 hours. The reaction mixture was quenched with saturated ammonium chloride solution (5 ml) and extracted with ethyl acetate (3 x 10 ml). The combined organic extract was washed with water (2 x 20 ml) & brine (20 ml), dried over sodium sulfate and evaporated under reduced pressure. Crude product was purified by column chromatography using 100-200 mesh silica gel column and 50% ethyl acetate in *n*-hexane as an eluent to get pure product (0.1 g, 24.18%) as colorless oil.

¹H NMR (DMSO-*d*₆) δ : 1.61-1.69 (m, 2H), 1.91-1.99 (m, 2H), 2.24-2.28 (m, 2H), 2.66-2.69 (m, 2H), 3.50 (s, 2H), 4.48-4.54 (m, 1H), 4.68 (d, *J* = 6.8 Hz, 2H), 4.76 (d, *J* = 6.8 Hz, 2H), 6.30 (s, 1H), 7.13 (d, *J* = 8.8 Hz, 2H), 7.33 (d, *J* = 8.8 Hz, 2H), 7.55 (d, *J* = 8.4 Hz, 2H), 7.61 (d, *J* = 8.8 Hz, 2H); ESI-MS: *m/z* 408.15 (M+H)⁺, 100%.

Example- 4 : (4-(3-hydroxyoxetan-3-yl)phenyl)(4-(4-((trifluoromethyl)sulfonyl)phenoxy)piperidin-1-yl)methanone



20

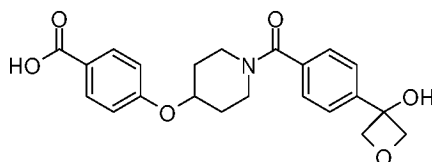
To a stirred solution of (4-(3-hydroxyoxetan-3-yl)phenyl)(4-(4-((trifluoromethyl)thio)phenoxy)piperidin-1-yl)methanone (500 mg, 1.103 mmol) in dichloromethane (50 ml), *meta*-chloroperoxybenzoic acid (951 mg, 5.51 mmol) was added at 30 °C and stirring was continued for 24 hours. The reaction mixture was poured into saturated sodium bicarbonate solution (50 ml) and extracted with dichloromethane (3 x 25 ml). The combined organic layer was washed with water (2 x 20 ml) & brine (20 ml), dried over sodium sulfate and evaporated under vacuum. The crude product was purified by column chromatography using 230-400 silica gel column and 2-4% methanol in chloroform as an eluent to yield (4-(3-hydroxyoxetan-3-yl)phenyl)(4-(4-((trifluoromethyl)sulfonyl)phenoxy)piperidin-1-yl)methanone (150 mg, 28.0% yield) as a white solid.

30

¹H NMR (DMSO-*d*₆) δ : 1.70 (m, 2H), 2.00-2.07 (m, 2H), 3.33-3.50 (m, 2H), 3.50-3.61 (m, 1H), 3.95-4.05 (m, 1H), 4.69 (d, *J* = 6.4 Hz, 2H), 4.94-4.97 (m, 2H), 4.97-5.05 (m, 1H), 6.45 (s, -OH), 7.40 (d, *J* = 9.4 Hz, 2H), 7.46 (d, *J* = 8.0 Hz, 2H), 7.68 (d, *J* = 8.0 Hz, 2H), 8.03 (d, *J* = 9.2 Hz, 2H); ESI-MS: *m/z*, 486.12 (M+H)⁺, 100%.

5

Example- 5 : 4-((1-(4-(3-hydroxyoxetan-3-yl)benzoyl)piperidin-4-yl)oxy)benzoic acid



Step 1: Preparation of ethyl 4-((1-(4-(3-hydroxyoxetan-3-yl)benzoyl)piperidin-4-yl)oxy)benzoate

To a stirred solution of 4-(3-hydroxyoxetan-3-yl)benzoic acid (257 mg, 1.324 mmol), ethyl 4-(piperidin-4-yloxy)benzoate (300 mg, 1.203 mmol) and HBTU (685 mg, 1.805 mmol) in N,N-dimethylformamide (5.0 ml), N,N-diisopropylethylamine (0.631 ml, 3.61 mmol) was added under nitrogen atmosphere at 30 °C and stirring was continued for 16 hours. Reaction mixture was poured into ice cold water (50 ml) and extracted with ethyl acetate (3 x 20 ml). The combined organic layer was washed with water (3 x 30 ml) & brine (30 ml), dried over sodium sulfate and concentrated under reduced pressure. Crude product was purified by column chromatography using 230-400 silica gel column and 60% ethyl acetate in *n*-hexane as an eluent to yield the product as a thick liquid which was triturated with *n*-hexane to yield ethyl 4-((1-(4-(3-hydroxyoxetan-3-yl)benzoyl)piperidin-4-yl)oxy)benzoate (500 mg, 98% yield) as a pink solid on drying.

¹H NMR (DMSO-*d*₆) δ : 1.30 (t, *J* = 6.8 Hz, 3H), 1.55-1.66 (m, 2H), 1.90-2.15 (m, 2H), 3.33-3.43 (m, 2H), 3.57-3.64 (m, 1H), 3.90-4.15 (m, 1H), 4.27 (q, *J* = 7.6 Hz, 2H), 4.69 (d, *J* = 6.4 Hz, 2H), 4.70-4.80 (m, 3H), 6.44 (s, -OH), 7.10 (d, *J* = 8.8 Hz, 2H), 7.46 (d, *J* = 8.0 Hz, 2H), 7.67 (d, *J* = 8.0 Hz, 2H), 7.90 (d, *J* = 8.4 Hz, 2H); ESI-MS: *m/z*, 426.20 (M+H)⁺, 100%.

25

Step 2: Preparation of 4-((1-(4-(3-hydroxyoxetan-3-yl)benzoyl)piperidin-4-yl)oxy)benzoic acid

To a stirred solution of ethyl 4-((1-(4-(3-hydroxyoxetan-3-yl)benzoyl)piperidin-4-yl)oxy)benzoate (330 mg, 0.776 mmol) in a mixture of methanol (15 ml) and tetrahydrofuran (30.0 ml), another solution of lithium hydroxide hydrate (65.1 mg, 1.551 mmol) in water (15.0 ml) was added at 30 °C and stirring was continued for 24 hours.

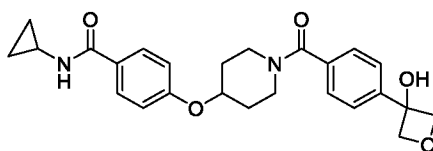
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Reaction mixture was concentrated under reduced pressure, the residue was dissolved in water (50 ml) and washed with ethyl acetate (15 ml). The aqueous layer was then acidified with citric acid (pH = 7) and extracted with ethyl acetate (3 x 25 ml). Combined organic layer was washed with water (15 ml) & brine (15 ml), dried over sodium sulfate and concentrated under reduced pressure to yield 4-((1-(4-(3-hydroxyoxetan-3-yl)benzoyl)piperidin-4-yl)oxy)benzoic acid (50 mg, 15.96% yield) as a thick liquid.

¹H NMR (DMSO-*d*₆) δ : 1.66 (m, 2H), 1.99-2.02 (m, 2H), 3.33-3.58 (m, 3H), 4.00-4.04 (m, 1H), 4.69 (d, *J* = 6.8 Hz, 2H), 4.78-4.79 (m, 3H), 6.44 (s, 1H), 7.07 (d, *J* = 8.8 Hz, 2H), 7.46 (d, *J* = 8.0 Hz, 2H), 7.67 (d, *J* = 8.0 Hz, 2H), 7.88 (d, *J* = 8.0 Hz, 2H), 12.61 (-COOH);

ESI-MS: *m/z*, 398.16 (M+H)⁺, 100%.

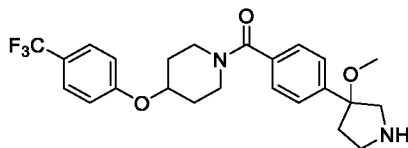
Example- 6 : N-cyclopropyl-4-((1-(4-(3-hydroxyoxetan-3-yl)benzoyl)piperidin-4-yl)oxy)benzamide



To a stirred solution of 4-((1-(4-(3-hydroxyoxetan-3-yl)benzoyl)piperidin-4-yl)oxy)benzoic acid (60 mg, 0.151 mmol), cyclopropylamine (0.013 ml, 0.181 mmol) and HBTU (86 mg, 0.226 mmol) in N,N-dimethylformamide (5.0 ml), N,N-diisopropylethylamine (0.079 ml, 0.453 mmol) was added at 30 °C and stirring was continued for 16 hours. Reaction mixture was poured into water (20 ml) and extracted with ethyl acetate (2 x 20 ml). Combined organic layer was washed with water (3 x 30 ml) & brine (30 ml), dried over sodium sulfate and concentrated under reduced pressure. The crude product was purified by column chromatography using 230-400 mesh silica gel column and 90% ethyl acetate in *n*-hexane as an eluent to yield pure N-cyclopropyl-4-((1-(4-(3-hydroxyoxetan-3-yl) benzoyl)piperidin-4-yl)oxy)benzamide (10 mg, 15.14 % yield) as a white solid.

¹H NMR (DMSO-*d*₆) δ : 0.66-0.68 (m, 2H), 0.84-0.85 (m, 2H), 1.64 (m, 2H), 1.91-2.01 (m, 2H), 2.80-2.81 (m, 1H), 3.32-3.70 (m, 3H), 4.00 (br s, 1H), 4.69 (d, *J* = 6.4 Hz, 2H), 4.78-4.79 (m, 3H), 6.43 (s, 1H), 7.03 (d, *J* = 8.8 Hz, 2H), 7.43 (d, *J* = 8.4 Hz, 2H), 7.68 (d, *J* = 8.0 Hz, 2H), 7.78 (d, *J* = 8.4 Hz, 2H), 8.25 (d, *J* = 3.2 Hz, 1H); ESI-MS: *m/z*, 437.25 (M+H)⁺, 100%.

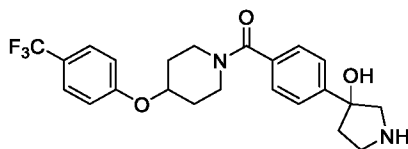
Example- 7 : (4-(3-methoxypyrrolidin-3-yl)phenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone



To a stirred solution of *tert*-butyl 3-methoxy-3-(4-(4-(4-(trifluoromethyl)phenoxy)piperidine-1-carbonyl)phenyl)pyrrolidine-1-carboxylate (0.3 g, 0.547 mmol) in 1, 2 dichloromethane (4 ml), trifluoroacetic acid (0.421 ml, 5.47 mmol) was added at 0-5 °C and stirring was continued for further 2 hours at ambient temperature. Reaction mixture was concentrated on rotavapor under vacuum. Residue was diluted with 1, 2-dichloromethane (10 ml) and saturated sodium bicarbonate solution (10 ml). Organic layer was separated and aqueous layer was extracted again with 1, 2 dichloromethane (20 ml). Combined organic layer was dried over sodium sulfate and concentrated on rotavapour under vacuum. Crude product was triturated with di-isopropyl ether to yield (4-(3-methoxypyrrolidin-3-yl)phenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone (0.210 g, 80% Yield) as a light brown solid.

¹H NMR (DMSO-*d*₆) δ : 1.63-1.69 (m, 2H), 2.01-2.09 (m, 3H), 2.20-2.29 (m, 1H), 2.91-2.95 (m, 4H), 3.02-3.14 (m, 2H), 3.34-3.37 (m, 2H), 3.45-3.48 (m, 1H), 3.95-4.03 (m, 2H), 4.80 (s, 1H), 7.18 (d, *J* = 8.4 Hz, 2H), 7.42-7.46 (m, 4H), 7.65 (d, *J* = 8.4 Hz, 2H); ESI-MS: *m/z* 449.27 (M+H)⁺, 100%.

Example- 8 : (4-(3-hydroxypyrrolidin-3-yl)phenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone

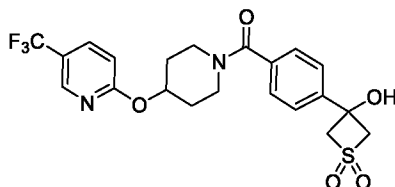


The title product (0.490 g, 93% yield) was prepared from *tert*-butyl 3-hydroxy-3-(4-(4-(4-(trifluoromethyl)phenoxy)piperidine-1-carbonyl)phenyl)pyrrolidine-1-carboxylate (0.6 g, 1.122 mmol) according to the procedure described in **Example-7** as light brown solid.

¹H NMR (DMSO-*d*₆) δ : 1.63-1.69 (m, 2H), 2.02-2.13 (m, 3H), 2.98-3.01 (m, 1H), 3.09-3.15 (m, 4H), 3.18-3.25 (m, 3H), 3.96-4.01 (m, 1H), 4.78-4.82 (m, 1H), 5.43 (br s, 1H),

7.18 (d, $J = 8.8$ Hz, 2H), 7.40 (d, $J = 8.4$ Hz, 2H), 7.56 (d, $J = 8.4$ Hz, 2H), 7.65 (d, $J = 8.8$ Hz, 2H); ESI-MS: m/z 435.26 ($M+H$)⁺, 100%.

Example- 9 : (4-(3-hydroxy-1,1-dioxidothietan-3-yl)phenyl)(4-((5-(trifluoromethyl)pyridin-2-yl)oxy)piperidin-1-yl)methanone

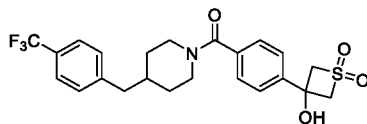


To a stirred solution of (4-(3-hydroxythietan-3-yl)phenyl)(4-((5-(trifluoromethyl)pyridin-2-yl)oxy)piperidin-1-yl)methanone (0.150 g, 0.342 mmol) in a mixture of acetone (4 ml) and water (1 ml), oxone (0.631 g, 1.026 mmol) was added at 0-5 °C and stirring was continued for 6 hours at ambient temperature. Reaction mixture was concentrated on rotavapor under vacuum. Residue was transferred to a Buckner funnel, washed with water (20 ml) and dried over phosphorous pentaoxide to yield (4-(3-hydroxy-1,1-dioxidothietan-3-yl)phenyl)(4-((5-(trifluoromethyl)pyridin-2-yl)oxy)piperidin-1-yl)methanone (0.134 g, 81% yield) as an off white solid.

¹H NMR (DMSO-*d*₆) δ : 1.68-1.73 (m, 2H), 1.91-2.09 (m, 2H), 2.48-2.49 (m, 1H), 3.43-3.54 (m, 2H), 3.98-4.04 (m, 1H), 4.39 (d, $J = 15.2$ Hz, 2H), 4.72 (d, $J = 15.2$ Hz, 2H), 5.32-5.39 (m, 1H), 6.81 (s, 1H), 7.01 (d, $J = 8.8$ Hz, 1H), 7.47 (d, $J = 8.4$ Hz, 2H), 7.62 (d, $J = 8.4$ Hz, 2H), 8.08 (dd, $J = 8.8$ Hz & 2.6 Hz, 1H), 8.58 (d, $J = 2.6$ Hz, 1H); ESI-MS: m/z 471.00 ($M+H$)⁺, 100%.

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Example- 10 : (4-(3-hydroxy-1,1-dioxidothietan-3-yl)phenyl)(4-(4-(trifluoromethyl)benzyl)piperidin-1-yl)methanone

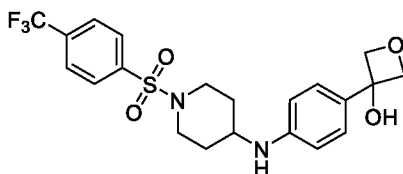


The title product (70 mg, 65% yield) was prepared from (4-(3-hydroxythietan-3-yl)phenyl)(4-(4-(trifluoromethyl)benzyl)piperidin-1-yl)methanone (0.1 gm, 0.230 mmol) according to the procedure described in **Example-9** as a white solid.

¹H NMR (DMSO-*d*₆) δ : 1.16-1.18 (m, 2H), 1.64 (m, 2H), 1.81-1.84 (m, 1H), 2.64 (d, $J = 7.2$ Hz, 2H), 2.67 (m, 1H), 2.71 (br s, 1H), 3.55 (m, 1H), 4.37-4.41 (m, 3H), 4.668-4.72 (m,

2H), 6.81 (s, 1H), 7.41 (d, $J = 8.4$ Hz, 4H), 7.60 (d, $J = 8.4$ Hz, 2H), 7.65 (d, $J = 8.0$ Hz, 2H); ESI-MS: m/z 466.13 (M+H)⁺, 100%.

Example- 11: 3-(4-((1-((4-(trifluoromethyl)phenyl)sulfonyl)piperidin-4-yl)amino)phenyl)oxetan-3-ol



Step 1: Preparation of 1-((4-(trifluoromethyl)phenyl)sulfonyl)piperidin-4-one

To a stirred solution of piperidin-4-one hydrochloride (0.500 g, 3.69 mmol) in dichloromethane (10 ml), 4-(Trifluoromethyl)benzenesulfonyl chloride (0.902 g, 3.69 mmol) was added followed by the addition of triethylamine (1.542 ml, 11.06 mmol) at 30 °C and stirring was continued at for 20 hours. Reaction mixture was poured to ice cold water (25 ml) and extracted with dichloromethane (2 x 25 ml). The combined organic layer was washed with water (2 x 15 ml) & brine (10 ml), dried over sodium sulfate and evaporated under vacuum. The crude product was triturated with 10% ethyl acetate in hexane (2 x 10 ml), the resulting solid was collected by filtration, washed with 10% ethyl acetate in hexane and dried to yield 1-((4-(trifluoromethyl)phenyl)sulfonyl)piperidin-4-one (1.020 g, 90% yield) as yellow solid.

¹H NMR (CDCl₃) δ : 2.57-2.60 (m, 2H), 3.45-3.48 (m, 2H), 7.85 (d, $J = 8.4$ Hz, 2H), 7.96 (d, $J = 8.0$ Hz, 2H); ESI-MS: m/z , 308.05 (M-H)⁺, 30%.

Step 2: Preparation of 3-(4-((1-((4-(trifluoromethyl)phenyl)sulfonyl)piperidin-4-yl)amino)phenyl)oxetan-3-ol

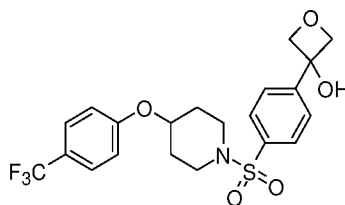
To a stirred solution of 3-(4-aminophenyl)oxetan-3-ol (50 mg, 0.303 mmol) and 1-((4-(trifluoromethyl)phenyl)sulfonyl)piperidin-4-one (93 mg, 0.303 mmol) in 1, 2-dichloroethane (10 ml), sodium triacetoxyborohydride (96 mg, 0.454 mmol) was added at 30 °C and stirring was continued for 20 hours. The reaction mixture was poured into water (50 ml) and extracted with dichloromethane (2 x 20 ml). The combined organic layer was washed with water (2 x 15 ml) & brine (15 ml), dried over sodium sulfate and evaporated under vacuum. The crude product was purified by column chromatography using 230-400 mesh silica gel column and 50% ethyl acetate in *n*-hexane as an eluent to yield 3-(4-((1-

((4-(trifluoromethyl)phenyl)sulfonyl)piperidin-4-yl)amino)phenyl)oxetan-3-ol (6.0 mg, 3.97% yield) as a white solid.

¹H NMR (DMSO-*d*₆) δ : 1.57-1.69 (m, 2H), 2.08-2.16 (m, 2H), 2.54-2.59 (m, 2H), 3.30-3.33 (m, 1H), 3.77-3.80 (m, 2H), 4.88 (s, 4H), 4.93 (s, -OH), 6.71 (d, *J* = 8.4 Hz, 2H), 7.40 (d, *J* = 8.4 Hz, 2H), 7.84 (d, *J* = 8.4 Hz, 2H), 7.92 (d, *J* = 8.0 Hz, 2H);

ESI-MS: *m/z*, 457.19 (M+H)⁺, 100%.

Example- 12 : 3-(4-((4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)sulfonyl)phenyl)oxetan-3-ol



Step 1: Preparation of 1-((4-bromophenyl)sulfonyl)-4-(4-(trifluoromethyl)phenoxy)piperidine.

To a stirred solution of 4-(4-(trifluoromethyl)phenoxy)piperidine hydrochloride (0.500 g, 1.775 mmol) in dichloromethane (20 ml), triethylamine (0.742 ml, 5.32 mmol) was added followed by the addition of 4-bromobenzenesulfonyl chloride (0.590 g, 2.307 mmol) at 0°C and stirring was continued at 0°C for 30 minute. The reaction mixture was poured into water (20 ml) and extracted with dichloromethane (3 x 20 ml). The combined organic layers were washed with water (2 x 20 ml) & brine (20 ml), dried over sodium sulfate and evaporated under vacuum to yield 1-((4-bromophenyl)sulfonyl)-4-(4-(trifluoromethyl)phenoxy)piperidine (0.700 g, 85% yield) as a white solid.

¹H NMR (CDCl₃) δ : 1.94-2.10 (m, 4H), 3.12-3.31 (m, 4H), 4.48-4.51 (m, 1H), 6.89 (d, *J* = 8.8 Hz, 2H), 7.52 (d, *J* = 8.4 Hz, 2H), 7.66 (d, *J* = 8.8 Hz, 2H), 7.72 (d, *J* = 8.0 Hz, 2H).

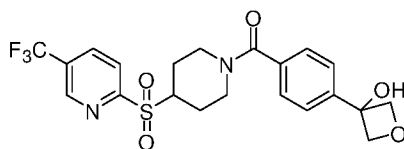
Step 2: Preparation of 3-(4-((4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)sulfonyl)phenyl)oxetan-3-ol

To a stirred solution of 1-((4-bromophenyl)sulfonyl)-4-(4-(trifluoromethyl)phenoxy)piperidine (0.700 g, 1.508 mmol) in tetrahydrofuran (10 ml), *n*-butyllithium (0.784 ml, 1.960 mmol) was added dropwise at -78 °C over period of 5.0 minutes and stirring was continued for 1.0 hour at -78 °C. To this another solution of oxetan-3-one (0.326 g, 4.52 mmol) in tetrahydrofuran (1.0 ml) was added and stirring was continued at -78 °C for 1.0 hour. Then the reaction mixture was slowly warmed to ambient

temperature over a period of 2.0 hours. The reaction mixture was poured into 0.1M hydrochloric acid (20 ml) and extracted with ethyl acetate (3 x 25 ml). The combined organic layer was washed with water (3 x 20 ml) & brine (20 ml), dried over sodium sulfate and evaporated under vacuum. The crude product was purified by column chromatography using 230-400 mesh silica gel column and 30% ethyl acetate in *n*-hexane as an eluent to yield 3-(4-((4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)sulfonyl)phenyl)oxetan-3-ol (40 mg, 5.45% yield) as a white solid.

¹H NMR (DMSO-*d*₆) δ : 1.68-1.74 (m, 2H), 2.01-2.04 (m, 2H), 2.79-2.85 (m, 2H), 3.31-3.34 (m, 2H), 4.55-4.59 (m, 1H), 4.70 (d, *J* = 6.8 Hz, 2H), 4.83 (d, *J* = 6.8 Hz, 2H), 6.67 (m, 1H), 7.08 (d, *J* = 8.4 Hz, 2H), 7.58 (d, *J* = 8.8 Hz, 2H), 7.81 (d, *J* = 8.4 Hz, 2H), 7.90 (d, *J* = 8.4 Hz, 2H); ESI-MS: *m/z*, 458.12 (M+H)⁺, 60%.

Example- 13 : (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((5-(trifluoromethyl)pyridin-2-yl)sulfonyl)piperidin-1-yl)methanone



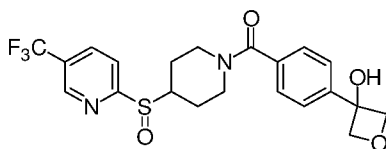
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To a stirred solution of (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((5-(trifluoromethyl)pyridin-2-yl)thio)piperidin-1-yl)methanone (200 mg, 0.456 mmol) in dichloromethane (10 ml), *meta*-chloroperoxybenzoic acid (315 mg, 0.912 mmol) was added at 30 °C and stirring was continued for 5.0 hours. The reaction mixture was poured into saturated sodium bicarbonate solution (15 ml) and extracted with dichloromethane (3 x 15 ml). The combined organic layer was washed with water (3 x 10 ml) & brine (20 ml), dried over sodium sulfate and evaporated under vacuum. The crude product was purified by column chromatography using 230-400 mesh silica gel column and 6% methanol in ethyl acetate as an eluent to yield (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((5-(trifluoromethyl)pyridin-2-yl)sulfonyl)piperidin-1-yl)methanone (90 mg, 40.7% yield) as a white solid.

¹H NMR (DMSO-*d*₆) δ : 1.57-1.65 (m, 2H), 1.92-1.99 (m, 2H), 2.86-3.15 (m, 2H), 3.70 (s, 1H), 3.95-4.06 (m, 1H), 4.53 (m, 1H), 4.68 (d, *J* = 6.4 Hz, 2H), 4.78 (d, *J* = 6.8 Hz, 2H), 6.45 (s, -OH), 7.42 (d, *J* = 8.0 Hz, 2H), 7.66 (d, *J* = 8.0 Hz, 2H), 8.28 (d, *J* = 8.0 Hz, 1H), 8.63 (d, *J* = 8.4 Hz, 1H), 9.29 (s, 1H); ESI-MS: *m/z*, 471.12 (M+H)⁺, 100%.

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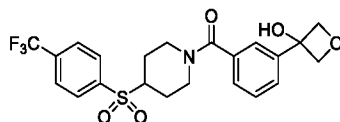
Example- 14 : (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((5-(trifluoromethyl)pyridin-2-yl)sulfinyl)piperidin-1-yl)methanone



The title product (24 mg, 4.21 % yield) was isolated as a polar byproduct during the purification of **Example-13** as white solid.

¹H NMR (DMSO-*d*₆) δ : 1.25-1.27 (m, 2H), 1.92-2.02 (m, 2H), 2.23-2.35 (m, 2H), 2.71-2.92 (m, 3H), 3.29-3.35 (m, 1H), 3.78-3.97 (m, 1H), 4.84 (d, *J* = 6.4 Hz, 2H), 4.94 (d, *J* = 6.8 Hz, 2H), 7.39 (d, *J* = 8.0 Hz, 2H), 7.64 (d, *J* = 8.0 Hz, 2H), 8.14 (d, *J* = 8.4 Hz, 1H), 8.22 (d, *J* = 7.2 Hz, 1H), 8.93 (s, 1H); ESI-MS: *m/z*, 455.15 (M+H)⁺, 60%.

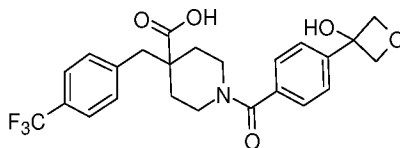
Example- 15 : (3-(3-hydroxyoxetan-3-yl)phenyl)(4-((4-(trifluoromethyl)phenyl)sulfonyl)piperidin-1-yl)methanone



To a stirred solution of (3-(3-hydroxyoxetan-3-yl)phenyl)(4-((4-(trifluoromethyl)phenyl)thio)piperidin-1-yl)methanone (100 mg, 0.229 mmol) in acetone (2 ml), another solution of oxone (281 mg, 0.457 mmol) in water (1 ml) was added under nitrogen atmosphere at ambient temperature and stirring was continued for 12 hours. Solvent was removed on rotavapor under vacuum and the residue was poured into water (25 ml). White solid was filtered, washed with water and dried over phosphorous pentoxide under vacuum to yield (3-(3-hydroxyoxetan-3-yl)phenyl)(4-((4-(trifluoromethyl)phenyl)sulfonyl)piperidin-1-yl)methanone (78 mg, 66% yield) as a white solid.

¹H NMR (DMSO-*d*₆) δ : 1.51-1.53 (m, 2H), 1.88-1.91 (m, 2H), 3.02-3.04 (m, 2H), 3.71-3.77 (m, 2H), 4.02-4.06 (m, 1H), 4.67 (d, *J* = 6.8 Hz, 2H), 4.78 (d, *J* = 6.8 Hz, 2H), 6.44 (s, 1H), 7.31 (d, *J* = 6.4 Hz, 1H), 7.47 (t, *J* = 7.6 Hz, 1H), 7.68 (s, 1H), 7.69 (d, *J* = 6.8 Hz, 1H), 8.06-8.11 (m, 4H); ESI-MS: *m/z* 470.11 (M+H)⁺, 100%.

Example- 16 : 1-(4-(3-hydroxyoxetan-3-yl)benzoyl)-4-(4-(trifluoromethyl)benzyl)piperidine-4-carboxylic acid



Step 1: Preparation of ethyl 1-(4-(3-hydroxyoxetan-3-yl)benzoyl)-4-(4-(trifluoromethyl)benzyl)piperidine-4-carboxylate

To a stirred solution of ethyl 4-(4-(trifluoromethyl)benzyl)piperidine-4-carboxylate (375 mg, 1.189 mmol), 4-(3-hydroxyoxetan-3-yl)benzoic acid (254 mg, 1.308 mmol) and HBTU (676 mg, 1.784 mmol) in N,N-dimethylformamide (5.0 ml), N,N-diisopropylethylamine (0.623 ml, 3.57 mmol) was added under nitrogen atmosphere at 30 °C and continued the stirring 16 hours. Reaction mixture was poured into water (20 ml) and extracted with ethyl acetate (2 x 20 ml). The combined organic layer was washed with water (2 x 20 ml) & brine (10 ml), dried over sodium sulfate and evaporated under vacuum. The crude product was purified by column chromatography using 230-400 mesh silica gel column and 50% ethyl acetate in *n*-hexane as an eluent to yield ethyl 1-(4-(3-hydroxyoxetan-3-yl)benzoyl)-4-(4-(trifluoromethyl)benzyl)piperidine-4-carboxylate (275 mg, 47.0% yield) as a white solid.

ESI-MS: *m/z*, 492.19 (M+H)⁺, 100%.

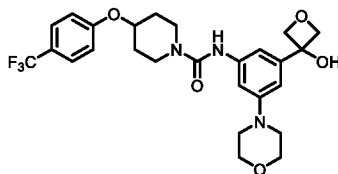
Step 2: Preparation of 1-(4-(3-hydroxyoxetan-3-yl)benzoyl)-4-(4-(trifluoromethyl)benzyl)piperidine-4-carboxylic acid

To a stirred solution of ethyl 1-(4-(3-hydroxyoxetan-3-yl)benzoyl)-4-(4-(trifluoromethyl)benzyl)piperidine-4-carboxylate (275 mg, 0.560 mmol) in methanol (10 ml), another solution of sodium hydroxide (67.1 mg, 1.679 mmol) in water (2.0 ml) was added at 30 °C and stirring was continued for 20 hours. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in water (15 ml), acidified with aqueous hydrochloric acid and extracted with ethyl acetate (2 x 20 ml). The combined organic layer was washed with water (2 x 20 ml) & brine (10 ml), dried over sodium sulfate and evaporated under vacuum. The crude product was purified by column chromatography using 230-400 mesh silica gel column and 4% methanol in chloroform as an eluent to yield pure 1-(4-(3-hydroxyoxetan-3-yl)benzoyl)-4-(4-(trifluoromethyl)benzyl)piperidine-4-carboxylic acid (40 mg, 15.22% yield) as a white solid.

¹H NMR (DMSO-*d*₆) δ : 1.50-1.67 (m, 2H), 1.84-1.99 (m, 2H), 2.74-2.76 (m, 1H), 3.04-3.53 (m, 4H), 4.31 (m, 1H), 4.69 (d, *J* = 6.0 Hz, 2H), 4.79 (d, *J* = 6.4 Hz, 2H), 6.41 (s, -

OH), 7.35 (d, $J = 7.6$ Hz, 2H), 7.42 (d, $J = 8.0$ Hz, 2H), 7.53-7.73 (m, 4H); ESI-MS: m/z , 464.19 (M+H)⁺, 100%.

Example- 17 : N-(3-(3-hydroxyoxetan-3-yl)-5-morpholinophenyl)-4-(4-(trifluoromethyl)phenoxy) piperidine-1-carboxamide



Step 1: Preparation of 4-(3-bromo-5-nitrophenyl)morpholine

To a solution of 1-bromo-3-fluoro-5-nitrobenzene (5 g, 22.73 mmol) in N,N-dimethylacetamide (50 ml), morpholine (2.97 ml, 34.1 mmol) and potassium carbonate (6.28 g, 45.5 mmol) were added under nitrogen atmosphere at 27 °C. Then the reaction mixture was stirred at 120 °C for 18 hours under nitrogen atmosphere. The reaction mixture was cooled to ambient temperature and poured into ice cold water (50 ml). The solid separated was filtered, washed with water and dried over P₂O₅ under vacuum to yield 4-(3-bromo-5-nitrophenyl)morpholine (6.0 g, 92 % yield) as yellow solid.

¹H NMR (CDCl₃) δ : 3.26-3.28 (m, 4H), 3.88-3.90 (m, 4H), 7.28 (dd, $J = 2.4$ & 1.6 Hz, 1H), 7.64 (t, $J = 2.2$ Hz, 1H), 7.81 (d, $J = 1.6$ Hz, 1H); ESI-MS: m/z : 288.9 (M+H)⁺, 100%.

Step 2: Preparation of 3-bromo-5-morpholinoaniline

To a solution of 4-(3-bromo-5-nitrophenyl)morpholine (6.0 g, 20.90 mmol) in ethanol (150 ml), tin(II) chloride dihydrate (18.86 g, 84 mmol) was added and the reaction mixture was refluxed for 1 hour. The reaction mixture was cooled to room temperature and solvent was evaporated on rotavapor under vacuum. The residue was dissolved in ethyl acetate (100 ml) and the solution was basified by dropwise addition of saturated aqueous ammonia solution. The solid separated was filtered and washed with ethyl acetate (50 ml). The filtrate was dried over sodium sulfate and evaporated under reduced pressure to yield 3-bromo-5-morpholinoaniline (5.3 g, 99 % yield) as a thick liquid. The product was directly used for the next step without purification.

Step 3: Preparation of N,N-dibenzyl-3-bromo-5-morpholinoaniline

To a solution of 3-bromo-5-morpholinoaniline (5.3 g, 20.61 mmol) in acetonitrile (100 ml), potassium carbonate (8.55 g, 61.8 mmol) was added followed by the addition of benzyl bromide (5.39 ml, 45.3 mmol) under nitrogen atmosphere at 28 °C and refluxed for

18 hrs. The reaction mixture was cooled to room temperature. The solid separated was filtered and washed with ethyl acetate (50 ml). The filtrate was dried over sodium sulfate and evaporated under reduced pressure to yield N,N-dibenzyl-3-bromo-5-morpholinoaniline (7.5 g, 83 % yield) as a thick liquid.

