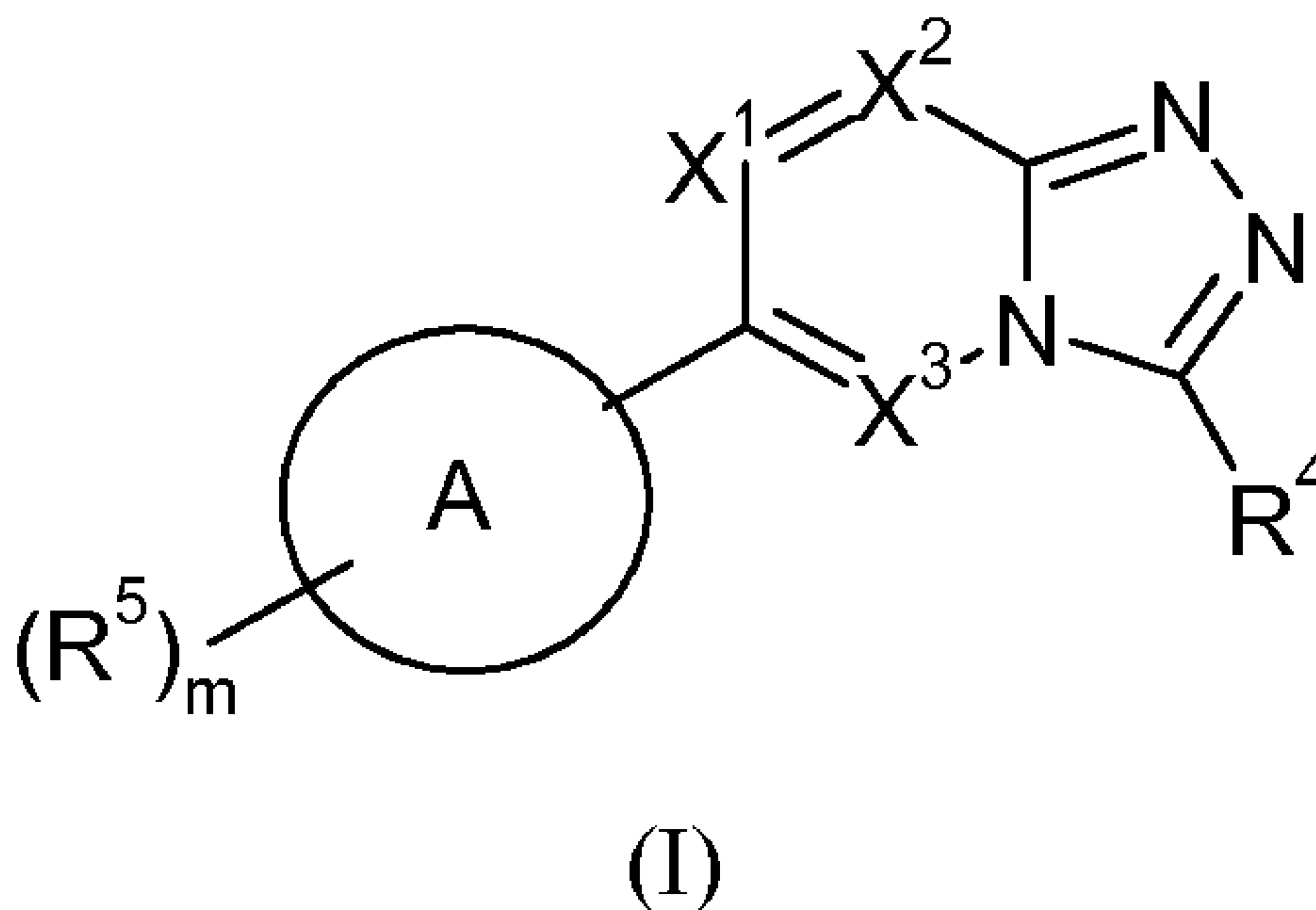




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ASSOCIEES AU RECEPTEUR DES ANDROGENES  
(54) Title: BICYCLIC DERIVATIVES FOR USE IN THE TREATMENT OF ANDROGEN RECEPTOR ASSOCIATED  
CONDITIONS



(57) **Abrégé/Abstract:**

The invention concerns bicyclic compounds of Formula (I), wherein the integers  $X^1$ ,  $X^2$ ,  $X^3$ , Ring A,  $R^4$ ,  $R^5$  and  $m$  are as defined in the description. The present invention also relates to processes for the preparation of such compounds, pharmaceutical compositions containing them and their use in the manufacture of a medicament for use in the prevention or treatment of androgen-receptor associated conditions.





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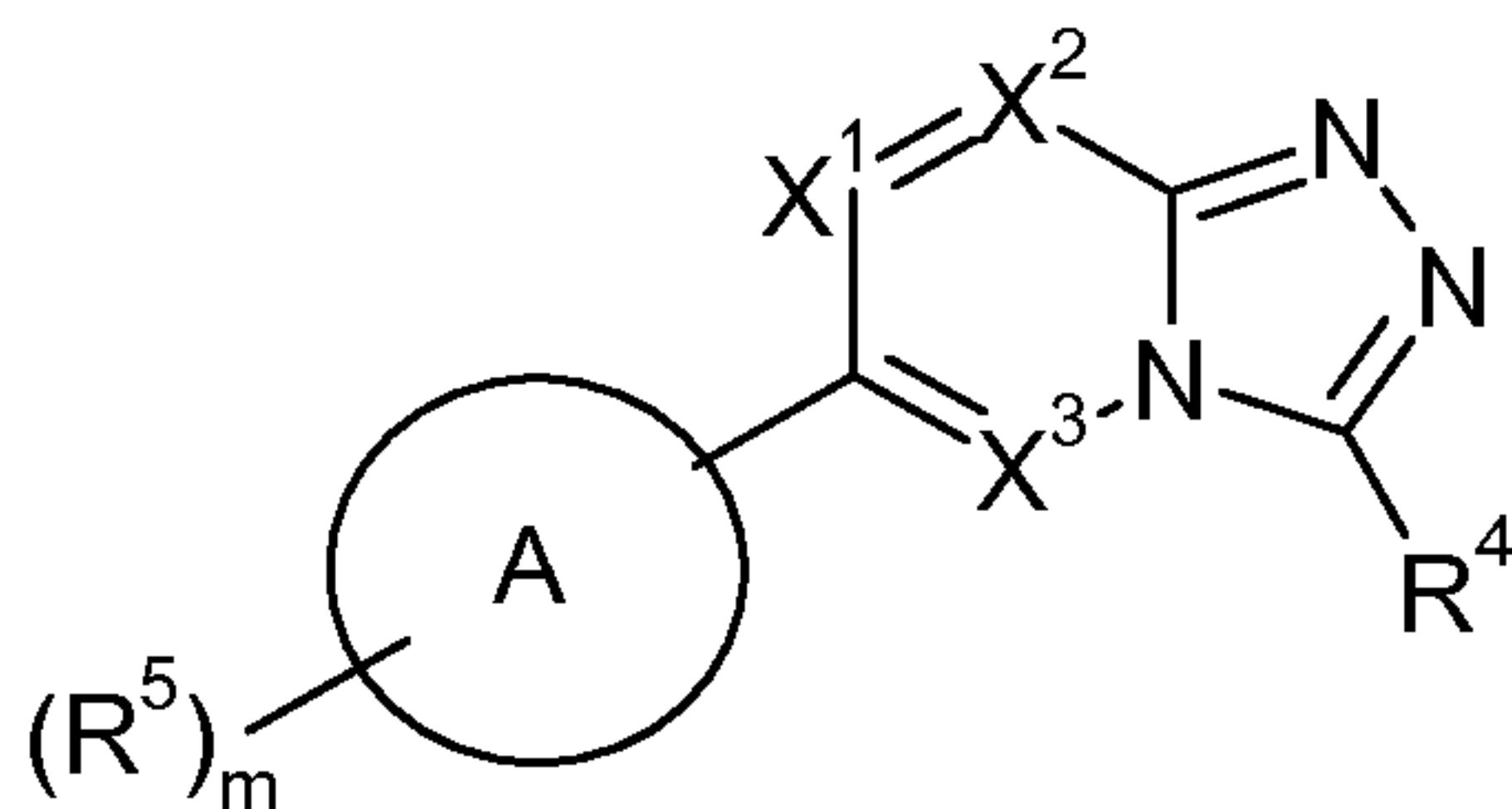
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(54) **Title:** BICYCLIC DERIVATIVES FOR USE IN THE TREATMENT OF ANDROGEN RECEPTOR ASSOCIATED CONDITIONS



(I)

(57) **Abstract:** The invention concerns bicyclic compounds of Formula (I), wherein the integers  $X^1$ ,  $X^2$ ,  $X^3$ , Ring A,  $R^4$ ,  $R^5$  and  $m$  are as defined in the description. The present invention also relates to processes for the preparation of such compounds, pharmaceutical compositions containing them and their use in the manufacture of a medicament for use in the prevention or treatment of androgen-receptor associated conditions.

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## BICYCLIC DERIVATIVES FOR USE IN THE TREATMENT OF ANDROGEN RECEPTOR ASSOCIATED CONDITIONS

This invention relates to new bicyclic derivatives and, more particularly, to bicyclic  
5 derivatives that act as ligands of the androgen receptor (AR). This invention also relates to  
methods for the preparation of such bicyclic derivatives, and novel intermediates in the  
preparation thereof, to pharmaceutical compositions containing such bicyclic derivatives,  
to the use of such bicyclic derivatives in the preparation of medicines, and to the use of  
such bicyclic derivatives in the treatment of androgen-receptor associated condition such  
10 as prostate cancer.

Prostate cancer is the second most common cause of death from cancer amongst  
men in developed countries. Four percent of deaths amongst men over 55 can be attributed  
to prostate cancer. Although the death rate is relatively low, it is currently increasing  
yearly at a rate of about 14%. The proportion of men for whom prostate cancer is likely to  
15 be diagnosed has risen by 30% in recent years, an increase which is attributable largely to  
better diagnostic methods and to a general increase in the age of the population, rather than  
to any increased incidence of new disease (E.J. Small, D.M. Reese, Curr. Opinion.  
Oncology, 2000,12,265-272).

The early stages of prostate cancer tumour growth are androgen-dependent.  
20 Provided that the tumour is confined to the prostate itself, it can usually be treated by  
surgical removal, radiation therapy and/or by chemotherapy. In more advanced cases in  
which the tumour is no longer confined to the prostate, but has formed metastatic tumours  
elsewhere in the body, the tumour may be treated palliatively by reducing blood  
testosterone levels. Such a reduction in blood testosterone levels may be achieved by  
25 surgical castration (orchidectomy) or medicinally by treatment with antiandrogens  
(Casodex, cyproterone acetate, flutamide), LHRH-Agonists (Zoladex, Buserelin), LHRH  
antagonists (Cetrorelix), or 5 $\alpha$ -reductase inhibitors (Finasteride). Since adrenal androgen  
synthesis is unaffected by surgical castration, a recent trend has been to combine surgical  
and medicinal treatment. This treatment has only temporary success since after an interval  
30 of up to 2 years renewed growth of the tumour normally occurs and this renewed tumour  
growth is usually not hormonally dependent (L.J. Denis and K. Griffith, Seminars in Surg.  
Onc., 2000, 18, 52-74). Despite extensive research on this topic during the past 50 years



there is still no effective treatment for the advanced stages of prostate cancer. For patients with advanced prostate cancer the 5-year survival rate is under 15%.

There is evidence that the androgen receptor plays an important role in the development and growth of prostate cancer not only in the early hormone-dependent stages but also in the advanced hormone-independent stages.

The androgen receptor belongs to the family of steroid hormone receptors, which function as transcription factors. The binding of an androgen to the androgen receptor results in the stabilisation of the receptor and protects it from undergoing a rapid proteolytic degradation. The complex of androgen and androgen receptor is transported into the nucleus, where it regulates the expression of androgen responsive genes by binding to their androgen response DNA elements in the promoter region of such androgen responsive genes (D.J. Lamb et al. *Vitam. Horm.* 2001, 62,199-230).

Investigation of prostate tumours shows that in 30% of advanced cases an amplification of the androgen receptor gene locus had occurred; in other cases a range of mutations of the androgen receptor were found in various domains of the androgen receptor and that lead to androgen receptors with altered properties. Such mutated receptors can have a higher than normal affinity for androgens, can be constitutively active, can have altered ligand specificity resulting in activation by other steroid hormones or even by antiandrogens, can be activated by interaction with molecules from other growth promoting signal transduction pathways, can alter interactions with other co-factors, or can activate other target genes (J.P. Elo, T. Visakorpi, *Ann. Med.* 2001,33,130-141).

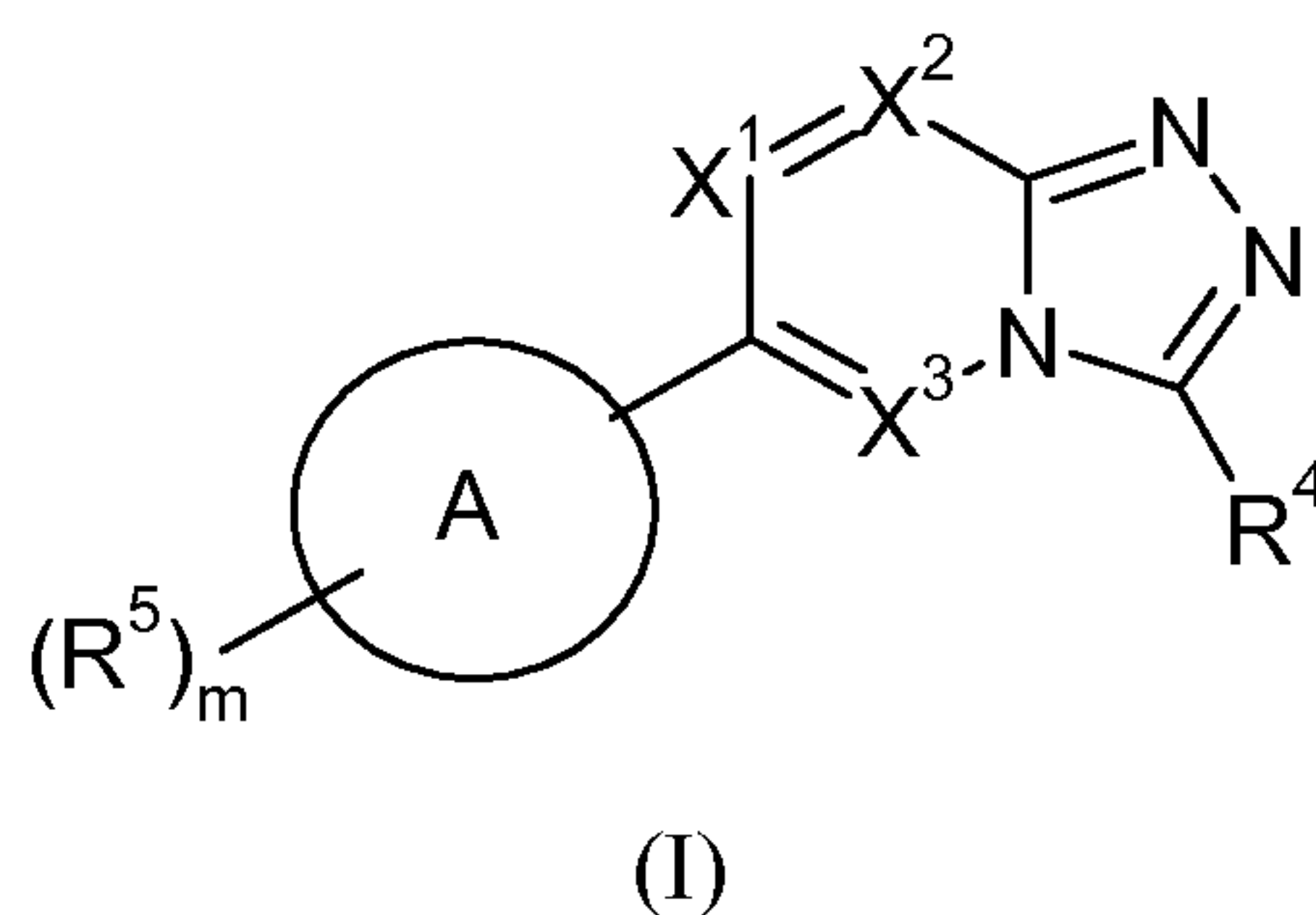
The identification of antiandrogens that would inhibit not only the natural form of the androgen receptor but also its mutated forms and thereby so alter the receptor molecule that it became unstable would be very useful in the treatment of prostate tumours at various stages of growth. Such compounds could inhibit a recurrence of tumour growth or at least prolong the disease free interval. In the case of oestrogen receptors, such ligands have been identified that destabilise the receptor and lead to a reduction in the receptor content both in vitro and in vivo (S. Dauvois et al., *Proc Natl. Acad. Sci. USA*, 1992, 89,4037-41; R.A. McClelland et al. *Eur. J. Cancer*, 1996, 32A, 413-416).

Non-steroidal antiandrogens have been described in US5411981 (phenylimidazolidine derivatives), in WO97/00071 (specifically substituted



phenyldimethyl hydantoins and their imino- and thio-derivatives), in WO00/37430 (phenylalanines, phenylhydantoins, and phenylureas), in WO01/58855 (aminopropanilides), and in EP1122242 (substituted cyanophenylpiperazines).

A series of bicyclic derivatives capable of inducing cellular down-regulation of the androgen receptor is described herein. According to a first aspect of the present invention there is therefore provided the use of a compound of Formula (I) for the treatment of an androgen receptor associated condition;



wherein

$X^1$  is selected from  $-N-$  and  $-C(R^1)-$ ;

$X^2$  is selected from  $-N-$  and  $-C(R^2)-$ ;

$X^3$  is selected from  $-N-$  and  $-C(R^3)-$ ;

Wherein at least one of  $X^1$ ,  $X^2$  and  $X^3$  is not  $-N-$ ;

Ring A is selected from a mono or bicyclic heterocyclic ring and a carbocyclic ring;

$R^1$ ,  $R^2$  and  $R^3$  are independently selected from hydrogen,  $C_{1-6}$ alkyl,  $C_{1-6}$ alkoxy,

$C_{1-6}$ alkylthio, halo and cyano wherein an alkyl chain in  $R^1$ ,  $R^2$  and  $R^3$  is optionally substituted by up to three halo groups;

$R^4$  is selected from hydrogen, hydroxy, halo, cyano, amino,  $N-C_{1-6}$ alkylamino,

$N,N$ -di- $C_{1-6}$ alkylamino,  $C_{1-6}$ alkyl,  $C_{2-6}$ alkenyl,  $C_{2-6}$ alkynyl,  $C_{1-6}$ alkoxy,

$C_{1-6}$ alkyl- $S(O)_n-$  wherein  $n$  is an integer from 0-2 and a  $C_{3-4}$ carbocyclic ring, wherein an alkyl, alkenyl or alkynyl chain within  $R^4$  can optionally be substituted with up to 5 groups selected from cyano, halo, amino,  $C_{1-6}$ alkoxy,  $C_{1-4}$ alkoxy $C_{1-4}$ alkyl and

$C_{1-6}$ alkylthio and when  $R^4$  comprises an alkyl chain the chain can be perfluorinated;

$R^5$  is selected from oxo or the group  $-L^1-J-L^2-K$

wherein

$L^1$  and  $L^2$  are independently selected from a direct bond,  $C_{1-6}$ alkylene,  $C_{2-6}$ alkenylene

$C_{2-6}$ alkynylene,  $C_{1-6}$ alkylidene, wherein an alkyl, alkenyl, alkynyl or



alkylidenyl chain within  $L^1$  and  $L^2$  can optionally be substituted with up to 3 groups selected from  $R^7$  and wherein  $L^1$  and  $L^2$  can also be selected from one of the following groups or an alkyl, alkenyl, alkynyl or alkylidenyl chain into which is inserted one of the following groups, said groups independently selected from: -O-, -C(O)-, -C(O)-O-, -O-C(O)-, -N( $R^6$ )-, -N( $R^6$ )-C(O)-; -C(O)-N( $R^6$ )-, -N( $R^6$ )-C(O)-O-, -O-C(O)-N( $R^6$ )-, -C(O)-N( $R^6$ )-O-; -O-N( $R^6$ )-C(O)-, -N( $R^6$ )-C(O)-N( $R^6$ )-, -S(O)<sub>0-2</sub>-, -O-S(O<sub>2</sub>)-, S-(O<sub>2</sub>)-O-, -N( $R^6$ )-S(O)<sub>2</sub>- and -S(O)<sub>2</sub>-N( $R^6$ )-;

J is selected from a direct bond, C<sub>1-4</sub>alkylene, aryl, heterocyclyl and heteroaryl

wherein J is optionally substituted by up to five groups selected from  $R^8$ ;

K is selected from C<sub>1-6</sub>alkyl, C<sub>2-6</sub>alkenyl, C<sub>2-6</sub>alkynyl, a carbocyclic ring, aryl, heterocyclyl and heteroaryl wherein K is optionally substituted by up to five groups selected from  $R^8$ ;

$R^6$  is selected from hydrogen and C<sub>1-6</sub>alkyl;

$R^7$  is selected from hydroxy, carboxy, carbamoyl, C<sub>1-6</sub>alkyl, C<sub>2-6</sub>alkenyl, C<sub>2-6</sub>alkynyl, C<sub>1-6</sub>alkoxy, C<sub>1-4</sub>alkyloxyC<sub>1-4</sub>alkyl, C<sub>1-6</sub>alkoxycarbonyl, C<sub>1-6</sub>alkyl-S(O)<sub>n</sub>- wherein n is an integer from 0 to 2, aminosulphonyl, carbamoyl, N-C<sub>1-4</sub>alkylamino, N,N-di-C<sub>1-4</sub>alkylamino, N-C<sub>1-4</sub>alkylaminocarbonyl, N,N-di-C<sub>1-4</sub>alkylaminocarbonyl, N-C<sub>1-4</sub>alkylaminosulphonyl, N,N-di-C<sub>1-4</sub>alkylaminosulphonyl, oxo, C<sub>1-6</sub>alkyl(C<sub>1-6</sub>alkoxy)oxophosphinyl, diC<sub>1-6</sub>alkyloxophosphinyl, aryl, carbocyclyl, heterocyclyl, heteroaryl wherein  $R^7$  is optionally substituted by up to three groups selected from hydroxy, halo, cyano, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy and a carbocyclic ring and an N,N-di-C<sub>1-4</sub>alkylamino group within  $R^7$  is optionally cyclized to form a ring;

$R^8$  is selected from hydroxy, oxo, cyano, halo, nitro, hydroxy, carboxy, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkenyl, C<sub>1-6</sub>alkynyl, C<sub>1-6</sub>alkoxy, C<sub>1-6</sub>alkoxycarbonyl, cyanoC<sub>1-6</sub>alkoxy, C<sub>1-6</sub>alkenyloxy, C<sub>1-6</sub>alkanoyl, C<sub>1-4</sub>alkoxycarbonyl, C<sub>1-6</sub>alkyl-S(O)<sub>n</sub>- wherein n is an integer from 0 to 2, amino, C<sub>1-6</sub>alkylsulphonyloxy, carbamoyl, aminosulphonyl, N-C<sub>1-4</sub>alkylaminosulphonyl, N,N-di-C<sub>1-4</sub>alkylaminosulphonyl, N-C<sub>1-4</sub>alkylamino, N,N-di-C<sub>1-4</sub>alkylamino, carbamoyl, N-C<sub>1-4</sub>alkylaminocarbonyl, N,N-di-C<sub>1-4</sub>alkylaminocarbonyl, aryl, carbocyclyl, heterocyclyl and heteroaryl wherein an alkyl chain or ring in  $R^8$  is optionally substituted by up to five groups selected from halo, amino, hydroxy, carboxy, C<sub>1-4</sub>alkoxy, N-C<sub>1-4</sub>alkylamino,

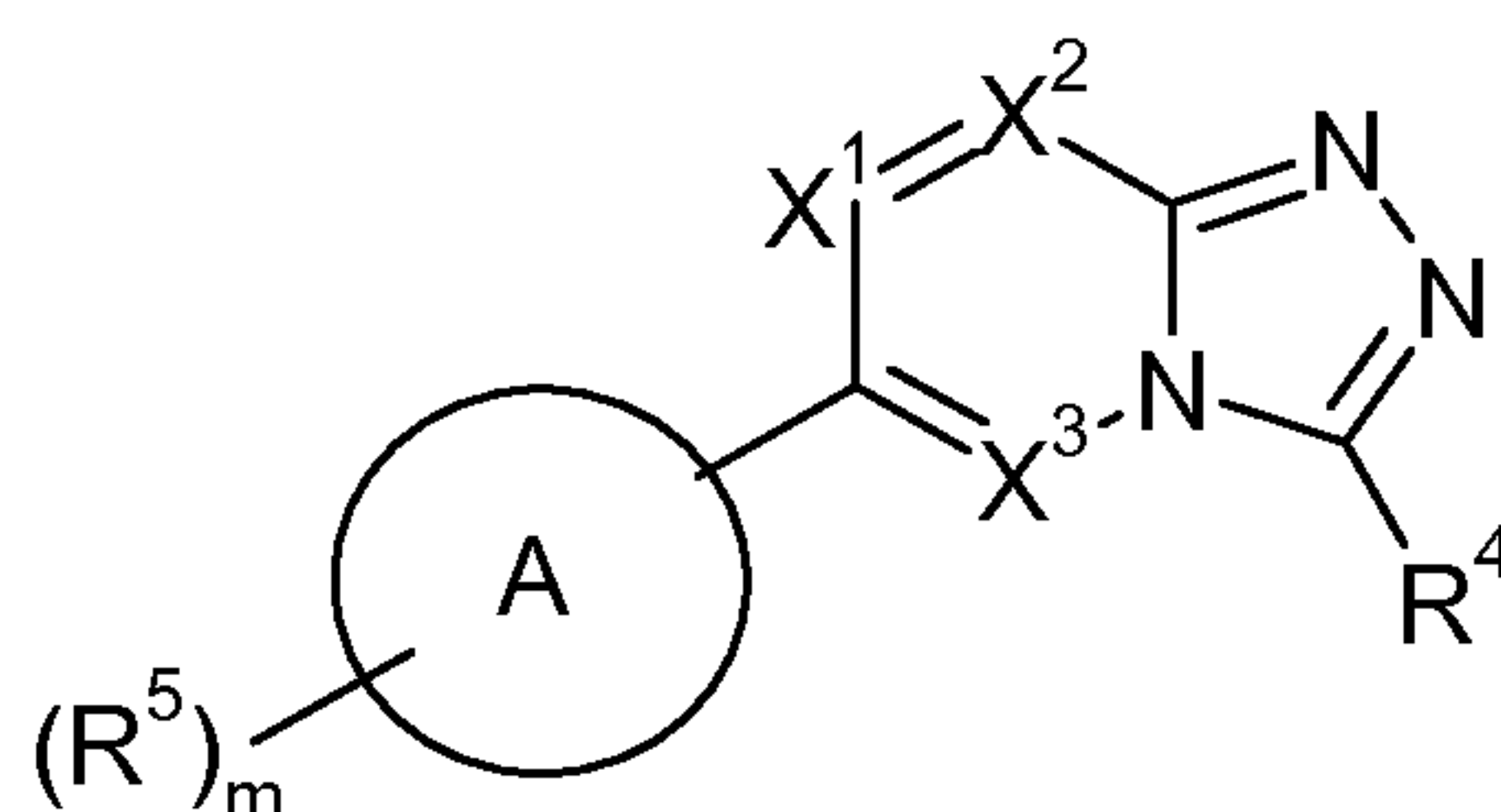


N,N-di-C<sub>1-4</sub>alkylamino, carbamoyl, N-C<sub>1-4</sub>alkylaminocarbonyl,  
N,N-di-C<sub>1-4</sub>alkylaminocarbonyl and oxo and an N,N-di-C<sub>1-4</sub>alkylamino group within  
R<sup>8</sup> is optionally cyclized to form a ring; and

m is an integer from 1 to 4;

5 or a pharmaceutically acceptable salt thereof.

