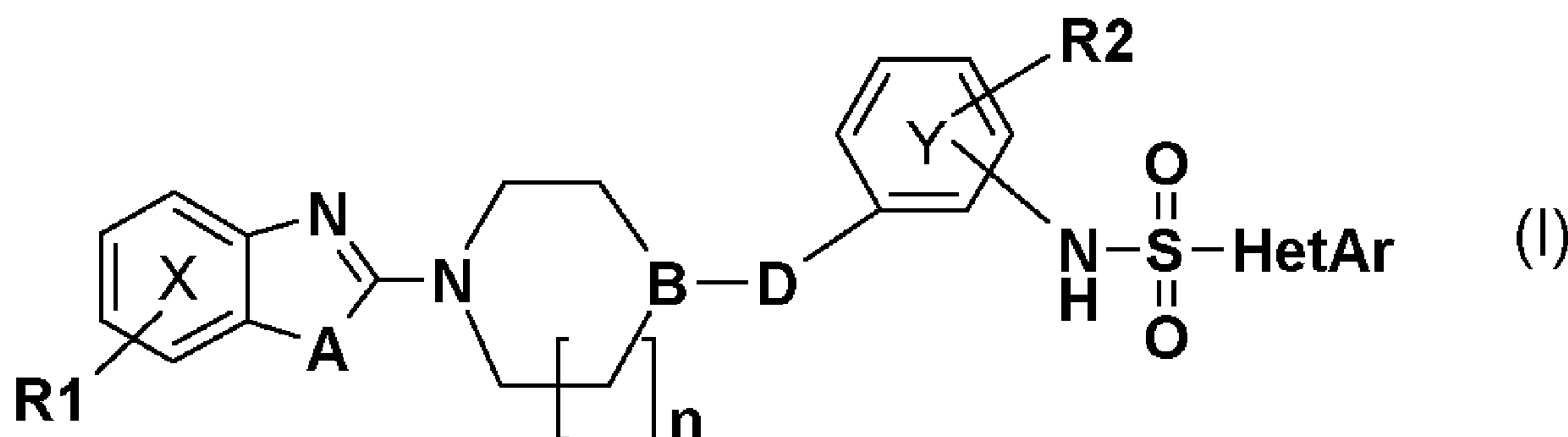




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(54) Title: DERIVATIVES OF HETEROARYLSULFONAMIDES, THEIR PREPARATION AND THEIR APPLICATION IN HUMAN THERAPY



(57) **Abrégé/Abstract:**

The present invention concerns derivatives of heteroarylsulfonamides, notably as blockers of Kv potassium channels, and more particularly of channels Kv1.5, Kv4.3 or Kv11.1, their application in clinical therapy and their preparation methods. These compounds correspond to the following general formula (I): where R1 represents one or more substituents of the phenyl core X such as: hydrogen, halogen, trifluoromethyl, trifluoromethoxy, linear or branched C₁-C₄ alkyl, or linear or branched C₁-C₄ alkoxy, A represents oxygen or sulphur, B represents nitrogen when n=1 or 2 and D represents -C(=O)-, or B represents CH when n=0 and D represents -CH₂O- or when n=1 and D represents -O-, R2 represents a hydrogen, a methyl, a fluorine or chlorine atom or a methoxy, HetAr represents a pyridyl or quinolyl group, possibly substituted by a group such as a linear or branched C₁-C₄ alkyl, a linear or branched C₁-C₄ alkoxy, a halogen, or a trifluoromethyl, and to their pharmaceutically acceptable salts.



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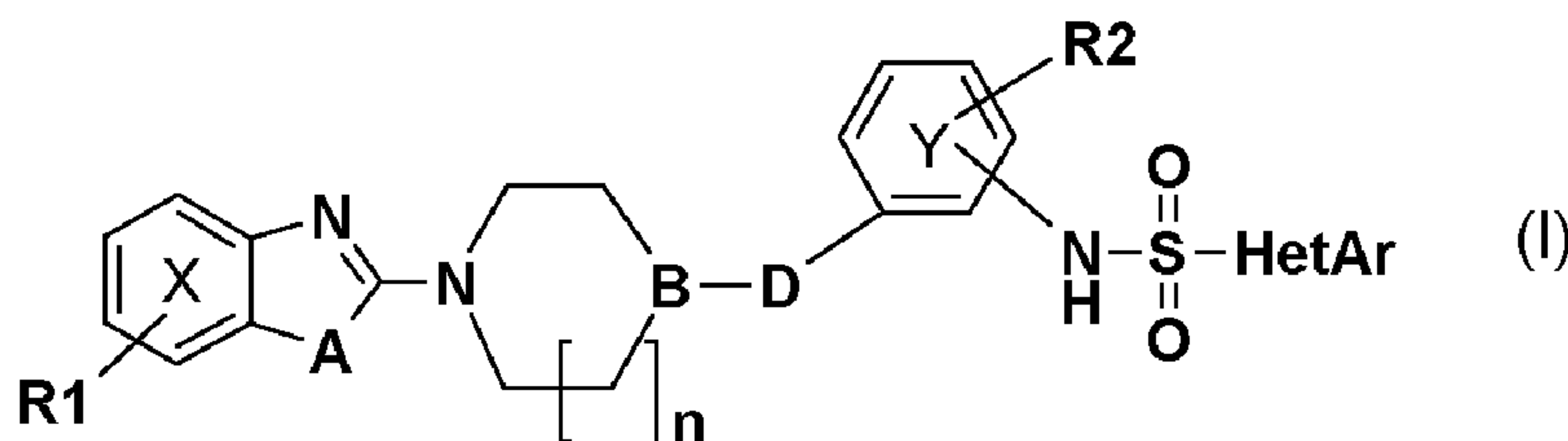
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(57) **Abstract**: The present invention concerns derivatives of heteroarylsulfonamides, notably as blockers of Kv potassium channels, and more particularly of channels Kv1.5, Kv4.3 or Kv11.1, their application in clinical therapy and their preparation methods. These compounds correspond to the following general formula (I): where R1 represents one or more substituents of the phenyl core X such as: hydrogen, halogen, trifluoromethyl, trifluoromethoxy, linear or branched C₁-C₄ alkyl, or linear or branched C₁-C₄ alkoxy, A represents oxygen or sulphur, B represents nitrogen when n=1 or 2 and D represents -C(=O)-, or B represents CH when n=0 and D represents -CH₂O- or when n=1 and D represents -O-, R2 represents a hydrogen, a methyl, a fluorine or chlorine atom or a methoxy, HetAr represents a pyridyl or quinolyl group, possibly substituted by a group such as a linear or branched C₁-C₄ alkyl, a linear or branched C₁-C₄ alkoxy, a halogen, or a trifluoromethyl, and to their pharmaceutically acceptable salts.

DERIVATIVES OF HETEROARYLSULFONAMIDES, THEIR PREPARATION AND THEIR APPLICATION IN HUMAN THERAPY

The present invention concerns derivatives of heteroarylsulfonamides, their
5 preparation and their applications in human therapy, as blockers of Kv potassium
channels and specifically channels Kv1.5, Kv4.3 and Kv11.1.

Potassium channels represent the largest family of ion channels in the human
genome, with approximately 80 genes (Tamargo et al., Cardiovasc. Res. 2004, 62: 9-
33). These potassium channels can be subdivided into 3 sub-families: channels
10 activated by potential or voltage (K_v channels) and calcium (K_{Ca} channels), inward
rectifier channels (K_{ir}) and two-pore potassium channels (K_{2p}). The sub-family of
voltage-activated channels is the one most represented in the human organism, with
an almost ubiquitous distribution in excitable cells (cardiac cells, neurons, striated or
smooth muscle cells) and non-excitable cells such as pancreatic, prostatic, parathyroid
15 cells, etc. (for review, Gutman G et al., Pharmacol. Rev. 2005, 57:473-508).

The main function of the Kv potassium channels in excitable cells is the control
of the resting membrane potential and of the action potential duration (Nerbonne and
Kass, Physiol. Rev. 2005, 85:1205-1253). As such, several Kv channels are involved in
this control, in both the heart auricles and ventricles. The Kv4.3 channels associated
20 with the KChIP 2 sub-units form the current I_{to} which is involved in the premature
repolarisation phase of the action potential (PA), the KVLQT1/MinK and hERG
channels which are involved in the late repolarisation phase of the PA (generating
respectively currents I_{Ks} and I_{Kr}). The abovementioned channels are distributed
uniformly between the heart auricles and ventricles. However, two other types of
25 potassium channels show a distribution only in the auricles. The potential-dependent
potassium channels ($K_{v1.5}$) responsible for the current I_{Kur} and the acetylcholine-
activated inward rectifier channels (Kir3.1 and Kir3.4 responsible for current I_{K-Ach}).

Modifications of the membranous electrical activity are observed in many
pathologies, notably heart rhythm disorder pathologies. Among the latter, atrial
30 fibrillation (FA) is a serious rhythm disorder which corresponds to totally
desynchronised activity of the atrial myocytes resulting in interrupted, rapid and
irregular electrical activity. FA is caused by the appearance of electrical reentry circuits
in the atrial tissue (Miyasaka Y et al., Circulation 2006, 114:119-125). There is currently
no specific anti-arhythmic treatment of the atrial stage to reduce the incidence of FA,

which therefore constitutes an important medical need (Page and Roden, Nat. Rev. Drug Discov. 2005, 4:899-910).

The presence of many simultaneously activated micro-reentry circuits explains the anarchic character of the electrical activity observed either by intracavitary means or in electrocardiograms. This rhythmic disorder generally develops on a pathological atrial myocardium in electrophysiological terms, the refractory periods of which are too short and too unequal, and therefore very vulnerable to the smallest extrasystole. These anomalies form part of a phenomenon of myocardial remodelling, following a pressure overload or a stretching causing morphological alterations (hypertrophy, dilatation, fibrosis), as well as modifications in the regulation of the trans-membranous ionic currents, modifying the electrophysiological characteristics of the atrial myocytes. Given that each FA access maintains, or aggravates, this mechanical and electrophysiological remodelling process, it will be understood that FA has a great potential risk of recurrence, and that its natural development is towards chronicity. Conversely, focal-type FAs have recently been identified, originating in a precise point, which is almost always found to be an extension of the atrial myocardium in the pulmonary veins.

These quite rare cases of FA have a quite monomorphous character, and in any event one which is comparable to that of atrial extrasystoles initiating access, or observed intermittently between crises. In all cases, the consequence of the loss of the atrial systole is a reduction in the heart rate of between 20 and 30%, and higher the more the rate is reduced to the basal state. Simultaneously, the existence of blood stasis in the atrial cavities, notably in certain pockets such as the auricles, accounts for the thromboembolic risk. However, the embolic risk is only partially conditional on the presence of the FA alone, since atrial stasis is also related to the increase of intracavitary pressures (systolic or diastolic left ventricular dysfunction, valvular heart disease or valve replacement).

Electrical remodelling therefore constitutes the major substrate of the genesis of the FA; it results from a diminution of the activity of the L-type calcic channels allowing the Kv1.5 potassium channels to play fully their repolarising role through the ultra-rapid potassium current (Bhakta and Miller, Expert Opin. Ther. Targets 2007, 11:1161-1178). Its consequence is a dramatic shortening of the refractory period, which constitutes the triggering factor of micro-reentries. Bearing in mind that the Kv1.5 potassium channels are not expressed functionally in the ventricular stage, a blocker of these channels will therefore constitute a selected anti-arhythmic of the atrial stage without affecting the

ventricular electrophysiology. Its pharmacological effect takes the form of a lengthening of the refractory period, and therefore a lesser incidence of micro-reentry circuits. A quantity of experimental data obtained with reference products confirms the interest of the blockage of Kv1.5 as a therapeutic target (Gögelein et al., Naunyn Schmiedeberg's Arch. Pharmacol. 2004, 370:183-192; Regan et al., J. Pharmacol. Exp. Ther. 2008, 324:322-330).

Rapid changes of membrane potential are well-known in excitable cells, but slow variations of potential are observed in all the cells and are associated with the control of the cell cycle. The cell cycle is a key parameter in cell behaviour, which must be regulated and coordinated for development, tissue regeneration and cell proliferation (Pardo, Physiology, 2004, 19:285-292; Blackiston et al., Cell Cycle, 2009, 8-21:3527-3536). Generally speaking, the blockage of the potassium channels leads to reduced proliferation in physiological models (as in lymphocytes) and pathological models (cancer). The role of the potassium channels in regulating the cell cycle has been demonstrated in many cell types, whether physiological or pathological (cancer cell lines or tumours) originating from human melanoma, lung cancer, lymphoma, mesothelioma, hepatocellular carcinoma, lymphocytes, monocytes (for review Pardo et al., J. Membr. Biol, 2005, 205:115-124).

As used previously, the term "Kv" indicates the family of voltage-dependent potassium channels, and includes various sub-families (Kv1., Kv2., Kv3. etc.) among which are the Kv1.1, Kv1.2, Kv1.3 channels, ... "A blocker of the Kv channels" denotes a molecule which reduces or blocks the K⁺ ion flow through the channel.

As used here, the term "salts" designates acid or base addition salts, notably mineral ones, of the compounds of the present invention, and notably base addition salts using bases such as LiOH, KOH or NaOH or acid addition salts using acids such as HCl. The salts are preferably pharmaceutically acceptable, i.e. they are non-toxic for the patient to whom they are administered. The term "pharmaceutically acceptable" refers to molecular entities and compositions producing no adverse or allergic effect, or other undesirable reaction when administered to an animal or a human. When used here, the term "pharmaceutically acceptable excipient" includes all diluents, additives or excipients, such as preservative agents, fillers, disintegrating agents, wetting agents, emulsifiers, dispersants, anti-bacterials or antifungals, or also agents allowing intestinal and digestive absorption and resorption to be slowed. The use of these media or vectors is well-known in the art. Unless the agent is chemically incompatible with a derivative of heteroarylsulfonamides its use in pharmaceutical compositions with the

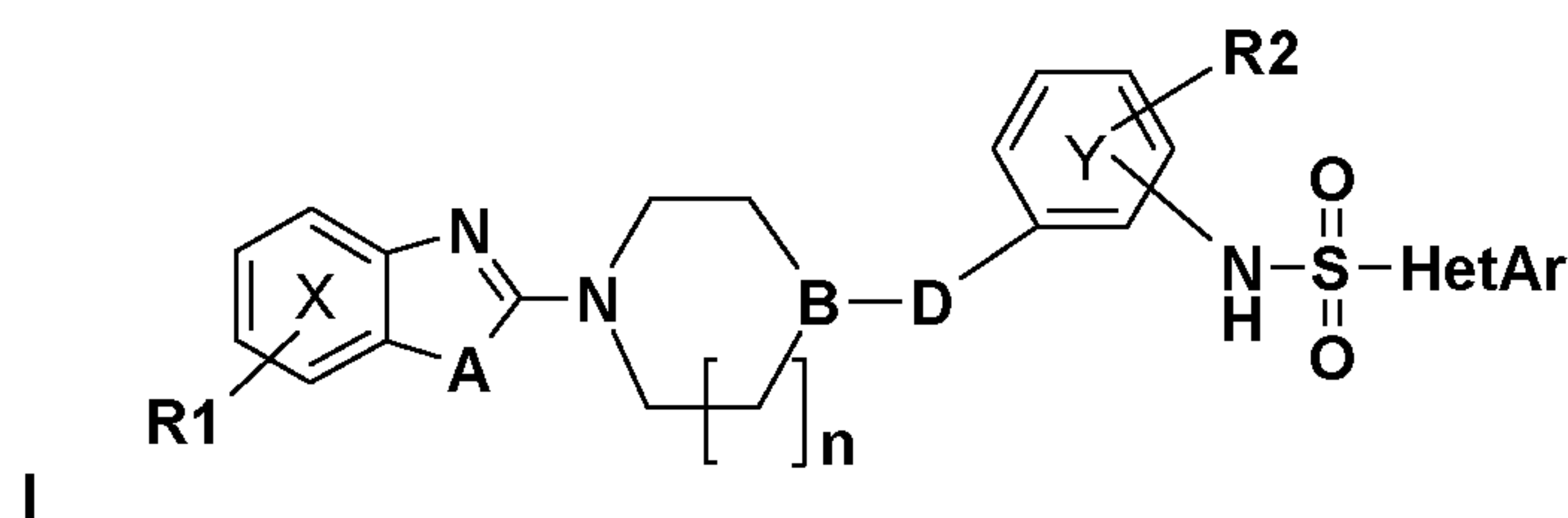
compounds according to the invention is envisaged. In the context of the invention, the term "treatment", as used here, means preventing or inhibiting the occurrence or progress of the affection to which the term applies, or one or more symptoms of this affection.

5

The purpose of the present invention is derivatives of heteroarylsulfonamides which are blockers of the Kv potassium channels (more specifically the Kv1.5, Kv4.3 and Kv11.1 channels) and their application in clinical therapy.

10

These compounds have the following general formula I:



where

15

R1 represents one or more substituents of the phenyl core X chosen from among the group consisting of: hydrogen, halogen (such as F, Cl, Br), trifluoromethyl, trifluoromethoxy, linear or branched C₁-C₄ alkyl, and linear or branched C₁-C₄ alkoxy,

n represents 0, 1 or 2,

A represents oxygen or sulphur,

20

D represents -C(=O)-, -CH₂O- or -O-,

B represents nitrogen when n=1 or 2 and **D** represents -C(=O)-,

or **B** represents CH when n=0 and **D** represents -CH₂O- or when n=1 and **D** represents -O-,

R2 represents a hydrogen, a methyl, a fluorine or chlorine atom or a methoxy,

25

HetAr represents a pyridyl or quinolyl group, possibly substituted by a group such as a linear or branched C₁-C₄ alkyl, a linear or branched C₁-C₄ alkoxy, a halogen (such as F, Cl, Br), or trifluoromethyl,

as well as their pharmaceutically acceptable salts.

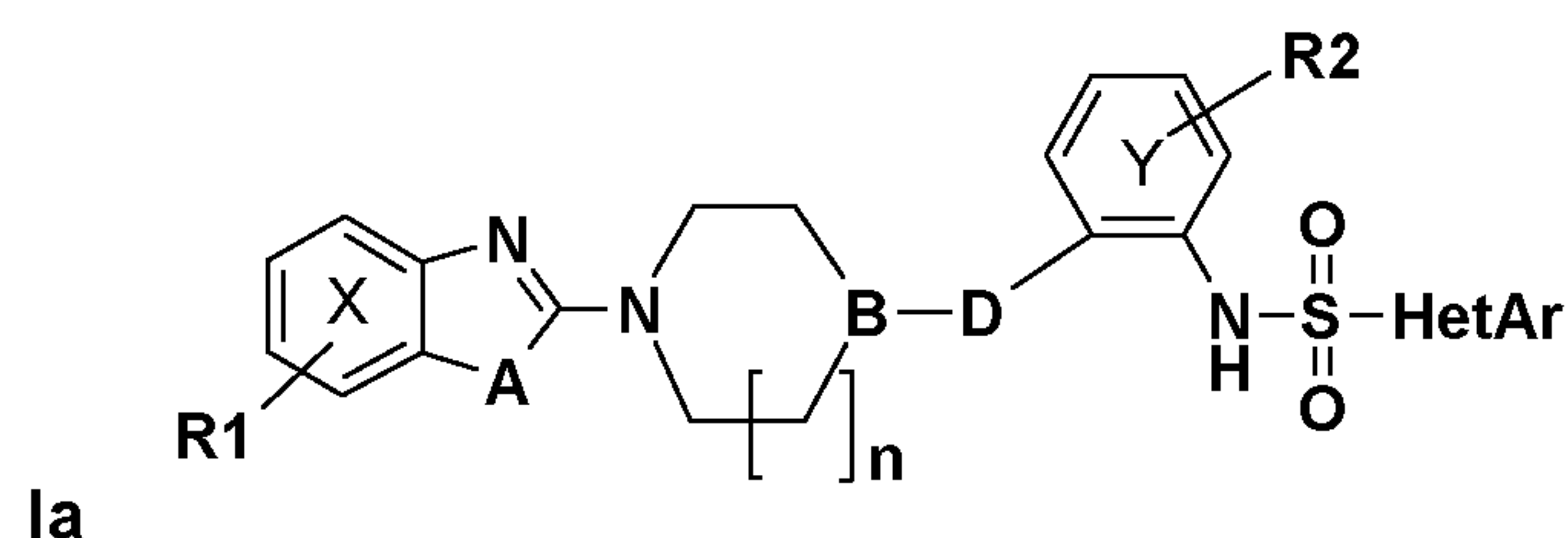
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The sulfonamide group (-NH-SO₂HetAr) can be located on the phenyl core Y in ortho, meta or para of the position occupied by group D.

“Linear or branched C₁-C₄ alkyl” means, in the sense of the present invention, a linear or branched hydrocarbon chain, including 1 to 4 carbon atoms, such as the methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl and tert-butyl groups.

“Linear or branched C₁-C₄ alkoxy”, means, in the sense of the present invention, a linear or branched C₁-C₄ alkyl group as defined above linked to the remainder of the molecule through an oxygen atom, such as the methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, sec-butoxy, isobutoxy and tert-butoxy groups.

According to an embodiment of the invention, the compounds of general formula I are those matching the following formula (Ia):



where **R1**, **R2**, **A**, **B**, **D**, **n** and **HetAr** are as defined above, as well as their pharmaceutically acceptable salts.

According to another embodiment of the invention, compounds of general formula I or Ia are those for which:

R1 represents one or more substituents of the phenyl core X chosen from among the group consisting of: hydrogen, halogen (such as F, Cl, Br), trifluoromethyl, trifluoromethoxy, linear or branched C₁-C₄ alkyl, and methoxy,

n represents 1,

A represents oxygen or sulphur,

D represents -C(=O)- or -O-,

B represents nitrogen when **D** represents -C(=O)-, or **B** represents CH when **D** represents -O-,

R2 represents a hydrogen,

HetAr represents a 2-pyridyl or 8-quinolyl group, possibly substituted by a group such as methyl or trifluoromethyl,

and the sulfonamide group (-NH-SO₂HetAr) is notably located on the phenyl core Y in ortho of the position occupied by group **D**,

as well as their pharmaceutically acceptable salts.

According to another embodiment of the invention, compounds of general formula **I** or **Ia** are those for which:

R1 represents one or more substituents of the phenyl group X chosen from among the group consisting of: hydrogen, halogen (such as F, Cl, Br), trifluoromethyl, trifluoromethoxy, linear or branched C₁-C₄ alkyl, and methoxy,

A represents sulphur,

n represents 1,

D represents -C(=O)-,

B represents nitrogen,

R2 represents a hydrogen,

HetAr represents a 2-pyridyl group, possibly substituted by a group such as methyl or trifluoromethyl,

and the sulfonamide group (-NH-SO₂HetAr) is located on the phenyl core Y in ortho of the position occupied by group **D**,

as well as their pharmaceutically acceptable salts.

The present invention concerns the compounds of general formula **I** characterised in that they are chosen from among:

- 1) N-(2-(4-(6-fluorobenzo[d]oxazol-2-yl)piperazine-1-carbonyl)phenyl)-5-(trifluoromethyl)pyridine-2-sulfonamide,
- 2) N-(2-(4-(6-fluorobenzo[d]thiazol-2-yl)piperazine-1-carbonyl)phenyl)-pyridine-2-sulfonamide,
- 3) N-(2-(4-(6-bromobenzo[d]thiazol-2-yl)piperazine-1-carbonyl)phenyl)-pyridine-2-sulfonamide,
- 4) N-(2-(4-(6-chlorobenzo[d]thiazol-2-yl)piperazine-1-carbonyl)phenyl)-pyridine-2-sulfonamide hydrochloride,
- 5) N-(2-(4-(4-methylbenzo[d]thiazol-2-yl)piperazine-1-carbonyl)phenyl)-pyridine-2-sulfonamide,
- 6) N-(2-(4-(7-chlorobenzo[d]thiazol-2-yl)piperazine-1-carbonyl)phenyl)-pyridine-2-sulfonamide,
- 7) N-(2-(4-(5-(trifluoromethyl)benzo[d]thiazol-2-yl)piperazine-1-carbonyl)phenyl)pyridine-2-sulfonamide,
- 8) N-(2-(4-(6-chlorobenzo[d]thiazol-2-yl)piperazine-1-carbonyl)phenyl)-5-(trifluoromethyl)pyridine-2-sulfonamide,

- 9) N-(2-(4-(6-bromobenzo[d]thiazol-2-yl)piperazine-1-carbonyl)phenyl)-6-methylpyridine-2-sulfonamide dihydrochloride,
- 10) N-(3-(4-(6-chlorobenzo[d]oxazol-2-yl)piperazine-1-carbonyl)-phenyl)-pyridine-2-sulfonamide,
- 5 11) N-(3-(4-(6-chlorobenzo[d]thiazol-2-yl)piperazine-1-carbonyl)-phenyl)-pyridine-2-sulfonamide,
- 12) N-(3-(4-(6-chlorobenzo[d]thiazol-2-yl)piperazine-1-carbonyl)-phenyl)-6-methylpyridine-2-sulfonamide,
- 13) N-(4-(4-(6-fluorobenzo[d]oxazol-2-yl)piperazine-1-carbonyl)-phenyl)-pyridine-2-sulfonamide,
- 10 14) N-(4-(4-(6-chlorobenzo[d]oxazol-2-yl)piperazine-1-carbonyl)-phenyl)-pyridine-2-sulfonamide,
- 15) N-(4-(4-(6-chlorobenzo[d]thiazol-2-yl)piperazine-1-carbonyl)-phenyl)-pyridine-2-sulfonamide,
- 15 16) N-(2-(4-(6-bromobenzo[d]thiazol-2-yl)piperazine-1-carbonyl)-phenyl)-quinoline-8-sulfonamide,
- 17) N-(2-(4-(6-chlorobenzo[d]oxazol-2-yl)piperazine-1-carbonyl)-phenyl)-quinoline-8-sulfonamide,
- 18) N-(2-(4-(6-chlorobenzo[d]thiazol-2-yl)piperazine-1-carbonyl)-phenyl)-quinoline-8-sulfonamide,
- 20 19) N-(2-(4-(6-(trifluoromethoxy)benzo[d]thiazol-2-yl)piperazine-1-carbonyl)-phenyl)quinoline-8-sulfonamide,
- 20) N-(2-(4-(4-methylbenzo[d]thiazol-2-yl)-1,4-diazepane-1-carbonyl)-phenyl)quinoline-8-sulfonamide,
- 25 21) N-(2-(1-(6-methylbenzo[d]oxazol-2-yl)piperidin-4-yloxy)phenyl)-pyridine-2-sulfonamide,
- 22) N-(2-(1-(6-chlorobenzo[d]oxazol-2-yl)piperidin-4-yloxy)phenyl)-pyridine-2-sulfonamide,
- 23) N-(2-(1-(5-tert-butylbenzo[d]oxazol-2-yl)piperidin-4-yloxy)phenyl)-pyridine-2-sulfonamide,
- 30 24) N-(2-(1-(5-chlorobenzo[d]oxazol-2-yl)piperidin-4-yloxy)phenyl)pyridine-2-sulfonamide,
- 25) N-(2-(1-(benzo[d]thiazol-2-yl)piperidin-4-yloxy)phenyl)pyridine-2-sulfonamide,

- 26) N-(2-(1-(6-chlorobenzo[d]thiazol-2-yl)piperidin-4-yloxy)phenyl-pyridine-2-sulfonamide,
- 27) N-(2-(1-(6-bromobenzo[d]thiazol-2-yl)piperidin-4-yloxy)phenyl)-pyridine-2-sulfonamide,
- 5 28) N-(2-((1-(benzo[d]thiazol-2-yl)pyrrolidin-3-yl)methoxy)phenyl)-pyridine-2-sulfonamide,
- 29) N-(2-((1-(6-fluorobenzo[d]thiazol-2-yl)pyrrolidin-3-yl)methoxy)phenyl)-pyridine-2-sulfonamide,
- 30) N-(2-((1-(6-chlorobenzo[d]thiazol-2-yl)pyrrolidin-3-yl)methoxy)phenyl)pyridine-2-sulfonamide,
- 10 31) N-(2-((1-(4-methylbenzo[d]thiazol-2-yl)pyrrolidin-3-yl)methoxy)phenyl)-pyridine-2-sulfonamide,
- 32) N-(2-((1-(4-methoxybenzo[d]thiazol-2-yl)pyrrolidin-3-yl)methoxy)phenyl)-pyridine-2-sulfonamide,
- 15 33) lithium N-(2-(4-(6-bromobenzo[d]thiazol-2-yl)piperazine-1-carbonyl)phenyl)-pyridine-2-sulfonamide,
- 34) sodium N-(2-(4-(6-bromobenzo[d]thiazol-2-yl)piperazine-1-carbonyl)phenyl)-pyridine-2-sulfonamide, and
- 35) potassium N-(2-(4-(6-bromobenzo[d]thiazol-2-yl)piperazine-1-carbonyl)phenyl)-pyridine-2-sulfonamide.
- 20

The purpose of the invention also concerns the pharmaceutically acceptable salts of the compounds of general formula I.

25 The present invention also concerns the compounds of general formula I as well as their pharmaceutically acceptable salts for their use as a medicine.

The present invention also concerns the compounds of general formula I as well as their pharmaceutically acceptable salts for their use as blockers of Kv potassium channels, and more particularly of the Kv1.5, Kv4.3 or Kv11.1 channels.

30

The invention also concerns the compounds of general formula I as well as their pharmaceutically acceptable salts for their use as medicine intended for the treatment and/or prevention of illnesses requiring blockers of Kv potassium channels, and more particularly channels Kv1.5, Kv4.3 and Kv11.1.

35

The invention also concerns the compounds of general formula I as well as their pharmaceutically acceptable salts for their use as medicine intended for the treatment and/or prevention of atrial fibrillation, heart rhythm disorders of the auricles and/or the ventricles, and pathologies in which the cell cycle and/or cell proliferation and/or
5 regeneration are impaired (cancer, chronic inflammation).

“Impaired” is understood to mean a deterioration from an initial state.

The invention also extends to pharmaceutical compositions characterised in
10 that they contain as their active principle a compound of general formula I or one of its pharmaceutically acceptable salts.

The invention also concerns a pharmaceutical composition characterised in that it contains a compound of general formula I or one of its pharmaceutically acceptable
15 salts in association with at least one pharmaceutically acceptable excipient.

The pharmaceutical compositions according to the invention can be administered orally, sublingually, subcutaneously, intramuscularly, intravenously, transdermally, locally or rectally. In this case the active ingredient may be administered
20 in the form of administration units, blended with traditional pharmaceutical supports, to animals or to human beings. The appropriate administration unit forms include orally administered forms such as pills, capsules, powders, granules and oral solutions or suspensions, sublingual and by-mouth forms of administration, the subcutaneous, topical, intramuscular, intravenous, intranasal or intraocular forms of administration,
25 and the rectal forms of administration. The formulations appropriate for the chosen form of administration are known by the skilled man in the art and described, for example, in: Remington, The science and Practice of Pharmacy, 19th edition, 1995, Mack Publishing Company.

30 The dosages of the compounds of formula I in the compositions of the invention can be adjusted to obtain a quantity of active substance which is effective in obtaining the desired therapeutic response for a composition particular to the method of administration. The effective dose of a compound of the invention varies according to numerous parameters such as, for example, the chosen method of administration,
35 weight, age, sex, the nature of the pathology and the sensitivity of the individual

requiring treatment. Accordingly, the optimum posology must be determined in accordance with parameters judged relevant, by the specialist in the field.

The present invention also extends to the methods of chemical preparation of the compounds of general formula I as notably defined below.

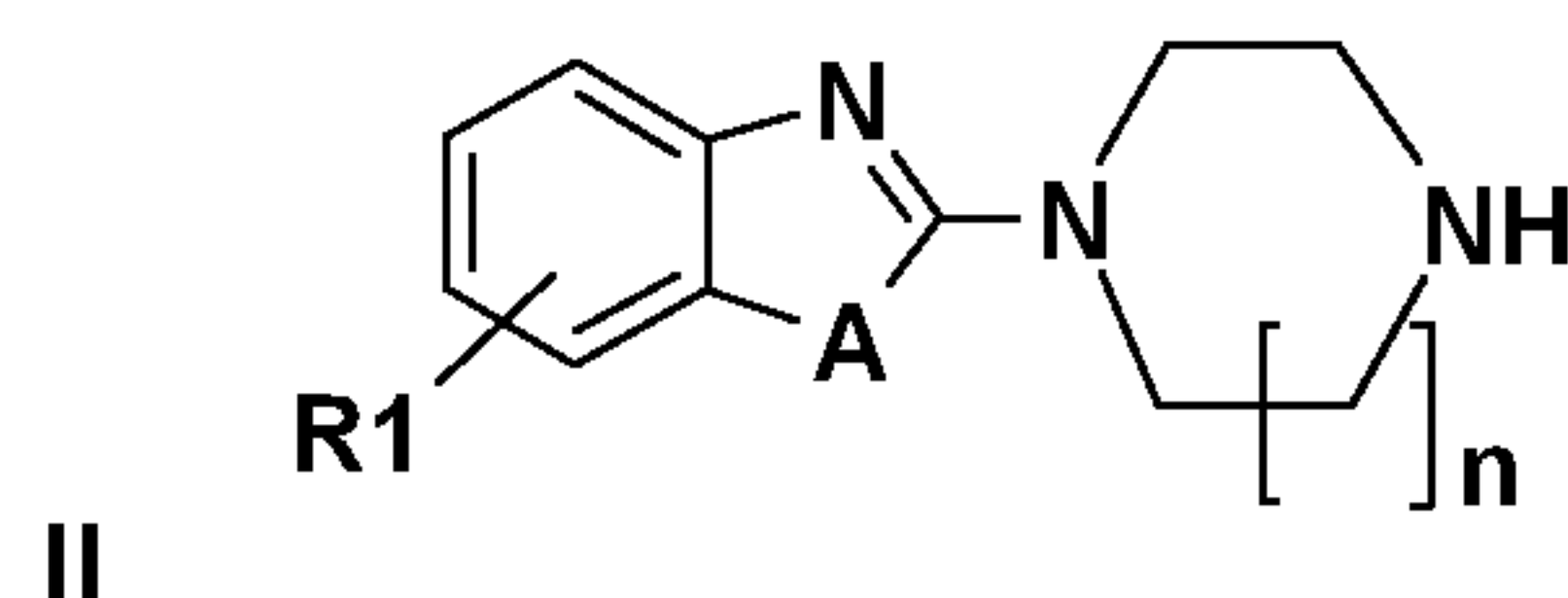
SYNTHESIS

The compounds of the present invention can be synthesised by using the methods of synthesis described below, or by using methods of synthesis known to the skilled man in the art.

Method 1 (when B = N)

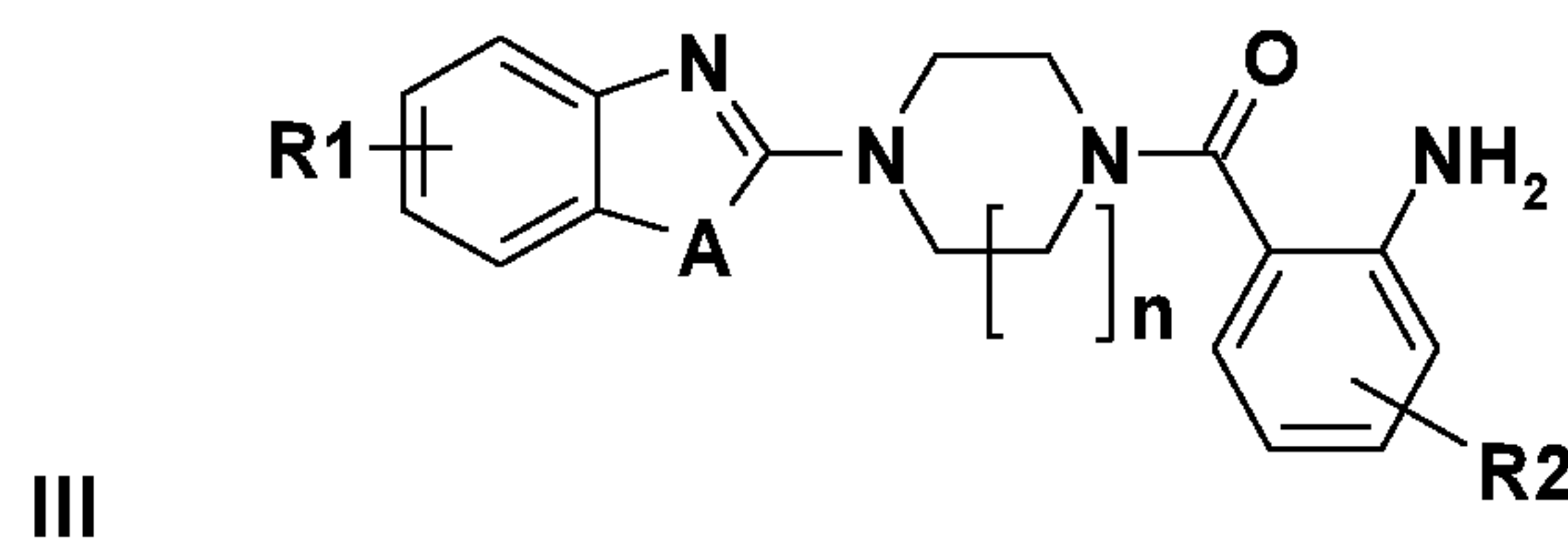
This method of synthesis of the compounds of general formula I with **B** = N (diagram 1) is characterised by the following successive steps:

(a1) A derivative of general formula II for which **R1**, **A** and **n** are as defined in general formula I is condensed,

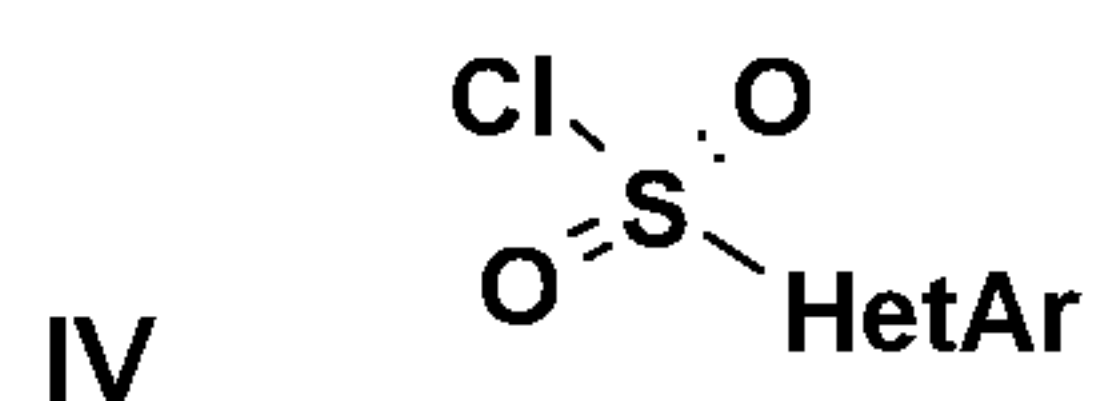


with a derivative of isatoic anhydride **XV** for which **R2** is as defined in general formula I, in the presence of a base such as DMAP, notably in a blend of solvents such as THF and DMF.

(a2) The intermediate III obtained

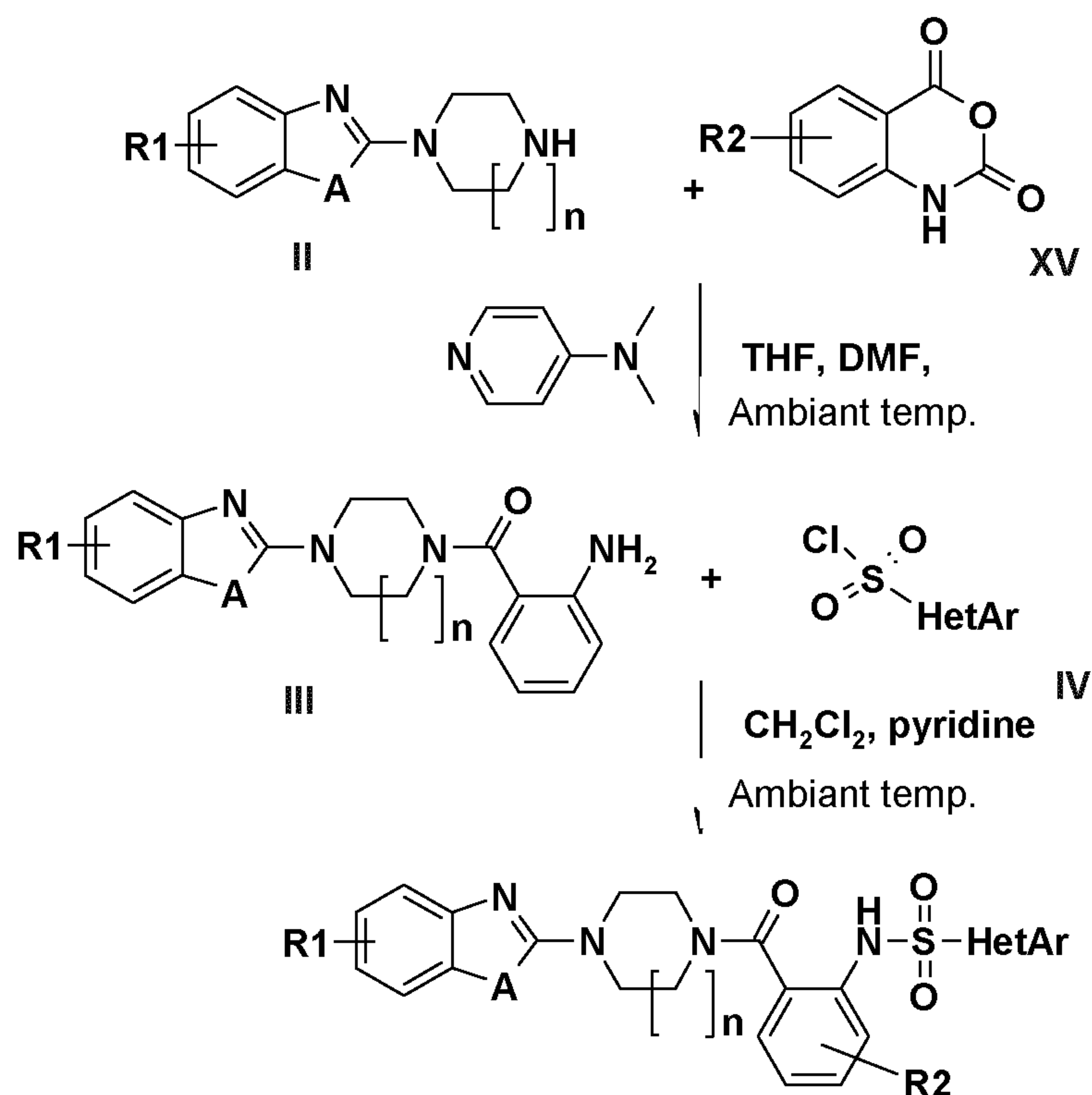


is then condensed with a sulfonyl chloride of general formula IV for which **HetAr** is as defined in general formula I



in the presence of a base such as pyridine, notably in a solvent such as dichloromethane.

(a3) The compound of formula I obtained in the previous step (a2) may be salified in the presence of a pharmaceutically acceptable base or acid in order to give a pharmaceutically acceptable salt of the compound of formula I.