- 5 ¹H NMR (CDCl₃) δ : 2.99-3.05 (m, 4H), 3.75-3.78 (m, 4H), 4.72 (s, 4H), 6.13 (t, J = 2.0 Hz, 1H), 6.43 (t, J = 1.8 Hz, 1H), 6.49 (t, J = 1.8 Hz, 1H), 7.23-7.40 (m, 10H); ESI-MS: m/z : 439.19 (M+H)⁺, 100%.

Step 4: Preparation of 3-(3-(dibenzylamino)-5-morpholinophenyl)oxetan-3-ol

- To a solution of N,N-dibenzyl-3-bromo-5-morpholinoaniline (0.75 g, 1.71 mmol) in THF (10 ml), *n*-butyllithium (2.5M in hexane) (1.03 ml, 2.57 mmol) was added dropwise under nitrogen atmosphere at -78 °C over a period of 10 minutes. The reaction mixture was stirred at the same temperature for 30 minutes. To this another solution of oxetan-3-one (0.247 g, 3.43 mmol) in THF (1 ml) was added dropwise at -78 °C. The reaction mixture was allowed to warm to ambient temperature and stirred for 30 minutes. under nitrogen atmosphere. The reaction mixture was poured into saturated aqueous ammonium chloride solution (10 mL) and extracted by ethyl acetate (3 x 25 ml). The combined organic layer was washed with water (20 ml) & brine (20 ml), dried over sodium sulfate and evaporated under vacuum. The crude product was purified by column chromatography using 230-400 mesh silica gel column and 20-50% ethyl acetate in *n*-hexane as an eluent to obtain 3-(3-(dibenzylamino)-5-morpholinophenyl)oxetan-3-ol (500 mg, 68% Yield) as thick liquid.
- 10 ¹H NMR (DMSO-*d*₆) δ : 3.05-3.07 (m, 4H), 3.78-3.81 (m, 4H), 4.68 (s, 4H), 4.80-4.84 (m, 4H), 6.24 (s, 1H), 6.50 (s, 2H), 7.25-7.36 (m, 10H); ESI-MS: m/z : 431.31 (M+H)⁺, 100%.

Step 5: Preparation of 3-(3-amino-5-morpholinophenyl)oxetan-3-ol

- To a suspension of Pd/C (10%) (66 mg) in methanol (2 ml), a solution of 3-(3-(dibenzylamino)-5-morpholinophenyl)oxetan-3-ol (0.33 g, 0.76 mmol) in methanol (10 ml) was added and the reaction mixture was stirred under hydrogen at a pressure of 50 psi for 18 hrs. The reaction mixture was filtered through celite and washed with methanol (10 ml). The combined filtrate was evaporated under vacuum to yield 3-(3-amino-5-morpholinophenyl)oxetan-3-ol (170 mg, 89% Yield) as a thick liquid.
- 25 ¹H NMR (DMSO-*d*₆) δ : 3.16-3.19 (m, 4H), 3.85-3.87 (m, 4H), 4.87-4.92 (m, 4H), 6.21 (t, J = 2.2 Hz, 1H), 6.47 (t, J = 1.6 Hz, 1H), 6.56 (t, J = 1.8 Hz, 1H); ESI-MS: m/z : 251.19 (M+H)⁺, 100%.
- 30

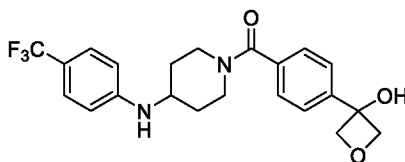
Step 6: N-(3-(3-hydroxyoxetan-3-yl)-5-morpholinophenyl)-4-(4-(trifluoromethyl)phenoxy) piperidine-1-carboxamide

To a stirred solution of 4-(4-(trifluoromethyl)phenoxy)piperidine hydrochloride (90 mg, 0.367 mmol) in acetonitrile (3 ml), N,N-diisopropylethyl amine (0.192 ml, 1.101 mmol) was added under nitrogen atmosphere at ambient temperature and followed by the dropwise addition of another solution of 3-(3-amino-5-morpholinophenyl)oxetan-3-ol (101 mg, 0.404 mmol), triphosgene (35.9 mg, 0.330 mmol) in tetrahydrofuran (3 ml) at 0 °C over the period of 10 minutes. The reaction mixture was stirred for 12 hours at ambient temperature, poured into water (25 ml) and extracted with ethyl acetate (2 x 25 ml). The combined organic layers was washed with water (2 x 25 ml) & brine (20 ml), dried over sodium sulphate and evaporated in rotavapor under vacuum. The crude product was purified by column chromatography using 100-200 mesh silica gel column and 50% ethyl acetate in *n*-hexane as an eluent to yield N-(3-(3-hydroxyoxetan-3-yl)-5-morpholinophenyl)-4-(4-(trifluoromethyl)phenoxy) piperidine-1-carboxamide (17 mg, 9% yield) as white solid.

¹H NMR (DMSO-*d*₆) δ: 1.59-1.63 (m, 2H), 1.94-2.02 (m, 2H), 3.05-3.08 (m, 4H), 3.26-3.28 (m, 2H), 3.72-3.75 (m, 4H), 3.81-3.85 (m, 2H), 4.64 (d, *J* = 6.4 Hz, 2H), 4.71 (d, *J* = 6.4 Hz, 2H), 4.72-4.75 (m, 1H), 6.75 (s, 1H), 7.14 (s, 1H), 7.18 (d, *J* = 8.4 Hz, 2H), 7.23 (s, 1H), 7.64 (d, *J* = 8.8 Hz, 2H); ESI-MS: *m/z*: 522.6 (M+H)⁺, 100%.

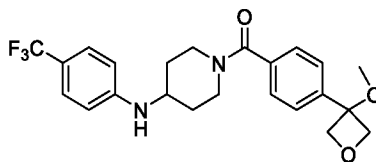
The following compounds were prepared by procedure similar to that described in Example 1-17 with appropriate variations of reactants, reaction conditions and quantities of reagents.

Example-18 : (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((4-(trifluoromethyl)phenyl)amino)piperidin-1-yl)methanone



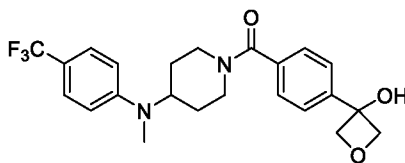
¹H NMR (DMSO-*d*₆) δ: 1.16-1.24 (m, 2H), 1.91-1.99 (m, 2H), 3.08-3.12 (m, 2H), 3.60-3.3.63 (m, 2H), 4.35-4.36 (m, 1H), 4.69 (d, *J* = 6.4 Hz, 2H), 4.78 (d, *J* = 6.4 Hz, 2H), 6.32 (d, *J* = 7.6 Hz, 1H), 6.45 (s, 1H), 6.70 (d, *J* = 8.8 Hz, 2H), 7.35 (d, *J* = 8.4 Hz, 2H), 7.41 (d, *J* = 8.0 Hz, 2H), 7.69 (d, *J* = 8.0 Hz, 2H); ESI-MS: *m/z* 421.4 (M+H)⁺, 100%.

Example-19 : (4-(3-methoxyoxetan-3-yl)phenyl)(4-((4-(trifluoromethyl)phenyl)amino)piperidin-1-yl)methanone



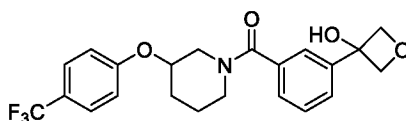
¹H NMR (DMSO-*d*₆) δ : 1.23-1.35 (m, 2H), 1.91-1.99 (m, 2H), 3.05 (s, 3H), 3.07 (s, 1H)
 5 3.10-3.11 (m, 1H), 3.61-3.63 (m, 2H), 4.36 (s, 1H), 4.75-4.81 (m, 4H), 6.31 (d, *J* = 8.0 Hz, 1H), 6.70-6.73 (m, 2H), 7.35 (d, *J* = 8.8 Hz, 2H), 7.45 (d, *J* = 8.4 Hz, 2H), 7.52 (d, *J* = 8.4 Hz, 2H); ESI-MS: *m/z* 435.1 (M)⁺, 100%.

Example-20 : (4-(3-hydroxyoxetan-3-yl)phenyl)(4-(methyl(4-(trifluoromethyl)phenyl)amino)piperidin-1-yl)methanone



¹H NMR (DMSO-*d*₆) δ : 1.16-1.24 (m, 1H), 1.60-1.72 (m, 1H), 1.74-1.82 (m, 3H), 2.81 (s, 3H),
 10 3.27-3.30 (m, 1H), 3.8-4.02 (m, 1H), 4.18-4.20 (m, 1H), 4.50 (br s, 1H), 4.69 (d, *J* = 6.8 Hz, 2H), 4.78 (d, *J* = 6.8 Hz, 2H), 6.45 (s, 1H), 6.93 (d, *J* = 8.8 Hz, 2H), 7.45-7.49
 15 (m, 4H), 7.67 (d, *J* = 8.0 Hz, 2H); ESI-MS: *m/z* 435.4 (M+H)⁺, 100%.

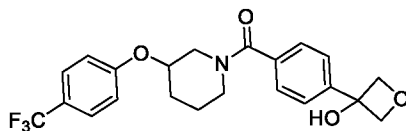
Example-21 : (3-(3-hydroxyoxetan-3-yl)phenyl)(3-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone



¹H NMR (DMSO-*d*₆) δ : 1.24-1.30 (m, 1H), 1.78-1.94 (m, 3H), 2.67-2.68 (m, 2H), 3.33-
 20 3.37 (m, 1H), 3.54-3.60 (m, 2H), 4.75-4.78 (m, 1H), 4.80-4.85 (m, 2H), 6.45 (s, 1H), 7.01-
 7.03 (m, 1H), 7.23-7.28 (m, 1H), 7.33-7.36 (m, 1H), 7.52-7.55 (m, 1H), 7.56-7.59 (m, 1H),
 7.60-7.68 (m, 2H), 7.67-7.70 (m, 1H), 7.95-8.05 (m, 1H); ESI-MS: *m/z* 422.14 (M+H)⁺,
 100%.

25

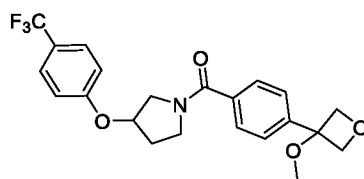
Example-22 : (4-(3-hydroxyoxetan-3-yl)phenyl)(3-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone



^1H NMR ($\text{DMSO}-d_6$) δ : 1.24-1.30 (m, 1H), 1.78-1.94 (m, 3H), 3.33-3.37 (m, 1H), 3.54-3.60 (m, 2H), 4.01-4.05 (m, 1H), 4.80-4.85 (m, 5H), 6.45 (s, 1H), 7.01-7.03 (m, 1H), 7.23-7.28 (m, 3H), 7.33-7.36 (m, 3H), 7.67-7.70 (m, 1H); ESI-MS: m/z 422.14 ($\text{M}+\text{H}$) $^+$, 100%.

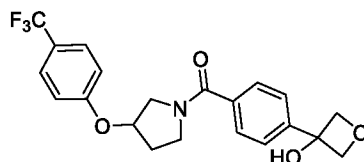
5

Example-23 : (4-(3-methoxyoxetan-3-yl)phenyl)(3-(4-(trifluoromethyl)phenoxy)pyrrolidin-1-yl)methanone



^1H NMR (CDCl_3) δ : 2.10-2.15 (m, 1H), 2.16-2.18 (m, 1H), 2.21-2.27 (m, 1H), 3.16 (s, 3H), 3.63-3.66 (m, 1H), 3.68-3.72 (m, 1H), 3.85-3.89 (m, 1H), 4.11-4.15 (m, 1H), 4.83 (d, $J = 6.4$ Hz, 2H), 4.96 (d, $J = 6.4$ Hz, 2H), 6.99-7.01 (m, 1H), 7.05-7.08 (m, 1H), 7.28-7.33 (m, 3H), 7.54-7.57 (m, 2H), 7.61-7.65 (m, 1H); ESI-MS: m/z 422.15 ($\text{M}+\text{H}$) $^+$, 100%.

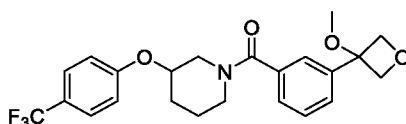
Example-24 : (4-(3-hydroxyoxetan-3-yl)phenyl)(3-(4-(trifluoromethyl)phenoxy)pyrrolidin-1-yl)methanone



^1H NMR (CDCl_3) δ : 2.10-2.15 (m, 1H), 2.16-2.20 (m, 1H), 2.98-3.0 (m, 1H), 3.38-3.40 (m, 1H), 3.49-3.51 (m, 1H), 3.61-3.68 (m, 1H), 3.69-3.72 (m, 1H), 3.85-3.89 (m, 1H), 4.82-4.88 (m, 4H), 6.90-6.92 (m, 1H), 7.01-7.08 (m, 1H), 7.28-7.35 (m, 3H), 7.47-7.50 (m, 1H), 7.72-7.75 (m, 1H); ESI-MS: m/z 408.1 ($\text{M}+\text{H}$) $^+$, 100%.

20

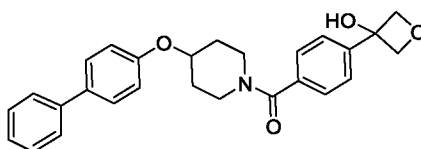
Example-25 : (3-(3-methoxyoxetan-3-yl)phenyl)(3-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone



¹H NMR (CDCl₃) δ : 1.27-1.30 (m, 1H), 1.89-2.03 (m, 3H), 2.80-2.95 (m, 2H), 3.15-3.18 (m, 1H), 3.35 (s, 3H), 4.12-4.15 (m, 1H), 4.30-4.32 (m, 1H), 4.74-4.76 (m, 2H), 4.83-4.92 (m, 2H), 6.80-6.85 (m, 1H), 7.08-7.10 (m, 1H), 7.24-7.28 (m, 2H), 7.50-7.54 (m, 2H), 7.57-7.76 (m, 2H); ESI-MS: m/z 436.16 (M+H)⁺, 100%.

5

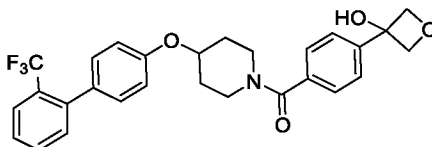
Example-26 : (4-([1,1'-biphenyl]-4-yloxy)piperidin-1-yl)(4-(3-hydroxyoxetan-3-yl)phenyl)methanone



¹H NMR (CDCl₃) δ : 1.93-2.11 (m, 4H), 3.15 (s, 1H), 3.42 (m, 1H), 3.71 (m, 1H), 3.91-3.92 (m, 2H), 4.63-4.68 (m, 1H), 4.84 (d, *J* = 7.2 Hz, 2H), 4.95 (d, *J* = 7.2 Hz, 2H), 7.03 (d, *J* = 6.8 & 2.0 Hz, 2H), 7.31-7.36 (m, 1H), 7.42-7.46 (m, 4H), 7.53-7.57 (m, 4H), 7.67 (d, *J* = 8.4 Hz, 2H); ESI-MS: m/z, 430.20 (M+H)⁺, 100%.

Example-27 : (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((2'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)oxy)piperidin-1-yl)methanone

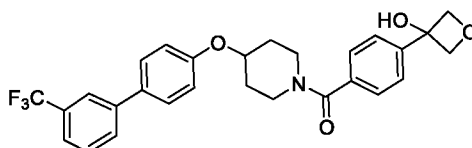
15



¹H NMR (CDCl₃) δ : 1.93-2.06 (m, 4H), 3.26 (m, 1H), 3.60-3.83 (m, 3H), 4.66 (m, 1H), 4.85 (d, *J* = 6.8 Hz, 2H), 4.74 (d, *J* = 6.0 Hz, 2H), 6.95-7.05 (m, 2H), 7.16-7.28 (m, 3H), 7.32-7.76 (m, 8H); ESI-MS: m/z, 498.18 (M+H)⁺, 100%.

20

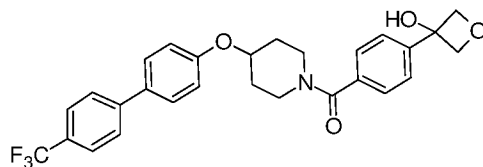
Example-28 : (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((3'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)oxy)piperidin-1-yl)methanone



¹H NMR (CDCl₃) δ : 1.88-2.08 (m, 4H), 3.23-3.29 (m, 2H), 3.43-3.70 (m, 1H), 3.79-4.07 (m, 2H), 4.68 (m, 1H), 4.84 (d, *J* = 6.8 Hz, 2H), 4.95 (d, *J* = 7.2 Hz, 2H), 7.03 (d, *J* = 8.4 Hz, 2H), 7.28 (s, 2H), 7.36-7.59 (m, 4H), 7.65 (d, *J* = 8.0 Hz, 2H), 7.73 (d, *J* = 7.2 Hz, 1H), 7.80 (s, 1H); ESI-MS: m/z, 498.22 (M+H)⁺, 100%.

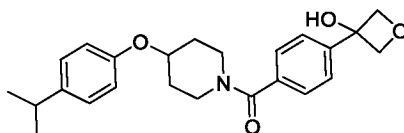
25

Example-29 : (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((4'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)oxy)piperidin-1-yl)methanone



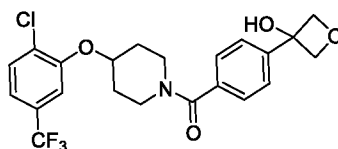
¹H NMR (DMSO-*d*₆) δ : 1.68 (m, 2H), 2.01 (m, 2H), 3.32-3.70 (m, 3H), 4.01 (m, 1H), 4.70 (d, *J* = 8.4 Hz, 2H), 4.76-4.80 (m, 3H), 6.44 (s, 1H), 7.13 (d, *J* = 8.4 Hz, 2H), 7.46 (d, *J* = 8.0 Hz, 2H), 7.68-7.70 (m, 4H), 7.77 (d, *J* = 8.4 Hz, 2H), 7.85 (d, *J* = 8.0 Hz, 2H). ESI-MS: *m/z*, 498.24 (M+H)⁺, 100%

Example-30 : (4-(3-hydroxyoxetan-3-yl)phenyl)(4-(4-isopropylphenoxy)piperidin-1-yl)methanone



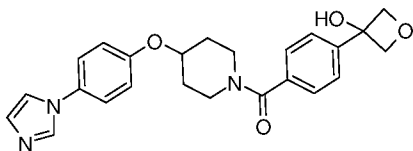
¹H NMR (DMSO-*d*₆) δ : 1.17 (d, *J* = 6.8 Hz, 6H), 1.61 (m, 2H), 1.96 (m, 2H), 2.80-2.84 (m, 1H), 3.33-3.43 (m, 2H), 3.45-3.65 (m, 1H), 3.80-3.95 (m, 1H), 4.57-4.61 (m, 1H), 4.69 (d, *J* = 6.8 Hz, 2H), 4.78 (d, *J* = 6.8 Hz, 2H), 6.44 (s, 1H), 6.88-6.92 (m, 2H), 7.12-7.15 (m, 2H), 7.44 (d, *J* = 6.4 & 1.6 Hz, 2H), 7.67 (dd, *J* = 6.4 & 2.0 Hz, 2H); ESI-MS: *m/z*, 396.24 (M+H)⁺, 100%.

Example-31 : (4-(2-chloro-5-(trifluoromethyl)phenoxy)piperidin-1-yl)(4-(3-hydroxyoxetan-3-yl)phenyl)methanone



¹H NMR (DMSO-*d*₆) δ : 1.71 (m, 2H), 1.98-2.02 (m, 2H), 3.33-3.59 (m, 1H), 3.74 (m, 2H), 3.86 (m, 1H), 4.69 (d, *J* = 6.4 Hz, 2H), 4.78 (d, *J* = 6.8 Hz, 2H), 4.99-5.01 (m, 1H), 6.45 (s, 1H), 7.34 (d, *J* = 8.4 Hz, 1H), 7.48 (d, *J* = 8.4, 2H), 7.61 (d, *J* = 1.2 Hz, 1H), 7.66-7.71 (m, 3H); ESI-MS: *m/z*, 356.11 (M+H)⁺, 100%.

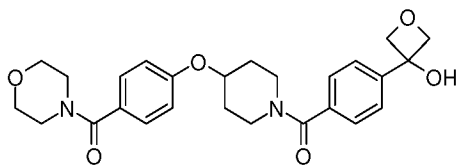
Example-32 : (4-(4-(1H-imidazol-1-yl)phenoxy)piperidin-1-yl)(4-(3-hydroxyoxetan-3-yl)phenyl)methanone



^1H NMR ($\text{DMSO}-d_6$) δ : 1.65-1.86 (m, 2H), 1.88-2.20 (m, 2H), 3.32-3.80 (m, 3H), 3.94-4.17 (m, 1H), 4.94-5.03 (m, 5H), 6.44 (s, 1H), 6.09-7.14 (m, 3H), 7.32-7.99 (m, 7H), 8.32-8.35 (m, 1H); ESI-MS: m/z , 420.24 ($\text{M}+\text{H}$) $^+$, 100%.

5

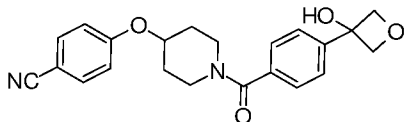
Example-33 : (4-((1-(4-(3-hydroxyoxetan-3-yl)benzoyl)piperidin-4-yl)oxy)phenyl)(morpholino)methanone



^1H NMR ($\text{DMSO}-d_6$) δ : 1.64 (m, 2H), 1.99 (m, 2H), 3.32-3.70 (m, 11H), 4.00 (m, 1H), 4.68-4.79 (m, 5H), 6.45 (s, 1H), 7.03 (d, $J = 7.6$ Hz, 2H), 7.37 (d, $J = 8.0$ Hz, 2H), 7.45 (d, $J = 7.2$ Hz, 2H), 7.68 (d, $J = 7.2$ Hz, 2H); ESI-MS: m/z , 467.28 ($\text{M}+\text{H}$) $^+$, 100%.

10

Example-34 : 4-((1-(4-(3-hydroxyoxetan-3-yl)benzoyl)piperidin-4-yl)oxy)benzonitrile

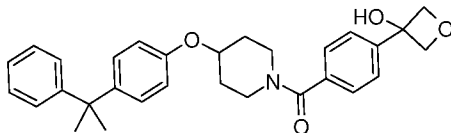


15

^1H NMR ($\text{DMSO}-d_6$) δ : 1.65 (m, 2H), 2.01 (m, 2H), 3.34-3.81 (m, 3H), 4.01 (m, 1H), 4.70-5.04 (m, 5H), 6.45 (s, 1H), 7.18 (m, 2H), 7.46 (m, 2H), 7.67-7.95 (m, 4H); ESI-MS: m/z , 379.15 ($\text{M}+\text{H}$) $^+$, 100%.

Example-35 : (4-(3-hydroxyoxetan-3-yl)phenyl)(4-(4-(2-phenylpropan-2-yl)phenoxy)piperidin-1-yl)methanone

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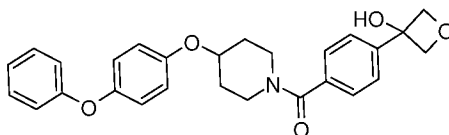


^1H NMR ($\text{DMSO}-d_6$) δ : 1.60 (m, 8H), 1.99 (m, 2H), 3.28-3.45 (m, 2H), 3.55 (m, 1H), 3.96 (m, 1H), 4.57-4.61 (m, 1H), 4.69 (d, $J = 6.8$ Hz, 2H), 4.78 (d, $J = 6.8$ Hz, 2H), 6.45

(s, 1H), 6.87-6.90 (m, 2H), 7.10-7.46 (m, 7H), 7.66 (d, $J = 4.8$ Hz, 2H), 7.95 (s, 2H).

ESI-MS: m/z , 372.20 (M+H)⁺, 100%.

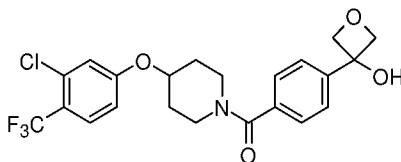
Example-36 : (4-(3-hydroxyoxetan-3-yl)phenyl)(4-(4-phenoxyphenoxy)piperidin-1-yl)methanone



¹H NMR (DMSO-*d*₆) δ : 1.60 (m, 2H), 1.98-2.14 (m, 2H), 3.38-3.80 (m, 3H), 3.99 (m, 1H), 4.61-5.09 (m, 5H), 6.45 (s, 1H), 6.60-7.35 (m, 7H), 7.46-7.89 (m, 4H), 7.95-8.09 (m, 2H);

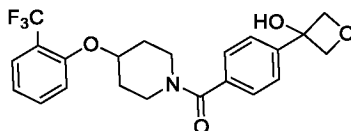
ESI-MS: m/z , 446.26 (M+H)⁺, 100%.

Example-37 : (4-(3-chloro-4-(trifluoromethyl)phenoxy)piperidin-1-yl)(4-(3-hydroxyoxetan-3-yl)phenyl)methanone



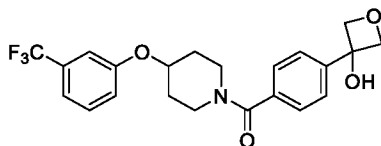
¹H NMR (DMSO-*d*₆) δ : 1.65 (m, 2H), 1.99 (m, 2H), 3.33-3.56 (m, 3H), 3.99 (s, 1H), 4.69 (d, $J = 6.8$ Hz, 2H), 4.78 (d, $J = 6.8$ Hz, 2H), 4.86-4.88 (m, 1H), 6.44 (s, 1H), 7.15 (d, $J = 8.8$ & 1.6 Hz, 1H), 7.38 (d, $J = 2.0$ Hz, 1H), 7.46 (d, $J = 8.4$ Hz, 2H), 7.67 (d, $J = 8.0$ Hz, 2H), 7.75 (d, $J = 9.2$ Hz, 1H); ESI-MS: m/z , 456.06 (M+H)⁺, 100%.

Example-38 : (4-(3-hydroxyoxetan-3-yl)phenyl)(4-(2-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone



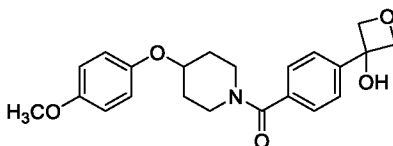
¹H NMR (DMSO-*d*₆) δ : 1.71 (m, 2H), 1.97 (m, 2H), 3.33 (m, 1H), 3.49 (m, 1H), 3.70 (m, 2H), 4.69 (d, $J = 5.6$ Hz, 2H), 4.79 (d, $J = 5.6$ Hz, 2H), 4.92 (m, 1H), 6.45 (s, 1H), 7.07-7.10 (m, 1H), 7.47 (d, $J = 7.6$ Hz, 1H), 7.62 (d, $J = 7.6$ Hz, 2H), 7.79-7.86 (m, 4H); ESI-MS: m/z 422.15 (M+H)⁺, 100%.

Example-39 : (4-(3-hydroxyoxetan-3-yl)phenyl)(4-(3-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone



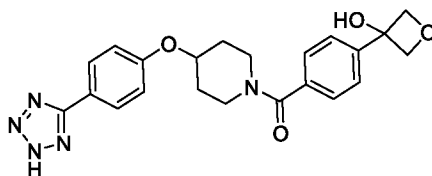
¹H NMR (DMSO-*d*₆) δ : 1.65 (m, 2H), 1.99-2.01 (m, 2H), 3.34-3.57 (m, 3H), 3.99 (m, 1H), 4.69 (d, *J* = 6.4 Hz, 2H), 4.80-4.83 (m, 3H), 6.45 (s, 1H), 7.28-7.33 (m, 3H), 7.46 (d, *J* = 8.4 Hz, 2H), 7.51-7.55 (m, 1H), 7.67 (d, *J* = 8.4 Hz, 2H); ESI-MS: *m/z* 422.13 (M+H)⁺, 100%.

Example-40 : (4-(3-hydroxyoxetan-3-yl)phenyl)(4-(4-methoxyphenoxy)piperidin-1-yl)methanone



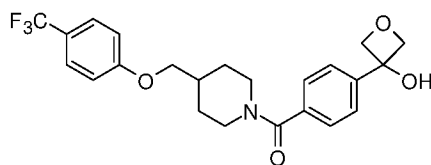
¹H NMR (DMSO-*d*₆) δ : 1.60 (m, 2H), 1.93-2.05 (m, 2H), 3.40-3.56 (m, 3H), 3.69 (s, 3H), 3.96 (s, 1H), 4.50 (s, 1H), 4.69 (d, *J* = 6.0 Hz, 2H), 4.79 (d, *J* = 6.4 Hz, 2H), 6.45 (s, 1H), 6.85 (d, *J* = 8.48 Hz, 2H), 6.93 (d, *J* = 8.8 Hz, 2H), 7.45 (d, *J* = 8.0 Hz, 2H), 7.67 (d, *J* = 8.0 Hz, 2H); ESI-MS: *m/z* 384.10 (M+H)⁺, 100%.

Example-41 : (4-(4-(2H-tetrazol-5-yl)phenoxy)piperidin-1-yl)(4-(3-hydroxyoxetan-3-yl)phenyl)methanone



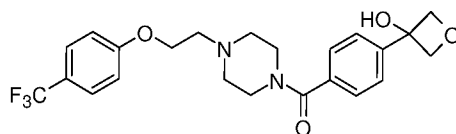
¹H NMR (DMSO-*d*₆) δ : 1.67 (m, 2H), 2.02 (m, 2H), 3.20-3.53 (m, 2H), 3.72-3.76 (m, 1H), 3.80-4.18 (m, 1H), 4.70 (d, *J* = 6.0 Hz, 2H), 4.78-4.79 (m, 3H), 6.47 (br s, 1H), 7.17 (d, *J* = 8.8 Hz, 2H), 7.46 (d, *J* = 8.0 Hz, 2H), 7.68 (d, *J* = 8.0 Hz, 2H), 7.95 (d, *J* = 8.8 Hz, 2H); ESI-MS: *m/z* 422.17 (M+H)⁺, 100%.

Example-42 : (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((4-(trifluoromethyl)phenoxy)methyl)piperidin-1-yl)methanone



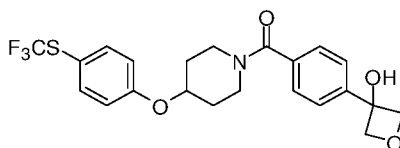
¹H NMR (DMSO-*d*₆) δ : 1.29 (m, 2H), 1.75-1.86 (m, 2H), 2.08 (m, 1H), 2.82 (m, 1H), 3.09 (m, 1H), 3.65 (m, 1H), 3.96 (d, *J* = 5.2 Hz, 2H), 4.53 (s, 1H), 4.69 (d, *J* = 6.0 Hz, 2H), 4.79 (d, *J* = 6.0 Hz, 2H), 6.45 (s, -OH), 7.12 (d, *J* = 8.0 Hz, 2H), 7.42 (d, *J* = 7.6 Hz, 2H), 7.63-7.68 (m, 4H); ESI-MS: *m/z*, 436.18 (M+H)⁺, 100%.

Example-43 : (4-(3-hydroxyoxetan-3-yl)phenyl)(4-(2-(4-(trifluoromethyl)phenoxy)ethyl)piperazin-1-yl)methanone



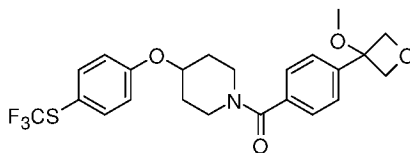
¹H NMR (CDCl₃) δ : 2.55-2.69 (m, 4H), 1.90 (t, *J* = 6.4 Hz, 2H), 3.47 (m, 2H), 3.84 (m, 2H), 4.17 (t, *J* = 6.8 Hz, 2H), 4.82 (d, *J* = 6.8 Hz, 2H), 4.94 (d, *J* = 7.2 Hz, 2H), 6.97 (d, *J* = 8.8 Hz, 2H), 7.38 (d, *J* = 8.0 Hz, 2H), 7.56 (d, *J* = 8.8 Hz, 2H), 7.63 (d, *J* = 8.4 Hz, 2H); ESI-MS: *m/z*, 451.20 (M+H)⁺, 100%.

Example-44 : (4-(3-hydroxyoxetan-3-yl)phenyl)(4-(4-((trifluoromethyl)thio)phenoxy)piperidin-1-yl)methanone



¹H NMR (DMSO-*d*₆) δ : 1.66 (m, 2H), 2.02 (m, 2H), 3.27-3.37 (m, 2H), 3.50-3.60 (m, 1H), 3.90-4.10 (m, 1H), 4.79 (d, *J* = 5.6 Hz, 2H), 4.75-5.00 (m, 3H), 6.44 (s, -OH), 7.14 (d, *J* = 6.8 Hz, 2H), 7.45 (d, *J* = 6.8 Hz, 2H), 7.62-7.68 (m, 4H); ESI-MS: *m/z*, 454.12 (M+H)⁺, 100%.

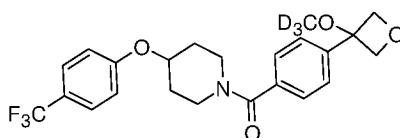
Example-45 : (4-(3-methoxyoxetan-3-yl)phenyl)(4-(4-((trifluoromethyl)thio)phenoxy)piperidin-1-yl)methanone



^1H NMR (DMSO- d_6) δ : 1.67 (m, 2H), 1.90-2.10 (m, 2H), 3.05 (s, 3H), 3.27-3.42 (m, 2H), 3.45-3.55 (m, 1H), 3.90-4.10 (m, 1H), 4.75-4.80 (m, 5H), 7.15 (d, $J = 8.4$ Hz, 2H), 7.48-7.53 (m, 4H), 7.63 (d, $J = 8.4$ Hz, 2H); ESI-MS: m/z , 468.14 ($M+H$) $^+$, 100%.

5

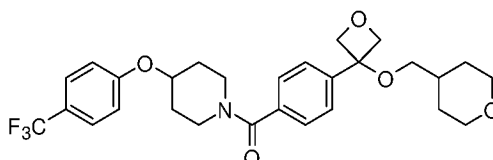
Example-46 : (4-(3-(methoxy-d3)oxetan-3-yl)phenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone



^1H NMR (CDCl_3) δ : 1.95-2.06 (m, 4H), 3.46 (m, 1H), 3.71-3.80 (m, 1H), 3.91 (m, 2H), 4.67-4.71 (m, 1H), 4.82 (d, $J = 7.6$ Hz, 2H), 4.96 (d, $J = 7.2$ Hz, 2H), 7.00 (d, $J = 8.4$ Hz, 2H), 7.49-7.58 (m, 6H); ESI-MS: m/z , 439.19 ($M+H$) $^+$, 100%.