According to a second aspect of the present invention there is provided the use of a  
compound of Formula (Ia) as a medicament;



(Ia)

10 wherein X<sup>1</sup>, X<sup>2</sup>, X<sup>3</sup>, Ring A, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> are as defined above in the definition of  
a compound of Formula (I)

with the proviso that

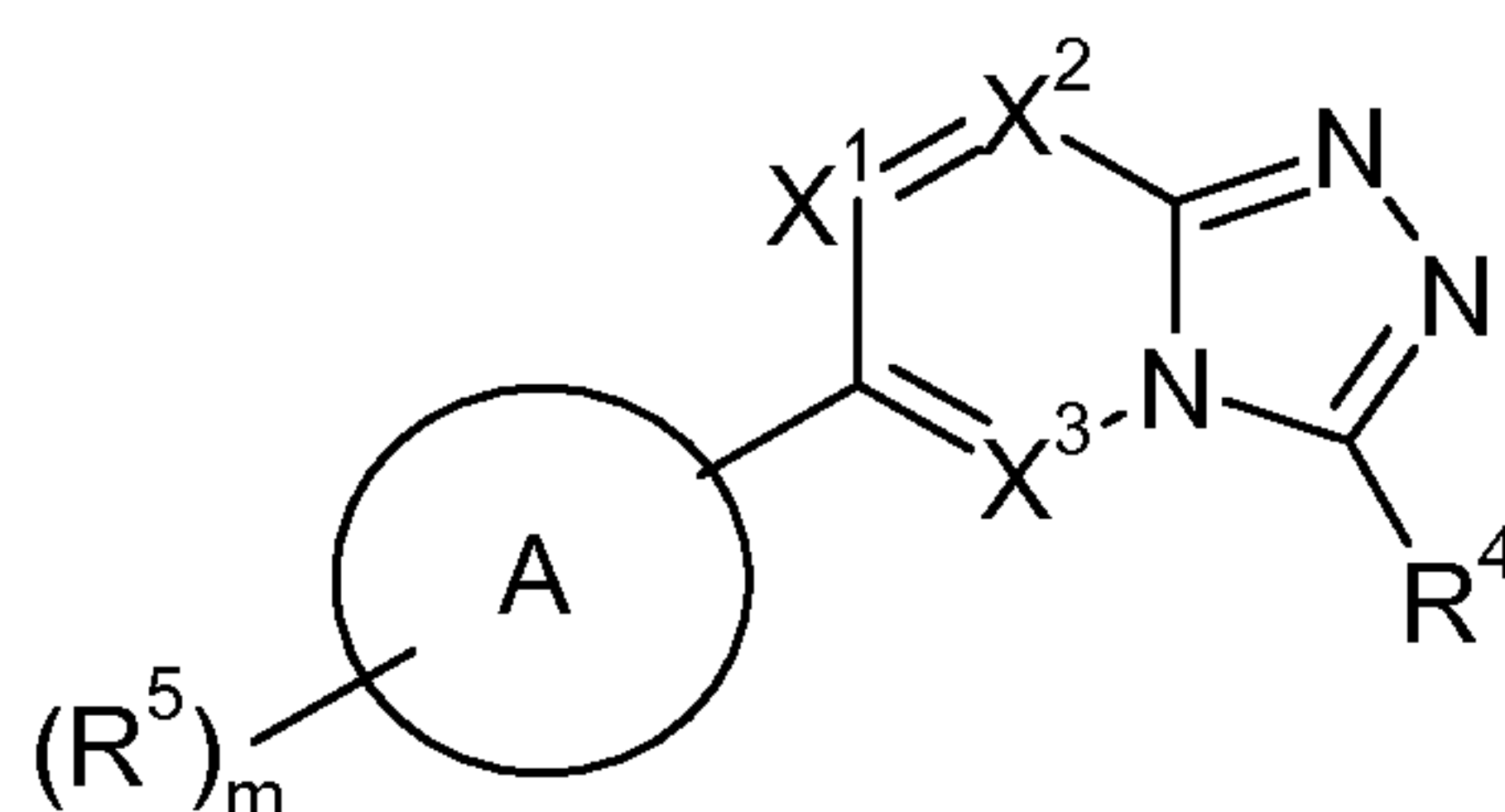
- (i) when m is 1 then (R<sup>5</sup>)<sub>m</sub> cannot be hydroxy, oxo or C<sub>1-6</sub>alkyl and when m is 2 then  
(R<sup>5</sup>)<sub>m</sub> cannot be dihydroxy;
- 15 (ii) -L<sup>1</sup>-J-L<sup>2</sup>-K cannot be trifluorophenylpiperidin-1-yl when the piperidine group is  
substituted by amino or C<sub>1-4</sub>alkylcarbonylamino;
- (iii) When Ring A is pyrrolidin-1-yl, m is 2 and (R<sup>5</sup>)<sub>m</sub> is substituted piperidine-1-  
ylcarbonyl and substituted phenyl or substituted piperidine-1-ylcarbonyl and  
substituted pyridyl then the phenyl or pyridyl ring cannot be substituted by fluoro,  
20 chloro, cyano, trifluoromethyl or methoxy.
- (iv) when Ring A is indoline and m is 1 then R<sup>5</sup> cannot be unsubstituted or substituted  
pyrrolidinylcarbonyl or unsubstituted or substituted piperidinylcarbonyl.

or a pharmaceutically acceptable salt thereof.

According to a third aspect of the present invention there is provided a compound  
25 of Formula (Ib);



6



(Ib)

wherein  $X^1$ ,  $X^2$ ,  $X^3$ , Ring A,  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$  and  $R^5$  are as defined above in the definition of a compound of Formula (I)

5 the proviso that

- (i) when  $m$  is 1 then  $(R^5)_m$  cannot be hydroxy,  $C_{1-6}$ alkyl, oxo, acetyl, carbamoyl, ethoxycarbonyl, methylsulphonyl, methylsulphonylamino, isopropylaminocarbonylmethyl or isobutylaminocarbonylmethyl and when  $m$  is 2  $(R^5)_m$  cannot be dihydroxy and cannot be cyano and amino;
- 10 (ii) when  $R^4$  is trifluoromethyl or methyl and Ring A is piperazin-1-yl substituted at the 4 position by phenyl, benzyl phenethyl, phenylsulphonyl, phenylcarbonyl or anilincarbonyl then the phenyl ring cannot be unsubstituted or substituted by 2-methyl, 2,3-dimethyl, 2,4-dimethyl, 2,6-dimethyl, 2-methoxy, 4-methoxy, 3-chloro, 4-chloro, 3-fluoro, 4-fluoro, 2,6-difluoro, 3-trifluoromethyl, 2-nitro, 4-nitro or 2,3,5,6-tetrafluoro-4-trifluoromethyl;
- 15 (iii) when  $R^4$  is trifluoromethyl or methyl and Ring A is piperazinyl substituted by  $-L^1-J-L^2-K$  at the 4-position and  $m$  is 1 then  $-L^1-J-L^2-K$  cannot be unsubstituted  $\alpha$ -carbamoylbenzyl,  $\alpha$ -phenylbenzyl, unsubstituted pyrrolidin-1-ylcarbonyl, unsubstituted morpholinocarbonylmethyl, unsubstituted thien-3-ylmethyl, unsubstituted thiazol-2-yl, unsubstituted pyridin-2-yl, unsubstituted pyridin-4-ylmethyl, unsubstituted pyrazin-2-yl, unsubstituted pyrimidin-2-yl, unsubstituted tetrazolo[1,5-b]pyridazin-6-yl, unsubstituted quinolin-8-ylmethyl, unsubstituted 1,3-benzodioxol-5-ylmethyl, 2,6-difluorophenylsulphonyl, 5-chlorothiophen-2-ylsulphonyl, 2-methylthiazol-4-ylmethyl, 2-(4-methoxyphenyl)thiazol-4-ylmethyl;
- 20 (iv)  $-L^1-J-L^2-K$  cannot be trifluorophenylpiperidin-1-yl when the piperidine group is substituted by amino or  $C_{1-4}$ alkylcarbonylamino; and
- 25 (v) When Ring A is pyrrolidin-1-yl,  $m$  is 2 and  $(R^5)_m$  is substituted piperidine-1-ylcarbonyl and substituted phenyl or substituted piperidine-1-ylcarbonyl and



substituted pyridyl then the phenyl or pyridyl ring cannot be substituted by fluoro, chloro, cyano, trifluoromethyl or methoxy;

(vi) when Ring A is indoline and m is 1 then R<sup>5</sup> cannot be unsubstituted or substituted pyrrolidinylcarbonyl or unsubstituted or substituted piperidinylcarbonyl.

5 (vii) when R<sup>4</sup> is trifluoromethyl or methyl and Ring A is piperidinyl substituted by -L<sup>1</sup>-J-L<sup>2</sup>-K at the 4-position and m is 1 then -L<sup>1</sup>-J-L<sup>2</sup>-K cannot be mono or disubstituted carbamoyl;

(viii) The following compounds are excluded:

- 10 6-[2-(2,4-dimethoxyphenyl)-1-pyrrolidinyl]-3-(trifluoromethyl)-1,2,4-Triazolo[4,3-b]pyridazine;
- 6-[4-(7-ethyl-1H-indol-3-yl)-3,6-dihydro-1(2H)-pyridinyl]-3-(trifluoromethyl)-1,2,4-Triazolo[4,3-b]pyridazine,
- 6-[4-(1H-indol-3-yl)-3,6-dihydro-1(2H)-pyridinyl]-3-(trifluoromethyl)-1,2,4-Triazolo[4,3-b]pyridazine;
- 15 6,7,8,9-tetrahydro-3-[1-[3-(trifluoromethyl)-1,2,4-triazolo[4,3-b]pyridazin-6-yl]-3-piperidinyl]-5H-1,2,4-triazolo[4,3-a]azepine;
- 6-[4-[2-(3,5-dimethoxyphenyl)ethyl]-1-piperidinyl]-3-(trifluoromethyl)-1,2,4-triazolo[4,3-b]pyridazine;
- 20 2-thienyl[4-[3-(trifluoromethyl)-1,2,4-triazolo[4,3-b]pyridazin-6-yl]-1-piperazinyl]-methanone;
- N-cyclopentyl-N-methyl-1-(3-methyl-1,2,4-triazolo[4,3-b]pyridazin-6-yl)-4-piperidinamine;
- 6-[4-(2-benzoxazolyl)-1-piperidinyl]-3-(trifluoromethyl)-1,2,4-triazolo[4,3-b]pyridazine
- 25 6-(3-phenylpyrrolidin-1-yl)-1,2,4-triazolo[4,3-b]pyridazine; and
- 1-[[2,3-dihydro-1-(3-methyl-1,2,4-triazolo[4,3-b]pyridazin-6-yl)-1H-indol-2-yl]carbonyl]-3-methyl-piperidine;

or a salt thereof.

Whilst pharmaceutically-acceptable salts of compounds of the invention are  
30 preferred, other non-pharmaceutically-acceptable salts of compounds of the invention may also be useful, for example in the preparation of pharmaceutically-acceptable salts of compounds of the invention.



It is to be understood that, insofar as certain of the compounds of Formula (I) defined above may exist in optically active or racemic forms by virtue of one or more asymmetric carbon atoms, the invention includes in its definition any such optically active or racemic form which possesses the above-mentioned activity. The synthesis of optically  
5 active forms may be carried out by standard techniques of organic chemistry well known in the art, for example by synthesis from optically active starting materials or by resolution of a racemic form. Similarly, the above-mentioned activity may be evaluated using the standard laboratory techniques referred to hereinafter.

Examples of suitable methods for separating the enantiomers of a racemic  
10 compound include chromatography using a suitable chiral stationary phase; or conversion of a racemic mixture into diastereomeric derivatives, separation of the mixture of diastereomeric derivatives into two single diastereomers, and regeneration of a separate single enantiomer from each separate single diastereomer.

Examples of suitable methods for separating a mixture of diastereomers include  
15 fractional crystallisation, normal-phase chromatography, or reverse-phase chromatography.

It is to be understood that certain compounds of Formula (I) defined above may exhibit the phenomenon of tautomerism. In particular, tautomerism may affect any heterocyclic groups that bear 1 or 2 oxo substituents. It is to be understood that the present invention includes in its definition any such tautomeric form, or a mixture thereof, which  
20 possesses the above-mentioned activity and is not to be limited merely to any one tautomeric form utilised within the formulae drawings or named in the Examples.

It is to be understood that certain compounds of Formula (I) above may exist in unsolvated forms as well as solvated forms, such as, for example, hydrated forms. It is to be understood that the present invention encompasses all such solvated forms that possess  
25 androgen receptor ligand activity.

It is also to be understood that certain compounds of the Formula (I) may exhibit polymorphism, and that the present invention encompasses all such forms which possess androgen receptor ligand activity.

In this specification the generic term "alkyl", unless specifically specified  
30 otherwise, includes both straight-chain and branched-chain alkyl groups such as propyl, isopropyl and tert-butyl. However, references to individual alkyl groups such as "propyl" are specific for the straight-chain version only, and references to individual branched-chain



alkyl groups such as “isopropyl” are specific for the branched-chain version only. The same principle also applies to generic terms “alkenyl” and “alkynyl”, unless specified otherwise.

The term “fluoroC<sub>1-6</sub>alkyl” is intended to mean a saturated carbon chain of 1 to 6 carbon atoms in length which may be straight-chained or branched wherein at least one of the hydrogen atoms have been replaced by fluorine. For example, “fluoroC<sub>1-6</sub>alkyl” includes, but is not limited to, fluoromethyl, fluoroethyl, fluoropropyl, fluoroisopropyl, fluorobutyl, fluoroisobutyl, fluoro-tert-butyl, fluoropentyl, fluoroisopentyl, fluorohexyl, fluoroisohexyl, trifluoromethyl, pentafluoroethyl, heptafluoropropyl, nonafluorobutyl, undecafluoropentyl and tridecafluorohexyl. The term “fluoroC<sub>1-4</sub>alkyl” should be construed accordingly.

The term “C<sub>1-6</sub> alkoxy” is intended to mean a saturated carbon chain of 1 to 6 carbon atoms in length, which may be straight-chained or branched, linked to oxygen. For example, “C<sub>1-6</sub> alkoxy” includes, but is not limited to, methoxy, ethoxy, propoxy, butoxy, pentoxy and hexoxy.

The term “C<sub>2-6</sub>alkanoyl” is intended to mean a saturated carbon chain of 1 to 5 carbon atoms in length which may be straight-chained or branched, linked to carbonyl. For example, “C<sub>2-6</sub>alkanoyl” includes, but is not limited to, ethanoyl, propanoyl, butanoyl, pentanoyl and hexanoyl.

The term “C<sub>1-6</sub>alkoxyC<sub>1-6</sub>alkyl” is intended to mean a saturated carbon chain of 1 to 6 carbon atoms in length, which may be straight-chained or branched, linked via oxygen to another saturated carbon chain of 1 to 6 carbon atoms in length, which may be straight-chained or branched. For example, “C<sub>1-6</sub>alkoxyC<sub>1-6</sub>alkyl” includes, but is not limited to, methoxyethyl, methoxypropyl, ethoxypropyl, propoxyethyl and butoxypropyl.

The term “hydroxyC<sub>1-6</sub>alkyl” is intended to mean a saturated carbon chain of 1 to 6 carbon atoms in length, which may be straight-chained or branched, comprising a single hydroxyl group. For example “hydroxyC<sub>1-6</sub>alkyl” includes, but is not limited to, hydroxymethyl, hydroxyethyl, 2-hydroxypropyl, 3-hydroxypropyl, 1-hydroxyisopropyl, 4-hydroxybutyl, hydroxypentyl, hydroxyhexyl and hydroxyisohexyl.

The term “C<sub>1-6</sub>alkylsulphanyl” is intended to mean a saturated carbon chain of 1 to 6 carbon atoms in length, which may be straight-chained or branched, linked to sulphur. For example, “C<sub>1-6</sub>alkylsulphanyl” includes, but is not limited to, methylsulphanyl,



ethylsulphanyl, propylsulphanyl, isopropylsulphanyl, butylsulphanyl, isobutylsulphanyl, *tert*-butylsulphanyl, pentylsulphanyl and hexylsulphanyl.

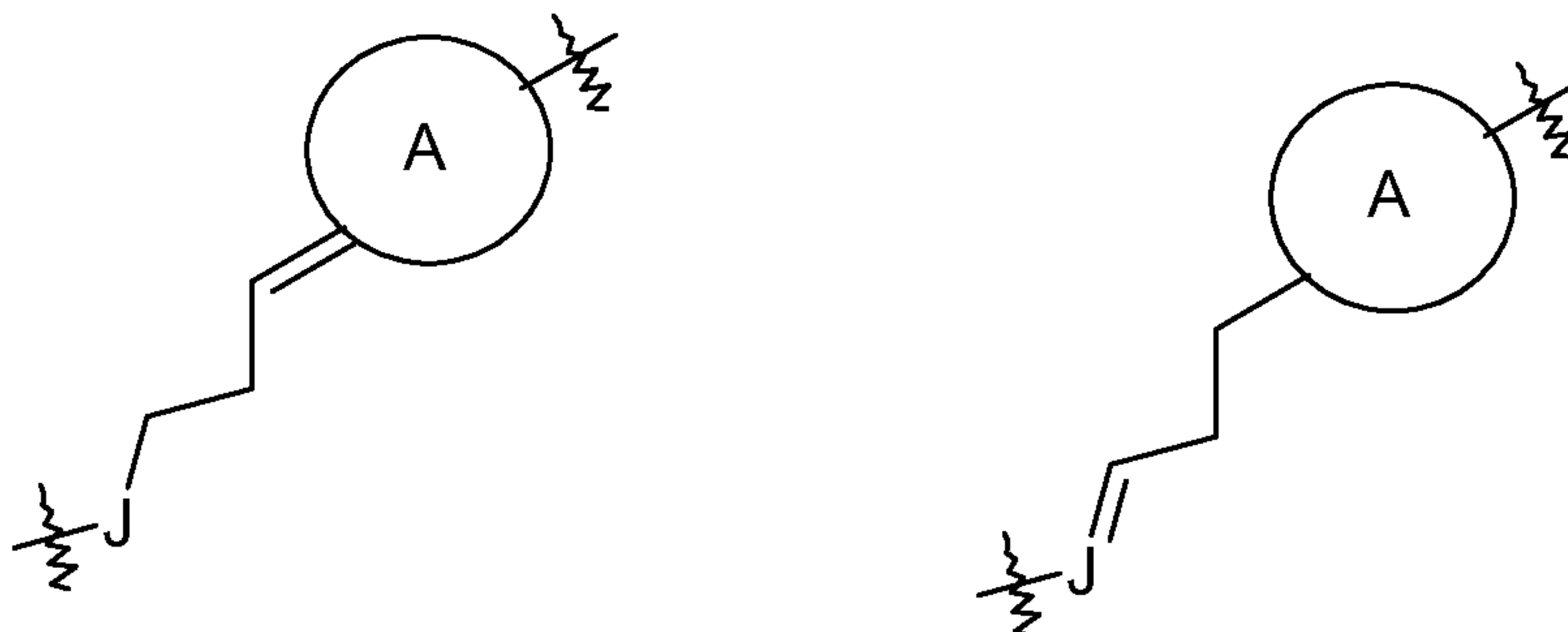
The term “C<sub>1-6</sub>alkylsulphinyl” is intended to mean a saturated carbon chain of 1 to 6 carbon atoms in length, which may be straight-chained or branched, linked to sulfoxide. For example, “C<sub>1-6</sub>alkylsulphinyl” includes, but is not limited to, methylsulphinyl, ethylsulphinyl, propylsulphinyl, isopropylsulphinyl, butylsulphinyl, isobutylsulphinyl, *tert*-butylsulphinyl, pethylsulphinyl and hexylsulphinyl.

The term “C<sub>1-6</sub>alkylsulphonyl” is intended to mean a saturated carbon chain of 1 to 6 carbon atoms in length, which may be straight-chained or branched, linked to sulphur dioxide. For example, “C<sub>1-6</sub>alkylsulphonyl” includes, but is not limited to, methylsulphonyl, ethylsulphonyl, propylsulphonyl, isopropylsulphonyl, butylsulphonyl, isobutylsulphonyl, *tert*-butylsulphonyl, pentylsulphonyl and hexylsulphonyl.

The term “N-C<sub>1-4</sub>alkylamino” is intended to mean a saturated carbon chain of 1 to 4 carbon atoms in length, which may be straight-chained or branched, linked to a secondary amino group. For example, “N-C<sub>1-4</sub>alkylamino” includes, but is not limited to, methylamino, ethylamino, propylamino and butylamino.

The term “N,N-di-C<sub>1-4</sub>alkylamino” is intended to mean a saturated carbon chain of 1 to 4 carbon atoms in length, which may be straight-chained or branched, linked to a tertiary amino group, which is in turn linked to a further saturated carbon chain of the same length. For example, “N,N-di-C<sub>1-4</sub>alkylamino” includes, but is not limited to, N,N-dimethylamino, N,N-diethylamino, N,N-dipropylamino and N,N-dibutylamino.

The term alkylidene is used to denote an alkylidene chain which can be in either orientation within the molecule, thus for example where L<sup>1</sup> is propylidene this would cover the following two structures:



The term “halo” is used herein to denote fluoro, chloro, bromo and iodo.



The term “haloC<sub>1-4</sub>alkyl” is intended to mean a saturated carbon chain of 1 to 4 carbon atoms in length which may be straight-chained or branched wherein at least one of the hydrogen atoms have been replaced by a halo atom. For example, “haloC<sub>1-4</sub>alkyl” includes, but is not limited to, difluoromethyl, trifluoromethyl, chloro(difluoro)methyl, difluoroethyl and difluoropropyl.

The term “aryl” refers to phenyl or naphthyl.

The term “carbamoyl” refers to the group –C(O)NH<sub>2</sub>.

Unless stated otherwise, the term “heteroaryl” refers to a 4-10 membered aromatic mono or, bicyclic ring containing up to 5 heteroatoms independently selected from nitrogen, oxygen or sulphur, linked via ring carbon atoms or ring nitrogen atoms where a bond from a nitrogen is allowed, for example no bond is possible to the nitrogen of a pyridine ring, but a bond is possible through the 1-nitrogen of a pyrazole ring. In one embodiment the term “heteroaryl” refers to a 5-10 membered aromatic mono or bicyclic ring containing up to 5 heteroatoms independently selected from nitrogen, oxygen or sulphur, linked via ring carbon atoms or ring nitrogen atoms where a bond from a nitrogen is allowed, for example no bond is possible to the nitrogen of a pyridine ring, but a bond is possible through the 1-nitrogen of a pyrazole ring. In another embodiment the term “heteroaryl” refers to a 5 or 6 membered aromatic monocyclic ring containing up to 4 heteroatoms independently selected from nitrogen, oxygen or sulphur, linked via ring carbon atoms or ring nitrogen atoms where a bond from a nitrogen is allowed, for example no bond is possible to the nitrogen of a pyridine ring, but a bond is possible through the 1-nitrogen of a pyrazole ring. Examples of 5- or 6-membered heteroaryl rings include pyrrole, furan, imidazole, triazole, tetrazole, pyrazine, pyrazole, pyrimidine, pyridazine, pyridine, pyrrole, isoxazole, oxazole, 1,2,4 oxadiazole, isothiazole, thiazole, thiadiazole, 1,2,4-triazole and thiophene. Examples of 5/6 and 6/6 bicyclic ring systems include benzofuran, benzimidazole, benzthiophene, benzthiazole, benzisothiazole, benzoxazole, benzisoxazole, 1,3-benzodioxole, indole, pyridoimidazole, pyrimidoimidazole, quinoline, isoquinoline, quinoxaline, quinazoline, phthalazine, cinnoline and naphthyridine. This definition further comprises sulphur-containing rings wherein the sulphur atom has been oxidised to an S(O) or S(O<sub>2</sub>) group.

Unless stated otherwise, the term “heterocyclyl” refers to a 4-10 membered saturated or partially saturated mono or bicyclic ring containing up to 5 heteroatoms

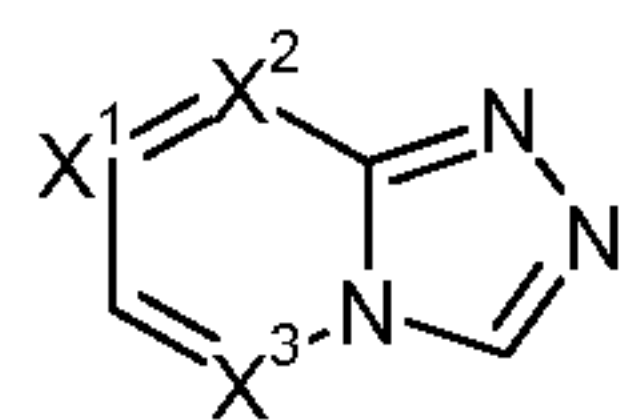


selected from nitrogen, oxygen or sulphur linked via ring carbon atoms or ring nitrogen atoms. Examples of 'heterocyclyl' include tetrahydrofuranyl, 2,3-dihydro-4H-pyranyl, tetrahydro-2H-pyranyl, pyrrolinyl, pyrrolidinyl, 1,3-thiazolidine, morpholinyl, oxetanyl, piperidinyl, piperazinyl, dihydropyridinyl, dihydropyrimidinyl and azepane. Particular  
 5 examples of 'heterocyclyl' include pyrrolinyl, pyrrolidinyl, morpholinyl, piperidinyl, piperazinyl, dihydropyridinyl and dihydropyrimidinyl. This definition further comprises sulphur-containing rings wherein the sulphur atom has been oxidised to an S(O) or S(O<sub>2</sub>) group.

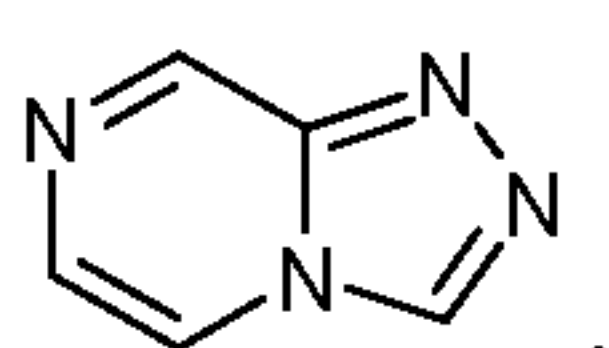
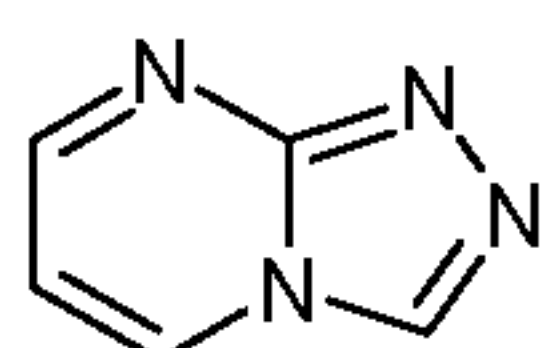
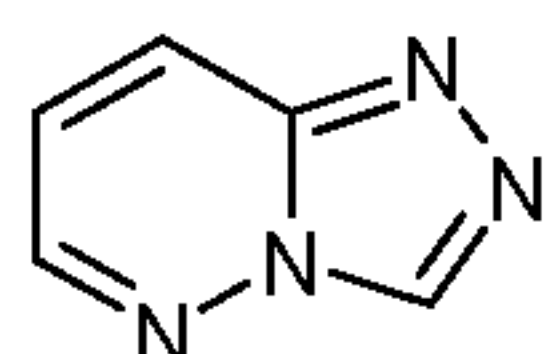
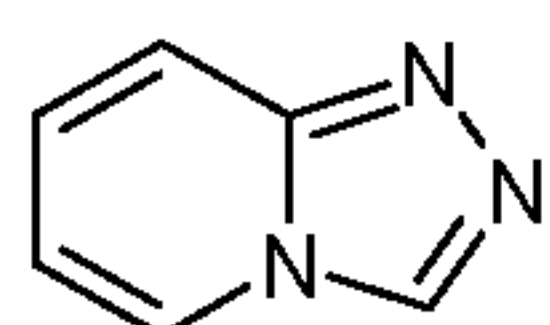
The term "carbocyclyl" or carbocyclic ring refers to a totally saturated or partially  
 10 saturated mono, bicyclic 3-10 membered carbon ring. Examples of carbocyclic rings are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, bicyclo[4,2,0]octane or 2,3-dihydroindene.