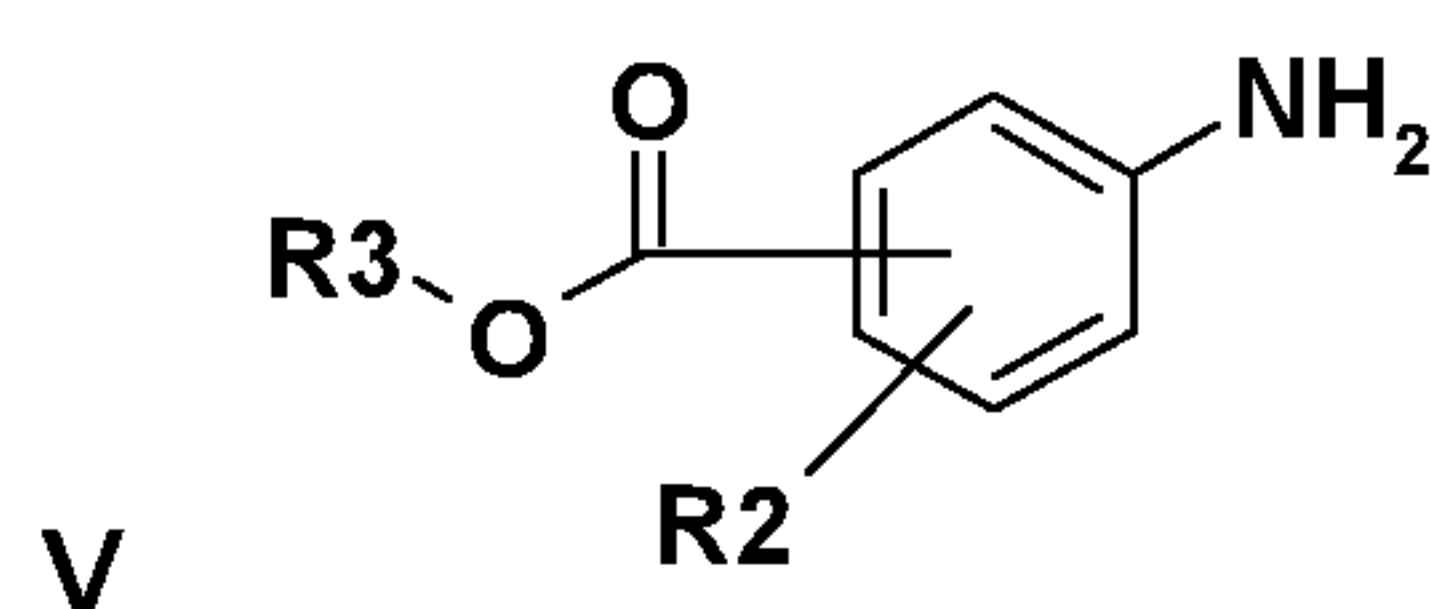
5

Diagram 1:

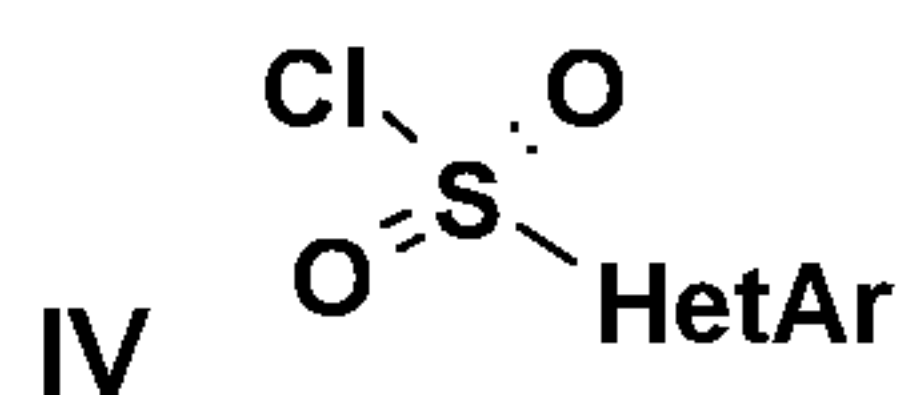
Method 2 (when B = N)

This method of synthesis of the compounds of general formula I with B = N (diagram 2) is characterised by the following successive steps:

- 10 (b1) A derivative of general formula V for which R3 represents a linear or branched C₁-C₄ alkyl such as a methyl or ethyl and R2 is such as defined in general formula I is condensed,

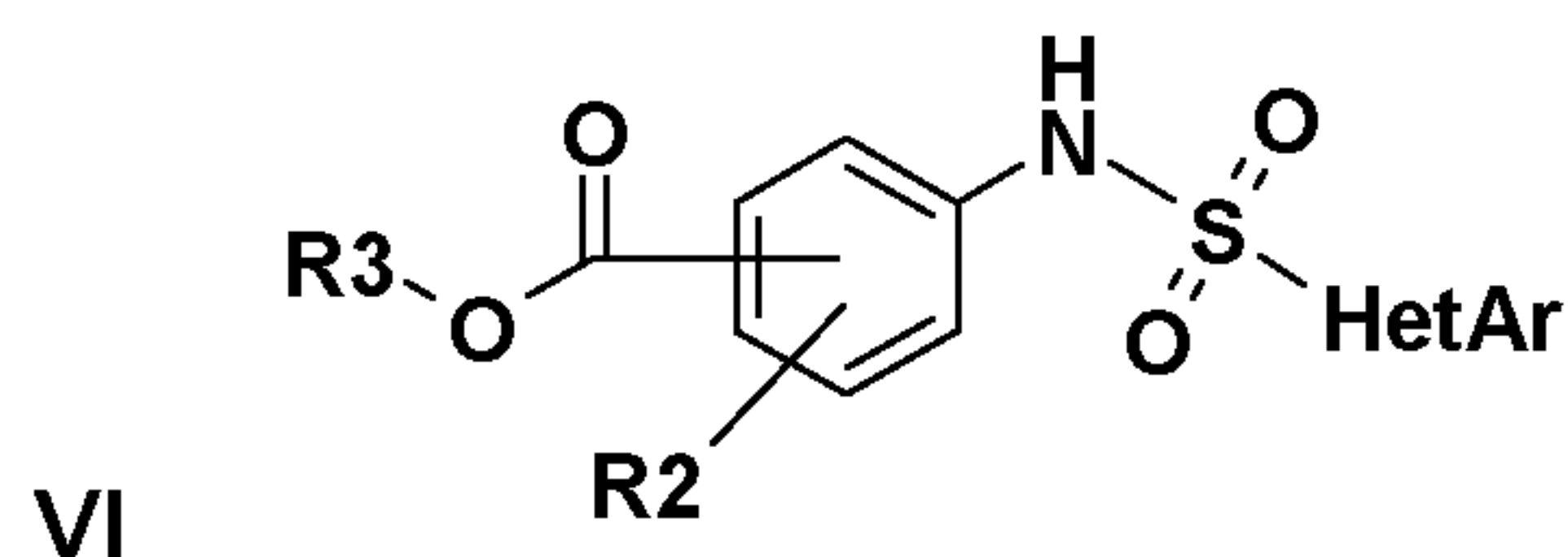


15 with a sulfonyl chloride of general formula IV for which HetAr is as defined in general formula I.

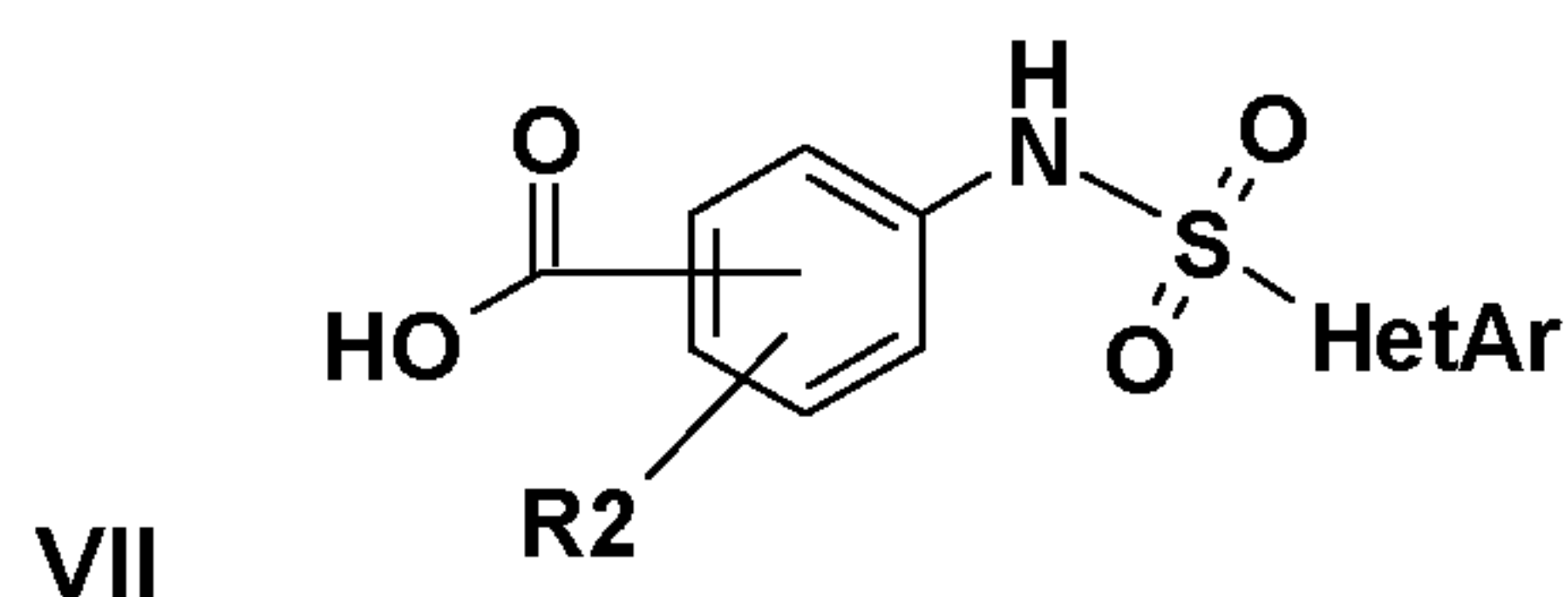


in the presence of a base such as pyridine, notably in a solvent such as dichloromethane.

(b2) The compound VI obtained in this manner



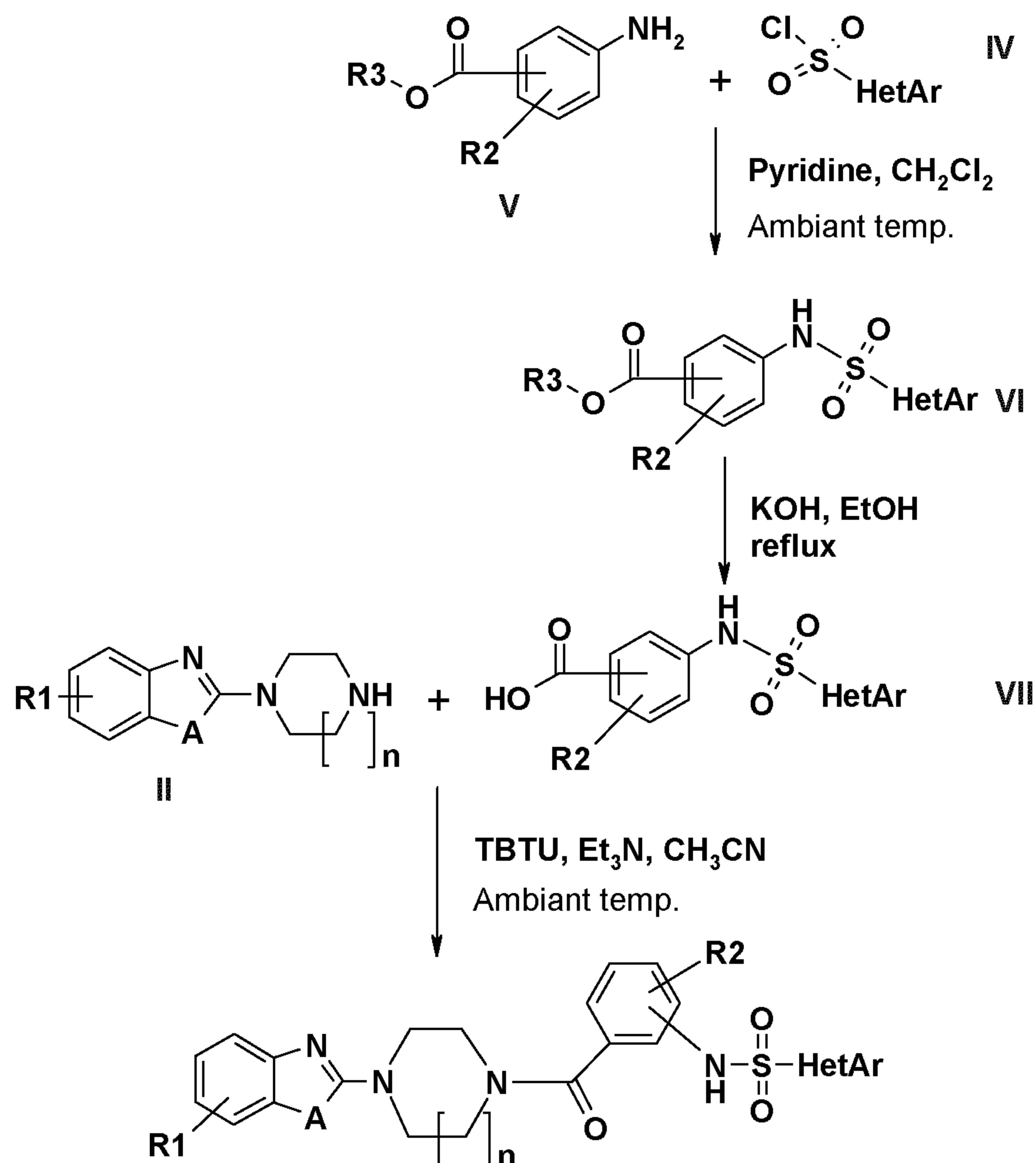
5 is saponified, notably in the presence of a base such as potash, in particular in a solvent such as ethanol, to give the compound VII.



(b3) The latter is coupled with the previously defined intermediate II to give the compound of formula I, notably under process conditions such as in the presence of TBTU and Et₃N in a solvent such as acetonitrile.

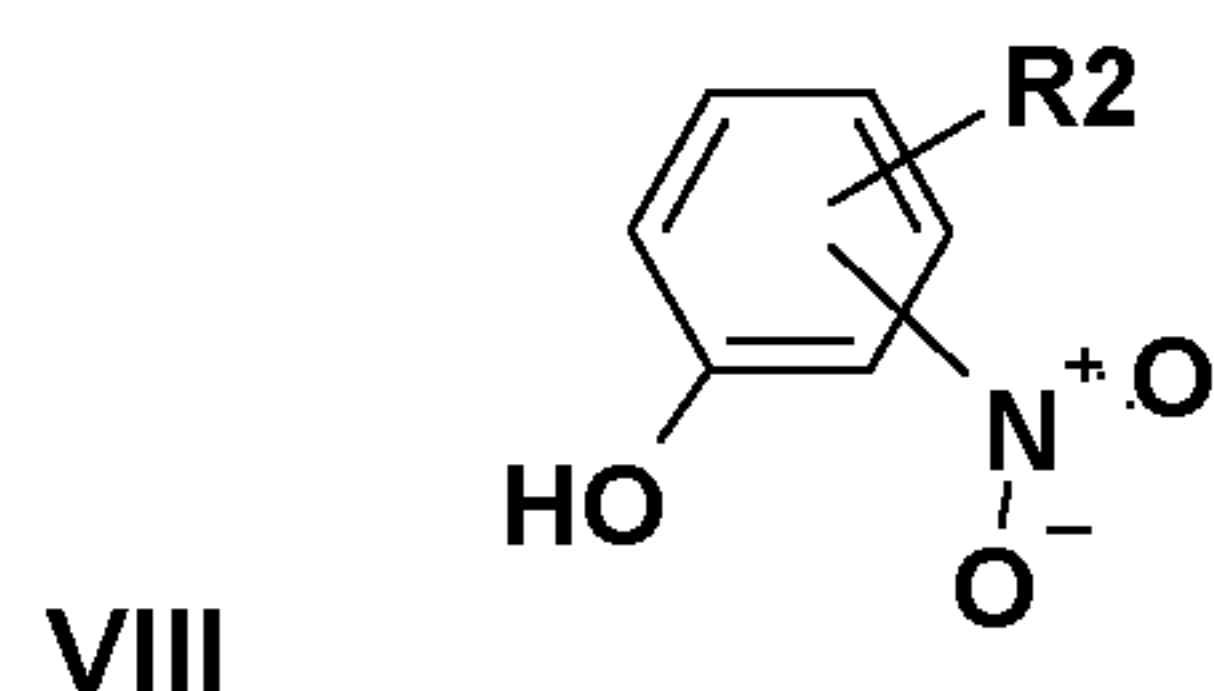
(b4) The compound of formula I obtained in the previous step (b3) may be converted into a salt in the presence of a pharmaceutically acceptable base or acid in order to give a pharmaceutically acceptable salt of the compound of formula I.

13

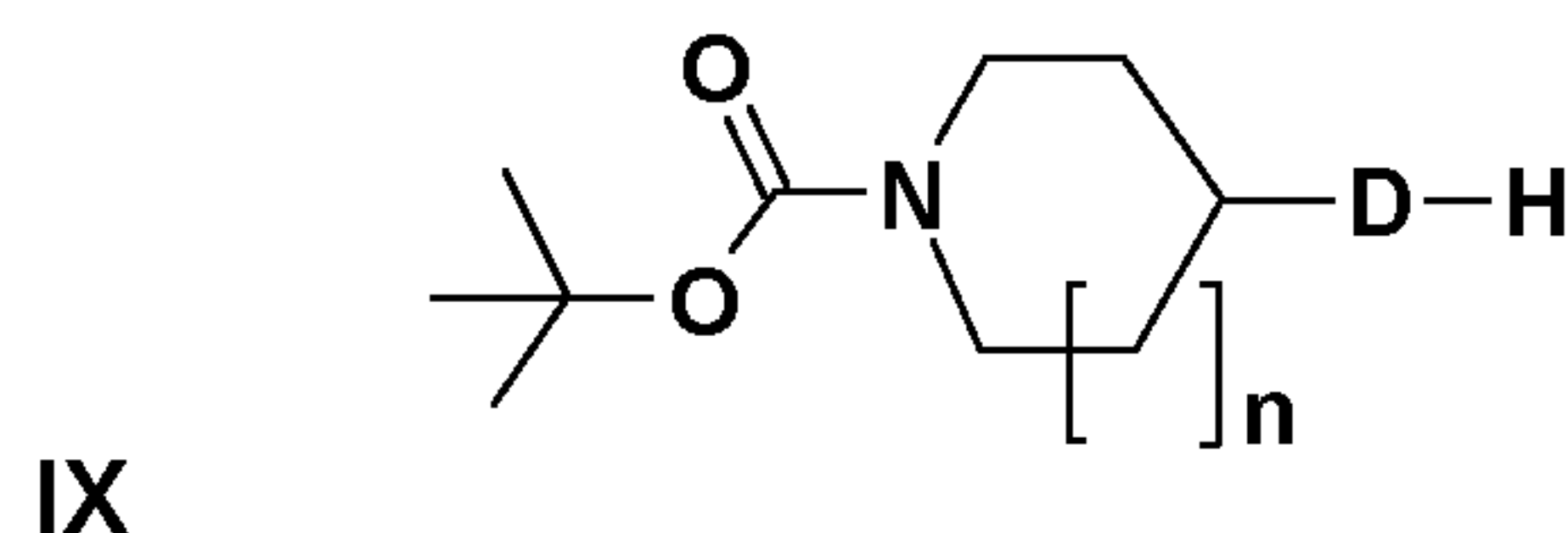
Method 3 (when B = CH)

- 5 This method of synthesis of the compounds of general formula I with **B** = CH (diagram 3) is characterised by the following successive steps:

(c1) A derivative of general formula VIII for which **R2** is as defined in general formula I is condensed,

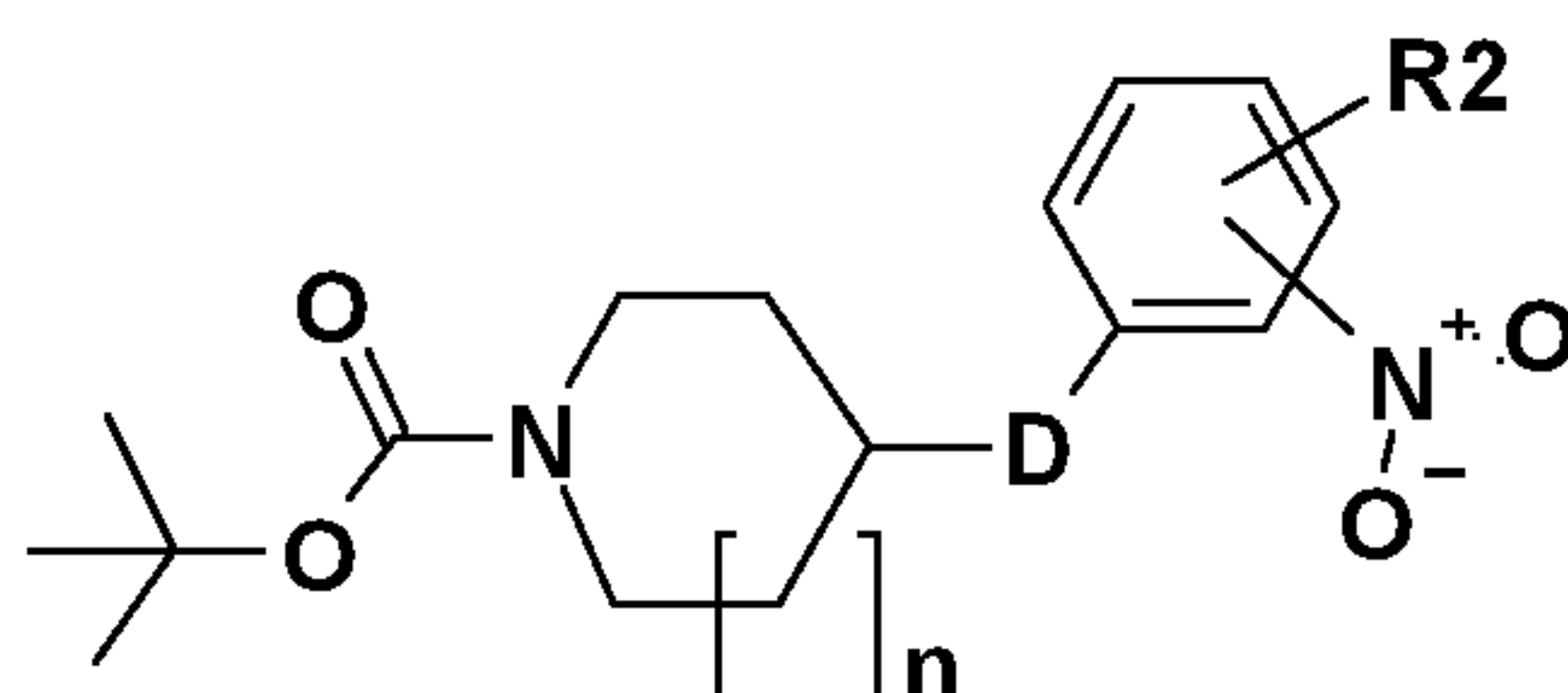


- 10 with a derivative of general formula IX for which **D** and **n** are as defined in general formula I when **B** represents CH.

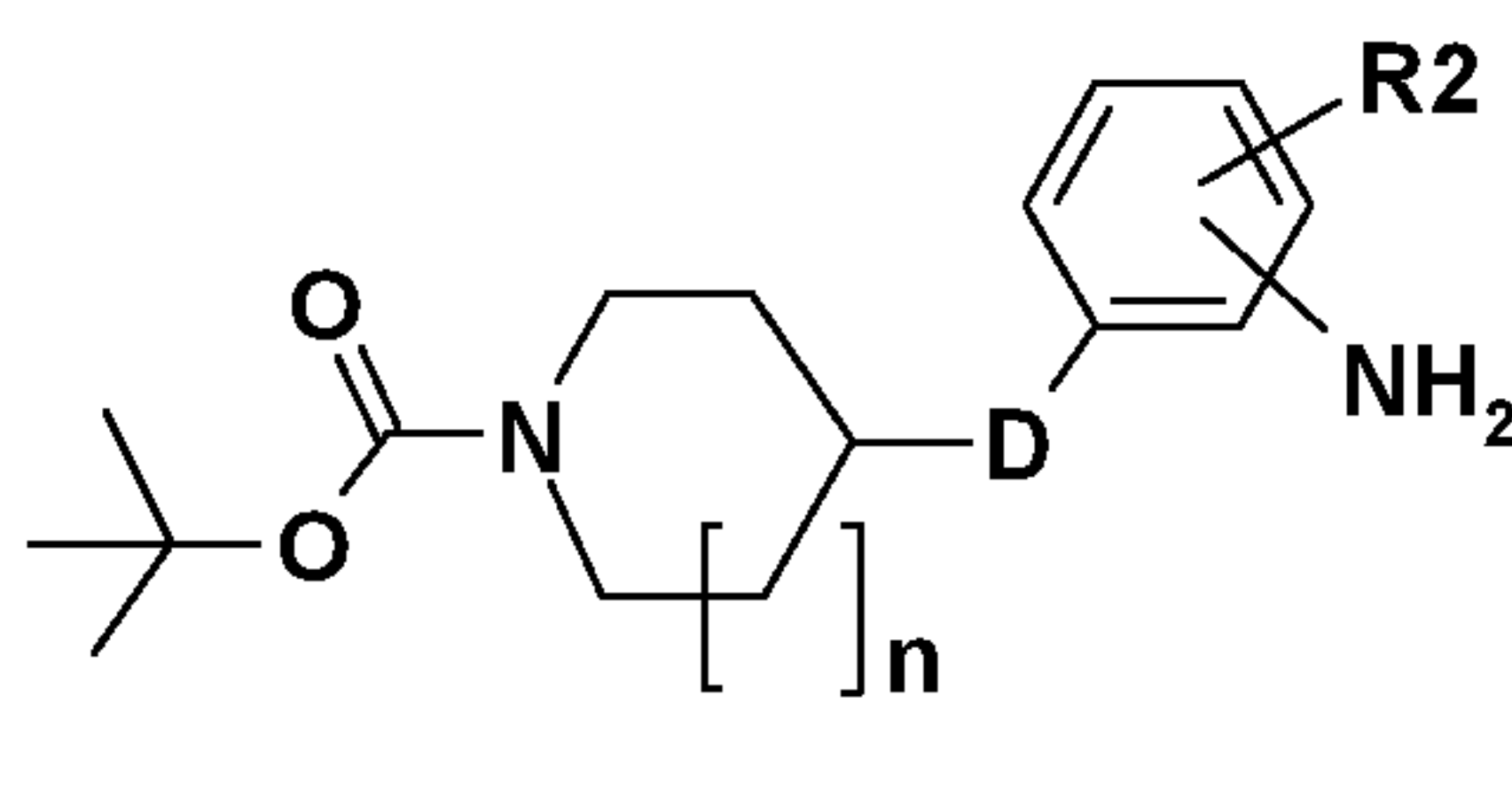


notably under process conditions such as those of Mitsunobu coupling in the presence of triphenylphosphine, of diethylazodicarboxylate in THF.

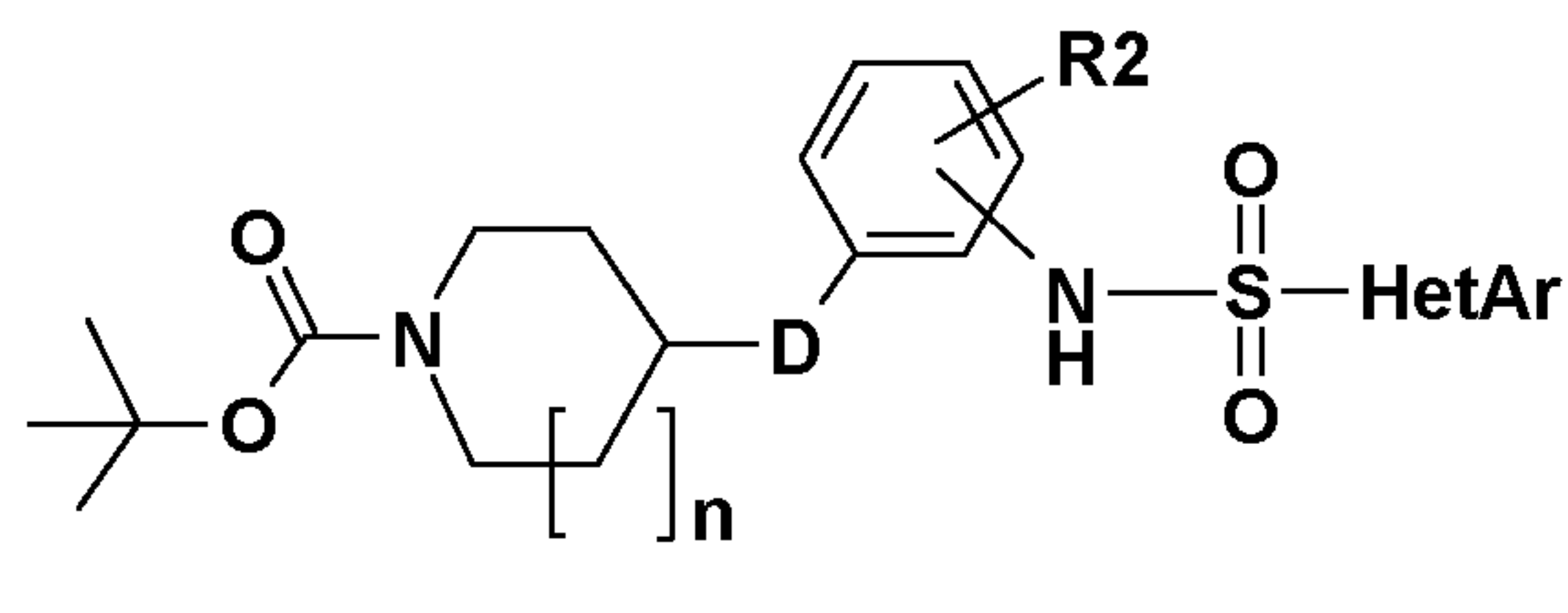
(c2) The intermediate **X** obtained in this manner



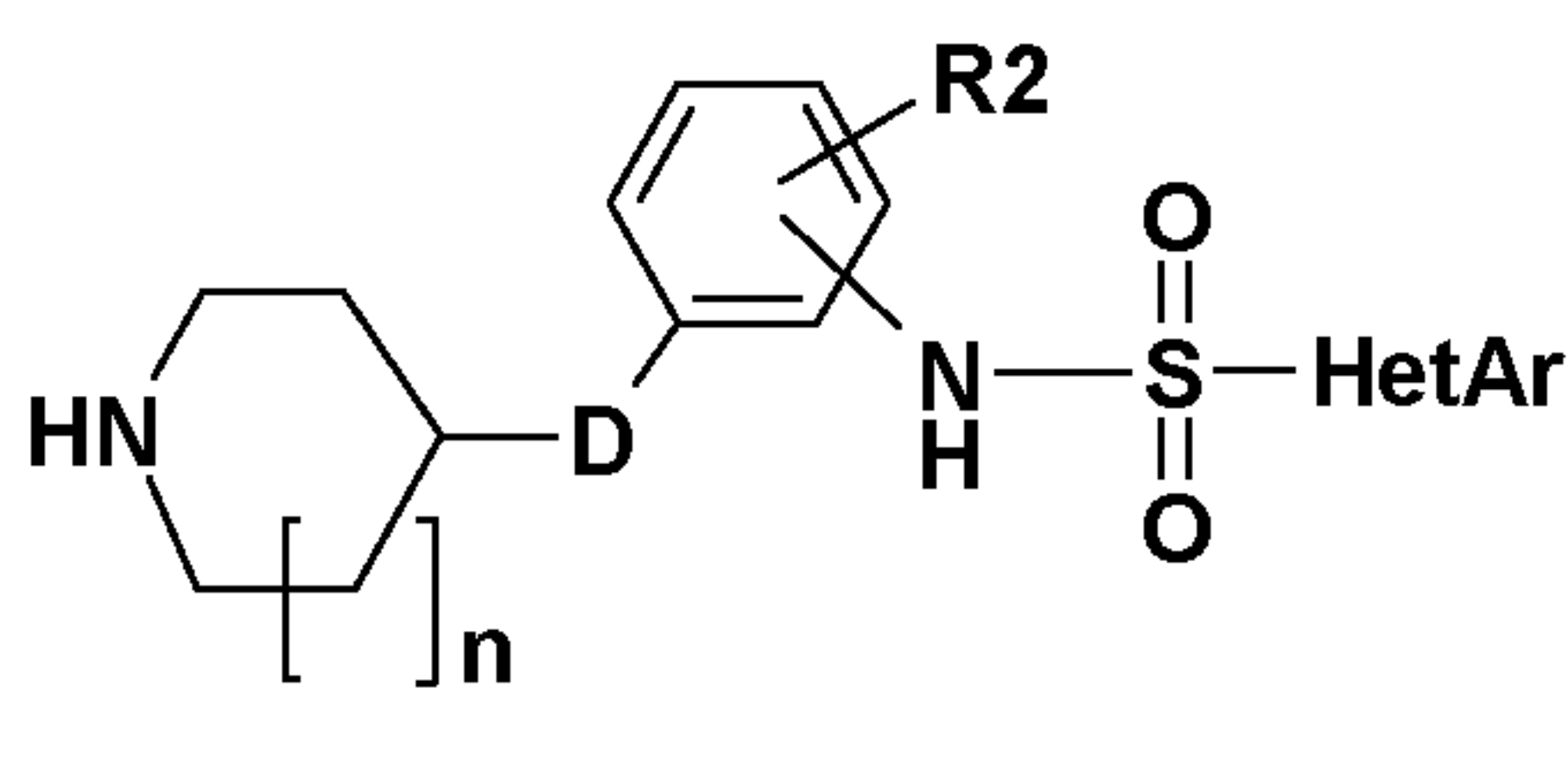
is then reduced, notably by using process conditions such as palladium on carbon in an atmosphere of hydrogen in a solvent such as ethanol, which enables intermediate **XI** to be isolated.



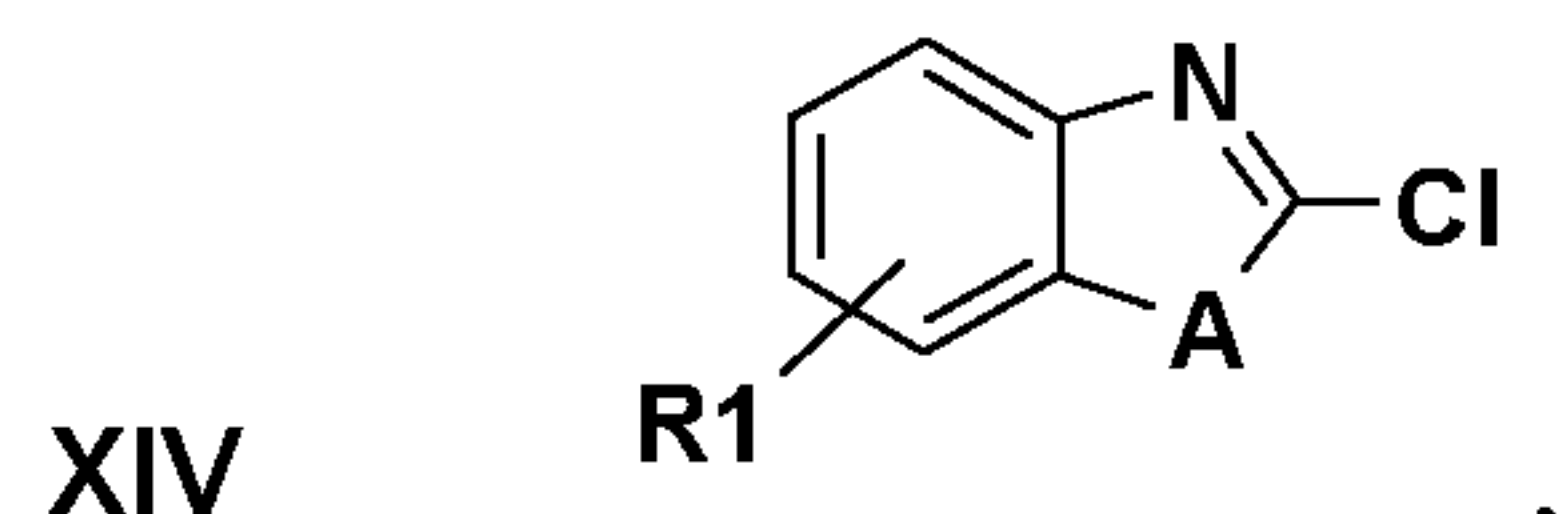
(c3) The latter is coupled with a sulfonyl chloride of general formula **IV** for which **HetAr** is as defined in general formula **I**, in the presence of a base such as pyridine, notably in a solvent such as dichloromethane, leading to intermediate **XII**.



(c4) The amide group of the latter is hydrolysed, notably in the presence of trifluoroacetic acid, notably in a solvent such as dichloromethane to give intermediate **XIII**.



(c5) The compound **XIII** is then coupled with intermediate **XIV** for which **R1** and **A** are as defined in general formula I,



notably under process conditions such as in the presence of bicarbonate of soda in a
5 blend of solvents such as ethanol and water, to give the compound of general formula I.

(c6) The compound of formula I obtained in the previous step (c5) may be salified in the presence of a pharmaceutically acceptable base or acid in order to give a pharmaceutically acceptable salt of the compound of formula I.

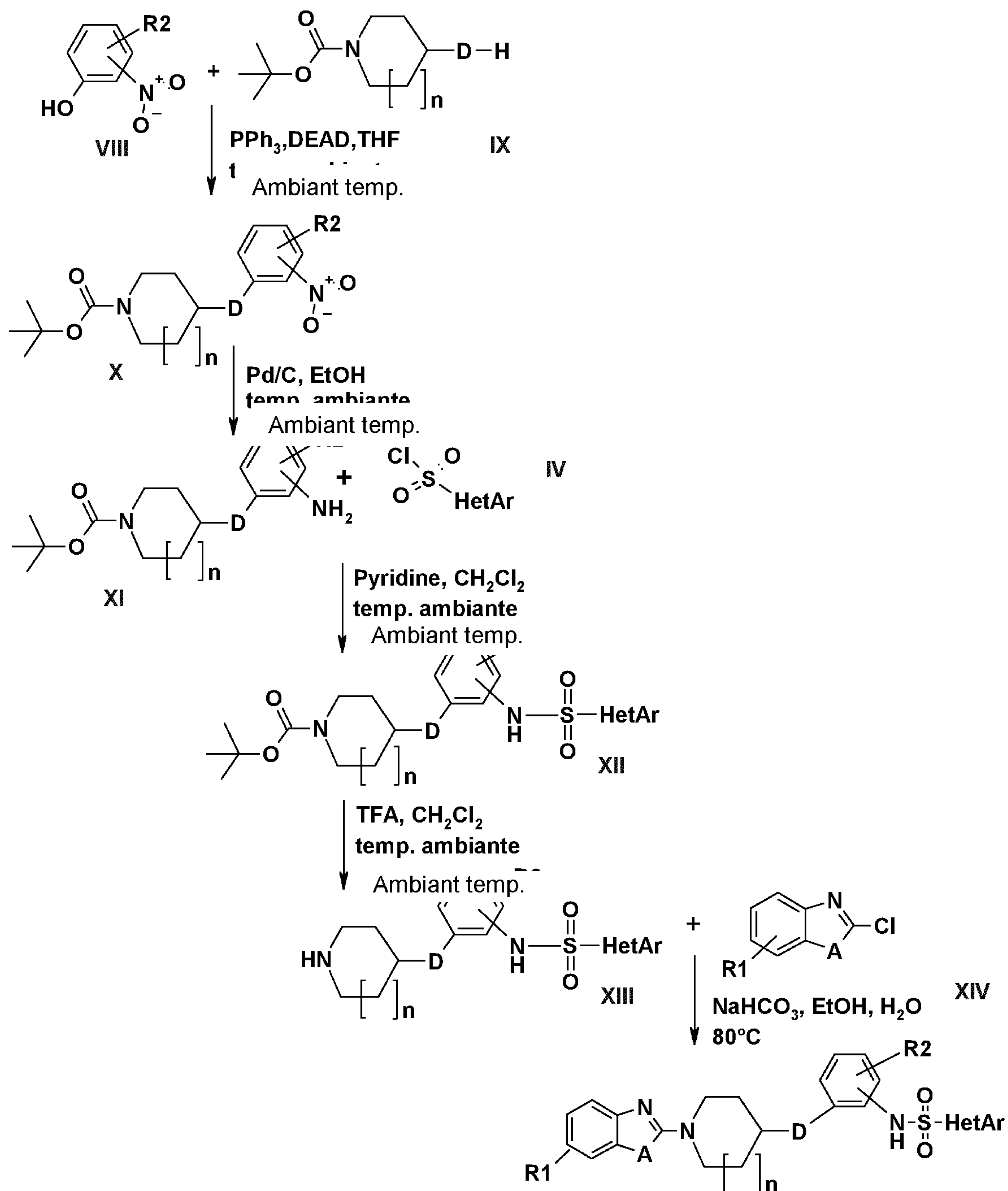


Diagram 3

The intermediate and final compounds may if desired be purified using one or more methods of purification chosen from among extraction, filtration, chromatography on silica gel, preparatory HPLC in the normal or reverse phase, or crystallisation.

The starting materials used in the methods described above are commercial or easily accessible to the skilled man in the art using methods described in the literature.

The following examples illustrate the invention without limiting its scope.

The elementary analyses and the mass spectra and NMR confirm the structures of the compounds.