10

Example-47 : (4-(3-((tetrahydro-2H-pyran-4-yl)methoxy)oxetan-3-yl)phenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone



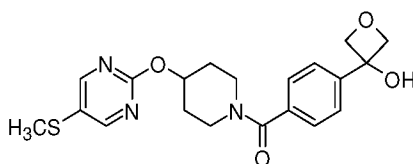
15

^1H NMR (CDCl_3) δ : 1.23-1.41 (m, 3H), 1.69 (dd, $J = 6.6$ Hz, 2H), 1.83-2.06 (m, 5H), 3.04 (d, $J = 6.4$ Hz, 2H), 3.38-3.45 (m, 3H), 3.71 (m, 1H), 3.91-4.01 (m, 3H), 4.68-4.71 (m, 1H), 4.82 (d, $J = 6.8$ Hz, 2H), 4.94 (d, $J = 6.8$ Hz, 2H), 7.00 (d, $J = 8.8$ Hz, 2H), 6.49-7.58 (m, 6H);

ESI-MS: m/z , 520.23 ($M+H$) $^+$, 100%.

20

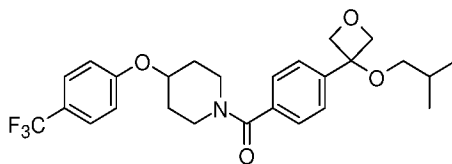
Example-48 : (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((5-(methylthio)pyrimidin-2-yl)oxy)piperidin-1-yl)methanone



^1H NMR ($\text{DMSO-}d_6$) δ : 1.71 (m, 2H), 2.00-2.06 (m, 2H), 2.50 (s, 3H), 3.31-3.43 (m, 2H), 3.51-3.56 (m, 1H), 4.02 (m, 1H), 4.70 (d, $J = 6.8$ Hz, 2H), 4.78 (d, $J = 6.8$ Hz, 2H), 5.18-5.22 (m, 1H), 6.44 (s, -OH), 7.46 (d, $J = 8.0$ Hz, 2H), 7.67 (d, $J = 8.4$ Hz, 2H), 8.61 (s, 2H); ESI-MS: m/z , 402.14 ($\text{M}+\text{H}$) $^+$, 100%.

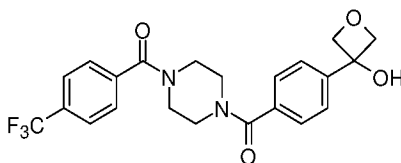
5

Example-49 : (4-(3-isobutoxyoxetan-3-yl)phenyl)(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone



^1H NMR (CDCl_3) δ : 0.94 (d, $J = 6.8$ Hz, 6H), 1.83-2.11 (m, 5H), 2.96 (d, $J = 6.4$ Hz, 2H), 3.35-3.55 (m, 1H), 3.60-3.99 (m, 3H), 4.68-4.71 (m, 1H), 4.80 (d, $J = 7.2$ Hz, 2H), 4.97 (d, $J = 7.2$ Hz, 2H), 7.00 (d, $J = 8.8$ Hz, 2H), 7.50 (dd, $J = 6.8$ & 2.0 Hz, 2H), 7.54-7.58 (m, 4H); ESI-MS: m/z , 478.22 ($\text{M}+\text{H}$) $^+$, 100%.

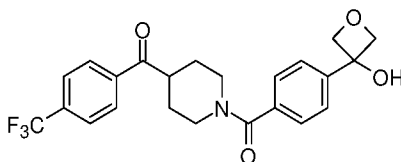
Example-50: (4-(4-(3-hydroxyoxetan-3-yl)benzoyl)piperazin-1-yl)(4-(trifluoromethyl)phenyl)methanone



^1H NMR (CDCl_3) δ : 3.19 (s, -OH), 3.52-4.07 (m, 8H), 4.85 (d, $J = 6.0$ Hz, 2H), 6.94 (d, $J = 6.8$ Hz, 2H), 7.45 (d, $J = 7.6$ Hz, 2H), 7.55 (d, $J = 7.6$ Hz, 2H), 7.69-7.73 (m, 4H); ESI-MS: m/z , 435.15 ($\text{M}+\text{H}$) $^+$, 100%.

20

Example-51 : (1-(4-(3-hydroxyoxetan-3-yl)benzoyl)piperidin-4-yl)(4-(trifluoromethyl)phenyl)methanone

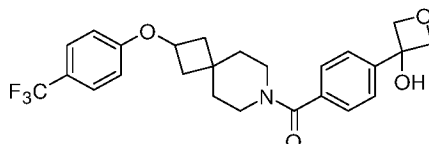


^1H NMR (CDCl_3) δ : 1.72-1.89 (m, 4H), 3.05-3.20 (m, 2H), 3.46 (s, 1H), 3.54-3.68 (m, 1H), 3.88 (m, 1H), 4.61-4.70 (m, 1H), 4.84 (d, $J = 6.8$ Hz, 2H), 4.94 (d, $J = 6.8$ Hz, 2H),

7.41 (d, $J = 8.4$ Hz, 2H), 7.65 (d, $J = 8.4$ Hz, 2H), 7.78 (d, $J = 8.0$ Hz, 2H), 8.05 (d, $J = 8.0$ Hz, 2H);

ESI-MS: m/z , 434.15 (M+H)⁺, 100%.

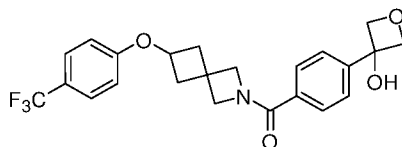
5 **Example-52: (4-(3-hydroxyoxetan-3-yl)phenyl)(2-(4-(trifluoromethyl)phenoxy)-7-azaspiro[3.5]nonan-7-yl)methanone**



¹H NMR (CDCl₃) δ : 1.78 (m, 2H), 2.04 (m, 2H), 2.50 (m, 2H), 3.32-3.37 (m, 2H), 3.46 (s, 2H), 3.70-3.76 (m, 2H), 4.76 (s, 2H), 4.84 (d, $J = 6.8$ Hz, 2H), 4.94 (d, $J = 6.8$ Hz, 2H), 6.86 (d, $J = 8.4$ Hz, 2H), 7.37 (d, $J = 8.4$ Hz, 2H), 7.54 (d, $J = 8.8$ Hz, 2H), 7.62 (d, $J = 8.0$ Hz, 2H);

ESI-MS: m/z , 462.18 (M+H)⁺, 100%.

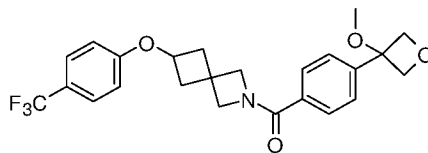
15 **Example-53 : (4-(3-hydroxyoxetan-3-yl)phenyl)(6-(4-(trifluoromethyl)phenoxy)-2-azaspiro[3.3]heptan-2-yl)methanone**



¹H NMR (DMSO-*d*₆) δ : 2.25-2.43 (m, 2H), 2.78-2.83 (m, 2H), 4.06 (s, 1H), 4.15 (s, 1H), 4.32 (s, 1H), 4.41 (s, 1H), 4.67-4.79 (m, 5H), 6.49 (s, -OH), 7.02 (d, $J = 8.0$ Hz, 2H), 7.63-7.68 (m, 6H); ESI-MS: m/z , 434.15 (M+H)⁺, 100%.

20

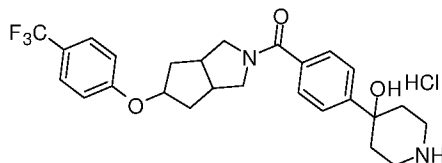
Example-54 : (4-(3-methoxyoxetan-3-yl)phenyl)(6-(4-(trifluoromethyl)phenoxy)-2-azaspiro[3.3]heptan-2-yl)methanone



¹H NMR (DMSO-*d*₆) δ : 2.28-2.33 (m, 2H), 2.78-2.83 (m, 2H), 3.04 (s, 3H), 4.07 (s, 1H), 4.16 (s, 1H), 4.33 (s, 1H), 4.41 (s, 1H), 4.71-4.80 (m, 5H), 7.00-7.039 (m, 2H), 7.51-7.55 (m, 2H), 7.63-7.71 (m, 4H); ESI-MS: m/z , 448.15 (M+H)⁺, 100%.

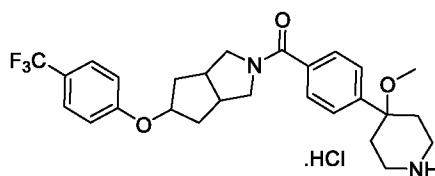
25

Example-55 : (4-(4-hydroxypiperidin-4-yl)phenyl)(5-(4-(trifluoromethyl)phenoxy)hexahydrocyclopenta[c]pyrrol-2(1H)-yl)methanone hydrochloride



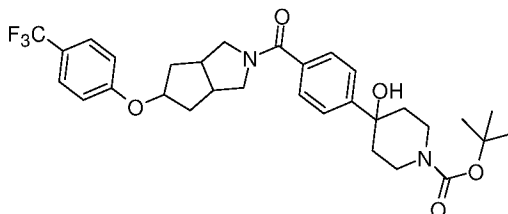
5 ^1H NMR (CD_3OD) δ : 1.18-1.19 (m, 1H), 1.21-1.41 (m, 2H), 1.70-1.81 (m, 1H), 1.93-1.96 (m, 3H), 2.27-2.36 (m, 4H), 3.32-3.35 (m, 2H), 3.47-3.51 (m, 3H), 3.75-3.79 (m, 2H), 3.81-3.85 (m, 1H), 4.98-5.01 (m, 1H), 7.03 (d, $J = 8.4$ Hz, 2H), 7.48 (d, $J = 8.4$ Hz, 2H), 7.57-7.61 (m, 4H); ESI-MS: m/z 475.4 ($\text{M}+\text{H}$) $^+$, 100%.

10 **Example-56 : (4-(4-methoxypiperidin-4-yl)phenyl)(5-(4-(trifluoromethyl)phenoxy)hexahydrocyclopenta[c]pyrrol-2(1H)-yl)methanone hydrochloride**



15 ^1H NMR ($\text{DMSO}-d_6$) δ : 1.58-1.61 (m, 1H), 1.73-1.77 (m, 1H), 2.07-2.10 (m, 4H), 2.29-2.33 (m, 2H), 2.77-2.80 (m, 2H), 2.91 (s, 3H), 3.20-3.23 (m, 2H), 3.34-3.39 (m, 3H), 3.59-3.67 (m, 3H), 4.95-4.96 (m, 1H), 7.05 (d, $J = 8.8$ Hz, 2H), 7.41 (d, $J = 8.8$ Hz, 2H), 7.51 (d, $J = 8.4$ Hz, 2H), 7.62 (d, $J = 8.8$ Hz, 2H), 8.92 (m, 2H); ESI-MS: m/z 430.8 (M) $^+$, 100%.

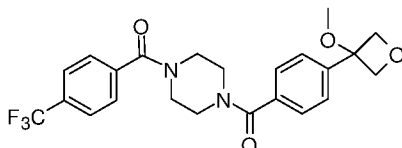
20 **Example-57 : *tert*-butyl 4-hydroxy-4-(4-(5-(4-(trifluoromethyl)phenoxy)octahydrocyclopenta[c]pyrrole-2-carbonyl)phenyl)piperidine-1-carboxylate**



25 ^1H NMR (CDCl_3) δ : 1.49 (s, 9H), 1.65-1.69 (m, 3H), 2.05-2.07 (m, 1H), 2.27-2.31 (m, 3H), 2.33-2.35 (m, 2H), 2.80-2.82 (m, 1H), 3.24 (s, 2H), 3.47-3.51 (m, 2H), 3.67-3.69 (m,

1H), 3.77-3.79 (m, 1H), 3.92-3.94 (m, 1H), 4.12-4.14 (m, 1H), 5.3-5.35 (m, 1H), 6.92 (d, $J = 8.4$ Hz, 2H), 7.44 (m, 4H), 7.53 (d, $J = 8.4$ Hz, 2H); ESI-MS: m/z 575.2 (M+H)⁺, 100%.

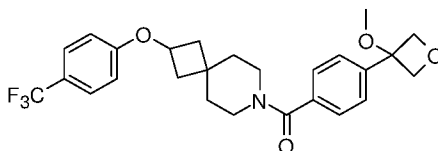
5 **Example-58 : (4-(4-(3-methoxyoxetan-3-yl)benzoyl)piperazin-1-yl)(4-(trifluoromethyl)phenyl)methanone**



¹H NMR (DMSO-*d*₆) δ : 3.04 (s, 3H), 3.29-3.80 (m, 8H), 4.76-4.80 (m, 4H), 7.52 (d, $J = 5.6$ Hz, 4H), 7.64 (d, $J = 7.2$ Hz, 2H), 7.84 (d, $J = 5.6$ Hz, 2H);

10 ESI-MS: m/z , 449.16 (M+H)⁺, 100%.

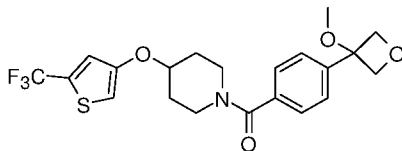
Example-59 : (4-(3-methoxyoxetan-3-yl)phenyl)(2-(4-(trifluoromethyl)phenoxy)-7-azaspiro[3.5]nonan-7-yl)methanone



15 ¹H NMR (CDCl₃) δ : 1.53-1.61 (m, 4H), 1.97-2.10 (m, 2H), 2.51 (m, 2H), 3.17 (s, 3H), 3.34-3.48 (m, 2H), 3.71-3.77 (m, 2H), 4.77 (s, 1H), 4.82 (d, $J = 6.8$ Hz, 2H), 4.96 (d, $J = 6.8$ Hz, 2H), 6.86 (d, $J = 8.8$ Hz, 2H), 7.47 (d, $J = 8.0$ Hz, 2H), 7.52-7.55 (m, 4H);

ESI-MS: m/z , 476.20 (M+H)⁺, 100%

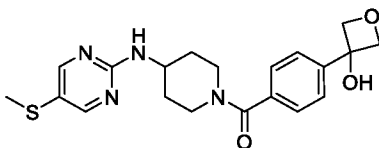
20 **Example-60 : (4-(3-methoxyoxetan-3-yl)phenyl)(4-((5-(trifluoromethyl)thiophen-3-yl)oxy)piperidin-1-yl)methanone**



¹H NMR (CDCl₃) δ : 1.84-2.06 (m, 4H), 3.44 (m, 2H), 3.68 (m, 2H), 3.88 (m, 2H), 4.44-4.49 (m, 1H), 4.82 (d, $J = 6.8$ Hz, 2H), 4.96 (m, 2H), 6.50 (s, 1H), 7.14 (s, 2H), 7.49-7.51

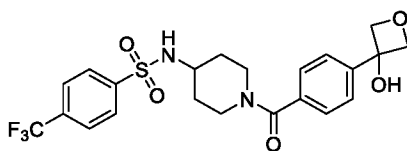
25 (m, 2H), 7.54 (dd, $J = 6.4$ & 1.6 Hz, 2H); ESI-MS: m/z , 442.10 (M+H)⁺, 100%.

Example-61 : (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((5-(methylthio)pyrimidin-2-yl)amino)piperidin-1-yl)methanone



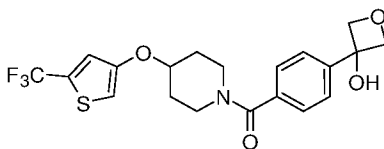
¹H NMR (CDCl₃) δ : 1.28-1.64 (m, 2H), 2.06-2.21 (m, 2H), 2.38 (s, 3H), 3.10-3.28 (m, 2H), 3.79 (m, 1H), 4.06-4.15 (m, 1H), 4.64 (m, 1H), 4.88 (d, J = 7.2 Hz, 2H), 4.95 (d, J = 7.2 Hz, 2H), 5.20 (s, J = 7.6 Hz, -NH), 7.43 (dd, J = 6.8 & 2.0 Hz, 2H), 7.66 (dd, J = 6.4 & 1.6 Hz, 2H), 8.37 (s, 2H); ESI-MS: m/z , 401.16 (M+H)⁺, 100%.

Example-62 : N-(1-(4-(3-hydroxyoxetan-3-yl)benzoyl)piperidin-4-yl)-4-(trifluoromethyl)benzenesulfonamide



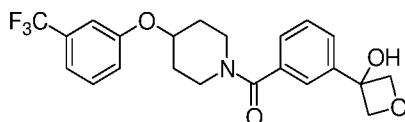
¹H NMR (DMSO-*d*₆) δ : 1.19-1.32 (m, 2H), 1.50-1.63 (m, 2H), 2.89-3.02 (m, 2H), 3.35-3.36 (m, 1H), 3.50 (m, 1H), 4.20 (m, 1H), 4.67 (d, J = 6.8 Hz, 2H), 4.77 (d, J = 6.8 Hz, 2H), 6.43 (s, -OH), 7.36 (dd, J = 6.4 & 1.6 Hz, 2H), 7.64-7.66 (m, 2H), 8.00 (d, J = 8.4 Hz, 2H), 8.51 (d, J = 8.0 Hz, 2H), 8.14 (d, J = 6.8 Hz, -NH); ESI-MS: m/z , 485.13 (M+H)⁺, 100%.

Example-63 : (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((5-(trifluoromethyl)thiophen-3-yl)oxy)piperidin-1-yl)methanone



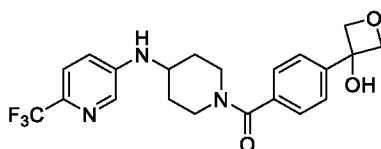
¹H NMR (CDCl₃) δ : 1.80 - 2.20 (m, 4H), 3.02 (s, -OH), 3.41-3.43 (m, 1H), 3.66 (m, 1H), 3.80 (m, 2H), 4.44-4.49 (m, 1H), 4.88 (d, J = 6.8 Hz, 2H), 4.95 (d, J = 6.8 Hz, 2H), 6.49 (s, 1H), 7.14 (s, 1H), 7.45 (d, J = 8.4 Hz, 2H), 7.68 (d, J = 8.4 Hz, 2H); ESI-MS: m/z , 428.12 (M+H)⁺, 100%.

Example-64 : (3-(3-hydroxyoxetan-3-yl)phenyl)(4-(3-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone



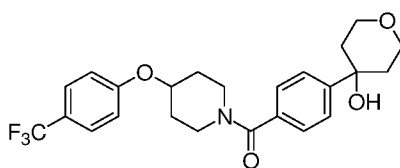
¹H NMR (CDCl₃) δ : 1.83-2.10 (m, 4H), 3.43 (m, 1H), 3.56 (s, -OH), 3.67 (m, 1H), 3.91 (m, 2H), 4.64-4.69 (m, 1H), 4.83 (d, J = 6.8 Hz, 2H), 4.90 (d, J = 6.8 Hz, 2H), 7.10 (dd, J = 8.0 & 2.0 Hz, 1H), 7.16 (s, 1H), 7.23-7.28 (m, 1H), 7.35-7.49 (m, 3H), 7.15 (d, J = 1.2 Hz, 1H), 7.73 (dd, J = 2.8 & 1.6 Hz, 1H); ESI-MS: m/z , 422.16 (M+H)⁺, 100%.

Example-65 : (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((6-(trifluoromethyl)pyridin-3-yl)amino)piperidin-1-yl)methanone



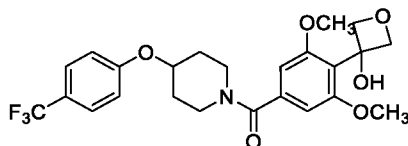
¹H NMR (DMSO-*d*₆) δ : 1.24-1.40 (m, 2H), 1.80-2.05 (m, 2H), 3.00-3.20 (m, 2H), 3.60-3.70 (m, 2H), 4.40 (m, 1H), 7.69 (d, J = 6.8 Hz, 2H), 4.79 (d, J = 6.8 Hz, 2H), 6.44 (s, -OH), 6.63 (d, J = 7.6 Hz, 1H), 7.07 (dd, J = 8.4 & 2.0 Hz, 1H), 7.43 (d, J = 8.0 Hz, 2H), 7.52 (d, J = 8.4 Hz, 1H), 7.68 (d, J = 8.0 Hz, 2H), 8.07 (d, J = 2.0 Hz, 1H); ESI-MS: m/z , 422.17 (M+H)⁺, 100%.

Example-66 : (4-(4-hydroxytetrahydro-2H-pyran-4-yl)phenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone



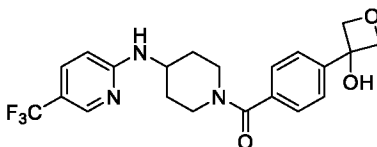
¹H NMR (DMSO-*d*₆) δ : 1.53 (d, J = 12.8 Hz, 2H), 1.65 (m, 2H), 1.94-2.01 (m, 4H), 3.32-3.42 (m, 2H), 3.55-3.57 (m, 1H), 3.69-3.81 (m, 4H), 3.97 (m, 1H), 4.78-4.80 (m, 1H), 5.11 (s, -OH), 7.17 (d, J = 8.8 Hz, 2H), 7.38 (d, J = 8.0 Hz, 2H), 7.55 (d, J = 8.0 Hz, 2H), 7.64 (d, J = 8.0 Hz, 2H); ESI-MS: m/z , 450.19 (M+H)⁺, 100%.

Example-67 : (4-(3-hydroxyoxetan-3-yl)-3,5-dimethoxyphenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone



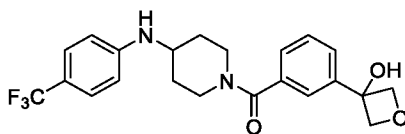
¹H NMR (DMSO-*d*₆) δ : 1.69 (m, 2H), 1.90-2.10 (m, 2H), 3.31-3.33 (m, 1H), 3.44 (m, 1H), 3.57 (m, 1H), 3.75 (s, 6H), 3.95-4.05 (m, 1H), 4.49 (d, *J* = 8.0 Hz, 2H), 4.79-4.82 (m, 1H), 4.89 (d, *J* = 8.0 Hz, 2H), 5.74 (s, -OH), 6.66 (s, 2H), 7.18 (d, *J* = 8.8 Hz, 2H), 7.65 (d, *J* = 8.8 Hz, 2H); ESI-MS: *m/z*, 482.12 (M+H)⁺, 100%.

Example-68 : (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((5-(trifluoromethyl)pyridin-2-yl)amino)piperidin-1-yl)methanone



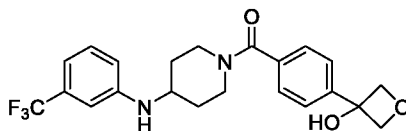
¹H NMR (DMSO-*d*₆) δ : 1.34-1.40 (m, 2H), 1.91-2.01 (m, 2H), 3.06 (m, 1H), 3.20 (m, 1H), 3.62 (m, 1H), 4.09 (m, 1H), 4.36 (m, 1H), 4.69 (d, *J* = 6.8 Hz, 2H), 4.79 (d, *J* = 6.4 Hz, 2H), 6.44 (s, 1H), 6.59 (d, *J* = 7.2 Hz, 1H), 7.34 (d, *J* = 6.8 Hz, 1H), 7.42 (d, *J* = 8.4 Hz, 2H), 7.63 (dd, *J* = 8.8 & 2.0 Hz, 1H), 7.68 (d, *J* = 8.4 Hz, 2H), 8.29 (s, 1H); ESI-MS: *m/z*, 422.17 (M+H)⁺, 100%.

Example-69 : (3-(3-hydroxyoxetan-3-yl)phenyl)(4-((4-(trifluoromethyl)phenyl)amino)piperidin-1-yl)methanone



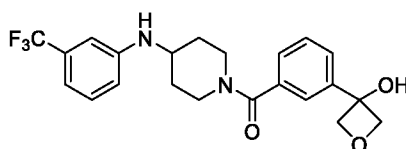
¹H NMR (DMSO-*d*₆) δ : 1.24-1.35 (m, 2H), 1.89-2.01 (m, 2H), 3.07-3.21 (m, 2H), 3.61-3.63 (m, 2H), 4.37 (m, 1H), 4.68 (d, *J* = 6.4 Hz, 2H), 4.79 (d, *J* = 6.4 Hz, 2H), 6.33 (d, *J* = 8.0 Hz, 1H), 6.47 (s, -OH), 6.71 (d, *J* = 8.4 Hz, 2H), 7.31-7.37 (m, 3H), 7.47-7.51 (m, 1H), 7.59 (s, 1H), 7.70 (d, *J* = 6.8 Hz, 1H); ESI-MS: *m/z*, 421.18 (M+H)⁺, 100%.

Example-70 : (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((3-(trifluoromethyl)phenyl)amino)piperidin-1-yl)methanone



¹H NMR (DMSO-*d*₆) δ : 1.34 (m, 2H), 1.90-1.99 (m, 2H), 3.05-3.20 (m, 2H), 3.61-3.63 (m, 2H), 4.32 (m, 1H), 4.69 (d, *J* = 6.4 Hz, 2H), 4.79 (d, *J* = 6.4 Hz, 2H), 6.08 (d, *J* = 8.0 Hz, 1H), 6.45 (s, -OH), 6.79 (d, *J* = 7.2 Hz, 2H), 6.86 (d, *J* = 6.4 Hz, 2H), 7.25-7.29 (m, 1H),
 5 7.42 (d, *J* = 8.0 Hz, 2H), 7.68 (d, *J* = 8.4 Hz, 1H); ESI-MS: *m/z*, 421.18 (M+H)⁺, 100%.

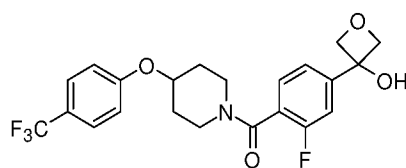
Example-71 : (3-(3-hydroxyoxetan-3-yl)phenyl)(4-((3-(trifluoromethyl)phenyl)amino)piperidin-1-yl)methanone



10 ¹H NMR (DMSO-*d*₆) δ : 1.34 (m, 2H), 1.90-1.99 (m, 2H), 3.05-3.20 (m, 2H), 3.61-3.63 (m, 2H), 4.35 (m, 1H), 4.68 (d, *J* = 6.4 Hz, 2H), 4.79 (d, *J* = 6.4 Hz, 2H), 6.08 (d, *J* = 8.0 Hz, 1H), 6.46 (s, -OH), 6.79 (d, *J* = 7.6 Hz, 1H), 6.86 (d, *J* = 6.4 Hz, 2H), 7.25-7.29 (m, 1H), 7.33 (d, *J* = 7.6 Hz, 1H), 7.47-7.51 (m, 1H), 7.59 (s, -OH), 7.70 (d, *J* = 8.0 Hz, 1H);
 ESI-MS: *m/z*, 421.18 (M+H)⁺, 100%.

15

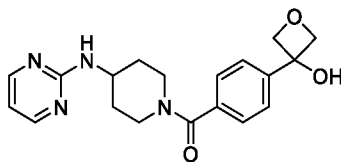
Example-72 : (2-fluoro-4-(3-hydroxyoxetan-3-yl)phenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone



20 ¹H NMR (DMSO-*d*₆) δ : 1.60-1.69 (m, 2H), 1.93 (m, 1H), 2.02-2.04 (m, 1H), 3.26-3.33 (m, 1H), 3.43-3.51 (m, 2H), 4.01-4.02 (m, 1H), 4.68 (d, *J* = 6.4 Hz, 2H), 4.77-4.83 (m, 3H), 6.58 (s, -OH), 7.18 (d, *J* = 8.4 Hz, 2H), 7.43-7.56 (m, 3H), 7.65 (d, *J* = 8.4 Hz, 2H);
 ESI-MS: *m/z*, 440.20 (M+H)⁺, 100%

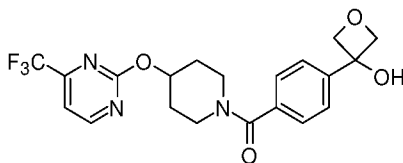
Example-73 : (4-(3-hydroxyoxetan-3-yl)phenyl)(4-(pyrimidin-2-ylamino)piperidin-1-yl)methanone

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¹H NMR (DMSO-*d*₆) δ : 1.44 (m, 2H), 1.84-1.99 (m, 2H), 2.99 (m, 1H), 3.17 (m, 1H), 3.62 (m, 1H), 3.94-4.04 (m, 1H), 4.39 (m, 1H), 4.70 (d, *J* = 6.8 Hz, 2H), 4.79 (d, *J* = 6.4 Hz, 2H), 6.44 (s, -OH), 6.56 (t, *J* = 4.4 Hz, 1H), 7.15 (d, *J* = 8.0 Hz, 1H), 7.41 (d, *J* = 8.4 Hz, 2H), 7.68 (d, *J* = 8.0 Hz, 2H), 8.26 (d, *J* = 4.8 Hz, 2H); ESI-MS: *m/z*, 355.24 (M+H)⁺, 100%.

Example-74 : (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((4-(trifluoromethyl)pyrimidin-2-yl)oxy)piperidin-1-yl)methanone

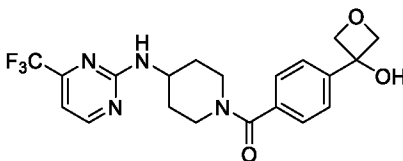


10

¹H NMR (DMSO-*d*₆) δ : 1.77 (m, 2H), 1.90-2.05 (m, 2H), 3.37 (m, 1H), 3.54 (m, 2H), 3.97 (m, 1H), 4.70 (d, *J* = 6.0 Hz, 2H), 4.79 (d, *J* = 6.0 Hz, 2H), 5.30 (s, 1H), 6.44 (s, -OH), 7.47 (d, *J* = 8.0 Hz, 2H), 7.63-7.69 (m, 3H), 8.99 (d, *J* = 4.4 Hz, 1H); ESI-MS: *m/z*, 424.14 (M+H)⁺, 100%.

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Example-75 : (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((4-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)methanone

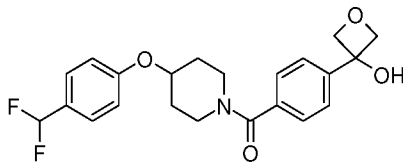


¹H NMR (DMSO-*d*₆) δ : 1.47 (m, 2H), 1.82-1.99 (m, 2H), 3.09 (m, 1H), 3.18 (m, 1H), 3.49 (m, 1H), 4.05 (m, 1H), 4.40 (m, 1H), 4.70 (d, *J* = 6.4 Hz, 2H), 4.79 (d, *J* = 6.8 Hz, 2H), 6.44 (s, -OH), 6.97 (d, *J* = 5.2 Hz, 1H), 7.42 (d, *J* = 8.4 Hz, 2H), 7.68 (d, *J* = 8.4 Hz, 2H), 7.97 (s, -NH), 8.62 (s, 1H); ESI-MS: *m/z*, 423.16 (M+H)⁺, 100%.

20

Example-76 : (4-(4-(difluoromethyl)phenoxy)piperidin-1-yl)(4-(3-hydroxyoxetan-3-yl)phenyl)methanone

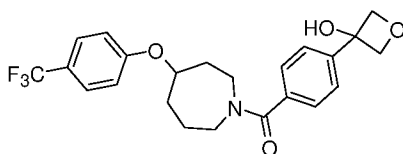
25



^1H NMR (DMSO- d_6) δ : 1.65 (m, 2H), 2.00 (m, 2H), 3.30-3.56 (m, 4H), 3.99 (m, 1H), 4.69 (d, J = 6.4 Hz, 2H), 4.75-4.79 (m, 3H), 6.44 (s, -OH), 7.11 (d, J = 8.4 Hz, 2H), 7.45-7.51 (m, 4H), 7.67 (d, J = 8.0 Hz, 2H); ESI-MS: m/z , 404.16 ($M+H$) $^+$, 100%.

5

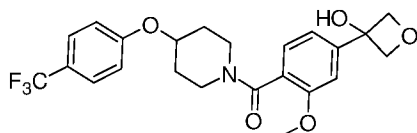
Example-77 : (4-(3-hydroxyoxetan-3-yl)phenyl)(4-(4-(trifluoromethyl)phenoxy)azepan-1-yl)methanone



^1H NMR (DMSO- d_6) δ : 1.63-2.16 (m, 6H), 3.33-3.57 (m, 2H), 3.64-3.79 (m, 2H), 4.69-4.89 (m, 5H), 6.43 (s, -OH), 7.09-7.15 (m, 2H), 7.45 (s, 2H), 7.64 (s, 4H); ESI-MS: m/z , 436.22 ($M+H$) $^+$, 100%.

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Example-78 : (4-(3-hydroxyoxetan-3-yl)-2-methoxyphenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone

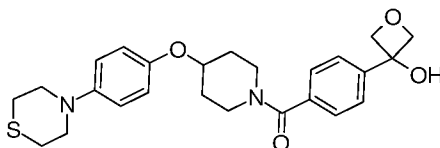


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^1H NMR (DMSO- d_6) δ : 1.52-1.66 (m, 2H), 1.90 (m, 1H), 2.00 (m, 1H), 3.10-3.28 (m, 1H), 3.33-3.45 (m, 2H), 3.84 (s, 3H), 4.02-4.06 (m, 1H), 4.72 (d, J = 6.4 Hz, 2H), 4.76-4.78 (m, 3H), 6.44 (s, -OH), 7.18 (t, J = 6.8 Hz, 2H), 7.25-7.27 (m, 3H), 7.64 (d, J = 8.8 Hz, 2H); ESI-MS: m/z , 452.22 ($M+H$) $^+$, 100%.

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Example-79 : (4-(3-hydroxyoxetan-3-yl)phenyl)(4-(4-thiomorpholinophenoxy)piperidin-1-yl)methanone

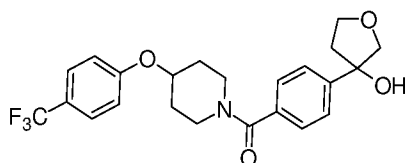


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^1H NMR (DMSO- d_6) δ : 1.59 (m, 2H), 1.87-2.05 (m, 2H), 2.67-2.69 (m, 4H), 3.30-3.58 (m, 5H), 3.42-3.57 (m, 2H), 3.96 (m, 1H), 4.49-4.51 (m, 1H), 4.69 (d, J = 6.8 Hz, 2H), 4.79 (d, J = 6.4 Hz, 2H), 6.44 (s, -OH), 6.88 (s, 4H), 7.44 (d, J = 8.4 Hz, 2H), 7.67 (d, J = 8.4 Hz, 2H); ESI-MS: m/z , 455.29 (M+H) $^+$, 100%.