Particular novel compounds of the invention include, for example, compounds of Formula (I), or pharmaceutically-acceptable salts thereof, wherein, unless otherwise stated,  
 15 each of R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup>, A, J, K, L<sup>1</sup>, L<sup>2</sup> and m have any of the meanings defined hereinbefore or in paragraphs (1) to (56) hereinafter:-

- (1) X<sup>1</sup> and X<sup>2</sup> and X<sup>3</sup> are all -C(H)-;
- (2) X<sup>1</sup> is -C(R<sup>1</sup>)-, X<sup>2</sup> is -C(R<sup>2</sup>)- and X<sup>3</sup> is -C(R<sup>3</sup>)-;
- (3) The ring



is selected from one of the following



;

- (4) X<sup>1</sup> is -C(R<sup>1</sup>)-, X<sup>2</sup> is -C(R<sup>2</sup>)- and X<sup>3</sup> is -N-;
- (5) X<sup>1</sup> and X<sup>2</sup> are both C(H) and X<sup>3</sup> is -N-;
- (6) Ring A is selected from pyrrolidinyl, , piperidinyl, 1,2-dihydropyridyl, 1,2,5,6-  
 25 tetrahydropyridyl, morpholinyl, thiomorpholinyl, oxazepanyl, thiazepanyl, azepanyl, 1,2,5,6-1H-tetrahydroazepinyl, piperazinyl, diazepanyl, tetrahydroimidazolyl, octahydro-1H-indolyl, octahydro-2H-isoindolyl,



azabicyclo[2.2.1]heptanyl, azabicyclo[3.3.0]octanyl, azabicyclo[3.2.1]octanyl, triazaspirodecanyl, octahydropyrido[1,2-a]pyrazinyl, hexahydropyrrolo[3,4-c]pyrrolyl, diazabicyclo[3.2.1]octanyl and diazabicycloheptanyl;

- (7) In another embodiment Ring A is selected from tetrahydrofuranyl, tetrahydropyranyl, and 5,6-dihydro-2H-pyranyl;
- (8) Ring A is selected from piperidinyl, pyrrolidinyl, piperazinyl and diazepanyl;
- (9) Ring A is selected from piperidinyl, piperazinyl, diazepanyl, 1,3,8-triazaspiro[4.5]decan-4-onyl, 1,3,4,6,7,8,9,9a-octahydropyrido[1,2-a]pyrazinyl, ,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrolyl, 3,8-diazabicyclo[3.2.1]octanyl and 2,5-diazabicyclo[2.2.1]heptanyl.
- (10) Ring A is selected from piperidinyl, piperazinyl, 3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrolyl, and diazepanyl;
- (11) Ring A is selected from piperazinyl and 3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrolyl;
- (12)  $R^1$  is  $C_{1-4}$ alkyl and  $R^2$  is  $C_{1-4}$ alkyl;
- (13)  $R^1$  is hydrogen and  $R^2$  is  $C_{1-4}$ alkyl;
- (14)  $R^1$  is  $C_{1-4}$ alkyl and  $R^2$  is hydrogen;
- (15)  $R^1$  is selected from methyl and ethyl;
- (16)  $R^1$  is selected from hydrogen and methyl;
- (17)  $R^2$  is selected from hydrogen and methyl;
- (18)  $R^3$  is selected from hydrogen and methyl;
- (19)  $R^3$  is hydrogen;
- (20)  $R^4$  is selected from halo,  $C_{1-6}$ alkyl optionally substituted by up to 5 halo substituents,  $C_{1-6}$ alkylS(O) $n$ - where in  $n$  is an integer from 0 to 2 and amino;
- (21)  $R^4$  is selected from halo,  $C_{1-4}$ alkyl optionally substituted by up to 5 halo substituents,  $C_{1-4}$ alkylthio and amino;
- (22)  $R^4$  is selected from chloro, difluoromethyl, trifluoromethyl, 1,1,2,2-tetrafluoroethyl, methylthio or amino;
- (23)  $R^5$  is the group  $-L^1-J-L^2-K$ ;
- (24)  $R^5$  is the group  $-L^1-K$ ;
- (25)  $R^5$  is the group  $-L^1-J-K$ ;
- (26)  $R^5$  is the group  $-K$ ;



- (27)  $R^5$  is the group  $-L^1-L^2-K$ ;
- (28)  $L^1$  and  $L^2$  are independently selected from a direct bond,  $C_{1-6}$ alkylene wherein an alkyl chain within  $L^1$  and  $L^2$  can optionally be substituted with up to 3 groups selected from  $R^7$  and wherein  $L^1$  and  $L^2$  can also be selected from one of the following groups or an alkyl chain into which is inserted one of the following groups, said groups independently selected from:  $-O-$ ,  $-C(O)-$ ,  $-C(O)-O-$ ,  $-O-C(O)-$ ,  $-N(R^6)-$ ,  $-N(R^6)-C(O)-$ ;  $-C(O)-N(R^6)-$ ,  $-N(R^6)-C(O)-O-$ ,  $-O-C(O)-N(R^6)-$ ,  $-C(O)-N(R^6)-O-$ ;  $-O-N(R^6)-C(O)-$ ,  $-N(R^6)-C(O)-N(R^6)-$ ,  $-S(O)_{0-2}-$ ,  $-O-S(O_2)-$ ,  $S-(O_2)-O-$ ,  $-N(R^6)-S(O)_2-$  and  $-S(O)_2-N(R^6)-$ ;
- (29)  $L^1$  and  $L^2$  are independently selected from a direct bond,  $C_{1-6}$ alkylene wherein an alkyl chain within  $L^1$  and  $L^2$  can optionally be substituted with up to 3 groups selected from  $R^7$  and wherein  $L^1$  and  $L^2$  can also be selected from one of the following groups or an alkyl chain into which is inserted one of the following groups, said groups independently selected from:  $-O-$ ,  $-C(O)-$  and  $-S(O)_{0-2}-$ ;
- (30)  $L^1$  and  $L^2$  are independently selected from a direct bond,  $C_{1-4}$ alkylene,  $-O-$ ,  $-C(O)-$ ,  $-OC(O)-$ ,  $-C(O)O-$ ,  $-N(R^6)-$ ,  $-N(R^6)C(O)-$ ,  $-C(O)N(R^6)-$ ,  $-N(R^6)C(O)O-$ ,  $-S(O)_n-$  wherein  $n$  is an integer from 0 to 2,  $-OS(O)_2-$ ,  $-S(O)_2N(R^5)-$  and  $-N(R^5)S(O)_2-$ ;
- (31)  $L^1$  and  $L^2$  are independently selected from a direct bond,  $C_{1-4}$ alkylene,  $-O-$ ,  $-C(O)-$ ,  $-C(O)O-$ ,  $-N(R^6)-$ ,  $-N(R^6)C(O)-$ ,  $-C(O)N(R^6)-$ ,  $-N(R^6)C(O)O-$ ,  $-S-$ ,  $-S(O)_2-$ ,  $-OS(O)_2-$ ,  $-S(O)_2N(R^6)-$  and  $-N(R^6)S(O)_2-$ ;
- (32)  $L^1$  and  $L^2$  are independently selected from a direct bond,  $C_{1-2}$ alkylene,  $-O-$ ,  $-S(O)_2N(R^6)-$  and  $-N(R^6)S(O)_2-$ ;
- (33)  $L^1$  is independently selected from a direct bond,  $C_{1-2}$ alkylene,  $-O-$ ,  $-S(O)_2N(R^6)-$  and  $-N(R^6)S(O)_2-$  and  $L^2$  is a direct bond;
- (34)  $L^1$  is selected from a direct bond,  $C_{1-4}$ alkylene,  $-C(O)-$ ,  $-C(O)O-$ ,  $-C(O)N(R^6)-$ ,  $-S(O)_2-$  and  $-S(O)_2N(R^6)-$ ;
- (35)  $L^2$  is selected from a direct bond,  $-O-$ ,  $-C(O)O-$ ,  $-N(R^6)-$ ,  $-N(R^6)C(O)-$ ,  $-C(O)N(R^6)-$ ,  $-N(R^6)C(O)O-$ ,  $-S-$ ,  $-S(O)_2-$ ,  $-OS(O)_2-$ ,  $-N(R^6)S(O)_2-$ ;
- (36)  $L^2$  is a direct bond;
- (37)  $J$  is selected from a direct bond, aryl and heteroaryl ring wherein  $J$  is optionally substituted by up to five groups selected from  $R^8$ ;
- (38)  $J$  is selected from a direct bond, phenyl, imidazolyl and pyridyl;



- (39) J is a direct bond;
- (40) K is selected from aryl and heteroaryl ring wherein K is optionally substituted by up to five groups selected from R<sup>8</sup>;
- (41) K is selected from C<sub>1-6</sub>alkyl, C<sub>2-6</sub>ethenyl, cyclohexyl, phenyl, naphthyl, , furanyl, pyrrolidinyl, pyrrolyl, morpholinyl, piperaziyl, thienyl, thiazolyl, thiadiazolyl, pyrazolyl, piperidinyl, pyridyl, 2,3-dihydropyridyl, pyrazinyl, pyrimidinyl, quinolinyl, quinoxalinyl, benzothiophenyl, 1-benzofuranyl, 2,3-dihydro-1-benzofuranyl, 1,2,3,4-tetrahydroquinolinyl, 1,4-dihydro-2H-3,1-benzoxazinyl, 1,3-benzoxazolyl, 2,3-dihydro-1,4-benzodioxinyl, 1,3-benzodioxolyl, 2,3-dihydro-1,4-benzodioxinyl, 1,3-benzothiazolyl and benzimidazolyl;
- (42) K is selected from methyl, ethyl, propyl, butyl, ethenyl, prop-2-enyl, cyclohexyl, phenyl, naphthyl, , furanyl, pyrrolidinyl, pyrrolyl, morpholinyl, piperazinyl, thienyl, thiazolyl, thiadiazolyl, pyrazolyl, piperidinyl, pyridyl, 2,3-dihydropyridyl, pyrazinyl, pyrimidinyl, quinolinyl, quinoxalinyl, benzothiophenyl, 1-benzofuranyl, 2,3-dihydro-1-benzofuranyl, 1,2,3,4-tetrahydroquinolinyl, 1,4-dihydro-2H-3,1-benzoxazinyl, 1,3-benzoxazolyl, 2,3-dihydro-1,4-benzodioxinyl, 1,3-benzodioxolyl, 2,3-dihydro-1,4-benzodioxinyl, 1,3-benzothiazolyl and benzimidazolyl;
- (43) K is selected from phenyl, naphthyl, , furanyl, pyrrolyl, , thienyl, thiazolyl, thiadiazolyl, pyrazolyl, piperidinyl, pyridyl, pyrazinyl, pyrimidinyl, quinolinyl, quinoxalinyl, benzothiophenyl, 1-benzofuranyl, 1,2,3,4-tetrahydroquinolinyl, 1,4-dihydro-2H-3,1-benzoxazinyl, 1,3-benzoxazolyl, 2,3-dihydro-1,4-benzodioxinyl, 1,3-benzodioxolyl, 2,3-dihydro-1,4-benzodioxinyl, 1,3-benzothiazolyl and benzimidazolyl;
- (44) R<sup>6</sup> is selected from hydrogen and C<sub>1-4</sub>alkyl;
- (45) R<sup>6</sup> is selected from hydrogen, methyl;
- (46) R<sup>7</sup> is selected from C<sub>1-4</sub>alkyl, hydroxyC<sub>1-4</sub>alkyl and phenyl;
- (47) R<sup>7</sup> is selected from phenyl;
- (48) R<sup>8</sup> is selected from oxo, cyano, halo, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy, C<sub>1-6</sub>alkoxycarbonyl, C<sub>1-6</sub>alkyl-S(O)<sub>n</sub>— wherein n is an integer from 0 to 2, C<sub>1-6</sub>alkylsulphonyloxy, carbamoyl, aminosulphonyl, N-C<sub>1-4</sub>alkylaminosulphonyl, N,N-di-C<sub>1-4</sub>alkylaminosulphonyl, N-C<sub>1-4</sub>alkylaminocarbonyl, N,N-di-C<sub>1-4</sub>alkylaminocarbonyl, aryl, carbocyclyl, heterocyclyl and heteroaryl



wherein an alkyl chain or ring in  $R^8$  is optionally substituted by up to five groups selected from halo, carboxy,  $C_{1-4}$ alkoxy, N,N-di- $C_{1-4}$ alkylamino, carbamoyl, N- $C_{1-4}$ alkylaminocarbonyl, N,N-di- $C_{1-4}$ alkylaminocarbonyl and oxo and an N,N-di- $C_{1-4}$ alkylamino group within  $R^8$  is optionally cyclized to form a ring;

- 5 (49)  $R^8$  is selected from  $C_{1-6}$ alkyl,  $C_{1-6}$ alkenyl,  $C_{1-6}$ alkynyl,  $C_{1-6}$ alkoxy,  $C_{1-6}$ alkoxycarbonyl, hydroxy, carbamoyl, cyano, halo, nitro, amino, N- $C_{1-4}$ alkylamino, N,N-di- $C_{1-4}$ alkylamino and oxo wherein an alkyl, chain in  $R^8$  is optionally substituted by up to 5 halo groups;
- 10 (50)  $R^8$  is selected from  $C_{1-6}$ alkyl,  $C_{1-6}$ alkenyl,  $C_{1-6}$ alkynyl,  $C_{1-6}$ alkoxy,  $C_{1-6}$ alkoxycarbonyl, hydroxy, carbamoyl, cyano, halo, nitro, amino, N,N-di- $C_{1-4}$ alkylamino and oxo wherein an alkyl, chain in  $R^8$  is optionally substituted by up to 5 halo groups;
- (51)  $R^8$  is selected from methyl, propyl, isopropyl, 2-methylpropyl, t-butyl, ethynyl, trifluoromethyl, methoxy, ethoxy, butoxy, difluoromethoxy, trifluoromethoxy, ethoxycarbonyl, hydroxy, carbamoyl, cyano, chloro, bromo, fluoro, amino, dimethylamino; diethylamino and oxo;
- 15 (52) m is an integer from 0 to 3;
- (53) m is 1;
- (54) m is 2;
- 20 (55) m is 3;
- (56) m is 4;

Particular novel compounds of the invention include any one of the following:

- 6-[4-(4-nitrophenyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine
- 6-[4-[(3-bromophenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine
- 25 6-[4-(naphthalen-1-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine
- 6-[4-[(3-chlorophenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine
- 30 6-[4-[3-chloro-5-(trifluoromethyl)pyridin-2-yl]-1,4-diazepan-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine
- 6-(4-phenethylpiperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine



6-[4-(1-benzothiophen-3-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

3-(trifluoromethyl)-6-[4-[[3-(trifluoromethyl)phenyl]methyl]piperazin-1-yl]-[1,2,4]triazolo[4,3-a]pyridine

5 6-[4-(3,5-dichloropyridin-4-yl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

4-[[5-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-2-yl]methyl]benzonitrile

10 3-(trifluoromethyl)-6-[4-[[3-(trifluoromethyl)phenyl]methyl]-1,4-diazepan-1-yl]-[1,2,4]triazolo[4,3-b]pyridazine

4-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]-1,4-diazepan-1-yl]methyl]benzonitrile

6-[4-[(4-chlorophenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

15 3-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]-1,4-diazepan-1-yl]methyl]benzonitrile

6-[4-(thiophen-2-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

20 3-(trifluoromethyl)-6-[4-[[3-(trifluoromethyl)phenyl]methyl]piperazin-1-yl]-[1,2,4]triazolo[4,3-b]pyridazine

6-[4-[(3-chlorophenyl)methyl]-1,4-diazepan-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

6-[4-[(2-chlorophenyl)methyl]-1,4-diazepan-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

25 6-[4-(1H-indol-6-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

6-[4-[(2,2-difluoro-1,3-benzodioxol-4-yl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

30 6-[4-[(2-chlorophenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

5-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]isoquinoline



6-[4-[(4-nitrophenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

6-[4-[(4-fluorophenyl)methyl]-1,4-diazepan-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

5 6-[4-(2,6-dimethylphenyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

6-[4-[(4-chlorophenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridine

6-[4-[(3-fluorophenyl)methyl]-1,4-diazepan-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine  
10

3-[[5-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-2-yl]methyl]benzonitrile

6-[4-[(4-chlorophenyl)methyl]-1,4-diazepan-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

15 6-[4-[(3-fluorophenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

6-[4-[(3-methylphenyl)methyl]-1,4-diazepan-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

6-[4-[(2-fluorophenyl)methyl]-1,4-diazepan-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine  
20

6-[4-(1H-indol-3-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

6-[4-[(4-methylsulfonylphenyl)methyl]-1,4-diazepan-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

25 3-(trifluoromethyl)-6-[4-[[2-(trifluoromethyl)phenyl]methyl]-1,4-diazepan-1-yl]-[1,2,4]triazolo[4,3-b]pyridazine

6-[4-(3-methylphenyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

6-[4-[(4-methylsulfonylphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

30 6-[4-[[3-(difluoromethoxy)phenyl]methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine



6-[4-[(4,5-dimethylfuran-2-yl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-  
[1,2,4]triazolo[4,3-b]pyridazine

6-[4-[phenyl-[4-(trifluoromethyl)phenyl]methyl]piperazin-1-yl]-3-(trifluoromethyl)-  
[1,2,4]triazolo[4,3-b]pyridazine

5 3-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-  
yl]methyl]benzonitrile

3-(trifluoromethyl)-6-[4-[[2-(trifluoromethyl)phenyl]methyl]piperazin-1-yl]-  
[1,2,4]triazolo[4,3-b]pyridazine

6-[4-[(2-fluorophenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-  
10 b]pyridazine

4-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-  
yl]methyl]benzonitrile

6-[4-[(4-methoxyphenyl)-phenylmethyl]piperazin-1-yl]-3-(trifluoromethyl)-  
[1,2,4]triazolo[4,3-b]pyridazine

15 6-[4-[(3-fluorophenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-  
a]pyridine

3-(trifluoromethyl)-6-[4-[[3-(trifluoromethylsulfanyl)phenyl]methyl]piperazin-1-yl]-  
[1,2,4]triazolo[4,3-b]pyridazine

6-[4-[(4-fluorophenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-  
20 b]pyridazine

6-[4-[4,4-bis(4-fluorophenyl)butyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-  
b]pyridazine

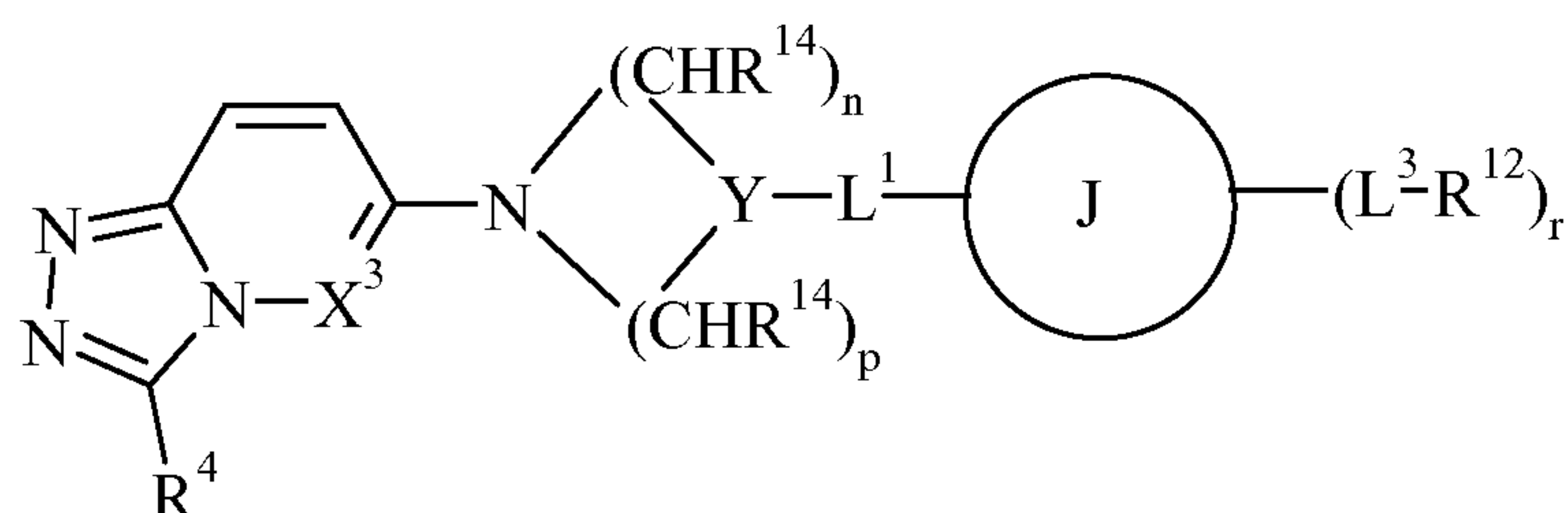
6-[2-[(3-chlorophenyl)methyl]-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-5-yl]-3-  
(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

25 or pharmaceutically acceptable salts thereof.

According to a fourth aspect of the present invention there is provided a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, for use as a medicament:



20



(Ic)

wherein

$X^3$  represents CH or N;

5  $R^4$  represents halo $C_{1-4}$ alkyl;

$Y$  represents CH, COH or N;

$R^{14}$ , identically or differently on each occurrence, represents hydrogen or methyl;

$n$  and  $p$  independently represent 1 or 2;

10  $L^1$  represents a direct bond,  $-(CR^9R^{10})_t-$ ,  $-(CR^9R^{10})_v-O-(CR^9R^{10})_v-$ ,  $-N(R^{11})-(CH_2)_q-$ ,  $-S-$ ,  $-S(O)-$  or  $-S(O)_2-$ ;

$R^9$  and  $R^{10}$ , identically or differently on each occurrence, represent hydrogen or methyl;

$q$ , identically or differently on each occurrence, represents 0, 1, 2 or 3;

$t$  represents 1, 2 or 3;

$v$ , identically or differently on each occurrence, represents 0, 1 or 2;

15  $J$  represents:

aryl;

a totally saturated monocyclic 3 to 6 membered carbocyclic ring;

a monocyclic 4, 5, 6 or 7 membered heterocyclic ring which comprises 1, 2, 3 or 4 heteroatoms independently selected from O, N or S;

20 a monocyclic 5 or 6 membered heteroaryl ring which comprises 1, 2, 3 or 4 heteroatoms independently selected from O, N or S; or

a bicyclic 9 or 10 membered heteroaryl ring system which comprises 1, 2, 3, 4 or 5 heteroatoms independently selected from O, N or S;

25  $L^3$  represents a direct bond,  $-(CR^9R^{10})_t-$ ,  $-C(O)N(R^{11})-(CH_2)_q-$ ,  $-C(O)N(R^{11})-(CH_2)_q-S(O)_2-$ ,  $-NR^{11}C(O)-(CH_2)_q-$ ,  $-C(O)-(CH_2)_q-$ ,  $-O-(CH_2)_q-$ ,  $-O-(CH_2)_q-NR^{11}-(CH_2)_q-$ ,  $-O-(CH_2)_q-C(O)NR^{11}-(CH_2)_q-$ ,  $-S-$ ,  $-S(O)-$  or  $-S(O)_2-$ ;

$R^{11}$  represents hydrogen or methyl;

$R^{12}$  represents:



halo, C<sub>1-6</sub>alkyl, C<sub>2-6</sub>alkenyl, C<sub>2-6</sub>alkynyl, carboxy, C<sub>1-6</sub>alkoxy, cyano, oxo, fluoroC<sub>1-6</sub>alkyl, hydroxy, amino, N-C<sub>1-4</sub>alkylamino or N,N-di-C<sub>1-4</sub>alkylamino; aryl, wherein the aryl ring is optionally substituted with 1, 2 or 3 substituents selected from R<sup>13</sup>;

a monocyclic 5 or 6 membered heteroaryl ring which comprises 1, 2, 3 or 4 heteroatoms independently selected from O, N or S and wherein the heteroaryl ring is optionally substituted with 1, 2 or 3 substituents selected from R<sup>13</sup>; or

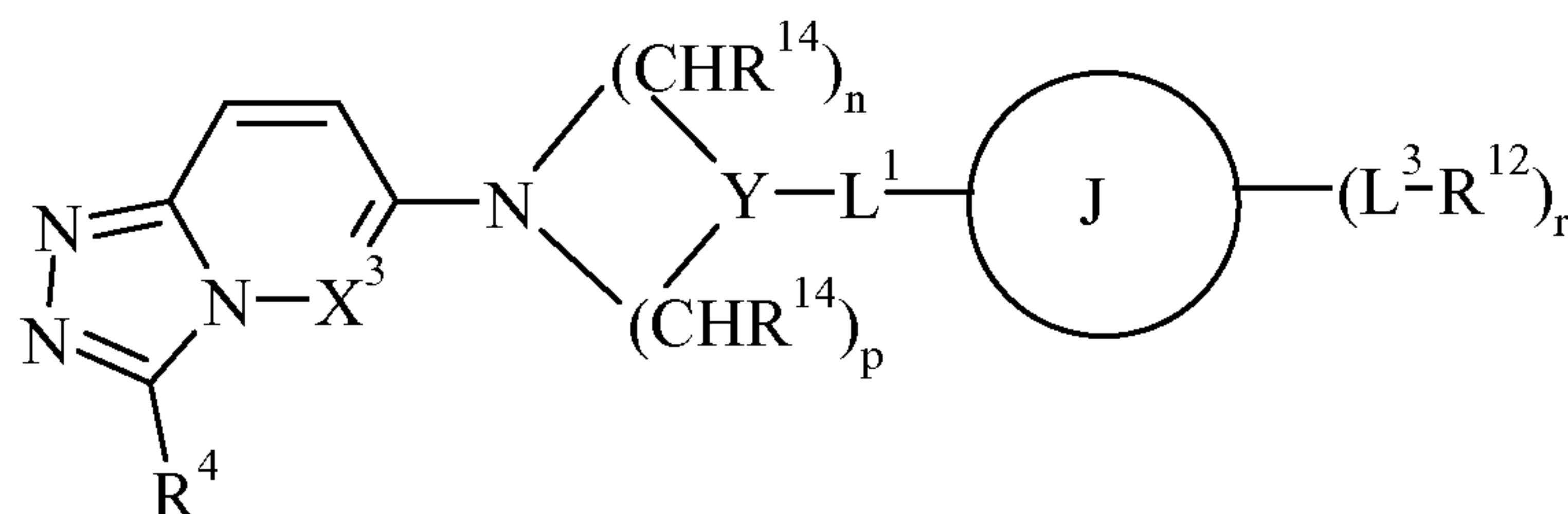
a monocyclic 4, 5, 6 or 7 membered heterocyclic ring which comprises 1, 2, 3 or 4 heteroatoms independently selected from O, N or S and wherein the heterocyclic ring is optionally substituted with 1, 2 or 3 substituents selected from R<sup>13</sup>;

R<sup>13</sup> represents amino, halo, C<sub>1-6</sub>alkyl, C<sub>2-6</sub>alkenyl, C<sub>2-6</sub>alkynyl, C<sub>1-6</sub>alkoxy, C<sub>2-6</sub>alkanoyl, C<sub>1-6</sub>alkoxyC<sub>1-6</sub>alkyl, carboxy, cyano, oxo, fluoroC<sub>1-6</sub>alkyl, hydroxy, hydroxyC<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkylsulphanyl, C<sub>1-6</sub>alkylsulphinyl, C<sub>1-6</sub>alkylsulphonyl, N-C<sub>1-4</sub>alkylamino, N,N-di-C<sub>1-4</sub>alkylamino or -C(O)NR<sup>14</sup>R<sup>15</sup> wherein R<sup>14</sup> and R<sup>15</sup>

independently represent hydrogen or methyl; and

r represents 0, 1, 2 or 3.

According to a fifth aspect of the present invention there is provided a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, for use in the treatment of prostate cancer:



(Ic)

wherein

X<sup>3</sup> represents CH or N;

R<sup>4</sup> represents haloC<sub>1-4</sub>alkyl;

Y represents CH, COH or N;

R<sup>14</sup>, identically or differently on each occurrence, represents hydrogen or methyl;

n and p independently represent 1 or 2;

L<sup>1</sup> represents a direct bond, -(CR<sup>9</sup>R<sup>10</sup>)<sub>t</sub>-, -(CR<sup>9</sup>R<sup>10</sup>)<sub>v</sub>-O-(CR<sup>9</sup>R<sup>10</sup>)<sub>v</sub>-, -N(R<sup>11</sup>)-(CH<sub>2</sub>)<sub>q</sub>-, -S-,



-S(O)- or -S(O)<sub>2</sub>-;

R<sup>9</sup> and R<sup>10</sup>, identically or differently on each occurrence, represent hydrogen or methyl;

q, identically or differently on each occurrence, represents 0, 1, 2 or 3;

t represents 1, 2 or 3;

5 v, identically or differently on each occurrence, represents 0, 1 or 2;

J represents:

aryl;

a totally saturated monocyclic 3 to 6 membered carbocyclic ring;

a monocyclic 4, 5, 6 or 7 membered heterocyclic ring which comprises 1, 2, 3 or 4

10 heteroatoms independently selected from O, N or S;

a monocyclic 5 or 6 membered heteroaryl ring comprising 1, 2, 3 or 4 heteroatoms independently selected from O, N or S; or

a bicyclic 9 or 10 membered heteroaryl ring system comprising 1, 2, 3, 4 or 5 heteroatoms independently selected from O, N or S;

15 L<sup>3</sup> represents a direct bond, -(CR<sup>9</sup>R<sup>10</sup>)<sub>t</sub>-, -C(O)N(R<sup>11</sup>)-(CH<sub>2</sub>)<sub>q</sub>-, -C(O)N(R<sup>11</sup>)-(CH<sub>2</sub>)<sub>q</sub>-S(O)<sub>2</sub>-, -NR<sup>11</sup>C(O)-(CH<sub>2</sub>)<sub>q</sub>-, -C(O)-(CH<sub>2</sub>)<sub>q</sub>-, -O-(CH<sub>2</sub>)<sub>q</sub>-, -O-(CH<sub>2</sub>)<sub>q</sub>-NR<sup>11</sup>-(CH<sub>2</sub>)<sub>q</sub>-, -O-(CH<sub>2</sub>)<sub>q</sub>-C(O)NR<sup>11</sup>-(CH<sub>2</sub>)<sub>q</sub>-, -S-, -S(O)- or -S(O)<sub>2</sub>-;

R<sup>11</sup> represents hydrogen or methyl;

R<sup>12</sup> represents:

20 halo, C<sub>1-6</sub>alkyl, C<sub>2-6</sub>alkenyl, C<sub>2-6</sub>alkynyl, carboxy, C<sub>1-6</sub>alkoxy, cyano, oxo, fluoroC<sub>1-6</sub>alkyl, hydroxy, amino, N-C<sub>1-4</sub>alkylamino or N,N-di-C<sub>1-4</sub>alkylamino;

aryl, wherein the aryl ring is optionally substituted with 1, 2 or 3 substituents selected from R<sup>13</sup>;

a monocyclic 5 or 6 membered heteroaryl ring which comprises 1, 2, 3 or 4

25 heteroatoms independently selected from O, N or S and wherein the heteroaryl ring is optionally substituted with 1, 2 or 3 substituents selected from R<sup>13</sup>; or

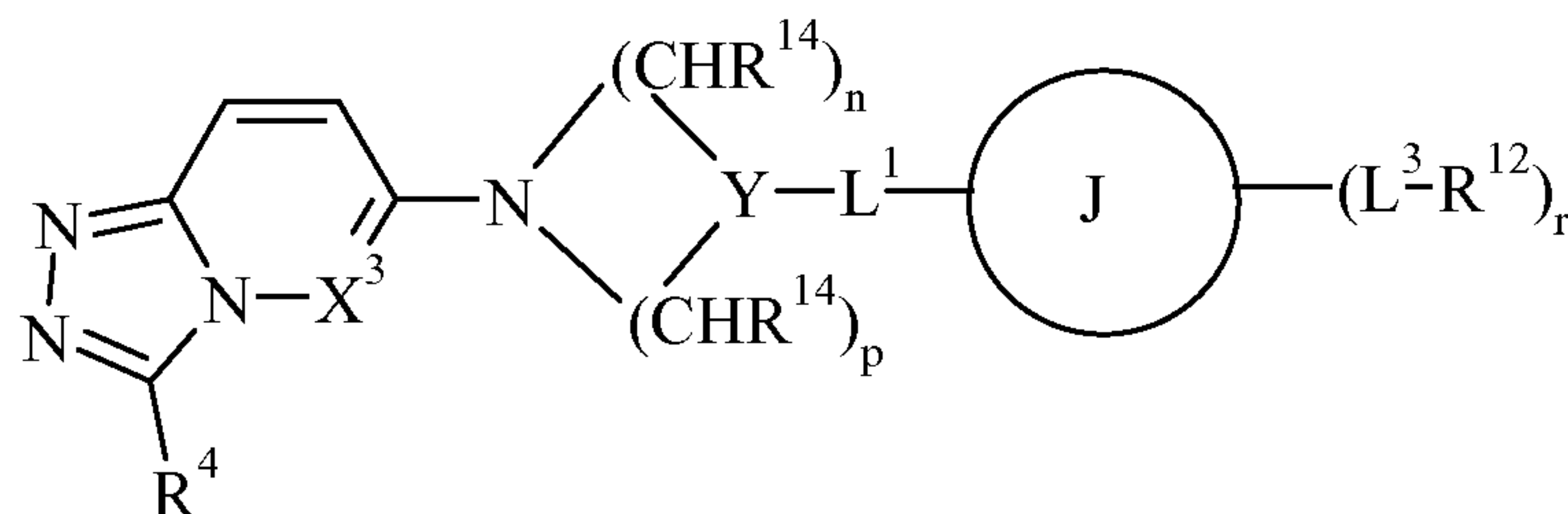
a monocyclic 4, 5, 6 or 7 membered heterocyclic ring which comprises 1, 2, 3 or 4 heteroatoms independently selected from O, N or S and wherein the heterocyclic ring is optionally substituted with 1, 2 or 3 substituents selected from R<sup>13</sup>;

30 R<sup>13</sup> represents amino, halo, C<sub>1-6</sub>alkyl, C<sub>2-6</sub>alkenyl, C<sub>2-6</sub>alkynyl, C<sub>1-6</sub>alkoxy, C<sub>2-6</sub>alkanoyl, C<sub>1-6</sub>alkoxyC<sub>1-6</sub>alkyl, carboxy, cyano, oxo, fluoroC<sub>1-6</sub>alkyl, hydroxy, hydroxyC<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkylsulphanyl, C<sub>1-6</sub>alkylsulphinyl, C<sub>1-6</sub>alkylsulphonyl,



N-C<sub>1-4</sub>alkylamino, N,N-di-C<sub>1-4</sub>alkylamino or -C(O)NR<sup>14</sup>R<sup>15</sup> wherein R<sup>14</sup> and R<sup>15</sup> independently represent hydrogen or methyl; and  
r represents 0, 1, 2 or 3.