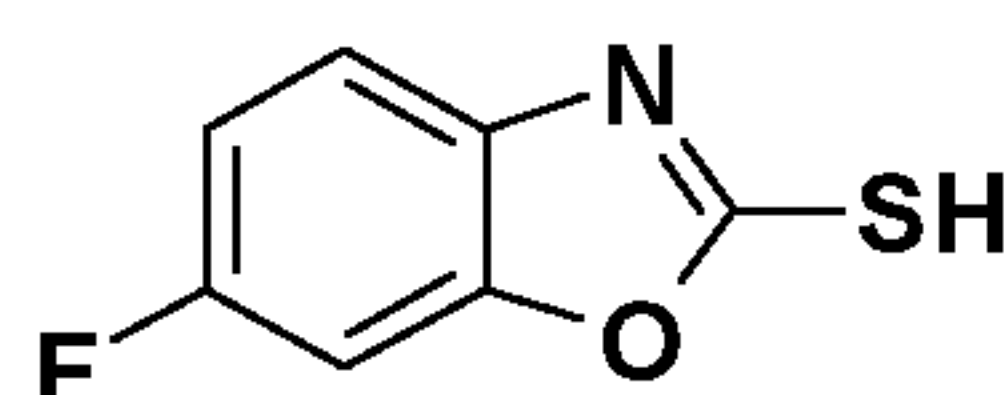
EXAMPLES

5

A) INTERMEDIATES

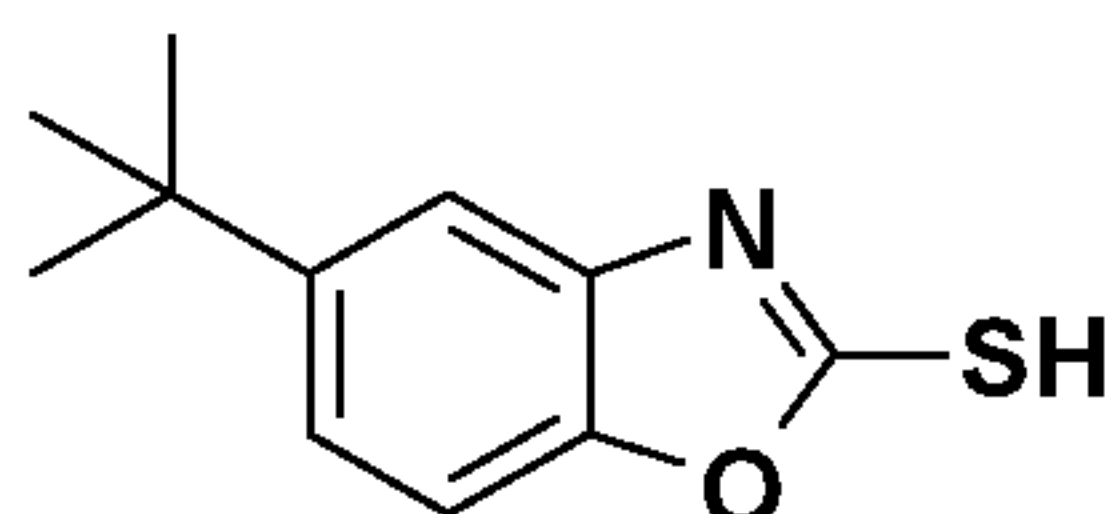
Intermediates 1:

a) 6-Fluoro-benzoxazole-2-thiol (1a)



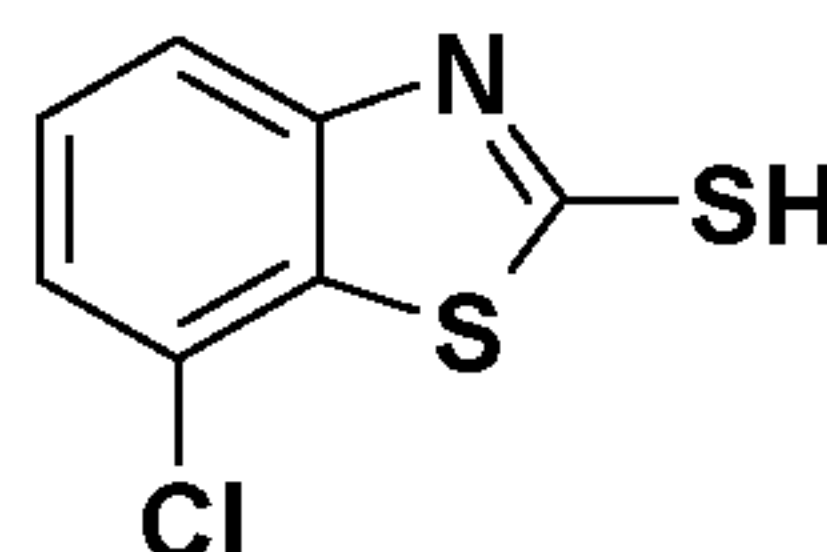
10 2-amino-5-fluoro-phenol (10 g, 79 mmol) is placed in the presence of potassium O-ethylcarbonodithioate (27.7 g, 173 mmol) in 100 mL of ethanol at reflux overnight. After reduction to dryness the residue is triturated in a solution of HCl 1N, filtered and then rinsed with HCl 1N. After drying under vacuum, 13.8 g of a brown solid is isolated (quantitative yield).

15 b) 5-tert-Butyl-benzoxazole-2-thiol (1b)



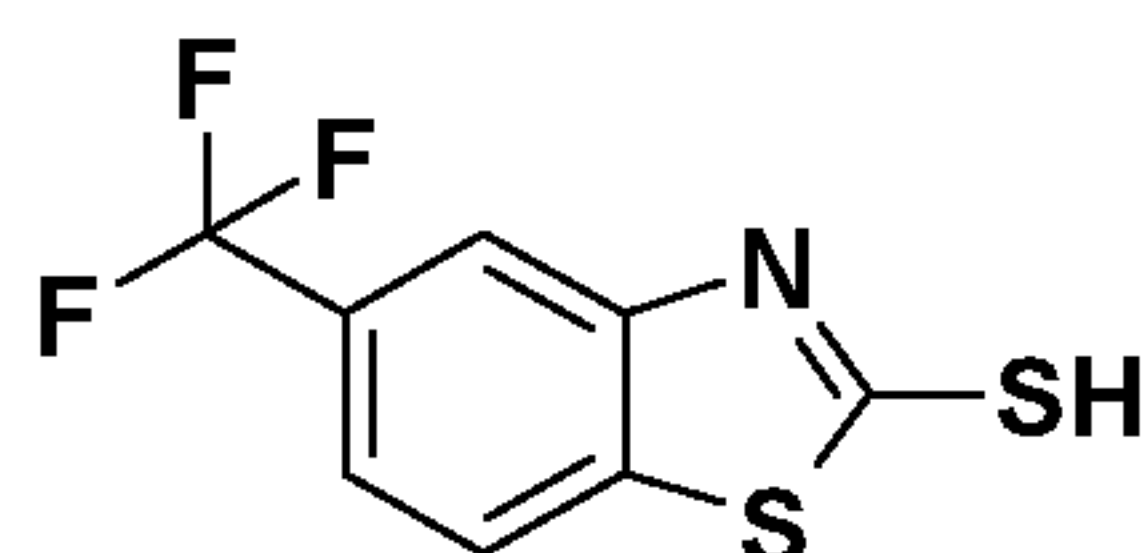
Intermediate **1b** (solid) is prepared from 2-amino-4-tert-butyl-phenol using the procedure described for intermediate **1a** (yield 94%). *TLC silica gel 60 F 254 Merck, CH₂Cl₂-MeOH:90-10, R_f=0.83.*

20 c) 7-Chloro-benzothiazole-2-thiol (1c)



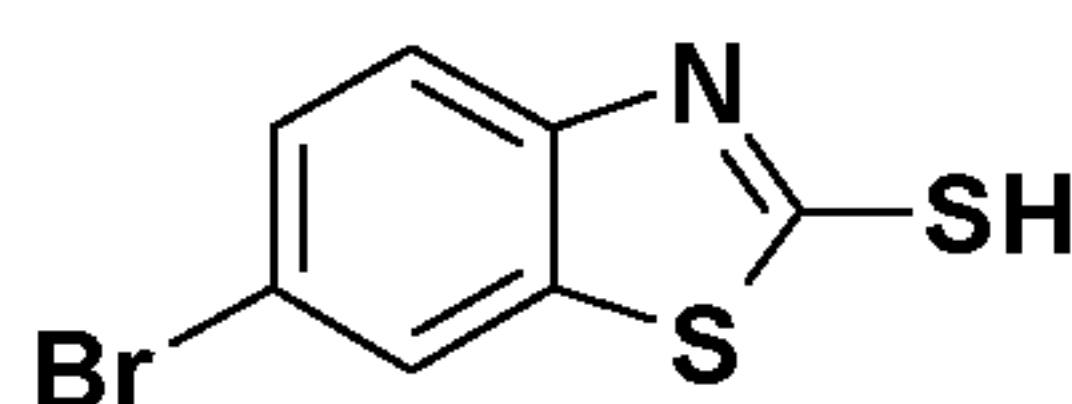
Intermediate **1c** (solid) is prepared from 3-chloro-2-fluoro-phenylamine using the procedure described for intermediate **1a** using DMF at reflux (quantitative yield). *TLC silica gel 60 F 254 Merck, CH₂Cl₂-MeOH:95-5, R_f=0.70.*

25 d) 5-Trifluoromethyl-benzothiazole-2-thiol (1d)



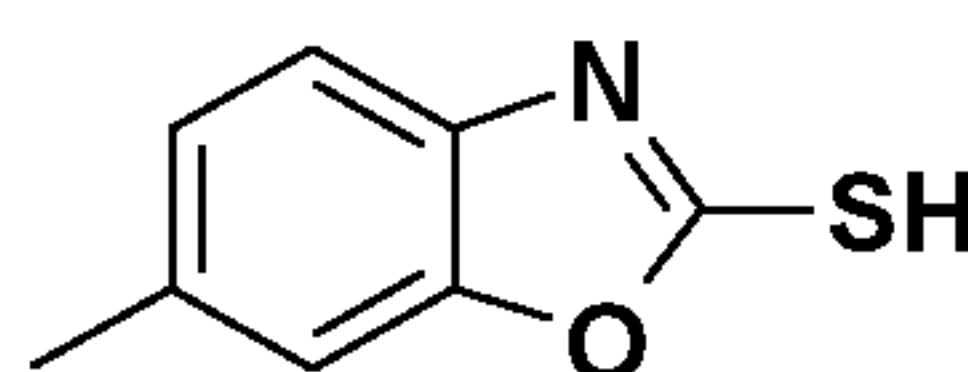
Intermediate **1d** (solid) is prepared from 2-bromo-5-trifluoromethyl-phenylamine using DMF as solvent using the procedure described for intermediate **1a** (yield 28%). *TLC silica gel 60 F 254 Merck, CH₂Cl₂-MeOH:95-5, R_f=0.73.*

e) 6-Bromo-benzothiazole-2-thiol (**1e**)



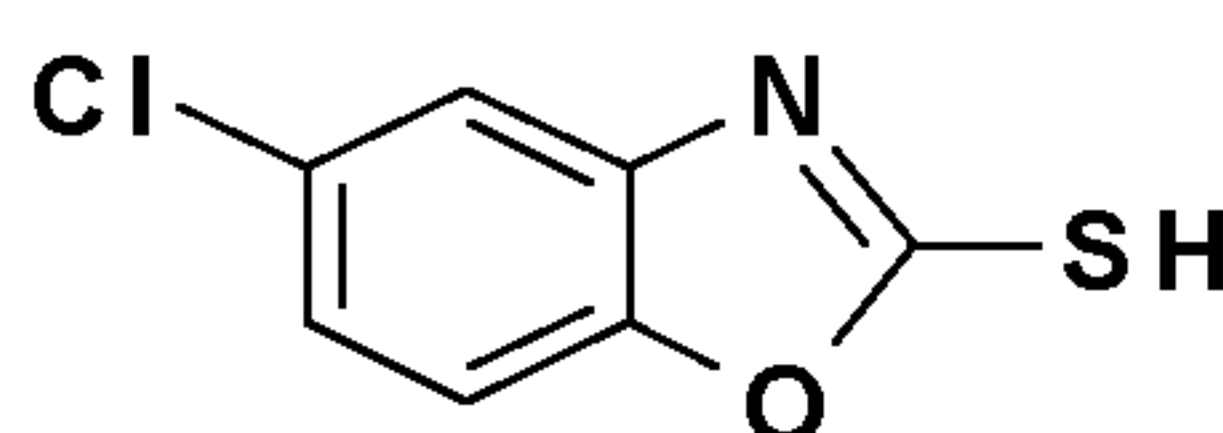
Intermediate **1e** (solid) is prepared from 4-bromo-2-fluoro-phenylamine using the procedure described for intermediate **1a** (quantitative yield). *TLC silica gel 60 F 254 Merck, CH₂Cl₂-MeOH:95-5, R_f=0.75.*

f) 6-Methyl-benzoxazole-2-thiol (**1f**)



8 g (65 mmol) of 2-amino-5-methyl-phenol is placed in the presence of potash (4.37 g, 78 mmol) in a mixture of 100 mL of CS₂ and 150 mL of EtOH and heated at 100°C for 8h. After reduction to dryness the medium is taken up in the water and extracted using AcOEt and after drying the organic phases are reduced to dryness. The residue is taken up by Et₂O and the crystals obtained are filtered and then rinsed in petroleum ether. 10 g of beige crystals is isolated (yield: 94%). *TLC silica gel 60 F 254 Merck, CH₂Cl₂-MeOH:95-5, R_f=0.75.*

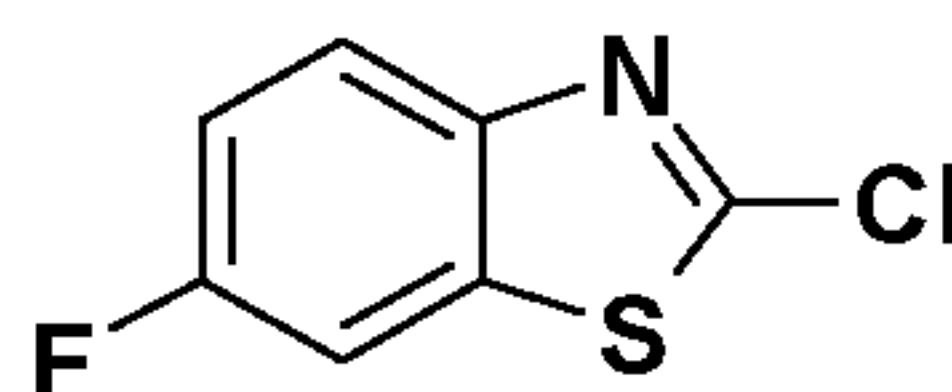
g) 5-Chloro-benzoxazole-2-thiol (**1g**)



Intermediate **1b** (solid) is prepared from 2-amino-4-chloro-phenol using the procedure described for intermediate **1f** (yield: 46%). *TLC silica gel 60 F 254 Merck, Petroleum ether-AcOEt:50-50, R_f=0.70.*

Intermediates 2:

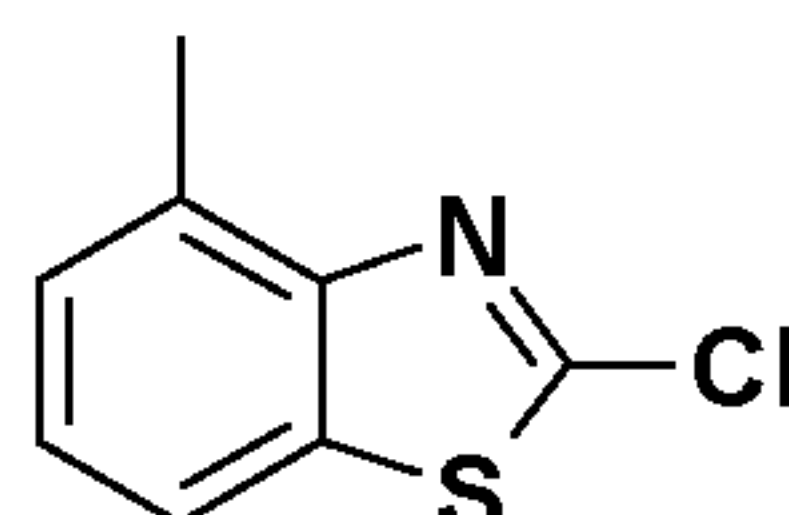
a) 2-Chloro-6-fluoro-benzothiazole (**2a**)



0.5 g (2.97 mmol) of 6-fluoro-benzothiazol-2-ylamine is placed in the presence of isoamyl nitrite (0.52 g, 4.46 mmol) and CuCl₂·2H₂O (0.61 g, 0.57 mmol) in 10 mL of acetonitrile. The reaction medium is heated to 65°C for 3h and then reduced to

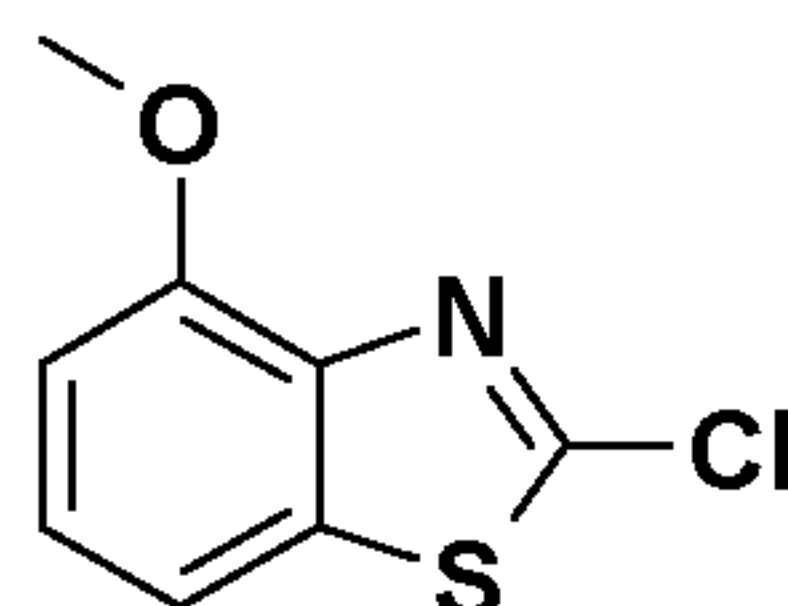
dryness; the residue is taken up by water and extracted using ethyl acetate. The organic phases are dried and then evaporated, and the residue obtained is purified by flash chromatography on silica (CH_2Cl_2 -AcOEt, gradient 100-0 to 97-3 over 30 min). 0.36 g of solid is obtained (yield 64%). *TLC silica gel 60 F 254 Merck, CH_2Cl_2 -MeOH:95-5, $R_f=0.84$.*

b) 2-Chloro-4-methyl-benzothiazole (2b)



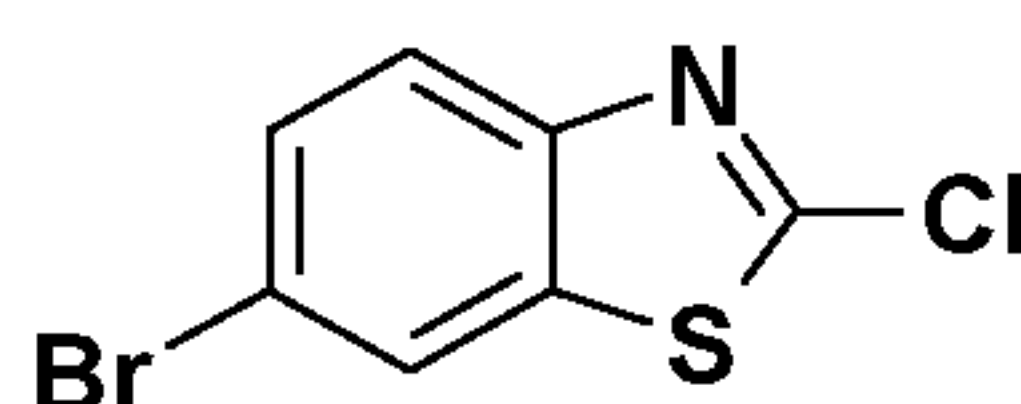
Intermediate **2b** (solid) is prepared from 4-methyl-benzothiazol-2-ylamine using the procedure described for intermediate **2a** (yield: 89%). *TLC silica gel 60 F 254 Merck, CH_2Cl_2 -MeOH:95-5, $R_f=0.83$.*

c) 2-Chloro-4-methoxy-benzothiazole (2c)



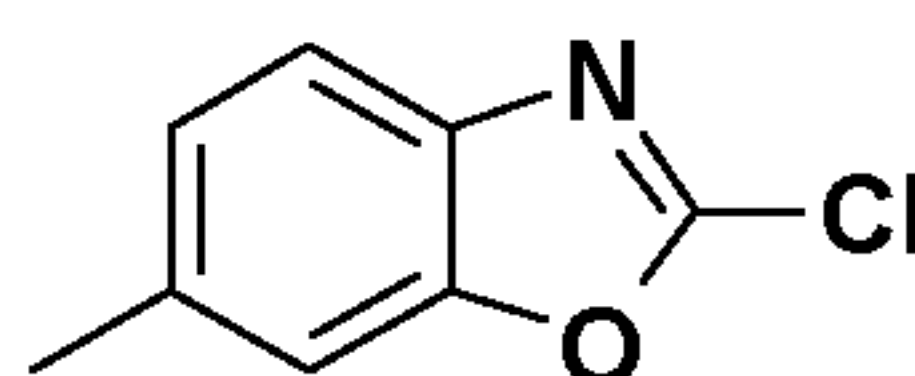
Intermediate **2c** (solid) is prepared from 4-methoxy-benzothiazol-2-ylamine using the procedure described for intermediate **2a** (yield: 47%). *TLC silica gel 60 F 254 Merck, Petroleum ether-AcOEt:70-30, $R_f=0.77$.*

d) 6-Bromo-2-chloro-benzothiazole (2d)



Intermediate **2c** (solid) is prepared from 6-bromo-benzothiazol-2-ylamine using the procedure described for intermediate **2a** (yield: 75%). *TLC silica gel 60 F 254 Merck, CH_2Cl_2 -MeOH:95-5, $R_f=0.83$.*

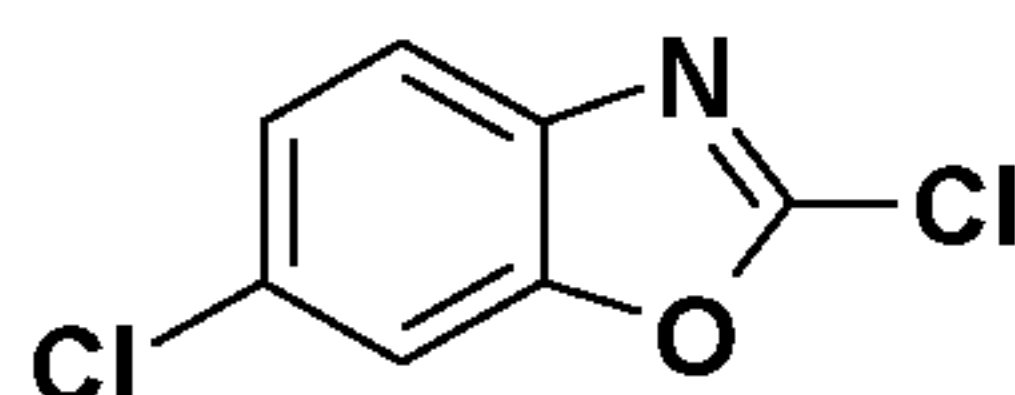
e) 2-Chloro-6-methyl-benzooxazole (2e)



Intermediate **1f** is placed at 0°C in 1.76 mL of thionyl chloride. 0.47 mL of DMF is poured drop-by-drop in such a way as to keep the reaction medium at 0°C, after which it is stirred for 1h at this temperature. After evaporation under vacuum the medium is taken up by water and extracted using ethyl acetate. The organic phases are dried and reduced to dryness. The residue obtained is purified by flash chromatography on silica

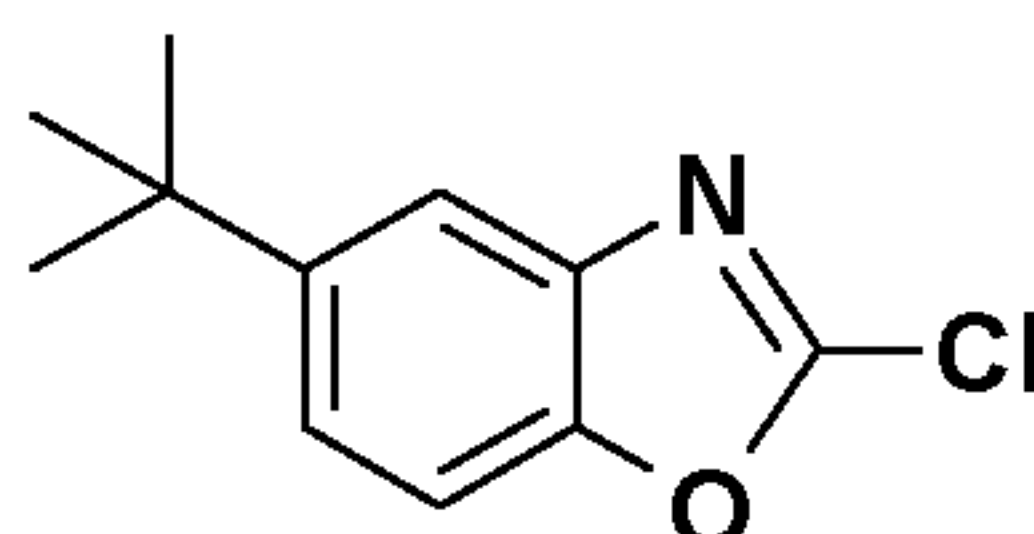
(Petroleum ether-AcOEt, gradient 100-0 to 80-20 over 20 min). 0.66 g of oil is obtained (yield 65%). *TLC silica gel 60 F 254 Merck, CH₂Cl₂-MeOH:90-10, R_f=0.80.*

f) 2,6-Dichloro-benzooxazole (2f)



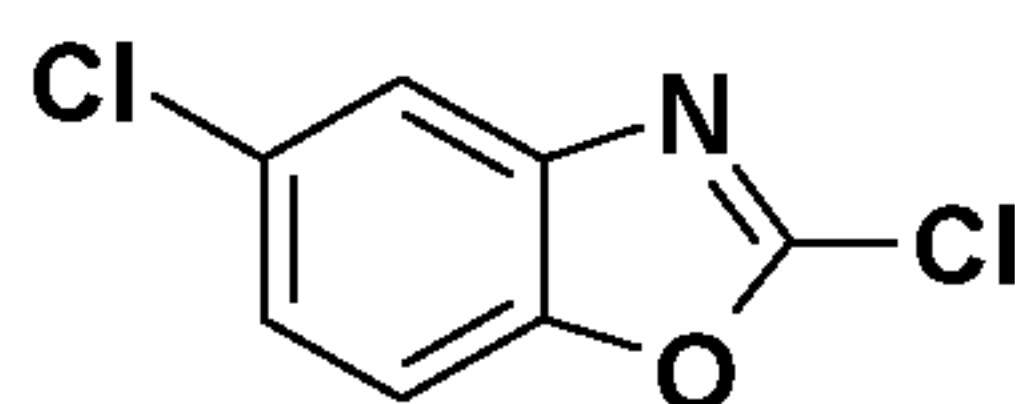
- 5 Intermediate **2f** (solid) is prepared from 6-chloro-benzooxazole-2-thiol using the procedure described for intermediate **2e** (yield: 42%). *TLC silica gel 60 F 254 Merck, AcOEt, R_f=0.87.*

g) 5-tert-Butyl-2-chloro-benzooxazole (2g)



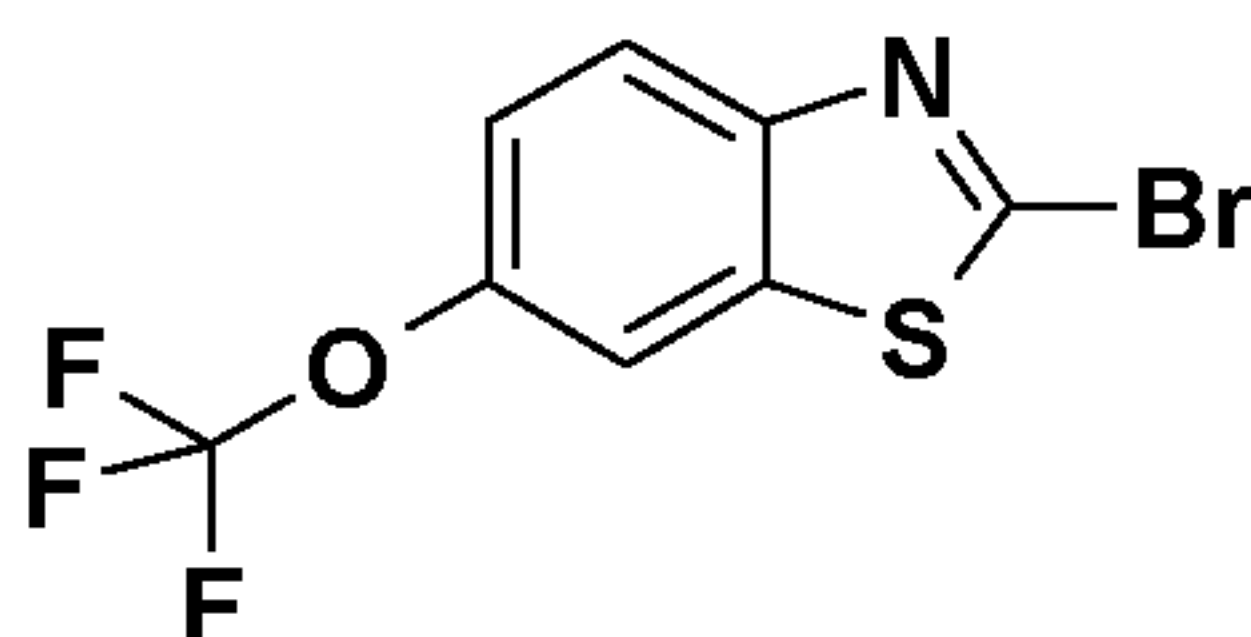
- 10 Intermediate **2g** (oil) is prepared from intermediate **1b** using the procedure described for intermediate **2e** (yield: 42%). *TLC silica gel 60 F 254 Merck, Petroleum ether-AcOEt:50-50, R_f=0.76.*

h) 2,5-Dichloro-benzooxazole (2h)



- 15 Intermediate **2h** (solid) is prepared from intermediate **1g** using the procedure described for intermediate **2e** (yield: quantitative). *TLC silica gel 60 F 254 Merck, Petroleum ether-AcOEt:50-50, R_f=0.68.*

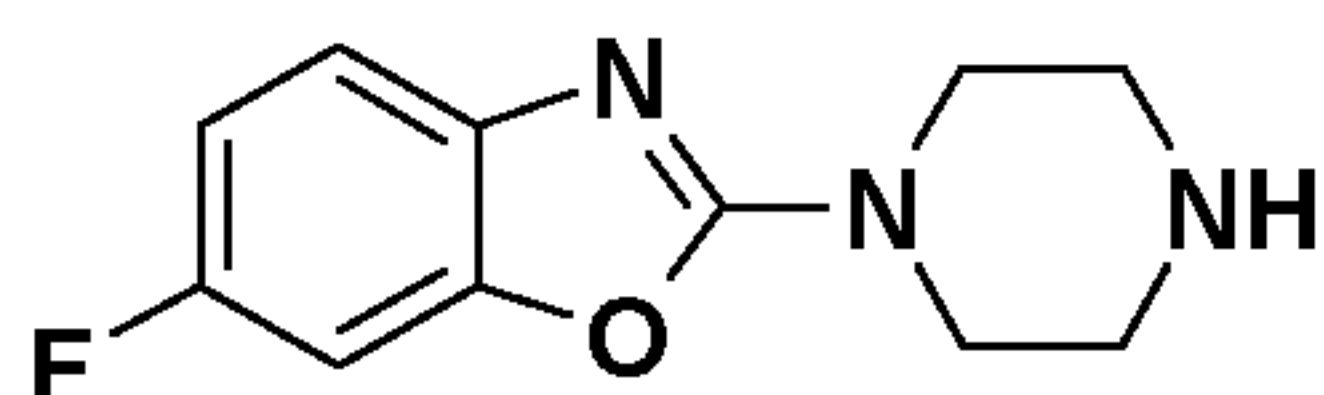
i) 2-bromo-6-(trifluoromethoxy)benzo[d]thiazole (2i)



- 20 Intermediate **2i** (solid) is prepared from 2-amino-6-(trifluoromethoxy)benzothiazole using the procedure described for intermediate **2a** using CuBr₂ (yield: 90%). *TLC silica gel 60 F 254 Merck, CH₂Cl₂-MeOH:95-5, R_f=0.93.*

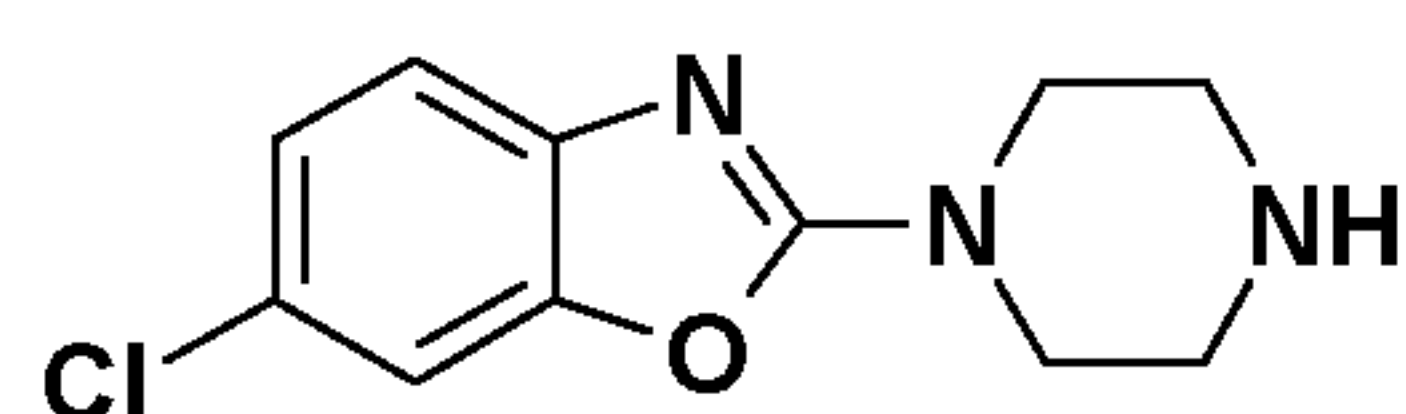
Intermediates 3:

- 25 a) 6-Fluoro-2-piperazin-1-yl-benzooxazole (3a)



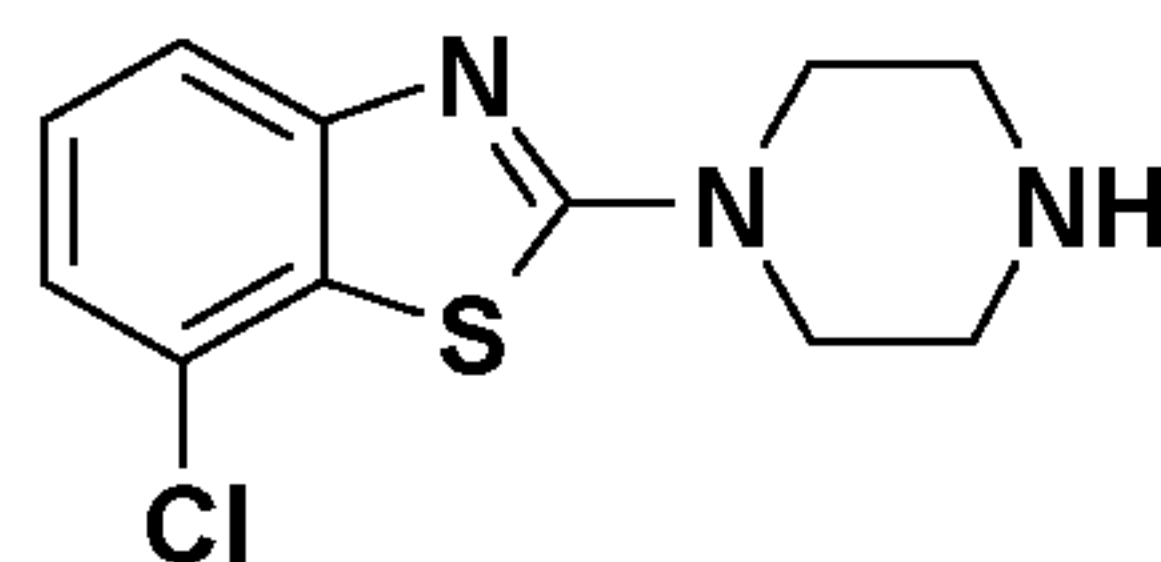
intermediate **1a** (9 g, 53.2 mmol) is placed in the presence of piperazine (22.91 g, 266 mmol) in 45 mL of butanol at 180°C for 40 min under microwaves. After reduction to dryness the medium is taken up by water and extracted using ethyl acetate. The organic phases are dried and then evaporated, and the residue obtained is purified by
 5 flash chromatography on silica (CH₂Cl₂-MeOH, gradient 98-2 to 80-20 over 20 min). 2.73 g of brown oil is obtained (yield 23%). *TLC silica gel 60 F 254 Merck, CH₂Cl₂-MeOH:90-10, R_f=0.11.*

b) 6-Chloro-2-piperazin-1-yl-benzoxazole (**3b**)



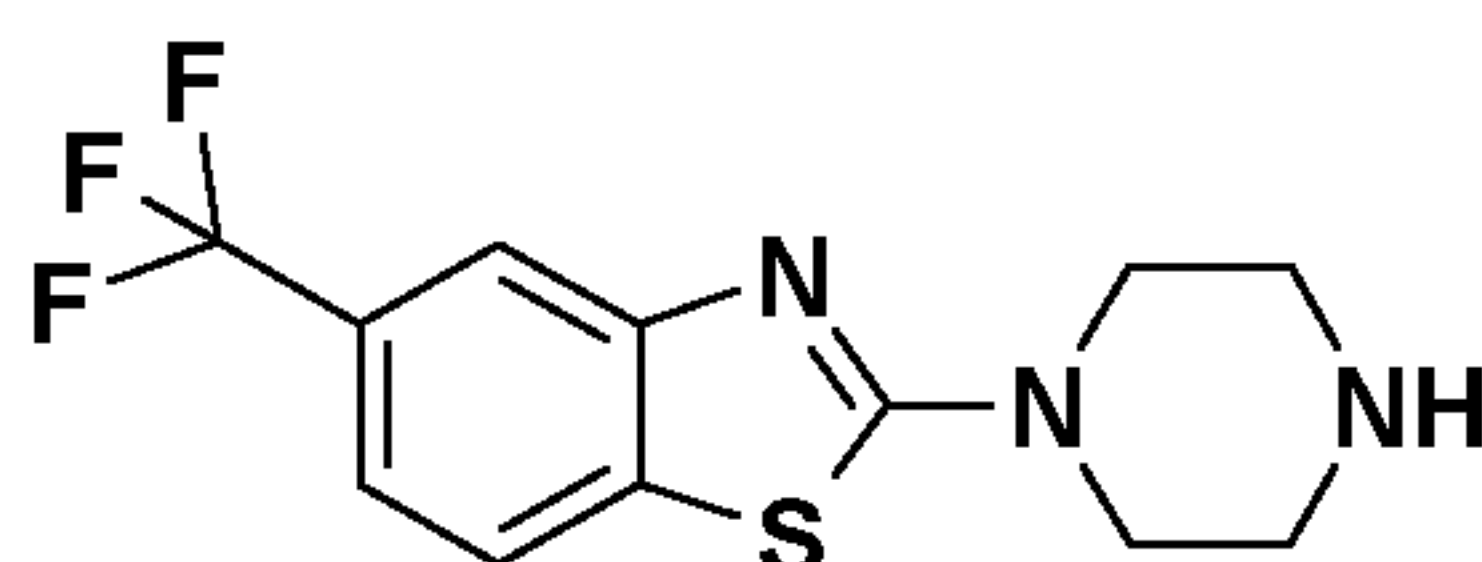
10 Intermediate **3b** (oil) is prepared from 6-chloro-2-benzoxazole-2-thiol using the procedure described for intermediate **3a** (yield: 92%). *TLC silica gel 60 F 254 Merck, CH₂Cl₂-MeOH:90-10, R_f=0.11.*

c) 7-Chloro-2-piperazin-1-yl-benzothiazole (**3c**)



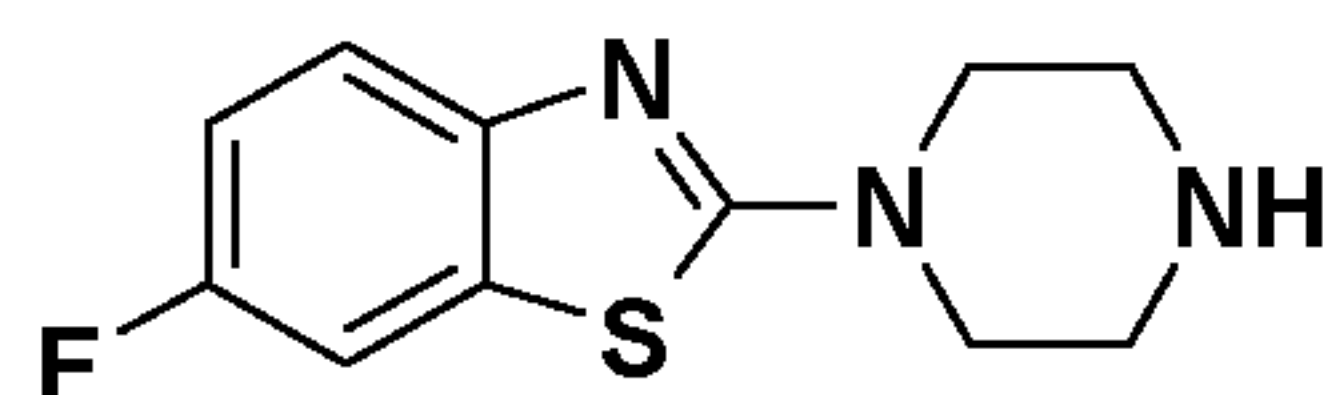
15 Intermediate **3c** (solid) is prepared from intermediate **1c** using the procedure described for intermediate **3a** (yield: 79%). *TLC silica gel 60 F 254 Merck, CH₂Cl₂-MeOH:90-10, R_f=0.15.*

d) 2-Piperazin-1-yl-5-trifluoromethyl-benzothiazole (**3d**)



20 Intermediate **3d** (solid) is prepared from intermediate **1d** using the procedure described for intermediate **3a** (yield: 91%). *TLC silica gel 60 F 254 Merck, CH₂Cl₂-MeOH:95-5, R_f=0.20.*

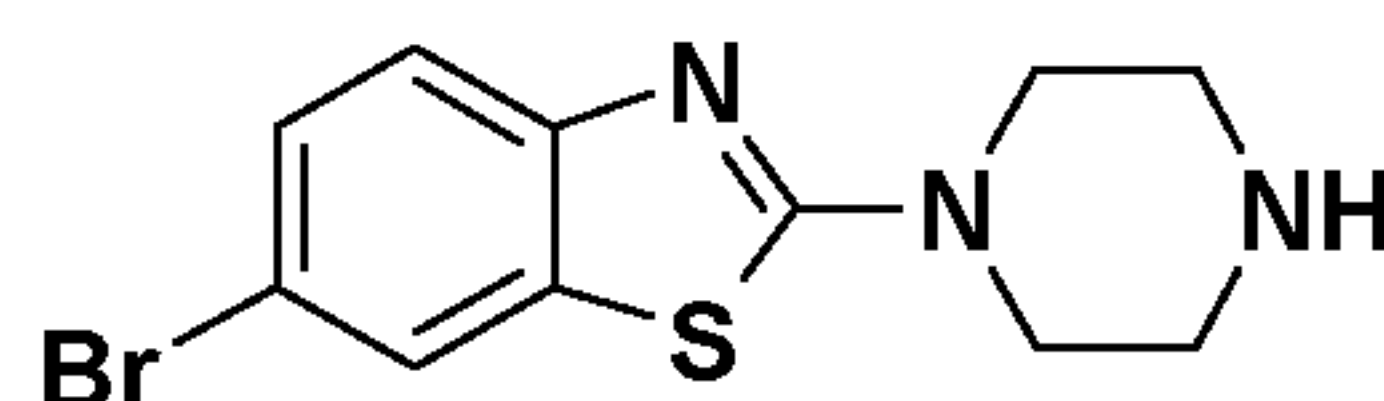
e) 6-Fluoro-2-piperazin-1-yl-benzothiazole (**3e**)