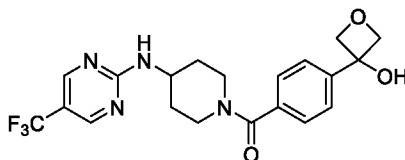
5

Example-80 : (4-(3-hydroxytetrahydrofuran-3-yl)phenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone



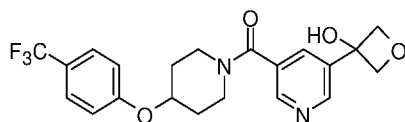
^1H NMR (DMSO- d_6) δ : 1.66 (m, 2H), 1.90-2.10 (m, 2H), 2.13-2.16 (m, 1H), 2.23-2.28 (m, 1H), 3.30-3.66 (m, 3H), 3.75 (d, J = 8.8 Hz, 1H), 3.80 (d, J = 8.8 Hz, 1H), 3.99-4.03 (m, 3H), 4.79-4.81 (m, 1H), 5.44 (s, -OH), 7.18 (d, J = 6.8 Hz, 2H), 7.40 (d, J = 8.4 Hz, 2H), 7.56 (d, J = 8.4 Hz, 2H), 7.65 (d, J = 8.8 Hz, 2H); ESI-MS: m/z , 436.27 (M+H) $^+$, 100%.

Example-81 (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)methanone



^1H NMR (DMSO- d_6) δ : 1.47 (m, 2H), 1.86-2.00 (m, 2H), 2.99 (m, 1H), 3.17 (m, 1H), 3.59-3.63 (m, 1H), 4.05-4.15 (m, H), 4.41 (m, 1H), 4.69 (d, J = 6.4 Hz, 2H), 4.78 (d, J = 6.4 Hz, 2H), 6.44 (s, -OH), 7.42 (d, J = 8.0 Hz, 2H), 7.68 (d, J = 8.0 Hz, 2H), 8.12 (d, J = 7.6 Hz, 1H), 8.63 (d, J = 9.6 Hz, 2H); ESI-MS: m/z , 423.10 (M+H) $^+$, 100%.

Example-82 : (5-(3-hydroxyoxetan-3-yl)pyridin-3-yl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone

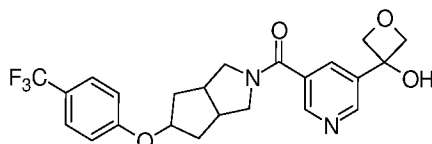


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^1H NMR (DMSO- d_6) δ : 1.91-2.11 (m, 4H), 3.47-3.51 (m, 1H), 3.69-3.70 (m, 1H), 3.84-3.91 (m, 1H), 3.96-4.00 (m, 1H), 4.70-4.73 (m, 1H), 4.86 (d, J = 8.0 Hz, 2H), 4.97 (d, J =

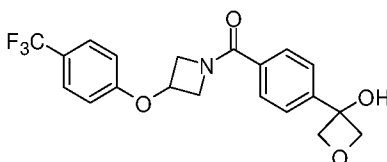
7.6 Hz, 2H), 6.99 (d, $J = 8.8$ Hz, 2H), 7.57 (d, $J = 8.8$ Hz, 2H), 8.05 (d, $J = 2.0$ Hz, 1H), 8.64 (d, $J = 2.0$ Hz, 1H), 9.00 (d, $J = 2.0$ Hz, 1H); ESI-MS: m/z 423.13 ($M+H$)⁺, 100%.

Example-83 : (5-(3-hydroxyoxetan-3-yl)pyridin-3-yl)(5-(4-(trifluoromethyl)phenoxy)hexahydrocyclopenta[c]pyrrol-2(1H)-yl)methanone



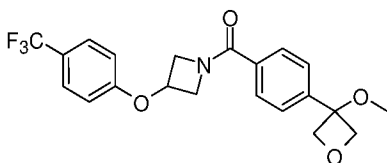
¹H NMR (DMSO-*d*₆) δ : 1.82-2.86 (m, 1H), 2.00-2.04 (m, 1H), 2.29-2.36 (m, 2H), 2.88-2.94 (m, 2H), 3.48-3.52 (m, 1H), 3.71-3.73 (m, 1H), 3.88-3.93 (m, 2H), 4.84 (d, $J = 7.2$ Hz, 2H), 4.90-4.94 (m, 1H), 4.95 (d, $J = 7.6$ Hz, 2H), 6.92 (d, $J = 8.8$ Hz, 2H), 7.55 (d, $J = 8.4$ Hz, 2H), 8.07 (d, $J = 2.0$ Hz, 1H), 8.68 (d, $J = 2.0$ Hz, 1H), 8.98 (d, $J = 2.4$ Hz, 1H); ESI-MS: m/z 449.15 ($M+H$)⁺, 100%.

Example-84 : (4-(3-hydroxyoxetan-3-yl)phenyl)(3-(4-(trifluoromethyl)phenoxy)azetidin-1-yl)methanone



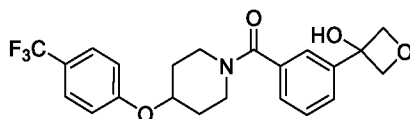
¹H NMR (DMSO-*d*₆) δ : 4.02-4.05 (m, 1H), 4.36-4.38 (m, 1H), 4.56-4.60 (m, 1H), 4.66 (d, $J = 6.8$ Hz, 2H), 4.73-4.75 (m, 1H), 4.78 (d, $J = 6.8$ Hz, 2H), 5.17-5.22 (m, 1H), 7.05 (d, $J = 8.8$ Hz, 2H), 7.67-7.72 (m, 6H); ESI-MS: m/z 394.11 ($M+H$)⁺, 100%.

Example-85 : (4-(3-methoxyoxetan-3-yl)phenyl)(3-(4-(trifluoromethyl)phenoxy)azetidin-1-yl)methanone



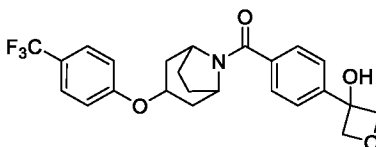
¹H NMR (DMSO-*d*₆) δ : 3.17 (s, 3H), 4.31-4.39 (m, 2H), 4.68-4.69 (m, 2H), 4.79 (d, $J = 7.6$ Hz, 2H), 4.96 (d, $J = 7.2$ Hz, 2H), 5.06-5.11 (m, 1H), 6.84 (d, $J = 8.8$ Hz, 2H), 7.55-7.60 (m, 4H), 7.72-7.74 (m, 2H). ESI-MS: m/z 408.14 ($M+H$)⁺, 100%.

Example-86 : (3-(3-hydroxyoxetan-3-yl)phenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone



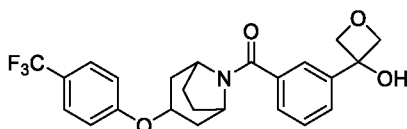
¹H NMR (DMSO-*d*₆) δ : 1.66-1.68 (m, 2H), 1.96-2.02 (m, 2H), 3.38-3.55 (m, 3H), 3.99-4.03 (m, 1H), 4.69 (d, *J* = 6.8 Hz, 2H), 4.78-4.83 (m, 3H), 6.46 (s, 1H), 7.18 (d, *J* = 8.8 Hz, 2H), 7.36 (d, *J* = 7.6 Hz, 1H), 7.48 (t, *J* = 7.6 Hz, 1H), 7.62-7.70 (m, 4H); ESI-MS: *m/z* 422.20 (M+H)⁺, 100%.

Example-87 : (4-(3-hydroxyoxetan-3-yl)phenyl)(3-(4-(trifluoromethyl)phenoxy)-8-azabicyclo[3.2.1]octan-8-yl)methanone



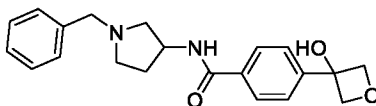
¹H NMR (DMSO-*d*₆) δ : 1.88-2.28 (m, 7H), 2.32-2.35 (m, 1H), 3.93-3.96 (m, 1H), 4.60-4.64 (m, 1H), 4.70 (d, *J* = 6.8 Hz, 2H), 4.79 (d, *J* = 6.8 Hz, 2H), 4.85-4.89 (m, 1H), 6.55 (br s, 1H), 7.08 (d, *J* = 8.8 Hz, 2H), 7.52 (d, *J* = 8.4 Hz, 2H), 7.57-7.70 (m, 4H); ESI-MS: *m/z* 448.14 (M+H)⁺, 100%.

Example-88 : (3-(3-hydroxyoxetan-3-yl)phenyl)(3-(4-(trifluoromethyl)phenoxy)-8-azabicyclo[3.2.1]octan-8-yl)methanone



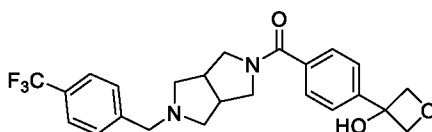
¹H NMR (DMSO-*d*₆) δ : 1.54-1.58 (m, 1H), 1.74-1.78 (m, 1H), 1.93-1.98 (m, 4H), 2.14-2.18 (m, 1H), 2.20-2.25 (m, 1H), 4.00-4.14 (m, 1H), 4.68-4.69 (m, 3H), 4.79 (d, *J* = 6.8 Hz, 2H), 4.98-5.03 (m, 1H), 6.47 (s, 1H), 7.20 (d, *J* = 8.4 Hz, 2H), 7.43-7.45 (m, 1H), 7.50 (t, *J* = 7.6 Hz, 1H), 7.62 (d, *J* = 8.8 Hz, 2H), 7.70-7.75 (m, 2H); ESI-MS: *m/z* 448.14 (M+H)⁺, 100%.

Example-89 : N-(1-benzylpyrrolidin-3-yl)-4-(3-hydroxyoxetan-3-yl)benzamide



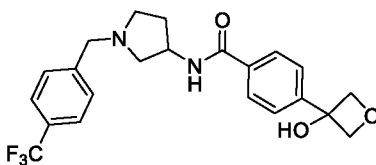
¹H NMR (DMSO-*d*₆) δ : 2.06-2.08 (m, 1H), 2.23-2.25 (m, 1H), 3.10-3.29 (m, 1H), 3.34-3.37 (m, 1H), 3.47-3.56 (m, 1H), 3.56-3.74 (m, 1H), 4.40-4.44 (m, 2H), 4.49-4.60 (m, 1H), 4.67 (t, *J* = 6.0 Hz, 2H), 4.79-4.81 (m, 2H), 6.52 (s, 1H), 7.48-7.54 (m, 5H), 7.70-7.74 (m, 2H), 7.87-7.90 (m, 2H), 8.59-8.76 (m, 1H); ESI-MS: *m/z* 353.19 (M+H)⁺, 100%.

Example-90 : 4-(3-hydroxyoxetan-3-yl)phenyl(5-(4-(trifluoromethyl)benzyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methanone



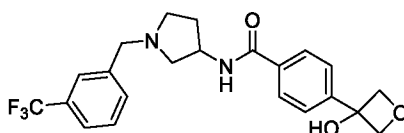
¹H NMR (DMSO-*d*₆) δ : 1.33-1.37 (m, 2H), 2.31-2.35 (m, 1H), 2.42-2.46 (m, 1H), 2.73-2.79 (m, 2H), 3.24-3.29 (m, 1H), 3.53-3.70 (m, 5H), 4.68 (d, *J* = 6.4 Hz, 2H), 4.79 (d, *J* = 6.4 Hz, 2H), 6.45 (s, 1H), 7.50-7.54 (m, 4H), 7.65-7.69 (m, 4H); ESI-MS: *m/z* 447.19 (M+H)⁺, 100%.

Example-91 : 4-(3-hydroxyoxetan-3-yl)-N-(1-(4-(trifluoromethyl)benzyl)pyrrolidin-3-yl)benzamide



¹H NMR (DMSO-*d*₆) δ : 1.80-1.84 (m, 1H), 2.13-2.21 (m, 1H), 2.43-2.48 (m, 1H), 2.58-2.67 (m, 2H), 2.80-2.86 (m, 1H), 3.70 (s, 2H), 4.40-4.43 (m, 1H), 4.67 (d, *J* = 6.8 Hz, 2H), 4.79 (d, *J* = 6.8 Hz, 2H), 6.47 (s, 1H), 7.56 (d, *J* = 7.6 Hz, 2H), 7.62-7.70 (m, 4H), 7.88 (d, *J* = 8.4 Hz, 2H), 8.48 (d, *J* = 6.8 Hz, 1H); ESI-MS: *m/z* 421.17 (M+H)⁺, 100%.

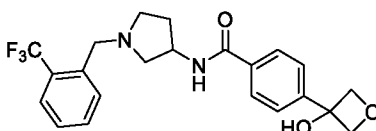
Example-92 : 4-(3-hydroxyoxetan-3-yl)-N-(1-(3-(trifluoromethyl)benzyl)pyrrolidin-3-yl)benzamide



^1H NMR (DMSO- d_6) δ : 1.80-1.87 (m, 1H), 2.12-2.21 (m, 1H), 2.42-2.46 (m, 1H), 2.53-2.55 (m, 1H), 2.62-2.68 (m, 1H), 2.80-2.84 (m, 1H), 3.70 (s, 2H), 4.36-4.45 (m, 1H), 4.67 (d, J = 6.8 Hz, 2H), 4.79 (d, J = 6.8 Hz, 2H), 6.47 (s, 1H), 7.55-7.68 (m, 6H), 7.88 (d, J = 8.4 Hz, 2H), 8.48 (d, J = 7.2 Hz, 1H); ESI-MS: m/z 421.17 ($M+H$) $^+$, 100%.

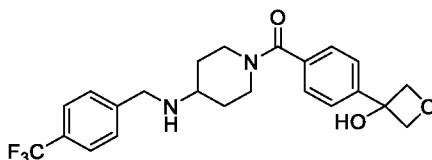
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Example-93 : 4-(3-hydroxyoxetan-3-yl)-N-(1-(2-(trifluoromethyl)benzyl)pyrrolidin-3-yl)benzamide



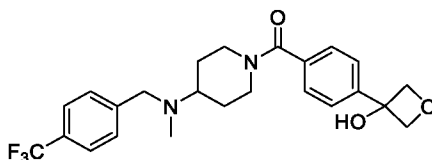
^1H NMR (DMSO- d_6) δ : 1.80-1.87 (m, 1H), 2.14-2.22 (m, 1H), 2.45-2.47 (m, 1H), 2.55-2.61 (m, 1H), 2.64-2.70 (m, 1H), 2.86-2.90 (m, 1H), 3.78 (s, 2H), 4.40-4.45 (m, 1H), 4.68 (d, J = 6.8 Hz, 2H), 4.79 (d, J = 6.8 Hz, 2H), 6.47 (s, 1H), 7.46 (t, J = 7.6 Hz, 1H), 7.64-7.70 (m, 4H), 7.82 (d, J = 7.6 Hz, 1H), 7.89 (d, J = 8.4 Hz, 2H), 8.48 (d, J = 6.8 Hz, 1H); ESI-MS: m/z 421.17 ($M+H$) $^+$, 100%.

Example-94 : (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((4-(trifluoromethyl)benzyl)amino)piperidin-1-yl)methanone



^1H NMR (DMSO- d_6) δ : 1.53-1.55 (m, 2H), 1.67-1.76 (m, 2H), 2.84-3.00 (m, 1H), 3.12-3.20 (m, 1H), 3.23-3.30 (m, 3H), 4.29-4.32 (m, 2H), 4.34-4.40 (m, 1H), 4.68 (d, J = 6.4 Hz, 2H), 4.79 (d, J = 6.4 Hz, 2H), 6.63 (s, 1H), 7.34 (d, J = 8.4 Hz, 2H), 7.57 (d, J = 8.4 Hz, 2H), 7.68-7.86 (m, 4H); ESI-MS: m/z 435.2 ($M+H$) $^+$, 100%.

Example-95 : (4-(3-hydroxyoxetan-3-yl)phenyl)(4-(methyl(4-(trifluoromethyl)benzyl)amino)piperidin-1-yl)methanone

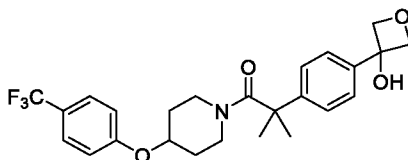


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^1H NMR (DMSO- d_6) δ : 1.50-1.58 (m, 2H), 1.67-1.70 (m, 1H), 1.91-1.95 (m, 2H), 2.26 (s, 3H), 3.23-3.30 (m, 2H), 3.67-3.70 (m, 2H), 4.12 (s, 2H), 4.68 (d, J = 6.4 Hz, 2H), 4.78

(d, $J = 6.4$ Hz, 2H), 6.40 (s, 1H), 7.42 (d, $J = 8.4$ Hz, 2H), 7.56 (d, $J = 8.4$ Hz, 2H), 7.66-7.68 (m, 4H); ESI-MS: m/z 449.2 (M+H)⁺, 100%.

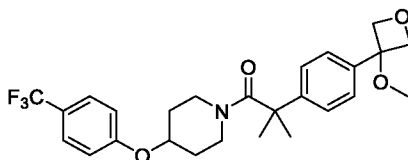
Example-96 : 2-(4-(3-hydroxyoxetan-3-yl)phenyl)-2-methyl-1-(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)propan-1-one



¹H NMR (DMSO-*d*₆) δ : 1.18-1.28 (m, 2H), 1.45 (s, 6H), 1.61-1.64 (m, 2H), 2.85-2.95 (m, 2H), 3.23-3.29 (m, 2H), 4.54-4.61 (m, 1H), 4.66 (d, $J = 6.8$ Hz, 2H), 4.76 (d, $J = 6.8$ Hz, 2H), 6.33 (s, 1H), 7.08 (d, $J = 8.4$ Hz, 2H), 7.26 (d, $J = 8.4$ Hz, 2H), 7.57-7.61 (m, 4H);

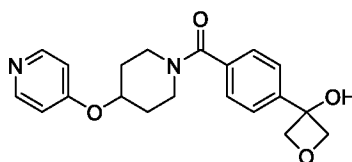
ESI-MS: m/z 464.21 (M+H)⁺, 100%.

Example-97 : 2-(4-(3-methoxyoxetan-3-yl)phenyl)-2-methyl-1-(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)propan-1-one



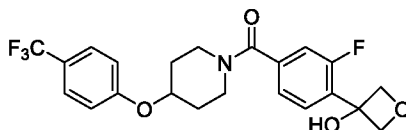
¹H NMR (CDCl₃) δ : 1.40-1.44 (m, 2H), 1.58 (s, 6H), 1.69-1.79 (m, 2H), 3.13 (s, 3H), 3.14-3.20 (m, 1H), 3.65-3.75 (m, 2H), 4.45-4.48 (m, 1H), 4.83 (d, $J = 7.2$ Hz, 2H), 4.95 (d, $J = 7.2$ Hz, 2H), 5.32 (s, 1H), 6.89 (d, $J = 8.4$ Hz, 2H), 7.33 (d, $J = 8.8$ Hz, 2H), 7.45 (d, $J = 8.8$ Hz, 2H), 7.51 (d, $J = 8.4$ Hz, 2H); ESI-MS: m/z 478.22 (M+H)⁺, 100%.

Example-98: (4-(3-hydroxyoxetan-3-yl)phenyl)(4-(pyridin-4-yloxy)piperidin-1-yl)methanone



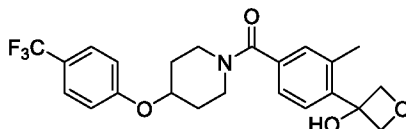
¹H NMR (DMSO-*d*₆) δ : 1.62-1.68 (m, 2H), 1.97-2.05 (m, 2H), 3.34-3.38 (m, 2H), 3.53-3.58 (m, 1H), 4.00-4.05 (m, 1H), 4.69 (d, $J = 6.8$ Hz, 2H), 4.79 (d, $J = 6.8$ Hz, 2H), 4.80-4.84 (m, 1H), 6.45 (s, 1H), 7.02 (d, $J = 6.4$ Hz, 2H), 7.46 (d, $J = 8.4$ Hz, 2H), 7.67 (d, $J = 8.4$ Hz, 2H), 8.38 (d, $J = 6.4$ Hz, 2H); ESI-MS: m/z 355.17 (M+H)⁺, 100%.

Example-99 : (3-fluoro-4-(3-hydroxyoxetan-3-yl)phenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone



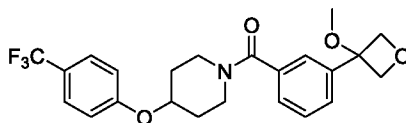
¹H NMR (DMSO-*d*₆) δ : 1.65-1.69 (m, 2H), 1.97-2.04 (m, 2H), 3.29-3.32 (m, 1H), 3.46-3.50 (m, 2H), 3.97-4.01 (m, 1H), 4.70 (d, *J* = 7.2 Hz, 2H), 4.79-4.82 (m, 1H), 4.98 (d, *J* = 7.2 Hz, 2H), 6.45 (s, 1H), 7.18 (d, *J* = 8.8 Hz, 2H), 7.25-7.33 (m, 2H), 7.51 (d, *J* = 8.0 Hz, 1H), 7.65 (d, *J* = 8.8 Hz, 2H); ESI-MS: *m/z* 440.15 (M+H)⁺, 100%.

Example-100 : (4-(3-hydroxyoxetan-3-yl)-3-methylphenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone



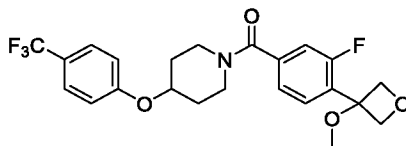
¹H NMR (DMSO-*d*₆) δ : 1.63-1.67 (m, 2H), 1.97-2.02 (m, 2H), 2.21 (s, 3H), 2.99-3.32 (m, 1H), 3.35-3.39 (m, 1H), 3.55-3.59 (m, 1H), 3.98-4.01 (m, 1H), 4.70 (d, *J* = 6.8 Hz, 2H), 4.78-4.82 (m, 1H), 5.04 (d, *J* = 6.8 Hz, 2H), 6.17 (s, 1H), 7.18 (d, *J* = 8.4 Hz, 2H), 7.21-7.24 (m, 2H), 7.29 (d, *J* = 7.6 Hz, 1H), 7.65 (d, *J* = 8.4 Hz, 2H); ESI-MS: *m/z* 436.17 (M+H)⁺, 100%.

Example-101 : (3-(3-methoxyoxetan-3-yl)phenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone



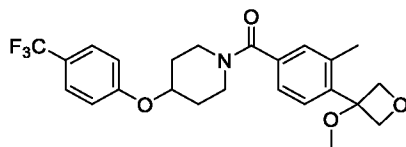
¹H NMR (CDCl₃) δ : 1.86-2.14 (m, 4H), 3.18 (s, 3H), 3.42-3.45 (m, 1H), 3.67-3.70 (m, 1H), 3.89-3.93 (m, 2H), 4.67-4.72 (m, 1H), 4.82 (d, *J* = 6.8 Hz, 2H), 4.96 (d, *J* = 6.8 Hz, 2H), 7.00 (d, *J* = 8.8 Hz, 2H), 7.41-7.43 (m, 1H), 7.51 (t, *J* = 7.6 Hz, 1H), 7.55-7.58 (m, 4H); ESI-MS: *m/z* 436.17 (M+H)⁺, 100%.

Example-102 : (3-fluoro-4-(3-methoxyoxetan-3-yl)phenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone



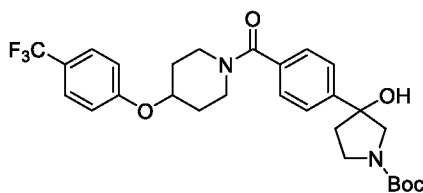
¹H NMR (CDCl₃) δ : 1.95-2.14 (m, 4H), 3.17 (s, 3H), 3.42-3.45 (m, 1H), 3.68-3.72 (m, 1H), 3.82-3.89 (m, 2H), 4.68-4.73 (m, 1H), 4.95 (d, J = 6.8 Hz, 2H), 5.05 (d, J = 6.8 Hz, 2H), 7.00 (d, J = 8.4 Hz, 2H), 7.18-7.21 (m, 1H), 7.25-7.31 (m, 2H), 7.58 (d, J = 8.4 Hz, 2H); ESI-MS: m/z 454.20 (M+H)⁺, 100%.

Example-103 : (4-(3-methoxyoxetan-3-yl)-3-methylphenyl)(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone



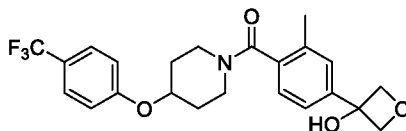
¹H NMR (CDCl₃) δ : 1.87-2.09 (m, 4H), 2.24 (s, 3H), 3.03 (s, 3H), 3.41-3.46 (m, 1H), 3.67-3.71 (m, 1H), 3.87-3.93 (m, 2H), 4.67-4.71 (m, 1H), 4.92 (d, J = 7.2 Hz, 2H), 5.00 (d, J = 7.2 Hz, 2H), 7.00 (d, J = 8.8 Hz, 2H), 7.20-7.27 (m, 3H), 7.57 (d, J = 8.8 Hz, 2H); ESI-MS: m/z 450.23 (M+H)⁺, 100%.

Example-104 : *tert*-butyl 3-hydroxy-3-(4-(4-(4-(trifluoromethyl)phenoxy)piperidine-1-carbonyl)phenyl)pyrrolidine-1-carboxylate



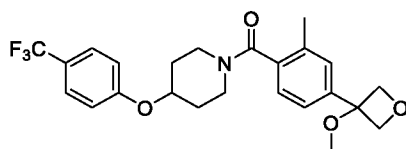
¹H NMR (DMSO-*d*₆) δ : 1.42 (d, J = 11.2 Hz, 9H), 1.63-1.69 (m, 2H), 1.99-2.05 (m, 3H), 2.21-2.28 (m, 1H), 3.41-3.55 (m, 7H), 3.99-4.03 (m, 1H), 4.78-4.81 (m, 1H), 5.50 (s, 1H), 7.18 (d, J = 8.4 Hz, 2H), 7.40 (d, J = 8.4 Hz, 2H), 7.57 (d, J = 8.4 Hz, 2H), 7.65 (d, J = 8.4 Hz, 2H).

Example-105 : (4-(3-hydroxyoxetan-3-yl)-2-methylphenyl)(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone



¹H NMR (DMSO-*d*₆) δ : 1.53-1.58 (m, 1H), 1.64-1.72 (m, 1H), 1.87-1.93 (m, 1H), 2.02-2.07 (m, 1H), 2.26 (s, 3H), 3.14-3.20 (m, 1H), 3.34-3.44 (m, 2H), 3.55-3.63 (m, 1H), 4.69 (d, *J* = 6.8 Hz, 2H), 4.76 (d, *J* = 6.8 Hz, 2H), 4.77-4.80 (m, 1H), 6.38 (s, 1H), 7.17 (d, *J* = 8.4 Hz, 2H), 7.23 (d, *J* = 8.0 Hz, 1H), 7.45-7.50 (m, 2H), 7.64 (d, *J* = 8.4 Hz, 2H); ESI-MS: *m/z* 436.25 (M+H)⁺, 100%.

Example-106 : (4-(3-methoxyoxetan-3-yl)-2-methylphenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone

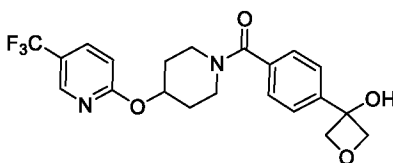


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¹H NMR (CDCl₃) δ : 1.77-1.82 (m, 1H), 1.87-1.92 (m, 1H), 1.95-2.00 (m, 1H), 2.06-2.10 (m, 1H), 2.39 (s, 3H), 3.16 (s, 3H), 3.23-3.29 (m, 1H), 3.50-3.57 (m, 1H), 3.87-3.91 (m, 1H), 3.98-4.02 (m, 1H), 4.67-4.71 (m, 1H), 4.82 (d, *J* = 6.8 Hz, 2H), 4.94 (d, *J* = 6.8 Hz, 2H), 6.99 (d, *J* = 8.8 Hz, 2H), 7.25-7.27 (m, 1H), 7.33 (d, *J* = 7.6 Hz, 2H), 7.57 (d, *J* = 8.8 Hz, 2H); ESI-MS: *m/z* 450.25 (M+H)⁺, 100%.

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Example-107 : (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((5-(trifluoromethyl)pyridin-2-yl)oxy)piperidin-1-yl)methanone

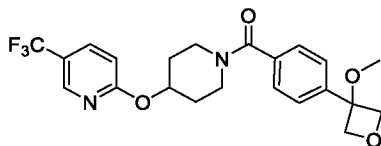


¹H NMR (DMSO-*d*₆) δ : 1.64-1.72 (m, 2H), 2.01-2.06 (m, 2H), 2.47-2.49 (m, 2H), 3.56-3.59 (m, 1H), 4.01-4.05 (m, 1H), 4.69 (d, *J* = 6.8 Hz, 2H), 4.79 (d, *J* = 6.8 Hz, 2H), 5.35-5.39 (m, 1H), 6.45 (s, 1H), 7.01 (d, *J* = 8.8 Hz, 1H), 7.46 (d, *J* = 8.4 Hz, 2H), 7.68 (d, *J* = 8.4 Hz, 2H), 8.08 (dd, *J* = 8.8 Hz & 2.4 Hz, 1H), 8.58 (d, *J* = 2.4 Hz, 1H); ESI-MS: *m/z* 423.15 (M+H)⁺, 100%.

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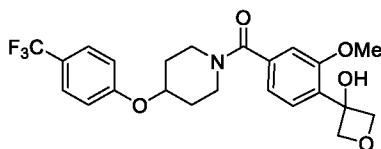
Example-108 : (4-(3-methoxyoxetan-3-yl)phenyl)(4-((5-(trifluoromethyl)pyridin-2-yl)oxy)piperidin-1-yl)methanone

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¹H NMR (DMSO-*d*₆) δ : 1.69-1.73 (m, 2H), 2.02-2.06 (m, 2H), 2.47-2.49 (m, 1H), 3.05 (s, 3H), 3.35-3.58 (m, 1H), 3.55-3.58 (m, 1H), 3.99-4.03 (m, 1H), 4.76 (d, *J* = 6.8 Hz, 2H), 4.80 (d, *J* = 6.8 Hz, 2H), 5.35-5.39 (m, 1H), 7.02 (d, *J* = 8.8 Hz, 1H), 7.49 (d, *J* = 8.4 Hz, 2H), 7.53 (d, *J* = 8.4 Hz, 2H), 8.08 (dd, *J* = 8.8 Hz & 2.4 Hz, 1H), 8.59 (d, *J* = 2.4 Hz, 1H); ESI-MS: *m/z* 437.05 (M+H)⁺, 100%.

Example-109 : (4-(3-hydroxyoxetan-3-yl)-3-methoxyphenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone

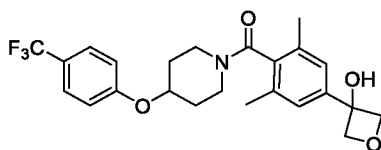


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¹H NMR (DMSO-*d*₆) δ : 1.66-1.69 (m, 2H), 1.96-2.01 (m, 2H), 2.29-2.33 (m, 1H), 3.36-3.45 (m, 1H), 3.52-3.62 (m, 1H), 3.80 (s, 3H), 3.96-4.04 (m, 1H), 4.63 (d, *J* = 6.8 Hz, 2H), 4.79-4.81 (m, 1H), 4.96 (d, *J* = 6.8 Hz, 2H), 5.93 (s, 1H), 6.98 (d, *J* = 8.0 Hz, 1H), 7.04 (s, 1H), 7.18 (d, *J* = 8.8 Hz, 2H), 7.27 (d, *J* = 8.0 Hz, 1H), 7.65 (d, *J* = 8.8 Hz, 2H); ESI-MS: *m/z* 452.22 (M+H)⁺, 100%.

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Example-110: (4-(3-hydroxyoxetan-3-yl)-2,6-dimethylphenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone

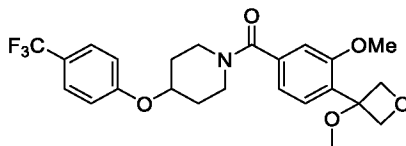


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¹H NMR (DMSO-*d*₆) δ : 1.53-1.56 (m, 1H), 1.66-1.69 (m, 1H), 1.89-1.91 (m, 1H), 2.04-2.09 (m, 1H), 2.20 (s, 3H), 2.22 (s, 3H), 3.15-3.18 (m, 1H), 3.28-3.32 (m, 1H), 3.49-3.54 (m, 1H), 4.08-4.12 (m, 1H), 4.68 (d, *J* = 6.8 Hz, 2H), 4.76 (d, *J* = 6.8 Hz, 2H), 4.77-4.81 (m, 1H), 6.32 (s, 1H), 7.17 (d, *J* = 8.8 Hz, 2H), 7.30 (s, 2H), 7.65 (d, *J* = 8.8 Hz, 2H); ESI-MS: *m/z* 450.24 (M+H)⁺, 100%.

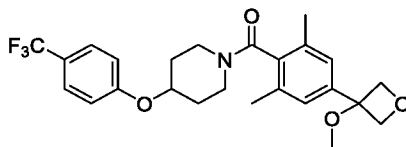
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Example-111 : (3-methoxy-4-(3-methoxyoxetan-3-yl)phenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone



¹H NMR (DMSO-*d*₆) δ : 1.66-1.69 (m, 2H), 1.97-2.00 (m, 2H), 2.97 (s, 3H), 3.34-3.45 (m, 1H), 3.78 (s, 3H), 3.76-3.79 (m, 1H), 4.71 (d, *J* = 7.6 Hz, 2H), 4.79-4.82 (m, 1H), 4.88 (d, *J* = 7.6 Hz, 2H), 7.01 (dd, *J* = 8.0 Hz & 1.2 Hz, 1H), 6.32 (s, 1H), 7.07 (d, *J* = 1.2 Hz, 2H), 7.18 (d, *J* = 8.4 Hz, 2H), 7.26 (d, *J* = 8.0 Hz, 1H), 7.65 (d, *J* = 8.4 Hz, 2H); ESI-MS: *m/z* 465.8 (M+H)⁺, 100%.

Example-112 : (4-(3-methoxyoxetan-3-yl)-2,6-dimethylphenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone

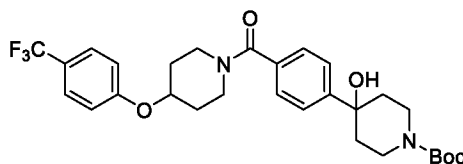


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¹H NMR (DMSO-*d*₆) δ : 1.56-1.60 (m, 1H), 1.64-1.71 (m, 1H), 1.89-1.93 (m, 1H), 2.03-2.08 (m, 1H), 2.21 (s, 3H), 2.23 (s, 3H), 3.02 (s, 3H), 3.12-3.18 (m, 1H), 3.19-3.28 (m, 1H), 3.49-3.55 (m, 1H), 4.08-4.12 (m, 1H), 4.75-4.80 (m, 5H), 7.15-7.19 (m, 4H), 7.65 (d, *J* = 8.8 Hz, 2H); ESI-MS: *m/z* 463.8 (M+H)⁺, 100%.