According to a sixth aspect of the present invention there is provided a compound  
5 of Formula (Ic), or a pharmaceutically acceptable salt thereof:



(Ic)

wherein

X<sup>3</sup> represents CH or N;

10 R<sup>4</sup> represents haloC<sub>1-4</sub>alkyl;

Y represents CH, COH or N;

R<sup>14</sup>, identically or differently on each occurrence, represents hydrogen or methyl;

n and p independently represent 1 or 2;

15 L<sup>1</sup> represents a direct bond, -(CR<sup>9</sup>R<sup>10</sup>)<sub>t</sub>-, -(CR<sup>9</sup>R<sup>10</sup>)<sub>v</sub>-O-(CR<sup>9</sup>R<sup>10</sup>)<sub>v</sub>-, -N(R<sup>11</sup>)-(CH<sub>2</sub>)<sub>q</sub>-, -S-,  
-S(O)- or -S(O)<sub>2</sub>-;

R<sup>9</sup> and R<sup>10</sup>, identically or differently on each occurrence, represent hydrogen or methyl;

q, identically or differently on each occurrence, represents 0, 1, 2 or 3;

t represents 1, 2 or 3;

v, identically or differently on each occurrence, represents 0, 1 or 2;

20 J represents:

aryl;

a totally saturated monocyclic 3 to 6 membered carbocyclic ring;

furanyl, imidazolyl, isothiazolyl, morpholinyl, oxadiazolyl, oxazolyl, isoxazolyl,

oxetanyl, tetrahydro-2H-pyranyl, pyrazolyl, pyridazinyl, pyridinyl, pyrrolyl or

25 thiadiazolyl; or

a bicyclic 9 membered heteroaryl ring system which comprises 1 or 2 nitrogen

atoms, 1 or 2 oxygen atoms, 1 sulphur atom, or 1 nitrogen atom and 1 sulphur atom;



$L^3$  represents a direct bond,  $-(CR^9R^{10})_t-$ ,  $-C(O)N(R^{11})-(CH_2)_q-$ ,  $-C(O)N(R^{11})-(CH_2)_q-S(O)_2-$ ,  $-NR^{11}C(O)-(CH_2)_q-$ ,  $-C(O)-(CH_2)_q-$ ,  $-O-(CH_2)_q-$ ,  $-O-(CH_2)_q-NR^{11}-(CH_2)_q-$ ,  $-O-(CH_2)_q-C(O)NR^{11}-(CH_2)_q-$ ,  $-S-$ ,  $-S(O)-$  or  $-S(O)_2-$ ;

$R^{11}$  represents hydrogen or methyl;

5  $R^{12}$  represents:

halo,  $C_{1-6}$ alkyl,  $C_{2-6}$ alkenyl,  $C_{2-6}$ alkynyl, carboxy,  $C_{1-6}$ alkoxy, cyano, oxo, fluoro $C_{1-6}$ alkyl, hydroxy, amino,  $N-C_{1-4}$ alkylamino or  $N,N$ -di- $C_{1-4}$ alkylamino; aryl, wherein the aryl ring is optionally substituted with 1, 2 or 3 substituents selected from  $R^{13}$ ;

10 a monocyclic 5 or 6 membered heteroaryl ring which comprises 1, 2, 3 or 4 heteroatoms independently selected from O, N or S and wherein the heteroaryl ring is optionally substituted with 1, 2 or 3 substituents selected from  $R^{13}$ ; or a monocyclic 4, 5, 6 or 7 membered heterocyclic ring which comprises 1, 2, 3 or 4 heteroatoms independently selected from O, N or S and wherein the heterocyclic  
15 ring is optionally substituted with 1, 2 or 3 substituents selected from  $R^{13}$ ;

$R^{13}$  represents amino, halo,  $C_{1-6}$ alkyl,  $C_{2-6}$ alkenyl,  $C_{2-6}$ alkynyl,  $C_{1-6}$ alkoxy,  $C_{2-6}$ alkanoyl,  $C_{1-6}$ alkoxy $C_{1-6}$ alkyl, carboxy, cyano, oxo, fluoro $C_{1-6}$ alkyl, hydroxy, hydroxy $C_{1-6}$ alkyl,  $C_{1-6}$ alkylsulphanyl,  $C_{1-6}$ alkylsulphinyl,  $C_{1-6}$ alkylsulphonyl,  $N-C_{1-4}$ alkylamino,  $N,N$ -di- $C_{1-4}$ alkylamino or  $-C(O)NR^{14}R^{15}$  wherein  $R^{14}$  and  $R^{15}$   
20 independently represent hydrogen or methyl;

$r$  represents 1, 2 or 3 when  $J$  represents aryl;

$r$  represents 0 when  $J$  represents a totally saturated monocyclic 3 to 6 membered carbocyclic ring; and

$r$  represents 0, 1, 2 or 3 when  $J$  represents furanyl, imidazolyl, isothiazolyl, morpholinyl, oxadiazolyl, oxazolyl, isoxazolyl, oxetanyl, tetrahydro-2*H*-pyranyl, pyrazolyl, pyridazinyl, pyridinyl, pyrrolyl, thiadiazolyl, or a bicyclic 9 membered heteroaryl ring system which  
25 comprises 1 or 2 nitrogen atoms, 1 or 2 oxygen atoms, 1 sulphur atom, or 1 nitrogen atom and 1 sulphur atom;

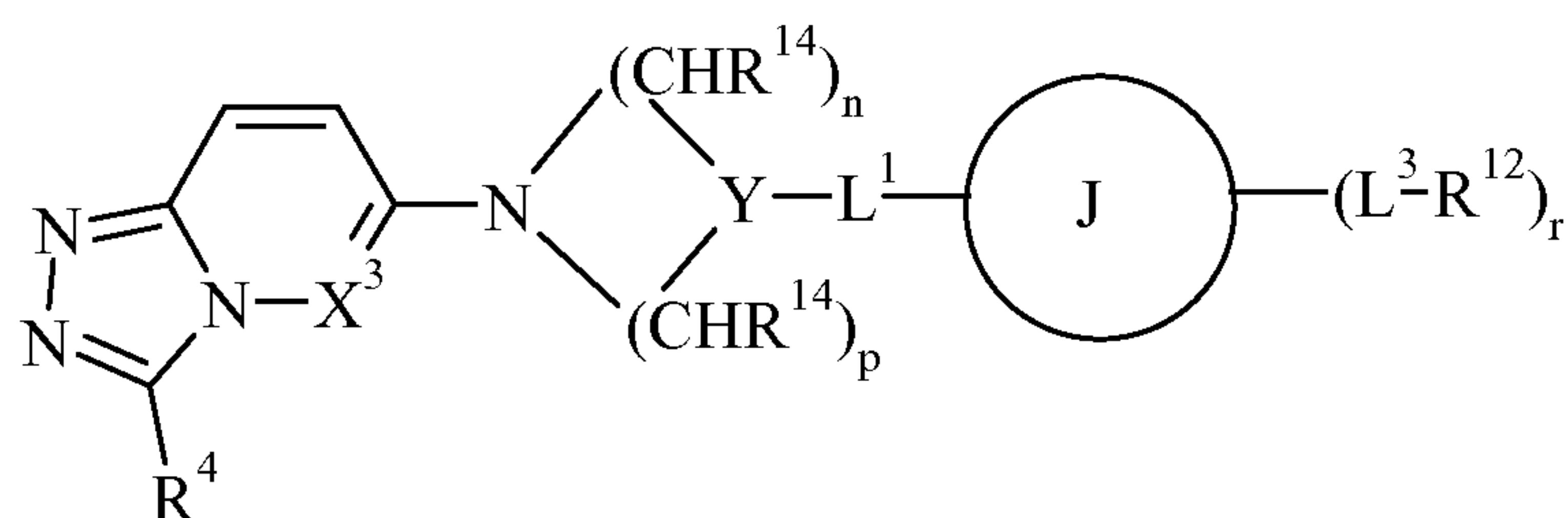
with the proviso that the compound of Formula (Ic) is other than:

30 4-{4-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]piperazin-1-yl}phenol;  
6-[4-(pyridin-3-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazine;



- 6-[4-(2-fluorobenzyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazine;  
 6-[4-(imidazo[1,2-*a*]pyridin-2-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazine;  
 6-[4-(3,4-dimethoxybenzyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazine;  
 5 6-[4-(1*H*-indol-3-yl)piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazine;  
 6-{4-[2-(3,5-dimethoxyphenyl)ethyl]piperidin-1-yl}-3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazine;  
 6-[4-(4-methoxybenzyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazine;  
 10 6-[4-(3-chlorobenzyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazine;  
 6-[4-(4-chlorobenzyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazine;  
 6-[4-(2-methylbenzyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazine;  
 6-[4-(pyridin-4-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazine;  
 15 6-[4-(2,6-dimethylphenyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazine;  
 6-[4-(4-methoxyphenyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazine;  
 6-[4-(3-chlorophenyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazine;  
 20 6-[4-(4-fluorophenyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazine;  
 or  
 6-{4-[(2,6-difluorophenyl)sulfonyl]piperazin-1-yl}-3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazine.

According to one embodiment of the sixth aspect of the present invention there is  
 25 provided a compound of Formula (Ic), or a pharmaceutically acceptable salt thereof:



(Ic)

wherein



X<sup>3</sup> represents CH or N;

R<sup>4</sup> represents difluoromethyl, trifluoromethyl or chloro(difluoro)methyl;

Y represents CH, COH or N;

R<sup>14</sup>, identically or differently on each occurrence, represents hydrogen or methyl;

5 n and p independently represent 1 or 2;

L<sup>1</sup> represents a direct bond, -(CR<sup>9</sup>R<sup>10</sup>)<sub>t</sub>-, -(CR<sup>9</sup>R<sup>10</sup>)<sub>v</sub>-O-(CR<sup>9</sup>R<sup>10</sup>)<sub>v</sub>- or -N(R<sup>11</sup>)-(CH<sub>2</sub>)<sub>q</sub>-;

R<sup>9</sup> and R<sup>10</sup>, identically or differently on each occurrence, represent hydrogen or methyl;

q represents 0, 1, 2 or 3;

t represents 1 or 2;

10 v represents 0, 1 or 2;

J represents:

aryl;

a totally saturated monocyclic 3 to 6 membered carbocyclic ring;

imidazolyl, isothiazolyl, morpholinyl, oxadiazolyl, oxazolyl, isoxazolyl, oxetanyl,

15 tetrahydro-2*H*-pyranyl, pyrazolyl, pyridazinyl, pyridinyl; or

a bicyclic 9 membered heteroaryl ring system comprising 1 or 2 nitrogen atoms or a single sulphur atom;

L<sup>3</sup> represents a direct bond, -(CH<sub>2</sub>)<sub>q</sub>-, -C(O)N(R<sup>11</sup>)-(CH<sub>2</sub>)<sub>q</sub>-, -NR<sup>11</sup>C(O)-(CH<sub>2</sub>)<sub>q</sub>-,

-C(O)-(CH<sub>2</sub>)<sub>q</sub>-, -O-(CH<sub>2</sub>)<sub>q</sub>-, -O-(CH<sub>2</sub>)<sub>q</sub>-NR<sup>11</sup>-, -O-(CH<sub>2</sub>)<sub>q</sub>-C(O)NR<sup>11</sup>-, -S-, -S(O)- or

20 -S(O)<sub>2</sub>-;

R<sup>11</sup> represents hydrogen or methyl;

R<sup>12</sup> represents:

halo, C<sub>1-6</sub>alkyl, C<sub>2-6</sub>alkenyl, C<sub>2-6</sub>alkynyl, carboxy, C<sub>1-6</sub>alkoxy, cyano, oxo, fluoroC<sub>1-6</sub>alkyl, hydroxy, amino, N-C<sub>1-4</sub>alkylamino or N,N-di-C<sub>1-4</sub>alkylamino;

25 a monocyclic 5 or 6 membered heteroaryl ring which comprises 1, 2, 3 or 4

heteroatoms independently selected from O, N or S and wherein the heteroaryl ring is optionally substituted with 1, 2 or 3 substituents selected from R<sup>13</sup>; or

a monocyclic 4, 5, 6 or 7 membered heterocyclic ring which comprises 1, 2, 3 or 4 heteroatoms independently selected from O, N or S and wherein the heterocyclic

30 ring is optionally substituted with 1, 2 or 3 substituents selected from R<sup>13</sup>;

R<sup>13</sup> represents amino, halo, C<sub>1-6</sub>alkyl, C<sub>2-6</sub>alkenyl, C<sub>2-6</sub>alkynyl, C<sub>1-6</sub>alkoxy,

C<sub>2-6</sub>alkanoyl, C<sub>1-6</sub>alkoxyC<sub>1-6</sub>alkyl, carboxy, cyano, oxo, fluoroC<sub>1-6</sub>alkyl, hydroxy,



hydroxyC<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkylsulphanyl, C<sub>1-6</sub>alkylsulphinyl, C<sub>1-6</sub>alkylsulphonyl, N-C<sub>1-4</sub>alkylamino, N,N-di-C<sub>1-4</sub>alkylamino or -C(O)NR<sup>14</sup>R<sup>15</sup> wherein R<sup>14</sup> and R<sup>15</sup> independently represent hydrogen or methyl;

r represents 1, 2 or 3 when J represents aryl;

5 r represents 0 when J represents a totally saturated monocyclic 3 to 6 membered carbocyclic ring; and

r represents 0, 1, 2 or 3 when J represents imidazolyl, isothiazolyl, morpholinyl, oxadiazolyl, oxazolyl, isoxazolyl, oxetanyl, tetrahydro-2*H*-pyranyl, pyrazolyl, pyridazinyl, pyridinyl or a bicyclic 9 membered heteroaryl ring system comprising 1 or 2 nitrogen  
10 atoms or a single sulphur atom;

with the proviso that the compound of Formula (Ic) is other than:

4-{4-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]piperazin-1-yl}phenol;

6-[4-(pyridin-3-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazine;

15 6-[4-(2-fluorobenzyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazine;

6-[4-(imidazo[1,2-*a*]pyridin-2-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazine;

6-[4-(3,4-dimethoxybenzyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazine;

20 6-[4-(1*H*-indol-3-yl)piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazine;

6-{4-[2-(3,5-dimethoxyphenyl)ethyl]piperidin-1-yl}-3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazine;

6-[4-(4-methoxybenzyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazine;

6-[4-(3-chlorobenzyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazine;

25 6-[4-(4-chlorobenzyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazine;

6-[4-(2-methylbenzyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazine;

6-[4-(pyridin-4-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazine;

6-[4-(2,6-dimethylphenyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazine;

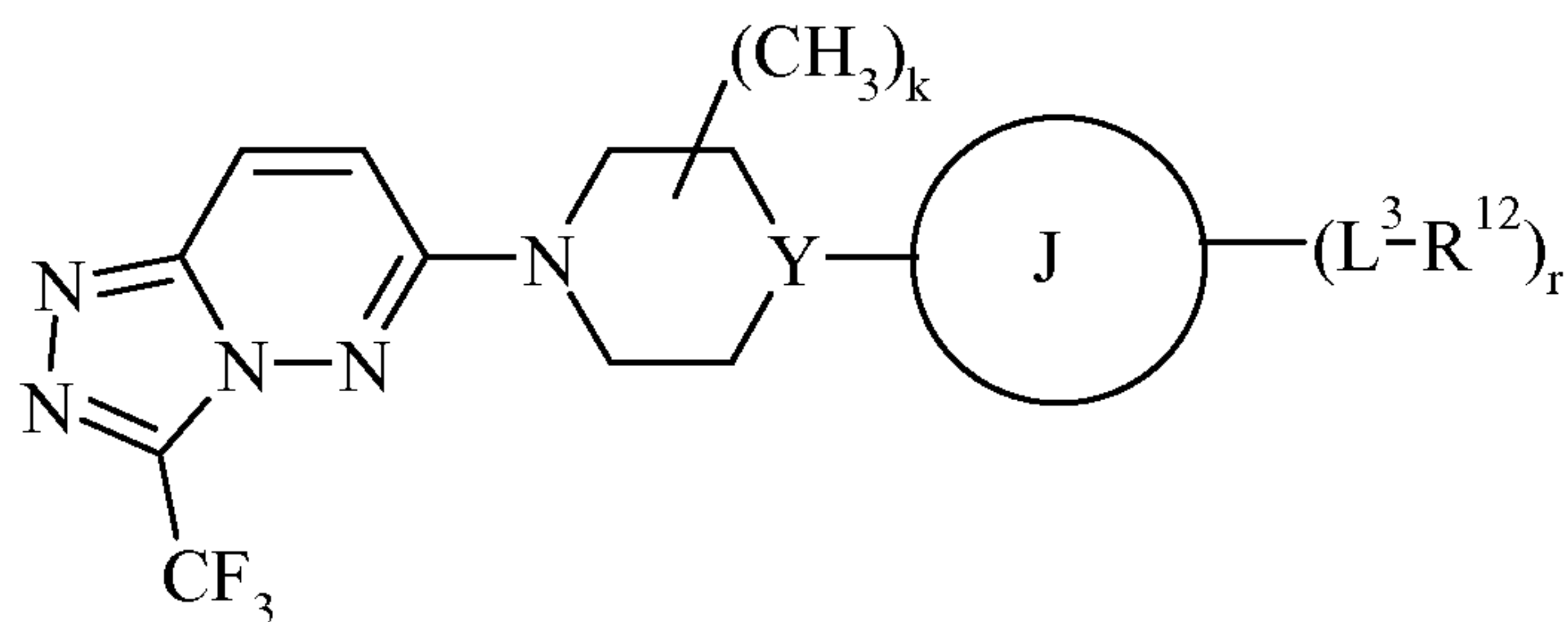
30 *b*]pyridazine;

6-[4-(4-methoxyphenyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazine; or



6-[4-(3-chlorophenyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazine.

According to a further embodiment of the sixth aspect of the present invention there is provided a compound of Formula (If), or a pharmaceutically acceptable salt thereof:



(If)

wherein

Y represents CH, COH or N;

k represents 0, 1 or 2;

10 J represents:

aryl;

a totally saturated monocyclic 3 to 6 membered carbocyclic ring;

furanyl, imidazolyl, isothiazolyl, morpholinyl, oxadiazolyl, oxazolyl, isoxazolyl,

oxetanyl, tetrahydro-2*H*-pyranyl, pyrazolyl, pyridazinyl, pyridinyl, pyrrolyl or

15 thiadiazolyl; or

a bicyclic 9 membered heteroaryl ring system which comprises 1 or 2 nitrogen

atoms, 1 or 2 oxygen atoms, 1 sulphur atom, or 1 nitrogen atom and 1 sulphur atom;

$L^3$  represents a direct bond,  $-(CR^9R^{10})_t-$ ,  $-C(O)N(R^{11})-(CH_2)_q-$ ,  $-C(O)N(R^{11})-(CH_2)_q-S(O)_2-$ ,

$-C(O)-(CH_2)_q-$ ,  $-O-(CH_2)_q-$ ,  $-O-(CH_2)_q-NR^{11}-(CH_2)_q-$ ,  $-O-(CH_2)_q-C(O)NR^{11}-(CH_2)_q-$ ,  $-S-$ ,

20  $-S(O)-$  or  $-S(O)_2-$ ;

$R^9$  and  $R^{10}$ , identically or differently on each occurrence, represent hydrogen or methyl;

q, identically or differently on each occurrence, represents 0, 1, 2 or 3;

t represents 1, 2 or 3;

$R^{11}$  represents hydrogen or methyl;

25  $R^{12}$  represents:

halo,  $C_{1-6}$ alkyl,  $C_{2-6}$ alkenyl,  $C_{2-6}$ alkynyl, carboxy,  $C_{1-6}$ alkoxy, fluoro $C_{1-6}$ alkyl,

hydroxy, amino, N- $C_{1-4}$ alkylamino or N,N-di- $C_{1-4}$ alkylamino;



aryl, wherein the aryl ring is optionally substituted with 1, 2 or 3 substituents selected from R<sup>13</sup>;

a monocyclic 5 or 6 membered heteroaryl ring which comprises 1, 2, 3 or 4 heteroatoms independently selected from O, N or S and wherein the heteroaryl ring is optionally substituted with 1, 2 or 3 substituents selected from R<sup>13</sup>; or

a monocyclic 4, 5, 6 or 7 membered heterocyclic ring which comprises 1, 2, 3 or 4 heteroatoms independently selected from O, N or S and wherein the heterocyclic ring is optionally substituted with 1, 2 or 3 substituents selected from R<sup>13</sup>;

R<sup>13</sup> represents amino, halo, C<sub>1-6</sub>alkyl, C<sub>2-6</sub>alkenyl, C<sub>2-6</sub>alkynyl, C<sub>1-6</sub>alkoxy,

C<sub>2-6</sub>alkanoyl, C<sub>1-6</sub>alkoxyC<sub>1-6</sub>alkyl, carboxy, cyano, oxo, fluoroC<sub>1-6</sub>alkyl, hydroxy, hydroxyC<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkylsulphanyl, C<sub>1-6</sub>alkylsulphinyl, C<sub>1-6</sub>alkylsulphonyl, N-C<sub>1-4</sub>alkylamino, N,N-di-C<sub>1-4</sub>alkylamino or -C(O)NR<sup>14</sup>R<sup>15</sup> wherein R<sup>14</sup> and R<sup>15</sup> independently represent hydrogen or methyl;

r represents 1, 2 or 3 when J represents aryl;

r represents 0 when J represents a totally saturated monocyclic 3 to 6 membered carbocyclic ring; and

r represents 0, 1, 2 or 3 when J represents furanyl, imidazolyl, isothiazolyl, morpholinyl, oxadiazolyl, oxazolyl, isoxazolyl, oxetanyl, tetrahydro-2H-pyran, pyrazolyl, pyridazinyl, pyridinyl, pyrrolyl, thiadiazolyl, or a bicyclic 9 membered heteroaryl ring system which comprises 1 or 2 nitrogen atoms, 1 or 2 oxygen atoms, 1 sulphur atom, or 1 nitrogen atom and 1 sulphur atom;

with the proviso that the compound of Formula (If) is other than:

4-{4-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]piperazin-1-yl}phenol;

6-[4-(1*H*-indol-3-yl)piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazine;

6-[4-(2,6-dimethylphenyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazine;

6-[4-(4-methoxyphenyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazine;

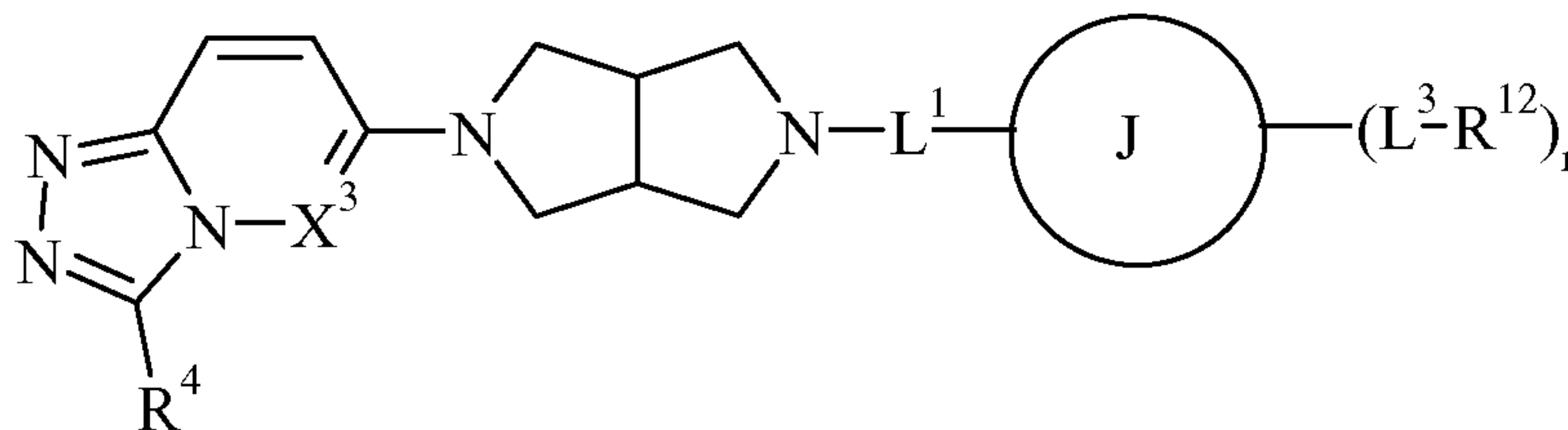
6-[4-(3-chlorophenyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazine;

or

6-[4-(4-fluorophenyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazine.