25 Piperazine (0.33 g, 3.84 mmol) is placed in 6 mL of ethanol, the sodium bicarbonate (0.56 g, 6.72 mmol) diluted in 8 mL of water is added, and then 0.36 g (1.92 mmol) of intermediate **2a** diluted in 8 mL of ethanol is poured drop-by-drop. The reaction

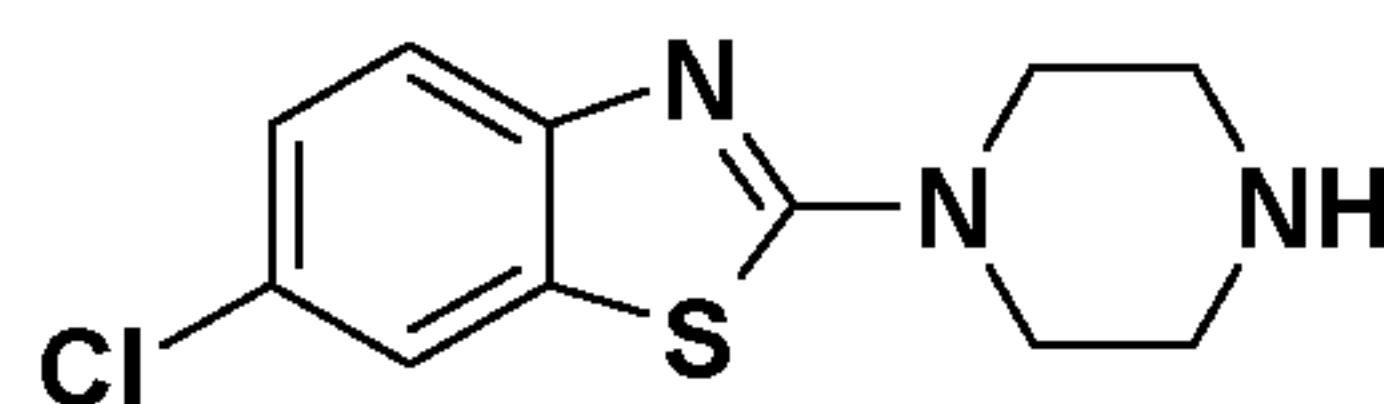
medium is heated to reflux overnight and then reduced to dryness. After extraction using ethyl acetate the organic phases are evaporated and the residue obtained is purified by flash chromatography on silica (CH_2Cl_2 -MeOH, gradient 100-0 to 90-10 over 45 min). 0.39 g of solid is obtained (yield 86%). *TLC silica gel 60 F 254 Merck, CH_2Cl_2 -MeOH:95-5, $R_f=0.05$.*

f) 6-Bromo-2-piperazin-1-yl-benzothiazole (3f)



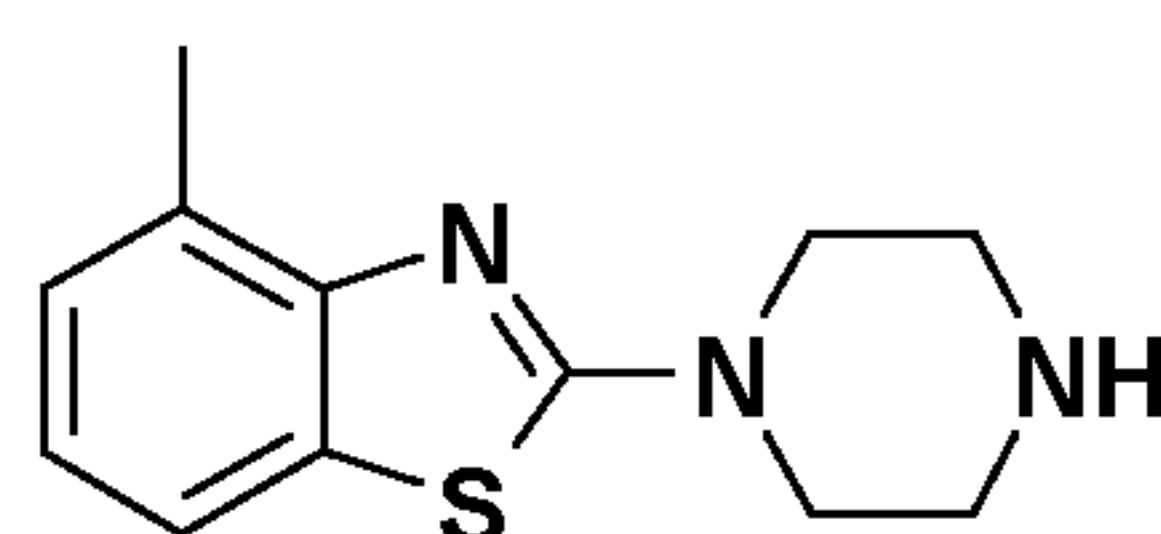
Intermediate **3f** (solid) is prepared from intermediate **2d** using the procedure described for intermediate **3e** (yield: 92%). *TLC silica gel 60 F 254 Merck, CH_2Cl_2 -MeOH:95-5, $R_f=0.14$.*

g) 6-Chloro-2-piperazin-1-yl-benzothiazole (3g)



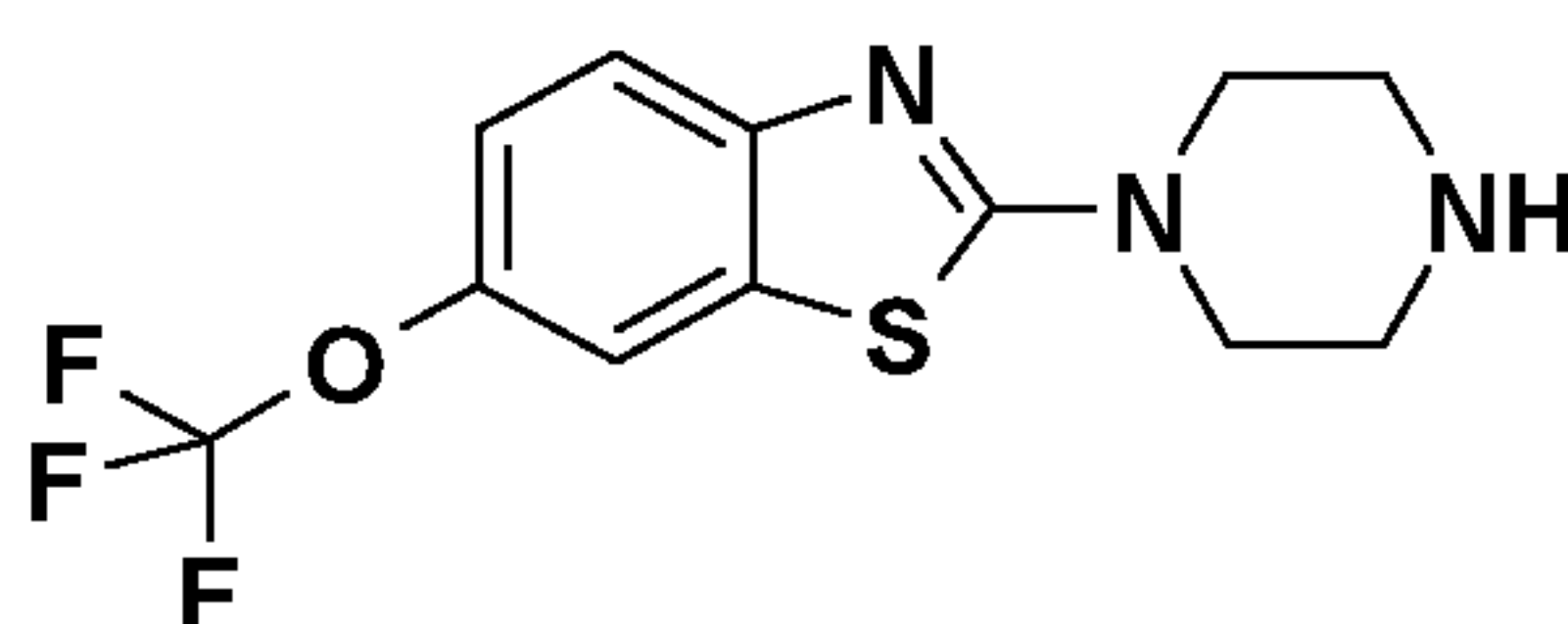
Intermediate **3g** (solid) is prepared from 2,6-dichloro-1,3-benzothiazole using the procedure described for intermediate **3e** (yield: 84%). *TLC silica gel 60 F 254 Merck, CH_2Cl_2 -MeOH:90-10, $R_f=0.23$.*

h) 4-Methyl-2-piperazin-1-yl-benzothiazole (3h)



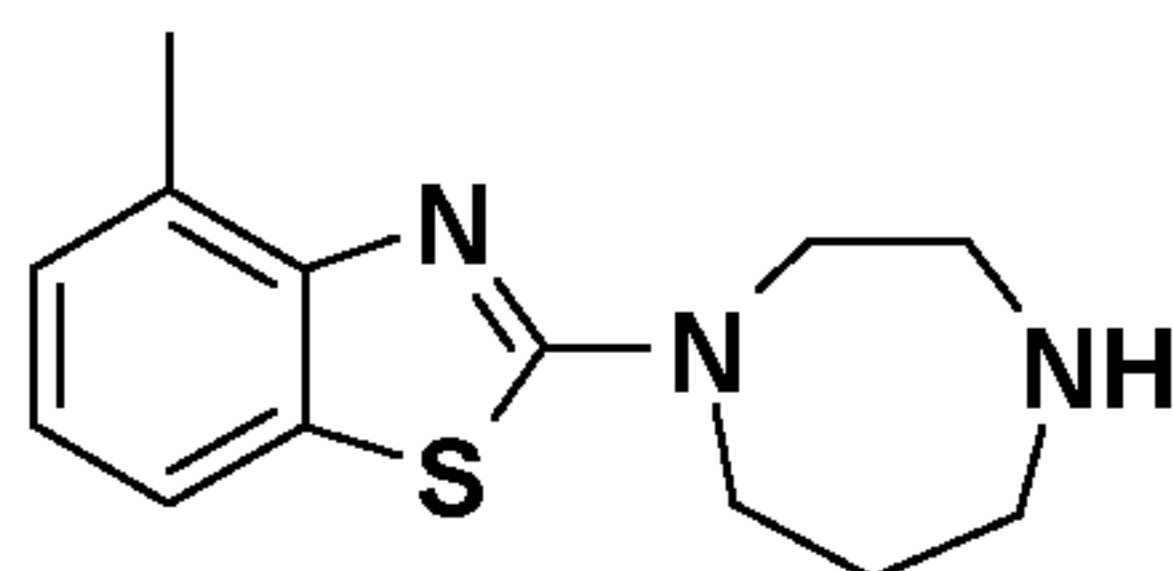
Intermediate **3h** (solid) is prepared from intermediate **2b** using the procedure described for intermediate **3e** (yield: 79%). *TLC silica gel 60 F 254 Merck, CH_2Cl_2 -AcOEt:95-5, $R_f=0.05$.*

i) 2-(Piperazin-1-yl)-6-(trifluoromethoxy)benzothiazole (3i)



Intermediate **3i** (solid) is prepared from intermediate **2i** using the procedure described for intermediate **3e** (yield: 88%). *TLC silica gel 60 F 254 Merck, CH_2Cl_2 -MeOH:95-5, $R_f=0.22$.*

j) 2-[1,4]Diazepan-1-yl-4-methyl-benzothiazole (3j)

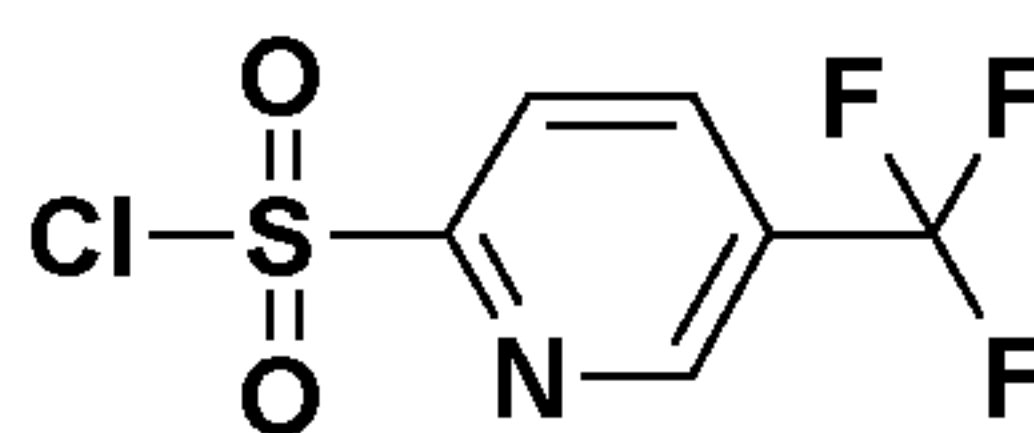


Intermediate **3j** (oil) is prepared from intermediate **2b** and [1,4]diazepane using the procedure described for intermediate **3e** (yield: 83%). *TLC silica gel 60 F 254 Merck, CH₂Cl₂-MeOH:95-5, R_f=0.10.*

5

Intermediates 4:

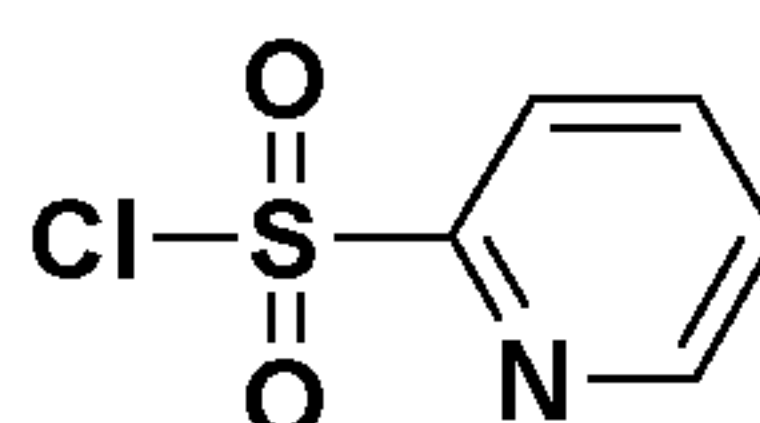
a) 5-Trifluoromethyl-pyridine-2-sulfonyl chloride (**4a**)



0.8 g (4.47 mmol) of 5-trifluoromethyl-pyridine-2-thiol is placed at -8°C in 16 mL of H₂SO₄. 16.96 mL (35.7 mmol) of a 13% sodium hypochlorite solution is poured gently such that the temperature of the reaction medium does not exceed 5°C. This mixture is then stirred for 45 min, taken up by water and then extracted using AcOEt. After drying followed by reduction to dryness of the organic phases, an oil is isolated (yield: 79%) and used as such for the next reactions.

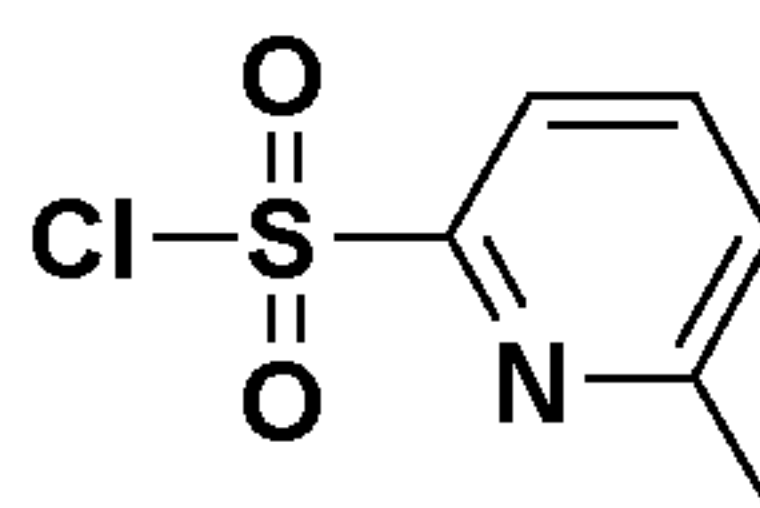
15

b) Pyridine-2-sulfonyl chloride (**4b**)



Intermediate **4b** (oil) is prepared from pyridine-2-thiol using the procedure described for **4a** (yield: 96%).

c) 6-methylpyridine-2-sulfonyl chloride (**4c**)



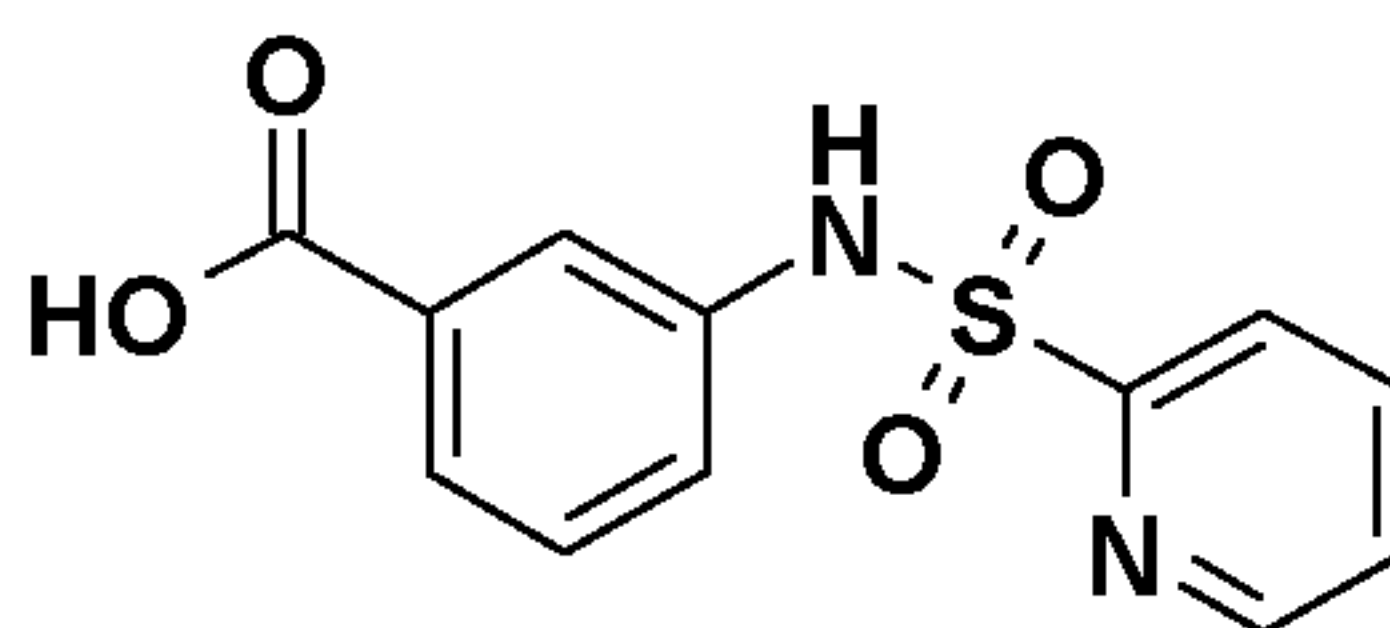
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Intermediate **4c** (oil) is prepared from 6-methylpyridine-2-thiol using the procedure described for **4a** (yield: 96%).

Intermediates 5:

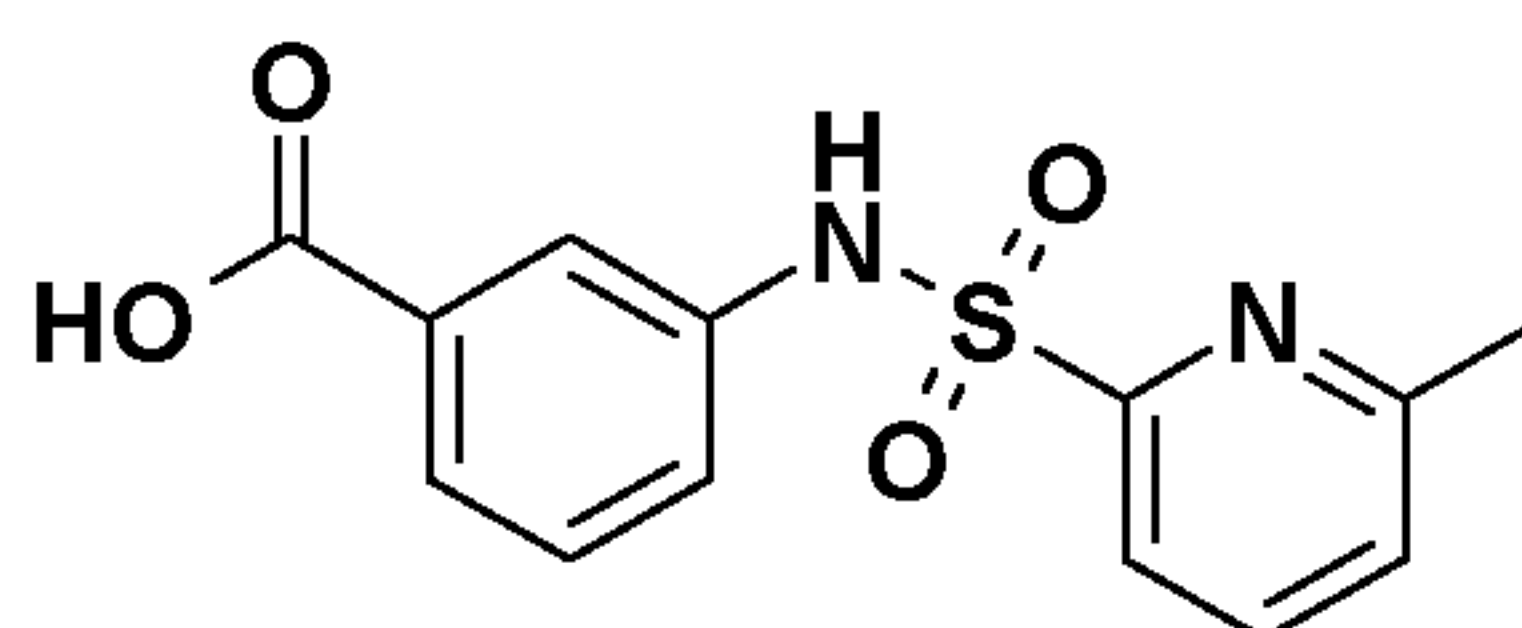
25

a) 3-(pyridine-2-sulfonamido)benzoic acid (**5a**)



0.68 g (4.13 mmol) of ethyl 3-aminobenzoate is placed in 10 mL of CH_2Cl_2 in the presence of 0.4 mL of pyridine and a solution of intermediate **4b** diluted in 3 mL of CH_2Cl_2 is poured drop-by-drop. The reaction medium is stirred for 8h and then reduced to dryness. The residue is taken up in water and then extracted using AcOEt. After drying followed by reduction to dryness of the organic phases, a solid is isolated and then purified by flash chromatography on silica (CH_2Cl_2 -AcOEt, gradient 100-0 to 90-10 over 45 min). 1.14 g of white solid is obtained (yield: 90%). *TLC silica gel 60 F 254 Merck, CH_2Cl_2 -AcOEt:90-10, $R_f=0.26$.* This solid (3.72 mmol) is placed in 17 mL of EtOH in the presence of 0.41 g (7.44 mmol) of soda and the mixture is heated to reflux for 9h30. After reduction to dryness the medium is taken up by water and extracted using AcOEt. The aqueous phase is then acidified (pH=1) with HCl 1N and then extracted using AcOEt. After drying followed by reduction to dryness of the organic phases, a solid is obtained. It is triturated in petroleum ether and then isolated by filtration (1 g, yield: 98%). *TLC silica gel 60 F 254 Merck, CH_2Cl_2 -MeOH:95-5, $R_f=0.20$.*

b) 3-(6-Methyl-pyridine-2-sulfonylamino)-benzoic acid (**5b**)

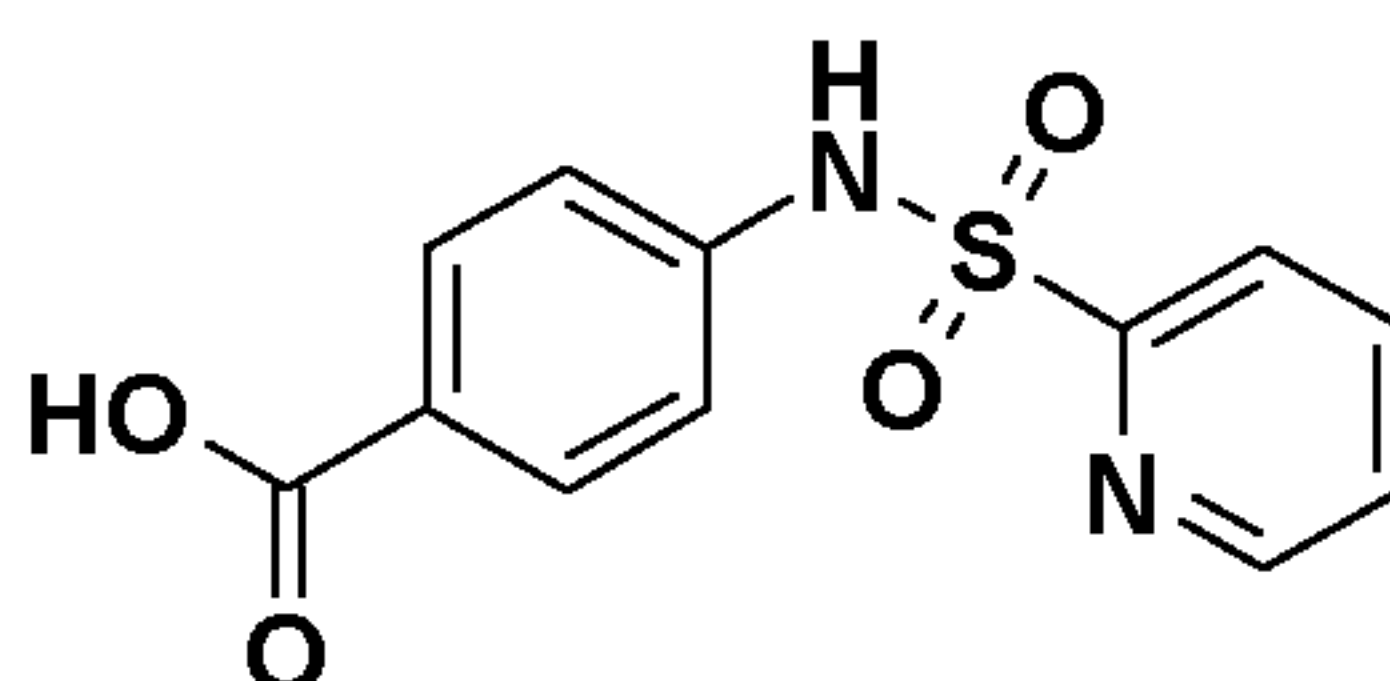


Intermediate **5b** (solid) is prepared using intermediate **4c** and ethyl 3-aminobenzoate using the procedure described for **5a**.

(yield: 94%).

TLC silica gel 60 F 254 Merck, CH_2Cl_2 -MeOH:85-15, $R_f=0.36$.

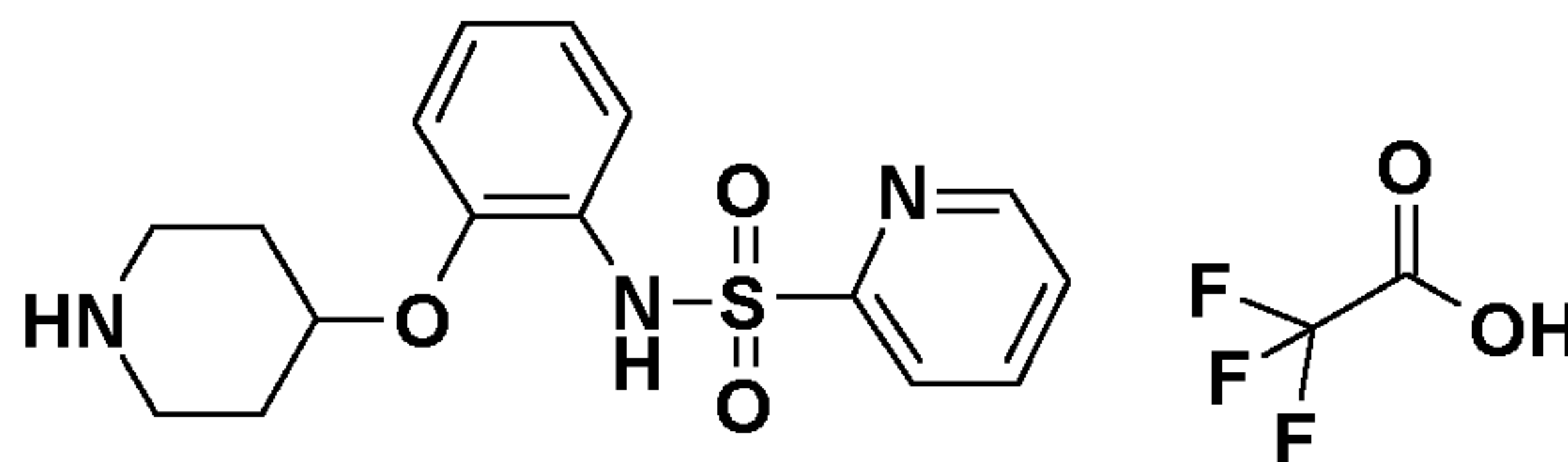
c) 4-(Pyridine-2-sulfonylamino)-benzoic acid (**5c**)



Intermediate **5c** (solid) is prepared using intermediate **4b** and ethyl 4-aminobenzoate using the procedure described for **5a**.

(yield: 50%).

TLC silica gel 60 F 254 Merck, CH_2Cl_2 -MeOH:85-15, $R_f=0.37$.

Intermediates 6:a) N-(2-(piperidin-4-yloxy)phenyl)pyridine-2-sulfonamide trifluoroacetate (6a)

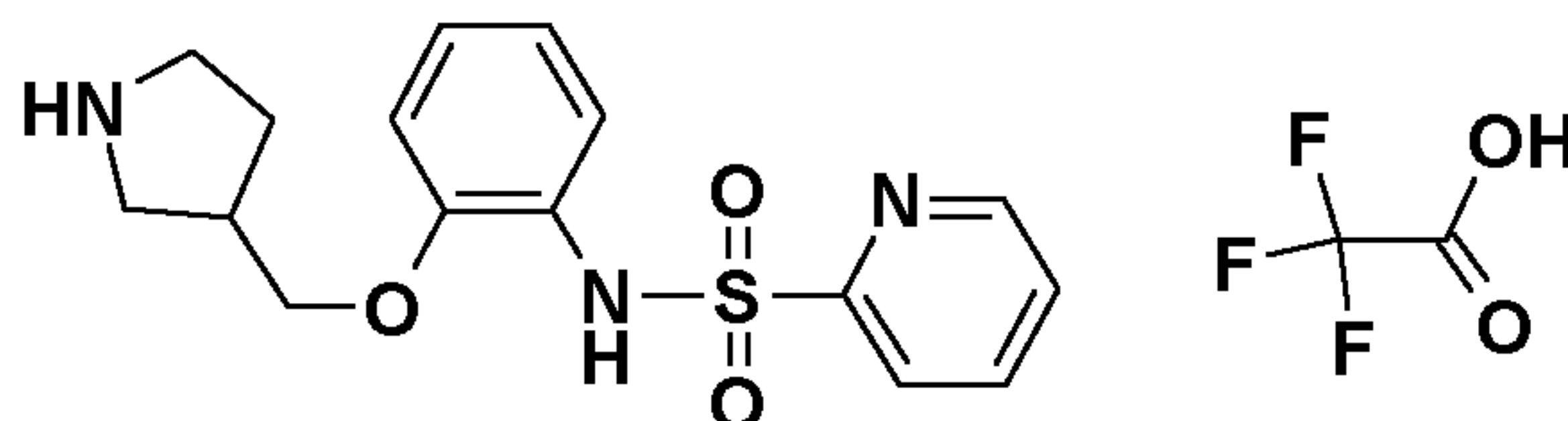
10 g (49.7 mmol) of tert-butyl 4-hydroxypiperidine-1-carboxylate is placed in the
 5 presence of 6.91 g (49.7 mmol) of 2-nitrophenol and 16.94 g (64.6 mmol) of PPh₃.
 11.25 g (64.6 mmol) of DEAD is added to this mixture per fraction and the reaction
 medium is stirred for 2h at ambient temperature and then reduced to dryness. The
 residue is taken up in water and extracted using AcOEt. After drying followed by
 evaporation of the organic phases the residue obtained is purified by flash
 10 chromatography on silica (Petroleum ether-AcOEt, gradient 80-20 to 60-40 over
 20 min). The yellow oil obtained crystallises after trituration in a mixture of petroleum
 ether-Et₂O and 13.2 g of solid is isolated (yield 82%). *TLC silica gel 60 F 254 Merck,*
Petroleum ether-AcOEt:50-50, R_f=0.40.

The solid previously obtained (41.9 mmol) is placed in a stainless steel reactor in the
 15 presence of 223 mg of Pd on carbon in 100 mL of MeOH under 5 bars of hydrogen and
 stirred for 2h at ambient temperature. After filtration on celite followed by evaporation,
 12.4 g of an orange oil is isolated (quantitative yield). *TLC silica gel 60 F 254 Merck,*
Petroleum ether-AcOEt:80-20, R_f=0.44.

4.5 g (15.39 mmol) of previously isolated oil is placed in 200 mL of CH₂Cl₂ in the
 20 presence of intermediate **4b** and of pyridine (1.46 g, 18.47 mmol) and stirred at
 ambient temperature for 3h. The reaction medium is taken up by water and then
 extracted using AcOEt. After drying followed by evaporation of the organic phases the
 residue obtained is purified by flash chromatography on silica (Petroleum ether-AcOEt,
 gradient 70-30 to 50-50 over 30 min). 5.5 g of brown solid is isolated (yield: 82%). *TLC*
 25 *silica gel 60 F 254 Merck, Petroleum ether-AcOEt:50-50, R_f=0.50.*

The solid previously obtained (12.7 mmol) is placed in the presence of 14.7 g
 (127 mmol) of trifluoroacetic acid in 40 mL of CH₂Cl₂ and stirred for 2h at ambient
 temperature. After evaporation under reduced pressure the residue is triturated in a
 mixture of Et₂O/acetone and 5.34 g of intermediate **6a** (a beige solid) is isolated by
 30 filtration (yield 94%). *TLC silica gel 60 F 254 Merck, Petroleum ether-AcOEt:50-50,*
R_f=0.36.

b) N-(2-(pyrrolidin-3-ylmethoxy)phenyl)pyridine-2-sulfonamide trifluoroacetate (6b)



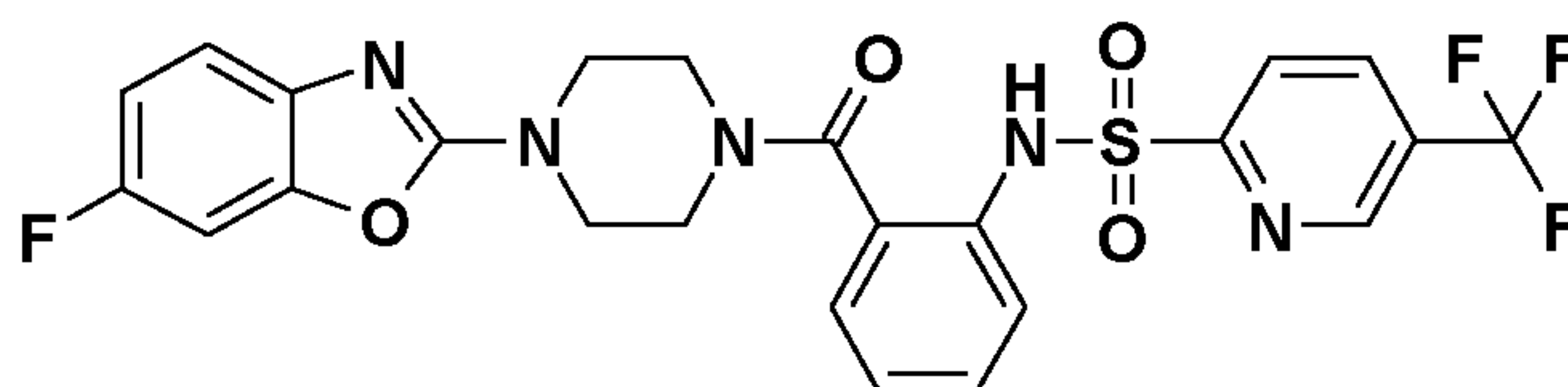
Intermediate **6b** (solid) is prepared using tert-butyl 3-(hydroxymethyl)pyrrolidine-1-carboxylate instead of tert-butyl 4-hydroxypiperidine-1-carboxylate using the procedure described for **6a** (yield: 39% over the 4 steps).

TLC silica gel 60 F 254 Merck, CH₂Cl₂-MeOH:90-10, R_f=0.25.

B) COMPOUNDS ACCORDING TO THE INVENTION

10

Example 1: N-(2-(4-(6-fluorobenzo[d]oxazol-2-yl)piperazine-1-carbonyl)phenyl)-5-(trifluoromethyl)pyridine-2-sulfonamide (1)



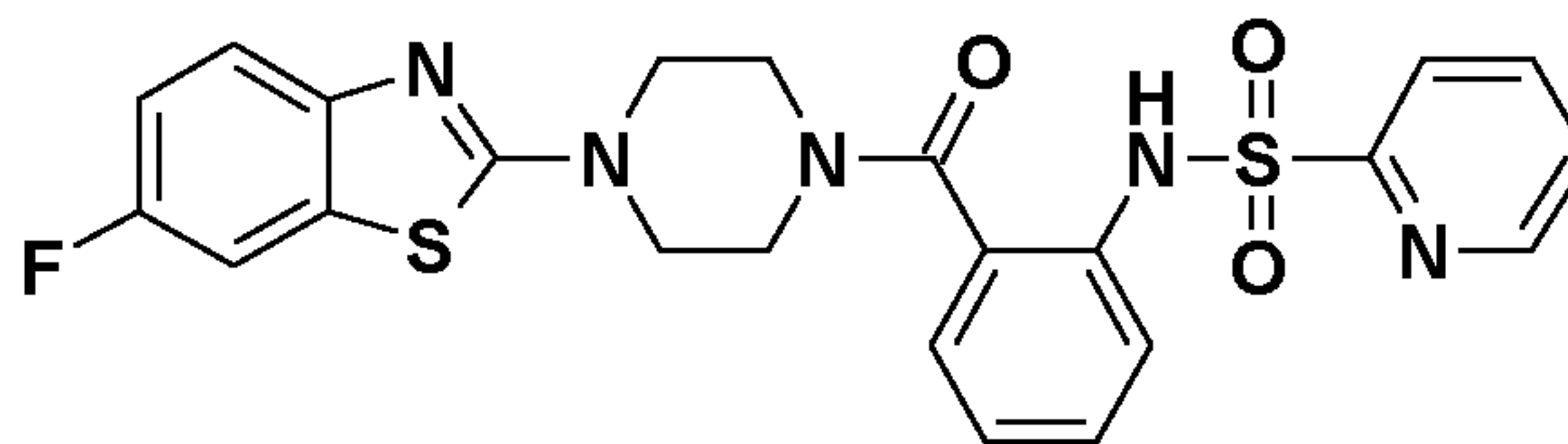
Compound **1** is prepared using synthesis method 1: intermediate **3a** (2.5 g, 11.30 mmol) is placed in the presence of 1H-benzo[d][1,3]oxazine-2,4-dione (1.83 g, 11.3 mmol) and of DMAP (138 mg, 1.13 mmol) in 25 mL of THF and 5 mL of DMF and the mixture is stirred overnight at ambient temperature. After reduction to dryness the residue is taken up in water and extracted using AcOEt. After the organic phases are dried and after reduction to dryness the residue obtained is purified by flash chromatography on silica (CH₂Cl₂-MeOH, gradient 100-0 to 95-5 over 40 min). 0.47 g of solid is obtained (yield: 32%). It is then placed in 3 mL of dichloromethane in the presence of 0.119 g (0.48 mmol) of intermediate **4a** and 39 µL of pyridine. The mixture is then stirred overnight at ambient temperature and then taken up by water and extracted using dichloromethane. After the organic phases are dried and after reduction to dryness the residue obtained is purified by flash chromatography (CH₂Cl₂-MeOH, gradient 100-0 to 95-5 over 65 min). 90 mg of solid is obtained (yield: 35%).

TLC silica gel 60 F 254 Merck, CH₂Cl₂-MeOH: 95-5, R_f=0.48.

NMR ¹H (CDCl₃) ppm: 8.94 (s, 1H), 8.69 (s, 1H), 8.19 (m, 2H), 7.74 (d, 1H), 7.41 (t, 1H), 7.26 (m, 2H), 7.17 (t, 1H), 7.07 (d, 1H), 6.95 (t, 1H), 3.76 (m, 8H).

MS (-ESI) m/z 548 (M-H-)

Example 2: N-(2-(4-(6-fluorobenzo[d]thiazol-2-yl)piperazine-1-carbonyl)phenyl)-pyridine-2-sulfonamide (2)



Compound 2 is prepared using synthesis method 1 using intermediate **3e** for the first step (yield: 87%) and intermediate **4b** for the second step (yield: 30%).

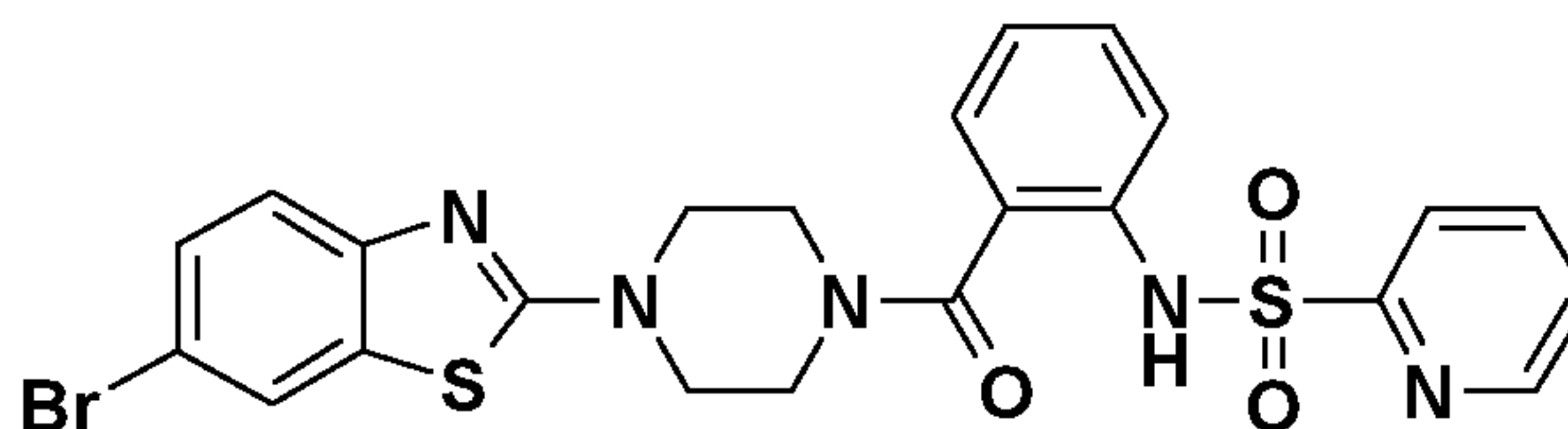
TLC silica gel 60 F 254 Merck, CH₂Cl₂-MeOH: 95-5, R_f=0.58.