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Example-113 : *tert*-butyl 4-hydroxy-4-(4-(4-(4-(trifluoromethyl)phenoxy)piperidine-1-carbonyl)phenyl)piperidine-1-carboxylate

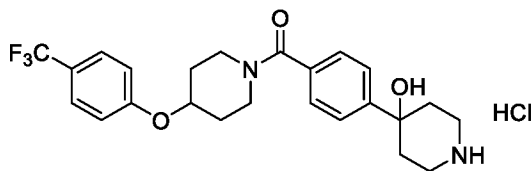


¹H NMR (CDCl₃) δ : 1.50 (s, 9H), 1.66-1.71 (m, 2H), 1.74-2.00 (m, 6H), 2.82 (s, 1H), 2.90 (s, 1H), 2.98 (s, 1H), 3.25 (m, 2H), 3.44 (m, 1H), 3.69-3.73 (m, 1H), 3.89 (m, 2H), 4.06 (m, 2H), 4.68 (m, 1H), 5.32 (s, 1H), 6.99 (d, *J* = 8.4 Hz, 2H), 7.41 (d, *J* = 8.4 Hz, 2H), 7.51 (d, *J* = 8.0 Hz, 2H), 7.57 (d, *J* = 8.4 Hz, 2H).

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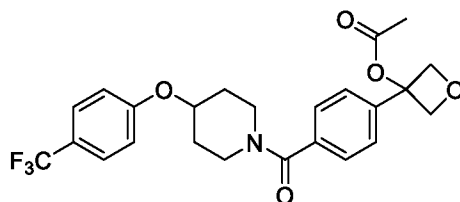
Example-114 : (4-(4-hydroxypiperidin-4-yl) phenyl)(4-(4-(trifluoromethyl) phenoxy) piperidin-1-yl) methanone hydrochloride

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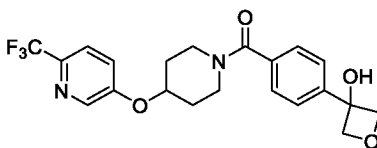
¹H NMR (DMSO-*d*₆) δ : 1.66-1.71 (m, 2H), 1.74-2.00 (m, 6H), 2.82 (s, 1H), 2.90 (s, 1H), 2.98 (s, 1H), 3.25 (m, 2H), 3.44 (m, 1H), 3.69-3.73 (m, 1H), 3.89 (m, 2H), 4.06 (m, 2H), 4.81 (m, 1H), 5.53 (s, 1H), 6.99 (d, *J* = 8.4 Hz, 2H), 7.41 (d, *J* = 8.4 Hz, 2H), 7.51 (d, *J* = 8.0 Hz, 2H), 7.57 (d, *J* = 8.4 Hz, 2H), 8.42 (br s, 2H); ESI-MS: *m/z* 449.12 (M+H)⁺, 100%.

Example-115 : 3-(4-(4-(4-(trifluoromethyl)phenoxy)piperidine-1-carbonyl)phenyl)oxetan-3-yl acetate



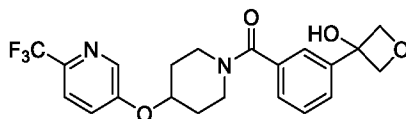
¹H NMR (CDCl₃) δ : 1.67 (m, 2H), 1.99 (m, 2H), 2.33 (s, 3H), 3.38-3.43 (m, 2H), 3.99 (m, 2H), 4.82 (d, *J* = 8.0 Hz, 3H), 4.95 (d, *J* = 8.0 Hz, 2H), 7.18 (d, *J* = 8.4 Hz, 2H), 7.48 (d, *J* = 8.4 Hz, 2H), 7.57 (d, *J* = 8.4 Hz, 2H), 7.65 (d, *J* = 8.8 Hz, 2H); ESI-MS: *m/z*, 464.20 (M+H)⁺, 100%.

Example-116 : (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((6-(trifluoromethyl)pyridin-3-yl)oxy)piperidin-1-yl)methanone.



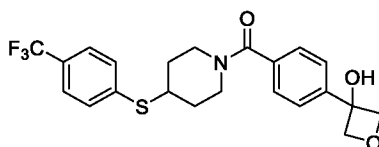
¹H NMR (DMSO-*d*₆) δ : 1.69 (m, 2H), 2.02 (m, 2H), 3.38 (m, 2H), 3.56-3.60 (m, 1H), 4.00-4.06 (m, 1H), 4.69 (d, *J* = 6.8 Hz, 2H), 4.79 (d, *J* = 6.8 Hz, 2H), 4.89-4.93 (m, 1H), 6.42 (s, 1H), 7.46 (d, *J* = 8.0 Hz, 2H), 7.67-7.72 (m, 3H), 7.85 (d, *J* = 9.2 Hz, 1H), 8.49 (s, 1H); ESI-MS: *m/z* 423.01 (M+H)⁺, 100%.

Example-117 : (3-(3-hydroxyoxetan-3-yl)phenyl)(4-((6-(trifluoromethyl)pyridin-3-yl)oxy)piperidin-1-yl)methanone.



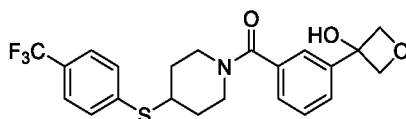
¹H NMR (DMSO-*d*₆) δ : 1.70 (m, 2H), 2.02 (m, 2H), 3.40-3.47 (m, 3H), 4.00 (m, 1H), 4.69 (d, *J* = 6.4 Hz, 2H), 4.79 (d, *J* = 6.4 Hz, 2H), 4.91 (s, 1H), 6.47 (s, 1H), 7.36 (d, *J* = 7.2 Hz, 1H), 7.49 (t, *J* = 8.0 Hz, 1H), 7.62 (s, 1H), 7.70 (d, *J* = 8.0 Hz, 2H), 7.85 (d, *J* = 8.8 Hz, 1H), 8.49 (s, 1H); ESI-MS: *m/z* 423.12 (M+H)⁺, 100%.

Example-118 : (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((4-(trifluoromethyl)phenyl)thio)piperidin-1-yl)methanone



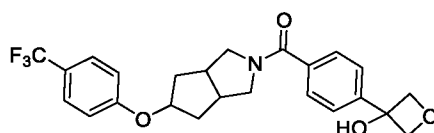
¹H NMR (DMSO-*d*₆) δ : 1.54 (m, 2H), 2.02 (m, 2H), 3.18 (m, 2H), 3.46-3.61 (m, 1H), 3.79 (s, 1H), 4.31 (m, 1H), 4.68 (d, *J* = 6.0 Hz, 2H), 4.78 (d, *J* = 6.0 Hz, 2H), 6.44 (s, 1H), 7.43 (d, *J* = 7.6 Hz, 2H), 7.58 (d, *J* = 8.0 Hz, 2H), 7.66 (m, 4H); ESI-MS: *m/z* 438.09 (M+H)⁺, 100%.

Example-119 : (3-(3-hydroxyoxetan-3-yl)phenyl)(4-((4-(trifluoromethyl)phenyl)thio)piperidin-1-yl)methanone



¹H NMR (DMSO-*d*₆) δ : 1.51-1.55 (m, 2H), 1.99-2.02 (m, 2H), 3.18 (m, 2H), 3.61 (m, 1H), 3.79 (s, 1H), 4.31 (m, 1H), 4.68 (d, *J* = 6.8 Hz, 2H), 4.79 (d, *J* = 6.8 Hz, 2H), 6.45 (s, 1H), 7.33 (d, *J* = 8.8 Hz, 1H), 7.47 (t, *J* = 7.8 Hz, 1H), 7.58 (d, *J* = 7.2 Hz, 3H), 7.66-7.70 (m, 3H); ESI-MS: *m/z* 438.16 (M+H)⁺, 100%.

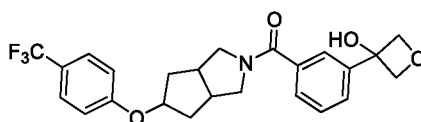
Example-120 : (4-(3-hydroxyoxetan-3-yl)phenyl)(5-(4-(trifluoromethyl)phenoxy)hexahydrocyclopenta[c]pyrrol-2(1H)-yl)methanone



^1H NMR (DMSO- d_6) δ : 1.45-1.49 (m, 2H), 1.91-2.05 (m, 1H), 2.10-2.15 (m, 1H), 2.49-2.50 (m, 4H), 3.70-3.80 (m, 3H), 4.67 (d, J = 6.8 Hz, 2H), 4.77 (d, J = 6.8 Hz, 2H), 6.43 (s, 1H), 7.06 (d, J = 8.4 Hz, 2H), 7.49 (d, J = 6.6 Hz, 2H), 7.63-7.95 (m, 4H); ESI-MS: m/z 448.16 (M+H) $^+$, 100%.

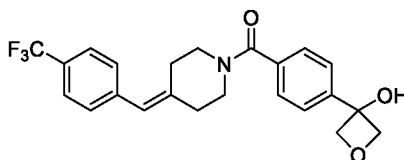
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Example-121 : (3-(3-hydroxyoxetan-3-yl)phenyl)(5-(4-(trifluoromethyl)phenoxy)hexahydrocyclopenta[c]pyrrol-2(1H)-yl)methanone



^1H NMR (DMSO- d_6) δ : 1.58-1.62 (m, 1H), 1.74-1.78 (m, 1H), 2.23-2.33 (m, 2H), 2.68-2.69 (m, 2H), 3.32 (d, J = 8.0 Hz, 1H), 3.56-3.68 (m, 4H), 4.65 (d, J = 6.4 Hz, 2H), 4.77 (d, J = 8.0 Hz, 2H), 4.95-4.99 (m, 1H), 7.06 (d, J = 8.4 Hz, 2H), 7.13-7.23 (m, 1H), 7.34-7.36 (m, 1H), 7.62-7.64 (m, 2H), 7.68-7.77 (m, 2H); ESI-MS: m/z 448.14 (M+H) $^+$, 80%.

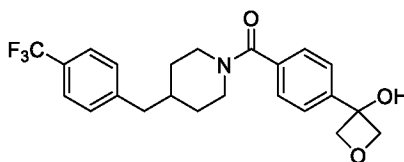
Example-122: (4-(3-hydroxyoxetan-3-yl)phenyl)(4-(4-(trifluoromethyl)benzylidene)piperidin-1-yl)methanone



^1H NMR (DMSO- d_6) δ : 2.01 (m, 2H), 2.23 (m, 2H), 3.43 (m, 2H), 3.83 (m, 2H), 4.69 (s, 2H), 4.78 (s, 2H), 6.46 (s, 1H), 6.49 (s, 1H), 7.43-7.48 (m, 4H), 7.665-7.69 (m, 4H); ESI-MS: m/z 418.21 (M+H) $^+$, 100%.

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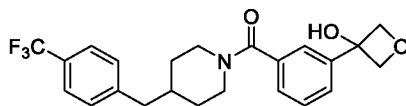
Example-123 : (4-(3-hydroxyoxetan-3-yl)phenyl)(4-(4-(trifluoromethyl)benzyl)piperidin-1-yl)methanone



^1H NMR (DMSO- d_6) δ : 1.01-1.09 (m, 2H), 1.16-1.26 (m, 2H), 1.81-1.87 (m, 1H), 2.64 (d, J = 7.2 Hz, 2H), 2.67 (m, 1H), 2.97 (m, 1H), 3.57 (m, 1H), 4.45 (m, 1H), 4.68 (d, J = 6.8 Hz, 2H), 4.78 (d, J = 6.8 Hz, 2H), 6.43 (s, 1H), 7.38-7.43 (m, 4H), 7.63-7.67 (m, 4H); ESI-MS: m/z 420.17 (M+H) $^+$, 100%.

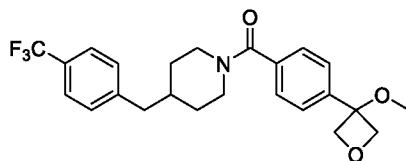
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Example-124 : (3-(3-hydroxyoxetan-3-yl)phenyl)(4-(4-(trifluoromethyl)benzyl)piperidin-1-yl)methanone



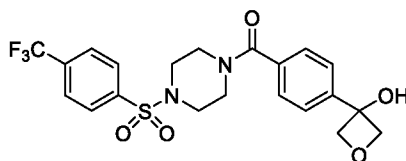
¹H NMR (DMSO-*d*₆) δ : 1.17 (m, 2H), 1.63 (m, 1H), 1.73 (m, 1H), 1.85 (m, 1H), 2.66 (d, $J = 7.6$ Hz, 2H), 2.71 (m, 1H), 2.98 (m, 1H), 3.56 (m, 1H), 4.46 (m, 1H), 4.67 (d, $J = 6.4$ Hz, 2H), 4.78 (d, $J = 6.4$ Hz, 2H), 6.45 (s, 1H), 7.29 (d, $J = 7.6$ Hz, 1H), 7.41-7.49 (m, 3H), 7.56 (s, 1H), 7.60-7.69 (m, 3H); ESI-MS: m/z 420.20 (M+H)⁺, 100%.

Example-125 : (4-(3-methoxyoxetan-3-yl)phenyl)(4-(4-(trifluoromethyl)benzyl)piperidin-1-yl)methanone



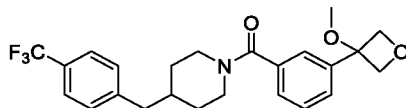
¹H NMR (DMSO-*d*₆) δ : 1.18 (m, 2H), 1.51 (m, 1H), 1.64 (m, 1H), 1.81-1.87 (m, 1H), 2.65 (d, $J = 7.2$ Hz, 2H), 2.67 (m, 1H), 2.97 (m, 1H), 3.07 (s, 3H), 3.55 (m, 1H), 4.46 (m, 1H), 4.74-4.80 (m, 4H), 7.42 (d, $J = 8.0$ Hz, 4H), 7.51 (d, $J = 8.4$ Hz, 2H), 7.65 (d, $J = 8.0$ Hz, 2H); ESI-MS: m/z 434.19 (M+H)⁺, 100%.

Example-126 : (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((4-(trifluoromethyl)phenyl)sulfonyl)piperazin-1-yl)methanone



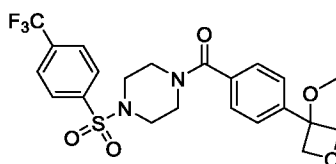
¹H NMR (DMSO-*d*₆) δ : 3.08 (m, 4H), 3.39 (m, 2H), 3.45 (m, 2H), 4.66 (d, $J = 6.8$ Hz, 2H), 4.77 (d, $J = 6.8$ Hz, 2H), 6.44 (s, 1H), 7.39 (d, $J = 7.6$ Hz, 2H), 7.63 (d, $J = 8.4$ Hz, 2H), 7.97 (d, $J = 8.4$ Hz, 2H), 8.05 (d, $J = 8.4$ Hz, 2H); ESI-MS: m/z 471.30 (M+H)⁺, 100%.

Example-127: (3-(3-methoxyoxetan-3-yl)phenyl)(4-(4-(trifluoromethyl)benzyl)piperidin-1-yl)methanone



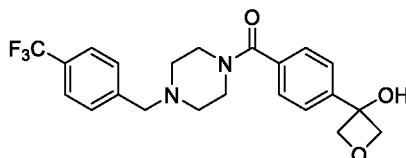
¹H NMR (DMSO-*d*₆) δ : 1.16-1.26 (m, 2H), 1.81-1.90 (m, 3H), 2.66 (d, *J* = 7.6 Hz, 2H), 2.71 (m, 1H), 2.98 (m, 1H), 3.16 (s, 3H), 3.56 (m, 1H), 4.46 (m, 1H), 4.67 (d, *J* = 6.4 Hz, 2H), 4.78 (d, *J* = 6.4 Hz, 2H), 7.29 (d, *J* = 7.6 Hz, 1H), 7.41-7.49 (m, 3H), 7.56 (s, 1H), 7.60-7.69 (m, 3H); ESI-MS: *m/z* 434.19 (M+H)⁺, 100%.

Example-128 : (4-(3-methoxyoxetan-3-yl)phenyl)(4-((4-(trifluoromethyl)phenyl)sulfonyl)piperazin-1-yl)methanone



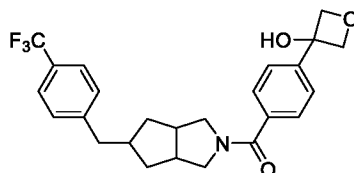
¹H NMR (DMSO-*d*₆) δ : 3.02 (s, 3H), 3.08 (m, 4H), 3.39 (m, 2H), 3.45 (m, 2H), 4.66 (d, *J* = 6.8 Hz, 2H), 4.77 (d, *J* = 6.8 Hz, 2H), 7.39 (d, *J* = 7.6 Hz, 2H), 7.63 (d, *J* = 8.4 Hz, 2H), 7.97 (d, *J* = 8.4 Hz, 2H), 8.05 (d, *J* = 8.4 Hz, 2H); ESI-MS: *m/z* 485.13 (M+H)⁺, 100%.

Example-129: (4-(3-hydroxyoxetan-3-yl)phenyl)(4-(4-(trifluoromethyl)benzyl)piperazin-1-yl)methanone



¹H NMR (DMSO-*d*₆) δ : 2.33-2.41 (m, 4H), 3.38 (m, 2H), 3.61 (m, 4H), 4.68 (d, *J* = 6.8 Hz, 2H), 4.78 (d, *J* = 6.8 Hz, 2H), 6.45 (s, 1H), 7.42 (d, *J* = 8.4 Hz, 2H), 7.56 (d, *J* = 8.0 Hz, 2H), 7.65-7.71 (m, 4H); ESI-MS: *m/z* 421.17 (M+H)⁺, 100%.

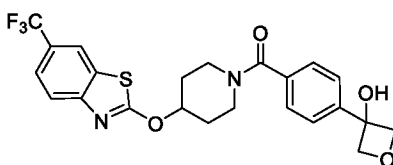
Example-130 : (4-(3-hydroxyoxetan-3-yl)phenyl)(5-(4-(trifluoromethyl)benzyl)hexahydrocyclopenta[c]pyrrol-2(1H)-yl)methanone



¹H NMR (DMSO-*d*₆) δ : 0.95 (m, 1H), 1.09 (m, 1H), 1.83 (m, 1H), 1.94 (m, 1H), 2.11-2.15 (m, 1H), 2.56 (m, 2H), 2.73 (d, *J* = 6.8 Hz, 2H), 3.49-3.63 (m, 4H), 4.69 (d, *J* = 6.8 Hz, 2H), 4.79 (d, *J* = 6.8 Hz, 2H), 6.45 (s, 1H), 7.42 (d, *J* = 8.0 Hz, 2H), 7.46-7.50 (m, 2H), 7.61-7.67 (d, *J* = 8.4 Hz, 4H); ESI-MS: *m/z* 446.19 (M+H)⁺, 100%.

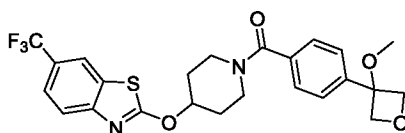
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Example-131 : (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((6-(trifluoromethyl)benzo[d]thiazol-2-yl)oxy)piperidin-1-yl)methanone



¹H NMR (DMSO-*d*₆) δ : 2.14 (m, 2H), 2.36 (m, 2H), 3.43-3.46 (m, 1H), 3.57 (m, 2H), 3.90 (m, 1H), 4.70 (d, *J* = 6.4 Hz, 2H), 4.79 (d, *J* = 6.8 Hz, 2H), 5.48 (s, 1H), 6.45 (s, 1H), 7.47 (d, *J* = 8.4 Hz, 2H), 7.68 (d, *J* = 8.4 Hz, 2H), 7.72 (d, *J* = 8.4 Hz, 1H), 7.85 (d, *J* = 8.4 Hz, 1H), 8.42 (s, 1H); ESI-MS: *m/z* 479.12 (M+H)⁺, 100%.

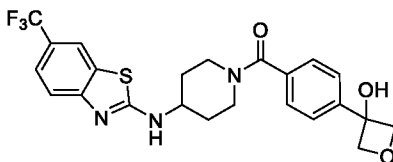
Example-132 : (4-(3-methoxyoxetan-3-yl)phenyl)(4-((6-(trifluoromethyl)benzo[d]thiazol-2-yl)oxy)piperidin-1-yl)methanone



¹H NMR (DMSO-*d*₆) δ : 2.14 (m, 2H), 2.36 (m, 2H), 3.18 (s, 3H), 3.43-3.46 (m, 1H), 3.57 (m, 2H), 3.90 (m, 1H), 4.70 (d, *J* = 6.4 Hz, 2H), 4.79 (d, *J* = 6.8 Hz, 2H), 5.48 (s, 1H), 7.47 (d, *J* = 8.4 Hz, 2H), 7.68 (d, *J* = 8.4 Hz, 2H), 7.72 (d, *J* = 8.4 Hz, 1H), 7.85 (d, *J* = 8.4 Hz, 1H), 8.42 (s, 1H); ESI-MS: *m/z* 493.14 (M+H)⁺, 100%.

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Example-133 : (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((6-(trifluoromethyl)benzo[d]thiazol-2-yl)amino)piperidin-1-yl)methanone



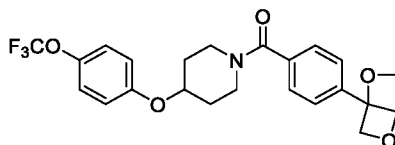
¹H NMR (DMSO-*d*₆) δ : 1.40-1.48 (m, 2H), 1.99-2.08 (m, 2H), 3.17-3.23 (m, 2H), 3.65 (m, 1H), 4.04-4.08 (m, 2H), 4.23 (m, 1H), 4.70 (d, *J* = 6.4 Hz, 2H), 4.79 (d, *J* = 6.4 Hz,

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2H), 6.44 (s, 1H), 7.44 (d, $J = 8.0$ Hz, 2H), 7.52 (s, 2H), 7.68 (d, $J = 8.0$ Hz, 2H), 8.48 (s, 1H); ESI-MS: m/z 478.14 (M+H)⁺, 100%.

Example-134 : (4-(3-methoxyoxetan-3-yl)phenyl)(4-(4-

5 **(trifluoromethoxy)phenoxy)piperidin-1-yl)methanone**

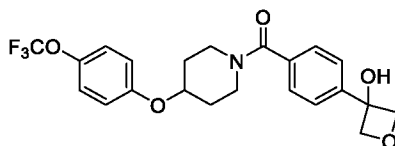


¹H NMR (DMSO-*d*₆) δ : 1.67 (m, 2H), 1.99 (m, 2H), 3.05 (m, 3H), 3.38-3.43 (m, 3H), 4.00 (m, 1H), 4.75 (m, 1H), 4.77-4.80 (m, 4H), 7.18 (d, $J = 6.8$ Hz, 2H), 7.43-7.49 (m, 4H), 7.52 (d, $J = 8.4$ Hz, 2H); ESI-MS: m/z 452.17 (M+H)⁺, 100%.

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Example-135 : (4-(3-hydroxyoxetan-3-yl)phenyl)(4-(4-

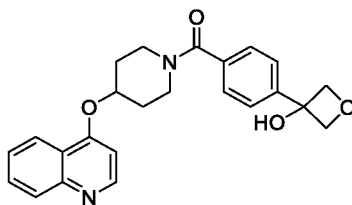
(trifluoromethoxy)phenoxy)piperidin-1-yl)methanone



¹H NMR (DMSO-*d*₆) δ : 1.62 (m, 2H), 1.94-1.96 (m, 2H), 3.38-3.43 (m, 3H), 4.00 (m, 1H), 4.64-4.67 (m, 1H), 4.69 (d, $J = 6.8$ Hz, 2H), 4.78 (d, $J = 6.8$ Hz, 2H), 6.44 (s, 1H), 6.97 (d, $J = 7.2$ Hz, 2H), 7.42-7.46 (m, 4H), 7.67 (d, $J = 8.4$ Hz, 2H).

15

Example-136 : (4-(3-hydroxyoxetan-3-yl)phenyl)(4-(quinolin-4-yloxy)piperidin-1-yl)methanone

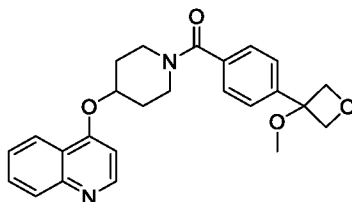


20

¹H NMR (DMSO-*d*₆) δ : 1.91-1.99 (m, 2H), 2.10-2.15 (m, 2H), 3.61-3.64 (m, 3H), 3.90-4.05 (m, 1H), 4.69 (d, $J = 6.4$ Hz, 2H), 4.78 (d, $J = 6.8$ Hz, 2H), 5.67-5.69 (m, 1H), 6.40 (s, 1H), 6.46 (d, $J = 5.6$ Hz, 2H), 7.47-7.68 (m, 3H), 7.91-7.97 (m, 2H), 8.23 (d, $J = 7.6$ Hz, 2H), 8.08 (s, 1H); ESI-MS: m/z 405.41 (M+H)⁺, 100%.

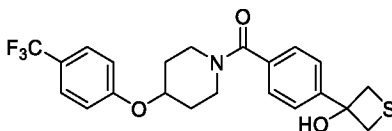
25

Example-137 : (4-(3-methoxyoxetan-3-yl)phenyl)(4-(quinolin-4-yloxy)piperidin-1-yl)methanone



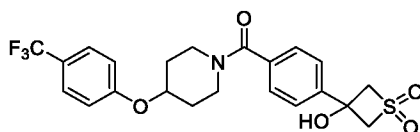
¹H NMR (DMSO-*d*₆) δ : 1.91-1.99 (m, 3H), 2.10-2.15 (m, 2H), 3.26 (s, 3H), 3.60-3.75 (m, 2H), 3.90-4.05 (m, 1H), 4.76-4.81 (m, 4H), 5.67-5.69 (m, 1H), 7.46-7.55 (m, 4H), 7.68-7.70 (m, 1H), 7.97-7.99 (m, 2H), 8.23 (d, *J* = 8.0 Hz, 2H), 8.08 (s, 1H); ESI-MS: *m/z* 419.4 (M+H)⁺, 100%.

Example-138 : (4-(3-hydroxythietan-3-yl)phenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone



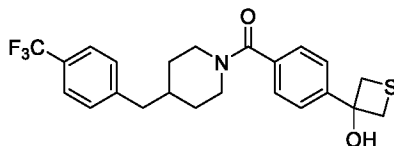
¹H NMR (CDCl₃) δ : 1.85-2.06 (m, 5H), 3.02 (m, 1H), 3.45 (m, 1H), 3.63 (s, 4H), 3.82 (m, 2H), 4.68 (m, 1H), 7.00 (d, *J* = 8.0 Hz, 2H), 7.48 (d, *J* = 8.4 Hz, 2H), 7.62 (d, *J* = 8.8 Hz, 2H), 7.77 (d, *J* = 8.4 Hz, 2H); ESI-MS: *m/z*, 438.13 (M+H)⁺, 100%.

Example-139 : (4-(3-hydroxy-1,1-dioxidothietan-3-yl)phenyl)(4-(4-(trifluoromethyl)phenoxy) piperidin-1-yl) methanone



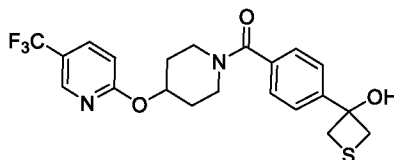
¹H NMR (DMSO-*d*₆) δ : 1.25 (s, 1H), 1.66 (m, 2H), 2.02 (m, 2H), 3.43-3.46 (m, 2H), 4.01 (m, 1H), 4.38 (d, *J* = 16.0 Hz, 2H), 4.71 (d, *J* = 15.2 Hz, 2H), 4.81 (m, 1H), 6.82 (s, 1H), 7.18 (d, *J* = 8.4 Hz, 2H), 7.48 (d, *J* = 8.4 Hz, 2H), 7.62 (d, *J* = 8.4 Hz, 2H), 7.65 (d, *J* = 9.2 Hz, 2H); ESI-MS: *m/z*, 470.12 (M+H)⁺, 100%.

Example-140 : (4-(3-hydroxythietan-3-yl)phenyl)(4-(4-(trifluoromethyl)benzyl)piperidin-1-yl)methanone



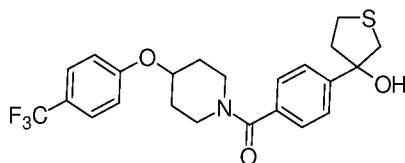
¹H NMR (DMSO-*d*₆) δ : 1.16-1.21 (m, 2H), 1.51-1.68 (m, 2H), 1.83 (m, 1H), 2.60 (d, *J* = 8.4 Hz, 2H), 2.64 (m, 1H), 2.98 (m, 1H), 3.38 (d, *J* = 10.0 Hz, 2H), 3.62-3.35 (m, 3H), 4.41 (m, 1H), 6.47 (s, 1H), 7.39 (d, *J* = 8.4 Hz, 2H), 7.43 (d, *J* = 8.0 Hz, 2H), 7.65 (d, *J* = 8.4 Hz, 2H), 7.77 (d, *J* = 8.4 Hz, 2H); ESI-MS: *m/z* 436.20 (M+H)⁺, 100%.

Example-141 : (4-(3-hydroxythietan-3-yl)phenyl)(4-((5-(trifluoromethyl)pyridin-2-yl)oxy)piperidin-1-yl)methanone



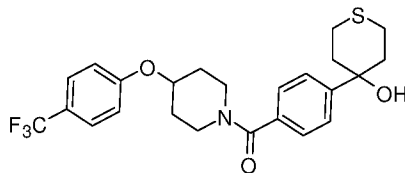
¹H NMR (DMSO-*d*₆) δ : 1.70-1.73 (m, 2H), 2.02-2.06 (m, 2H), 2.47-2.49 (m, 1H), 3.39 (d, *J* = 10.4 Hz, 3H), 3.62 (d, *J* = 10.4 Hz, 3H), 4.01-4.05 (m, 1H), 5.35-5.39 (m, 1H), 6.48 (s, 1H), 7.02 (d, *J* = 8.8 Hz, 1H), 7.45 (d, *J* = 8.4 Hz, 2H), 7.79 (d, *J* = 8.4 Hz, 2H), 8.08 (dd, *J* = 8.8 Hz & 2.4 Hz, 1H), 8.59 (d, *J* = 2.4 Hz, 1H); ESI-MS: *m/z* 439.13 (M+H)⁺, 100%.

Example-142 : (4-(3-hydroxytetrahydrothiophen-3-yl)phenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone



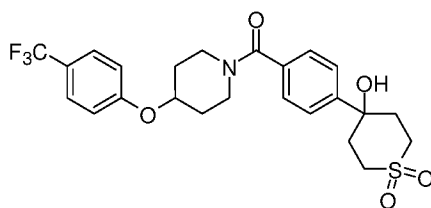
¹H NMR (DMSO-*d*₆) δ : 1.66 (m, 2H), 1.99 (m, 2H), 2.17-2.21 (m, 2H), 2.88-2.93 (m, 2H), 3.04-3.14 (m, 2H), 3.33-3.42 (m, 2H), 3.57 (m, 1H), 3.98-4.02 (m, 1H), 4.78-4.82 (m, 1H), 5.42 (s, -OH), 7.18 (d, *J* = 8.4 Hz, 2H), 7.40 (d, *J* = 8.4 Hz, 2H), 7.60-7.66 (m, 4H); ESI-MS: *m/z*, 452.23 (M+H)⁺, 100%.

Example-143 : (4-(4-hydroxytetrahydro-2H-thiopyran-4-yl)phenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone



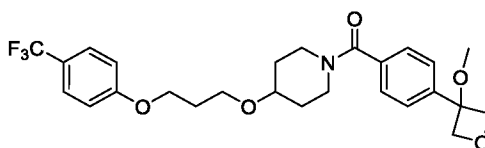
^1H NMR (DMSO- d_6) δ : 1.65 (m, 2H), 1.85 (d, $J = 12.8$ Hz, 2H), 1.96-2.02 (m, 4H), 2.39-2.41 (m, 2H), 3.06-3.13 (m, 2H), 3.33-3.42 (m, 2H), 3.57-3.61 (m, 1H), 3.90-4.04 (m, 1H), 4.80 (m, 1H), 5.10 (s, -OH), 7.18 (d, $J = 8.4$ Hz, 2H), 7.38 (d, $J = 8.0$ Hz, 2H), 7.53 (d, $J = 8.0$ Hz, 2H), 7.64 (d, $J = 8.4$ Hz, 2H); ESI-MS: m/z , 466.22 ($\text{M}+\text{H}$) $^+$, 100%.

Example-144 : (4-(4-hydroxy-1,1-dioxidotetrahydro-2H-thiopyran-4-yl)phenyl)(4-(trifluoromethyl)phenoxy)piperidin-1-ylmethanone



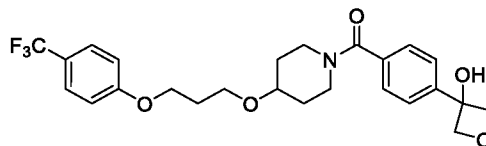
^1H NMR (DMSO- d_6) δ : 1.65 (m, 2H), 1.95-2.10 (m, 4H), 2.33-2.45 (m, 2H), 3.04 (d, $J = 12.4$ Hz, 2H), 3.33-3.41 (m, 4H), 3.54-3.56 (m, 1H), 3.94-4.04 (m, 1H), 4.80 (s, 1H), 5.72 (s, -OH), 7.18 (d, $J = 8.8$ Hz, 2H), 7.42 (d, $J = 8.0$ Hz, 2H), 7.57 (d, $J = 8.0$ Hz, 2H), 7.65 (d, $J = 8.8$ Hz, 2H); ESI-MS: m/z , 498.05 ($\text{M}+\text{H}$) $^+$, 100%.

Example-145 : (4-(3-methoxyoxetan-3-yl)phenyl)(4-(3-(4-(trifluoromethyl)phenoxy)propoxy)piperidin-1-ylmethanone



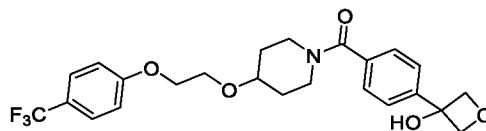
^1H NMR (CDCl_3) δ : 1.60-1.62 (m, 1H), 1.75-1.79 (m, 2H), 1.92-1.95 (m, 3H), 2.07-2.09 (m, 2H), 2.10-2.14 (m, 3H), 3.16 (s, 3H), 3.60-3.67 (m, 1H), 3.89-3.86 (m, 1H), 4.12-4.15 (m, 2H), 4.80 (d, $J = 6.4$ Hz, 2H), 4.94 (d, $J = 6.4$ Hz, 2H), 6.96 (d, $J = 8.8$ Hz, 2H), 7.44 (d, $J = 8.4$ Hz, 2H), 7.50-7.56 (m, 4H); ESI-MS: m/z 494.5 ($\text{M}+\text{H}$) $^+$, 100%.