According to a seventh aspect of the present invention there is provided a compound of Formula (Id), or a pharmaceutically acceptable salt thereof:



(Id)

5 wherein

$X^3$  represents CH or N;

$R^4$  represents haloC<sub>1-4</sub>alkyl;

$L^1$  represents a direct bond,  $-(CR^9R^{10})_t-$ ,  $-(CR^9R^{10})_v-O-(CR^9R^{10})_v-$ ,  $-N(R^{11})-(CH_2)_q-$ ,  $-S-$ ,  $-S(O)-$  or  $-S(O)_2-$ ;

10  $R^9$  and  $R^{10}$ , identically or differently on each occurrence, represent hydrogen or methyl;  
 $q$ , identically or differently on each occurrence, represents 0, 1, 2 or 3;

$t$  represents 1, 2 or 3;

$v$ , identically or differently on each occurrence, represents 0, 1 or 2;

$J$  represents:

15 aryl;

a totally saturated monocyclic 3 to 6 membered carbocyclic ring;

a monocyclic 4, 5, 6 or 7 membered heterocyclic ring which comprises 1, 2, 3 or 4 heteroatoms independently selected from O, N or S;

a monocyclic 5 or 6 membered heteroaryl ring which comprises 1, 2, 3 or 4

20 heteroatoms independently selected from O, N or S; or

a bicyclic 9 or 10 membered heteroaryl ring system which comprises 1, 2, 3, 4 or 5 heteroatoms independently selected from O, N or S;

$L^3$  represents a direct bond,  $-(CR^9R^{10})_t-$ ,  $-C(O)N(R^{11})-(CH_2)_q-$ ,  $-C(O)N(R^{11})-(CH_2)_q-S(O)_2-$ ,  $-NR^{11}C(O)-(CH_2)_q-$ ,  $-C(O)-(CH_2)_q-$ ,  $-O-(CH_2)_q-$ ,  $-O-(CH_2)_q-NR^{11}-(CH_2)_q-$ ,

25  $-O-(CH_2)_q-C(O)NR^{11}-(CH_2)_q-$ ,  $-S-$ ,  $-S(O)-$  or  $-S(O)_2-$ ;

$R^{11}$  represents hydrogen or methyl;

$R^{12}$  represents:



halo, C<sub>1-6</sub>alkyl, C<sub>2-6</sub>alkenyl, C<sub>2-6</sub>alkynyl, carboxy, C<sub>1-6</sub>alkoxy, cyano, oxo, fluoroC<sub>1-6</sub>alkyl, hydroxy, amino, N-C<sub>1-4</sub>alkylamino or N,N-di-C<sub>1-4</sub>alkylamino; aryl, wherein the aryl ring is optionally substituted with 1, 2 or 3 substituents selected from R<sup>13</sup>;

a monocyclic 5 or 6 membered heteroaryl ring which comprises 1, 2, 3 or 4 heteroatoms independently selected from O, N or S and wherein the heteroaryl ring is optionally substituted with 1, 2 or 3 substituents selected from R<sup>13</sup>; or

a monocyclic 4, 5, 6 or 7 membered heterocyclic ring which comprises 1, 2, 3 or 4 heteroatoms independently selected from O, N or S and wherein the heterocyclic ring is optionally substituted with 1, 2 or 3 substituents selected from R<sup>13</sup>;

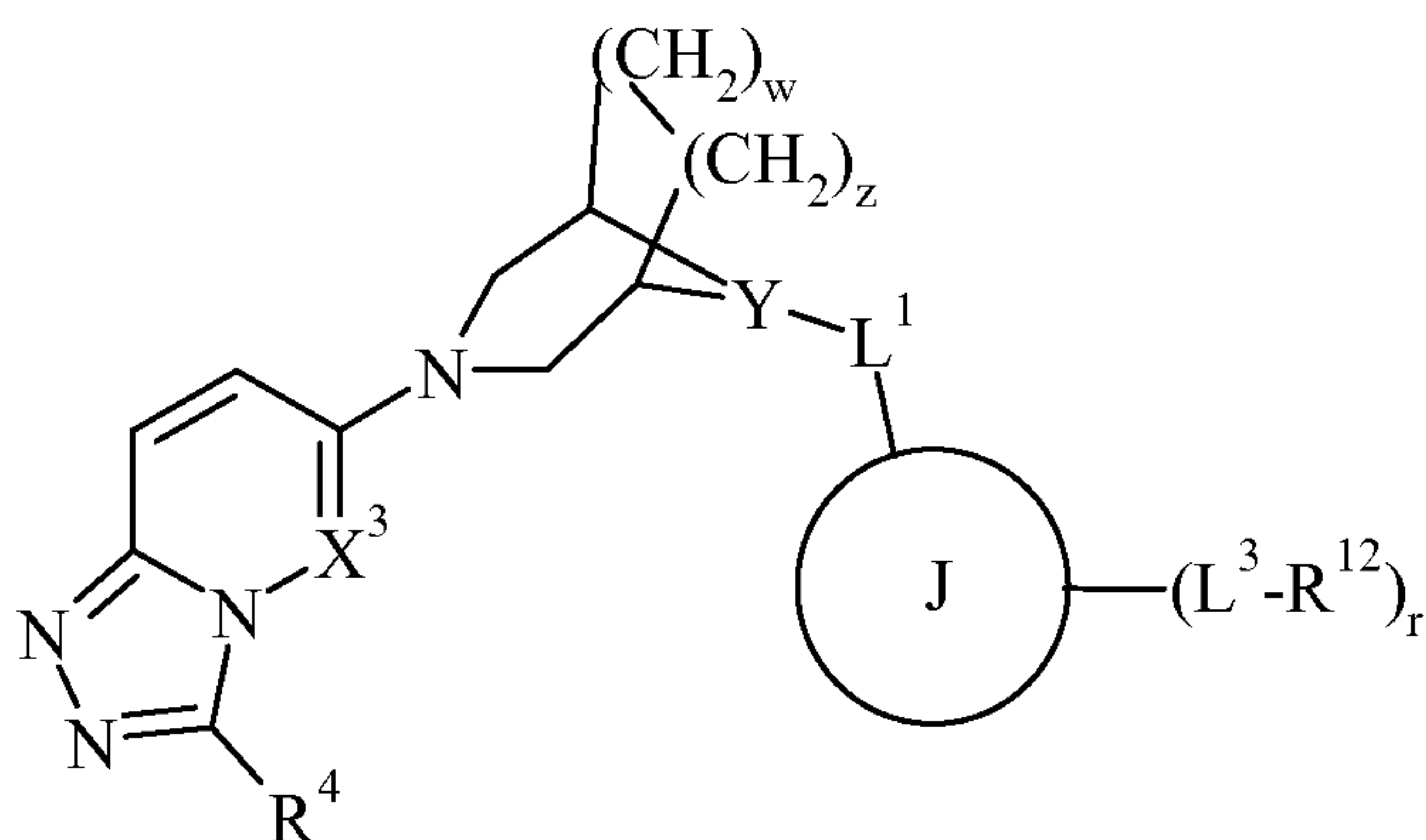
R<sup>13</sup> represents amino, halo, C<sub>1-6</sub>alkyl, C<sub>2-6</sub>alkenyl, C<sub>2-6</sub>alkynyl, C<sub>1-6</sub>alkoxy, C<sub>2-6</sub>alkanoyl, C<sub>1-6</sub>alkoxyC<sub>1-6</sub>alkyl, carboxy, cyano, oxo, fluoroC<sub>1-6</sub>alkyl, hydroxy, hydroxyC<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkylsulphanyl, C<sub>1-6</sub>alkylsulphinyl, C<sub>1-6</sub>alkylsulphonyl, N-C<sub>1-4</sub>alkylamino, N,N-di-C<sub>1-4</sub>alkylamino or -C(O)NR<sup>14</sup>R<sup>15</sup> wherein R<sup>14</sup> and R<sup>15</sup> independently represent hydrogen or methyl; and

r represents 0, 1, 2 or 3.

According to an eighth aspect of the present invention there is provided a compound of Formula (Id) as defined hereinbefore, or a pharmaceutically acceptable salt thereof, for use as a medicament.

According to a ninth aspect of the present invention there is provided a compound of Formula (Id) as defined hereinbefore, or a pharmaceutically acceptable salt thereof, for use in the treatment of prostate cancer.

According to a tenth aspect of the present invention there is provided a compound of Formula (Ie), or a pharmaceutically acceptable salt thereof:



(Ie)



wherein

$X^3$  represents CH or N;

$R^4$  represents haloC<sub>1-4</sub>alkyl;

Y represents CH, COH or N;

5 w and z independently represent 0 or 1;

$L^1$  represents a direct bond,  $-(CR^9R^{10})_t-$ ,  $-(CR^9R^{10})_v-O-(CR^9R^{10})_v-$ ,  $-N(R^{11})-(CH_2)_q-$ ,  $-S-$ ,  $-S(O)-$  or  $-S(O)_2-$ ;

$R^9$  and  $R^{10}$ , identically or differently on each occurrence, represent hydrogen or methyl;

q, identically or differently on each occurrence, represents 0, 1, 2 or 3;

10 t represents 1, 2 or 3;

v, identically or differently on each occurrence, represents 0, 1 or 2;

J represents:

aryl;

a totally saturated monocyclic 3 to 6 membered carbocyclic ring;

15 a monocyclic 4, 5, 6 or 7 membered heterocyclic ring which comprises 1, 2, 3 or 4 heteroatoms independently selected from O, N or S;

a monocyclic 5 or 6 membered heteroaryl ring which comprises 1, 2, 3 or 4 heteroatoms independently selected from O, N or S; or

a bicyclic 9 or 10 membered heteroaryl ring system which comprises 1, 2, 3, 4 or 5

20 heteroatoms independently selected from O, N or S;

$L^3$  represents a direct bond,  $-(CR^9R^{10})_t-$ ,  $-C(O)N(R^{11})-(CH_2)_q-$ ,  $-C(O)N(R^{11})-(CH_2)_q-S(O)_2-$ ,  $-NR^{11}C(O)-(CH_2)_q-$ ,  $-C(O)-(CH_2)_q-$ ,  $-O-(CH_2)_q-$ ,  $-O-(CH_2)_q-NR^{11}-(CH_2)_q-$ ,  $-O-(CH_2)_q-C(O)NR^{11}-(CH_2)_q-$ ,  $-S-$ ,  $-S(O)-$  or  $-S(O)_2-$ ;

$R^{11}$  represents hydrogen or methyl;

25  $R^{12}$  represents:

halo, C<sub>1-6</sub>alkyl, C<sub>2-6</sub>alkenyl, C<sub>2-6</sub>alkynyl, carboxy, C<sub>1-6</sub>alkoxy, cyano, oxo, fluoroC<sub>1-6</sub>alkyl, hydroxy, amino, N-C<sub>1-4</sub>alkylamino or N,N-di-C<sub>1-4</sub>alkylamino;

aryl, wherein the aryl ring is optionally substituted with 1, 2 or 3 substituents selected from  $R^{13}$ ;

30 a monocyclic 5 or 6 membered heteroaryl ring which comprises 1, 2, 3 or 4

heteroatoms independently selected from O, N or S and wherein the heteroaryl ring is optionally substituted with 1, 2 or 3 substituents selected from  $R^{13}$ ; or



a monocyclic 4, 5, 6 or 7 membered heterocyclic ring which comprises 1, 2, 3 or 4 heteroatoms independently selected from O, N or S and wherein the heterocyclic ring is optionally substituted with 1, 2 or 3 substituents selected from R<sup>13</sup>;

R<sup>13</sup> represents amino, halo, C<sub>1-6</sub>alkyl, C<sub>2-6</sub>alkenyl, C<sub>2-6</sub>alkynyl, C<sub>1-6</sub>alkoxy, C<sub>2-6</sub>alkanoyl, C<sub>1-6</sub>alkoxyC<sub>1-6</sub>alkyl, carboxy, cyano, oxo, fluoroC<sub>1-6</sub>alkyl, hydroxy, hydroxyC<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkylsulphanyl, C<sub>1-6</sub>alkylsulphinyl, C<sub>1-6</sub>alkylsulphonyl, N-C<sub>1-4</sub>alkylamino, N,N-di-C<sub>1-4</sub>alkylamino or -C(O)NR<sup>14</sup>R<sup>15</sup> wherein R<sup>14</sup> and R<sup>15</sup> independently represent hydrogen or methyl; and r represents 0, 1, 2 or 3.

According to an eleventh aspect of the present invention there is provided a compound of Formula (Ie) as defined hereinbefore, or a pharmaceutically acceptable salt thereof, for use as a medicament.

According to a twelfth aspect of the present invention there is provided a compound of Formula (Ie) as defined hereinbefore, or a pharmaceutically acceptable salt thereof, for use in the treatment of prostate cancer.

In further embodiments of the fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh and twelfth aspects of the present invention, each of the following definitions of J, L<sup>1</sup>, L<sup>3</sup>, n, p, r, w, z, R<sup>4</sup>, R<sup>9</sup>, R<sup>10</sup>, R<sup>11</sup>, R<sup>12</sup>, R<sup>13</sup>, R<sup>14</sup>, X<sup>3</sup> and Y in paragraphs (1) to (61) hereinafter may be used individually or in combination with one or more of the other following definitions to limit the broadest definitions of Formulae (Ic), (Id), (Ie) or (If).

- (1) X<sup>3</sup> represents N;
- (2) X<sup>3</sup> represents CH;
- (3) R<sup>4</sup> represents difluoromethyl, trifluoromethyl, chloro(difluoro)methyl, difluoroethyl or difluoropropyl;
- (4) R<sup>4</sup> represents difluoromethyl, trifluoromethyl or chloro(difluoro)methyl;
- (5) R<sup>4</sup> represents difluoromethyl
- (6) R<sup>4</sup> represents trifluoromethyl;
- (7) R<sup>4</sup> represents chloro(difluoro)methyl;
- (8) R<sup>14</sup> represents hydrogen;
- (9) n and p both represent 2;
- (10) n and p both represent 1;
- (11) Y represents CH or COH;



- (12) Y represents CH
- (13) Y represents COH;
- (14) Y represents N;
- (15)  $L^1$  represents a direct bond,  $-(CR^9R^{10})_t-$ ,  $-(CR^9R^{10})_v-O-(CR^9R^{10})_v-$  or  $-N(R^{11})-$   
 5  $(CH_2)_q-$ ;
- (16)  $L^1$  represents a direct bond,  $-CH_2-$ ,  $-CH(CH_3)-$  or  $-O-$ ;
- (17)  $L^1$  represents a direct bond;
- (18)  $L^1$  represents  $-CH_2-$ ;
- (19) J represents phenyl, pyridinyl, indolyl, indazolyl or pyrrolopyridinyl;
- 10 (20) J represents phenyl;
- (21) J represents pyridinyl;
- (22) J represents pyridin-3-yl;
- (23)  $L^3$  represents a direct bond;
- (24)  $L^3$  represents a direct bond,  $-(CR^9R^{10})_t-$ ,  $-C(O)N(R^{11})-(CH_2)_q-$ ,  $-NR^{11}C(O)-(CH_2)_q-$ ,  
 15  $-C(O)-(CH_2)_q-$ ,  $-O-(CH_2)_q-$  or  $-O-(CH_2)_q-C(O)NR^{11}-(CH_2)_q-$ ;
- (25)  $L^3$  represents  $-(CR^9R^{10})_t-$ ,  $-C(O)N(R^{11})-(CH_2)_q-$ ,  $-NR^{11}C(O)-(CH_2)_q-$ ,  $-C(O)-(CH_2)_q-$ ,  
 $-O-(CH_2)_q-$  or  $-O-(CH_2)_q-C(O)NR^{11}-(CH_2)_q-$ ;
- (26)  $L^3$  represents  $-C(O)N(R^{11})-(CH_2)_q-$ ,  $-NR^{11}C(O)-(CH_2)_q-$ ,  $-C(O)-(CH_2)_q-$ ,  $-O-(CH_2)_q-$   
 or  $-O-(CH_2)_q-C(O)NR^{11}-(CH_2)_q-$ ;
- 20 (27)  $L^3$  represents  $-C(O)N(R^{11})-(CH_2)_q-$ ,  $-NR^{11}C(O)-(CH_2)_q-$ ,  $-C(O)-(CH_2)_q-$  or  $-O-$   
 $(CH_2)_q-$ ;
- (28)  $L^3$  represents a direct bond,  $-C(O)N(R^{11})-(CH_2)_q-$  or  $-O-(CH_2)_q-$ ;
- (29)  $L^3$  represents  $-C(O)N(R^{11})-(CH_2)_q-$  or  $-O-(CH_2)_q-$ ;
- (30)  $L^3$  represents  $-O-(CH_2)_q-$ ;
- 25 (31)  $L^3$  represents  $-O-CH_2-CH_2-$ ;
- (32)  $R^9$  and  $R^{10}$  both represent hydrogen;
- (33)  $R^{11}$  represents hydrogen;
- (34)  $R^{11}$  represents methyl;
- (35) q represents 0, 1 or 2;
- 30 (36)  $R^{12}$  represents fluoro, chloro, methyl, methoxy, difluoromethyl, trifluoromethyl,  
 cyano, hydroxy, imidazolyl, pyrrolidinyl, piperidinyl, methylsulphonyl,  
 morpholinyl, pyrazolyl or phenyl;



- (37) R<sup>12</sup> represents fluoro, chloro, methyl, methoxy, difluoromethyl, trifluoromethyl, hydroxy, imidazolyl, pyrrolidinyl, piperidinyl, methylsulphonyl, morpholinyl, pyrazolyl or phenyl;
- (38) R<sup>12</sup> represents fluoro, chloro, methyl, methoxy, difluoromethyl, trifluoromethyl, cyano, hydroxy, methylsulphonyl, dimethylamino, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl or pyrazolyl;
- (39) R<sup>12</sup> represents fluoro, chloro, methyl, methoxy, difluoromethyl, trifluoromethyl, hydroxy, methylsulphonyl, dimethylamino, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl or pyrazolyl;
- (40) R<sup>12</sup> represents fluoro, chloro, methyl, methoxy, difluoromethyl, trifluoromethyl, cyano or hydroxy;
- (41) R<sup>12</sup> represents fluoro, chloro, methyl, methoxy, difluoromethyl, trifluoromethyl or hydroxy;
- (42) R<sup>12</sup> represents pyrrolidinyl, piperidinyl, methylsulphonyl, morpholinyl or pyrazolyl;
- (43) R<sup>12</sup> represents pyrazolyl;
- (44) R<sup>12</sup> represents pyrazol-5-yl;
- (45) R<sup>12</sup> represents 1-methyl-1H-pyrazol-5-yl;
- (46) r represents 1 or 2 when J represents aryl;
- (47) r represents 1 when J represents aryl;
- (48) r represents 0 or 1 when J represents imidazolyl, isothiazolyl, morpholinyl, oxadiazolyl, oxazolyl, isoxazolyl, oxetanyl, tetrahydro-2H-pyranyl, pyrazolyl, pyridazinyl, pyridinyl or a bicyclic 9 membered heteroaryl ring system comprising 1 or 2 nitrogen atoms or a single sulphur atom;
- (49) r represents 1 when J represents imidazolyl, isothiazolyl, morpholinyl, oxadiazolyl, oxazolyl, isoxazolyl, oxetanyl, tetrahydro-2H-pyranyl, pyrazolyl, pyridazinyl, pyridinyl or a bicyclic 9 membered heteroaryl ring system comprising 1 or 2 nitrogen atoms or a single sulphur atom;
- (50) r represents 0 when J represents imidazolyl, isothiazolyl, morpholinyl, oxadiazolyl, oxazolyl, isoxazolyl, oxetanyl, tetrahydro-2H-pyranyl, pyrazolyl, pyridazinyl,



pyridinyl or a bicyclic 9 membered heteroaryl ring system comprising 1 or 2 nitrogen atoms or a single sulphur atom;

(51) r represents 1 when J represents pyrazolyl;

(52)  $L^3$  represents  $-O-CH_2-CH_2-$ ,  $R^{12}$  represents 1-methyl-1H-pyrazol-5-yl and r represents 1;

(53)  $R^{13}$  represents methyl, methoxy, oxo, hydroxy, cyano, acetyl or methylsulphonyl;

(54)  $R^{13}$  represents methyl, methoxy, oxo, hydroxy, acetyl or methylsulphonyl;

(55)  $R^{13}$  represents methyl, oxo or hydroxy;

(56)  $R^{13}$  represents methyl;

(57) k represents 0;

(58) k represents 1;

(59) k represents 2;

(60) w and z both represent 1;

(61) w and z both represent 0.

Particular novel compounds of Formula (Ic) include, but are not limited to, the following compounds:

4-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]benzonitrile;

3-(trifluoromethyl)-6-[4-[[3-(trifluoromethyl)phenyl]methyl]piperazin-1-yl]-[1,2,4]triazolo[4,3-b]pyridazine;

4-pyridin-3-yl-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol;

3-(difluoromethyl)-6-{4-[(1R)-1-(4-fluorophenyl)ethyl]piperazin-1-yl}[1,2,4]triazolo[4,3-b]pyridazine;

4-(4-fluorophenyl)-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol;

N-(2-methoxyethyl)-N-methyl-4-{1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl}benzamide;

N-(2-hydroxyethyl)-N-methyl-4-{1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl}benzamide;

6-(4-{4-[(4-methylpiperazin-1-yl)carbonyl]phenyl}piperidin-1-yl)-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine;



N-[2-(2-oxopyrrolidin-1-yl)ethyl]-4-{1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl}benzamide;

6-[4-(1H-indazol-3-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine;

5 N-(2-methoxyethyl)-N-methyl-3-({1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl}oxy)benzamide;

2-morpholin-4-yl-N-(4-{1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl}phenyl)acetamide;

6-(4-{4-[2-(1-methyl-1H-pyrazol-5-yl)ethoxy]phenyl}piperidin-1-yl)-3-

10 (trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine;

6-{4-[2-(difluoromethyl)-5-fluorobenzyl]piperazin-1-yl}-3-

(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine;

6-{4-[(6-methylpyridin-3-yl)methyl]piperazin-1-yl}-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine;

15 6-[4-(1H-pyrrolo[2,3-b]pyridin-3-yl)piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine;

6-[4-(5-methoxy-1H-indol-3-yl)piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine;

1-[(4-{1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-

20 yl}phenyl)carbonyl]piperidin-4-ol;

N-methyl-N-[2-(methylsulfonyl)ethyl]-4-{1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl}benzamide;

6-[3-(4-methoxyphenoxy)azetidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine;

25 6-(4-{4-[2-(1-methyl-1H-pyrazol-5-yl)ethoxy]phenyl}piperazin-1-yl)-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine; and

4-[4-[2-(1-methyl-1H-pyrazol-5-yl)ethoxy]phenyl]-1-[3-

(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol;

and pharmaceutically acceptable salts thereof.

30 Crystalline forms of particular novel compounds of Formula (Ic), and a particular salt thereof, have also been identified.



According to the present invention there is therefore provided a crystalline form of 4-pyridin-3-yl-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol, Anhydrous Form A, which has an X-ray powder diffraction pattern with at least one specific peak at a  $2\theta$  value of about  $9.18^\circ$ ,  $15.51^\circ$ ,  $16.01^\circ$ ,  $18.94^\circ$  or  $24.59^\circ$  when measured using CuK $\alpha$  radiation, more particularly wherein said values may be plus or minus  $0.5^\circ 2\theta$ .

According to the present invention there is therefore provided a crystalline form of 4-pyridin-3-yl-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol, Anhydrous Form A, which has an X-ray powder diffraction pattern with specific peaks at  $2\theta$  values of about  $9.18^\circ$ ,  $15.51^\circ$ ,  $16.01^\circ$ ,  $18.94^\circ$  and  $24.59^\circ$  when measured using CuK $\alpha$  radiation, more particularly wherein said values may be plus or minus  $0.5^\circ 2\theta$ .

According to the present invention there is therefore provided a crystalline form of 4-pyridin-3-yl-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol, Anhydrous Form A, which has an X-ray powder diffraction pattern with specific peaks at  $2\theta$  values of  $8.30$ ,  $9.18$ ,  $9.96$ ,  $10.41$ ,  $14.35$ ,  $15.02$ ,  $15.51$ ,  $16.01$ ,  $17.03$ ,  $18.46$ ,  $18.94$ ,  $19.18$ ,  $19.82$ ,  $20.35$ ,  $20.61$ ,  $21.80$ ,  $22.65$ ,  $23.38$ ,  $24.15$ ,  $24.59$ ,  $25.43$ ,  $26.12$ ,  $26.35$ ,  $26.59$ ,  $27.43$ ,  $29.38$ ,  $31.83$  and  $37.33^\circ$  when measured using CuK $\alpha$  radiation, more particularly wherein said values may be plus or minus  $0.5^\circ 2\theta$ .

According to the present invention there is therefore provided a crystalline form of 4-pyridin-3-yl-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol, Anhydrous Form A, which has an X-ray powder diffraction pattern substantially the same as the X-ray powder diffraction pattern shown in Figure 1 when measured using CuK $\alpha$  radiation.

According to the present invention there is therefore provided a crystalline form of N-(2-methoxyethyl)-N-methyl-4-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]benzamide, Anhydrous Form A, which has an X-ray powder diffraction pattern with at least one specific peak at a  $2\theta$  value of about  $12.34^\circ$ ,  $15.78^\circ$ ,  $20.42^\circ$ ,  $23.75^\circ$  or  $24.73^\circ$  when measured using CuK $\alpha$  radiation, more particularly wherein said values may be plus or minus  $0.5^\circ 2\theta$ .

According to the present invention there is therefore provided a crystalline form of N-(2-methoxyethyl)-N-methyl-4-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]benzamide, Anhydrous Form A, which has an X-ray powder diffraction pattern with specific peaks at  $2\theta$  values of about  $12.34^\circ$ ,  $15.78^\circ$ ,  $20.42^\circ$ ,  $23.75^\circ$  and  $24.73^\circ$



when measured using CuK $\alpha$  radiation, more particularly wherein said values may be plus or minus 0.5° 2 $\theta$ .

According to the present invention there is therefore provided a crystalline form of N-(2-methoxyethyl)-N-methyl-4-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]benzamide, Anhydrous Form A, which has an X-ray powder diffraction pattern with specific peaks at 2 $\theta$  values of 6.28, 7.92, 9.65, 12.34, 12.69, 14.92, 15.78, 16.89, 18.78, 19.28, 20.42, 20.99, 21.57, 22.49, 23.31, 23.75, 24.34, 24.73, 25.38, 26.93, 28.14, 29.08, 31.16, 31.86, 32.50, 33.14, 34.79, 36.34, 36.78, 38.01 and 38.64° when measured using CuK $\alpha$  radiation, more particularly wherein said values may be plus or minus 0.5° 2 $\theta$ .

According to the present invention there is therefore provided a crystalline form of N-(2-methoxyethyl)-N-methyl-4-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]benzamide, Anhydrous Form A, which has an X-ray powder diffraction pattern substantially the same as the X-ray powder diffraction pattern shown in Figure 2 when measured using CuK $\alpha$  radiation.

According to the present invention there is therefore provided a crystalline form of 6-[4-[4-[2-(1-methyl-1H-pyrazol-5-yl)ethoxy]phenyl]piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine, Anhydrous Form A, which has an X-ray powder diffraction pattern with at least one specific peak at a 2 $\theta$  value of about 4.90°, 13.47°, 15.93°, 16.64° or 22.83° when measured using CuK $\alpha$  radiation, more particularly wherein said values may be plus or minus 0.5° 2 $\theta$ .

According to the present invention there is therefore provided a crystalline form of 6-[4-[4-[2-(1-methyl-1H-pyrazol-5-yl)ethoxy]phenyl]piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine, Anhydrous Form A, which has an X-ray powder diffraction pattern with specific peaks at 2 $\theta$  values of about 4.90°, 13.47°, 15.93°, 16.64° and 22.83° when measured using CuK $\alpha$  radiation, more particularly wherein said values may be plus or minus 0.5° 2 $\theta$ .

According to the present invention there is therefore provided a crystalline form of 6-[4-[4-[2-(1-methyl-1H-pyrazol-5-yl)ethoxy]phenyl]piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine, Anhydrous Form A, which has an X-ray powder diffraction pattern with specific peaks at 2 $\theta$  values of 4.90, 9.784, 11.50, 11.94, 12.97, 13.47, 14.72, 15.93, 16.64, 17.36, 18.32, 18.67, 19.195, 19.67, 20.26, 20.58, 20.87,



21.33, 21.64, 22.83, 23.7, 24, 24.40, 25.99, 26.75, 27.15, 28.10, 28.55, 29.02, 29.46, 29.74, 30.12, 30.65, 31.37, 31.85, 33.66, 34.28, 35.85, 36.42, 37.62 and 38.53° when measured using CuKα radiation, more particularly wherein said values may be plus or minus 0.5° 2θ.

According to the present invention there is therefore provided a crystalline form of  
5 6-[4-[4-[2-(1-methyl-1H-pyrazol-5-yl)ethoxy]phenyl]piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine, Anhydrous Form A, which has an X-ray powder diffraction pattern substantially the same as the X-ray powder diffraction pattern shown in Figure 3 when measured using CuKα radiation.

According to the present invention there is therefore provided a crystalline form of  
10 6-[4-[4-[2-(1-methyl-1H-pyrazol-5-yl)ethoxy]phenyl]piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine, Anhydrous Form A, which has an X-ray powder diffraction pattern with at least one specific peak at a 2θ value of about 6.90°, 15.38°, 21.55°, 24.48° or 27.56° when measured using CuKα radiation, more particularly wherein said values may be plus or minus 0.5° 2θ.

According to the present invention there is therefore provided a crystalline form of  
15 6-[4-[4-[2-(1-methyl-1H-pyrazol-5-yl)ethoxy]phenyl]piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine, Anhydrous Form A, which has an X-ray powder diffraction pattern with specific peaks at 2θ values of about 6.90°, 15.38°, 21.55°, 24.48° and 27.56° when measured using CuKα radiation, more particularly wherein said  
20 values may be plus or minus 0.5° 2θ.

According to the present invention there is therefore provided a crystalline form of  
6-[4-[4-[2-(1-methyl-1H-pyrazol-5-yl)ethoxy]phenyl]piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine, Anhydrous Form A, which has an X-ray powder diffraction pattern with specific peaks at 2θ values of 6.90, 9.6, 10.78, 12.82,  
25 13.16, 13.85, 14.44, 15.38, 16.44, 17.46, 18.25, 18.92, 19.27, 20.18, 21.03, 21.55, 22.36, 22.63, 23.55, 23.76, 24.48, 25.2, 25.76, 26.47, 27.56, 27.83, 28.21, 29.10, 29.93, 30.59, 31.20, 32.49, 33.33, 34.04, 34.62, 36.18, 36.54, 37.45, 38.17 and 39.32° when measured using CuKα radiation, more particularly wherein said values may be plus or minus 0.5° 2θ.

According to the present invention there is therefore provided a crystalline form of  
30 6-[4-[4-[2-(1-methyl-1H-pyrazol-5-yl)ethoxy]phenyl]piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine, Anhydrous Form A, which has an X-ray



powder diffraction pattern substantially the same as the X-ray powder diffraction pattern shown in Figure 4 when measured using CuK $\alpha$  radiation.

According to the present invention there is therefore provided a crystalline form of 6-[4-[4-[2-(1-methyl-1H-pyrazol-5-yl)ethoxy]phenyl]piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine fumarate which has an X-ray powder diffraction pattern with at least one specific peak at a 2 $\theta$  value of about 11.72°, 16.46°, 17.58° or 21.89° when measured using CuK $\alpha$  radiation, more particularly wherein said values may be plus or minus 0.5° 2 $\theta$ .

According to the present invention there is therefore provided a crystalline form of 6-[4-[4-[2-(1-methyl-1H-pyrazol-5-yl)ethoxy]phenyl]piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine fumarate which has an X-ray powder diffraction pattern with specific peaks at 2 $\theta$  values of about 11.72°, 16.46°, 17.58° and 21.89° when measured using CuK $\alpha$  radiation, more particularly wherein said values may be plus or minus 0.5° 2 $\theta$ .

According to the present invention there is therefore provided a crystalline form of 6-[4-[4-[2-(1-methyl-1H-pyrazol-5-yl)ethoxy]phenyl]piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine fumarate which has an X-ray powder diffraction pattern with specific peaks at 2 $\theta$  values of 4.51, 5.90, 11.72, 12.22, 13.23, 16.46, 17.58, 19.74, 20.26, 21.18, 21.89, 23.86, 24.17, 25.83, 26.75, 28.78, 30.54 and 31.51° when measured using CuK $\alpha$  radiation, more particularly wherein said values may be plus or minus 0.5° 2 $\theta$ .

According to the present invention there is therefore provided a crystalline form of 6-[4-[4-[2-(1-methyl-1H-pyrazol-5-yl)ethoxy]phenyl]piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine fumarate which has an X-ray powder diffraction pattern substantially the same as the X-ray powder diffraction pattern shown in Figure 5 when measured using CuK $\alpha$  radiation.