NMR ¹H (CDCl₃) ppm: 8.65 (d, 1H), 8.58 (s, 1H), 8.03 (d, 1H), 7.89 (t, 1H), 7.77 (d, 1H), 7.50 (m, 1H), 7.39 (m, 3H), 7.12 (m, 3H), 3.62 (m, 8H).

MS (+ESI) m/z 498 (MH⁺)

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Example 3: N-(2-(4-(6-bromobenzo[d]thiazol-2-yl)piperazine-1-carbonyl)phenyl)-pyridine-2-sulfonamide (3)



Compound 3 is prepared using synthesis method 1 using intermediate **3f** for the first step (quantitative yield) and intermediate **4b** for the second step (yield: 80%).

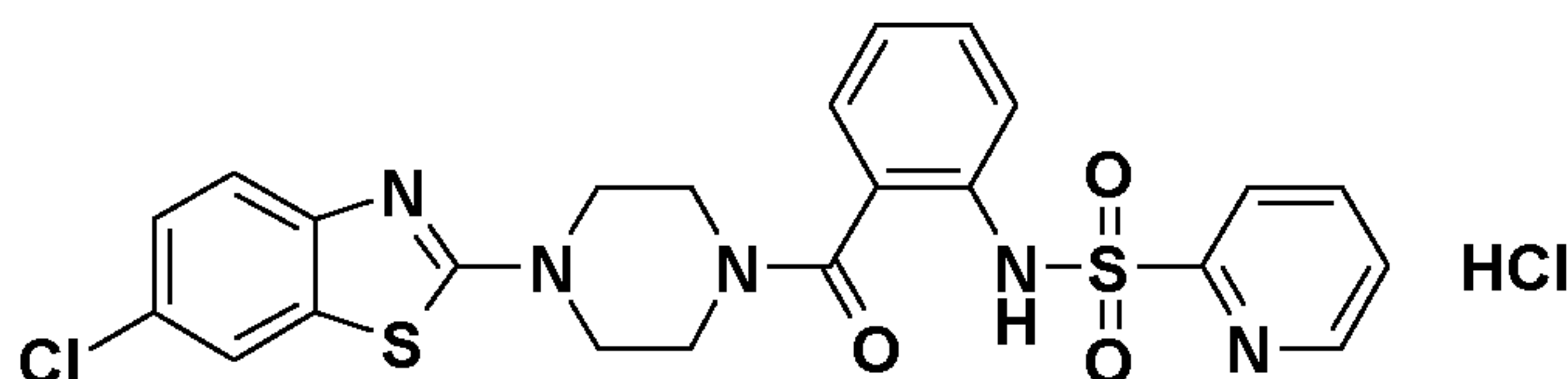
TLC silica gel 60 F 254 Merck, CH₂Cl₂-MeOH: 95-5, R_f=0.60.

mp=102°C

NMR ¹H (CDCl₃) ppm: 8.66 (d, 1H), 8.56 (s, 1H), 8.03 (d, 1H), 7.88 (t, 1H), 7.75 (m, 2H), 7.41 (m, 4H), 7.16 (m, 2H), 3.64 (m, 8H).

20 MS (+ESI) m/z 558 (MH⁺)

Example 4: N-(2-(4-(6-chlorobenzo[d]thiazol-2-yl)piperazine-1-carbonyl)phenyl)pyridine-2-sulfonamide hydrochloride (4)



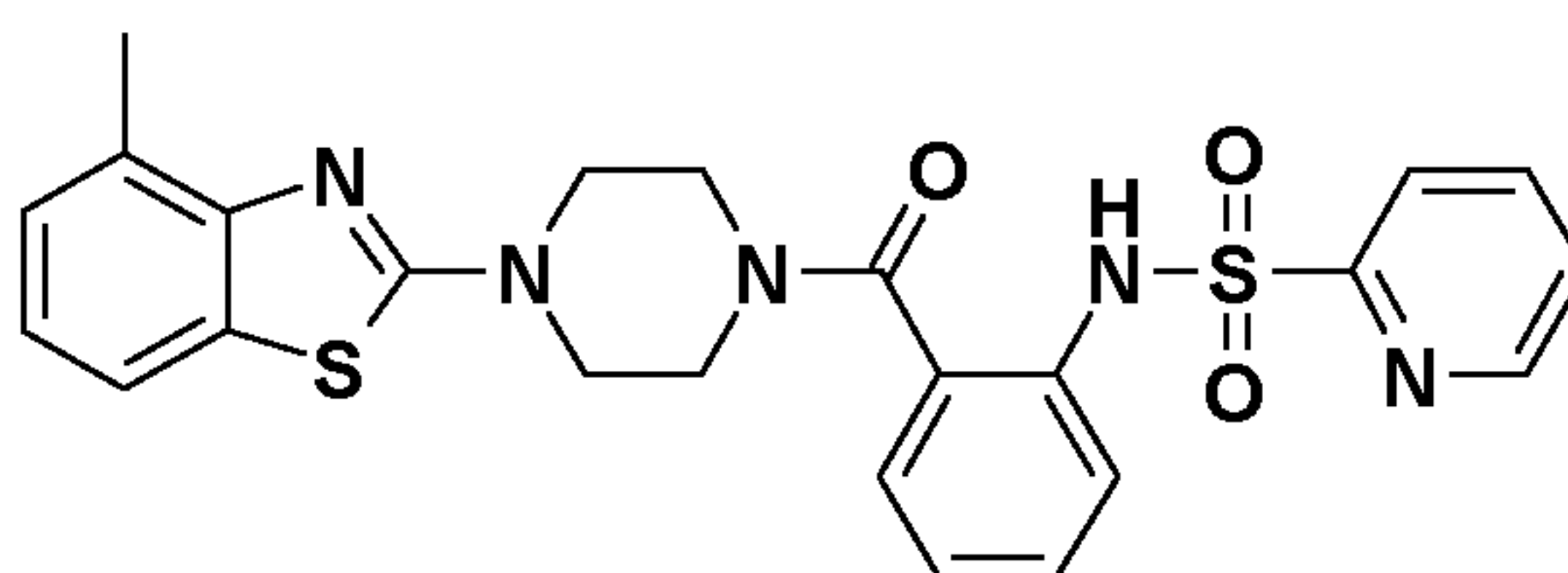
Compound 4 is prepared using synthesis method 1 using intermediate **3g** for the first step (yield: 72%) and intermediate **4b** for the second step (yield: 27%) and then salified in the form of hydrochloride.

25

NMR ^1H (DMSO) ppm: 10.70(s, 1H), 8.7(d, 1H), 8.0(m, 1H), 7.8(m, 2H), 7.6(m, 1H), 7.4(d, 1H), 7.3(m, 3H), 7.2(m, 1H), 7.1(d, 1H), 3.6(m, 8H).

MS (+ESI) m/z 514 (MH⁺ base)

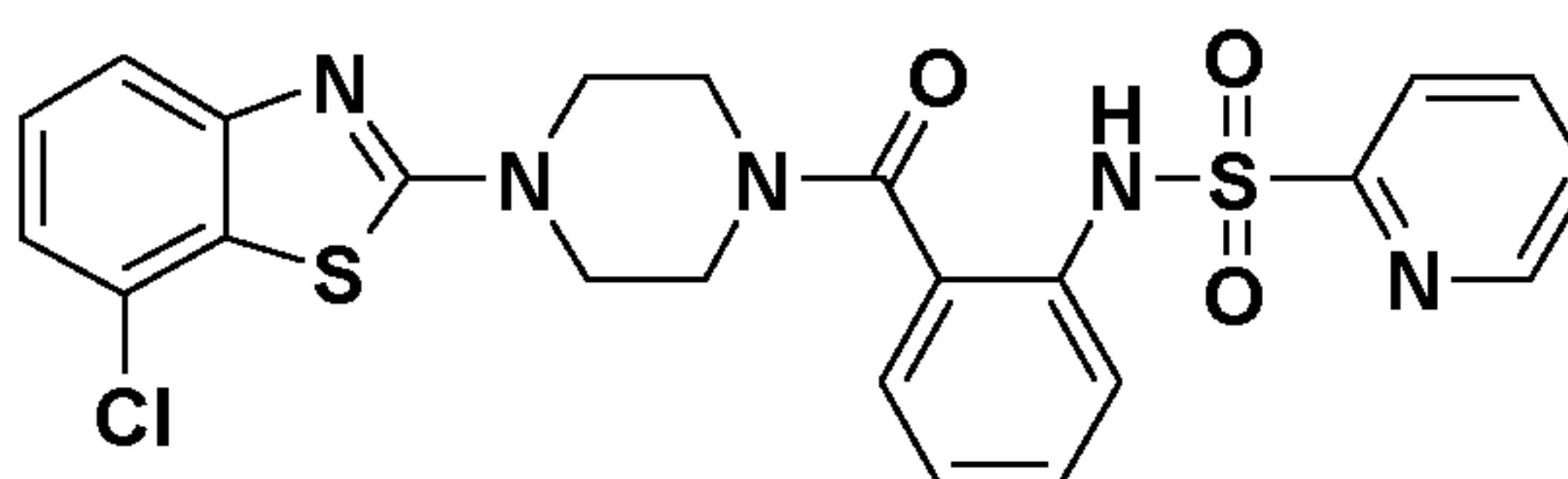
- 5 Example 5: N-(2-(4-(4-methylbenzo[d]thiazol-2-yl)piperazine-1-carbonyl)phenyl)-pyridine-2-sulfonamide (5)



Compound 5 is prepared using synthesis method 1 using intermediate **3h** for the first step (yield: 87%) and intermediate **4b** for the second step (yield: 23%).

- 10 TLC silica gel 60 F 254 Merck, CH₂Cl₂-MeOH: 95-5, R_f=0.70.
NMR ^1H (CDCl₃) ppm: 8.65 (m, 2H), 8.03 (d, 1H), 7.87 (t, 1H), 7.79 (d, 1H), 7.48 (d, 1H), 7.41 (m, 2H), 7.20 (d, 1H), 7.14 (m, 2H), 7.04 (t, 1H), 3.63 (m, 8H), 2.56 (s, 3H).
MS (+ESI) m/z 494 (MH⁺)

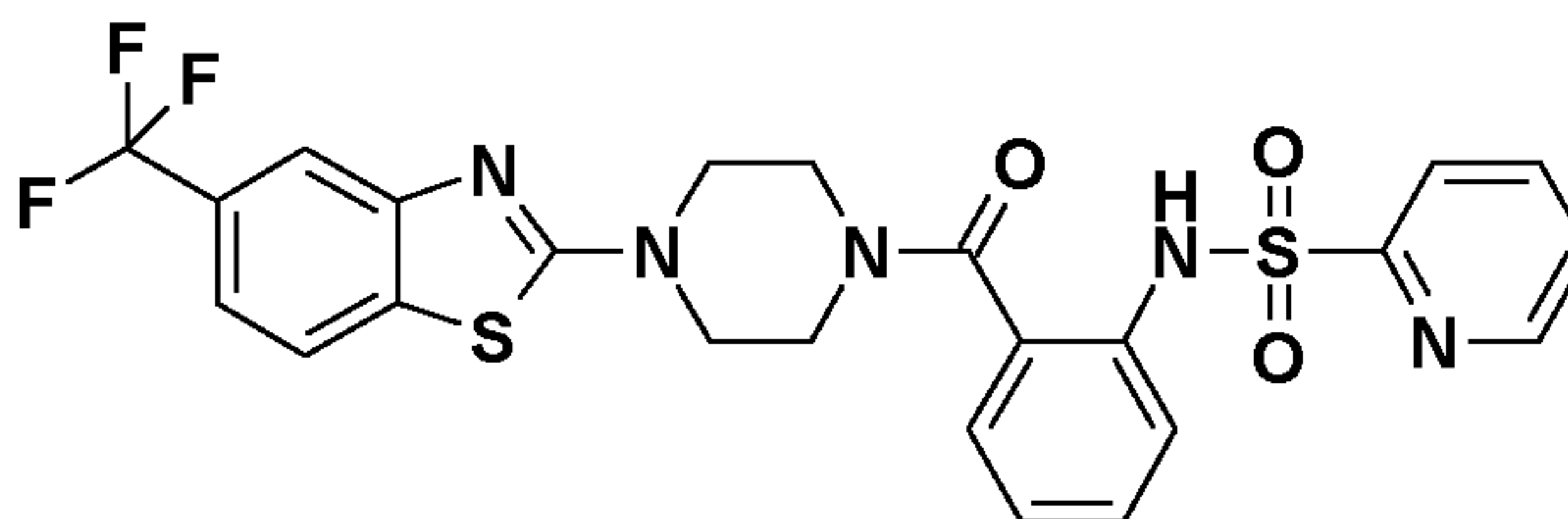
- 15 Example 6: N-(2-(4-(7-chlorobenzo[d]thiazol-2-yl)piperazine-1-carbonyl)phenyl)-pyridine-2-sulfonamide (6)



Compound 6 is prepared using synthesis method 1 using intermediate **3c** for the first step (quantitative yield) and intermediate **4b** for the second step (yield: 24%).

- 20 TLC silica gel 60 F 254 Merck, CH₂Cl₂-MeOH: 95-5, R_f=0.54.
NMR ^1H (CDCl₃) ppm: 8.66 (d, 1H), 8.57 (s, 1H), 8.04 (d, 1H), 7.89 (t, 1H), 7.77 (d, 1H), 7.42 (m, 3H), 7.29 (m, 1H), 7.16 (m, 3H), 3.66 (m, 8H).
MS (+ESI) m/z 514 (MH⁺)

- 25 Example 7: N-(2-(4-(5-(trifluoromethyl)benzo[d]thiazol-2-yl)piperazine-1-carbonyl)phenyl)pyridine-2-sulfonamide (7)



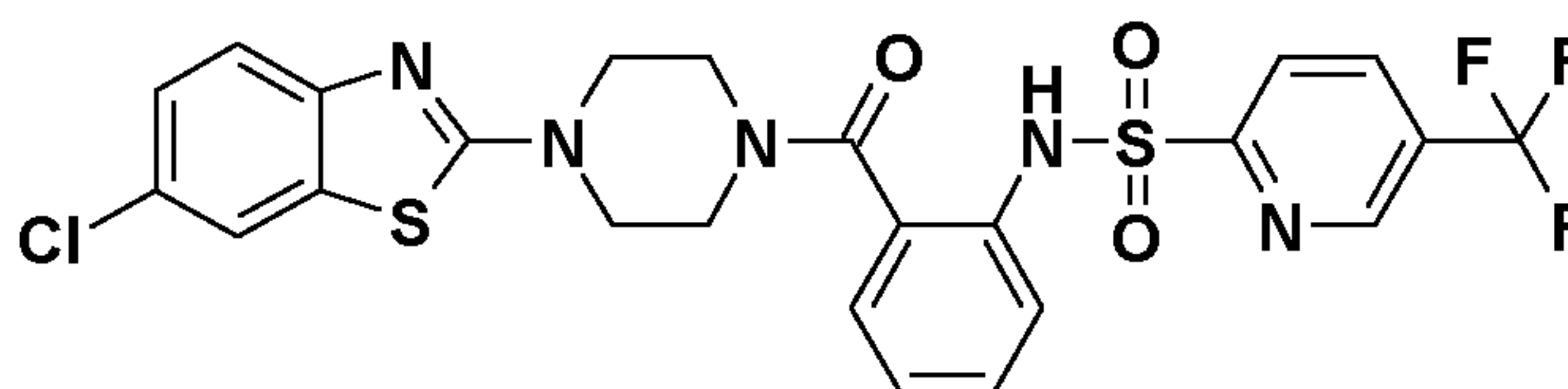
Compound 7 is prepared using synthesis method 1 using intermediate **3d** for the first step (yield: 74%) and intermediate **4b** for the second step (yield: 31%).

TLC silica gel 60 F 254 Merck, CH₂Cl₂-MeOH: 95-5, R_f=0.66.

5 NMR ¹H (CDCl₃) ppm: 8.67 (d, 1H), 8.55 (s, 1H), 8.04 (d, 1H), 7.89 (t, 1H), 7.76 (s, 1H), 7.74 (dd, 2H), 7.41 (m, 3H), 7.21 (d, 1H), 7.14 (t, 1H), 3.68 (m, 8H).

MS (+ESI) m/z 548 (MH⁺)

10 Example 8: N-(2-(4-(6-chlorobenzo[d]thiazol-2-yl)piperazine-1-carbonyl)phenyl)-5-(trifluoromethyl)pyridine-2-sulfonamide (8)



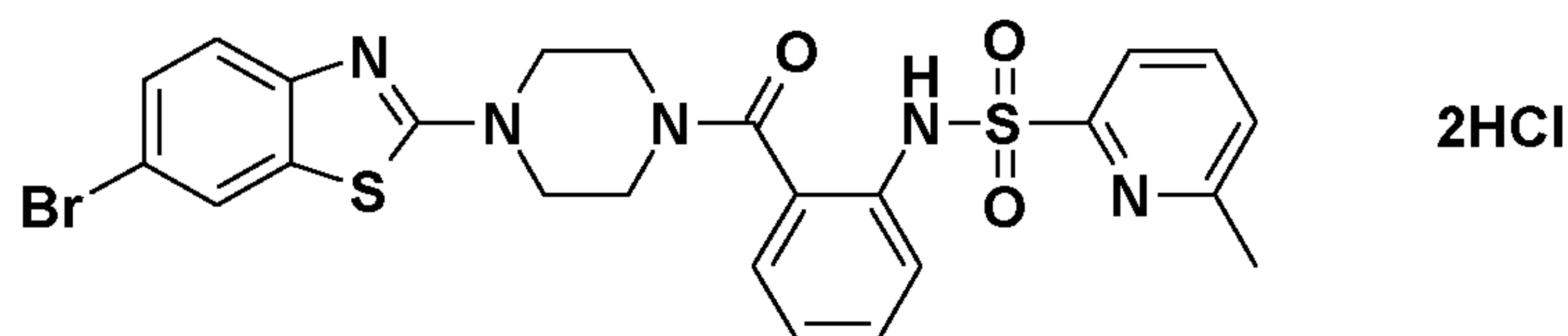
Compound 8 is prepared using synthesis method 1 using intermediate **3g** for the first step (yield: 94%) and intermediate **4a** for the second step (yield: 56%).

TLC silica gel 60 F 254 Merck, CH₂Cl₂- MeOH: 95-5, R_f=0.50.

15 NMR ¹H (CDCl₃) ppm: 8.93 (s, 1H), 8.71 (s, 1H), 8.18 (m, 2H), 7.74 (d, 1H), 7.60 (s, 1H), 7.47 (d, 1H), 7.40 (t, 1H), 7.26 (m, 2H), 7.16 (t, 1H), 3.69 (m, 8H).

MS (-ESI) m/z 580 (M-H⁻)

20 Example 9: N-(2-(4-(6-bromobenzo[d]thiazol-2-yl)piperazine-1-carbonyl)phenyl)-6-methylpyridine-2-sulfonamide dihydrochloride (9)



Compound 9 is prepared using synthesis method 1 using intermediate **3f** for the first step (quantitative yield) and intermediate **4c** for the second step (yield: 40%). The dihydrochloride is obtained by salt formation using a 5N solution of HCl in isopropanol (3 equivalents).

25 TLC silica gel 60 F 254 Merck, CH₂Cl₂- MeOH: 95-5, R_f=0.73.

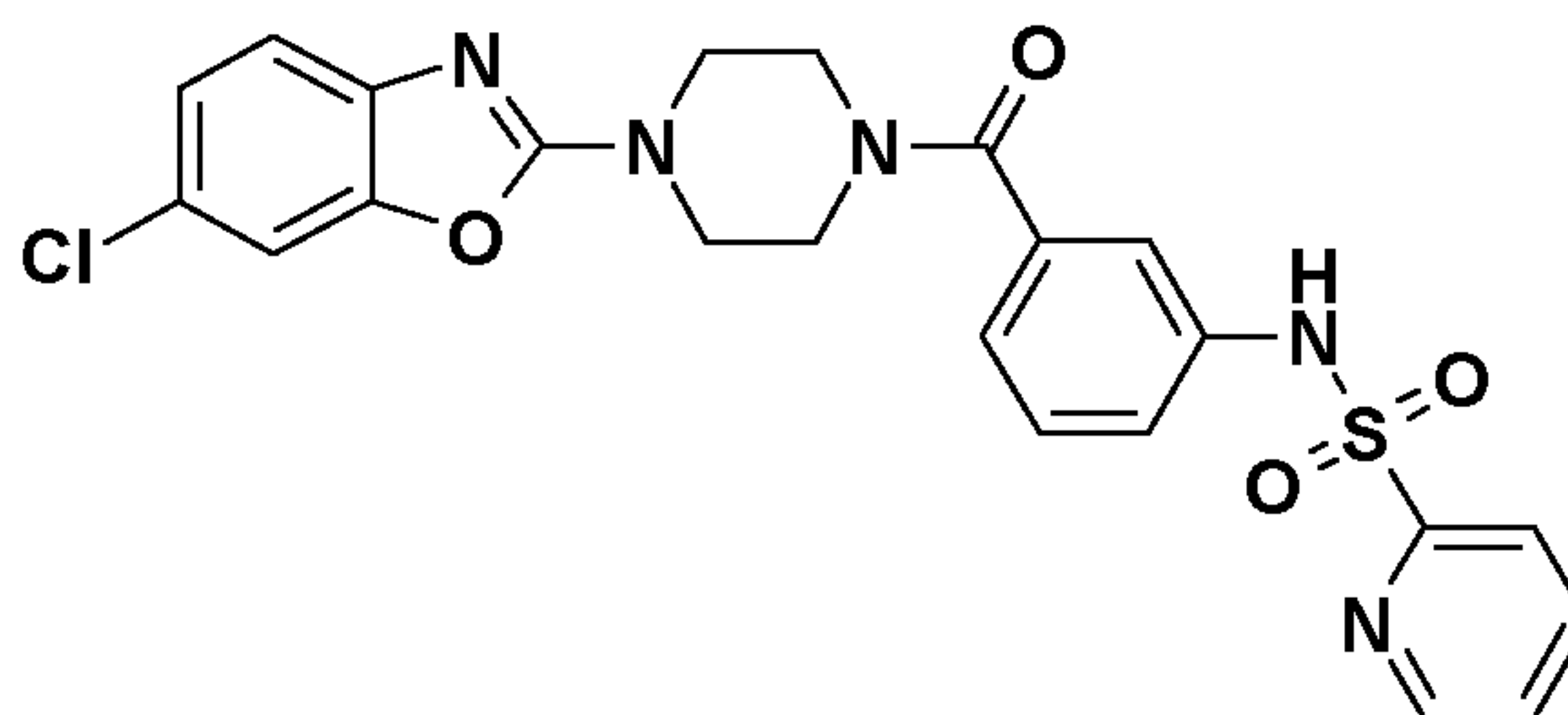
mp=180°C

NMR ^1H (DMSO- d_6) ppm: 10.03 (s, 1H), 8.07 (s, 1H), 7.93 (t, 1H), 7.70 (d, 1H), 7.53 (d, 1H), 7.42 (m, 2H), 7.33 (m, 2H), 7.21 (m, 2H), 3.68 (m, 8H), 2.55 (s, 3H).

MS (+ESI) m/z 572 (MH $^+$)

5

Example 10: N-(3-(4-(6-chlorobenzo[d]oxazol-2-yl)piperazine-1-carbonyl)-phenyl)pyridine-2-sulfonamide (10)



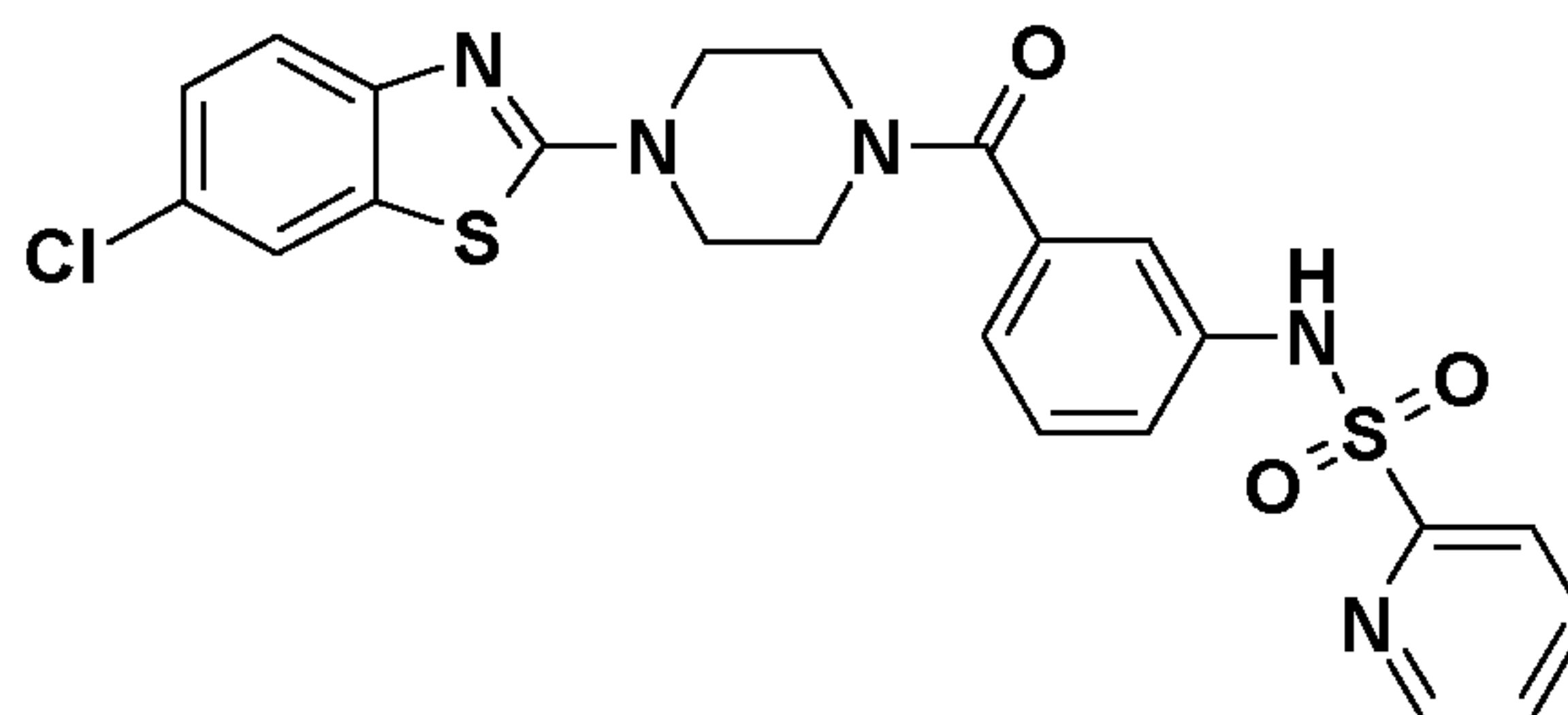
Compound 10 is prepared using synthesis method 2: intermediate **3b** (0.16 g, 0.67 mmol) is placed in 21 mL of acetonitrile in the presence of 0.18 g (0.67 mmol) of intermediate **5a** and 103 μL of Et_3N . 0.21 g (0.67 mmol) of TBTU is then added and the mixture is then stirred for 5h at ambient temperature. After evaporation under reduced pressure the residue is taken up by water and extracted using AcOEt. After the organic phases are dried and after reduction to dryness the residue obtained is purified by flash chromatography (CH_2Cl_2 -MeOH, gradient 99-1 to 95-5 over 65 min). 0.23 g of solid is obtained (yield: 68%).

TLC silica gel 60 F 254 Merck, CH_2Cl_2 -AcOEt: 95-5, R_f =0.30.

NMR ^1H (DMSO- d_6) ppm: 10.76 (s, 1H), 8.73 (d, 1H), 8.08 (t, 1H), 8.00 (d, 1H), 7.67 (t, 1H), 7.60 (s, 1H), 7.32 (m, 2H), 7.22 (m, 3H), 7.08 (d, 1H), 3.63 (m, 6H), 3.34 (m, 2H).

20 MS (+ESI) m/z 498 (MH $^+$)

Example 11: N-(3-(4-(6-chlorobenzo[d]thiazol-2-yl)piperazine-1-carbonyl)phenyl)-pyridine-2-sulfonamide (11)



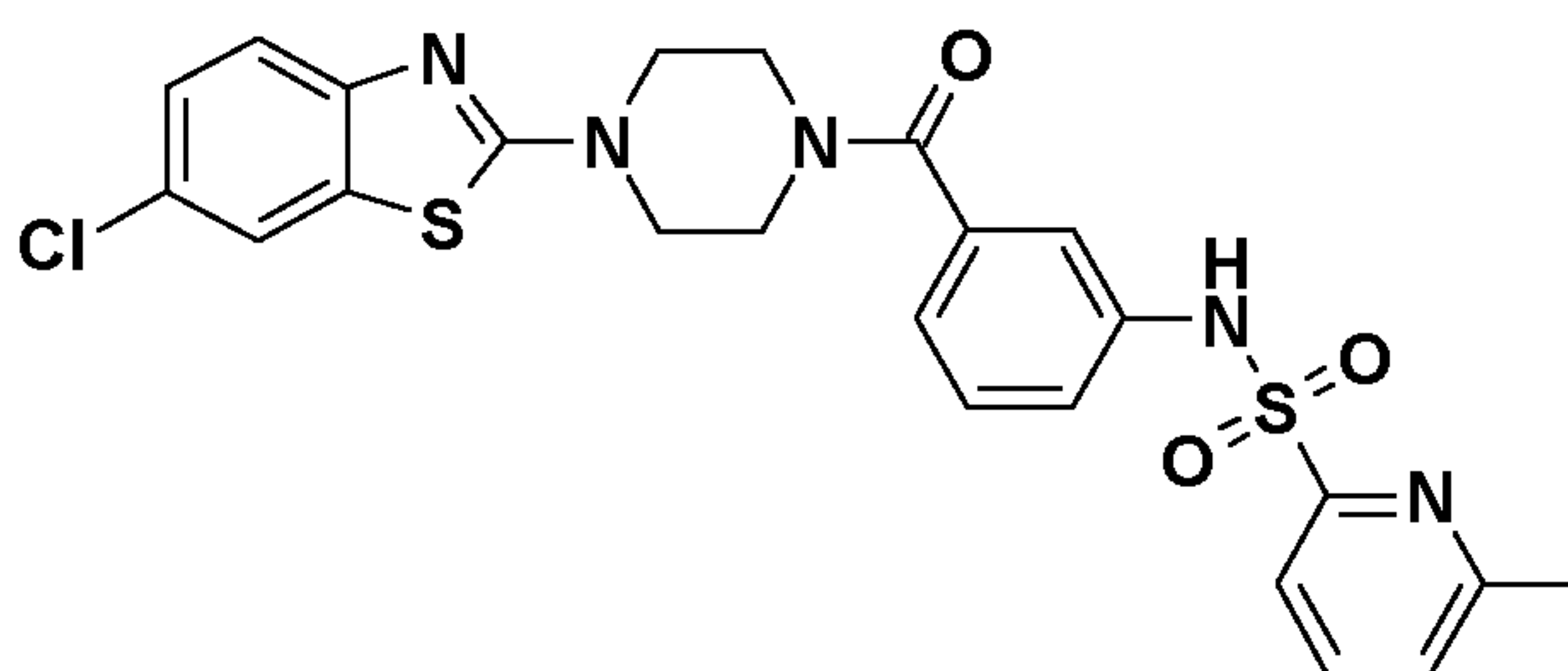
25 Compound 11 is prepared using synthesis method 2 using intermediates **3g** and **5a** (yield: 60%)

TLC silica gel 60 F 254 Merck, CH₂Cl₂- MeOH: 95-5, R_f=0.50.

NMR ¹H (DMSO-d₆) ppm: 10.77 (s, 1H), 8.73 (d, 1H), 8.09 (t, 1H), 8.00 (d, 1H), 7.94 (d, 1H), 7.67 (m, 1H), 7.46 (d, 1H), 7.32 (m, 2H), 7.22 (m, 2H), 7.09 (d, 1H), 3.66 (m, 6H), 3.34 (m, 2H).

5 MS (-ESI) m/z 512 (M-H-)

Example 12: N-(3-(4-(6-chlorobenzo[d]thiazol-2-yl)piperazine-1-carbonyl)-phenyl)-6-methylpyridine-2-sulfonamide (12)



10 Compound 12 is prepared using synthesis method 2 using intermediates **3g** and **5b** (yield: 15%).

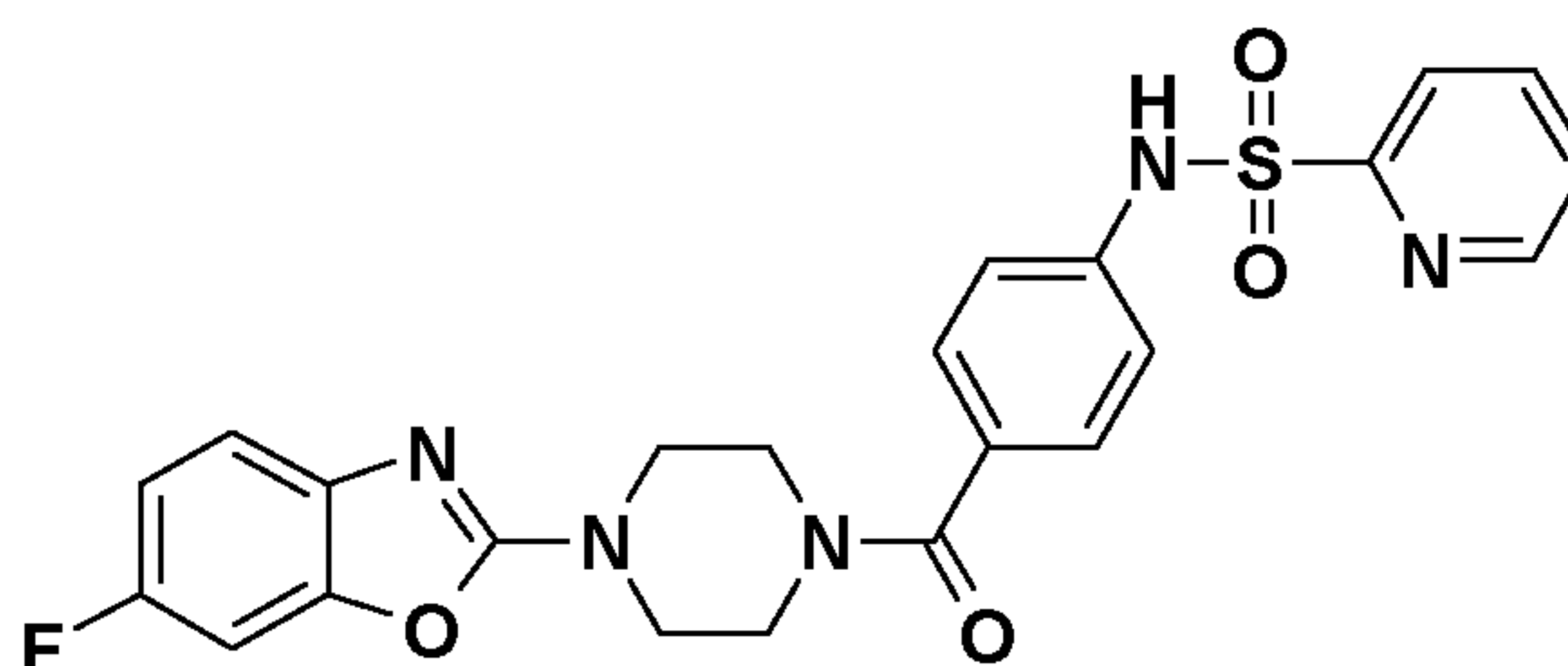
TLC silica gel 60 F 254 Merck, CH₂Cl₂- MeOH: 95-5, R_f=0.52.

NMR ¹H (DMSO-d₆) ppm: 10.71 (s, 1H), 7.95 (m, 2H), 7.79 (d, 1H), 7.52 (d, 1H), 7.46 (d, 1H), 7.32 (m, 2H), 7.23 (m, 2H), 7.09 (d, 1H), 3.62 (m, 6H), 3.38 (m, 2H), 2.52 (s, 3H).

15

MS (+ESI) m/z 528 (MH+)

Example 13: N-(4-(4-(6-fluorobenzo[d]oxazol-2-yl)piperazine-1-carbonyl)phenyl)pyridine-2-sulfonamide (13)



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Compound 13 is prepared using synthesis method 2 using intermediates **3a** and **5c** (yield: 53%).

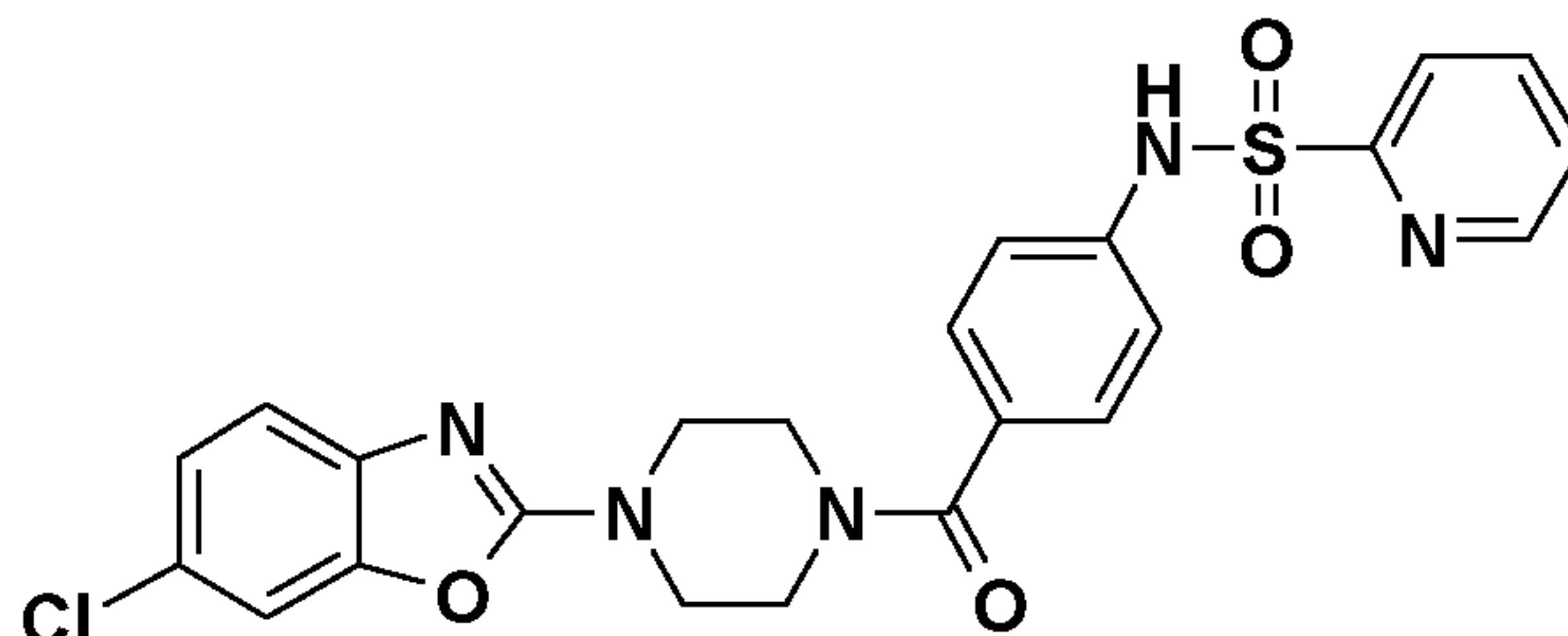
TLC silica gel 60 F 254 Merck, CH₂Cl₂- MeOH: 95-5, R_f=0.28.

NMR ¹H (DMSO-d₆) ppm: 10.87 (s, 1H), 8.72 (d, 1H), 8.06 (m, 2H), 7.67 (m, 1H), 7.44 (d, 1H), 7.33 (d, 1H), 7.27 (m, 3H), 7.21 (d, 1H), 7.02 (t, 1H), 3.61 (m, 8H).

25

MS (+ESI) m/z 482 (MH+)

Example 14: N-(4-(4-(6-chlorobenzo[d]oxazol-2-yl)piperazine-1-carbonyl)phenyl)pyridine-2-sulfonamide (14)



Compound 14 is prepared using synthesis method 2 using intermediates **3b** and **5c** (yield: 56%).

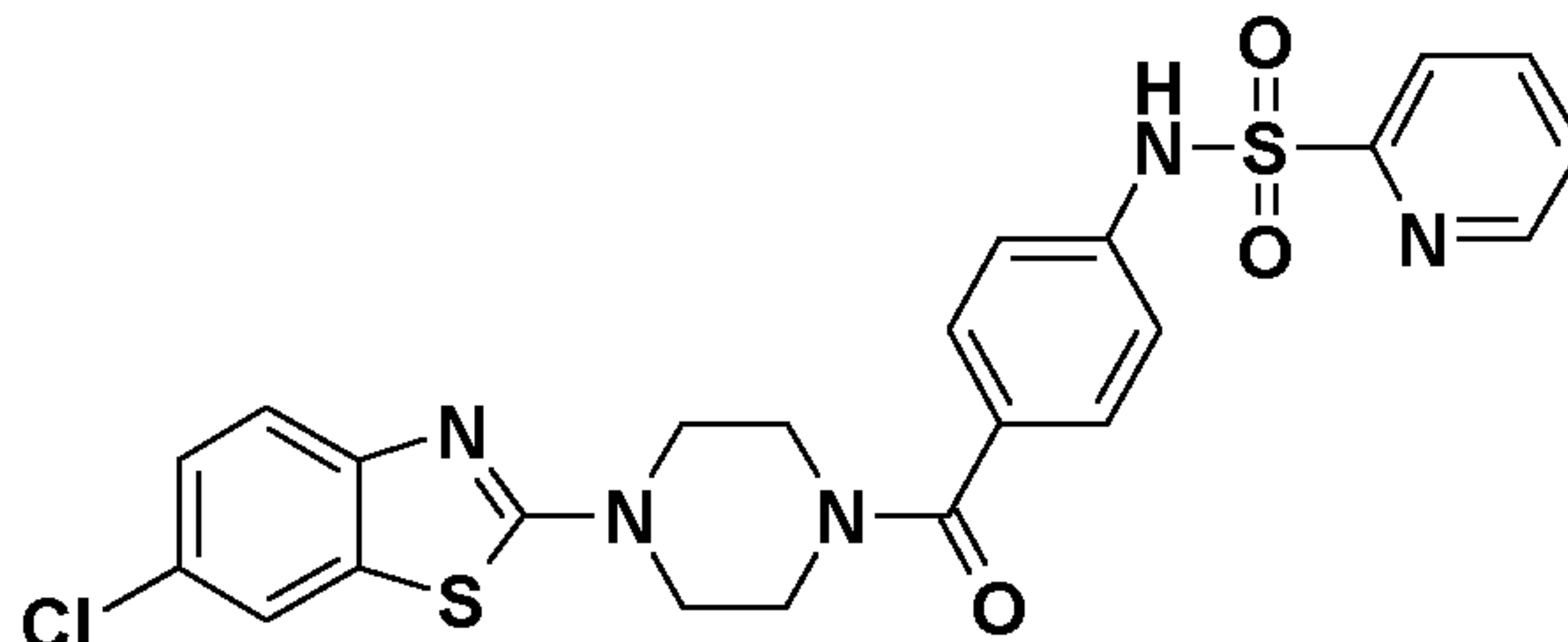
TLC silica gel 60 F 254 Merck, CH₂Cl₂- MeOH: 95-5, R_f=0.40.