Example-146 : (4-(3-hydroxyoxetan-3-yl)phenyl)(4-(3-(4-(trifluoromethyl)phenoxy)propoxy)piperidin-1-ylmethanone



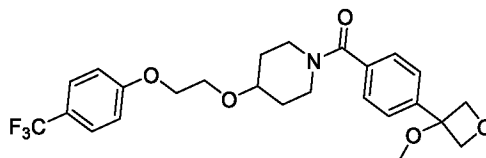
¹H NMR (CDCl₃) δ : 1.17-1.23 (m, 1H), 1.30-1.34 (m, 3H), 1.86-1.92 (m, 1H), 2.06-2.09 (m, 2H), 3.22-3.28 (m, 1H), 3.60-3.67 (m, 5H), 3.81-3.86 (m, 1H), 4.12-4.15 (m, 2H), 4.78 (d, J = 6.4 Hz, 2H), 4.92 (d, J = 6.4 Hz, 2H), 6.96 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 8.4 Hz, 2H), 7.40-7.61 (m, 4H); ESI-MS: m/z 480.2 (M+H)⁺, 100%.

Example-147 : (4-(3-hydroxyoxetan-3-yl)phenyl)(4-(2-(4-(trifluoromethyl)phenoxy)ethoxy)piperidin-1-yl)methanone



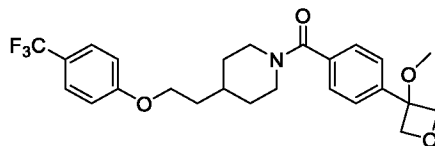
¹H NMR (DMSO-*d*₆) δ : 1.34-1.39 (m, 2H), 1.85-1.88 (m, 2H), 3.27-3.29 (m, 2H), 3.34-3.39 (m, 1H), 3.40-3.42 (m, 1H), 3.64-3.69 (m, 2H), 3.81-3.86 (m, 1H), 4.18-4.20 (m, 2H), 4.68 (d, J = 6.4 Hz, 2H), 4.78 (d, J = 6.4 Hz, 2H), 6.43 (s, 1H), 7.13 (d, J = 8.4 Hz, 2H), 7.40 (d, J = 8.0 Hz, 2H), 7.63-7.67 (m, 4H); ESI-MS: m/z 466.18 (M+H)⁺, 100%.

Example-148 : (4-(3-methoxyoxetan-3-yl)phenyl)(4-(2-(4-(trifluoromethyl)phenoxy)ethoxy)piperidin-1-yl)methanone



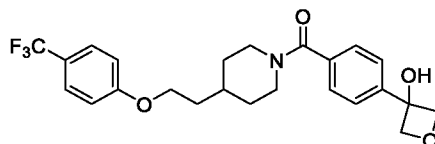
¹H NMR (CDCl₃) δ : 1.56-1.60 (m, 1H), 1.91-1.96 (m, 2H), 1.99-2.06 (m, 1H), 2.14-2.21 (m, 1H), 3.12 (s, 3H), 3.22-3.27 (m, 1H), 3.71-3.73 (m, 2H), 3.88-3.90 (m, 2H), 4.06-4.10 (m, 1H), 4.18-4.20 (m, 1H), 4.81 (d, J = 6.4 Hz, 2H), 4.95 (d, J = 6.4 Hz, 2H), 6.43 (s, 1H), 7.46 (d, J = 8.4 Hz, 2H), 7.52-7.57 (m, 4H), 7.98 (d, J = 8.4 Hz, 2H); ESI-MS: m/z 464.2 (M+H)⁺, 100%.

Example-149 : (4-(3-methoxyoxetan-3-yl)phenyl)(4-(2-(4-(trifluoromethyl)phenoxy)ethyl)piperidin-1-yl)methanone



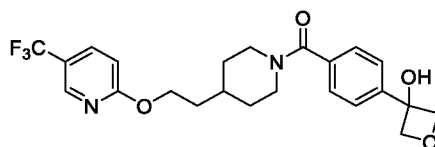
¹H NMR (DMSO-*d*₆) δ : 1.75-1.84 (m, 4H), 2.10-2.16 (m, 3H), 2.82-2.99 (m, 1H), 3.06-3.11 (m, 1H), 3.17 (s, 3H), 3.80-3.90 (m, 1H), 4.08-4.15 (m, 2H), 4.76-4.80 (m, 1H), 4.81 (d, *J* = 8.0 Hz, 2H), 4.95 (d, *J* = 8.0 Hz, 2H), 6.95 (d, *J* = 8.0 Hz, 2H), 7.47 (d, *J* = 8.0 Hz, 2H), 7.51-7.57 (m, 4H); ESI-MS: *m/z* 464.2 (M+H)⁺, 100%.

Example-150 : (4-(3-hydroxyoxetan-3-yl)phenyl)(4-(2-(4-(trifluoromethyl)phenoxy)ethyl)piperidin-1-yl)methanone



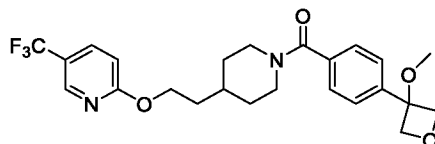
¹H NMR (DMSO-*d*₆) δ : 1.03-1.05 (m, 2H), 1.71-1.73 (m, 4H), 2.51-2.56 (m, 1H), 2.67-2.69 (m, 1H), 2.77-3.0 (m, 1H), 3.59-3.60 (m, 1H), 4.10-4.13 (m, 2H), 4.47-4.50 (m, 1H), 4.68 (d, *J* = 8.0 Hz, 2H), 4.78 (d, *J* = 8.0 Hz, 2H), 6.44 (s, 1H), 7.11 (d, *J* = 8.0 Hz, 2H), 7.40 (d, *J* = 6.8 Hz, 2H), 7.63-7.67 (m, 4H); ESI-MS: *m/z* 450.18 (M+H)⁺, 100%.

Example-151 : (4-(3-hydroxyoxetan-3-yl)phenyl)(4-(2-((5-(trifluoromethyl)pyridin-2-yl)oxy)ethyl)piperidin-1-yl)methanone



¹H NMR (DMSO-*d*₆) δ : 1.18-1.20 (m, 2H), 1.72-1.75 (m, 5H), 2.76-2.80 (m, 1H), 3.02-3.09 (m, 1H), 4.30-4.41 (m, 3H), 4.68 (d, *J* = 8.0 Hz, 2H), 4.77 (d, *J* = 8.0 Hz, 2H), 6.40 (s, 1H), 6.99 (d, *J* = 8.8 Hz, 2H), 7.39 (d, *J* = 8.0 Hz, 2H), 7.65 (d, *J* = 8.0 Hz, 2H), 8.01-8.06 (m, 1H), 8.57 (s, 1H); ESI-MS: *m/z* 451.18 (M+H)⁺, 100%.

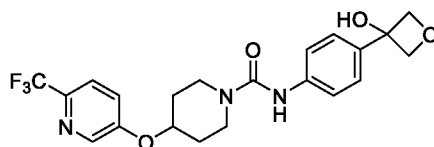
Example-152 (4-(3-methoxyoxetan-3-yl)phenyl)(4-(2-((5-(trifluoromethyl)pyridin-2-yl)oxy)ethyl)piperidin-1-yl)methanone



¹H NMR (CDCl₃) δ : 1.15-1.27 (m, 2H), 1.53-1.56 (m, 4H), 1.85-1.91 (m, 1H), 3.05-3.08 (s, 1H), 3.11-3.14 (m, 1H), 3.16 (s, 3H), 3.79-3.81 (m, 1H), 4.42-4.45 (m, 2H), 4.75-4.78 (m, 1H), 4.81 (d, J = 6.4 Hz, 2H), 4.94 (d, J = 8.0 Hz, 2H), 6.80 (d, J = 5.6 Hz, 1H), 7.46-7.52 (m, 4H), 7.77 (d, J = 8.8 Hz, 1H), 8.43 (s, 1H); ESI-MS: m/z 465.1 (M+H)⁺, 100%.

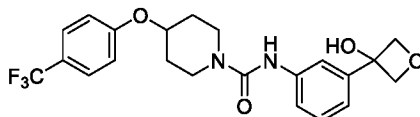
5

Example-153 (N-(4-(3-hydroxyoxetan-3-yl)phenyl)-4-((6-(trifluoromethyl)pyridin-3-yl)oxy)piperidine-1-carboxamide



¹H NMR (DMSO-*d*₆) δ : 1.62-1.64 (m, 2H), 2.01 (m, 2H), 3.28 (m, 2H), 3.83-3.87 (m, 2H), 4.66 (d, J = 6.4 Hz, 2H), 4.73 (d, J = 6.0 Hz, 2H), 4.85 (m, 1H), 6.21 (s, 1H), 7.43-7.49 (m, 4H), 7.71 (d, J = 8.4 Hz, 1H), 7.85 (d, J = 8.8 Hz, 1H), 8.49 (s, 1H), 8.61 (s, 1H); ESI-MS: m/z 436.12 (M-H), 100%.

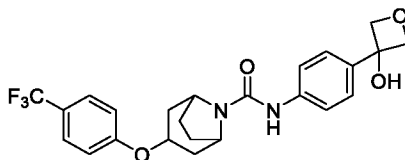
Example-154 : N-(3-(3-hydroxyoxetan-3-yl)phenyl)-4-(4-(trifluoromethyl)phenoxy)piperidine-1-carboxamide



¹H NMR (DMSO-*d*₆) δ : 1.60-1.64 (m, 2H), 1.99-2.02 (m, 2H), 3.27-3.31 (m, 2H), 3.83-3.88 (m, 2H), 4.66 (s, 2H), 4.76 (s, 3H), 6.28 (s, 1H), 7.16-7.26 (m, 4H), 7.47 (d, J = 8.0 Hz, 1H), 7.65 (d, J = 8.8 Hz, 2H), 7.70 (s, 1H), 8.62 (s, 1H); ESI-MS: m/z 437.13 (M+H)⁺, 100%.

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Example-155 :N-(4-(3-hydroxyoxetan-3-yl)phenyl)-3-(4-(trifluoromethyl)phenoxy)-8-azabicyclo[3.2.1]octane-8-carboxamide



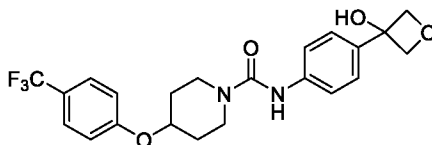
¹H NMR (DMSO-*d*₆) δ : 1.62-1.67 (m, 2H), 1.89-1.96 (m, 4H), 2.12-2.16 (m, 2H), 4.48 (m, 2H), 4.67 (d, J = 6.4 Hz, 2H), 4.74 (d, J = 6.8 Hz, 2H), 4.96-4.99 (m, 1H), 6.21 (s,

25

1H), 7.19 (d, $J = 8.8$ Hz, 2H), 7.45 (d, $J = 6.8$ Hz, 2H), 7.54 (d, $J = 8.8$ Hz, 2H), 7.61 (d, $J = 8.8$ Hz, 2H), 8.57 (s, 1H); ESI-MS: m/z 463.10 (M+H)⁺, 100%.

Example-156 : N-(4-(3-hydroxyoxetan-3-yl)phenyl)-4-(4-

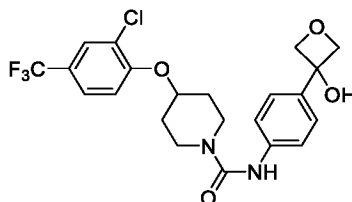
5 **(trifluoromethyl)phenoxy)piperidine-1-carboxamide**



¹H NMR (DMSO-*d*₆) δ : 1.57-1.65 (m, 2H), 1.99-2.03 (m, 2H), 3.27-3.31 (m, 3H), 3.81-3.86 (m, 2H), 4.65-4.77 (m, 5H), 7.19 (d, $J = 8.4$ Hz, 2H), 7.43-7.49 (m, 4H), 7.65 (d, $J = 8.4$ Hz, 2H), 8.60 (s, 1H); ESI-MS: m/z 437.00 (M+H)⁺, 100%.

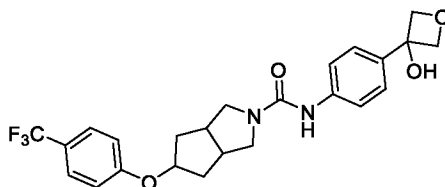
10

Example-157 : 4-(2-chloro-4-(trifluoromethyl)phenoxy)-N-(4-(3-hydroxyoxetan-3-yl)phenyl)piperidine-1-carboxamide



¹H NMR (DMSO-*d*₆) δ : 1.53-1.84 (m, 2H), 1.96-2.27 (m, 2H), 3.33-3.62 (m, 2H), 3.73-3.91 (m, 2H), 4.55-4.67 (m, 2H), 4.73-4.95 (m, 2H), 5.03 (m, 1H), 6.15-6.21 (m, 1H), 7.34 (d, $J = 6.8$ Hz, 1H), 7.47 (m, 4H), 7.61-7.92 (m, 2H), 8.60-8.71 (m, 1H); ESI-MS: m/z , 471.12 (M+H)⁺, 100%.

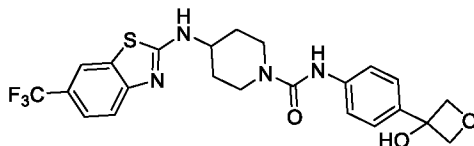
Example-158 : N-(4-(3-hydroxyoxetan-3-yl)phenyl)-5-(4-(trifluoromethyl)phenoxy)hexahydrocyclopenta[c]pyrrole-2(1H)-carboxamide



¹H NMR (DMSO-*d*₆) δ : 1.66-1.68 (m, 2H), 2.28-2.33 (m, 2H), 2.81-2.90 (m, 2H), 3.39-3.45 (m, 2H), 3.57-3.62 (m, 2H), 4.66 (d, $J = 6.4$ Hz, 2H), 4.74 (d, $J = 6.4$ Hz, 2H), 4.98-5.01 (m, 1H), 7.06 (d, $J = 8.8$ Hz, 2H), 7.08 (d, $J = 8.8$ Hz, 2H), 7.51 (d, $J = 8.8$ Hz, 2H), 7.60 (d, $J = 8.4$ Hz, 2H), 8.16 (s, 1H); ESI-MS: m/z 463.14 (M+H)⁺, 100%.

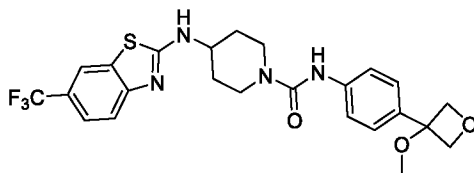
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Example-159 : N-(4-(3-hydroxyoxetan-3-yl)phenyl)-4-((6-(trifluoromethyl)benzo[d]thiazol-2-yl)amino)piperidine-1-carboxamide



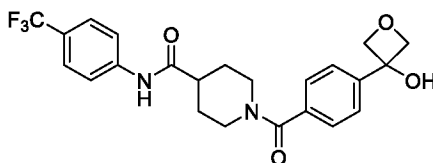
¹H NMR (DMSO-*d*₆) δ : 1.14-1.49 (m, 2H), 2.02-2.05 (m, 2H), 3.02-3.08 (m, 2H), 4.04-4.08 (m, 3H), 4.67 (d, *J* = 6.4 Hz, 2H), 4.74 (d, *J* = 6.4 Hz, 2H), 6.21 (s, 1H), 7.43-7.49 (m, 4H), 7.51 (d, *J* = 13.2 Hz, 2H), 8.14 (s, 1H), 8.45 (d, *J* = 7.2 Hz, 1H), 8.59 (s, 1H); ESI-MS: *m/z*, 493.22 (M+H)⁺, 100%.

Example-160 : N-(4-(3-methoxyoxetan-3-yl)phenyl)-4-((6-(trifluoromethyl)benzo[d]thiazol-2-yl)amino)piperidine-1-carboxamide



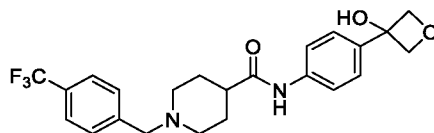
¹H NMR (DMSO-*d*₆) δ : 1.40-1.48 (m, 2H), 1.99-2.08 (m, 2H), 2.98 (s, 3H), 3.17-3.23 (m, 2H), 4.04-4.08 (m, 2H), 4.23 (m, 1H), 4.74 (s, 4H), 7.28 (d, *J* = 8.8 Hz, 2H), 7.52 (s, 4H), 8.14 (s, 1H), 8.45 (d, *J* = 7.6 Hz, 1H), 8.65 (s, 1H); ESI-MS: *m/z* 507.17 (M+H)⁺, 100%.

Example-161 : 1-(4-(3-hydroxyoxetan-3-yl)benzoyl)-N-(4-(trifluoromethyl)phenyl)piperidine-4-carboxamide



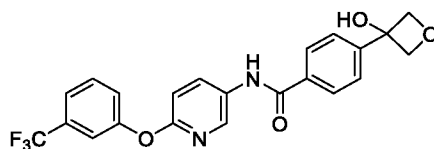
¹H NMR (DMSO-*d*₆) δ : 1.76-1.81 (m, 2H), 1.89-1.99 (m, 2H), 2.73 (m, 1H), 2.95 (m, 1H), 3.05 (m, 1H), 3.68 (m, 1H), 3.50-3.55 (m, 1H), 4.70 (d, *J* = 6.4 Hz, 2H), 4.79 (d, *J* = 6.8 Hz, 2H), 6.45 (s, 1H), 7.44 (d, *J* = 7.6 Hz, 2H), 7.67 (d, *J* = 7.6 Hz, 4H), 7.82 (d, *J* = 8.4 Hz, 2H), 10.32 (s, 1H); ESI-MS: *m/z* 449.16 (M+H)⁺, 100%.

Example-162 : N-(4-(3-hydroxyoxetan-3-yl)phenyl)-1-(4-(trifluoromethyl)benzyl)piperidine-4-carboxamide



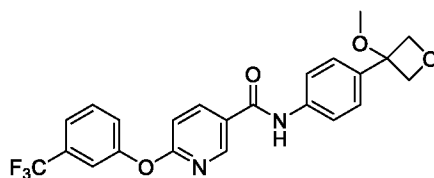
¹H NMR (DMSO-*d*₆) δ : 1.24 (s, 2H), 1.82-1.88 (m, 2H), 2.26-2.33 (m, 2H), 2.80-2.87 (m, 2H), 3.57 (m, 2H), 4.53 (m, 1H), 4.65 (d, *J* = 6.8 Hz, 2H), 4.74 (d, *J* = 6.8 Hz, 2H), 6.27 (s, 1H), 7.50 (d, *J* = 8.4 Hz, 2H), 7.61 (d, *J* = 8.4 Hz, 2H), 7.71-7.82 (m, 4H), 9.89 (br s, 1H); ESI-MS: *m/z* 435.18 (M+H)⁺, 100%.

Example-163 : 4-(3-hydroxyoxetan-3-yl)-N-(6-(3-(trifluoromethyl)phenoxy)pyridin-3-yl)benzamide



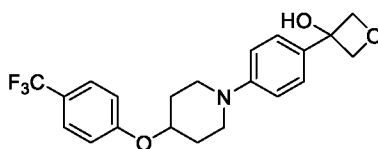
¹H NMR (DMSO-*d*₆) δ : 4.7 (d, *J* = 8.0 Hz, 2H), 4.81 (d, *J* = 6.8 Hz, 2H), 6.54 (s, 1H), 7.17 (d, *J* = 8.8 Hz, 1H), 7.45 (t, *J* = 8.0 Hz, 2H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.64 (m, 1H), 7.77 (d, *J* = 8.0 Hz, 2H), 8.01 (d, *J* = 8.0 Hz, 2H), 8.28 (t, *J* = 8.0 Hz, 1H), 8.55 (s, 1H), 10.46 (s, 1H); ESI-MS: *m/z* 430.8 (M)⁺, 100%.

Example-164 : N-(4-(3-methoxyoxetan-3-yl)phenyl)-6-(3-(trifluoromethyl)phenoxy)nicotinamide



¹H NMR (DMSO-*d*₆) δ : 3.0 (s, 3H), 4.7 (s, 4H), 7.27 (d, *J* = 8.4 Hz, 1H), 7.42 (d, *J* = 8.0 Hz, 2H), 7.54 (d, *J* = 8.0 Hz, 1H), 7.63-7.66 (m, 3H), 7.81 (d, *J* = 8.0 Hz, 2H), 8.40 (t, *J* = 8.0 Hz, 1H), 8.73 (s, 1H), 10.42 (s, 1H); ESI-MS: *m/z* 444.7 (M)⁺, 100%.

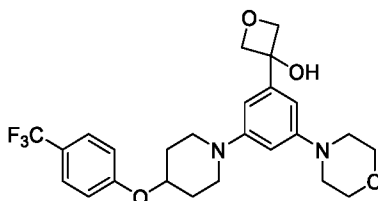
Example-165 : 3-(4-(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)phenyl)oxetan-3-ol



^1H NMR (DMSO- d_6) δ : 1.73-1.76 (m, 2H), 2.06-2.09 (m, 2H), 3.05-3.11 (m, 2H), 3.52-3.55 (m, 2H), 4.65 (d, J = 6.4 Hz, 2H), 4.72 (d, J = 6.4 Hz, 3H), 6.14 (s, 1H), 6.99 (d, J = 9.2 Hz, 2H), 7.18 (d, J = 8.8 Hz, 2H), 7.42 (d, J = 8.8 Hz, 2H), 7.65 (d, J = 8.8 Hz, 2H); ESI-MS: m/z 394.14 (M+H) $^+$, 100%.

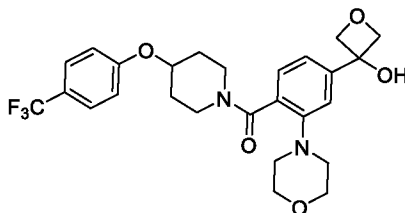
5

Example-166 : 3-(3-morpholino-5-(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)phenyl)oxetan-3-ol



^1H NMR (DMSO- d_6) δ : 1.71-1.76 (m, 2H), 1.99-2.06 (m, 2H), 3.04-3.11 (m, 6H), 3.51-3.54 (m, 2H), 3.72-3.74 (m, 4H), 4.69 (s, 5H), 6.14 (s, 1H), 6.44 (s, 1H), 6.61 (s, 1H), 6.67 (s, 1H), 7.18 (d, J = 8.8 Hz, 2H), 7.65 (d, J = 8.8 Hz, 2H); ESI-MS: m/z 479.19 (M+H) $^+$, 100%.

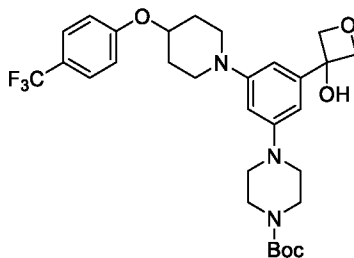
Example-167 : (4-(3-hydroxyoxetan-3-yl)-2-morpholinophenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone



^1H NMR (DMSO- d_6) δ : 1.67-1.72 (m, 2H), 2.02-2.06 (m, 2H), 2.78-2.81 (m, 2H), 3.13-3.19 (m, 3H), 3.28-3.31 (m, 1H), 3.45-3.51 (m, 1H), 3.71 (m, 4H), 4.09 (m, 1H), 4.68-4.71 (m, 2H), 4.76-4.79 (m, 3H), 6.42 (s, 1H), 7.16-7.23 (m, 4H), 7.28-7.36 (m, 1H), 7.64 (d, J = 8.8 Hz, 2H); ESI-MS: m/z 507.15 (M+H) $^+$, 100%.

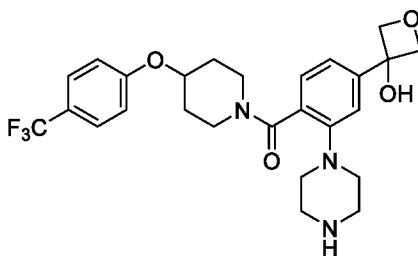
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Example-168 :tert-butyl 4-(3-(3-hydroxyoxetan-3-yl)-5-(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)phenyl)piperazine-1-carboxylate



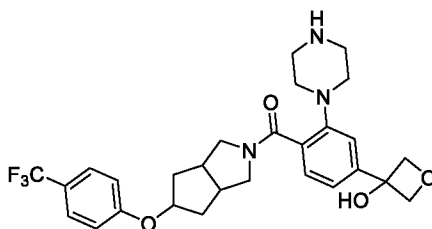
¹H NMR (CDCl₃) δ: 1.57 (s, 9H), 2.00 (m, 2H), 2.14 (m, 2H), 3.15-3.19 (m, 6H), 3.51-3.53 (m, 3H), 3.59-3.62 (m, 4H), 4.61 (m, 1H), 4.89-4.95 (m, 4H), 6.49 (s, 1H), 6.69 (s, 1H), 6.76 (s, 1H), 7.01 (d, *J* = 8.8 Hz, 2H), 7.57 (d, *J* = 8.8 Hz, 2H); ESI-MS: *m/z* 578.25 (M+H)⁺, 100%.

Example-169 : (4-(3-hydroxyoxetan-3-yl)-2-(piperazin-1-yl)phenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone



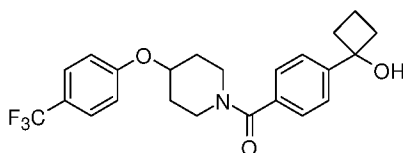
¹H NMR (CDCl₃) δ: 1.64-1.73 (m, 2H), 1.85-2.06 (m, 2H), 2.86-2.89 (m, 2H), 3.06-3.09 (m, 4H), 3.18-3.26 (m, 4H), 3.41-3.47 (m, 2H), 4.12 (m, 1H), 4.69 (d, *J* = 6.4 Hz, 2H), 4.77 (d, *J* = 6.8 Hz, 3H), 6.45 (s, 1H), 7.16-7.29 (m, 4H), 7.35 (d, *J* = 8.0 Hz, 1H), 7.64 (d, *J* = 8.4 Hz, 2H); ESI-MS: *m/z*, 506.17 (M+H)⁺, 100%.

Example-170 : (4-(3-hydroxyoxetan-3-yl)-2-(piperazin-1-yl)phenyl)(5-(4-(trifluoromethyl)phenoxy)hexahydrocyclopenta[c]pyrrol-2(1H)-yl)methanone



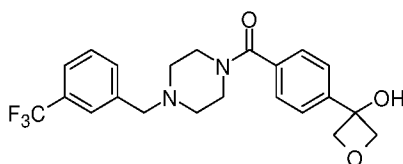
¹H NMR (DMSO-*d*₆) δ: 1.45-1.48 (m, 2H), 1.91-1.93 (m, 1H), 2.49-2.50 (m, 4H), 3.70-3.80 (m, 3H), 3.02-3.06 (m, 4H), 3.33-3.40 (m, 4H), 4.70-4.78 (m, 4H), 4.98-5.01 (m, 1H), 6.43 (s, 1H), 7.03 (d, *J* = 8.4 Hz, 2H), 7.48 (d, *J* = 8.4 Hz, 2H), 7.57-7.66 (m, 1H), 7.72 (s, 1H), 7.98 (d, *J* = 8.0 Hz, 1H), 8.92 (s, 1H); ESI-MS: *m/z* 532.5 (M+H)⁺, 100%.

Example-171 : (4-(1-hydroxycyclobutyl)phenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone



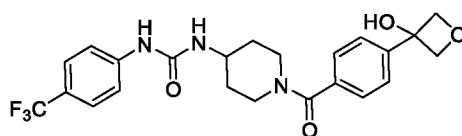
¹H NMR (DMSO-*d*₆) δ : 1.64-1.70 (m, 2H), 1.90-1.99 (m, 4H), 2.24-2.31 (m, 2H), 2.36-2.43 (m, 2H), 3.33-3.40 (m, 2H), 3.58 (m, 1H), 3.95-4.10 (m, 1H), 4.79-4.81 (m, 1H), 5.58 (s, -OH), 7.18 (d, *J* = 8.8 Hz, 2H), 7.39 (d, *J* = 8.4 Hz, 2H), 7.55 (d, *J* = 8.0 Hz, 2H), 7.65 (d, *J* = 8.4 Hz, 2H); ESI-MS: *m/z* 520.17 (M+H)⁺, 100%.

Example-172 : (4-(3-hydroxyoxetan-3-yl)phenyl)(4-(3-(trifluoromethyl)benzyl)piperazin-1-yl)methanone



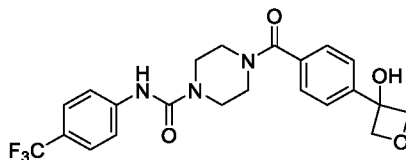
¹H NMR (CDCl₃) δ : 2.34-2.40 (m, 2H), 2.57-2.62 (m, 2H), 3.08 (s, 1H), 3.46-3.54 (m, 2H), 3.60 (s, 2H), 3.81-3.85 (m, 2H), 4.86 (d, *J* = 7.2 Hz, 2H), 4.94 (d, *J* = 7.2 Hz, 2H), 7.41-7.48 (m, 3H), 7.52-7.56 (m, 2H), 7.59-7.66 (m, 3H); ESI-MS: *m/z*, 421.17 (M+H)⁺, 100%.

Example-173 : 1-(1-(4-(3-hydroxyoxetan-3-yl)benzoyl)piperidin-4-yl)-3-(4-(trifluoromethyl)phenyl)urea



¹H NMR (DMSO-*d*₆) δ : 1.351.39 (m, 2H), 1.83-1.88 (m, 2H), 3.07-3.18 (m, 2H), 3.55-3.58 (m, 1H), 3.76-3.78 (m, 1H), 4.284.32 (m, 1H), 4.70 (d, *J* = 6.4 Hz, 2H), 4.79 (d, *J* = 6.8 Hz, 2H), 6.44 (d, *J* = 6.0 Hz, 2H), 7.43 (d, *J* = 8.4 Hz, 2H), 7.55-7.60 (m, 4H), 7.68 (d, *J* = 8.4 Hz, 2H), 8.91 (s, 1H).; ESI-MS: *m/z*, 464.16 (M+H)⁺, 100%.

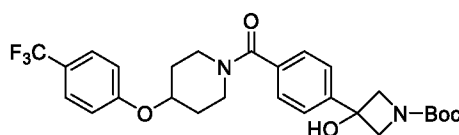
Example-174 : 4-(4-(3-hydroxyoxetan-3-yl)benzoyl)-N-(4-(trifluoromethyl)phenyl)piperazine-1-carboxamide



^1H NMR (DMSO- d_6) δ : 3.35-3.67 (m, 8H), 4.70 (d, J = 6.8 Hz, 2H), 4.80 (d, J = 6.8 Hz, 2H), 6.47 (s, 1H), 7.48 (d, J = 8.0 Hz, 2H), 7.60 (d, J = 8.8 Hz, 2H), 7.67-7.71 (m, 4H), 9.01 (s, 1H); ESI-MS: m/z , 450.15 ($M+H$) $^+$, 100%.

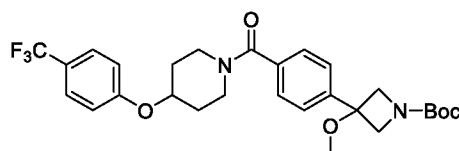
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Example-175 : *tert*-butyl 3-hydroxy-3-(4-(4-(4-(trifluoromethyl)phenoxy)piperidine-1-carbonyl)phenyl)azetidine-1-carboxylate



^1H NMR (DMSO- d_6) δ : 1.43 (s, 9H), 1.60-1.66 (m, 2H), 1.96-2.02 (m, 2H), 3.40-3.45 (m, 1H), 3.56-3.68 (m, 2H), 4.03-4.09 (m, 5H), 4.78-4.82 (m, 1H), 6.44 (s, 1H), 7.18 (d, J = 8.4 Hz, 2H), 7.44 (d, J = 8.4 Hz, 2H), 7.56 (d, J = 8.4 Hz, 2H), 7.65 (d, J = 8.4 Hz, 2H); ESI-MS: m/z 521.23 ($M+H$) $^+$, 15%.

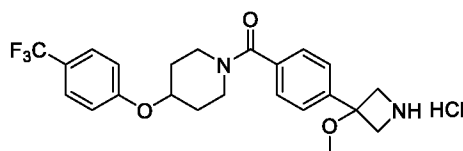
Example-176 : *tert*-butyl 3-methoxy-3-(4-(4-(4-(trifluoromethyl)phenoxy)piperidine-1-carbonyl)phenyl)azetidine-1-carboxylate



^1H NMR (DMSO- d_6) δ : 1.39 (s, 9H), 1.64-1.68 (m, 2H), 1.97-2.01 (m, 2H), 3.00 (s, 3H), 3.34-3.45 (m, 3H), 3.95-4.10 (m, 5H), 4.78-4.81 (m, 1H), 7.18 (d, J = 8.8 Hz, 2H), 7.46-7.48 (m, 4H), 7.64 (d, J = 8.8 Hz, 2H).

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Example-177 : (4-(3-methoxyazetidin-3-yl)phenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone hydrochloride

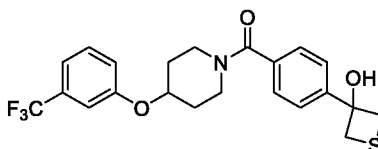


^1H NMR (DMSO- d_6) δ : 1.64-1.68 (m, 2H), 1.98-2.04 (m, 2H), 3.00 (s, 3H), 3.35-3.42 (m, 3H), 3.95-4.01 (m, 1H), 4.11-4.20 (m, 2H), 4.29-4.33 (m, 2H), 4.79-4.83 (m, 1H), 7.18 (d,

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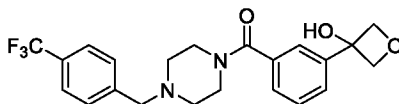
$J = 8.4$ Hz, 2H), 7.47-7.55 (m, 4H), 7.64 (d, $J = 8.4$ Hz, 2H), 9.55 (brs, 1H), 9.77 (brs, 1H); ESI-MS: m/z 435.19 (M+H)⁺, 50%.

Example-178 : (4-(3-hydroxythietan-3-yl)phenyl)(4-(3-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone



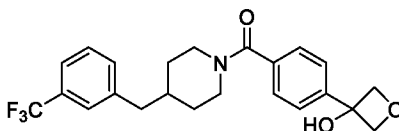
¹H NMR (DMSO-*d*₆) δ : 1.61-1.65 (m, 2H), 1.97-2.00 (m, 2H), 3.33-3.39 (m, 3H), 3.46-3.50 (m, 1H), 3.59-3.67 (m, 3H), 3.94-3.98 (m, 1H), 4.76-4.79 (m, 1H), 6.49 (s, 1H), 7.28 (d, $J = 6.4$ Hz, 3H), 7.43 (d, $J = 8.4$ Hz, 2H), 7.50-7.54 (m, 1H), 7.76 (d, $J = 8.4$ Hz, 2H); ESI-MS: m/z 438.12 (M+H)⁺, 100%.