Reference herein to a compound of Formula (I) should be understood to refer equally to a compound of Formula (Ic), (Id), (Ie) and (If).

A suitable pharmaceutically-acceptable salt of a compound of the Formula (I) is, for example, an acid-addition salt of a compound of the Formula I, for example an acid-addition salt with an inorganic or organic acid such as hydrochloric, hydrobromic, sulphuric, trifluoroacetic, citric or maleic acid; or, for example, a salt of a compound of the



Formula I which is sufficiently acidic, for example an alkali or alkaline earth metal salt such as a calcium or magnesium salt, or an ammonium salt, or a salt with an organic base such as methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine. A further suitable pharmaceutically-acceptable salt of a compound of the Formula I is, for example, a salt formed within the human or animal body after administration of a compound of the Formula I.

A suitable pharmaceutically-acceptable solvate of a compound of the Formula I is, for example, a hydrate such as a hemi-hydrate, a mono-hydrate, a di-hydrate or a tri-hydrate or an alternative quantity thereof.

The compounds of the invention may be administered in the form of a pro-drug, that is a compound that is broken down in the human or animal body to release a compound of the invention. A pro-drug may be used to alter the physical properties and/or the pharmacokinetic properties of a compound of the invention. A pro-drug can be formed when the compound of the invention contains a suitable group or substituent to which a property-modifying group can be attached. Examples of pro-drugs include *in vivo* cleavable ester derivatives that may be formed at a carboxy group or a hydroxy group in a compound of the Formula I and *in vivo* cleavable amide derivatives that may be formed at a carboxy group or an amino group in a compound of the Formula I.

Accordingly, the present invention includes those compounds of the Formula I as defined hereinbefore when made available by organic synthesis and when made available within the human or animal body by way of cleavage of a pro-drug thereof. Accordingly, the present invention includes those compounds of the Formula I that are produced by organic synthetic means and also such compounds that are produced in the human or animal body by way of metabolism of a precursor compound, that is a compound of the Formula I may be a synthetically-produced compound or a metabolically-produced compound.

A suitable pharmaceutically-acceptable pro-drug of a compound of the Formula I is one that is based on reasonable medical judgement as being suitable for administration to the human or animal body without undesirable pharmacological activities and without undue toxicity.

Various forms of pro-drug have been described, for example in the following documents :-



- a) Methods in Enzymology, Vol. 42, p. 309-396, edited by K. Widder, *et al.* (Academic Press, 1985);
- b) Design of Pro-drugs, edited by H. Bundgaard, (Elsevier, 1985);
- c) A Textbook of Drug Design and Development, edited by Krogsgaard-Larsen and H. Bundgaard, Chapter 5 “Design and Application of Pro-drugs”, by H. Bundgaard p. 113-191 (1991);
- d) H. Bundgaard, Advanced Drug Delivery Reviews, 8, 1-38 (1992);
- e) H. Bundgaard, *et al.*, Journal of Pharmaceutical Sciences, 77, 285 (1988);
- f) N. Kakeya, *et al.*, Chem. Pharm. Bull., 32, 692 (1984);
- g) T. Higuchi and V. Stella, “Pro-Drugs as Novel Delivery Systems”, A.C.S. Symposium Series, Volume 14; and
- h) E. Roche (editor), “Bioreversible Carriers in Drug Design”, Pergamon Press, 1987.

A suitable pharmaceutically-acceptable pro-drug of a compound of the Formula (I) that possesses a carboxy group is, for example, an *in vivo* cleavable ester thereof. An *in vivo* cleavable ester of a compound of the Formula (I) containing a carboxy group is, for example, a pharmaceutically-acceptable ester which is cleaved in the human or animal body to produce the parent acid. Suitable pharmaceutically-acceptable esters for carboxy include C<sub>1-6</sub>alkyl esters such as methyl, ethyl and *tert*-butyl, C<sub>1-6</sub>alkoxymethyl esters such as methoxymethyl esters, C<sub>1-6</sub>alkanoyloxymethyl esters such as pivaloyloxymethyl esters, 3-phthalidyl esters, C<sub>3-8</sub>cycloalkylcarbonyloxy- C<sub>1-6</sub>alkyl esters such as cyclopentylcarbonyloxymethyl and 1-cyclohexylcarbonyloxyethyl esters, 2-oxo-1,3-dioxolenylmethyl esters such as 5-methyl-2-oxo-1,3-dioxolen-4-ylmethyl esters and C<sub>1-6</sub>alkoxycarbonyloxy- C<sub>1-6</sub>alkyl esters such as methoxycarbonyloxymethyl and 1-methoxycarbonyloxyethyl esters.

A suitable pharmaceutically-acceptable pro-drug of a compound of the Formula (I) that possesses a hydroxy group is, for example, an *in vivo* cleavable ester or ether thereof.

An *in vivo* cleavable ester or ether of a compound of the Formula (I) containing a hydroxy group is, for example, a pharmaceutically-acceptable ester or ether which is cleaved in the human or animal body to produce the parent hydroxy compound. Suitable pharmaceutically-acceptable ester forming groups for a hydroxy group include inorganic esters such as phosphate esters (including phosphoramidic cyclic esters). Further suitable pharmaceutically-acceptable ester forming groups for a hydroxy group include



C<sub>1-10</sub>alkanoyl groups such as acetyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl groups, C<sub>1-10</sub>alkoxycarbonyl groups such as ethoxycarbonyl, N,N-[di-C<sub>1-4</sub>alkyl]carbamoyl, 2-dialkylaminoacetyl and 2-carboxyacetyl groups. Examples of ring substituents on the phenylacetyl and benzoyl groups include aminomethyl, N-alkylaminomethyl, N,N-dialkylaminomethyl, morpholinomethyl, piperazin-1-ylmethyl and 4-C<sub>1-4</sub>alkylpiperazin-1-ylmethyl. Suitable pharmaceutically-acceptable ether forming groups for a hydroxy group include  $\alpha$ -acyloxyalkyl groups such as acetoxymethyl and pivaloyloxymethyl groups.

A suitable pharmaceutically-acceptable pro-drug of a compound of the Formula (I) that possesses a carboxy group is, for example, an *in vivo* cleavable amide thereof, for example an amide formed with an amine such as ammonia, a C<sub>1-4</sub>alkylamine such as methylamine, a di-C<sub>1-4</sub>alkylamine such as dimethylamine, N-ethyl-N-methylamine or diethylamine, a C<sub>1-4</sub>alkoxy-C<sub>2-4</sub>alkylamine such as 2-methoxyethylamine, a phenyl-C<sub>1-4</sub>alkylamine such as benzylamine and amino acids such as glycine or an ester thereof.

A suitable pharmaceutically-acceptable pro-drug of a compound of the Formula (I) that possesses an amino group is, for example, an *in vivo* cleavable amide derivative thereof. Suitable pharmaceutically-acceptable amides from an amino group include, for example an amide formed with C<sub>1-10</sub>alkanoyl groups such as an acetyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl groups. Examples of ring substituents on the phenylacetyl and benzoyl groups include aminomethyl, N-alkylaminomethyl, N,N-dialkylaminomethyl, morpholinomethyl, piperazin-1-ylmethyl and 4-(C<sub>1-4</sub>)alkylpiperazin-1-ylmethyl.

The *in vivo* effects of a compound of the Formula (I) may be exerted in part by one or more metabolites that are formed within the human or animal body after administration of a compound of the Formula (I). As stated hereinbefore, the *in vivo* effects of a compound of the Formula (I) may also be exerted by way of metabolism of a precursor compound (a pro-drug).

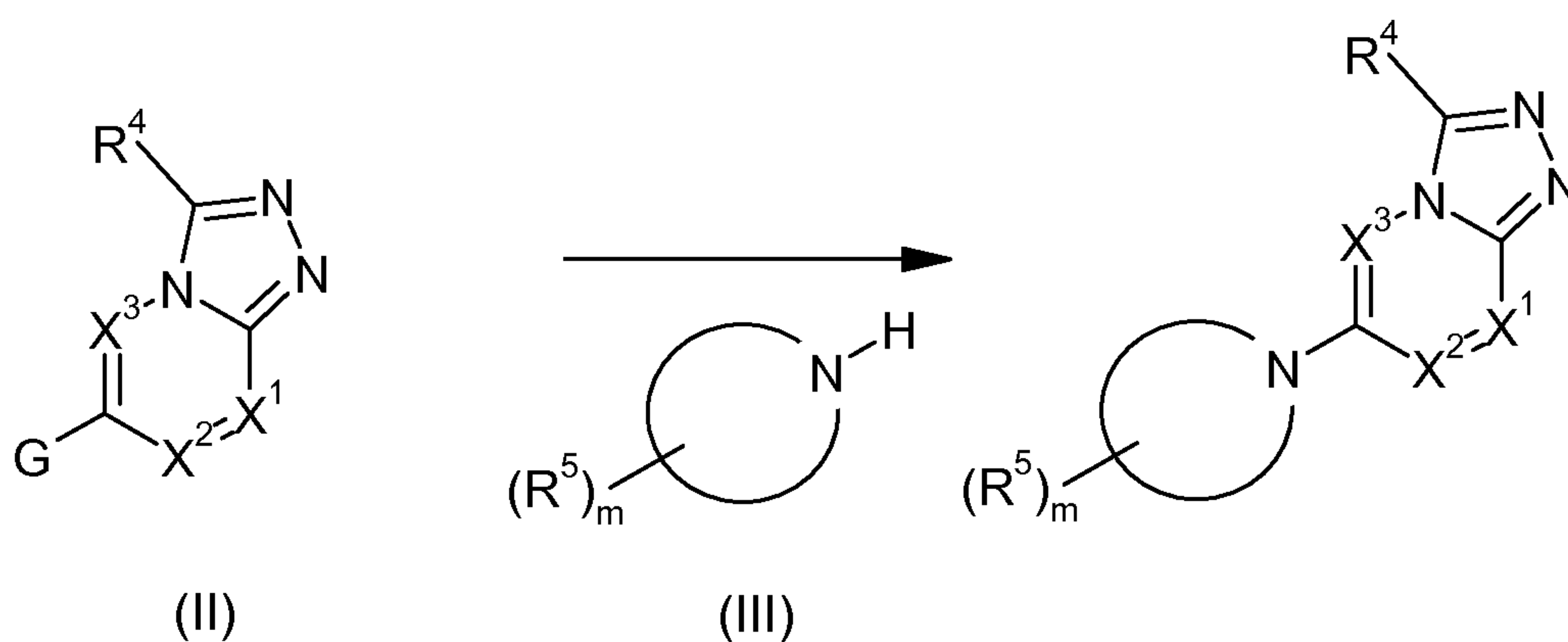
An example of a metabolite of a compound of the Formula (I) is 3-[4-hydroxy-1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]pyridine 1-oxide which is a metabolite of 4-pyridin-3-yl-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol.



The compounds of Formula (I) can be prepared by a process comprising a step selected from (1) to (10) as follows, these processes are provided as a further feature of the invention:-

### **Preparation of Compounds of Formula (I)**

1. A process for the manufacture of compounds of Formula (I) comprises reacting a compound of formula (II), wherein G is a leaving group such as halogen, alkane sulfonyloxy, or arylsulfonyloxy and  $R^4$ ,  $X^1$ ,  $X^2$ , and  $X^3$  are as defined above, with a monocyclic or bicyclic amine of Formula (III), wherein  $R^5$  and m are as defined above.

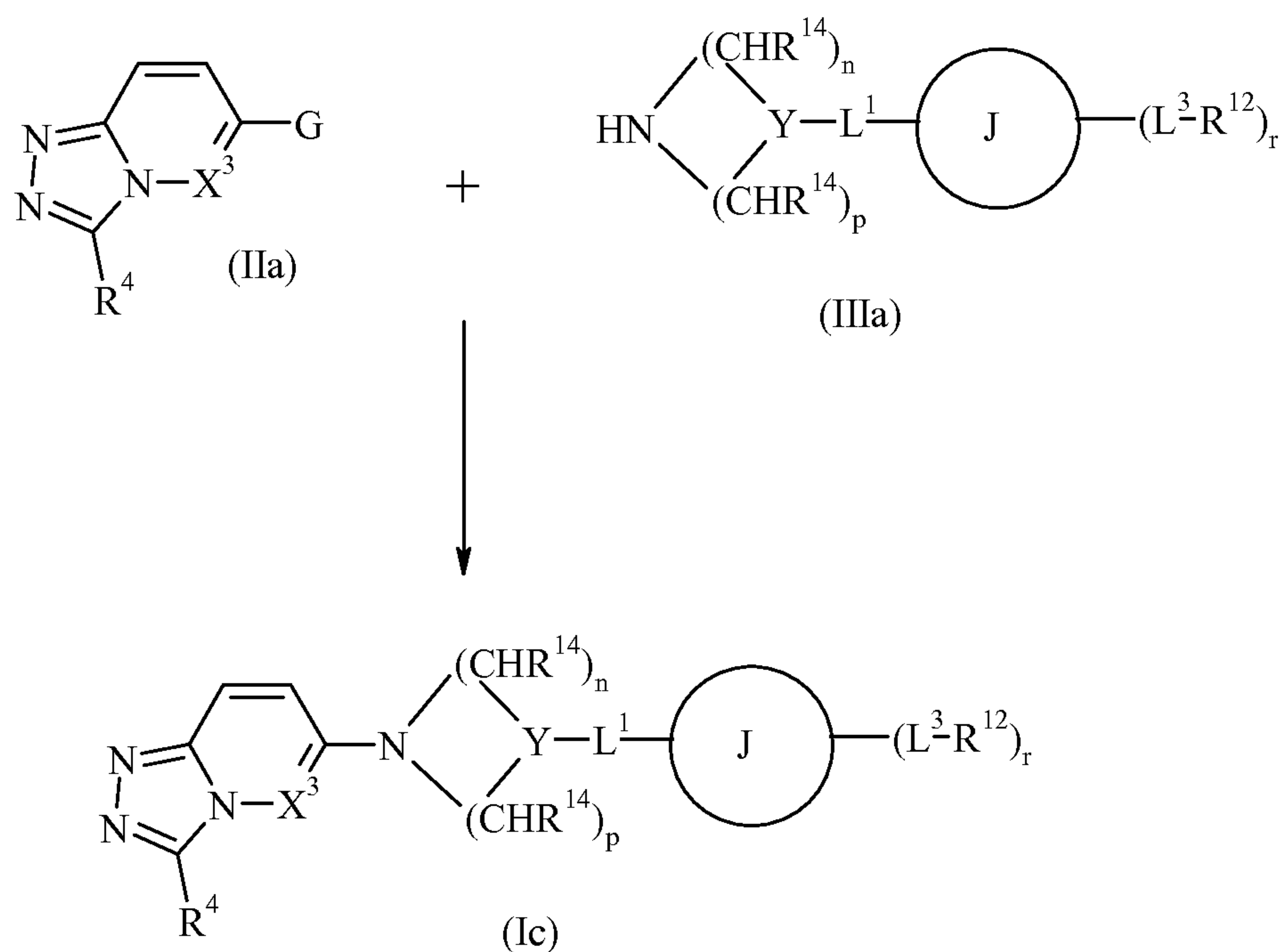


- The reaction may be carried out by combining the components in an inert solvent such as ethanol, xylene, or N-methylpyrrolidone at temperatures between 25°C and 250°C, preferably between 50°C and 150°C. The reaction may be advantageously catalysed by bases such as organic bases, for instance diisopropylethylamine or by low-valent transition metal catalysts such as Pd(0), for instance bis(dibenzylideneacetone) palladium(0). The reaction may be heated by a conventional heat source, such as an oil bath or a heating block, or by microwave heating.

- In one embodiment of the invention, there is provided a process for the preparation of compounds of Formula (Ic) which comprises reacting a compound of Formula (IIa), wherein G is a suitable leaving group such as halogen, for example chloro, and  $R^4$  and  $X^3$  are as defined hereinbefore in relation to Formula (Ic), with an amine of Formula (IIIa), wherein J, Y,  $L^1$ ,  $L^3$ ,  $R^{12}$ ,  $R^{14}$ , n, p and r are as defined hereinbefore in relation to Formula (Ic):



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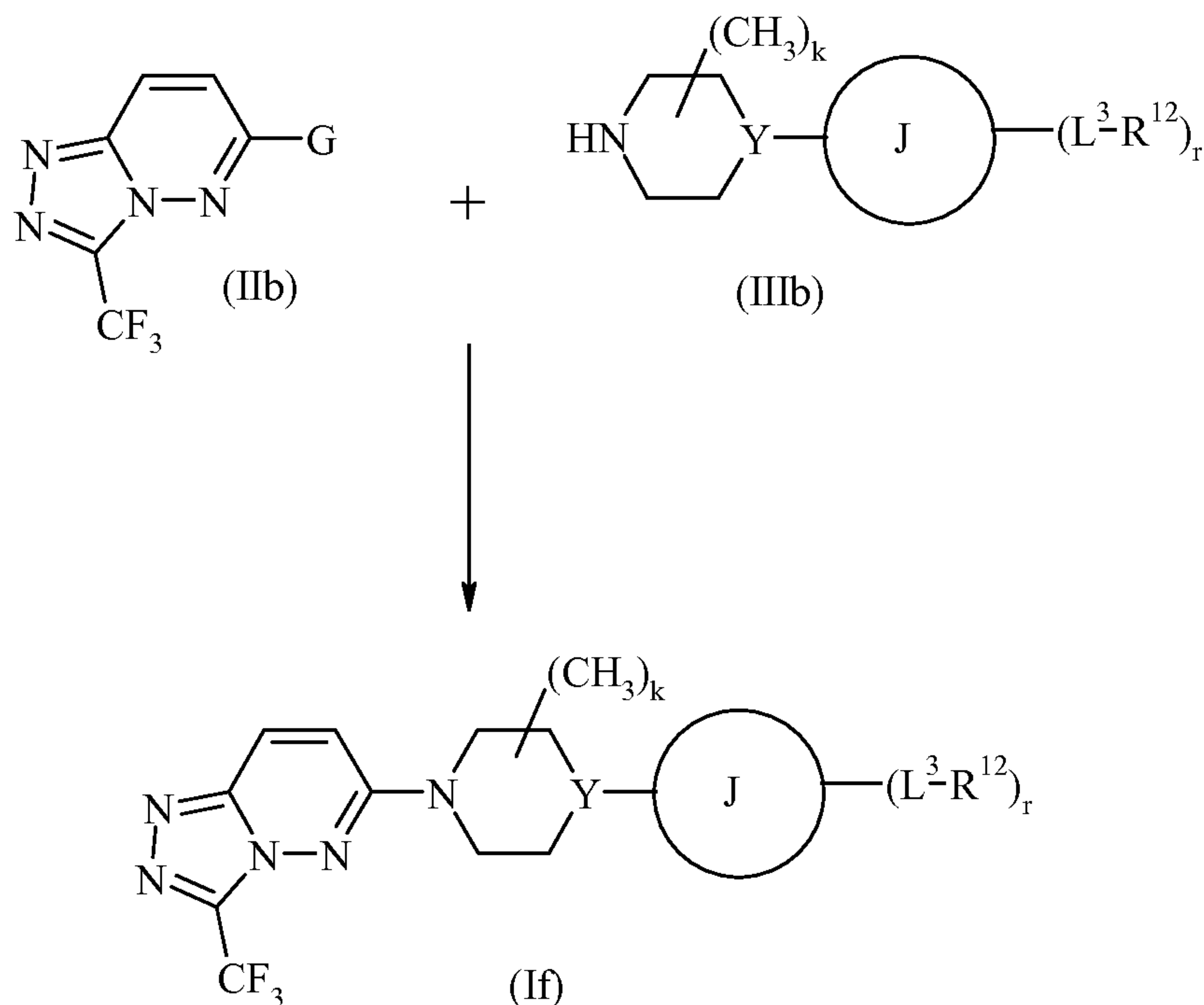
and thereafter, if necessary:

- (i) converting a functional group of one compound of the invention into another functional group;
- 5 (ii) introducing a new functional group into one compound of the invention;
- (iii) removing any protecting groups;
- (iv) for compounds of the invention in the form of a single enantiomer separating a racemic compound of the invention into separate enantiomers;
- (v) preparing a pharmaceutically acceptable salt thereof; and/or
- 10 (vi) preparing a crystalline form thereof.

In a further embodiment of the invention, there is provided a process for the preparation of compounds of Formula (If) which comprises reacting a compound of Formula (IIb), wherein  $G$  represents halogen, with an amine of Formula (IIIb), wherein  $Y$ ,  $J$ ,  $L^3$ ,  $R^{12}$ ,  $k$  and  $r$  are as defined hereinbefore in relation to Formula (If):



47



and thereafter, if necessary:

- (i) converting a functional group of one compound of the invention into another functional group;
- 5 (ii) introducing a new functional group into one compound of the invention;
- (iii) removing any protecting groups;
- (iv) for compounds of the invention in the form of a single enantiomer separating a racemic compound of the invention into separate enantiomers;
- (v) preparing a pharmaceutically acceptable salt thereof; and/or
- 10 (vi) preparing a crystalline form thereof.

The above reactions may be carried out by combining the components of formula (IIa) and (IIIa) or (IIb) and (IIIb) in a suitable solvent, for example dimethylformamide or dimethylacetamide, at a suitable temperature, for example between 25°C and 250°C, more particularly between 50°C and 150°C, in the presence of a suitable base, for example  
 15 diisopropylethylamine. The reaction may be heated by a conventional heat source, such as an oil bath or a heating block, or by microwave heating.

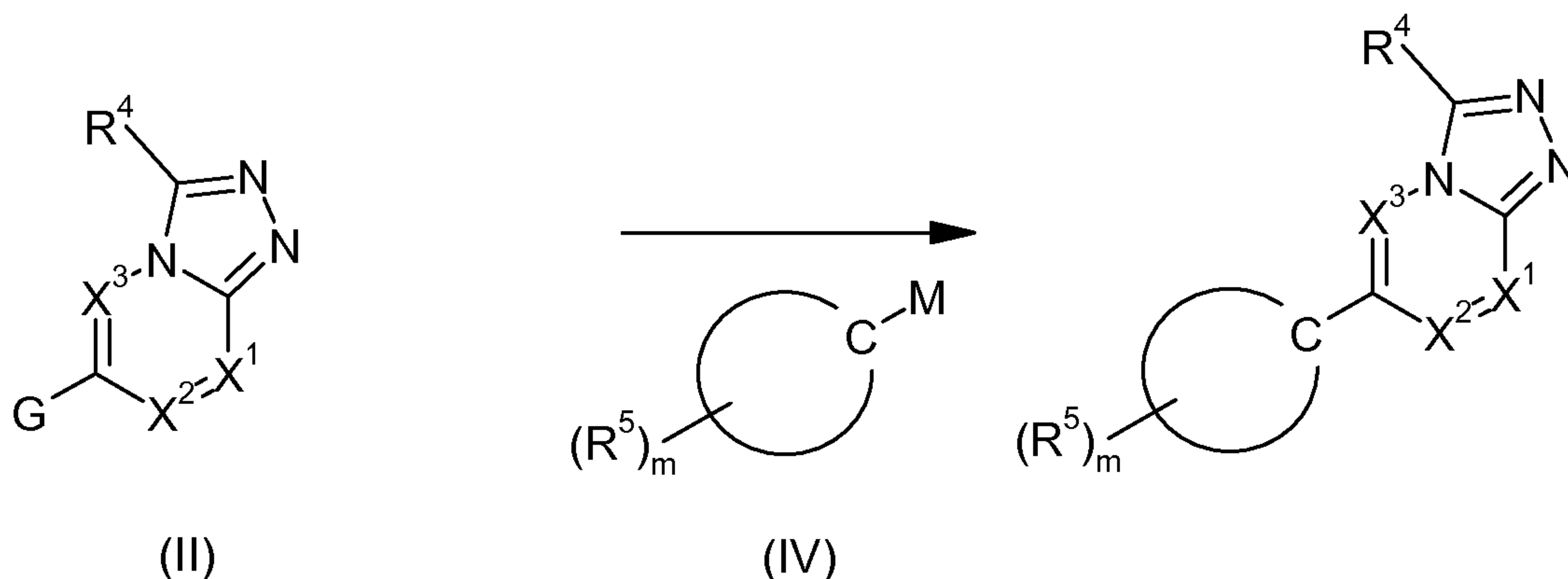
Compounds of formula (II), (IIa) or (IIb) may be made by methods well-known to those skilled in the art including methods according to or analogous to methods described in the chemical literature, for instance as described in W.L. Mosby, *Heterocyclic  
 20 Compounds*, Vol. 15 Part 1 and Part 2, *Systems with Bridgehead Nitrogen*, Interscience,



1961; R.N. Castle, *Heterocyclic Compounds*, Vol. 27, *Condensed Pyridazines*, Wiley, 1973; and *Heterocyclic Chemistry*, Vol. 35, *Condensed Pyrazines*, G.W.H. Cheeseman and R.F. Cookson, Wiley, 1979 and references therein.

Amines of formula (III), (IIIa) or (IIIb) may be made by methods well-known to those skilled in the art including methods according to or analogous to methods described in the chemical literature, for instance J.R. Malpass, *Aliphatic and Cyclic Amines* in *Comprehensive Organic Chemistry*, Volume 2, p3, D. Barton and D. Ollis Eds, Pergamon, 1979, J.M.J.Gladych and D. Hartley, *Polyfunctional Amines* in *Comprehensive Organic Chemistry*, Volume 2, p61, D. Barton and D. Ollis Eds, Pergamon, 1979; *Houben-Weyl Methods of Organic Chemistry*, Vol E 23 e *Cyclic Compounds I* (1999) to Vol E 23 j *Cyclic Compounds VI* (2000) and references therein and modified as required by functional group transformations well-known to those skilled in the art including methods according to or analogous to methods described in the chemical literature, for instance *Comprehensive Functional Group Transformations*, A.R. Katritzky, O. Meth-Cohn, and C.W. Rees Eds., Pergamon, 1995, and references therein.

2. A process for the manufacture of compounds of Formula (I) comprises reacting a compound of formula (II), wherein G is a leaving group such as iodide, bromide, chloride, alkane sulfonyloxy, or arylsulfonyloxy and  $R^4$ ,  $X^1$ ,  $X^2$ , and  $X^3$  are as defined above, with a monocyclic or bicyclic organometallic compound such as an organozinc compound of formula (IV) wherein  $R^5$  and m are as defined above and M is a suitable metal such as Zn-W wherein W is one or more inert ligand or ligands, such as bromide or iodide.



The reaction may be advantageously catalysed by low-valent transition metal catalysts such as Pd(0), for instance bis(diphenylphosphinoferrocene)palladium(II) dichloride (dppf).

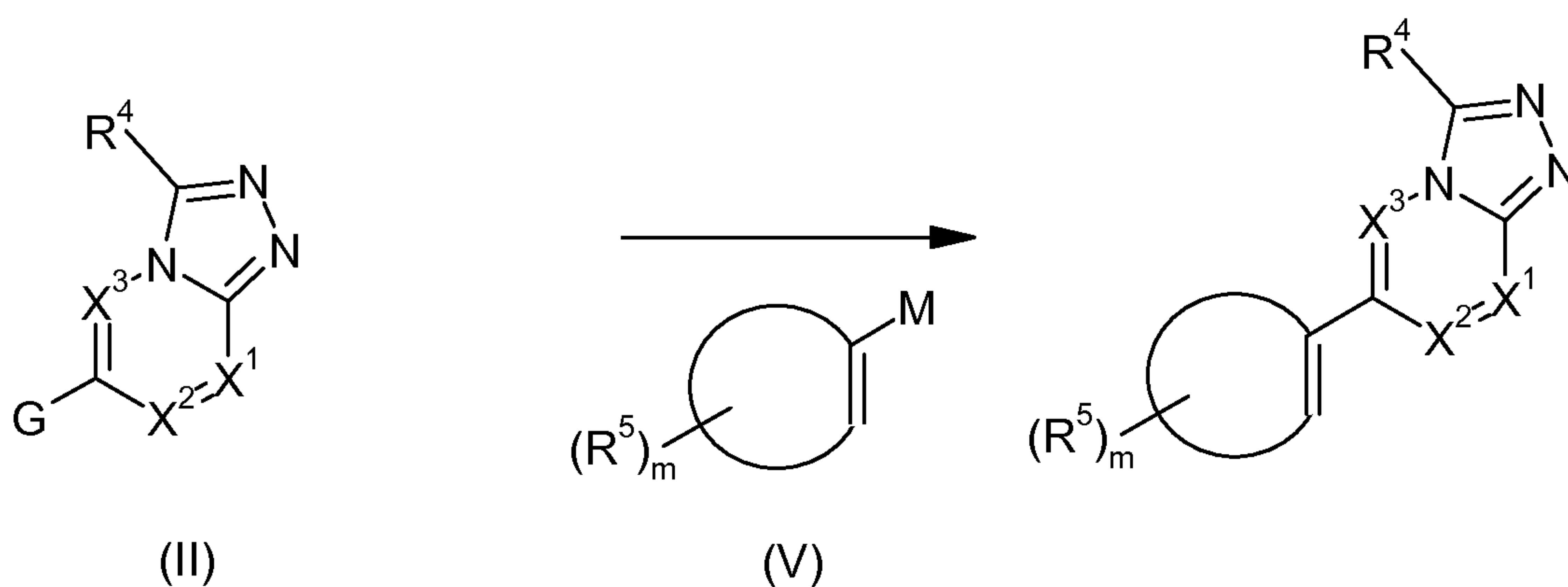
The reaction may be carried out by combining the components in an inert solvent such as



xylene or tetrahydrofuran at temperatures between 0°C and 150°C, preferably between 25°C and 100°C. The reaction may be heated by a conventional heat source, such as an oil bath or a heating block, or by microwave heating.