NMR ¹H (DMSO-d₆) ppm: 10.89 (s, 1H), 8.70 (d, 1H), 8.04 (m, 2H), 7.62 (m, 2H), 7.29 (m, 3H), 7.18 (m, 3H), 3.62 (m, 8H).

MS (+ESI) m/z 498 (MH⁺)

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Example 15: N-(4-(4-(6-chlorobenzo[d]thiazol-2-yl)piperazine-1-carbonyl)-phenyl)pyridine-2-sulfonamide (15)



Compound 15 is prepared using synthesis method 2 using intermediates **3g** and **5c** (yield: 80%).

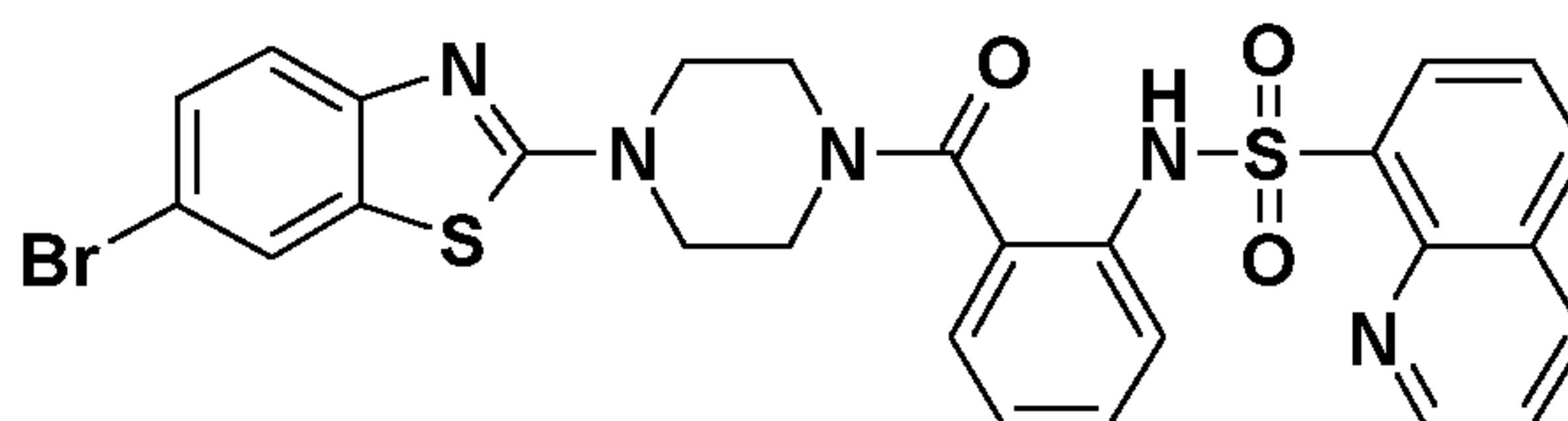
TLC silica gel 60 F 254 Merck, CH₂Cl₂- MeOH: 95-5, R_f=0.34.

NMR ¹H (DMSO-d₆) ppm: 10.87 (s, 1H), 8.73 (d, 1H), 8.07 (m, 2H), 7.93 (d, 1H), 7.65 (t, 1H), 7.44 (d, 1H), 7.32 (m, 3H), 7.21 (d, 2H), 3.60 (m, 8H).

MS (-ESI) m/z 512 (M-H⁻)

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Example 16: N-(2-(4-(6-bromobenzo[d]thiazol-2-yl)piperazine-1-carbonyl)phenyl)-quinoline-8-sulfonamide (16)



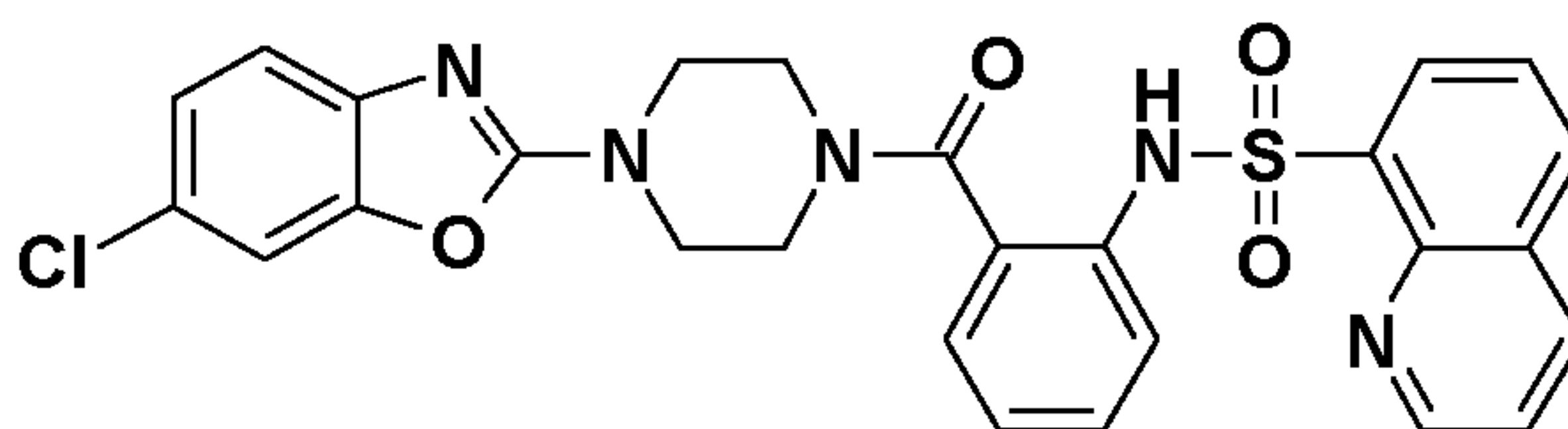
Compound 16 is prepared using synthesis method 1 using intermediate **3f** for the first step (yield: 97%) and quinoline-8-sulfonyl chloride for the second step (yield: 61%).

TLC silica gel 60 F 254 Merck, CH₂Cl₂- MeOH: 95-5, R_f=0.73.

NMR ¹H (CDCl₃) ppm: 9.16 (m, 2H), 8.39 (d, 1H), 8.17 (d, 1H), 7.93 (d, 1H), 7.75 (s, 1H), 7.58 (m, 3H), 7.42 (s, 2H), 7.31 (m, 1H), 7.10 (d, 2H), 3.30 (m, 8H).

MS (+ESI) m/z 608 (MH⁺)

Example 17: N-(2-(4-(6-chlorobenzo[d]oxazol-2-yl)piperazine-1-carbonyl)-phenyl)quinoline-8-sulfonamide (17)



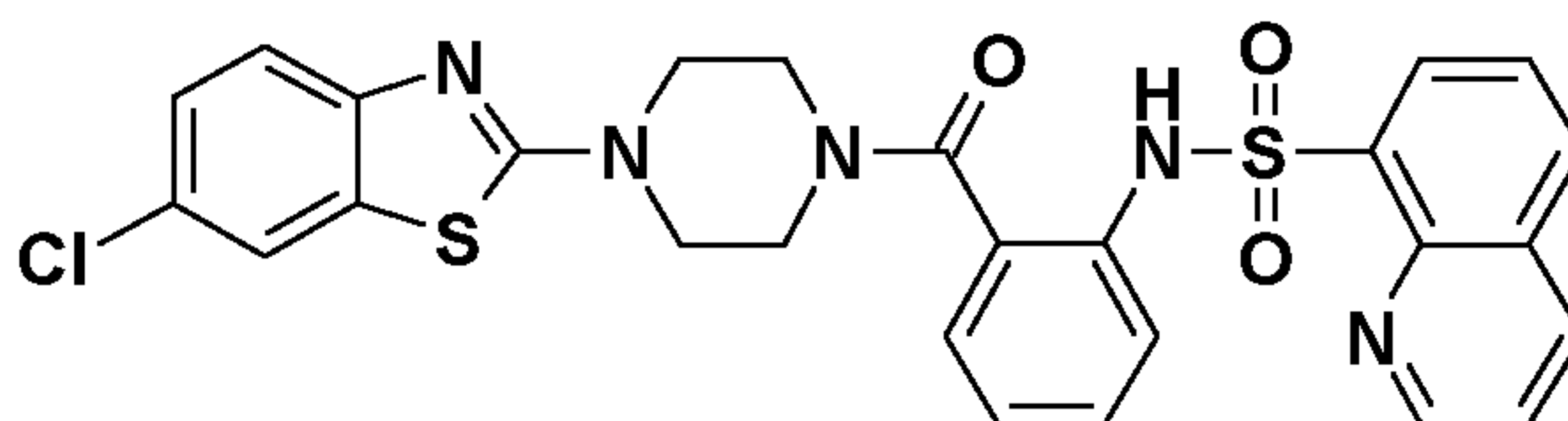
Compound 17 is prepared using synthesis method 1 using intermediate **3b** for the first step (yield: 73%) and quinoline-8-sulfonyl chloride for the second step (yield: 50%).

TLC silica gel 60 F 254 Merck, CH₂Cl₂- MeOH: 95-5, R_f=0.68.

NMR ¹H (CDCl₃) ppm: 9.15 (m, 2H), 8.40 (d, 1H), 8.20 (d, 1H), 7.96 (d, 1H), 7.57 (m, 3H), 7.31 (m, 3H), 7.18 (d, 1H), 7.10 (d, 2H), 3.30 (m, 8H).

MS (+ESI) m/z 548 (MH⁺)

Example 18: N-(2-(4-(6-chlorobenzo[d]thiazol-2-yl)piperazine-1-carbonyl)-phenyl)quinoline-8-sulfonamide (18)



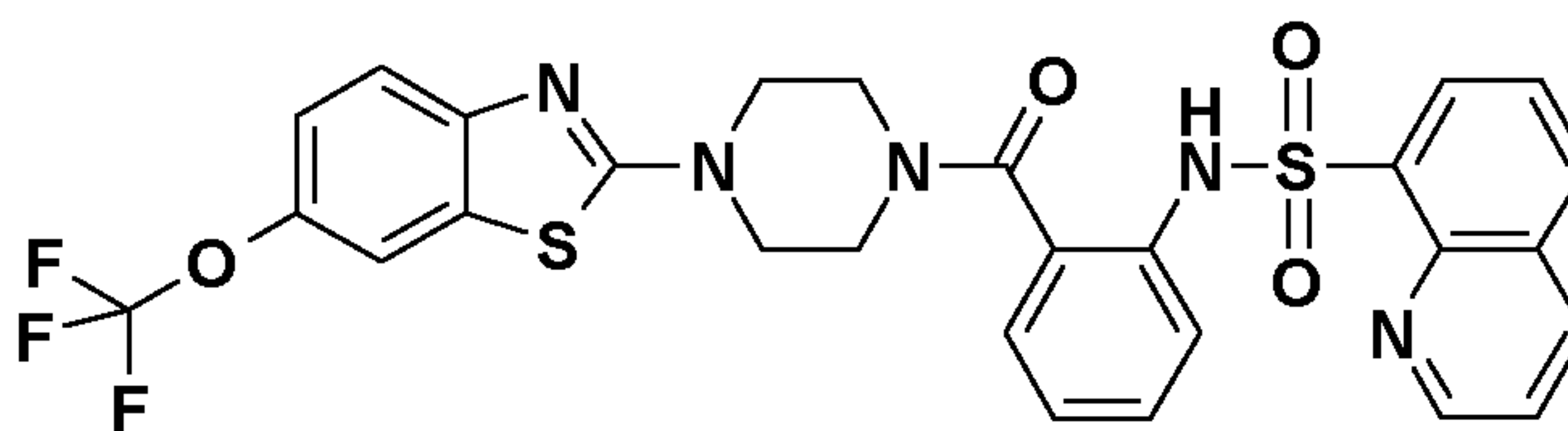
Compound 18 is prepared using synthesis method 1 using intermediate **3g** for the first step (yield: 94%) and quinoline-8-sulfonyl chloride for the second step (yield: 82%).

TLC silica gel 60 F 254 Merck, CH₂Cl₂- MeOH: 95-5, R_f=0.61.

NMR ¹H (CDCl₃) ppm: 9.15 (m, 2H), 8.39 (d, 1H), 8.17 (d, 1H), 7.93 (d, 1H), 7.58 (m, 4H), 7.47 (d, 1H), 7.30 (m, 2H), 7.10 (d, 2H), 3.30 (m, 8H).

MS (+ESI) m/z 564 (MH⁺)

Example 19: N-(2-(4-(6-(trifluoromethoxy)benzo[d]thiazol-2-yl)piperazine-1-carbonyl)-phenyl)quinoline-8-sulfonamide (19)



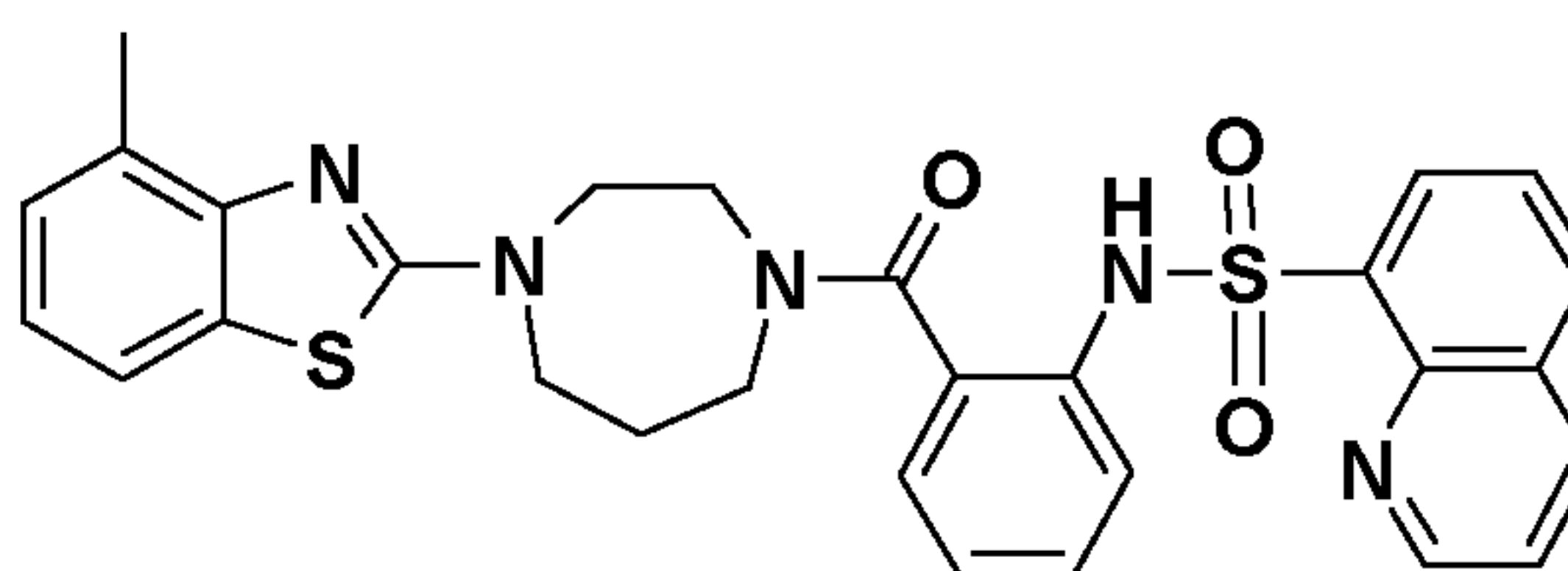
Compound 19 is prepared using synthesis method 1 using intermediate **3i** for the first step (yield: 91%) and quinoline-8-sulfonyl chloride for the second step (yield: 67%).

TLC silica gel 60 F 254 Merck, CH₂Cl₂- MeOH: 95-5, R_f=0.76.

5 NMR ¹H (DMSO-d₆) ppm: 9.39 (s, 1H), 9.10 (d, 1H), 8.49 (d, 1H), 8.26 (t, 2H), 7.97 (s, 1H), 7.71 (m, 2H), 7.54 (d, 1H), 7.47 (d, 1H), 7.37 (m, 1H), 7.27 (m, 2H), 7.14 (m, 1H), 3.62 (m, 6H), 2.77 (m, 2H).

MS (+ESI) m/z 614 (MH⁺)

10 Example 20: N-(2-(4-(4-methylbenzo[d]thiazol-2-yl)-1,4-diazepane-1-carbonyl)-phenyl)quinoline-8-sulfonamide (20)



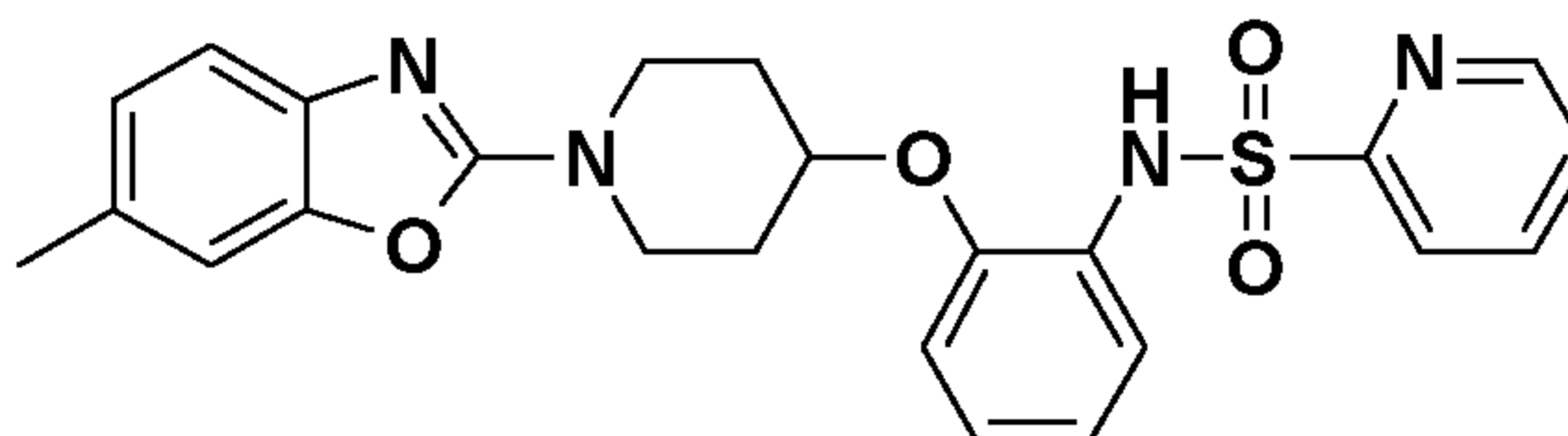
Compound 20 is prepared using synthesis method 1 using intermediate **3j** for the first step (quantitative yield) and quinoline-8-sulfonyl chloride for the second step (yield: 58%).

TLC silica gel 60 F 254 Merck, CH₂Cl₂- MeOH: 95-5, R_f=0.80.

15 NMR ¹H (CDCl₃) ppm: 9.13 (m, 1H), 8.86 (m, 1H), 8.62 (d, 1H), 8.41 (m, 1H), 8.20 (m, 1H), 7.98 (m, 1H), 7.55 (m, 2H), 7.47 (m, 1H), 7.28 (m, 1H), 7.12 (m, 1H), 6.99 (m, 2H), 6.85 (m, 1H), 3.71 (m, 4H), 3.51 (m, 2H), 3.20 (m, 2H), 2.47 (s, 3H), 2.09 (m, 2H).

20 MS (+ESI) m/z 558 (MH⁺)

Example 21: N-(2-(1-(6-methylbenzo[d]oxazol-2-yl)piperidin-4-yloxy)phenyl)pyridine-2-sulfonamide (21)



25 Compound 21 is prepared using synthesis method 3: intermediate **2e** (0.21 g, 1.25 mmol) and intermediate **6a** are placed in 5 mL of EtOH in the presence of 0.3 g

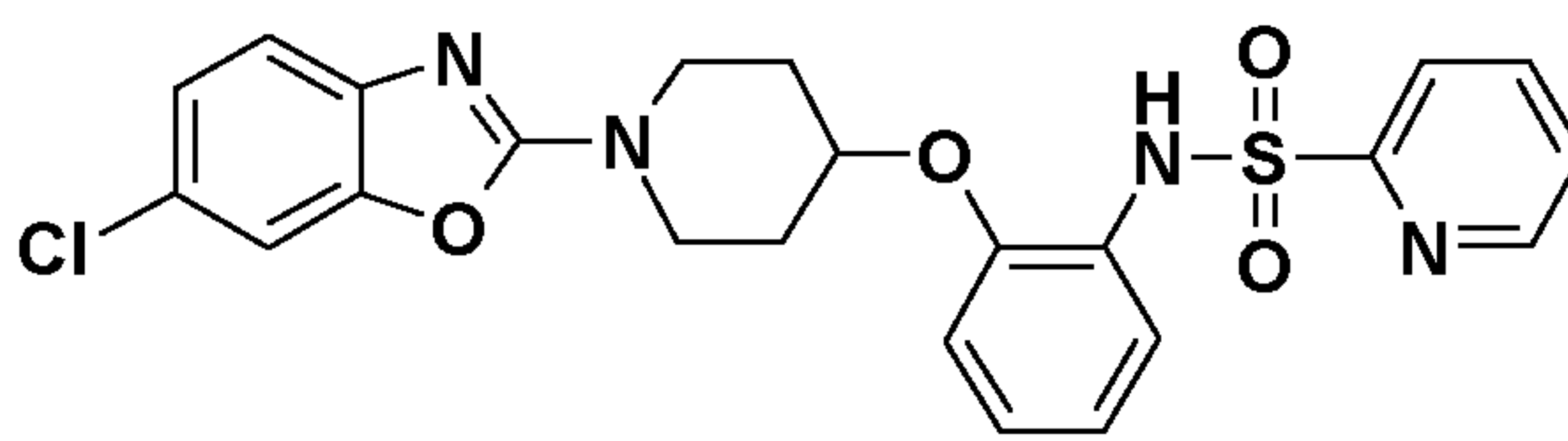
(3.58 mmol) of sodium bicarbonate, and the mixture is then stirred for 2h at 80°C. After evaporation under reduced pressure the residue is taken up by water and extracted using AcOEt. After drying of the organic phases and reduction to dryness the residue obtained is triturated in a mixture of EtOH/Et₂O and 0.32 g of solid is isolated by
5 filtration (yield: 77%).

TLC silica gel 60 F 254 Merck, CH₂Cl₂-AcOEt: 70-30, R_f=0.43.

NMR ¹H (DMSO-d₆) ppm: 9.57 (s, 1H), 8.61 (d, 1H), 7.96 (dt, 1H), 7.82 (d, 1H), 7.53 (m, 1H), 7.28 (dd, 1H), 7.24 (s, 1H), 7.18 (d, 1H), 7.11 (t, 1H), 6.98 (m, 2H), 6.86 (t, 1H), 4.53 (m, 1H), 3.72 (m, 2H), 3.48 (m, 2H), 2.35 (s, 3H), 1.77 (m, 2H), 1.48 (m, 2H).

10 MS (+ESI) m/z 465 (MH⁺)

Example 22: N-(2-(1-(6-chlorobenzo[d]oxazol-2-yl)piperidin-4-yloxy)phenyl)-pyridine-2-sulfonamide (22)



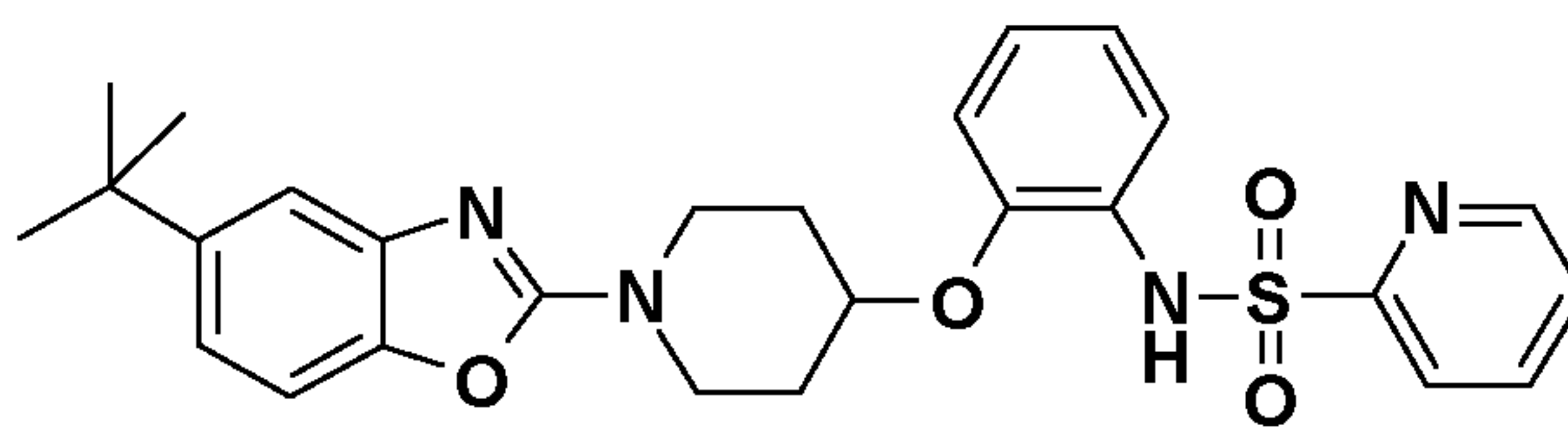
15 Compound 22 is prepared using synthesis method 3 using intermediates **2f** and **6a** (yield: 83%).

TLC silica gel 60 F 254 Merck, Petroleum ether-AcOEt: 70-30, R_f=0.46.

NMR ¹H (DMSO-d₆) ppm: 9.58 (s, 1H), 8.63 (d, 1H), 7.98 (dt, 1H), 7.83 (d, 1H), 7.59 (d, 1H), 7.55 (m, 1H), 7.28 (m, 2H), 7.20 (dd, 1H), 7.14 (t, 1H), 6.99 (d, 1H), 6.86 (t, 1H), 4.54 (m, 1H), 3.72 (m, 2H), 3.52 (m, 2H), 1.79 (m, 2H), 1.51 (m, 2H).

20 MS (+ESI) m/z 485 (MH⁺)

Example 23: N-(2-(1-(5-tert-butylbenzo[d]oxazol-2-yl)piperidin-4-yloxy)phenyl)pyridine-2-sulfonamide (23)



25

Compound 23 is prepared using synthesis method 3 using intermediates **2g** and **6a** (yield: 82%).

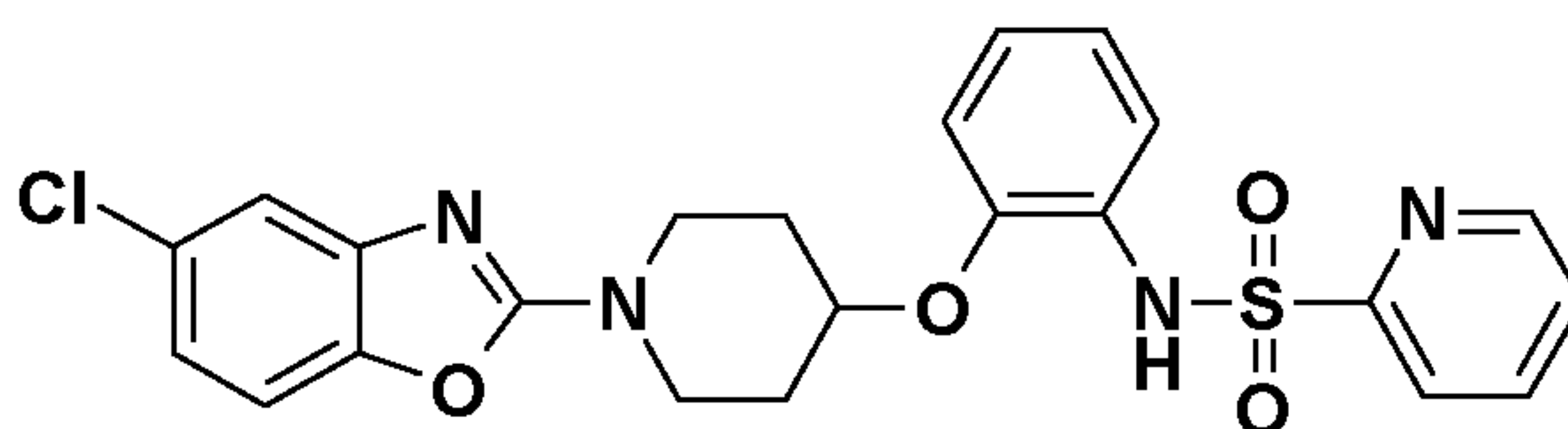
TLC silica gel 60 F 254 Merck, CH₂Cl₂- MeOH: 90-10, R_f=0.65.

NMR ^1H (DMSO- d_6) ppm: 9.57 (s, 1H), 8.63 (m, 1H), 7.97 (dt, 1H), 7.83 (d, 1H), 7.53 (m, 1H), 7.30 (m, 3H), 7.11 (dt, 1H), 7.05 (dd, 1H), 6.99 (d, 1H), 6.85 (dt, 1H), 4.54 (m, 1H), 3.74 (m, 2H), 3.50 (m, 2H), 1.78 (m, 2H), 1.48 (m, 2H), 1.30 (s, 9H).

MS (+ESI) m/z 507 (MH $^+$)

5

Example 24: N-(2-(1-(5-chlorobenzo[d]oxazol-2-yl)piperidin-4-yloxy)phenyl)-pyridine-2-sulfonamide (24)



Compound 24 is prepared using synthesis method 3 using intermediates **2h** and **6a** (yield: 92%).

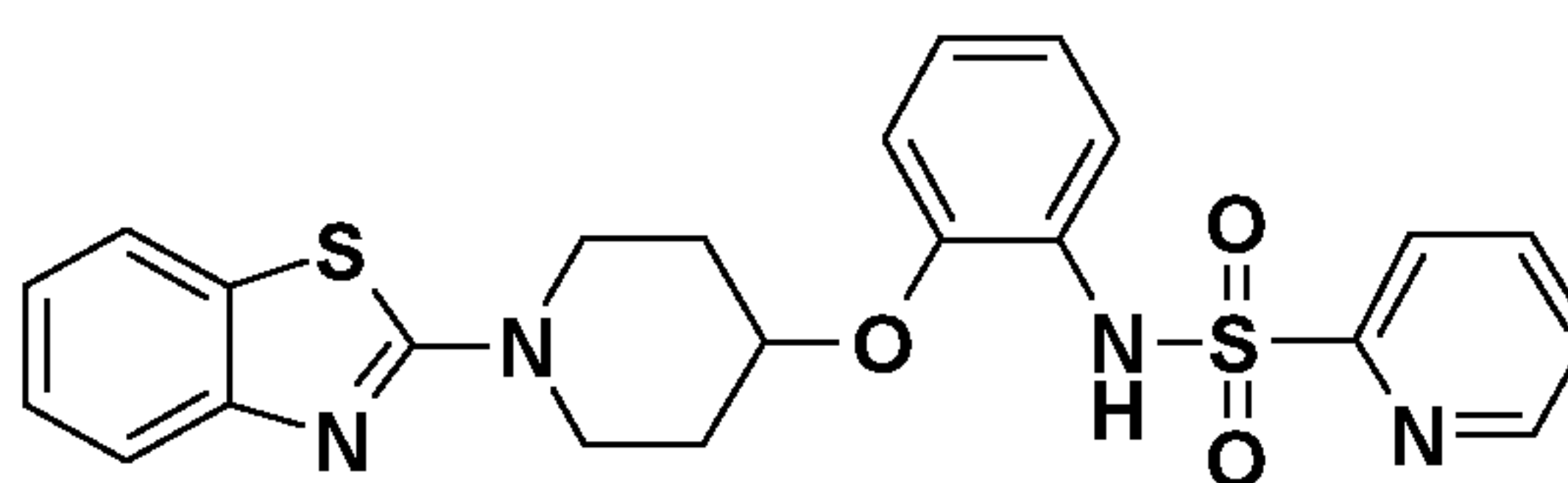
TLC silica gel 60 F 254 Merck, CH_2Cl_2 -AcOEt: 70-30, R_f =0.33.

NMR ^1H (DMSO- d_6) ppm: 9.57 (s, 1H), 8.63 (d, 1H), 7.98 (dt, 1H), 7.83 (d, 1H), 7.55 (m, 1H), 7.43 (d, 1H), 7.35 (d, 1H), 7.29 (dd, 1H), 7.12 (t, 1H), 7.04 (dd, 1H), 6.99 (d, 1H), 6.86 (t, 1H), 4.55 (m, 1H), 3.74 (m, 2H), 3.55 (m, 2H), 1.79 (m, 2H), 1.52 (m, 2H).

MS (+ESI) m/z 485 (MH $^+$)

15

Example 25: N-(2-(1-(benzo[d]thiazol-2-yl)piperidin-4-yloxy)phenyl)pyridine-2-sulfonamide (25)



Compound 25 is prepared using synthesis method 3 using intermediate **6a** and 2-chloro-1,3-benzothiazole (yield: 81%).

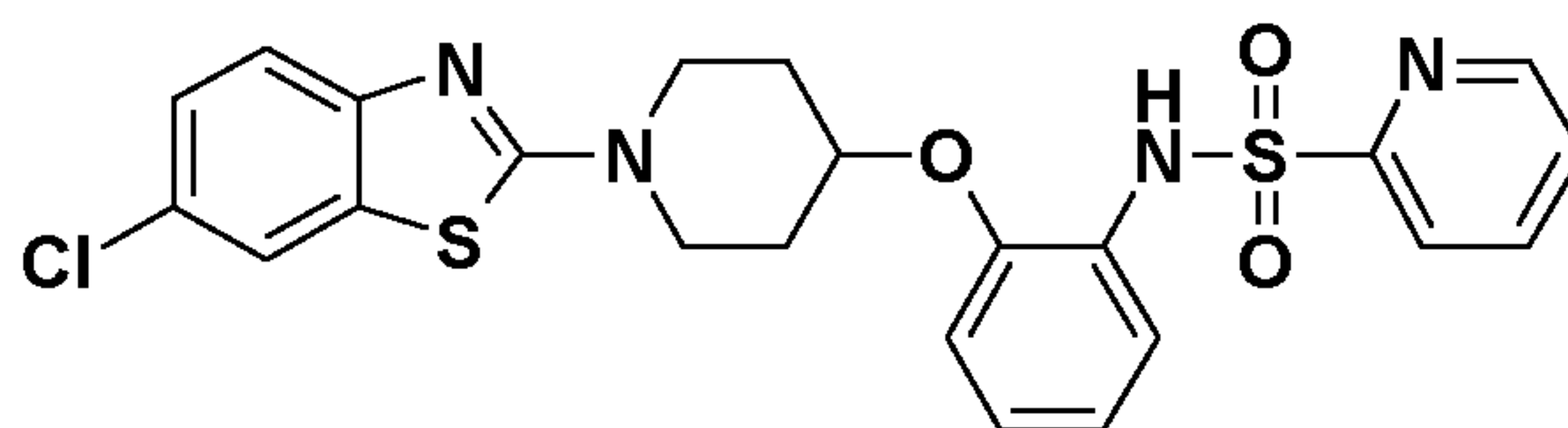
TLC silica gel 60 F 254 Merck, CH_2Cl_2 -AcOEt: 80-20, R_f =0.75.

NMR ^1H (DMSO- d_6) ppm: 9.59 (s, 1H), 8.62 (d, 1H), 7.97 (dt, 1H), 7.82 (d, 1H), 7.77 (d, 1H), 7.53 (m, 1H), 7.47 (d, 1H), 7.28 (m, 2H), 7.10 (m, 2H), 6.99 (d, 1H), 6.86 (t, 1H), 4.56 (m, 1H), 3.72 (m, 2H), 3.47 (m, 2H), 1.79 (m, 2H), 1.53 (m, 2H).

25

MS (+ESI) m/z 467 (MH $^+$)

Example 26: N-(2-(1-(6-chlorobenzo[d]thiazol-2-yl)piperidin-4-yloxy)phenyl)pyridine-2-sulfonamide (26)



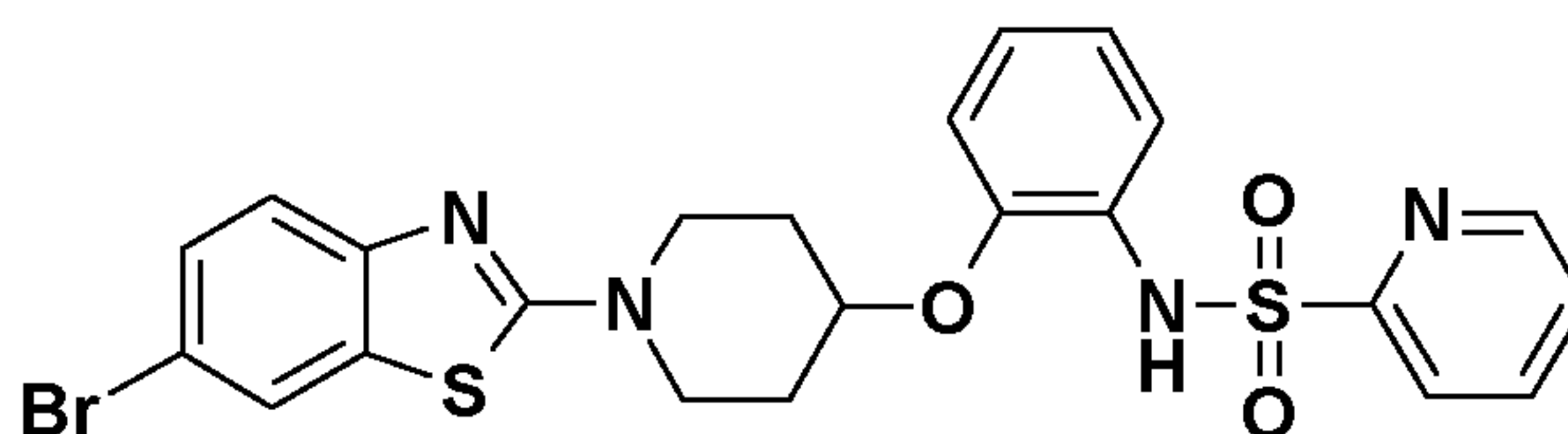
Compound 26 is prepared using synthesis method 3 using intermediate **6a** and 2,6-dichloro-1,3-benzothiazole (yield: 82%).

TLC silica gel 60 F 254 Merck, Petroleum ether-AcOEt: 60-40, R_f=0.20.

- 5 NMR ¹H (DMSO-d₆)ppm: 9.59 (s, 1H), 8.62 (d, 1H), 7.97 (dt, 1H), 7.91 (d, 1H), 7.82 (d, 1H), 7.54 (m, 1H), 7.44 (d, 1H), 7.29 (m, 2H), 7.12 (t, 1H), 6.99 (d, 1H), 6.86 (t, 1H), 4.56 (m, 1H), 3.72 (m, 2H), 3.49 (m, 2H), 1.78 (m, 2H), 1.52 (m, 2H).

MS (+ESI) m/z 501 (MH⁺)

- 10 Example 27: N-(2-(1-(6-bromobenzo[d]thiazol-2-yl)piperidin-4-yloxy)phenyl)-pyridine-2-sulfonamide (27)



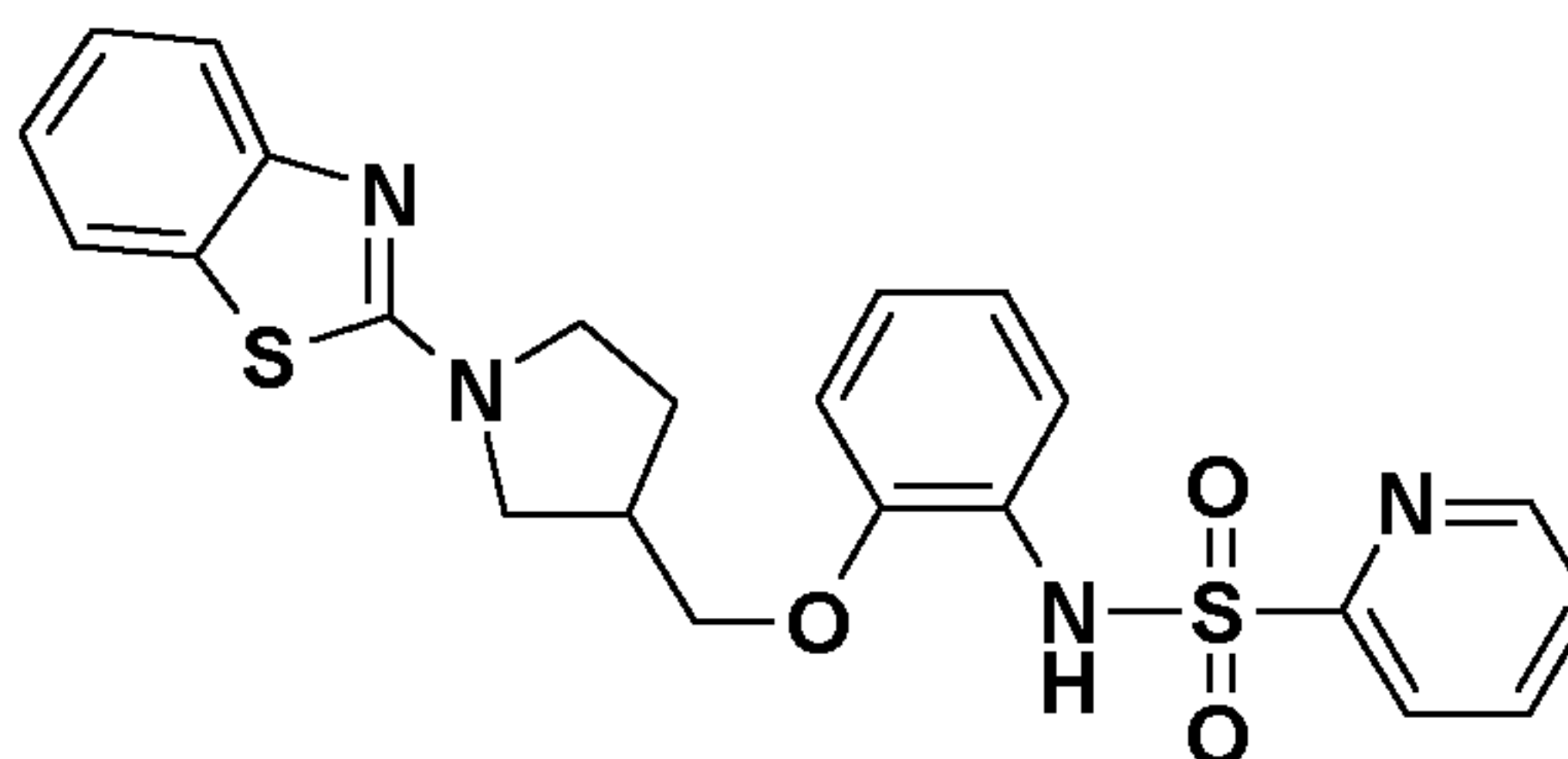
Compound 27 is prepared using synthesis method 3 using intermediates **2d** and **6a** (yield: 14%).