Example-179 : (3-(3-hydroxyoxetan-3-yl)phenyl)(4-(4-(trifluoromethyl)benzyl)piperazin-1-yl)methanone



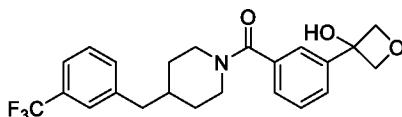
¹H NMR (CDCl₃) δ : 2.34-2.41 (m, 2H), 2.51-2.57 (m, 2H), 2.82 (s, 1H), 3.45-3.55 (m, 2H), 3.61 (s, 2H), 3.79-3.83 (m, 2H), 4.88 (d, $J = 7.2$ Hz, 2H), 4.93 (d, $J = 7.6$ Hz, 2H), 7.31 (s, 1H), 7.35-7.37 (m, 3H), 7.60 (d, $J = 8.0$ Hz, 2H), 7.71 (d, $J = 8.0$ Hz, 2H); ESI-MS: m/z 421.14 (M+H)⁺, 100%.

Example-180 : (4-(3-hydroxyoxetan-3-yl)phenyl)(4-(3-(trifluoromethyl)benzyl)piperidin-1-yl)methanone



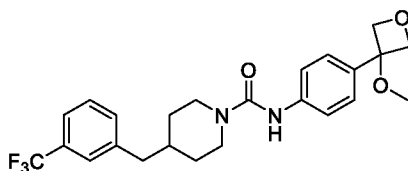
¹H NMR (DMSO-*d*₆) δ : 1.16-1.23 (m, 2H), 1.50-1.64 (m, 2H), 1.81-1.86 (m, 1H), 2.65 (d, $J = 6.4$ Hz, 2H), 2.68-2.72 (m, 1H), 2.96-2.99 (m, 1H), 3.55-3.59 (m, 1H), 4.43-4.47 (m, 1H), 4.69 (d, $J = 6.8$ Hz, 2H), 4.78 (d, $J = 6.8$ Hz, 2H), 6.44 (s, 1H), 7.39 (d, $J = 7.6$ Hz, 2H), 7.51-7.55 (m, 4H), 7.66 (d, $J = 8.4$ Hz, 2H); ESI-MS: m/z 420.16 (M+H)⁺, 100%.

Example-181 : (3-(3-hydroxyoxetan-3-yl)phenyl)(4-(3-(trifluoromethyl)benzyl)piperidin-1-yl)methanone



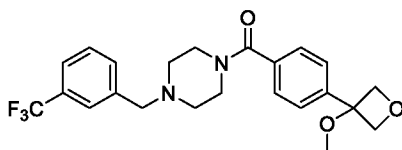
¹H NMR (CDCl₃) δ : 1.15-1.30 (m, 2H), 1.56-1.59 (m, 1H), 1.80-1.87 (m, 2H), 2.63-2.68 (m, 2H), 2.732.78 (m, 1H), 2.85-3.02 (m, 2H), 3.713.75 (m, 1H), 4.71-4.76 (m, 1H), 4.87 (d, $J = 7.2$ Hz, 2H), 4.92 (d, $J = 7.2$ Hz, 2H), 7.34 (d, $J = 7.6$ Hz, 2H), 7.41-7.50 (m, 4H), 7.65 (s, 1H), 7.70 (d, $J = 8.0$ Hz, 1H); ESI-MS: m/z 420.14 (M+H)⁺, 100%.

Example-182 : N-(4-(3-methoxyoxetan-3-yl)phenyl)-4-(3-(trifluoromethyl)benzyl)piperidine-1-carboxamide



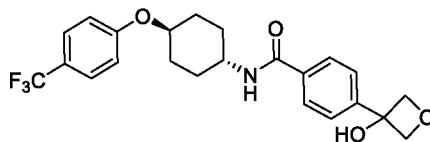
¹H NMR (DMSO-*d*₆) δ : 1.09-1.18 (m, 2H), 1.55-1.58 (m, 2H), 1.74-1.79 (m, 1H), 2.65 (d, $J = 7.2$ Hz, 2H), 2.73 (t, $J = 12.0$ Hz, 2H), 2.97 (s, 3H), 4.084.12 (m, 2H), 4.71-4.75 (m, 4H), 7.26 (d, $J = 7.2$ Hz, 2H), 7.49-7.57 (m, 6H), 8.54 (s, 1H); ESI-MS: m/z 449.19 (M+H)⁺, 100%.

Example-183 : (4-(3-methoxyoxetan-3-yl)phenyl)(4-(3-(trifluoromethyl)benzyl)piperazin-1-yl)methanone



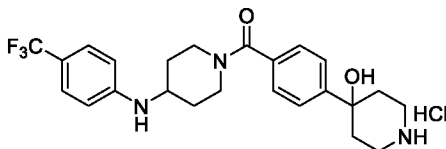
¹H NMR (DMSO-*d*₆) δ : 2.34-2.40 (m, 4H), 3.04 (s, 3H), 3.46-3.54 (m, 4H), 3.62 (s, 2H), 4.75 (d, $J = 7.2$ Hz, 2H), 4.79 (d, $J = 7.2$ Hz, 2H), 7.45 (d, $J = 8.4$ Hz, 2H), 7.51 (d, $J = 8.0$ Hz, 2H), 7.56-7.66 (m, 4H); ESI-MS: m/z 435.17 (M+H)⁺, 100%.

Example-184 : 4-(3-hydroxyoxetan-3-yl)-N-((1*r*,4*r*)-4-(4-(trifluoromethyl)phenoxy)cyclohexyl)benzamide



¹H NMR (DMSO-*d*₆) δ : 1.48-1.57 (m, 4H), 1.92-1.95 (m, 2H), 2.13-2.15 (m, 2H), 3.83-3.86 (m, 1H), 4.39-4.47 (m, 1H), 4.67 (d, *J* = 6.8 Hz, 2H), 4.79 (d, *J* = 6.8 Hz, 2H), 6.48 (s, 1H), 7.15 (d, *J* = 8.0 Hz, 2H), 7.62 (d, *J* = 8.4 Hz, 2H), 7.67 (d, *J* = 8.4 Hz, 2H), 7.88 (d, *J* = 8.0 Hz, 2H), 8.29 (d, *J* = 7.6 Hz, 1H); ESI-MS: *m/z* 436.15 (M+H)⁺, 100%.

Example-185 : (4-(4-hydroxypiperidin-4-yl)phenyl)(4-((4-(trifluoromethyl)phenyl)amino)piperidin-1-yl)methanone hydrochloride



¹H NMR (DMSO-*d*₆) δ : 1.35-1.37 (m, 2H), 1.78-1.80 (m, 2H), 1.99-2.01 (m, 2H), 2.22-2.25 (m, 2H), 3.07-3.19 (m, 6H), 3.37-3.39 (m, 2H), 3.61-3.63 (m, 1H), 5.76 (s, 1H), 6.73 (d, *J* = 8.4 Hz, 2H), 7.36-7.41 (m, 4H), 7.52 (d, *J* = 8.0 Hz, 2H), 8.97 (s, 1H), 9.17 (s, 1H); ESI-MS: *m/z* 448.15 (M+H)⁺, 100%.

The following compounds can be prepared by procedure similar to those described above with appropriate variations of reactions, reaction conditions and quantities of reagents.

- (4-(3-hydroxyoxetan-3-yl)phenyl)(3-methyl-4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((5-(trifluoromethyl)pyrimidin-2-yl)oxy)piperidin-1-yl)methanone;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(4-(methyl(5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)methanone;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(4-(2-((5-(trifluoromethyl)pyrimidin-2-yl)amino)ethyl)piperidin-1-yl)methanone;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(4-(2-((5-(trifluoromethyl)pyrimidin-2-yl)amino)ethoxy)piperidin-1-yl)methanone;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(4-(2-((5-(trifluoromethyl)pyrimidin-2-yl)amino)ethyl)piperazin-1-yl)methanone;

- (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((4-methoxy-5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)methanone;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((4-methoxy-5-(trifluoromethyl)pyrimidin-2-yl)oxy)piperidin-1-yl)methanone;
- 5 (4-((4-chloro-5-(trifluoromethyl)pyrimidin-2-yl)oxy)piperidin-1-yl)(4-(3-hydroxyoxetan-3-yl)phenyl)methanone;
- (4-((4-chloro-5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)(4-(3-hydroxyoxetan-3-yl)phenyl)methanone;
- 2-((1-(4-(3-hydroxyoxetan-3-yl)benzoyl)piperidin-4-yl)amino)-5-
- 10 (trifluoromethyl)pyrimidine-4-carbonitrile;
- 2-((1-(4-(3-hydroxyoxetan-3-yl)benzoyl)piperidin-4-yl)oxy)-5-
- (trifluoromethyl)pyrimidine-4-carbonitrile;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((5-(trifluoromethyl)pyrazin-2-yl)oxy)piperidin-1-yl)methanone;
- 15 (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((5-(trifluoromethyl)pyrazin-2-yl)amino)piperidin-1-yl)methanone;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((6-(trifluoromethyl)pyridazin-3-yl)amino)piperidin-1-yl)methanone;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((6-(trifluoromethyl)pyridazin-3-yl)oxy)piperidin-
- 20 1-yl)methanone;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((6-(4-(trifluoromethyl)phenyl)pyridazin-3-yl)oxy)piperidin-1-yl)methanone;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((6-(4-(trifluoromethyl)phenyl)pyridazin-3-yl)amino)piperidin-1-yl)methanone;
- 25 (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((5-(4-(trifluoromethyl)phenyl)pyrimidin-2-yl)oxy)piperidin-1-yl)methanone;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((5-(4-(trifluoromethyl)phenyl)pyridin-2-yl)oxy)piperidin-1-yl)methanone;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((8-(trifluoromethyl)quinolin-4-yl)oxy)piperidin-1-
- 30 yl)methanone;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((7-(trifluoromethyl)quinolin-4-yl)oxy)piperidin-1-yl)methanone;

- (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((3-(trifluoromethyl)quinolin-7-yl)oxy)piperidin-1-yl)methanone;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((4-(trifluoromethyl)naphthalen-1-yl)oxy)piperidin-1-yl)methanone;
- 5 (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((4-(trifluoromethyl)-5,6,7,8-tetrahydronaphthalen-1-yl)oxy)piperidin-1-yl)methanone;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((6-(trifluoromethyl)naphthalen-2-yl)oxy)piperidin-1-yl)methanone;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((5-(4-(trifluoromethyl)phenyl)pyrimidin-2-yl)amino)piperidin-1-yl)methanone;
- 10 (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((4-(4-(trifluoromethyl)phenoxy)phenyl)amino)piperidin-1-yl)methanone;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(2-methyl-4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;
- 15 (3-fluoro-4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)(4-(3-hydroxyoxetan-3-yl)phenyl)methanone;
- 1-(4-(3-hydroxyoxetan-3-yl)benzoyl)-4-(4-(trifluoromethyl)phenoxy)piperidine-3-carboxylic acid;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(3-methoxy-4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;
- 20 1-(4-(3-hydroxyoxetan-3-yl)benzoyl)-4-(4-(trifluoromethyl)phenoxy)piperidine-3-carbonitrile;
- (3,3-difluoro-4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)(4-(3-hydroxyoxetan-3-yl)phenyl)methanone;
- 25 (3-chloro-4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)(4-(3-hydroxyoxetan-3-yl)phenyl)methanone;
- (4-(3-hydroxyazetidin-3-yl)phenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(4-(4-morpholinophenoxy)piperidin-1-yl)methanone;
- 30 (4-(4-((2S,6R)-2,6-dimethylmorpholino)phenoxy)piperidin-1-yl)(4-(3-hydroxyoxetan-3-yl)phenyl)methanone;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(4-(4-(tetrahydro-1H-furo[3,4-c]pyrrol-5(3H)-yl)phenoxy)piperidin-1-yl)methanone;

- N-(4-(3-hydroxyoxetan-3-yl)phenyl)-1-((4-(trifluoromethyl)phenyl)sulfonyl)piperidine-4-sulfonamide;
- N-(4-(3-hydroxyoxetan-3-yl)phenyl)-1-(4-(trifluoromethyl)benzoyl)piperidine-4-sulfonamide;
- 5 4-(3-hydroxyoxetan-3-yl)-N-(1-(4-(trifluoromethyl)benzoyl)piperidin-4-yl)benzenesulfonamide;
- 4-(3-hydroxyoxetan-3-yl)-N-(1-((4-(trifluoromethyl)phenyl)sulfonyl)piperidin-4-yl)benzenesulfonamide;
- (4-((4-(3-hydroxyoxetan-3-yl)phenyl)amino)piperidin-1-yl)(4-
- 10 (trifluoromethyl)phenyl)methanone;
- (2,6-difluoro-4-(3-hydroxyoxetan-3-yl)phenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;
- (4-(3-hydroxyoxetan-3-yl)-3,5-dimethylphenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;
- 15 (4-(3-methoxy-1,1-dioxidothietan-3-yl)phenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;
- (4-(3-hydroxy-1,1-dioxidothietan-3-yl)phenyl)(4-(3-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;
- (4-(3-hydroxy-1,1-dioxidothietan-3-yl)phenyl)(4-((6-(trifluoromethyl)pyridin-3-
- 20 yl)oxy)piperidin-1-yl)methanone;
- (4-(3-hydroxy-1,1-dioxidothietan-3-yl)phenyl)(4-((5-(trifluoromethyl)pyrimidin-2-yl)oxy)piperidin-1-yl)methanone;
- (4-(3-hydroxy-1,1-dioxidothietan-3-yl)phenyl)(4-(4-(trifluoromethyl)benzyl)piperazin-1-yl)methanone;
- 25 (4-(3-hydroxy-1,1-dioxidothietan-3-yl)phenyl)(4-(3-(trifluoromethyl)benzyl)piperidin-1-yl)methanone;
- (3-(3-hydroxyoxetan-3-yl)phenyl)(4-(3-(trifluoromethyl)benzyl)piperazin-1-yl)methanone;
- (3-(3-hydroxyoxetan-3-yl)phenyl)(4-((6-(trifluoromethyl)pyridin-3-yl)methyl)piperidin-
- 30 1-yl)methanone;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((6-(trifluoromethyl)pyridin-3-yl)methyl)piperidin-1-yl)methanone;

- (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((6-(trifluoromethyl)pyridin-3-yl)methyl)piperazin-1-yl)methanone;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(6-(4-(trifluoromethyl)phenoxy)-3,4-dihydroquinolin-1(2H)-yl)methanone;
- 5 (4-(3-hydroxyoxetan-3-yl)phenyl)(2-((4-(trifluoromethyl)phenyl)sulfonyl)-2,6-dihydropyrrolo[3,4-c]pyrazol-5(4H)-yl)methanone;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(2-(4-(trifluoromethyl)phenoxy)-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methanone;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(5-(4-(trifluoromethyl)phenoxy)indolin-1-yl)methanone;
- 10 (4-(3-hydroxyoxetan-3-yl)phenyl)(5-(4-(trifluoromethyl)phenoxy)-1H-indol-1-yl)methanone;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(6-(4-(trifluoromethyl)phenoxy)-3,4-dihydroisoquinolin-2(1H)-yl)methanone;
- 15 N-(4-(3-hydroxyoxetan-3-yl)phenyl)-2-(4-(trifluoromethyl)phenoxy)pyrimidine-5-carboxamide;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((6-(trifluoromethyl)benzo[d]thiazol-2-yl)methyl)piperidin-1-yl)methanone;
- (3-(3-hydroxyoxetan-3-yl)phenyl)(4-((6-(trifluoromethyl)benzo[d]thiazol-2-yl)methyl)piperidin-1-yl)methanone;
- 20 N-(4-(3-hydroxyoxetan-3-yl)phenyl)-4-((6-(trifluoromethyl)benzo[d]thiazol-2-yl)methyl)piperidine-1-carboxamide;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((6-(trifluoromethyl)benzo[d]thiazol-2-yl)methyl)piperazin-1-yl)methanone;
- 25 N-(4-(3-hydroxyoxetan-3-yl)phenyl)-4-((6-(trifluoromethyl)benzo[d]thiazol-2-yl)methyl)piperazine-1-carboxamide;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((6-(trifluoromethyl)benzo[d]oxazol-2-yl)oxy)piperidin-1-yl)methanone;
- N-(4-(3-hydroxyoxetan-3-yl)phenyl)-4-((6-(trifluoromethyl)benzo[d]oxazol-2-yl)oxy)piperidine-1-carboxamide;
- 30 (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((6-(trifluoromethyl)-1H-benzo[d]imidazol-2-yl)oxy)piperidin-1-yl)methanone;

- (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((6-(trifluoromethyl)-1H-benzo[d]imidazol-2-yl)amino)piperidin-1-yl)methanone;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((6-(trifluoromethyl)benzofuran-2-yl)oxy)piperidin-1-yl)methanone;
- 5 (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((6-(trifluoromethyl)benzofuran-2-yl)amino)piperidin-1-yl)methanone;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((6-(trifluoromethyl)benzo[b]thiophen-2-yl)oxy)piperidin-1-yl)methanone;
- (4-fluoro-4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)(4-(3-hydroxyoxetan-3-yl)phenyl)methanone;
- 10 (4-(3-hydroxyoxetan-3-yl)phenyl)(4-methyl-4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(4-methyl-4-((6-(trifluoromethyl)benzo[d]thiazol-2-yl)oxy)piperidin-1-yl)methanone;
- 15 (4-(3-hydroxyoxetan-3-yl)phenyl)(4-(4-(trifluoromethyl)phenoxy)-4-(4-(trifluoromethyl)phenyl)piperidin-1-yl)methanone;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((6-(trifluoromethyl)benzo[d]thiazol-2-yl)oxy)-4-(4-(trifluoromethyl)phenyl)piperidin-1-yl)methanone;
- N-(4-(3-hydroxyoxetan-3-yl)phenyl)-4-(4-(trifluoromethyl)phenoxy)piperidine-1-sulfonamide;
- 20 1-(1-(4-(3-hydroxyoxetan-3-yl)benzoyl)piperidin-4-yl)-3-(4-(trifluoromethyl)phenyl)sulfonylurea;
- 1-(4-(3-hydroxyoxetan-3-yl)phenyl)-3-(1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)urea;
- 1-(4-(3-hydroxyoxetan-3-yl)phenyl)-3-(1-(4-(trifluoromethyl)benzyl)piperidin-4-yl)sulfonylurea;
- 25 (4-(3-hydroxyoxetan-3-yl)phenyl)(4-(3-(2-methoxyethoxy)-4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;
- (4-(3-hydroxyoxetan-3-yl)-3-(2-methoxyethoxy)phenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone
- 30 (4-(3-(2-(methylsulfonyl)ethoxy)oxetan-3-yl)phenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;
- (4-(difluoro(4-(trifluoromethyl)phenyl)methyl)piperidin-1-yl)(4-(3-hydroxyoxetan-3-yl)phenyl)methanone;

- (4-(3,3-difluoro-1-hydroxycyclobutyl)phenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;
- 3-(3-(morpholinosulfonyl)-5-(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)phenyl)oxetan-3-ol;
- 5 (4-(3-hydroxyoxetan-3-yl)phenyl)(5-((4-(trifluoromethyl)phenyl)sulfonyl)-3,5-dihydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methanone;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(5-((4-(trifluoromethyl)phenyl)sulfonyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methanone;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(5-((4-(trifluoromethyl)phenyl)sulfonyl)-3,4,5,6-
- 10 tetrahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methanone;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(5-(4-(trifluoromethyl)phenoxy)-3,4,5,6-tetrahydrocyclopenta[c]pyrrol-2(1H)-yl)methanone;

The compounds of the present invention are useful in lowering LDL. This was
 15 demonstrated by *in vitro* as well as *in vivo* animal experiments as provided below:

BODIPY-LDL uptake assay in HepG2 cells.

An established assay for PCSK9 inhibition features uptake of fluorescently labeled LDL nanoparticles (BODIPY-LDL) by hepatocytes and uptake of the BODIPY-containing
 20 particles is maximized in the absence of PCSK9.

In the LDL uptake assay, HepG2 cells were seeded at a density of 6x10⁴ cells/well in a 96-well plate. After 24 h, the test compounds at various concentrations were pre-incubated with 5 µg/ml PCSK9 in 0.2% DMSO for 60 min prior to the addition on to the cells. After 16h the medium was removed and 1 µg/ml BODIPY-LDL (Invitrogen) in serum free media
 25 was added and incubated for 5h. Then the cells were washed twice with 0.25% BSA in PBS. Then the fluorescence of the cells in PBS was measured using TECAN multimode reader (Excitation: 485nm and Emission: 520nm). The readings were taken in triplicate and the final values were normalized with the protein concentration from respective wells. The wells without test compound containing external PCSK9 is considered as zero uptake
 30 and the one without PCSK9 was considered as 100% uptake. The percentage increase in LDL uptake for the test compounds were calculated using these values. The results are presented in the table below.

Table 1

Example	% increase in LDL Uptake		
	1 μ M	10 μ M	30 μ M
1	29	117	99
2	22	42	0
3	6	51	63
4	36	111	0
9	0	0	59
11	0	41	0
12	7	14	41
18	0	51	129
20	0	64	103
21	0	34	130
22	5	5	37
25	0	3	53
34	0	2	95
36	0	33	129
37	56	0	0
38	0	0	12
39	6	16	111
40	0	0	77
42	6	79	35
43	15	140	8
52	1	40	0
53	0	48	30
54	17	40	0
61	3	12	128
62	10	80	0
63	15	94	0
65	19	25	78
68	0	31	58
70	30	75	0
71	29	77	119
72	41	132	7
74	30	43	0
75	0	14	76
76	0	47	98
77	39	178	34
82	28	86	80
83	1	0	100
86	24	137	0

87	39	21	120
88	3	0	53
99	19	45	18
106	82	0	0
107	0	35	81
108	18	128	77
109	0	84	39
114	2	0	43
115	0	49	97
116	5	140	146
117	19	0	49
118	0	33	59
119	0	94	127
120	12	86	0
121	30	72	102
122	35	76	140
123	25	89	142
124	28	79	0
125	9	48	68
127	48	125	87
129	0	71	55
131	6	58	0
133	25	109	39
135	0	76	0
137	10	163	136
138	1	10	60
139	29	73	0
140	0	66	10
147	0	70	56
148	0	116	22
151	4	65	0
155	16	39	43
156	37	82	95
166	36	53	56

LDL-C lowering activity- in high fat diet C57 mice

5 The *in-vivo* LDL-c lowering for test compound was tested in C57 mice which were kept on high fat diet for 4 weeks and the blood was collected by retro-orbital sinus puncture method under light ether anesthesia on day 0 (pretreatment). Animal are grouped based on LDL-c levels, after that 7 days treatment with vehicle or test compound orally at a dose of

30 mpk dose once a day was given. On completion of treatment on day 7 of the treatment the blood was collected for LDL-c and TC levels measurement. The percent change in LDL-c and TC in test compound group Vs Vehicle group was calculated and presented in the table 2 below

5 **Table 2**

Example No	Dose (mg/Kg)	% Change Vs Vehicle Control in LDLc
1	30	- 33.0 ± 7.0
18	30	-23.0 ± 5.0
21	30	7.0 ± 9.0
42	30	-27.0 ± 9.0
86	30	-31.0 ± 7.0
118	30	-4.0 ± 7.0
120	30	-24.0 ± 7.0
121	30	-23.0 ± 8.0
122	30	7.0 ± 5.0
124	30	-18.0 ± 4.6
125	30	-16.9 ± 5.8
126	30	-22.0 ± 5.0
159	30	-7.0 ± 5.0

Pharmacokinetic studies:

Pharmacokinetics of the test compounds was evaluated in rats/dogs. Animals were fasted for 16 hours with free access to water and food was supplied after 4 hours of administration of the test compound. Test substance was administered per oral as a homogenous suspension prepared in 1% tween 80 + 99% of 0.5% w/v Methyl cellulose in water at the dose of 3 mg/kg. Blood samples were withdrawn at various time intervals through retro-orbital plexus and collected into heparinized micro centrifuge tubes. Plasma was separated from collected blood by centrifugation at 4500 rpm for 10 min at 4°C and stored at -70°C until analysis using LC-MS/MS method. Pharmacokinetic parameters were calculated using Non-compartmental modelling of Phoenix (Certara) software.

Table 3

Example No	Species	T _{max} (H)	C _{max} (ng/mL)	AUC _(0-t) ng.h/ml)	T _{1/2} , po (h)	%F
Example 1	Rat	1.1	2344.52±665.09	16740.03±5675.49	2.42±0.24	100
	Dog	1 (0.5-1)	2032.4±174.2	21148.5±1416.5	5.6±0.4	87±6

PCSK9 protein expression

5 Effect of test compounds on secreted PCSK9 protein was analyzed using ELISA. Human hepatocytic cells, HepG2s were plated at 6 X 10⁴ density in multi-well tissue culture plates. After 24h, the culture media was removed and the media containing different concentrations of test compounds or DMSO as control was replaced and incubated at 37 °C with 5% CO₂ for 24 h. At the end of the incubation time, the media supernatant was

10 collected and PCSK9 protein was measured using the ELISA kit (R & D System kit DY3888). The procedure was used as per the directions given in the kit. The cells in the wells were washed and lysed with 0.1% Triton® X-100 and total protein was estimated using Bradford method. PCSK9 protein levels were normalized with the total protein concentration from respective wells. The modulation in PCSK9 protein with NCE

15 treatment was represented as the ratio compared to the control DMSO.

Table 4

Example No.	PCSK9 protein (Fold change)	
	10μM	30μM
1	-8.33	-20.0

In certain instances, it may be appropriate to administer at least one of the compounds described herein or a pharmaceutically acceptable salt, ester, or prodrug thereof in

20 combination with another therapeutic agent. Several reasons can be attributed for using a combination therapy depending on the need of the patient. As an example, if one of the side effects experienced by a patient upon receiving one of the compounds herein is hypertension, then it may be appropriate to administer an anti-hypertensive agent in combination with the initial therapeutic agent. Or, by way of example only, the benefit

experienced by a patient may be increased by administering one of the compounds described herein with another therapeutic agent (which also includes a therapeutic regimen) that also has therapeutic benefit. Several such instances are well known to a skilled person and the use of combination therapy may be envisaged for all such situations.

- 5 In any case, regardless of the disease, disorder or condition being treated, the overall benefit experienced by the patient may simply be additive of the two therapeutic agents or the patient may experience a synergistic benefit.

The pharmaceutical composition is prepared by employing conventional techniques. Preferably the composition is in unit dosage form containing an effective amount of the active component, i.e. the compounds of formula (I) according to this invention. In an embodiment of present invention there is provided a pharmaceutical composition comprising compound of formula (I) and pharmaceutically acceptable excipients. Pharmaceutically acceptable excipients include those which are commonly used for formulation of such compounds as is known in the art and may be selected from diluents, bulking agents, binders, disintegrants and other necessary excipients.

The quantity of active component, that is, the compounds of formula (I) according to this invention, in the pharmaceutical composition and unit dosage form thereof may be varied or adjusted widely depending upon the particular application method, the potency of the particular compound and the desired concentration. Generally, the quantity of active component will range between 0.5% to 90% by weight of the composition. Specific, non-limiting examples of possible combination therapies include use of certain compounds disclosed herein with agents found in the following pharmacotherapeutic classifications as indicated below. These lists should not be construed to be closed, but should instead serve as illustrative examples common to the relevant therapeutic area at present. Moreover, combination regimens may include a variety of routes of administration and should include oral, intravenous, intraocular, subcutaneous, dermal, and inhaled topical.

Specifically for the treatment of metabolic disorders, compounds disclosed herein may be administered with an agent selected from the group comprising: insulin, insulin derivatives and mimetics, insulin secretagogues, insulin sensitizers, biguanide agents, alpha-glucosidase inhibitors, insulinotropic sulfonylurea receptor ligands, meglitinides, GLP-1 (glucagon like peptide-1), GLP-1 analogs, DPPIV (dipeptidyl peptidase IV) inhibitors, GPR-119 inhibitors, sodium-dependent glucose co-transporter (SGLT2) inhibitors, PPAR modulators, non-glitazone type PPAR.delta. agonist, HMG-CoA

reductase inhibitors, cholesterol-lowering drugs, rennin inhibitors, anti-thrombotic and anti-platelet agents and anti-obesity agents.

For the treatment of metabolic disorders, compounds disclosed herein may be administered with an agent selected from the group comprising: insulin, metformin, 5 Glipizide, glyburide, Amaryl, gliclazide, meglitinides, nateglinide, repaglinide, amylin mimetics (for example, pramlintide), acarbose, miglitol, voglibose, Exendin-4, , vildagliptin, Liraglutide, naliglutide, saxagliptin, pioglitazone, rosiglitazone, HMG-CoA reductase inhibitors (for example, rosuvastatin, atrovastatin, simvastatin, lovastatin, pravastatin, fluvastatin, cerivastatin, rosuvastatin, pitavastatin and like), cholesterol- 10 lowering drugs (for example, fibrates which include: fenofibrate, benzaifibrate, clofibrate, gemfibrozil and like; cholesterol absorption inhibitors such as Ezetimibe, eflucimibe etc. In another embodiment of the present invention, use of compound of formula (I), their tautomeric form, their pharmaceutically acceptable salts or their pharmaceutical composition in the medicament for treating hyperlipidemia and related diseases is 15 disclosed. The compounds of the invention also have beneficial effect in cholesterol lowering.

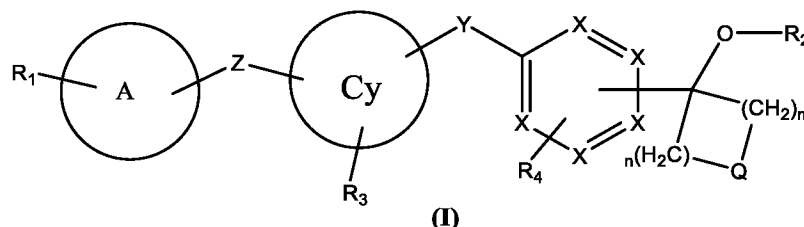
From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages 20 and conditions. Such different embodiments are also to be considered to be within the scope of the present invention.

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We claim:

1. Compounds of general formula (I)



5 their tautomeric forms, their stereoisomers, their pharmaceutically acceptable salts, and pharmaceutical compositions containing them wherein

‘A’ is selected from an optionally substituted single or fused group selected from aryl or heteroaryl groups;

‘Y’ is either a bond, or selected from (C₁-C₃)alkyl, -S(O)_o-, -C(O)-, -C(O)N(R₅)-,
 10 N(R₅)C(O)-, -N(R₅)-, -N(R₅)S(O)₂N(R₅)-, -N(R₅)C(O)N(R₅)-, -S(O)₂N(R₅)-, -N(R₅)S(O)₂-;
 ;

‘Z’ is selected from -O-, -S(O)_o-, -C(O)-, -N(R₅)-, -(C(R₅)₂)_p-, -O(C(R₅)₂)_p-, -
 (C(R₅)₂)_pO-, -O(C(R₅)₂)_pO-, -S(O)_o(C(R₅)₂)_p-, -(C(R₅)₂)_pS(O)_o-, -S(O)_o(C(R₅)₂)_pS(O)_o-, -
 N(R₅)(C(R₅)₂)_p-, -(C(R₅)₂)_pN(R₅)-, -N(R₅)(C(R₅)₂)_pN(R₅)-, -NHC(O)-, -C(O)NH-, -
 15 NHC(O)NH-, -NHS(O)₂NH-, -NHS(O)₂-, -S(O)₂NH- or ;

‘Q’ selected from O, C(R₅)₂, NR₆ or S(O)_o; wherein R₆ is selected from H, (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, -C(O)OR₅, -C(O)R₅, -C(O)NH₂;

‘o’ is an integer selected from 0-2;

‘m, n and p’ independently represent an integer selected from 0-4;

20 ‘Cy’ is a saturated or partially unsaturated or unsaturated, monocyclic, bicyclic or spirocyclic groups containing 0-4 heteroatoms selected from O, N or S;

‘X’ at each occurrence independently selected from either Carbon atom or Nitrogen atom;

R₁ at each occurrence is selected from halo, cyano, hydroxy or substituted or
 25 unsubstituted groups selected from alkyl, haloalkyl, perhaloalkyl, alkoxy, haloalkoxy, perhaloalkoxy, cycloalkyl, alkoxy, cycloalkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heterocyclylalkyl, heterocycloxy, heterocyclylalkoxy, heterocyclylalkoxyacyl, carboxylic acid and its derivatives such as esters and amides, carbonylamino, hydroxyalkyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthio,

thioalkyl, alkylsulfonyl, haloalkylsulfonyl, perhaloalkylsulfonyl, hydroxyl, sulfonic acid and its derivatives;

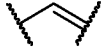
R_2 is selected from hydrogen, or substituted or unsubstituted groups selected from alkyl, haloalkyl, perhaloalkyl, cycloalkyl, aryl, aralkyl, heterocyl, heterocyclalkyl, heterocyclalkoxyacyl, Acyl, carbonylamino, hydroxyalkyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylsulfonyl;

Each of R_3 and R_4 at each occurrence independently selected from hydrogen, halo, cyano, hydroxy or substituted or unsubstituted groups selected from alkyl, haloalkyl, perhaloalkyl, alkoxy, haloalkoxy, perhaloalkoxy, cycloalkyl, alkoxy, cycloalkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyl, heterocyclalkyl, heterocycloxy, heterocyclalkoxy, heterocyclalkoxyacyl, carboxylic acid and its derivatives such as esters and amides, carbonylamino, hydroxyalkyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthio, thioalkyl, alkylsulfonyl, hydroxyl, sulfonic acid and its derivatives;

R_5 at each occurrence independently selected from H, (C_1-C_6) alkyl or (C_3-C_6) cycloalkyl.

2. The compound as claimed in claim 1 wherein A is optionally substituted phenyl, pyridine, thiophene, pyrimidine, benzo[d]thiazole and quinolone groups, preferably optionally substituted phenyl and benzo[d]thiazole group.

3. The compound as claimed in claim 1 wherein 'Y' is selected from $-C(O)-$, $-S(O)_o-$, $-(C_1-C_3)alkyl-$, $-C(O)N(R_5)-$, $-N(R_5)-$, $-C(O)CH(R_5)_2-$; preferably 'Y' is $-C(O)-$ and $-C(O)N(R_5)_2-$ wherein R_5 is as defined in claim 1.