Organometallic reagents of formula (IV) may be made by methods well-known to those skilled in the art including methods according to or analogous to methods described in the chemical literature, for instance E. Nakamura, *Organozinc Chemistry* p590 in *Organometallics in Synthesis*, M. Schlosser Ed., Wiley, 2002 and references therein.

3. A process for the manufacture of compounds of Formula (I) comprises reacting a compound of formula (II), wherein G is a leaving group such as iodide, bromide, chloride, alkane sulfonyloxy, or arylsulfonyloxy and  $R^4$ ,  $X^1$ ,  $X^2$ , and  $X^3$  are as defined above, with a monocyclic or bicyclic organometallic compound such as an organoborane compound of formula (V) wherein M is an organometallic residue such as  $B(OH)_2$  and wherein  $R^5$  and m are as defined above.



Alternatively, M is a leaving group such as iodide, bromide, chloride, alkane sulfonyloxy, or arylsulfonyloxy and R<sup>4</sup>, X<sup>1</sup>, X<sup>2</sup>, and X<sup>3</sup> are as defined above and G is an organometallic compound such as an organostannane and wherein R<sup>5</sup> and m are as defined above.

The reaction may be advantageously catalysed by low-valent transition metal catalysts such as Pd(0), for instance bis(dibenzylideneacetone)palladium/triphenylarsine.

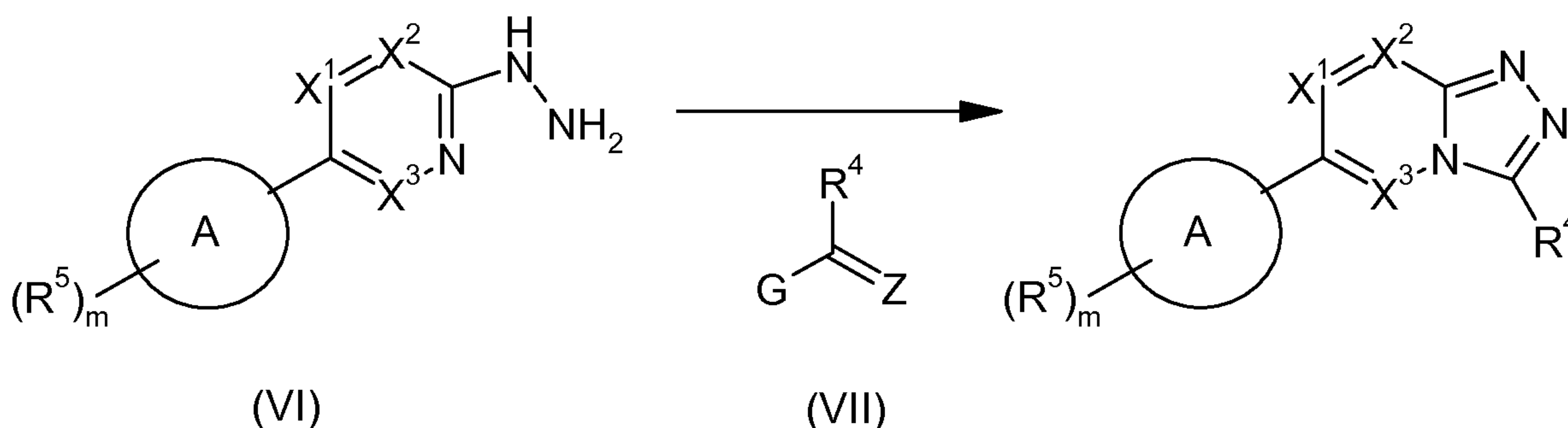
20 The reaction may be carried out by combining the components in an inert solvent such as xylene or tetrahydrofuran or N-methylpyrrolidone at temperatures between 0°C and 150°C, preferably between 25°C and 100°C. The reaction may be heated by a conventional heat source, such as an oil bath or a heating block, or by microwave heating.

For further details of such coupling reactions see for instance *Organometallics in*  
25 *Synthesis*, M. Schlosser Ed., Wiley, 2002, and references therein.



Organometallic reagents of formula (V) may be made by methods well-known to those skilled in the art including methods according to or analogous to methods described in the chemical literature, for instance *Comprehensive Organometallic Chemistry*, G. Wilkinson and F.G.A. Stone, Eds., Pergamon, 1982, and *Organometallics in Synthesis*, M. Schlosser Ed., Wiley, 2002, and references therein

4. A process for the manufacture of compounds of Formula (I) comprises reacting a compound of formula VI with an acylating agent, such as a carboxylic acid or a reactive derivative thereof wherein  $R^4$ ,  $X^1$ ,  $X^2$ , and  $X^3$ ,  $R^5$ , and  $m$  are as defined above. Suitable acylating reagents  $RC(Z)G$  are for instance carboxylic acid derivatives wherein  $G =$  is selected from Cl,  $O-C(=O)R$ ,  $O$ -Alkyl,  $S$ -Alkyl and  $Z$  is selected from  $O$ ,  $S$ ,  $N$ -Alkyl or  $N$ -Aryl, or wherein  $Z$  and  $G$  taken together with the carbon atom to which they are attached form a nitrile or an orthoester or an orthoamide.



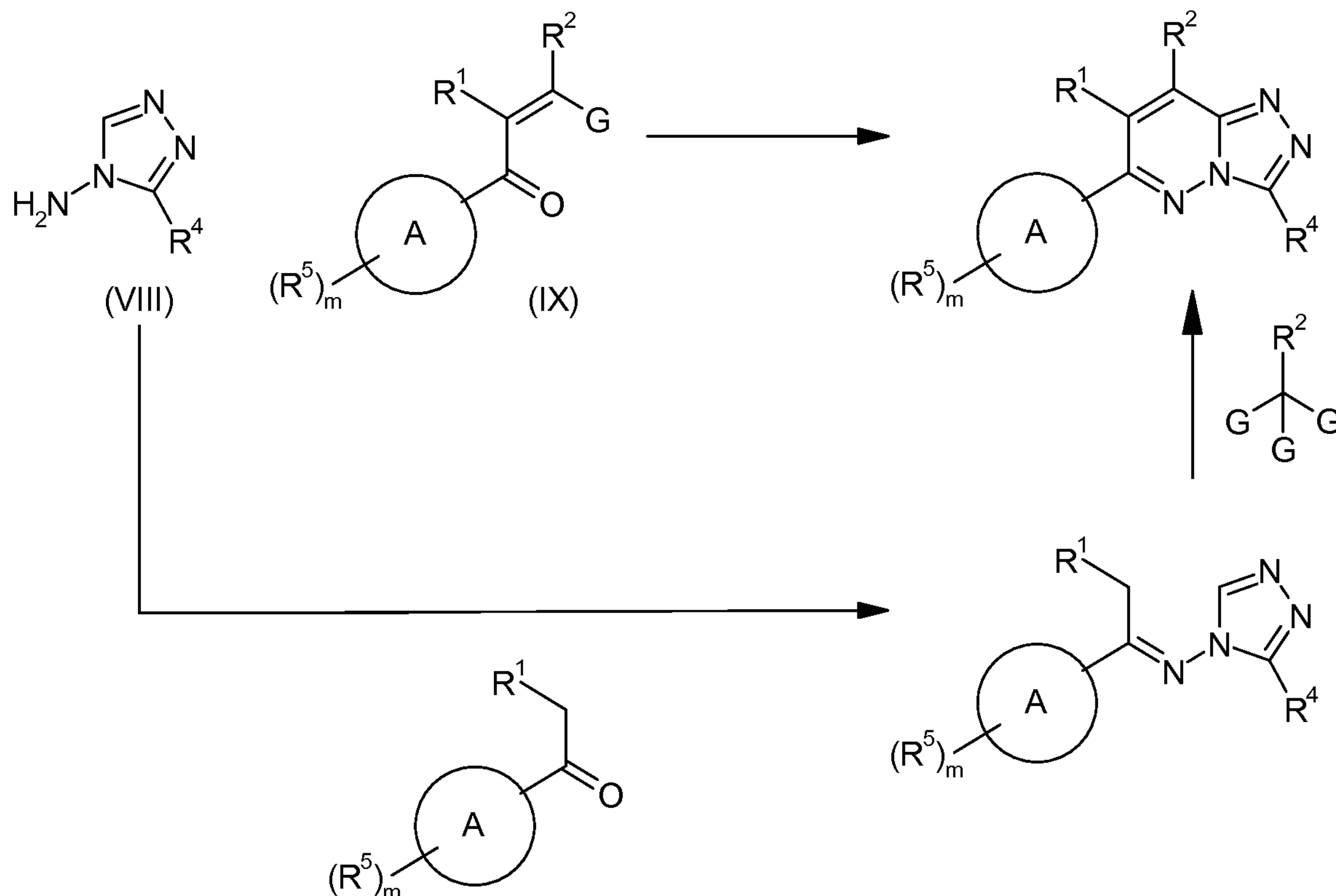
- The reaction may be carried out by combining the components in the absence of a solvent or in an inert solvent such as ortho-dichlorobenzene at temperatures between  $25^\circ\text{C}$  and  $250^\circ\text{C}$ , preferably between  $50^\circ\text{C}$  and  $150^\circ\text{C}$ . The reaction may be heated by a conventional heat source, such as an oil bath or a heating block, or by microwave heating.

- Compounds of formula (VI) may be made by methods well-known to those skilled in the art including methods according to or analogous to methods described in the chemical literature, for instance as described in W.L. Mosby, *Heterocyclic Compounds*, Vol. 15 Part 1 and Part 2, *Systems with Bridgehead Nitrogen*, Interscience, 1961; R.N. Castle, *Heterocyclic Compounds*, Vol. 27, *Condensed Pyridazines*, Wiley, 1973; and *Heterocyclic Chemistry*, Vol. 35, *Condensed Pyrazines*, G.W.H. Cheeseman and R.F. Cookson, Wiley, 1979 and references therein.

5. A process for the manufacture of compounds of Formula (I) wherein  $X^1$  and  $X^2$  are  $C(R^1)$  and  $C(R^2)$  respectively and  $X^3$  is nitrogen comprises reacting an N-amino-1,2,4-triazole (VIII) wherein  $R^4$  is as defined above with an unsaturated ketone or unsaturated



ester (IX) wherein G is a leaving group such as alkoxy or dialkylamino and  $R^1$ ,  $R^2$ ,  $R^5$  and m are as defined above



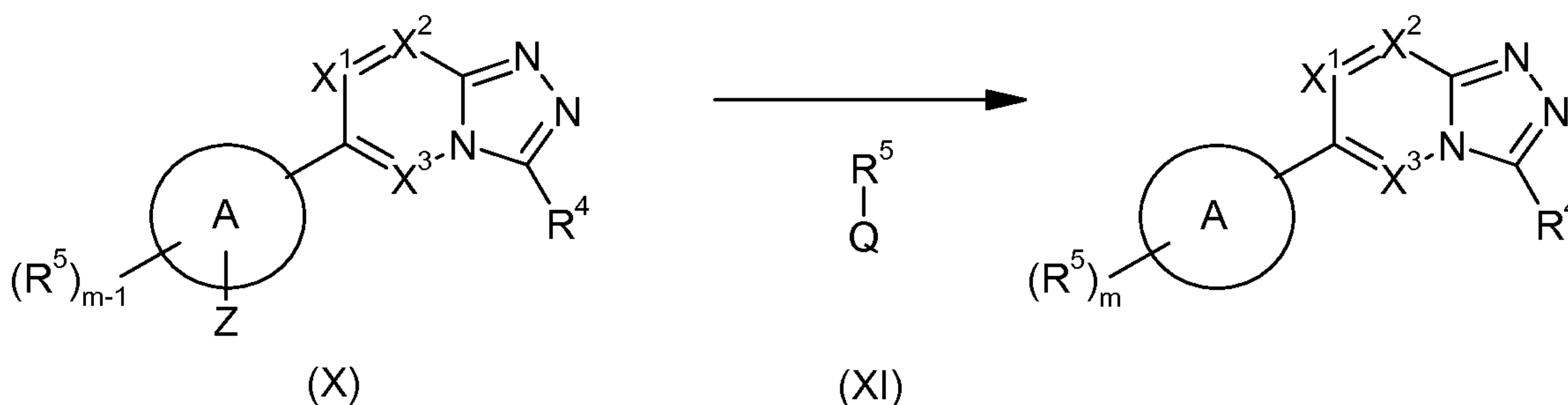
The reaction may be carried out in one or two steps as shown and the last step takes place in a solvent such as acetic acid at temperatures between 25°C and 250°C, preferably between 50°C and 150°C for instance according to the procedure of D.F. Lieberman and J.D. Albright, *J. Het. Chem.*, **1988**, 827.

Other useful and related processes for the manufacture of compounds of Formula (I) or for the preparation of starting materials for the manufacture of compounds of Formula (I) are disclosed in the literature for instance in W.L. Mosby, *Heterocyclic Compounds*, Vol. 15 Part 1 and Part 2, *Systems with Bridgehead Nitrogen*, Interscience, 1961; R.N. Castle, *Heterocyclic Compounds*, Vol. 27, *Condensed Pyridazines*, Wiley, 1973; and *Heterocyclic Chemistry*, Vol. 35, *Condensed Pyrazines*, G.W.H. Cheeseman and R.F. Cookson, Wiley, 1979 and references therein.

6. A process for the manufacture of compounds of Formula (I) comprises introducing a group  $R^5$  by reacting a compound of formula (X) wherein Z is a replaceable group such as a hydrogen of a primary or secondary amine, or Z is a leaving group such as halogen or alkyl or aryl sulfonyloxy, or Z is a counterion such as sodium(I) or magnesium(II) with a



compound of formula (XI) wherein  $R^5$  is as defined above and Q is a replaceable group such as a hydrogen of a primary or secondary amine, or Q is a leaving group such as halogen or alkyl or aryl sulfonyloxy, or Q is a counterion such as sodium(I) or magnesium(II).



Examples of reactions of this type include alkylations, acylations, and sulfonylations. Alternatively, if Z is the hydrogen of a secondary amine, preferably a cyclic secondary amine and  $R^5$ -Q is an aldehyde, the  $m^{\text{th}}$  group  $R^5$  may be introduced by reductive amination, for instance by reducing the mixture of aldehyde and secondary amine with sodium cyanoborohydride.

7. A process for the manufacture of compounds of Formula (I) comprises converting a functional group of one compound of the invention into another functional group using standard chemical reactions well-known to those skilled in the art to produce another compound of the invention. Such methods are described for instance in *Comprehensive Organic Chemistry*, Volume 2, p3, D. Barton and D. Ollis Eds, Pergamon, 1979, *Comprehensive Functional Group Transformations*, A.R. Katritzky, O. Meth-Cohn, and C.W. Rees Eds., Pergamon, 1995, and by various authors in *Houben-Weyl, Methods of Organic Chemistry*, Verlag Chemie, various years, and references therein.

8. A process for the manufacture of compounds of the invention comprises introducing a new functional group into one compound of the invention using standard chemical reactions well-known to those skilled in the art to produce another compound of the invention. Such methods are described for instance in *Comprehensive Organic Chemistry*, Volume 2, p3, D. Barton and D. Ollis Eds, Pergamon, 1979, *Comprehensive Functional Group Transformations*, A.R. Katritzky, O. Meth-Cohn, and C.W. Rees Eds., Pergamon, 1995, and by various authors in *Houben-Weyl, Methods of Organic Chemistry*, Verlag Chemie, various years, and references therein.



9. A process for the manufacture of compounds of the invention in the form of a single enantiomer comprises separating a racemic compound of the invention into separate enantiomers.

Examples of suitable methods for separating the enantiomers of a racemic  
5 compound include chromatography using a suitable chiral stationary phase; or conversion of a racemic mixture into diastereomeric derivatives, separation of the mixture of diastereomeric derivatives into two single diastereomers, and regeneration of a separate single enantiomer from each separate single diastereomer; or selective chemical reaction of one of the enantiomers of a racemic compound (kinetic resolution) using a  
10 diastereoselective reaction catalysed by a microbiological agent or an enzyme.

Examples of suitable methods for separating a mixture of diastereomers include fractional crystallisation, normal-phase chromatography or reverse-phase chromatography.

Examples of suitable diastereomeric derivatives where  $R^5$  contains an hydroxy- or amino-group include esters formed by acylation of  $R^5$  using an activated derivative of a  
15 single enantiomer of a carboxylic acid. An example of a suitable carboxylic acid is camphanic acid.

Examples of suitable diastereomeric derivatives where  $R^5$  contains a carboxylic acid include esters or amides formed by acylation of a single enantiomer of an alcohol or amine using an activated derivative of a compound of Formula (I) wherein at least one of  
20  $R^5$  contains a carboxylic acid. An example of a suitable amine is 1-phenylethylamine and an example of a suitable alcohol is menthol.

Examples of suitable agents to carry out a kinetic resolution of a racemic mixture of compounds of the invention include Hog Liver Esterase and Baker's Yeast.

10. A process for the manufacture of a compound of the invention in the form of a  
25 single enantiomer comprises carrying out one of the processes described in the preceding sections using chiral intermediates in resolved form.

It will be appreciated by a person skilled in the art that it may be necessary/desirable to protect any sensitive groups in the compounds in some of the processes/ reactions mentioned herein. The instances where protection is necessary or  
30 desirable, and suitable methods for providing such protection are known to those skilled in the art. Conventional protecting groups may be used in accordance with standard practice (for illustration see P.G.M. Wuts and T.W. Green, *Protective Groups in Organic Synthesis*,



4th Edition, John Wiley and Sons, 2002). Thus, if reactants include groups such as amino, carboxy or hydroxy it may be desirable to protect the group in some of the reactions mentioned herein.

Any protecting groups utilised in the processes described herein may in general be  
5 chosen from any of the groups described in the literature or known to the skilled chemist as appropriate for the protection of the group in question and may be introduced by conventional methods. Protecting groups may be removed by any convenient method as described in the literature or known to the skilled chemist as appropriate for the removal of the protecting group in question, such methods being chosen so as to effect removal of the  
10 protecting group with minimum disturbance of groups elsewhere in the molecule.

Specific examples of protecting groups are given below for the sake of convenience, in which "lower", as in, for example, lower alkyl, signifies that the group to which it is applied preferably has 1-4 carbon atoms. It will be understood that these examples are not exhaustive. Where specific examples of methods for the removal of  
15 protecting groups are given below these are similarly not exhaustive. The use of protecting groups and methods of deprotection not specifically mentioned is of course within the scope of the invention.

A suitable protecting group for an amino or alkylamino group is, for example, an acyl group, for example an alkanoyl group such as trifluoroacetyl, an alkoxycarbonyl  
20 group, for example a methoxycarbonyl, ethoxycarbonyl or *t*-butoxycarbonyl group, an arylmethoxycarbonyl group, for example benzyloxycarbonyl, or an aroyl or heteroaroyl group, for example picolinoyl. The deprotection conditions for the above protecting groups necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or alkoxycarbonyl group or an aroyl group may be removed for  
25 example, by hydrolysis with a suitable acid such as hydrochloric, sulphuric, or phosphoric acid or trifluoroacetic acid or a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an acyl group such as a *t*-butoxycarbonyl group may be removed, for example, by treatment with a suitable acid as hydrochloric, sulphuric or phosphoric acid or trifluoroacetic acid and an  
30 arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon, or by treatment with a Lewis acid for example boron tris(trifluoroacetate). A suitable alternative protecting



group for a primary amino group is, for example, a phthaloyl group which may be removed by treatment with an alkylamine, for example dimethylaminopropylamine, or with hydrazine.

A suitable protecting group for a hydroxy group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an aroyl group, for example benzoyl, or an arylmethyl group, for example benzyl. The deprotection conditions for the above protecting groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or an aroyl group may be removed, for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an arylmethyl group such as a benzyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

A suitable protecting group for a carboxy group is, for example, an esterifying group, for example a methyl or an ethyl group which may be removed, for example, by hydrolysis with a base such as sodium hydroxide, or for example a *t*-butyl group which may be removed, for example, by treatment with an acid, for example an organic acid such as trifluoroacetic acid, or for example a benzyl group which may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

The protecting groups may be removed at any convenient stage in the synthesis using conventional techniques well known in the chemical art.

### Biological Assays

The ability of compounds to reduce Androgen Receptor (AR) numbers was assessed in a cell based immuno-fluorescence assay using the LNCaP prostate epithelial cell line.

#### 25 a) LNCaP Androgen Receptor down-regulation cell assay

This immunofluorescence end point assay measures the ability of a test compound to down-regulate and reduce measured levels of the AR in the LNCaP prostate carcinoma cell line (LNCaP clone FGC (CRL-1740) obtained from the American Type Culture Collection (ATCC)).

30 LNCaP cells were cultured in Growth Medium (phenol red free Roswell Park Memorial Institute (RPMI) 1640 (Invitrogen Code no. 11835-063) containing 2mM L-Glutamine (Invitrogen Code no. 25030-024) and 1%(v/v) Penicillin/Streptomycin (10000



units/ml Penicillin and 10000 µg/ml of Streptomycin utilising penicillin G (sodium salt) and streptomycin sulphate: prepared in normal saline, Invitrogen Code no. 15140122) and 10%(v/v) foetal bovine serum (FBS)) in a 5% CO<sub>2</sub> air incubator at 37°C. Cells for assay were harvested from T175 stock flasks by washing once in PBS (phosphate buffered saline, pH 7.4) (Invitrogen Code no. 14190-094) and harvested using 5mls of 1 x Trypsin / ethylenediaminetetraacetic acid (EDTA) (10 x Trypsin-EDTA, 5.0 g/L Trypsin, 2.0 g/L of EDTA•4Na and 8.5 g/L of NaCl, without Phenol Red, Invitrogen Code no. 15400-054) diluted in PBS solution. A 5ml volume of Growth Medium was added to each flask (as above except that 5% (v/v) charcoal stripped FBS (HyClone Code no. SH30068.03) was included instead of 10% (v/v) FBS). Cells were syringed at least twice using a sterile 18G x 1.5" (1.2 x 40mm) broad gauge needle and cell density was measured using a haemocytometer. Cells were further diluted in Growth Medium plus 5% (v/v) charcoal stripped FBS and seeded at a density of 6.5x10<sup>3</sup> cells per well (in 90ul) into transparent, black, tissue culture treated 96 well plates (Packard, No. 6005182).

Test data reported herein was generated using two different compounds preparation and dosing methods. In method (1) a 10mM compound stock solution in 100% (v/v) DMSO was serially diluted in 4-fold steps in 100% (v/v) DMSO using a Thermo Scientific Matrix SerialMate. The diluted compounds were then further diluted 1 in 30 in assay media using a Thermo Scientific Matrix PlateMate and a 10µl aliquot of this dilution was dosed to cells manually using a multi-channel pipette. In method (2) starting with a 10mM compound stock solution, the Labcyte Echo 550 was used to generate a compound concentration response set diluted in 30µl of assay media. The Echo 550 is a liquid handler that uses acoustic technology to perform direct microplate-to-microplate transfers of DMSO compound solutions. The system can be programmed to transfer volumes as low as 2.5 nL in multiple increments between microplates and in so doing generates a serial dilution of compound which is then back-filled to normalise the DMSO concentration across the dilution range. A 10µl volume of diluted compound is then dosed to cells using a Thermo Scientific Matrix PlateMate.

Plates were incubated overnight at 37°C, 5% CO<sub>2</sub>. Wells were then dosed with compound prepared by one of the 2 methods above and further incubated for 20-22 hours at 37°C, 5% CO<sub>2</sub>. Plates were fixed by the addition of 20 µl of 10% (v/v) formaldehyde solution (in PBS) to each well (final formaldehyde conc.= 1.67%(v/v)) and left at room



temperature for 10 mins. This fixative solution was removed and cells were washed with 250µl of PBS/0.05% (v/v) Tween 20 (PBST) using an automated plate washer. This process was then repeated twice more.

Immunostaining was performed at room temperature. Cells were permeabilised by the addition of 35 µl of PBS containing 0.5% Tween 20 and incubated for 1 hour at room temperature. Permeabilisation solution was removed and cells were washed with 250µl of PBST using an automated plate washer. This process was then repeated twice more. 35 µl of Blocking Solution (PBST containing 3%(w/v) Marvel dried skimmed milk (Nestle)) was added to each well and plates were incubated at room temperature for a minimum of 1 hour. Following removal of the Blocking Solution with a plate washer, 35µl of mouse anti-human AR monoclonal antibody (clone AR441) (immunogen – synthetic peptide corresponding to amino acids 229-315 of the human AR coupled to keyhole limpet hemocyanin, DAKO, Code No. M3562), diluted 1:500 in Blocking Solution, was added to each well and incubated for 1 hour. Then this primary antibody solution was removed from the wells followed by 3 x 100µl PBST washes using a plate washer. Then 35µl of Alexa-Fluor 488 goat anti-mouse IgG secondary antibody (Invitrogen, Code No. A-11001), diluted 1:500 in Blocking Solution, was added to each well. Henceforth, wherever possible, plates were protected from light exposure. The plates were incubated for 1 hour and then the secondary antibody solution was removed from the wells followed by 3 x 100ul PBST washes using a plate washer. Then 50µl of PBST was added to each well and plates were covered with a black plate seal and stored at 4°C before being read. Plates were read within six hours of completing the immunostaining.

The Green Fluorescent AR-associated signal in each well was measured using an Acumen Explorer HTS Reader (TTP Labtech Ltd., Cambridge). AR-associated fluorescence emission can be detected at 530nm following excitation at 488nm. The instrument is a laser-scanning fluorescence microplate cytometer which samples the well at regular intervals and uses threshold algorithms to identify all fluorescent intensities above the solution background without the need to generate and analyse an image. These fluorescent objects can be quantified and provide a measure of the AR levels in cells. Fluorescence dose response data obtained with each compound was exported into a suitable software package (such as Origin) to perform curve fitting analysis. Down-



regulation of AR levels was expressed as an IC<sub>50</sub> value. This was determined by calculation of the concentration of compound that was required to give a 50% reduction of the AR signal.