- 15 TLC silica gel 60 F 254 Merck, Petroleum ether-AcOEt: 60-40, R_f=0.21.
NMR ¹H (DMSO-d₆) ppm: 9.59 (s, 1H), 8.62 (d, 1H), 8.03 (t, 1H), 7.98 (t, 1H), 7.82 (d, 1H), 7.53 (m, 1H), 7.40 (m, 2H), 7.26 (d, 1H), 7.12 (t, 1H), 6.99 (d, 1H), 6.86 (t, 1H), 4.56 (m, 1H), 3.72 (m, 2H), 3.49 (m, 2H), 1.79 (m, 2H), 1.53 (m, 2H).

MS (+ESI) m/z 545 (MH⁺)

20

- Example 28: N-(2-((1-(benzo[d]thiazol-2-yl)pyrrolidin-3-yl)methoxy)phenyl)-pyridine-2-sulfonamide (28)



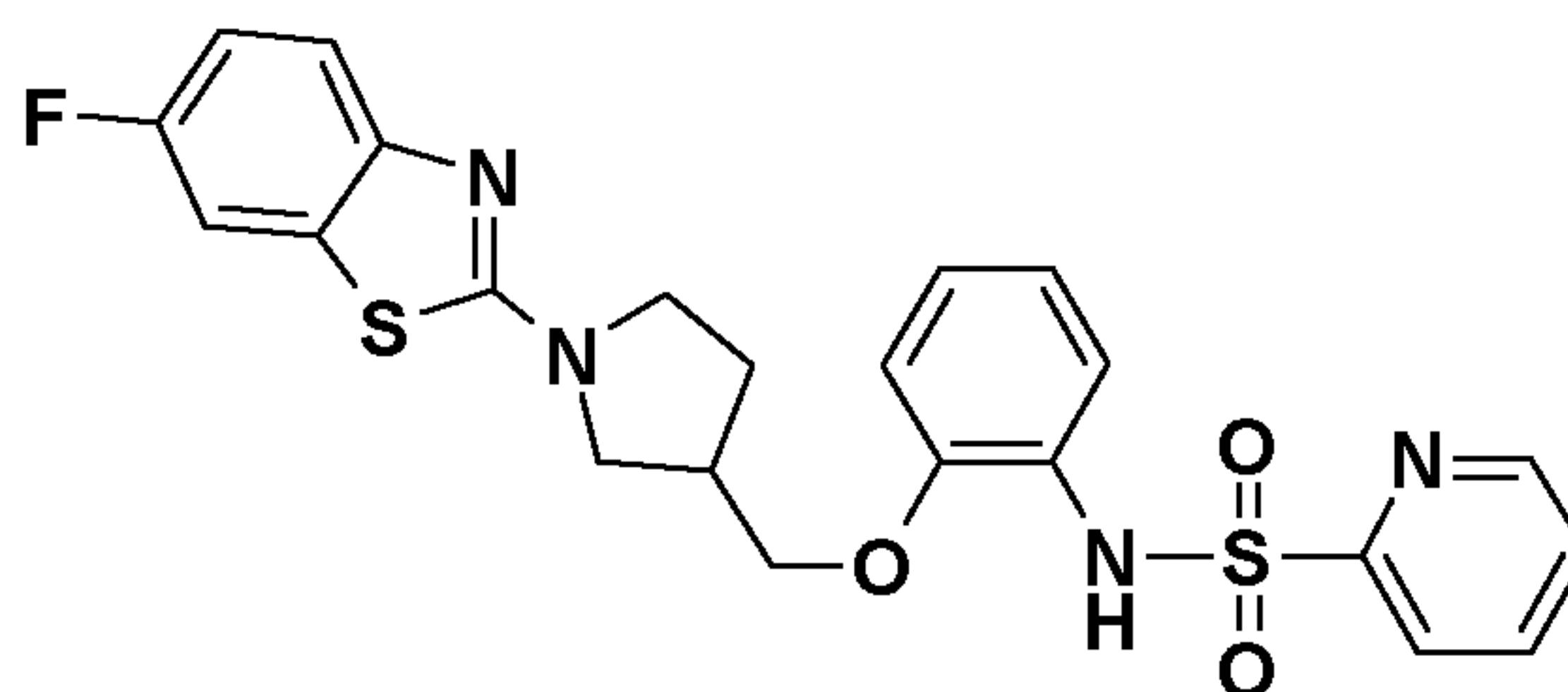
- 25 Compound 28 is prepared using synthesis method 3 using intermediate **6b** and 2-chloro-1,3-benzothiazole (yield: 66%).

TLC silica gel 60 F 254 Merck, CH₂Cl₂- MeOH: 90-10, R_f=0.44.

NMR ¹H (DMSO-d₆) ppm: 9.62 (s, 1H), 8.73 (d, 1H), 8.03 (dt, 1H), 7.76 (d, 1H), 7.64 (m, 1H), 7.46 (d, 1H), 7.28 (m, 2H), 7.12 (dt, 2H), 7.03 (t, 1H), 6.94 (d, 1H), 6.86 (t, 1H), 3.81 (d, 2H), 3.68 (m, 1H), 3.56 (m, 1H), 3.48 (m, 1H), 3.30 (m, 1H), 2.61 (m, 1H), 2.12 (m, 1H), 1.85 (m, 1H).

MS (+ESI) m/z 467 (MH⁺)

Example 29: N-(2-((1-(6-fluorobenzo[d]thiazol-2-yl)pyrrolidin-3-yl)methoxy)phenyl)pyridine-2-sulfonamide (29)



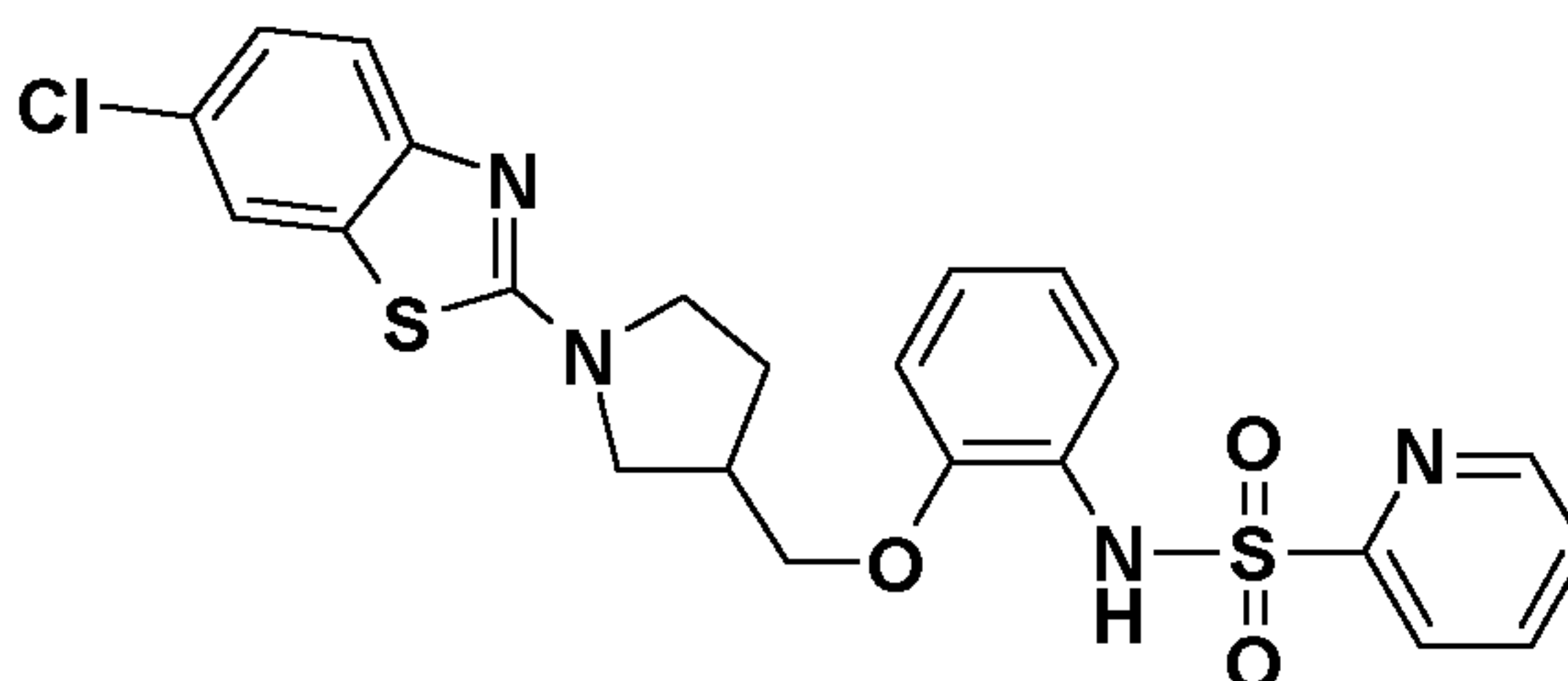
Compound 29 is prepared using synthesis method 3 using intermediates **2a** and **6b** (yield: 76%).

TLC silica gel 60 F 254 Merck, AcOEt, R_f=0.55.

NMR ¹H (DMSO-d₆) ppm: 9.61 (s, 1H), 8.72 (d, 1H), 8.03 (t, 1H), 7.84 (d, 1H), 7.71 (d, 1H), 7.63 (m, 1H), 7.45 (m, 1H), 7.26 (d, 1H), 7.12 (m, 2H), 6.94 (d, 1H), 6.86 (t, 1H), 3.83 (d, 2H), 3.67 (m, 1H), 3.53 (m, 1H), 3.48 (m, 1H), 3.30 (m, 1H), 2.62 (m, 1H), 2.09 (m, 1H), 1.85 (m, 1H).

MS (+ESI) m/z 485 (MH⁺)

Example 30: N-(2-((1-(6-chlorobenzo[d]thiazol-2-yl)pyrrolidin-3-yl)methoxy)phenyl)pyridine-2-sulfonamide (30)



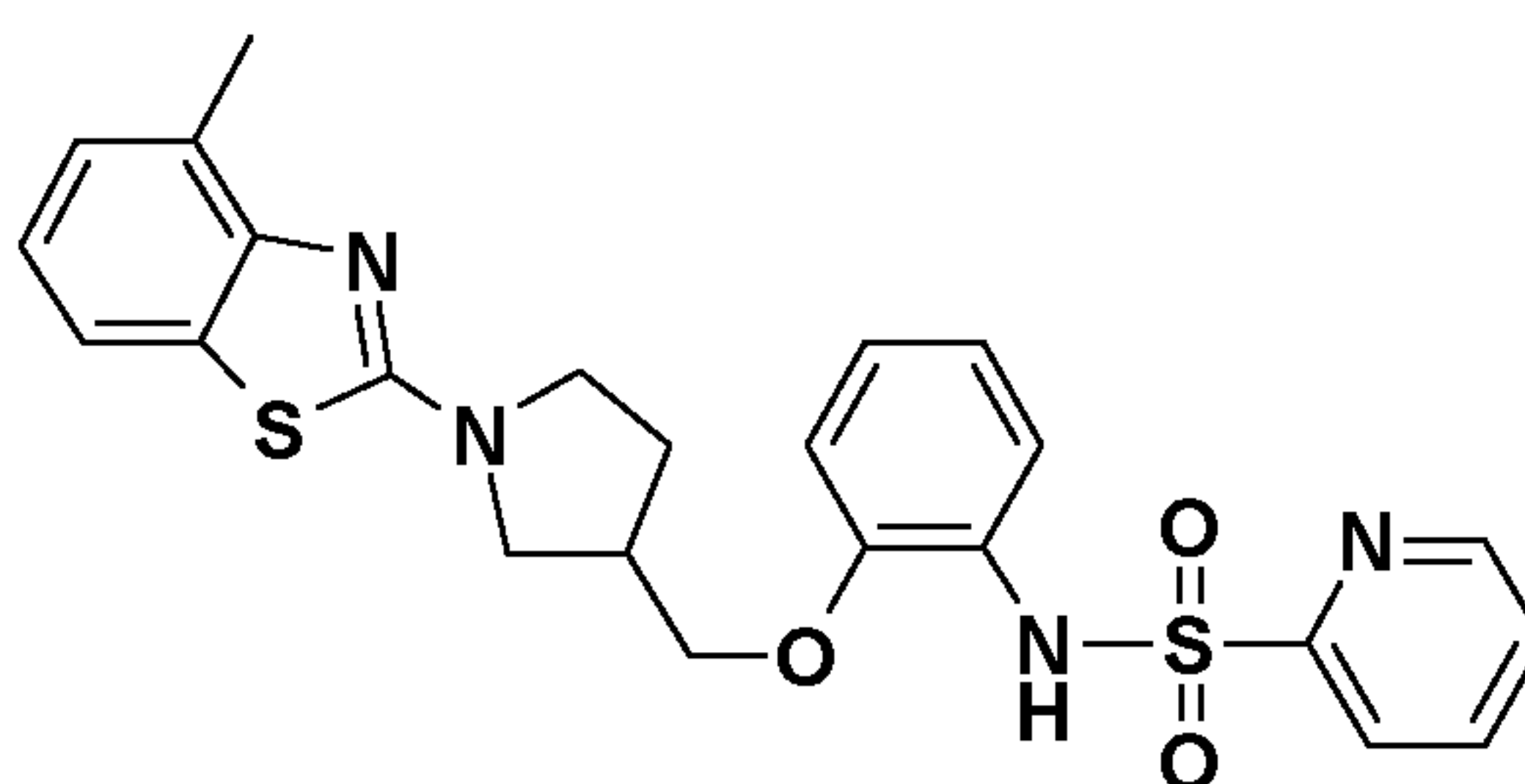
Compound 30 is prepared using synthesis method 3 using intermediate **6b** and 2,6-dichloro-1,3-benzothiazole (yield: 80%).

TLC silica gel 60 F 254 Merck, Petroleum ether-AcOEt: 50-50, R_f=0.23.

NMR ^1H (DMSO- d_6) ppm: 9.61 (s, 1H), 8.72 (d, 1H), 8.03 (dt, 1H), 7.91 (d, 1H), 7.84 (d, 1H), 7.63 (m, 1H), 7.43 (d, 1H), 7.28 (m, 2H), 7.10 (t, 1H), 6.94 (d, 1H), 6.86 (t, 1H), 4.03 (d, 2H), 3.66 (m, 1H), 3.53 (m, 2H), 3.30 (m, 1H), 2.61 (m, 1H), 2.11 (m, 1H), 1.84 (m, 1H).

5 MS (+ESI) m/z 501 (MH $^+$)

Example 31: N-(2-((1-(4-methylbenzo[d]thiazol-2-yl)pyrrolidin-3-yl)methoxy)phenyl)pyridine-2-sulfonamide (31)



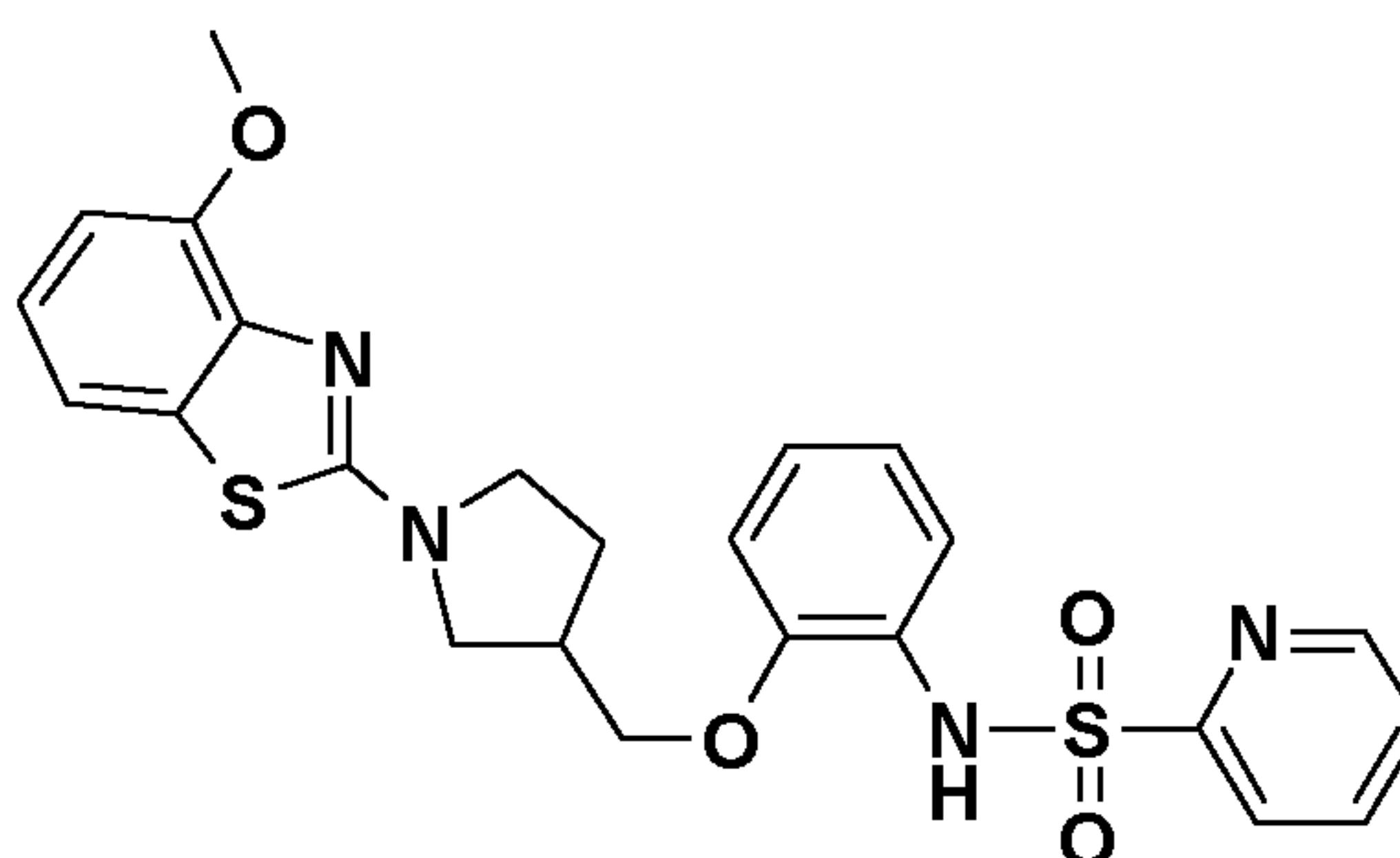
10 Compound 31 is prepared using synthesis method 3 using intermediates **2b** and **6b** (yield: 28%).

TLC silica gel 60 F 254 Merck, Petroleum ether-AcOEt: 50-50, R_f =0.36.

NMR ^1H (DMSO- d_6) ppm: 9.61 (s, 1H), 8.74 (d, 1H), 8.04 (t, 1H), 7.84 (d, 1H), 7.63 (m, 1H), 7.57 (d, 1H), 7.28 (d, 1H), 7.10 (m, 2H), 6.94 (m, 2H), 6.86 (t, 1H), 3.84 (d, 2H),
 15 3.72 (m, 1H), 3.58 (m, 1H), 3.52 (m, 1H), 3.30 (m, 1H), 2.63 (m, 1H), 2.5 (s, 3H), 2.10 (m, 1H), 1.80 (m, 1H).

MS (+ESI) m/z 481 (MH $^+$)

Example 32: N-(2-((1-(4-methoxybenzo[d]thiazol-2-yl)pyrrolidin-3-yl)methoxy)-
 20 phenyl)pyridine-2-sulfonamide (32)



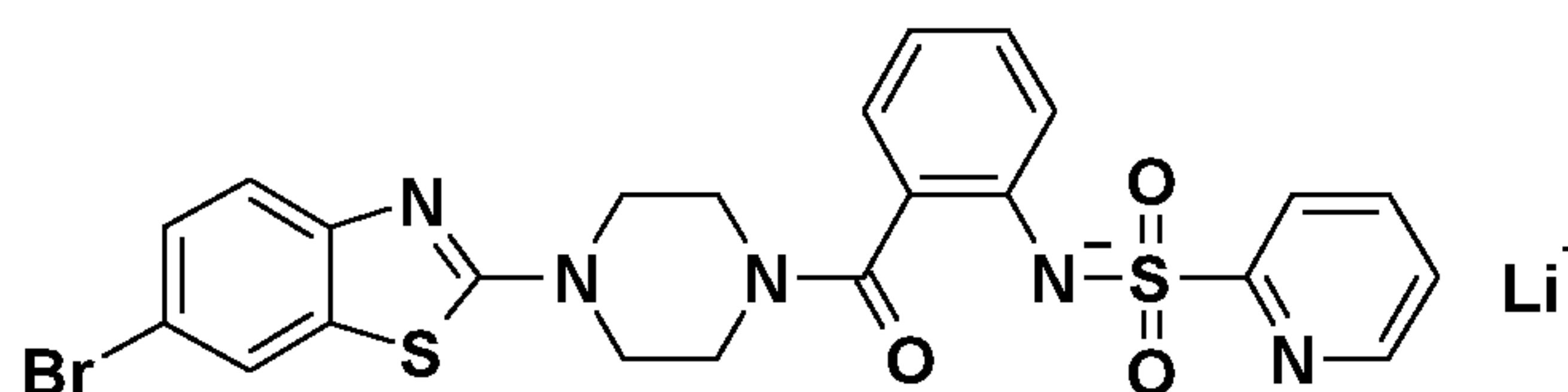
Compound 32 is prepared using synthesis method 3 using intermediates **2c** and **6b** (yield: 51%).

25 TLC silica gel 60 F 254 Merck, Petroleum ether-AcOEt: 50-50, R_f =0.63.

NMR ^1H (DMSO- d_6) ppm: 9.61 (s, 1H), 8.76 (d, 1H), 8.05 (t, 1H), 7.84 (d, 1H), 7.63 (m, 1H), 7.34 (d, 1H), 7.28 (d, 1H), 7.10 (t, 1H), 7.00 (t, 1H), 6.94 (d, 1H), 6.89 (m, 2H), 3.86 (s, 3H), 3.82 (d, 2H), 3.67 (m, 1H), 3.50 (m, 2H), 3.27 (m, 1H), 2.63 (m, 1H), 2.10 (m, 1H), 1.83 (m, 1H).

5 MS (+ESI) m/z 497 (MH $^+$)

Example 33: lithium N-(2-(4-(6-bromobenzo[d]thiazol-2-yl)piperazine-1-carbonyl)phenyl)-pyridine-2-sulfonamide (33)



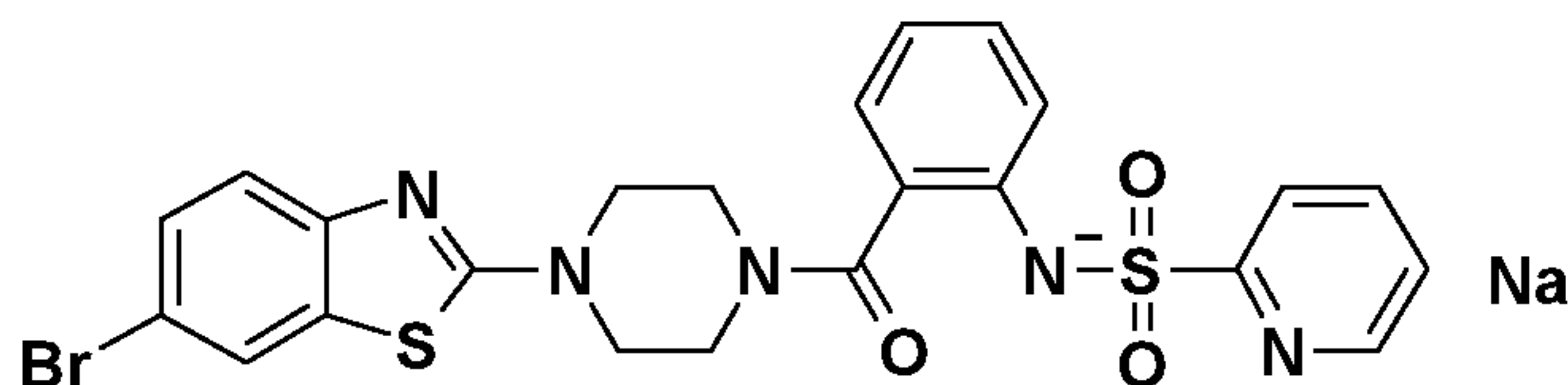
10 2.36 g (4.23 mmol) of compound 3 prepared according to example 3 are added to 30 mL of ethanol. Then, a 1M solution of LiOH (4.23 mL, 4.23 mmol) is added and the mixture is stirred for 30 min at room temperature. The solvent is concentrated until dryness; the residue is taken up in diethyl ether and stirred for 2h at room temperature. After filtration, compound 33 (2.45g) is isolated in the form of a solid and then dried
15 under vacuum.

mp=122.42°C

NMR ^1H (DMSO- d_6) ppm: 8.48 (d, 1H), 8.03 (s, 1H), 7.81 (d, 2H), 7.38 (m 2H), 7.38 (m, 1H), 7.18 (d, 1H), 6.86 (m, 2H), 6.46 (t, 1H), 4.02 (m, 2H), 3.78 (m, 1H), 3.44 (m, 4H), 3.14 (m, 1H).

20 MS (+ESI) m/z 558 (MH $^+$)

Example 34: sodium N-(2-(4-(6-bromobenzo[d]thiazol-2-yl)piperazine-1-carbonyl)phenyl)-pyridine-2-sulfonamide (34)



25 Compound 34 is prepared using synthesis method described in example 33 using a 1M solution of NaOH. After filtration, compound 34 (2.46g) is isolated in the form of a solid and then dried under vacuum.

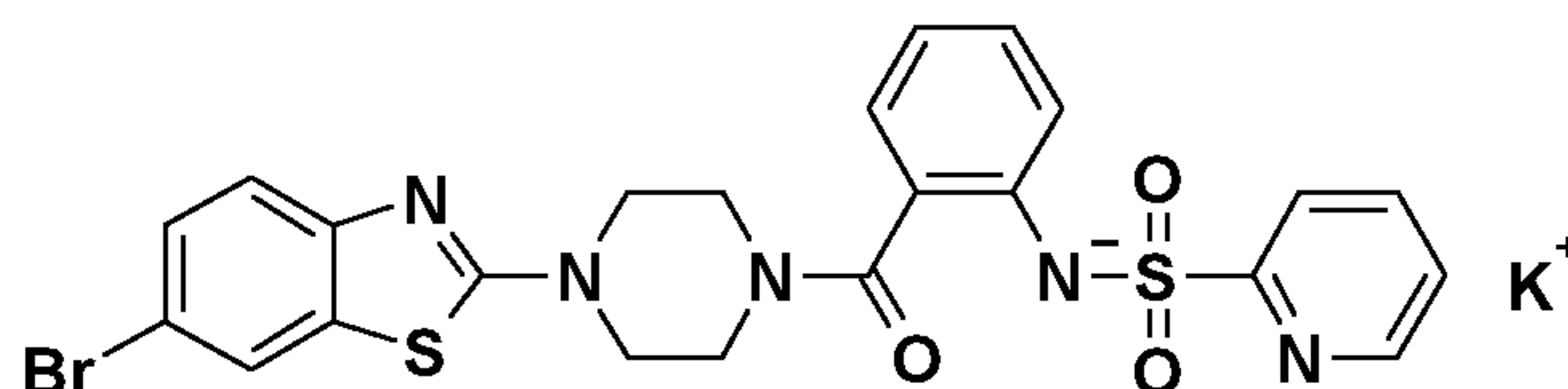
mp=330°C

NMR ^1H (DMSO- d_6) ppm: 8.48 (d, 1H), 8.03 (s, 1H), 7.82 (m, 2H), 7.39 (m 2H), 7.34 (m, 1H), 7.17 (d, 1H), 6.86 (m, 2H), 6.46 (t, 1H), 4.01 (m, 2H), 3.78 (m, 1H), 3.46 (m, 4H), 3.14 (m, 1H).

MS (+ESI) m/z 558 (MH $^+$)

5

Example 35: potassium N-(2-(4-(6-bromobenzo[d]thiazol-2-yl)pipérazine-1-carbonyl)phényl)-pyridine-2-sulfonamide (35)



10 Compound 35 is prepared using synthesis method described in example 33 using a 1M solution of KOH. After filtration, compound 35 (2.51g) is isolated in the form of a solid and then dried under vacuum.

mp=201°C

15 NMR ^1H (DMSO- d_6) ppm: 8.49 (d, 1H), 8.03 (s, 1H), 7.82 (m, 2H), 7.39 (m 2H), 7.34 (m, 1H), 7.18 (d, 1H), 6.87 (m, 2H), 6.46 (t, 1H), 4.00 (m, 2H), 3.78 (m, 1H), 3.42 (m, 4H), 3.14 (m, 1H).

MS (+ESI) m/z 558 (MH $^+$)

C) PHARMACOLOGICAL EVALUATION

20

The pharmacological evaluation of the compounds on potassium channel Kv1.5 was undertaken using a 96-well plate and FLIPR technology by thallium ion measurement.

25 The HEK293 cells, transfected in a stable manner with the human isoform of the Kv1.5 channels, are seeded 24h before the experiment in 96-well plates (15×10^6 cells/plate, 200 μl /well) with polylysine applied in the following culture medium: DMEM, 10% SVF, Penicillin/Streptomycin, G418 as the selection antibiotic.

The FLIPR experiment is undertaken using "FLIPR Potassium Ion Channel Assay Kit", as indicated by the manufacturer (Molecular Devices).

30 Briefly, the culture medium is replaced by the solution containing the thallium marker for 90min at 37°C. On conclusion of this step the compounds for testing are added to a final concentration of 10 μM in the well for 15 min at 37°C. The basic fluorescence is then read for 60 sec. The addition of depolarising medium (20 mM of potassium and

3 mM of final thallium) opens the potassium channels and causes an increase of the fluorescence of the thallium fluorophore corresponding to an influx of thallium ions through the hKv1.5 channels. The measurement is made 30 sec after the injection of the depolarising solution. The application of 10 μ M DPO (Tocris, blocker of the Kv1.5 channels) enables the fluorescence to be normalised.

Table 1

| Examples | % inhibition at 10 μ M |
|------------|----------------------------|
| BMS394136* | 99.6 |
| 1 | 61.4 |
| 2 | 100 |
| 3 | 100 |
| 4 | 100 |
| 5 | 90 |
| 6 | 91.8 |
| 7 | 94.9 |
| 8 | 94.7 |
| 9 | 62.8 |
| 10 | 58.9 |
| 11 | 75.1 |
| 12 | 52.6 |
| 13 | 100 |
| 14 | 68.7 |
| 15 | 70.2 |
| 16 | 68 |
| 17 | 70.8 |
| 18 | 91.5 |
| 19 | 50.2 |
| 20 | 82.8 |
| 21 | 54.6 |
| 22 | 58.8 |
| 23 | 51.8 |
| 24 | 81.0 |
| 25 | 90.2 |

| | |
|----|------|
| 26 | 65.8 |
| 27 | 100 |
| 28 | 76.0 |
| 29 | 64.5 |
| 30 | 54.1 |
| 31 | 56.0 |
| 32 | 53.7 |

* BMS394136 is a blocker of the Kv1.5 channel under development at Bristol-Myers Squibb (Abstract, D. Xing et al., Circulation 2009, 120 (18S3): 2515).

The results obtained show that compounds of general formula (I) block channel Kv1.5.

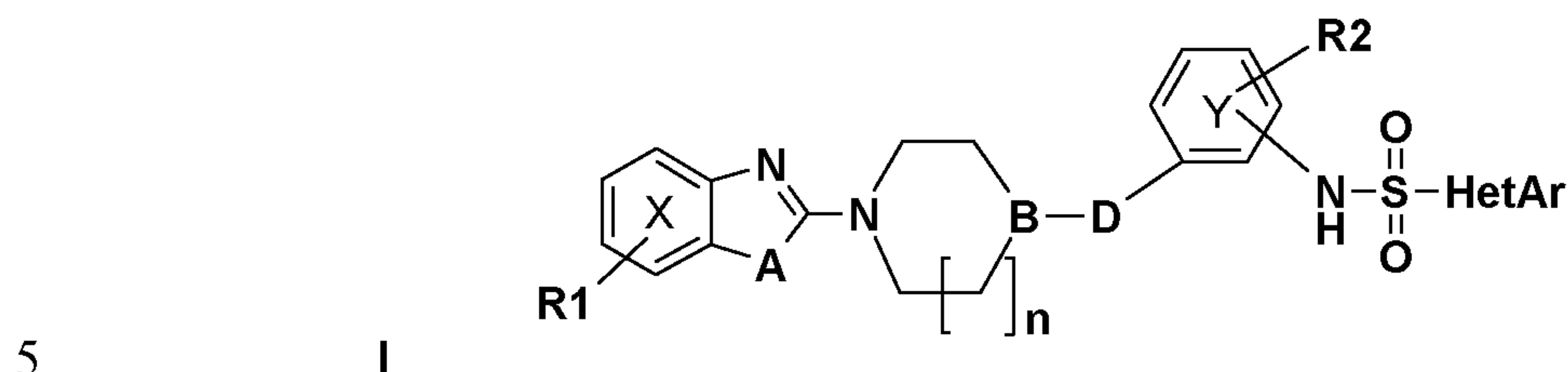
- 5 Compounds of general formula I can be used as blockers of channel Kv1.5.

D) ABBREVIATIONS

| | |
|----------------|---|
| DEAD | Diethyl azodicarboxylate |
| DMAP | N,N-4-Dimethylaminopyridine |
| DMF | Dimethylformamide |
| DMSO | Dimethyl sulfoxide |
| DPO | (2-isopropyl-5-methyl-cyclohexyl) diphenylphosphine oxide |
| ESI | Electrospray ionisation |
| HPLC | High-performance liquid chromatography |
| mp | Melting point |
| MS | Mass spectrum |
| NMR | Nuclear magnetic resonance |
| R _f | Retardation factor |
| Temp. | Temperature |
| TFA | Trifluoroacetic acid |
| THF | Tetrahydrofuran |
| TLC | Thin Layer Chromatography |

CLAIMS

1) A compound of general formula I:



where

R1 represents one or more substituents of the phenyl core X chosen from among the group consisting of: hydrogen, halogen such as F, Cl or Br, trifluoromethyl, trifluoromethoxy, linear or branched C₁-C₄ alkyl, and linear or branched C₁-C₄ alkoxy

10 **n** represents 0, 1 or 2,

A represents oxygen or sulphur,

D represents -C(=O)-, -CH₂O- or -O-,

B represents nitrogen when n=1 or 2 and **D** represents -C(=O)-, or then **B** represents CH when n=0 and **D** represents -CH₂O- or when n=1 and **D**

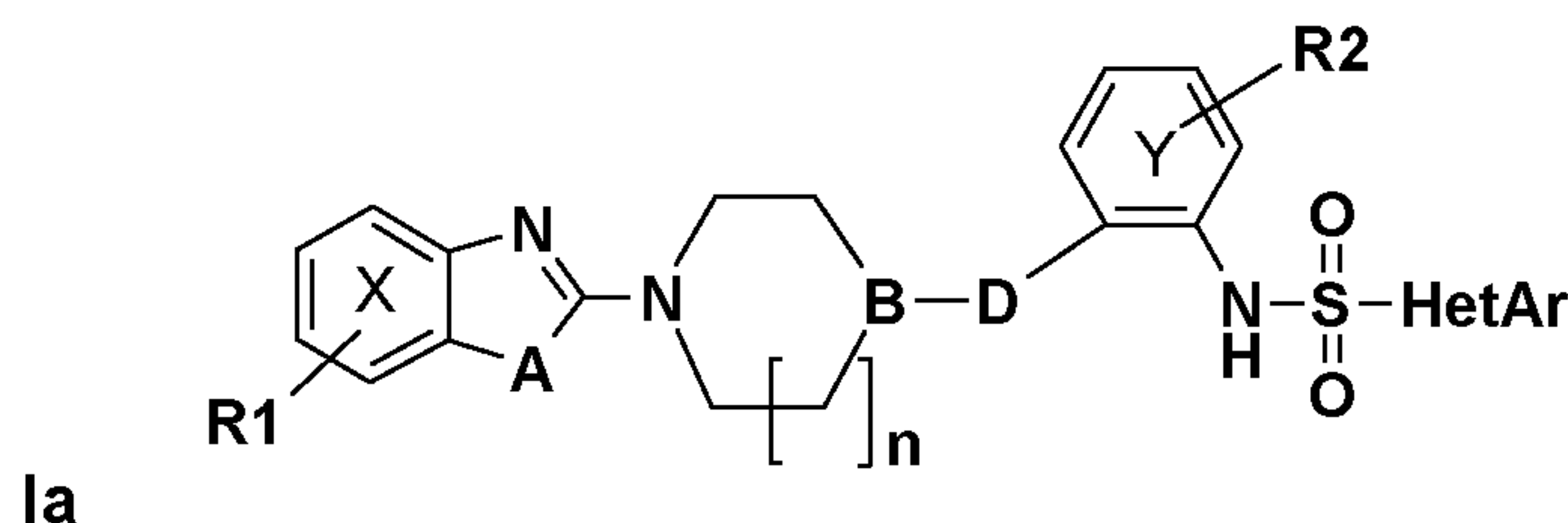
15 represents -O-,

R2 represents a hydrogen, a methyl, a fluorine or chlorine atom or a methoxy, and

HetAr represents a pyridyl or quinolyl group, possibly substituted by a group such as a linear or branched C₁-C₄ alkyl, a linear or branched C₁-C₄ alkoxy, a halogen such as F, Cl or Br, or trifluoromethyl,

20 or one of its pharmaceutically acceptable salts.

2) A compound of general formula I according to claim 1), characterised in that it is a compound of the following formula Ia:



25 for which **R1**, **R2**, **A**, **B**, **D**, **n** and **HetAr** are as defined in claim 1), or a pharmaceutically acceptable salt thereof.

3) A compound of general formula I according to either of claims 1 and 2, characterised in that:

R1 represents one or more substituents of the phenyl core chosen from among the group consisting of: hydrogen, halogen such as F, Cl or Br, trifluoromethyl, trifluoromethoxy, linear or branched C₁-C₄ alkyl, and methoxy,

n represents 1,

A represents oxygen or sulphur,

D represents -C(=O)- or -O-,

B represents nitrogen when **D** represents -C(=O)-,

10 or **B** represents CH when **D** represents -O-,

R2 represents a hydrogen, and

HetAr represents a 2-pyridyl or 8-quinolyl group, possibly substituted by a group such as methyl or trifluoromethyl,

or one of its pharmaceutically acceptable salts.

15

4) A compound of general formula I according to any of claims 1 to 3, characterised in that:

R1 represents one or more substituents of the phenyl core such as: hydrogen, halogen such as F, Cl or Br, trifluoromethyl, trifluoromethoxy, linear or branched C₁-C₄ alkyl, or methoxy,

20

A represents sulphur,

n represents 1,

D represents -C(=O)-,

B represents nitrogen,

25 **R2** represents a hydrogen, and

HetAr represents a 2-pyridyl group, possibly substituted by a group such as methyl or trifluoromethyl,

or one of its pharmaceutically acceptable salts.