4. The compound as claimed in claim 1 wherein 'Z' is selected from $-O-$, $-S(O)_o-$, $-C(O)-$, $-N(R_5)-$, $-(C(R_5)_2)_p-$, $-O(C(R_5)_2)_p-$, $-O(C(R_5)_2)_pO-$, $S(O)_o(C(R_5)_2)_p-$, $-S(O)_o(C(R_5)_2)_pS(O)_o-$, $-N(R_5)(C(R_5)_2)_p-$, $-NHC(O)-$, $-NHC(O)NH-$, or , preferably selected from $-O-$, $-S(O)_o-$, $-N(R_5)-$, $-(C(R_5)_2)_p-$, $-O(C(R_5)_2)_p-$, or , wherein R_5 is as defined in claim 1.

5. The compound as claimed in claim 1 wherein compound is selected from:

- (4-(3-hydroxyoxetan-3-yl)phenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;
- (4-(3-methoxyoxetan-3-yl)phenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;
- 5 3-(4-((4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methyl)phenyl)oxetan-3-ol;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(4-(4-((trifluoromethyl)sulfonyl)phenoxy)piperidin-1-yl)methanone;
- 4-((1-(4-(3-hydroxyoxetan-3-yl)benzoyl)piperidin-4-yl)oxy)benzoic acid;
- N-cyclopropyl-4-((1-(4-(3-hydroxyoxetan-3-yl)benzoyl)piperidin-4-
- 10 yl)oxy)benzamide;
- (4-(3-methoxypyrrolidin-3-yl)phenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;
- (4-(3-hydroxypyrrolidin-3-yl)phenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;
- 15 (4-(3-hydroxy-1,1-dioxidothietan-3-yl)phenyl)(4-((5-(trifluoromethyl)pyridin-2-yl)oxy)piperidin-1-yl)methanone;
- (4-(3-hydroxy-1,1-dioxidothietan-3-yl)phenyl)(4-(4-(trifluoromethyl)benzyl)piperidin-1-yl)methanone;
- 3-(4-((1-((4-(trifluoromethyl)phenyl)sulfonyl)piperidin-4-
- 20 yl)amino)phenyl)oxetan-3-ol;
- 3-(4-((4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)sulfonyl)phenyl)oxetan-3-ol;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((5-(trifluoromethyl)pyridin-2-yl)sulfonyl)piperidin-1-yl)methanone;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((5-(trifluoromethyl)pyridin-2-
- 25 yl)sulfinyl)piperidin-1-yl)methanone;
- (3-(3-hydroxyoxetan-3-yl)phenyl)(4-((4-(trifluoromethyl)phenyl)sulfonyl)piperidin-1-yl)methanone;
- 1-(4-(3-hydroxyoxetan-3-yl)benzoyl)-4-(4-(trifluoromethyl)benzyl)piperidine-4-carboxylic acid;
- 30 N-(3-(3-hydroxyoxetan-3-yl)-5-morpholinophenyl)-4-(4-(trifluoromethyl)phenoxy) piperidine-1-carboxamide;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((4-(trifluoromethyl)phenyl)amino)piperidin-1-yl)methanone;

- (4-(3-methoxyoxetan-3-yl)phenyl)(4-((4-(trifluoromethyl)phenyl)amino)piperidin-1-yl)methanone;
 (4-(3-hydroxyoxetan-3-yl)phenyl)(4-(methyl(4-(trifluoromethyl)phenyl)amino)piperidin-1-yl)methanone;
 5 (3-(3-hydroxyoxetan-3-yl)phenyl)(3-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;
 (4-(3-hydroxyoxetan-3-yl)phenyl)(3-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;
 (4-(3-methoxyoxetan-3-yl)phenyl)(3-(4-(trifluoromethyl)phenoxy)pyrrolidin-1-yl)methanone;
 10 (4-(3-hydroxyoxetan-3-yl)phenyl)(3-(4-(trifluoromethyl)phenoxy)pyrrolidin-1-yl)methanone;
 (3-(3-methoxyoxetan-3-yl)phenyl)(3-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;
 15 (4-([1,1'-biphenyl]-4-yloxy)piperidin-1-yl)(4-(3-hydroxyoxetan-3-yl)phenyl)methanone;
 (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((2'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)oxy)piperidin-1-yl)methanone;
 (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((3'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)oxy)piperidin-1-yl)methanone;
 20 (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((4'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)oxy)piperidin-1-yl)methanone;
 (4-(3-hydroxyoxetan-3-yl)phenyl)(4-(4-isopropylphenoxy)piperidin-1-yl)methanone;
 25 (4-(2-chloro-5-(trifluoromethyl)phenoxy)piperidin-1-yl)(4-(3-hydroxyoxetan-3-yl)phenyl)methanone;
 (4-(4-(1H-imidazol-1-yl)phenoxy)piperidin-1-yl)(4-(3-hydroxyoxetan-3-yl)phenyl)methanone;
 (4-((1-(4-(3-hydroxyoxetan-3-yl)benzoyl)piperidin-4-yl)oxy)phenyl)(morpholino)methanone;
 30 4-((1-(4-(3-hydroxyoxetan-3-yl)benzoyl)piperidin-4-yl)oxy)benzonitrile;
 (4-(3-hydroxyoxetan-3-yl)phenyl)(4-(4-(2-phenylpropan-2-yl)phenoxy)piperidin-1-yl)methanone;

- (4-(3-hydroxyoxetan-3-yl)phenyl)(4-(4-phenoxyphenoxy)piperidin-1-yl)methanone;
- (4-(3-chloro-4-(trifluoromethyl)phenoxy)piperidin-1-yl)(4-(3-hydroxyoxetan-3-yl)phenyl)methanone;
- 5 (4-(3-hydroxyoxetan-3-yl)phenyl)(4-(2-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(4-(3-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(4-(4-methoxyphenoxy)piperidin-1-yl)methanone;
- 10 (4-(4-(2H-tetrazol-5-yl)phenoxy)piperidin-1-yl)(4-(3-hydroxyoxetan-3-yl)phenyl)methanone;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((4-(trifluoromethyl)phenoxy)methyl)piperidin-1-yl)methanone;
- 15 (4-(3-hydroxyoxetan-3-yl)phenyl)(4-(2-(4-(trifluoromethyl)phenoxy)ethyl)piperazin-1-yl)methanone;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(4-(4-((trifluoromethyl)thio)phenoxy)piperidin-1-yl)methanone;
- (4-(3-methoxyoxetan-3-yl)phenyl)(4-(4-((trifluoromethyl)thio)phenoxy)piperidin-1-yl)methanone;
- 20 (4-(3-(methoxy-d3)oxetan-3-yl)phenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;
- (4-(3-((tetrahydro-2H-pyran-4-yl)methoxy)oxetan-3-yl)phenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;
- 25 (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((5-(methylthio)pyrimidin-2-yl)oxy)piperidin-1-yl)methanone;
- (4-(3-isobutoxyoxetan-3-yl)phenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;
- (4-(4-(3-hydroxyoxetan-3-yl)benzoyl)piperazin-1-yl)(4-(trifluoromethyl)phenyl)methanone;
- 30 (1-(4-(3-hydroxyoxetan-3-yl)benzoyl)piperidin-4-yl)(4-(trifluoromethyl)phenyl)methanone;

- (4-(3-hydroxyoxetan-3-yl)phenyl)(2-(4-(trifluoromethyl)phenoxy)-7-azaspiro[3.5]nonan-7-yl)methanone;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(6-(4-(trifluoromethyl)phenoxy)-2-azaspiro[3.3]heptan-2-yl)methanone;
- 5 (4-(3-methoxyoxetan-3-yl)phenyl)(6-(4-(trifluoromethyl)phenoxy)-2-azaspiro[3.3]heptan-2-yl)methanone;
- (4-(4-hydroxypiperidin-4-yl)phenyl)(5-(4-(trifluoromethyl)phenoxy)hexahydrocyclopenta[c]pyrrol-2(1H)-yl)methanone hydrochloride;
- 10 (4-(4-methoxypiperidin-4-yl)phenyl)(5-(4-(trifluoromethyl)phenoxy)hexahydrocyclopenta[c]pyrrol-2(1H)-yl)methanone hydrochloride;
- tert-butyl 4-hydroxy-4-(4-(5-(4-(trifluoromethyl)phenoxy)octahydrocyclopenta[c]pyrrole-2-carbonyl)phenyl)piperidine-1-carboxylate;
- 15 (4-(4-(3-methoxyoxetan-3-yl)benzoyl)piperazin-1-yl)(4-(trifluoromethyl)phenyl)methanone;
- (4-(3-methoxyoxetan-3-yl)phenyl)(2-(4-(trifluoromethyl)phenoxy)-7-azaspiro[3.5]nonan-7-yl)methanone;
- 20 (4-(3-methoxyoxetan-3-yl)phenyl)(4-((5-(trifluoromethyl)thiophen-3-yl)oxy)piperidin-1-yl)methanone;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((5-(methylthio)pyrimidin-2-yl)amino)piperidin-1-yl)methanone;
- N-(1-(4-(3-hydroxyoxetan-3-yl)benzoyl)piperidin-4-yl)-4-(trifluoromethyl)benzenesulfonamide;
- 25 (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((5-(trifluoromethyl)thiophen-3-yl)oxy)piperidin-1-yl)methanone;
- (3-(3-hydroxyoxetan-3-yl)phenyl)(4-(3-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;
- 30 (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((6-(trifluoromethyl)pyridin-3-yl)amino)piperidin-1-yl)methanone;
- (4-(4-hydroxytetrahydro-2H-pyran-4-yl)phenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;

- (4-(3-hydroxyoxetan-3-yl)-3,5-dimethoxyphenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;
(4-(3-hydroxyoxetan-3-yl)phenyl)(4-((5-(trifluoromethyl)pyridin-2-yl)amino)piperidin-1-yl)methanone;
- 5 (3-(3-hydroxyoxetan-3-yl)phenyl)(4-((4-(trifluoromethyl)phenyl)amino)piperidin-1-yl)methanone;
(4-(3-hydroxyoxetan-3-yl)phenyl)(4-((3-(trifluoromethyl)phenyl)amino)piperidin-1-yl)methanone;
(3-(3-hydroxyoxetan-3-yl)phenyl)(4-((3-(trifluoromethyl)phenyl)amino)piperidin-1-yl)methanone;
- 10 (2-fluoro-4-(3-hydroxyoxetan-3-yl)phenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;
(4-(3-hydroxyoxetan-3-yl)phenyl)(4-((4-(trifluoromethyl)pyrimidin-2-yl)oxy)piperidin-1-yl)methanone;
- 15 (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((4-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)methanone;
(4-(4-(difluoromethyl)phenoxy)piperidin-1-yl)(4-(3-hydroxyoxetan-3-yl)phenyl)methanone;
(4-(3-hydroxyoxetan-3-yl)phenyl)(4-(4-(trifluoromethyl)phenoxy)azepan-1-yl)methanone;
- 20 (4-(3-hydroxyoxetan-3-yl)-2-methoxyphenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;
(4-(3-hydroxyoxetan-3-yl)phenyl)(4-(4-thiomorpholinophenoxy)piperidin-1-yl)methanone;
- 25 (4-(3-hydroxytetrahydrofuran-3-yl)phenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;
(4-(3-hydroxyoxetan-3-yl)phenyl)(4-((5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidin-1-yl)methanone;
(5-(3-hydroxyoxetan-3-yl)pyridin-3-yl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;
- 30 (5-(3-hydroxyoxetan-3-yl)pyridin-3-yl)(5-(4-(trifluoromethyl)phenoxy)hexahydrocyclopenta[c]pyrrol-2(1H)-yl)methanone;

- (4-(3-hydroxyoxetan-3-yl)phenyl)(3-(4-(trifluoromethyl)phenoxy)azetidin-1-yl)methanone;
- (4-(3-methoxyoxetan-3-yl)phenyl)(3-(4-(trifluoromethyl)phenoxy)azetidin-1-yl)methanone;
- 5 (3-(3-hydroxyoxetan-3-yl)phenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(3-(4-(trifluoromethyl)phenoxy)-8-azabicyclo[3.2.1]octan-8-yl)methanone;
- (3-(3-hydroxyoxetan-3-yl)phenyl)(3-(4-(trifluoromethyl)phenoxy)-8-azabicyclo[3.2.1]octan-8-yl)methanone;
- 10 (4-(3-hydroxyoxetan-3-yl)phenyl)(5-(4-(trifluoromethyl)benzyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methanone;
- 4-(3-hydroxyoxetan-3-yl)-N-(1-(4-(trifluoromethyl)benzyl)pyrrolidin-3-yl)benzamide;
- 15 4-(3-hydroxyoxetan-3-yl)-N-(1-(3-(trifluoromethyl)benzyl)pyrrolidin-3-yl)benzamide;
- 4-(3-hydroxyoxetan-3-yl)-N-(1-(2-(trifluoromethyl)benzyl)pyrrolidin-3-yl)benzamide;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((4-(trifluoromethyl)benzyl)amino)piperidin-1-yl)methanone;
- 20 (4-(3-hydroxyoxetan-3-yl)phenyl)(4-(methyl(4-(trifluoromethyl)benzyl)amino)piperidin-1-yl)methanone;
- 2-(4-(3-hydroxyoxetan-3-yl)phenyl)-2-methyl-1-(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)propan-1-one;
- 25 2-(4-(3-methoxyoxetan-3-yl)phenyl)-2-methyl-1-(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)propan-1-one;
- (3-fluoro-4-(3-hydroxyoxetan-3-yl)phenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;
- (4-(3-hydroxyoxetan-3-yl)-3-methylphenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;
- 30 (3-(3-methoxyoxetan-3-yl)phenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;

- (3-fluoro-4-(3-methoxyoxetan-3-yl)phenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;
 (4-(3-methoxyoxetan-3-yl)-3-methylphenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;
 5 tert-butyl 3-hydroxy-3-(4-(4-(4-(trifluoromethyl)phenoxy)piperidine-1-carbonyl)phenyl)pyrrolidine-1-carboxylate;
 (4-(3-hydroxyoxetan-3-yl)-2-methylphenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;
 (4-(3-methoxyoxetan-3-yl)-2-methylphenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;
 10 (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((5-(trifluoromethyl)pyridin-2-yl)oxy)piperidin-1-yl)methanone;
 (4-(3-methoxyoxetan-3-yl)phenyl)(4-((5-(trifluoromethyl)pyridin-2-yl)oxy)piperidin-1-yl)methanone;
 15 (4-(3-hydroxyoxetan-3-yl)-3-methoxyphenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;
 (4-(3-hydroxyoxetan-3-yl)-2,6-dimethylphenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;
 (3-methoxy-4-(3-methoxyoxetan-3-yl)phenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;
 20 (4-(3-methoxyoxetan-3-yl)-2,6-dimethylphenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;
 tert-butyl 4-hydroxy-4-(4-(4-(4-(trifluoromethyl)phenoxy)piperidine-1-carbonyl)phenyl)piperidine-1-carboxylate;
 25 (4-(4-hydroxypiperidin-4-yl) phenyl)(4-(4-(trifluoromethyl) phenoxy) piperidin-1-yl) methanone hydrochloride;
 3-(4-(4-(4-(trifluoromethyl)phenoxy)piperidine-1-carbonyl)phenyl)oxetan-3-yl acetate;
 (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((6-(trifluoromethyl)pyridin-3-yl)oxy)piperidin-1-yl)methanone;
 30 (3-(3-hydroxyoxetan-3-yl)phenyl)(4-((6-(trifluoromethyl)pyridin-3-yl)oxy)piperidin-1-yl)methanone;

- (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((4-(trifluoromethyl)phenyl)thio)piperidin-1-yl)methanone;
(3-(3-hydroxyoxetan-3-yl)phenyl)(4-((4-(trifluoromethyl)phenyl)thio)piperidin-1-yl)methanone;
- 5 (4-(3-hydroxyoxetan-3-yl)phenyl)(5-(4-(trifluoromethyl)phenoxy)hexahydrocyclopenta[c]pyrrol-2(1H)-yl)methanone;
(3-(3-hydroxyoxetan-3-yl)phenyl)(5-(4-(trifluoromethyl)phenoxy)hexahydrocyclopenta[c]pyrrol-2(1H)-yl)methanone;
(4-(3-hydroxyoxetan-3-yl)phenyl)(4-(4-(trifluoromethyl)benzylidene)piperidin-1-yl)methanone;
- 10 (4-(3-hydroxyoxetan-3-yl)phenyl)(4-(4-(trifluoromethyl)benzyl)piperidin-1-yl)methanone;
(3-(3-hydroxyoxetan-3-yl)phenyl)(4-(4-(trifluoromethyl)benzyl)piperidin-1-yl)methanone;
- 15 (4-(3-methoxyoxetan-3-yl)phenyl)(4-(4-(trifluoromethyl)benzyl)piperidin-1-yl)methanone;
(4-(3-hydroxyoxetan-3-yl)phenyl)(4-((4-(trifluoromethyl)phenyl)sulfonyl)piperazin-1-yl)methanone;
(3-(3-methoxyoxetan-3-yl)phenyl)(4-(4-(trifluoromethyl)benzyl)piperidin-1-yl)methanone;
- 20 (4-(3-methoxyoxetan-3-yl)phenyl)(4-((4-(trifluoromethyl)phenyl)sulfonyl)piperazin-1-yl)methanone;
(4-(3-hydroxyoxetan-3-yl)phenyl)(4-(4-(trifluoromethyl)benzyl)piperazin-1-yl)methanone;
- 25 (4-(3-hydroxyoxetan-3-yl)phenyl)(5-(4-(trifluoromethyl)benzyl)hexahydrocyclopenta[c]pyrrol-2(1H)-yl)methanone;
(4-(3-hydroxyoxetan-3-yl)phenyl)(4-((6-(trifluoromethyl)benzo[d]thiazol-2-yl)oxy)piperidin-1-yl)methanone;
(4-(3-methoxyoxetan-3-yl)phenyl)(4-((6-(trifluoromethyl)benzo[d]thiazol-2-yl)oxy)piperidin-1-yl)methanone;
- 30 (4-(3-hydroxyoxetan-3-yl)phenyl)(4-((6-(trifluoromethyl)benzo[d]thiazol-2-yl)amino)piperidin-1-yl)methanone;

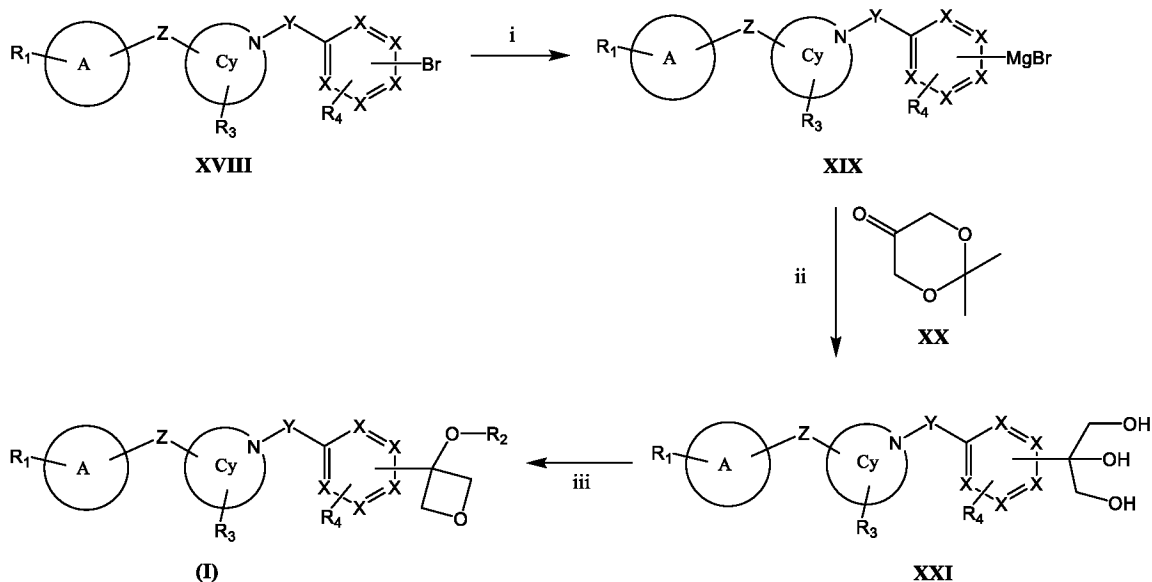
- (4-(3-methoxyoxetan-3-yl)phenyl)(4-(4-(trifluoromethoxy)phenoxy)piperidin-1-yl)methanone;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(4-(4-(trifluoromethoxy)phenoxy)piperidin-1-yl)methanone;
- 5 (4-(3-hydroxythietan-3-yl)phenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;
- (4-(3-hydroxy-1,1-dioxidothietan-3-yl)phenyl)(4-(4-(trifluoromethyl) phenoxy) piperidin-1-yl) methanone;
- (4-(3-hydroxythietan-3-yl)phenyl)(4-(4-(trifluoromethyl)benzyl)piperidin-1-yl)methanone;
- 10 (4-(3-hydroxythietan-3-yl)phenyl)(4-((5-(trifluoromethyl)pyridin-2-yl)oxy)piperidin-1-yl)methanone;
- (4-(3-hydroxytetrahydrothiophen-3-yl)phenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;
- 15 (4-(4-hydroxytetrahydro-2H-thiopyran-4-yl)phenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;
- (4-(4-hydroxy-1,1-dioxidotetrahydro-2H-thiopyran-4-yl)phenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;
- (4-(3-methoxyoxetan-3-yl)phenyl)(4-(3-(4-(trifluoromethyl)phenoxy)propoxy)piperidin-1-yl)methanone;
- 20 (4-(3-hydroxyoxetan-3-yl)phenyl)(4-(3-(4-(trifluoromethyl)phenoxy)propoxy)piperidin-1-yl)methanone;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(4-(2-(4-(trifluoromethyl)phenoxy)ethoxy)piperidin-1-yl)methanone;
- 25 (4-(3-methoxyoxetan-3-yl)phenyl)(4-(2-(4-(trifluoromethyl)phenoxy)ethoxy)piperidin-1-yl)methanone;
- (4-(3-methoxyoxetan-3-yl)phenyl)(4-(2-(4-(trifluoromethyl)phenoxy)ethyl)piperidin-1-yl)methanone;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(4-(2-(4-(trifluoromethyl)phenoxy)ethyl)piperidin-1-yl)methanone;
- 30 (4-(3-hydroxyoxetan-3-yl)phenyl)(4-(2-((5-(trifluoromethyl)pyridin-2-yl)oxy)ethyl)piperidin-1-yl)methanone;

- (4-(3-methoxyoxetan-3-yl)phenyl)(4-(2-((5-(trifluoromethyl)pyridin-2-yl)oxy)ethyl)piperidin-1-yl)methanone;
N-(4-(3-hydroxyoxetan-3-yl)phenyl)-4-((6-(trifluoromethyl)pyridin-3-yl)oxy)piperidine-1-carboxamide;
- 5 N-(3-(3-hydroxyoxetan-3-yl)phenyl)-4-(4-(trifluoromethyl)phenoxy)piperidine-1-carboxamide;
N-(4-(3-hydroxyoxetan-3-yl)phenyl)-3-(4-(trifluoromethyl)phenoxy)-8-azabicyclo[3.2.1]octane-8-carboxamide;
N-(4-(3-hydroxyoxetan-3-yl)phenyl)-4-(4-(trifluoromethyl)phenoxy)piperidine-1-
- 10 carboxamide;
4-(2-chloro-4-(trifluoromethyl)phenoxy)-N-(4-(3-hydroxyoxetan-3-yl)phenyl)piperidine-1-carboxamide;
N-(4-(3-hydroxyoxetan-3-yl)phenyl)-5-(4-(trifluoromethyl)phenoxy)hexahydrocyclopenta[c]pyrrole-2(1H)-carboxamide;
- 15 N-(4-(3-hydroxyoxetan-3-yl)phenyl)-4-((6-(trifluoromethyl)benzo[d]thiazol-2-yl)amino)piperidine-1-carboxamide;
N-(4-(3-methoxyoxetan-3-yl)phenyl)-4-((6-(trifluoromethyl)benzo[d]thiazol-2-yl)amino)piperidine-1-carboxamide;
1-(4-(3-hydroxyoxetan-3-yl)benzoyl)-N-(4-(trifluoromethyl)phenyl)piperidine-4-
- 20 carboxamide;
N-(4-(3-hydroxyoxetan-3-yl)phenyl)-1-(4-(trifluoromethyl)benzyl)piperidine-4-carboxamide;
4-(3-hydroxyoxetan-3-yl)-N-(6-(3-(trifluoromethyl)phenoxy)pyridin-3-yl)benzamide;
- 25 N-(4-(3-methoxyoxetan-3-yl)phenyl)-6-(3-(trifluoromethyl)phenoxy)nicotinamide;
3-(4-(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)phenyl)oxetan-3-ol;
3-(3-morpholino-5-(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)phenyl)oxetan-3-ol;
- 30 (4-(3-hydroxyoxetan-3-yl)-2-morpholinophenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;
tert-butyl 4-(3-(3-hydroxyoxetan-3-yl)-5-(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)phenyl)piperazine-1-carboxylate;

- (4-(3-hydroxyoxetan-3-yl)-2-(piperazin-1-yl)phenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;
- (4-(3-hydroxyoxetan-3-yl)-2-(piperazin-1-yl)phenyl)(5-(4-(trifluoromethyl)phenoxy)hexahydrocyclopenta[c]pyrrol-2(1H)-yl)methanone;
- 5 1-(1-(4-(3-hydroxyoxetan-3-yl)benzoyl)piperidin-4-yl)-3-(4-(trifluoromethyl)phenyl)urea;
- 4-(4-(3-hydroxyoxetan-3-yl)benzoyl)-N-(4-(trifluoromethyl)phenyl)piperazine-1-carboxamide;
- tert-butyl 3-hydroxy-3-(4-(4-(4-(trifluoromethyl)phenoxy)piperidine-1-carbonyl)phenyl)azetidine-1-carboxylate;
- 10 tert-butyl 3-methoxy-3-(4-(4-(4-(trifluoromethyl)phenoxy)piperidine-1-carbonyl)phenyl)azetidine-1-carboxylate;
- (4-(3-methoxyazetidin-3-yl)phenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone hydrochloride;
- 15 (4-(3-hydroxythietan-3-yl)phenyl)(4-(3-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;
- (3-(3-hydroxyoxetan-3-yl)phenyl)(4-(4-(trifluoromethyl)benzyl)piperazin-1-yl)methanone;
- (4-(3-hydroxyoxetan-3-yl)phenyl)(4-(3-(trifluoromethyl)benzyl)piperidin-1-yl)methanone;
- 20 (3-(3-hydroxyoxetan-3-yl)phenyl)(4-(3-(trifluoromethyl)benzyl)piperidin-1-yl)methanone;
- N-(4-(3-methoxyoxetan-3-yl)phenyl)-4-(3-(trifluoromethyl)benzyl)piperidine-1-carboxamide;
- 25 (4-(3-methoxyoxetan-3-yl)phenyl)(4-(3-(trifluoromethyl)benzyl)piperazin-1-yl)methanone;
- 4-(3-hydroxyoxetan-3-yl)-N-((1r,4r)-4-(4-(trifluoromethyl)phenoxy)cyclohexyl)benzamide;
- (4-(4-hydroxypiperidin-4-yl)phenyl)(4-((4-(trifluoromethyl)phenyl)amino)piperidin-1-yl)methanone hydrochloride;
- 30 (4-(1-hydroxycyclobutyl)phenyl)(4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)methanone;

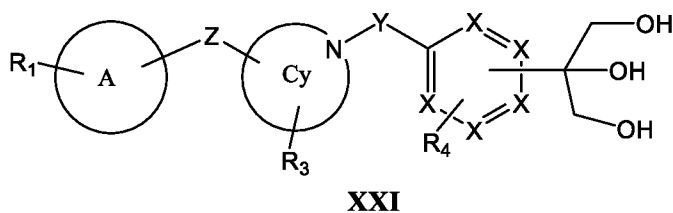
(4-(3-hydroxyoxetan-3-yl)phenyl)(4-(3-(trifluoromethyl)benzyl)piperazin-1-yl)methanone.

6. A process for the preparation of compound of formula (I) as claimed in claim 1 comprising following steps:



Wherein all symbols are as defined in claim 1; wherein reagents for step (i) is a suitable Grignard reagent and for step (ii) 2,2-dimethyl-1,3-dioxan-5-one; suitable solvents for step (i) and step (ii) are selected from as tetrahydrofuran, diethylether or suitable mixtures thereof; suitable temperature for range for reaction is selected from -78 °C to 28 °C.

7. An intermediate of formula XXI



Wherein all symbols are as defined in claim 1.

8. The compound of formula XXI as claimed in claim 7 is (4-(4-(trifluoromethyl)phenoxy)piperidin-1-yl)(4-(1,2,3-trihydroxypropan-2-yl)phenyl)methanone.

9. A pharmaceutical composition comprising a therapeutically effective amount of compound of formula (I) as claimed in claim 1 and suitable pharmaceutically acceptable excipients.
- 5 10. A pharmaceutical composition comprising compounds of formula (I) as claimed in claim 9 in combination with one or more pharmaceutically active agents selected from group comprising insulin, insulin derivatives and mimetics, insulin secretagogues, insulin sensitizers, biguanide agents, alpha-glucosidase inhibitors, insulinotropic sulfonylurea receptor ligands, meglitinides, GLP-1 (glucagon like
10 peptide-1), GLP- 1 analogs, dipeptidyl peptidase IV(DPP-IV) inhibitors, GPR- 1 19 activators, sodium-dependent glucose co-transporter (SGLT2) inhibitors, PPAR modulators, non-glitazone type PPAR.delta. agonist, HMG-CoA reductase inhibitors, cholesterol-lowering drugs, rennin inhibitors, anti-thrombotic and anti-platelet agents and anti-obesity agents or pharmaceutically acceptable salts thereof.
- 15 11. The use of compounds as claimed in claim 1 or pharmaceutical composition thereof for the treatment of hyperlipidemia, and other disorders related to hyperlipidemia.
- 20 12. Method of treating hyperlipidemia and disorders related to hyperlipidemia comprising the administering to a patient in need thereof therapeutically effective amount of a compound as claimed in claim 1 or pharmaceutical composition thereof.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2021/061988

A. CLASSIFICATION OF SUBJECT MATTER A61K45/06, C07D295/155, C07D477/00, C07D401/10, C07D305/08, A61P3/06, A61P3/04 Version=2022.01 According to International Patent Classification (IPC) or to both national classification and IPC																				
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) A61K, C07D, A61P Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) CAS REGISTRY, MARPAT, CAPLUS, PatSeer, IPO Internal Database																				
C. DOCUMENTS CONSIDERED TO BE RELEVANT <table border="1"> <thead> <tr> <th>Category*</th> <th>Citation of document, with indication, where appropriate, of the relevant passages</th> <th>Relevant to claim No.</th> </tr> </thead> <tbody> <tr> <td>X</td> <td>WO 2011/142359 A1 (NISSAN CHEMICAL INDUSTRIES, LTD., [JP]) 17 November 2011 (17.11.2011) Abstract, Paragraphs [0003], [0004], [0244], [0377], and Example 1;</td> <td>1-4, 9-11</td> </tr> <tr> <td>A</td> <td>Abstract, Paragraphs [0003], [0004], [0244], [0377], and Examples 1, 111-4;</td> <td>5-8</td> </tr> <tr> <td>X</td> <td>CAS REGISTRY Database [RN: 443910-67-6, Entered STN on 14 August 2002 (14.08.2002), RN: 2030748-57-1, Entered STN on 14 November 2016 (14.11.2016), RN: 1574166-92-9, Entered STN on 26 March 2014 (26.03.2014)] Respective compounds;</td> <td>1-4</td> </tr> <tr> <td>A</td> <td>WO 2011/029808 A1 (HOFFMANN-LA ROCHE AG, [CH]) 17 March 2011 (17.03.2011) Abstract, Page 5 lines 7-15, Claims 15, 16, and Examples 1-7;</td> <td>1-11</td> </tr> <tr> <td>A</td> <td>WO 2014/192023 A1 (CADILA HEALTHCARE LIMITED, [IN]) 4 December 2014 (14.12.2014) Abstract, Claims 7-13, and Examples 23-27, 29-34;</td> <td>1-11</td> </tr> </tbody> </table>			Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.	X	WO 2011/142359 A1 (NISSAN CHEMICAL INDUSTRIES, LTD., [JP]) 17 November 2011 (17.11.2011) Abstract, Paragraphs [0003], [0004], [0244], [0377], and Example 1;	1-4, 9-11	A	Abstract, Paragraphs [0003], [0004], [0244], [0377], and Examples 1, 111-4;	5-8	X	CAS REGISTRY Database [RN: 443910-67-6, Entered STN on 14 August 2002 (14.08.2002), RN: 2030748-57-1, Entered STN on 14 November 2016 (14.11.2016), RN: 1574166-92-9, Entered STN on 26 March 2014 (26.03.2014)] Respective compounds;	1-4	A	WO 2011/029808 A1 (HOFFMANN-LA ROCHE AG, [CH]) 17 March 2011 (17.03.2011) Abstract, Page 5 lines 7-15, Claims 15, 16, and Examples 1-7;	1-11	A	WO 2014/192023 A1 (CADILA HEALTHCARE LIMITED, [IN]) 4 December 2014 (14.12.2014) Abstract, Claims 7-13, and Examples 23-27, 29-34;	1-11
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☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.																				
* Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "D" document cited by the applicant in the international application "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family																				
Date of the actual completion of the international search 07-04-2022		Date of mailing of the international search report 07-04-2022																		
Name and mailing address of the ISA/ Indian Patent Office Plot No.32, Sector 14, Dwarka, New Delhi-110075 Facsimile No.		Authorized officer Veera R Kattula Telephone No. +91-1125300200																		

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2021/061988

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 12
because they relate to subject matter not required to be searched by this Authority, namely:
The subject matter of claim 12 is related to a method of treatment of the human or animal body by surgery or therapy or to a diagnostic method, which does not require an international search by this Authority in accordance with PCT Article 17(2)(a)(i) and Rule 39.1(iv).
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IB2021/061988

Citation	Pub.Date	Family	Pub.Date
WO 2011142359 A1	17-11-2011	TW 201211053 A	16-03-2012
		JP WO2011142359 A1	22-07-2013
WO 2011029808 A1	17-03-2011	US 20110065707 A1	17-03-2011
		EP 2475644 B1	08-01-2014
		IN 2012DN01232 A	15-05-2015
		CN 102498099 B	29-10-2014
		JP 5642793 B2	17-12-2014
		KR 101369551 B1	04-03-2014
WO 2014192023 A1	04-12-2014	IN 2013MN01811 A	08-05-2015