30 5) A compound of general formula I according to any of claims 1 to 4, characterised in that it is chosen from among:

1) N-(2-(4-(6-fluorobenzo[d]oxazol-2-yl)piperazine-1-carbonyl)phenyl)-5-(trifluoromethyl)pyridine-2-sulfonamide,

2) N-(2-(4-(6-fluorobenzo[d]thiazol-2-yl)piperazine-1-carbonyl)phenyl)-pyridine-2-sulfonamide,

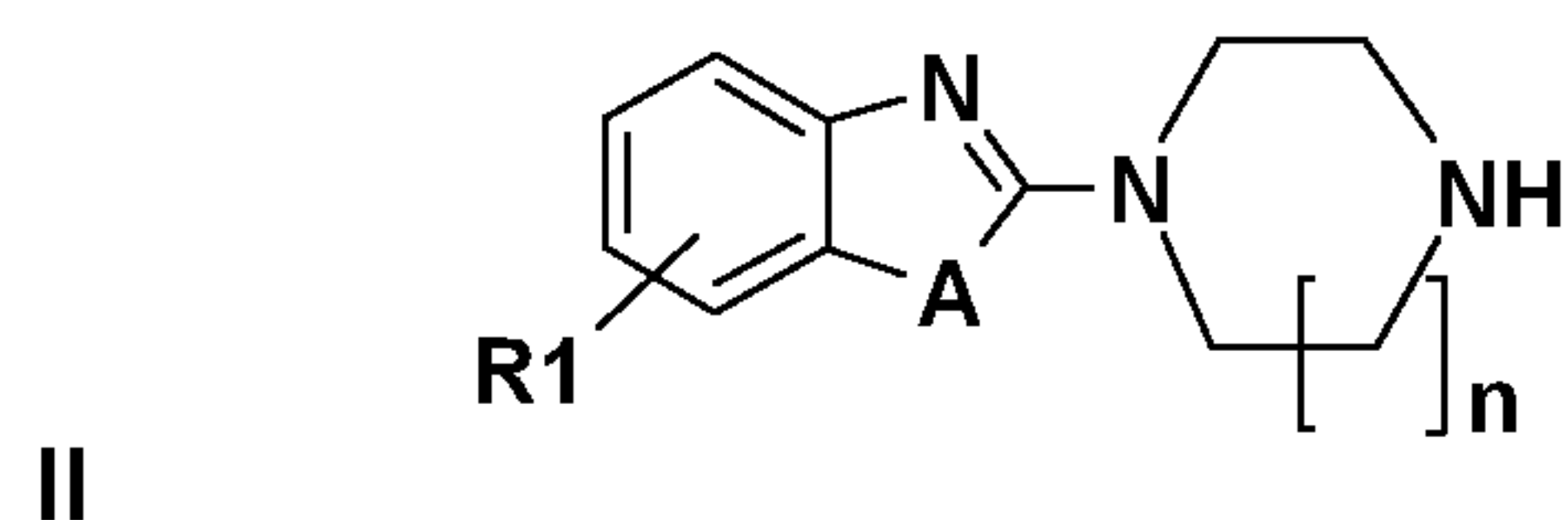
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- 3) N-(2-(4-(6-bromobenzo[d]thiazol-2-yl)piperazine-1-carbonyl)phenyl)-pyridine-2-sulfonamide,
- 4) N-(2-(4-(6-chlorobenzo[d]thiazol-2-yl)piperazine-1-carbonyl)phenyl)-pyridine-2-sulfonamide hydrochloride,
- 5) N-(2-(4-(4-methylbenzo[d]thiazol-2-yl)piperazine-1-carbonyl)phenyl)-pyridine-2-sulfonamide,
- 6) N-(2-(4-(7-chlorobenzo[d]thiazol-2-yl)piperazine-1-carbonyl)-phenyl)-pyridine-2-sulfonamide,
- 7) N-(2-(4-(5-(trifluoromethyl)benzo[d]thiazol-2-yl)piperazine-1-carbonyl)-phenyl)-pyridine-2-sulfonamide,
- 8) N-(2-(4-(6-chlorobenzo[d]thiazol-2-yl)piperazine-1-carbonyl)phenyl)-5-(trifluoromethyl)pyridine-2-sulfonamide,
- 9) N-(2-(4-(6-bromobenzo[d]thiazol-2-yl)piperazine-1-carbonyl)phenyl)-6-methylpyridine-2-sulfonamide dihydrochloride,
- 10) N-(3-(4-(6-chlorobenzo[d]oxazol-2-yl)piperazine-1-carbonyl)-phenyl)-pyridine-2-sulfonamide,
- 11) N-(3-(4-(6-chlorobenzo[d]thiazol-2-yl)piperazine-1-carbonyl)-phenyl)-pyridine-2-sulfonamide,
- 12) N-(3-(4-(6-chlorobenzo[d]thiazol-2-yl)piperazine-1-carbonyl)-phenyl)-6-methylpyridine-2-sulfonamide,
- 13) N-(4-(4-(6-fluorobenzo[d]oxazol-2-yl)piperazine-1-carbonyl)-phenyl)-pyridine-2-sulfonamide,
- 14) N-(4-(4-(6-chlorobenzo[d]oxazol-2-yl)piperazine-1-carbonyl)-phenyl)-pyridine-2-sulfonamide,
- 15) N-(4-(4-(6-chlorobenzo[d]thiazol-2-yl)piperazine-1-carbonyl)-phenyl)-pyridine-2-sulfonamide,
- 16) N-(2-(4-(6-bromobenzo[d]thiazol-2-yl)piperazine-1-carbonyl)-phenyl)-quinoline-8-sulfonamide,
- 17) N-(2-(4-(6-chlorobenzo[d]oxazol-2-yl)piperazine-1-carbonyl)-phenyl)-quinoline-8-sulfonamide,
- 18) N-(2-(4-(6-chlorobenzo[d]thiazol-2-yl)piperazine-1-carbonyl)-phenyl)-quinoline-8-sulfonamide,
- 19) N-(2-(4-(6-(trifluoromethoxy)benzo[d]thiazol-2-yl)piperazine-1-carbonyl)-phenyl)quinoline-8-sulfonamide,

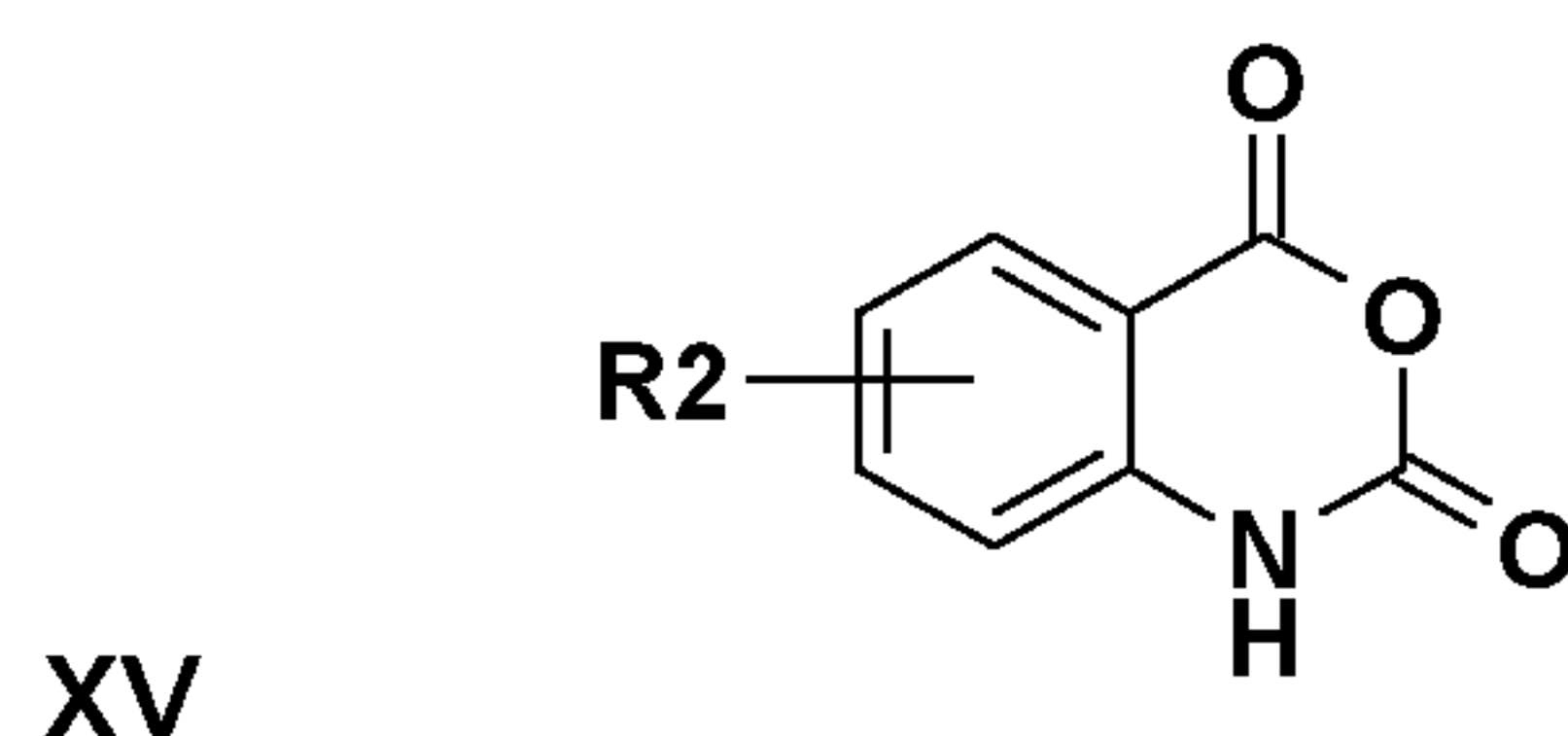
- 20) N-(2-(4-(4-methylbenzo[d]thiazol-2-yl)-1,4-diazepane-1-carbonyl)-phenyl)quinoline-8-sulfonamide,
- 21) N-(2-(1-(6-methylbenzo[d]oxazol-2-yl)piperidin-4-yloxy)phenyl)-pyridine-2-sulfonamide,
- 5 22) N-(2-(1-(6-chlorobenzo[d]oxazol-2-yl)piperidin-4-yloxy)phenyl)pyridine-2-sulfonamide,
- 23) N-(2-(1-(5-tert-butylbenzo[d]oxazol-2-yl)piperidin-4-yloxy)phenyl)-pyridine-2-sulfonamide,
- 24) N-(2-(1-(5-chlorobenzo[d]oxazol-2-yl)piperidin-4-yloxy)phenyl)pyridine-2-sulfonamide,
- 10 25) N-(2-(1-(benzo[d]thiazol-2-yl)piperidin-4-yloxy)phenyl)pyridine-2-sulfonamide,
- 26) N-(2-(1-(6-chlorobenzo[d]thiazol-2-yl)piperidin-4-yloxy)phenyl)-pyridine-2-sulfonamide,
- 15 27) N-(2-(1-(6-bromobenzo[d]thiazol-2-yl)piperidin-4-yloxy)phenyl)-pyridine-2-sulfonamide,
- 28) N-(2-((1-(benzo[d]thiazol-2-yl)pyrrolidin-3-yl)methoxy)phenyl)-pyridine-2-sulfonamide,
- 29) N-(2-((1-(6-fluorobenzo[d]thiazol-2-yl)pyrrolidin-3-yl)methoxy)phenyl)-pyridine-2-sulfonamide,
- 20 30) N-(2-((1-(6-chlorobenzo[d]thiazol-2-yl)pyrrolidin-3-yl)methoxy)phenyl)-pyridine-2-sulfonamide,
- 31) N-(2-((1-(4-methylbenzo[d]thiazol-2-yl)pyrrolidin-3-yl)methoxy)phenyl)-pyridine-2-sulfonamide,
- 25 32) N-(2-((1-(4-methoxybenzo[d]thiazol-2-yl)pyrrolidin-3-yl)methoxy)phenyl)-pyridine-2-sulfonamide,
- 33) lithium N-(2-(4-(6-bromobenzo[d]thiazol-2-yl)piperazine-1-carbonyl)phenyl)-pyridine-2-sulfonamide,
- 34) sodium N-(2-(4-(6-bromobenzo[d]thiazol-2-yl)piperazine-1-carbonyl)phenyl)-pyridine-2-sulfonamide, and
- 30 35) potassium N-(2-(4-(6-bromobenzo[d]thiazol-2-yl)piperazine-1-carbonyl)phenyl)-pyridine-2-sulfonamide.

6) A method of preparation of a compound of general formula I according to any of claims 1 to 5 for which **B** = N, including the following successive steps:

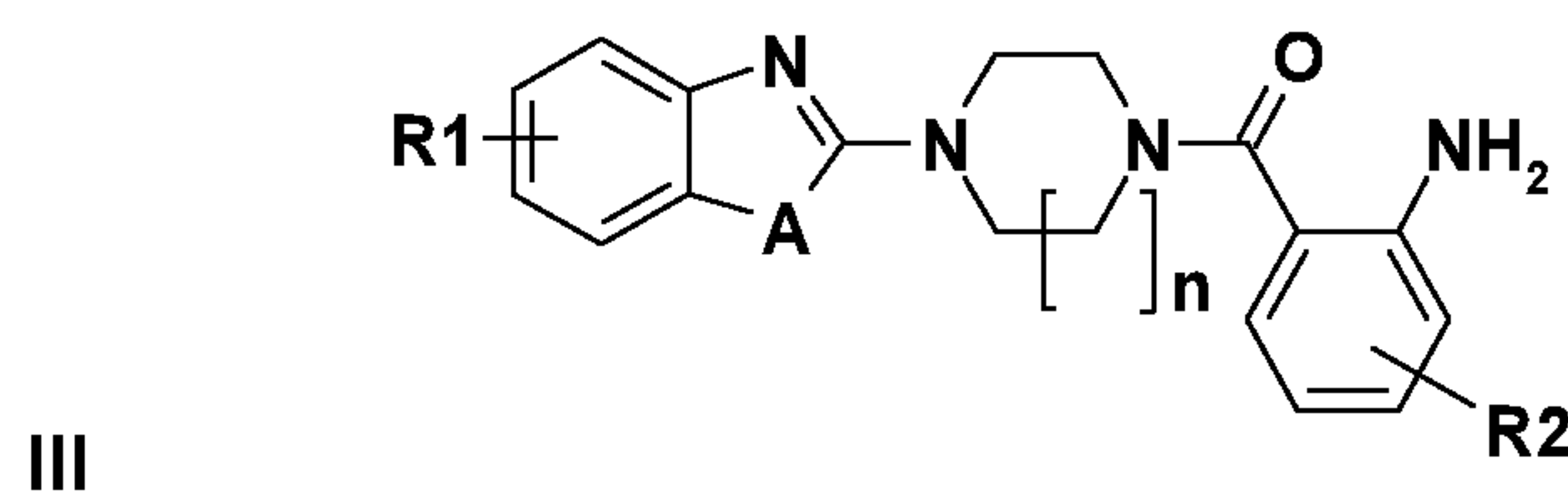
(a1) condensation of a compound of the following general formula II



5 for which **R1**, **A** and **n** are as defined in claim 1),
with a derivative of isatoic anhydride of the following formula **XV**:



for which **R2** is as defined in claim 1),
in the presence of a base such as dimethylaminopyridine,
10 to give an intermediate of the following formula **III**:



for which **R1**, **R2**, **A** and **n** are as defined in claim 1,

(a2) condensation of the intermediate of formula **III** with a sulfonyl chloride of the following general formula **IV**:



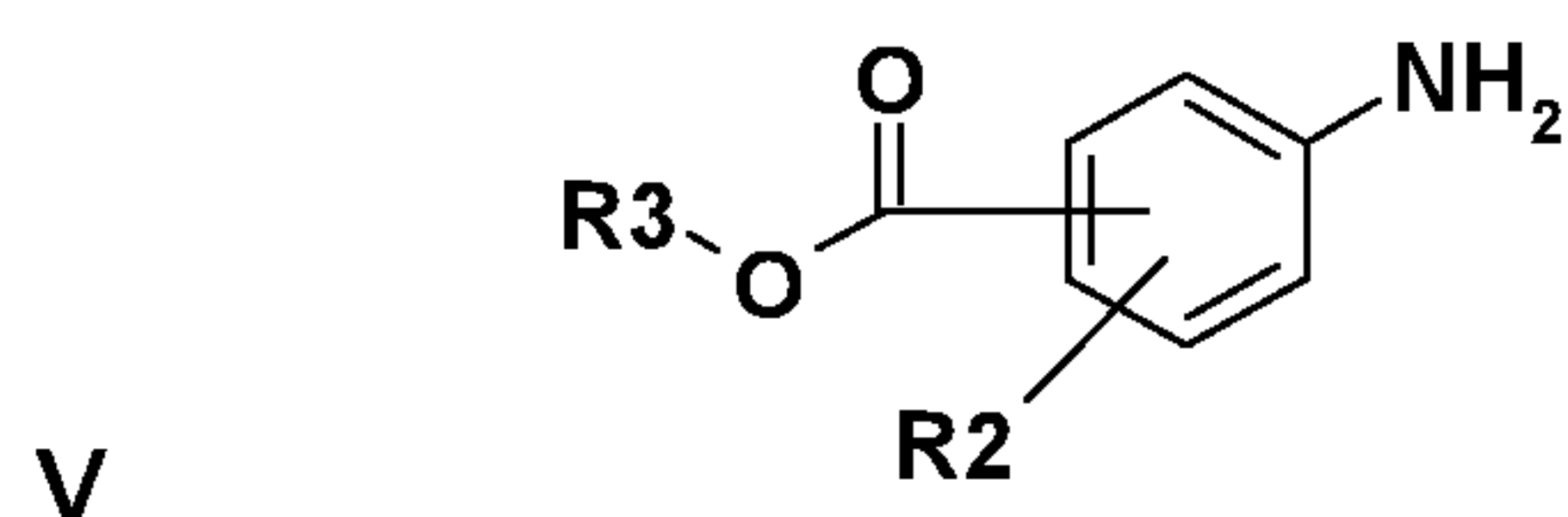
for which **HetAr** is as defined in claim 1,

in the presence of a base such as pyridine to give a compound of formula I, and

(a3) optionally salt formation of the compound of formula I obtained in the previous step (a2) in the presence of a pharmaceutically acceptable base or acid in order to give
20 a pharmaceutically acceptable salt of the compound of formula I.

7) A method of preparation of a compound of general formula I according to any of claims 1 to 5 for which **B** = N, including the following successive steps:

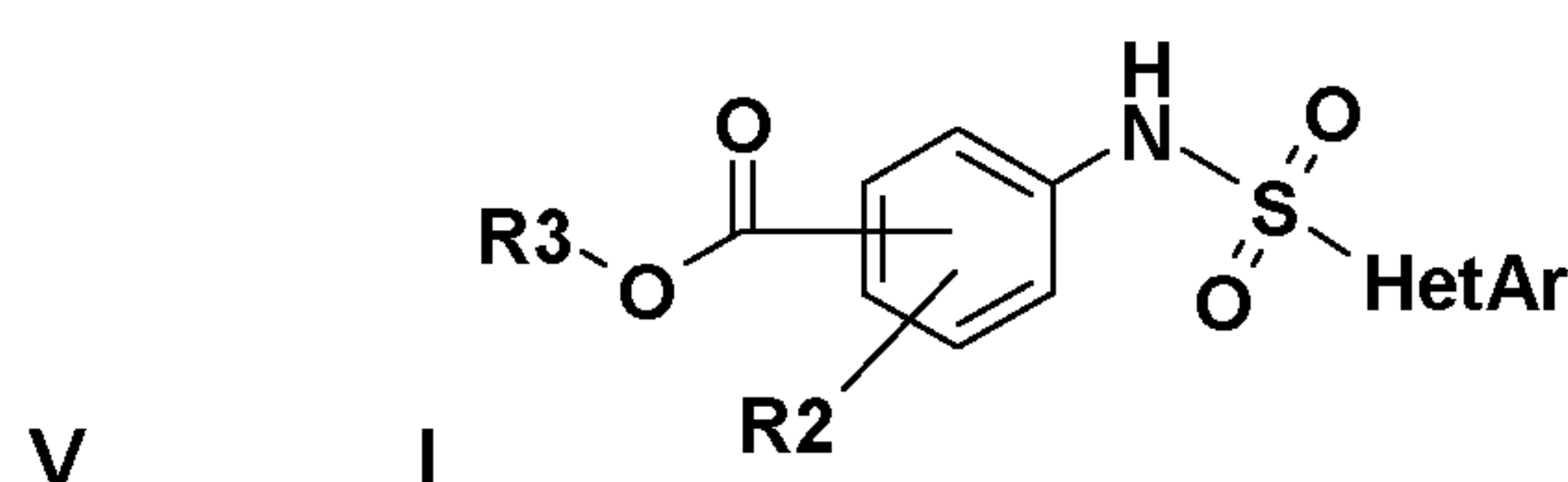
(b1) condensation of a compound of the following general formula **V**:



for which **R3** represents a linear or branched C₁-C₄ alkyl and **R2** is as defined in claim 1,

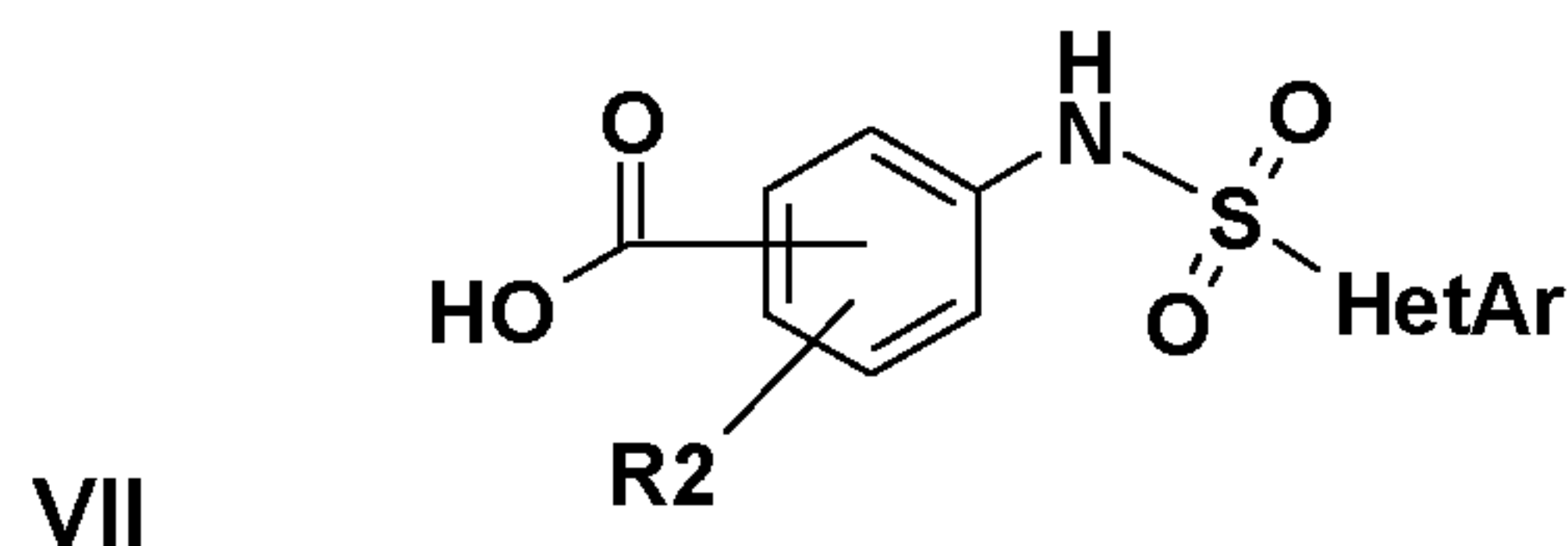
with a sulfonyl chloride of general formula **IV** as defined in claim 7,

5 in the presence of a base such as pyridine to give a compound of the following formula **VI**:



for which **R3** is as defined previously, and **R2** and **HetAr** are as defined in claim 1,

(b2) saponification of the compound of formula **VI**, notably in the presence of a base
 10 such as potash, to give the compound of the following formula **VII**:



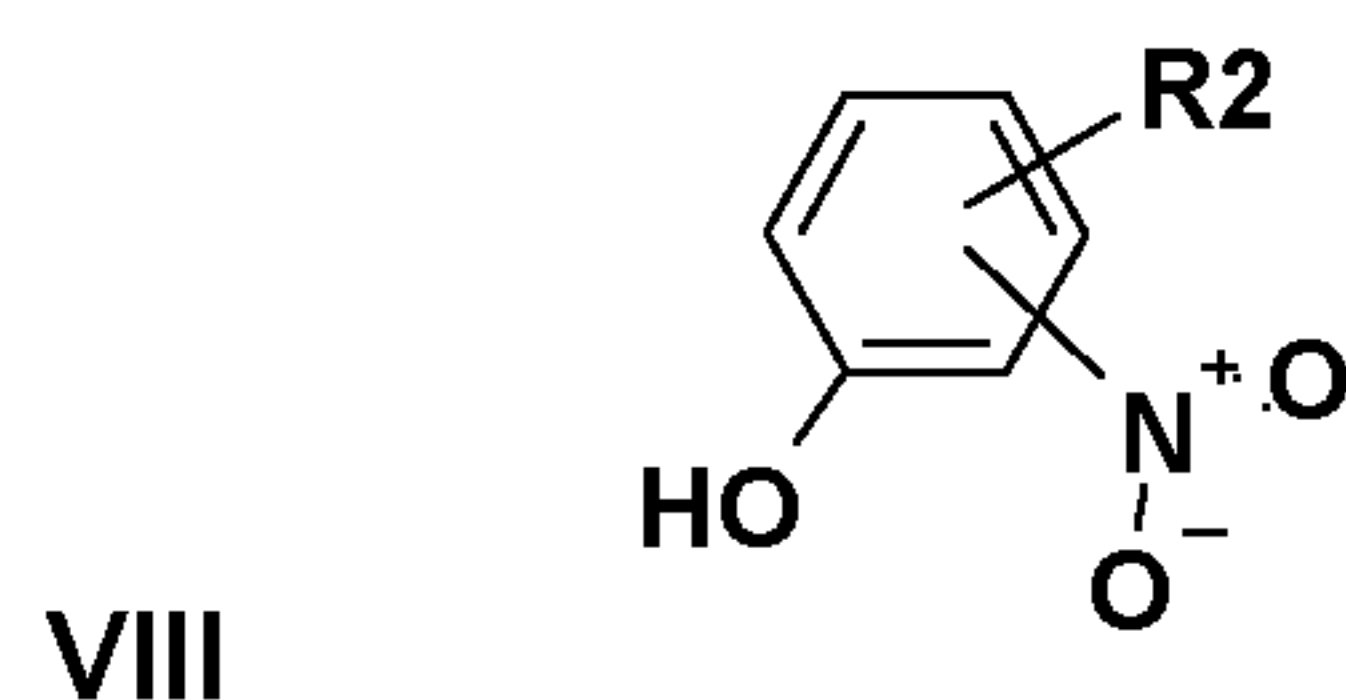
for which **R2** and **HetAr** are as defined in claim 1,

(b3) coupling of the compound of formula **VII** with the compound of formula **II** as defined in claim 6 to give a compound of formula **I**, and

15 (b4) optionally salt formation of the compound of formula **I** obtained in the previous step (b3) in the presence of a pharmaceutically acceptable base or acid in order to give a pharmaceutically acceptable salt of the compound of formula **I**.

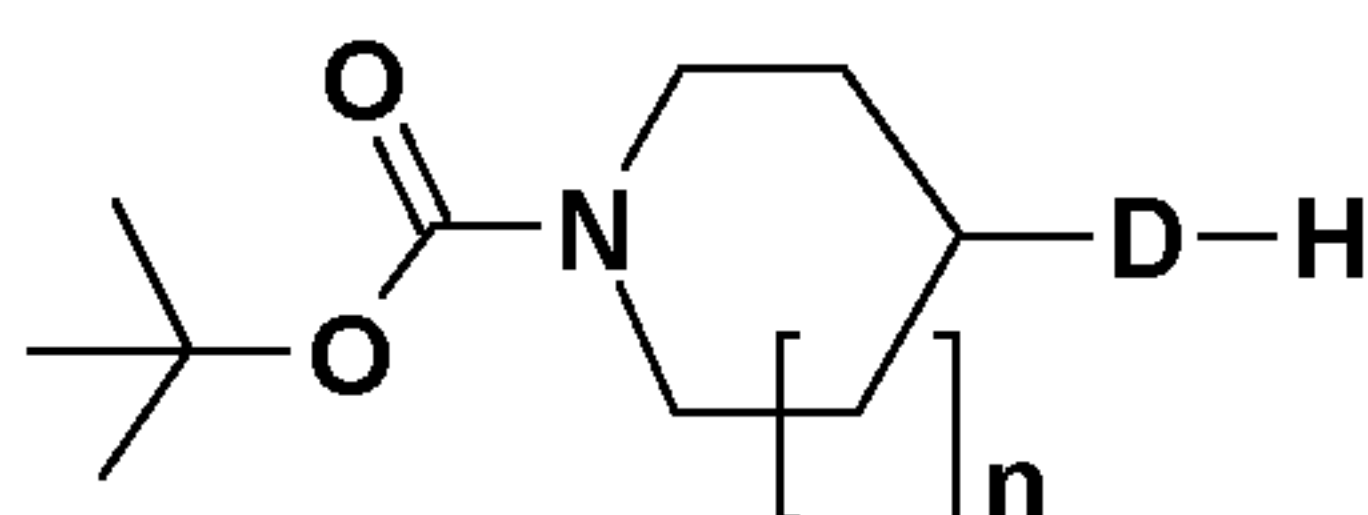
8) A method of preparation of a compound of general formula **I** according to any of
 20 claims 1 to 5 for which **B** = CH, including the following successive steps:

(c1) condensation of a compound of the following general formula **VIII**:



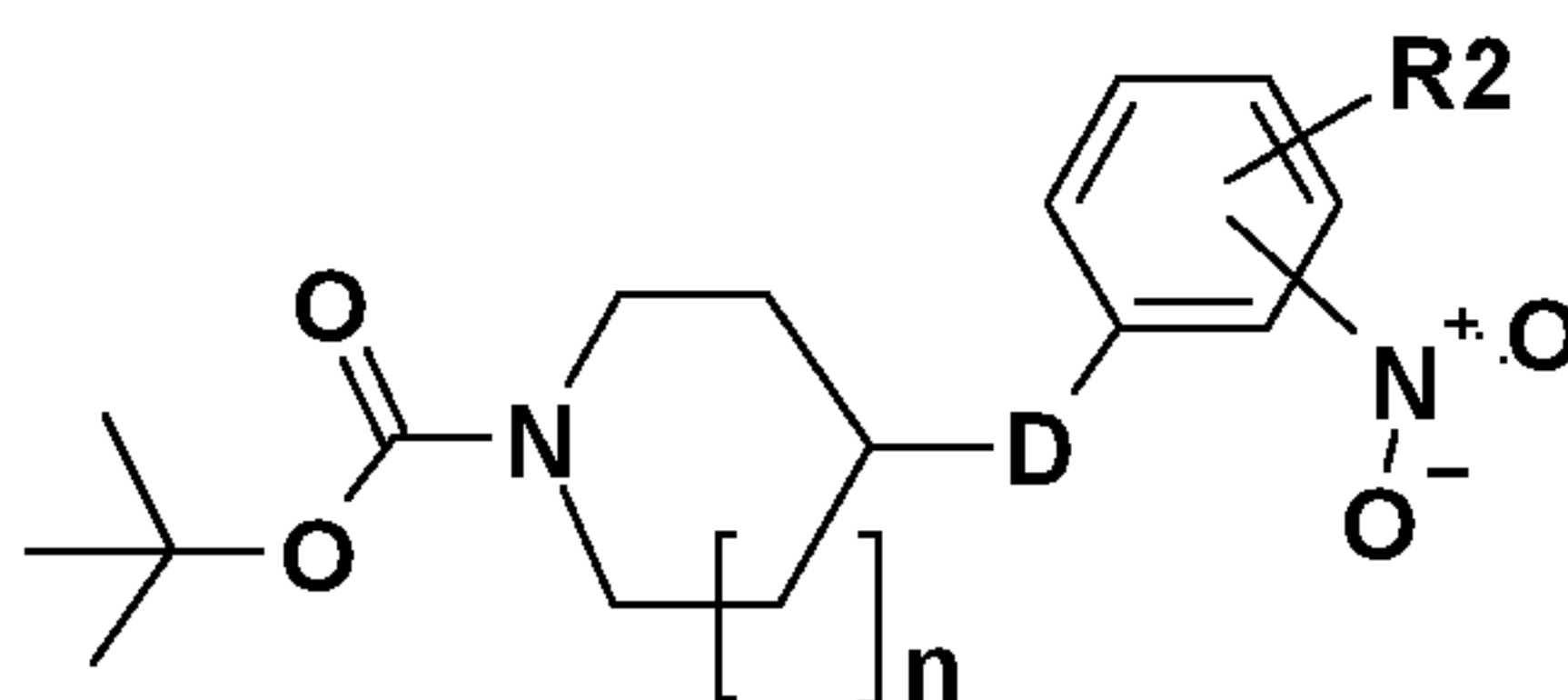
for which **R2** is as defined in general formula **I**,

with a compound of the following general formula **IX**:



IX

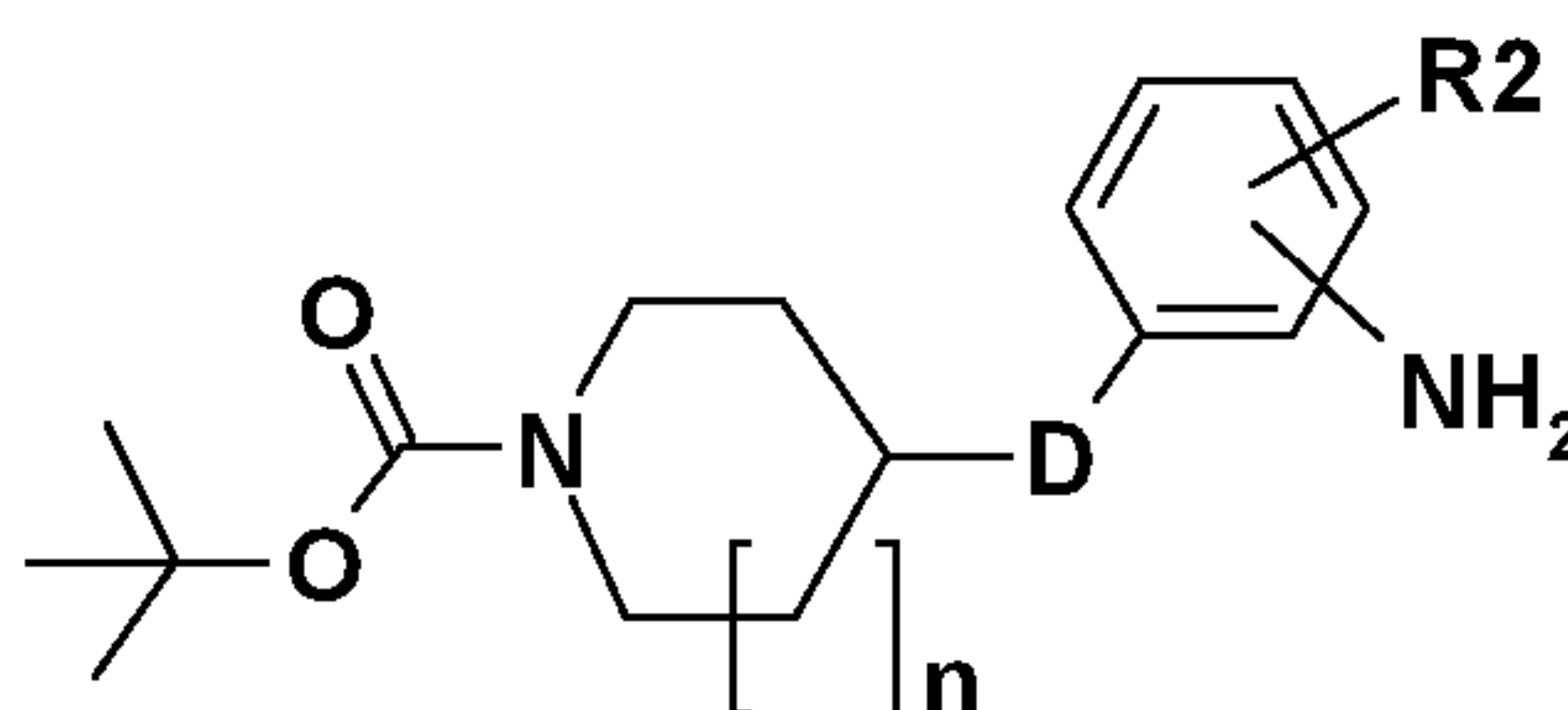
for which **D** and **n** are as defined in claim 1,
to give a compound of the following formula **X**:



X

5 for which **R2**, **D** and **n** are as defined in claim 1,

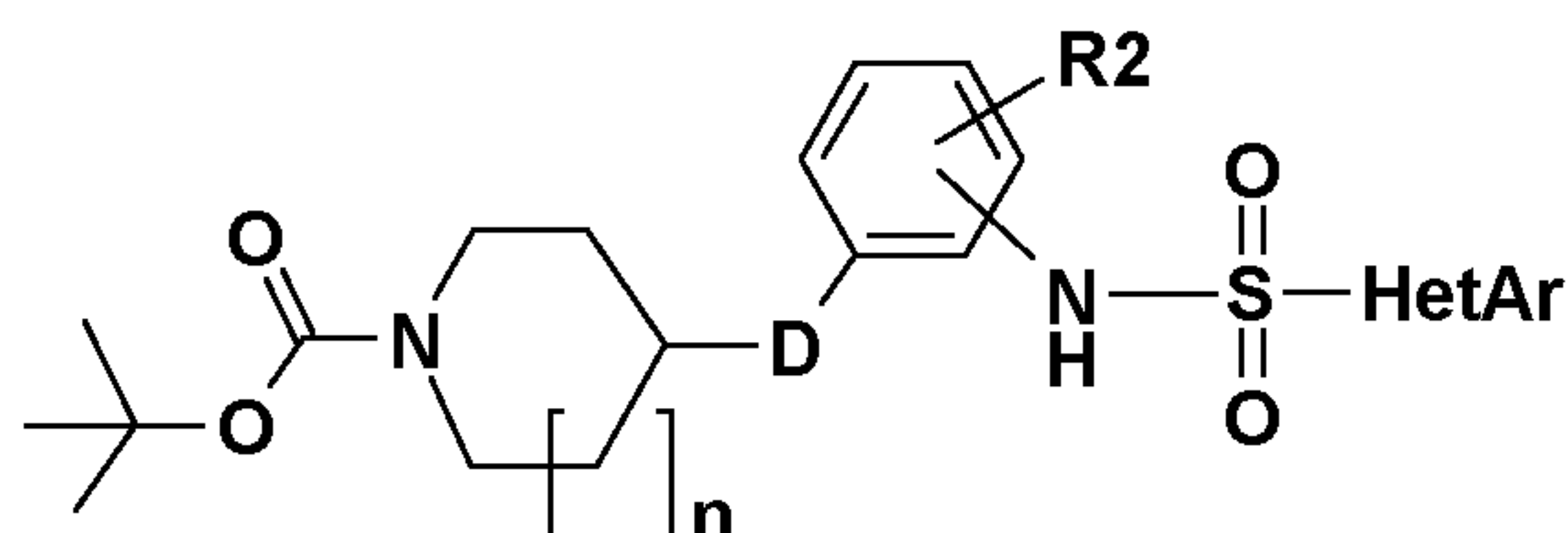
(c2) reduction of the compound of formula **X** to give a compound of the following formula **XI**:



XI

for which **R2**, **D** and **n** are as defined in claim 1,

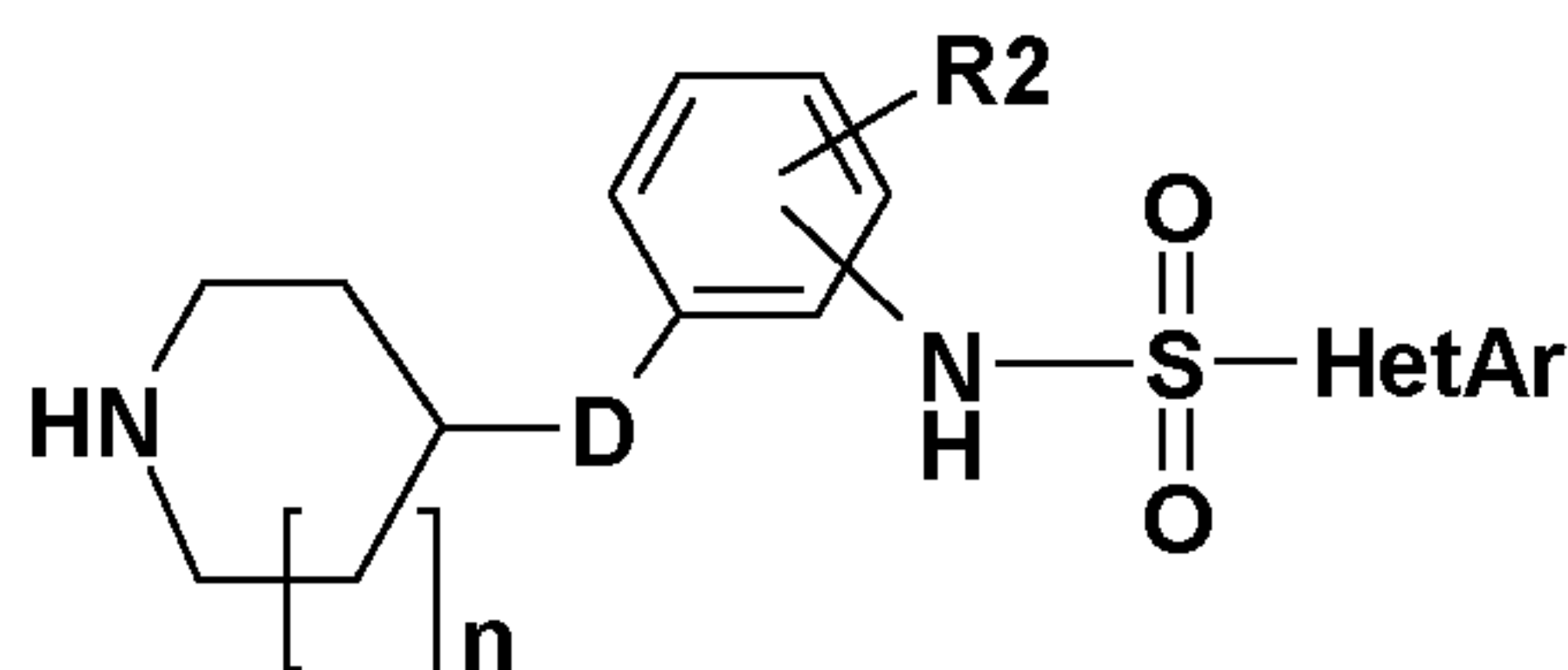
10 (c3) coupling of the compound of formula **XI** with the sulfonyl chloride of general formula **IV** as defined in claim 6) in the presence of a base such as pyridine, to give the compound of the following formula **XII**:



XII

for which **HetAr**, **R2**, **D** and **n** are as defined in claim 1,

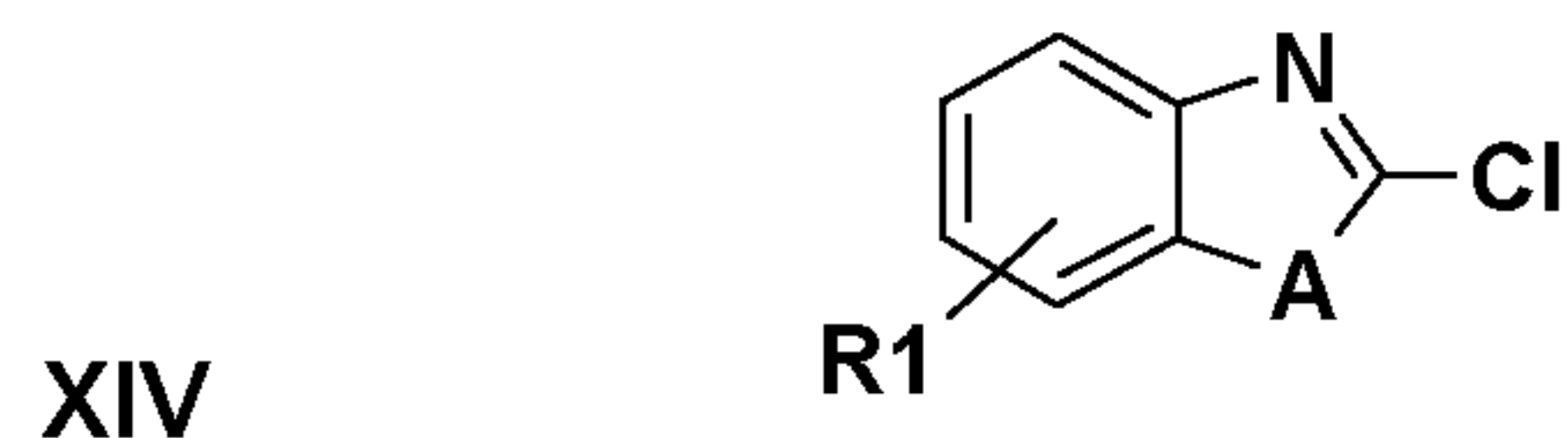
15 (c4) hydrolysis of the amide group of the compound of formula **XII** to give the compound of the following formula **XIII**:



XIII

for which **HetAr**, **R2**, **D** and **n** are as defined in claim 1,

(c5) coupling of the compound of formula XIII with the compound of the following formula XIV:



for which R1 and A are as defined in claim 1

5 to give a compound of formula I, and

(c6) optionally salt formation of the compound of formula I obtained in the previous step (c5) in the presence of a pharmaceutically acceptable base or acid in order to give a pharmaceutically acceptable salt of the compound of formula I.

10 9) A compound of general formula I according to any of claims 1 to 5 for its use as a medicine.

10) A compound of general formula I according to any of claims 1 to 5 for its use as a blocker of the Kv potassium channels, and more particularly of channels Kv1.5, Kv4.3
15 or Kv11.1.

11) A compound according to claim 9 for its use as a medicine intended for the treatment and/or prevention of diseases requiring blockers of Kv potassium channels, and more particularly of channels Kv1.5, Kv4.3 or Kv11.1.

20

12) A compound according to claim 9 for its use as medicine intended for the treatment and/or prevention of atrial fibrillation, heart rhythm disorders of the auricles and/or the ventricles, pathologies in which the cell cycle and/or cell proliferation and/or regeneration are impaired, such as cancer or chronic inflammation.

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13) A pharmaceutical composition including a compound of general formula I according to any of claims 1 to 5 in association with at least one pharmaceutically acceptable excipient.

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