The following table discloses biological data for compounds of the present invention using the aforementioned down-regulation assay.

| Example Number | Androgen Receptor Down-regulation Assay (a) IC <sub>50</sub> /μM | Example Number | Androgen Receptor Down-regulation Assay (a) IC <sub>50</sub> /μM | Example Number | Androgen Receptor Down-regulation Assay (a) IC <sub>50</sub> /μM |
|----------------|------------------------------------------------------------------|----------------|------------------------------------------------------------------|----------------|------------------------------------------------------------------|
| 1              | 3.4                                                              | 21             | 0.27                                                             | 41             | 28                                                               |
| 2              | 8.3                                                              | 22             | 1.4                                                              | 42             | 12.0                                                             |
| 3              | 11                                                               | 23             | 0.45                                                             | 43             | 1.5                                                              |
| 4              | 2.5                                                              | 24             | >26                                                              | 44             | 1.3                                                              |
| 5              | 1.6                                                              | 25             | 1.1                                                              | 45             | 1.4                                                              |
| 6              | 7.5                                                              | 26             | 1.0                                                              | 46             | 1.3                                                              |
| 7              | 18                                                               | 27             | 1.2                                                              | 47             | 1.5                                                              |
| 8              | 1.7                                                              | 28             | 2.8                                                              | 48             | 1.5                                                              |
| 9              | 1.7                                                              | 29             | 4.2                                                              | 49             | 3.2                                                              |
| 10             | 14                                                               | 30             | 0.38                                                             | 50             | 1.4                                                              |
| 11             | 2.5                                                              | 31             | 2.1                                                              | 51             | 8.4                                                              |
| 12             | 4.3                                                              | 32             | 1.6                                                              | 52             | 1.3                                                              |
| 13             | 8.4                                                              | 33             | 0.68                                                             | 53             | 7.9                                                              |
| 14             | 0.69                                                             | 34             | 20                                                               | 54             | 6.7                                                              |
| 15             | 2.5                                                              | 35             | 3.0                                                              | 55             | 8.8                                                              |
| 16             | 0.77                                                             | 36             | 0.99                                                             | 56             | 2.1                                                              |
| 17             | 2.5                                                              | 37             | 1.4                                                              | 57             | 4.3                                                              |
| 18             | 1.2                                                              | 38             | 1.2                                                              | 58             | 3.1                                                              |
| 19             | 0.52                                                             | 39             | 5.0                                                              | 59             | 2.7                                                              |
| 20             | 1.8                                                              | 40             | 3.3                                                              | 60             | 0.61                                                             |



| Example Number | Androgen Receptor Down-regulation Assay (a) IC <sub>50</sub> /μM |
|----------------|------------------------------------------------------------------|
| 61             | 7.4                                                              |
| 62             | 0.72                                                             |
| 63             | 1.5                                                              |
| 64             | 2.5                                                              |
| 65             | 0.76                                                             |
| 66             | 0.33                                                             |
| 67             | 1.0                                                              |
| 68             | 1.20                                                             |
| 69             | 1.4                                                              |
| 70             | 0.64                                                             |
| 71             | 1.4                                                              |
| 72             | 1.0                                                              |
| 73             | 12                                                               |
| 74             | 5.6                                                              |
| 75             | 2.3                                                              |
| 76             | 2.3                                                              |
| 77             | 1.4                                                              |
| 78             | 1.20                                                             |
| 79             | 2.4                                                              |
| 80             | 16                                                               |
| 81             | 7.2                                                              |
| 82             | 1.6                                                              |
| 83             | 2.5                                                              |
| 84             | 1.8                                                              |
| 85             | 1.6                                                              |

| Example Number | Androgen Receptor Down-regulation Assay (a) IC <sub>50</sub> /μM |
|----------------|------------------------------------------------------------------|
| 86             | 1.2                                                              |
| 87             | 5.2                                                              |
| 88             | 1.5                                                              |
| 89             | 23                                                               |
| 90             | 3.2                                                              |
| 91             | 1.2                                                              |
| 92             | 12                                                               |
| 93             | 1.3                                                              |
| 94             | 0.93                                                             |
| 95             | 0.67                                                             |
| 96             | >1.3                                                             |
| 97             | 0.36                                                             |
| 98             | 2.3                                                              |
| 99             | 2.9                                                              |
| 100            | 1.8                                                              |
| 101            | 1.7                                                              |
| 102            | 2.9                                                              |
| 103            | 6.2                                                              |
| 104            | 9.5                                                              |
| 105            | 3.2                                                              |
| 106            | 4.4                                                              |
| 107            | 7.2                                                              |
| 108            | 2.3                                                              |
| 109            | 7.2                                                              |
| 110            | 1.3                                                              |

| Example Number | Androgen Receptor Down-regulation Assay (a) IC <sub>50</sub> /μM |
|----------------|------------------------------------------------------------------|
| 111            | 0.77                                                             |
| 112            | 4.7                                                              |
| 113            | 7.1                                                              |
| 114            | 6.5                                                              |
| 115            | 2.5                                                              |
| 116            | 1.1                                                              |
| 117            | 1.7                                                              |
| 118            | 0.30                                                             |
| 119            | 2.2                                                              |
| 120            | 1.7                                                              |
| 121            | 4.8                                                              |
| 122            | 4.3                                                              |
| 123            | 4.1                                                              |
| 124            | 1.7                                                              |
| 125            | 1.9                                                              |
| 126            | 2.0                                                              |
| 127            | 1.5                                                              |
| 128            | 2.3                                                              |
| 129            | 0.99                                                             |
| 130            | 1.8                                                              |
| 131            | 4.1                                                              |
| 132            | 2.6                                                              |
| 133            | 1.3                                                              |
| 134            | 1.8                                                              |
| 135            | 4.9                                                              |



| Example Number | Androgen Receptor Down-regulation Assay (a) IC <sub>50</sub> /μM |
|----------------|------------------------------------------------------------------|
| 136            | 1.2                                                              |
| 137            | 1.5                                                              |
| 138            | 13                                                               |
| 139            | 2.0                                                              |
| 140            | 7.1                                                              |
| 141            | 9.7                                                              |
| 142            | 5.1                                                              |
| 143            | 8.8                                                              |
| 144            | 4.9                                                              |
| 145            | 1.2                                                              |
| 146            | 7.3                                                              |
| 147            | 2.5                                                              |
| 148            | 3.4                                                              |
| 149            | 7.9                                                              |
| 150            | 7.6                                                              |
| 151            | 3.1                                                              |
| 152            | 6.7                                                              |
| 153            | 7.9                                                              |
| 154            | 1.6                                                              |
| 155            | 18                                                               |
| 156            | 11                                                               |
| 157            | 2.4                                                              |
| 158            | 3.0                                                              |
| 159            | 1.4                                                              |
| 160            | 6.6                                                              |

| Example Number | Androgen Receptor Down-regulation Assay (a) IC <sub>50</sub> /μM |
|----------------|------------------------------------------------------------------|
| 161            | 1.4                                                              |
| 162            | 1.0                                                              |
| 163            | 3.6                                                              |
| 164            | 1.7                                                              |
| 165            | 1.7                                                              |
| 166            | 0.93                                                             |
| 167            | 2.4                                                              |
| 168            | 1.6                                                              |
| 169            | 0.92                                                             |
| 170            | 0.61                                                             |
| 171            | 0.62                                                             |
| 172            | 0.81                                                             |
| 173            | 1.2                                                              |
| 174            | 0.94                                                             |
| 175            | 0.68                                                             |
| 176            | 0.85                                                             |
| 177            | 0.77                                                             |
| 178            | 0.88                                                             |
| 179            | 0.59                                                             |
| 180            | 1.2                                                              |
| 181            | 2.1                                                              |
| 182            | 1.2                                                              |
| 183            | 1.2                                                              |
| 184            | 14                                                               |
| 185            | 0.68                                                             |

| Example Number | Androgen Receptor Down-regulation Assay (a) IC <sub>50</sub> /μM |
|----------------|------------------------------------------------------------------|
| 186            | 2.8                                                              |
| 187            | 4.7                                                              |
| 188            | 2.2                                                              |
| 189            | 1.1                                                              |
| 190            | 0.79                                                             |
| 191            | 2.1                                                              |
| 192            | 8.7                                                              |
| 193            | 2.0                                                              |
| 194            | 2.4                                                              |
| 195            | 4.0                                                              |
| 196            | 1.5                                                              |
| 197            | 0.82                                                             |
| 198            | 1.2                                                              |
| 199            | 1.9                                                              |
| 200            | 1.3                                                              |
| 201            | 1.7                                                              |
| 202            | 11                                                               |
| 203            | 1.7                                                              |
| 204            | 1.5                                                              |
| 205            | 0.53                                                             |
| 206            | 2.0                                                              |
| 207            | 7.6                                                              |
| 208            | 13                                                               |
| 209            | 12                                                               |
| 210            | 1.8                                                              |



| Example Number | Androgen Receptor Down-regulation Assay (a) IC <sub>50</sub> /μM |
|----------------|------------------------------------------------------------------|
| 211            | 8.2                                                              |
| 212            | 3.7                                                              |
| 213            | 4.5                                                              |
| 214            | 15                                                               |
| 215            | 7.4                                                              |
| 216            | 6.8                                                              |
| 217            | 3.7                                                              |
| 218            | >7.3                                                             |
| 219            | 3.5                                                              |
| 220            | 3.6                                                              |
| 221            | 3.1                                                              |
| 222            | 2.6                                                              |
| 223            | 4.7                                                              |
| 224            | 12                                                               |
| 225            | 9.2                                                              |
| 226            | 11                                                               |
| 227            | 13                                                               |
| 228            | 15                                                               |
| 229            | 1.9                                                              |
| 230            | 2.1                                                              |
| 231            | 2.1                                                              |
| 232            | 3.6                                                              |
| 233            | 1.5                                                              |
| 234            | 2                                                                |
| 235            | 1.9                                                              |

| Example Number | Androgen Receptor Down-regulation Assay (a) IC <sub>50</sub> /μM |
|----------------|------------------------------------------------------------------|
| 236            | 5.3                                                              |
| 237            | 5.3                                                              |
| 238            | 5                                                                |
| 239            | 2.8                                                              |
| 240            | 3                                                                |
| 241            | 13                                                               |
| 242            | 7.4                                                              |
| 243            | 3.7                                                              |
| 244            | 15                                                               |
| 245            | 17                                                               |
| 246            | 23                                                               |
| 247            | 12                                                               |
| 248            | 1.7                                                              |
| 249            | 6.3                                                              |
| 250            | 4.9                                                              |
| 251            | 9.3                                                              |
| 252            | 8.9                                                              |
| 253            | 3.7                                                              |
| 254            | 1.3                                                              |
| 255            | 1.8                                                              |
| 256            | 7.4                                                              |
| 257            | 9                                                                |
| 258            | 6.4                                                              |
| 259            | 4.8                                                              |
| 260            | 5.6                                                              |

| Example Number | Androgen Receptor Down-regulation Assay (a) IC <sub>50</sub> /μM |
|----------------|------------------------------------------------------------------|
| 261            | 7.9                                                              |
| 262            | 25                                                               |
| 263            | 11                                                               |
| 264            | 0.95                                                             |
| 265            | 3.8                                                              |
| 266            | 0.63                                                             |
| 267            | 0.85                                                             |
| 268            | 0.91                                                             |
| 269            | 2                                                                |
| 270            | 10                                                               |
| 271            | 1.8                                                              |
| 272            | 1.8                                                              |
| 273            | 10                                                               |
| 274            | 6.1                                                              |
| 275            | 6                                                                |
| 276            | 15                                                               |
| 277            | 2                                                                |
| 278            | 0.65                                                             |
| 279            | 13                                                               |
| 280            | 0.78                                                             |
| 281            | 0.8                                                              |
| 282            | 2.4                                                              |
| 283            | 0.78                                                             |
| 284            | 0.98                                                             |
| 285            | 2.7                                                              |



| Example Number | Androgen Receptor Down-regulation Assay (a) IC <sub>50</sub> /μM |
|----------------|------------------------------------------------------------------|
| 286            | 8.5                                                              |
| 287            | 2                                                                |
| 288            | 3.3                                                              |
| 289            | 2.7                                                              |
| 290            | 5.8                                                              |
| 291            | >9.7                                                             |
| 292            | 7                                                                |
| 293            | 11                                                               |
| 294            | 9.5                                                              |
| 295            | 3.4                                                              |
| 296            | 2.1                                                              |
| 297            | 15                                                               |
| 298            | 5.7                                                              |
| 299            | 0.84                                                             |
| 300            | 1                                                                |
| 301            | 1.8                                                              |
| 302            | 1.1                                                              |
| 303            | 5.8                                                              |
| 304            | 1.8                                                              |
| 305            | 4                                                                |
| 306            | 1.3                                                              |
| 307            | 3.4                                                              |
| 308            | 1.4                                                              |
| 309            | 1.6                                                              |
| 310            | 3.2                                                              |

| Example Number | Androgen Receptor Down-regulation Assay (a) IC <sub>50</sub> /μM |
|----------------|------------------------------------------------------------------|
| 311            | 5                                                                |
| 312            | 2.6                                                              |
| 313            | 1.8                                                              |
| 314            | 4.6                                                              |
| 315            | 2                                                                |
| 316            | 12                                                               |
| 317            | 4.1                                                              |
| 318            | 3.7                                                              |
| 319            | 11                                                               |
| 320            | 8.6                                                              |
| 321            | 8                                                                |
| 322            | 9.6                                                              |
| 323            | >8.1                                                             |
| 324            | 5.9                                                              |
| 325            | >1.2                                                             |
| 326            | 2                                                                |
| 327            | 1                                                                |
| 328            | 0.75                                                             |
| 329            | 3.6                                                              |
| 330            | 3.7                                                              |
| 331            | 16                                                               |
| 332            | 16                                                               |
| 333            | 2.7                                                              |
| 334            | 1.1                                                              |
| 335            | 1.5                                                              |

| Example Number | Androgen Receptor Down-regulation Assay (a) IC <sub>50</sub> /μM |
|----------------|------------------------------------------------------------------|
| 336            | 2.4                                                              |
| 337            | 1.5                                                              |
| 338            | 8.5                                                              |
| 339            | 0.77                                                             |
| 340            | 1.5                                                              |
| 341            | 1.3                                                              |
| 342            | 2.1                                                              |
| 343            | 1.7                                                              |
| 344            | 0.29                                                             |
| 345            | 1.1                                                              |
| 346            | 8.5                                                              |
| 347            | 0.97                                                             |
| 348            | 1                                                                |
| 349            | 1.7                                                              |
| 350            | 0.74                                                             |
| 351            | 1.9                                                              |
| 352            | 0.57                                                             |
| 353            | 0.69                                                             |
| 354            | 2.7                                                              |
| 355            | 0.72                                                             |
| 356            | 2.2                                                              |
| 357            | 2.1                                                              |
| 358            | 6.7                                                              |
| 359            | 2.6                                                              |
| 360            | 1                                                                |



| Example Number | Androgen Receptor Down-regulation Assay (a) IC <sub>50</sub> /μM |
|----------------|------------------------------------------------------------------|
| 361            | 4.7                                                              |
| 362            | 1                                                                |
| 363            | 22                                                               |
| 364            | 16                                                               |
| 365            | 19                                                               |
| 366            | >33                                                              |
| 367            | 4.1                                                              |
| 368            | 3.4                                                              |
| 369            | 8.7                                                              |
| 370            | 11                                                               |
| 371            | 6.2                                                              |
| 372            | 1.3                                                              |
| 373            | 4                                                                |
| 374            | 0.93                                                             |
| 375            | 11                                                               |
| 376            | 3                                                                |
| 377            | 5.9                                                              |
| 378            | 11                                                               |
| 379            | 18                                                               |
| 380            | 4.2                                                              |
| 381            | 2.1                                                              |
| 382            | 1.8                                                              |
| 383            | 1.3                                                              |
| 384            | 2.9                                                              |
| 385            | 2.1                                                              |

| Example Number | Androgen Receptor Down-regulation Assay (a) IC <sub>50</sub> /μM |
|----------------|------------------------------------------------------------------|
| 386            | 2.4                                                              |
| 387            | 1.1                                                              |
| 388            | 1.6                                                              |
| 389            | 1.5                                                              |
| 390            | 1.7                                                              |
| 391            | 2.7                                                              |
| 392            | 4.5                                                              |
| 393            | 1.9                                                              |
| 394            | 5.6                                                              |
| 395            | 10                                                               |
| 396            | 1.8                                                              |
| 397            | 3.9                                                              |
| 398            | 1.9                                                              |
| 399            | 3.7                                                              |
| 400            | 1.8                                                              |
| 401            | 1.6                                                              |
| 402            | 2.8                                                              |
| 403            | 4.8                                                              |
| 404            | 2.7                                                              |
| 405            | 3                                                                |
| 406            | 6.3                                                              |
| 407            | 5.7                                                              |
| 408            | 1.7                                                              |
| 409            | 3.9                                                              |
| 410            | 2.1                                                              |

| Example Number | Androgen Receptor Down-regulation Assay (a) IC <sub>50</sub> /μM |
|----------------|------------------------------------------------------------------|
| 411            | 2.2                                                              |
| 412            | 9.1                                                              |
| 413            | 1.9                                                              |
| 414            | >10                                                              |
| 415            | 1.4                                                              |
| 416            | 2.7                                                              |
| 417            | 4.6                                                              |
| 418            | >14                                                              |
| 419            | 4                                                                |
| 420            | 5.9                                                              |
| 421            | 4                                                                |
| 422            | 4.2                                                              |
| 423            | 7.4                                                              |
| 424            | 2.2                                                              |
| 425            | 3.6                                                              |
| 426            | 2.2                                                              |
| 427            | 4.3                                                              |
| 428            | 15                                                               |
| 429            | 2.6                                                              |
| 430            | 1.7                                                              |
| 431            | 1.5                                                              |
| 432            | 1.2                                                              |
| 433            | 0.9                                                              |
| 434            | 0.83                                                             |
| 435            | 0.98                                                             |



| Example Number | Androgen Receptor Down-regulation Assay (a) IC <sub>50</sub> /μM |
|----------------|------------------------------------------------------------------|
| 436            | 0.75                                                             |
| 437            | 0.53                                                             |
| 438            | 1.6                                                              |
| 439            | 0.48                                                             |
| 440            | 2.3                                                              |
| 441            | 0.22                                                             |
| 442            | 0.44                                                             |
| 443            | 1.5                                                              |
| 444            | 1.2                                                              |
| 445            | 1.6                                                              |
| 446            | 0.7                                                              |
| 447            | 16                                                               |
| 448            | 6.3                                                              |
| 449            | 4.8                                                              |
| 450            | 8.2                                                              |
| 451            | 9.7                                                              |
| 452            | 16                                                               |
| 453            | 5.7                                                              |
| 454            | 9.2                                                              |
| 455            | 10                                                               |
| 456            | 21                                                               |
| 457            | 11                                                               |
| 458            | 21                                                               |
| 459            | 15                                                               |
| 460            | 5.1                                                              |

| Example Number | Androgen Receptor Down-regulation Assay (a) IC <sub>50</sub> /μM |
|----------------|------------------------------------------------------------------|
| 461            | 13                                                               |
| 462            | 7.7                                                              |
| 463            | 0.98                                                             |
| 464            | 1.4                                                              |
| 465            | 4                                                                |
| 466            | >19                                                              |
| 467            | 4.9                                                              |
| 468            | >11                                                              |
| 469            | 1.8                                                              |
| 470            | 4.6                                                              |
| 471            | 2                                                                |
| 472            | 3.9                                                              |
| 473            | 3.2                                                              |
| 474            | 0.96                                                             |
| 475            | >15                                                              |
| 476            | 3.5                                                              |
| 477            | 6.3                                                              |
| 478            | 1.3                                                              |
| 479            | 17                                                               |
| 480            | 9.6                                                              |
| 481            | 6.6                                                              |
| 482            | 1.8                                                              |
| 483            | >30                                                              |
| 484            | >14                                                              |
| 485            | 10                                                               |

| Example Number | Androgen Receptor Down-regulation Assay (a) IC <sub>50</sub> /μM |
|----------------|------------------------------------------------------------------|
| 486            | >13                                                              |
| 487            | 16                                                               |
| 488            | 3.1                                                              |
| 489            | 3.6                                                              |
| 490            | 5.9                                                              |
| 491            | 7.2                                                              |
| 492            | >30                                                              |
| 493            | 18                                                               |
| 494            | 0.43                                                             |
| 495            | 0.35                                                             |
| 496            | 11                                                               |
| 497            | 2.8                                                              |
| 498            | 2.4                                                              |
| 499            | 1.7                                                              |
| 500            | >18                                                              |
| 501            | 1.2                                                              |
| 502            | 2.2                                                              |
| 503            | 4.3                                                              |
| 504            | 1.9                                                              |
| 505            | >19                                                              |
| 506            | 9.8                                                              |
| 507            | 0.53                                                             |
| 508            | 2.2                                                              |
| 509            | 1.8                                                              |
| 510            | 3.7                                                              |



| Example Number | Androgen Receptor Down-regulation Assay (a) IC <sub>50</sub> /μM |
|----------------|------------------------------------------------------------------|
| 511            | 10                                                               |
| 512            | 0.87                                                             |
| 513            | 0.24                                                             |
| 514            | 0.87                                                             |
| 515            | 1.4                                                              |
| 516            | 1.4                                                              |
| 517            | 1.5                                                              |
| 518            | 11                                                               |
| 519            | 1.2                                                              |
| 520            | 1.4                                                              |
| 521            | 5.4                                                              |
| 522            | 3.9                                                              |
| 523            | 1                                                                |
| 524            | 3.2                                                              |
| 525            | 5.2                                                              |
| 526            | 2.5                                                              |
| 527            | 0.67                                                             |
| 528            | 2.2                                                              |
| 529            | 1.9                                                              |
| 530            | 1.6                                                              |
| 531            | 1.8                                                              |
| 532            | 0.98                                                             |
| 533            | 2.3                                                              |
| 534            | 2.3                                                              |
| 535            | 1.9                                                              |

| Example Number | Androgen Receptor Down-regulation Assay (a) IC <sub>50</sub> /μM |
|----------------|------------------------------------------------------------------|
| 536            | 1.4                                                              |
| 537            | 3                                                                |
| 538            | 2.3                                                              |
| 539            | 1.5                                                              |
| 540            | 1.5                                                              |
| 541            | 4                                                                |
| 542            | 2.6                                                              |
| 543            | 3.2                                                              |
| 544            | 2.9                                                              |
| 545            | 3.6                                                              |
| 546            | 1.7                                                              |
| 547            | 1.2                                                              |
| 548            | 2.2                                                              |
| 549            | 1.6                                                              |
| 550            | 7.2                                                              |
| 551            | 4                                                                |
| 552            | 7.8                                                              |
| 553            | 2.6                                                              |
| 554            | 4.9                                                              |
| 555            | 1.4                                                              |
| 556            | 4.4                                                              |
| 557            | 3.1                                                              |
| 558            | 2.6                                                              |
| 559            | 2                                                                |
| 560            | 8.8                                                              |

| Example Number | Androgen Receptor Down-regulation Assay (a) IC <sub>50</sub> /μM |
|----------------|------------------------------------------------------------------|
| 561            | 2.9                                                              |
| 562            | 2                                                                |
| 563            | 1.3                                                              |
| 564            | 6.7                                                              |
| 565            | 3.5                                                              |
| 566            | 16                                                               |
| 567            | >16                                                              |
| 568            | 3.3                                                              |
| 569            | 2.7                                                              |
| 570            | 4.5                                                              |
| 571            | 0.96                                                             |
| 572            | 3.4                                                              |
| 573            | 10                                                               |
| 574            | 4                                                                |
| 575            | 2.5                                                              |
| 576            | 5                                                                |
| 577            | 5                                                                |
| 578            | 2.5                                                              |
| 579            | 4.1                                                              |
| 580            | 2                                                                |
| 581            | 3.3                                                              |
| 582            | 2.4                                                              |
| 583            | 4.1                                                              |
| 584            | 2.8                                                              |
| 585            | 1.5                                                              |



| Example Number | Androgen Receptor Down-regulation Assay (a) IC <sub>50</sub> /μM |
|----------------|------------------------------------------------------------------|
| 586            | 2.1                                                              |
| 587            | >17                                                              |
| 588            | 5.3                                                              |
| 589            | 4.8                                                              |
| 590            | 22                                                               |
| 591            | 20                                                               |
| 592            | 9.6                                                              |
| 593            | 7.2                                                              |
| 594            | 22                                                               |
| 595            | 6.8                                                              |
| 596            | 4.2                                                              |
| 597            | 2.9                                                              |
| 598            | 4.2                                                              |
| 599            | 5.8                                                              |
| 600            | 0.85                                                             |
| 601            | 2.2                                                              |
| 602            | 1.6                                                              |
| 603            | 3.5                                                              |
| 604            | 1.7                                                              |
| 605            | 5                                                                |
| 606            | 2.7                                                              |
| 607            | 7.4                                                              |
| 608            | 2.7                                                              |
| 609            | 6.6                                                              |
| 610            | 3.2                                                              |

| Example Number | Androgen Receptor Down-regulation Assay (a) IC <sub>50</sub> /μM |
|----------------|------------------------------------------------------------------|
| 611            | 1.6                                                              |
| 612            | >13                                                              |
| 613            | 3.3                                                              |
| 614            | >12                                                              |
| 615            | 0.88                                                             |
| 616            | 1.7                                                              |
| 617            | 4.3                                                              |
| 618            | >4                                                               |
| 619            | 4.5                                                              |
| 620            | >13                                                              |
| 621            | 2.3                                                              |
| 622            | 7.4                                                              |
| 623            | 0.89                                                             |
| 624            | 3.1                                                              |
| 625            | 1.4                                                              |
| 626            | 1.1                                                              |
| 627            | 1.7                                                              |
| 628            | 2.7                                                              |
| 629            | 1.3                                                              |
| 630            | 2.4                                                              |
| 631            | 1.1                                                              |
| 632            | 1.2                                                              |
| 633            | 1.9                                                              |
| 634            | 1.1                                                              |
| 635            | 2.9                                                              |

| Example Number | Androgen Receptor Down-regulation Assay (a) IC <sub>50</sub> /μM |
|----------------|------------------------------------------------------------------|
| 636            | 20                                                               |
| 637            | 1.8                                                              |
| 638            | 0.9                                                              |
| 639            | 1.2                                                              |
| 640            | 0.92                                                             |
| 641            | 1.4                                                              |
| 642            | 1.4                                                              |
| 643            | 6                                                                |
| 644            | 1.5                                                              |
| 645            | 2.3                                                              |
| 646            | 6.1                                                              |
| 647            | 1.7                                                              |
| 648            | 2.1                                                              |
| 649            | 2.3                                                              |
| 650            | 3.1                                                              |
| 651            | 1.9                                                              |
| 652            | 3.1                                                              |
| 653            | 1                                                                |
| 654            | 2.6                                                              |
| 655            | 1.1                                                              |
| 656            | 1.1                                                              |
| 657            | 3.2                                                              |
| 658            | 0.94                                                             |
| 659            | 1                                                                |
| 660            | 0.63                                                             |



| Example Number | Androgen Receptor Down-regulation Assay (a) IC <sub>50</sub> /μM |
|----------------|------------------------------------------------------------------|
| 661            | 0.65                                                             |
| 662            | 5.4                                                              |
| 663            | 2.7                                                              |
| 664            | 3.6                                                              |
| 665            | 0.82                                                             |
| 666            | 0.94                                                             |
| 667            | 1                                                                |
| 668            | 1.1                                                              |
| 669            | 0.6                                                              |
| 670            | 0.67                                                             |
| 671            | 1.6                                                              |
| 672            | 0.58                                                             |
| 673            | 0.73                                                             |
| 674            | 1.1                                                              |
| 675            | 1.5                                                              |
| 676            | 0.56                                                             |
| 677            | 4.5                                                              |
| 678            | 15                                                               |
| 679            | 0.58                                                             |
| 680            | 0.6                                                              |
| 681            | 1.3                                                              |
| 682            | 0.58                                                             |
| 683            | 0.49                                                             |
| 684            | 0.69                                                             |
| 685            | 5.7                                                              |

| Example Number | Androgen Receptor Down-regulation Assay (a) IC <sub>50</sub> /μM |
|----------------|------------------------------------------------------------------|
| 686            | 4.2                                                              |
| 687            | 3.8                                                              |
| 688            | 6.6                                                              |
| 689            | 4.1                                                              |
| 690            | 17                                                               |
| 691            | >28                                                              |
| 692            | 4.2                                                              |
| 693            | 2.3                                                              |
| 694            | 3.2                                                              |
| 695            | 3.3                                                              |
| 696            | 4.2                                                              |
| 697            | >22                                                              |
| 698            | 5.6                                                              |
| 699            | 2.1                                                              |
| 700            | 7.1                                                              |
| 701            | 14                                                               |
| 702            | >12                                                              |
| 703            | 5.5                                                              |
| 704            | 4.2                                                              |
| 705            | 5.3                                                              |
| 706            | 2.9                                                              |
| 707            | 7.9                                                              |
| 708            | 6.2                                                              |
| 709            | 1.7                                                              |
| 710            | 2.1                                                              |

| Example Number | Androgen Receptor Down-regulation Assay (a) IC <sub>50</sub> /μM |
|----------------|------------------------------------------------------------------|
| 711            | 2.5                                                              |
| 712            | 3                                                                |
| 713            | 0.81                                                             |
| 714            | >9.9                                                             |
| 715            | 1.2                                                              |
| 716            | 0.81                                                             |
| 717            | 2.9                                                              |
| 718            | 3.6                                                              |
| 719            | 3.5                                                              |
| 720            | 2.7                                                              |
| 721            | 2.9                                                              |
| 722            | 4.1                                                              |
| 723            | 0.9                                                              |
| 724            | 0.69                                                             |
| 725            | 1.2                                                              |
| 726            | 1.4                                                              |
| 727            | 1.2                                                              |
| 728            | 1.5                                                              |
| 729            | 0.92                                                             |
| 730            | 0.72                                                             |
| 731            | 1.1                                                              |
| 732            | 1.1                                                              |
| 733            | 0.6                                                              |
| 734            | 2.5                                                              |
| 735            | 1.9                                                              |



| Example Number | Androgen Receptor Down-regulation Assay (a) IC <sub>50</sub> /μM |
|----------------|------------------------------------------------------------------|
| 736            | 0.4                                                              |
| 737            | 0.74                                                             |
| 738            | 3.3                                                              |
| 739            | 3.2                                                              |
| 740            | 2                                                                |
| 741            | 2.2                                                              |
| 742            | 17                                                               |
| 743            | 14                                                               |
| 744            | 9.6                                                              |
| 745            | 3.4                                                              |
| 746            | 3.3                                                              |
| 747            | 23                                                               |
| 748            | 5.6                                                              |
| 749            | >22                                                              |
| 750            | 2.6                                                              |
| 751            | 6.3                                                              |
| 752            | 18                                                               |
| 753            | 2.1                                                              |
| 754            | 2.5                                                              |
| 755            | 2.2                                                              |
| 756            | 3.2                                                              |
| 757            | >12                                                              |
| 758            | 1.3                                                              |
| 759            | 3.9                                                              |
| 760            | >3.1                                                             |

| Example Number | Androgen Receptor Down-regulation Assay (a) IC <sub>50</sub> /μM |
|----------------|------------------------------------------------------------------|
| 761            | 1.5                                                              |
| 762            | 1.2                                                              |
| 763            | >9.8                                                             |
| 764            | 2.5                                                              |
| 765            | 8.8                                                              |
| 766            | >17                                                              |
| 767            | >12                                                              |
| 768            | 4.7                                                              |
| 769            | 11                                                               |
| 770            | 6.3                                                              |
| 771            | 3.1                                                              |
| 772            | 14                                                               |
| 773            | 3.1                                                              |
| 774            | 8                                                                |
| 775            | 6.8                                                              |
| 776            | 6.9                                                              |
| 777            | 4.6                                                              |
| 778            | 2.6                                                              |
| 779            | 0.54                                                             |
| 780            | 0.51                                                             |
| 781            | 0.82                                                             |
| 782            | 2                                                                |
| 783            | 0.84                                                             |
| 784            | 2.2                                                              |
| 785            | 1.7                                                              |

| Example Number | Androgen Receptor Down-regulation Assay (a) IC <sub>50</sub> /μM |
|----------------|------------------------------------------------------------------|
| 786            | 8.4                                                              |
| 787            | 1.3                                                              |
| 788            | 2.2                                                              |
| 789            | 2.1                                                              |
| 790            | 2                                                                |
| 791            | 0.96                                                             |
| 792            | 16                                                               |
| 793            | 1.6                                                              |
| 794            | 1.1                                                              |
| 795            | 2.4                                                              |
| 796            | 0.63                                                             |
| 797            | 2.4                                                              |
| 798            | 1                                                                |
| 799            | 1.6                                                              |
| 800            | 1.1                                                              |
| 801            | 1.3                                                              |
| 802            | 1.2                                                              |
| 803            | 7                                                                |
| 804            | 1.3                                                              |
| 805            | 1                                                                |
| 806            | 2.3                                                              |
| 807            | 7.5                                                              |
| 808            | 1                                                                |
| 809            |                                                                  |
| 810            | 1.9                                                              |



| Example Number | Androgen Receptor Down-regulation Assay (a) IC <sub>50</sub> /μM | Example Number | Androgen Receptor Down-regulation Assay (a) IC <sub>50</sub> /μM | Example Number | Androgen Receptor Down-regulation Assay (a) IC <sub>50</sub> /μM |
|----------------|------------------------------------------------------------------|----------------|------------------------------------------------------------------|----------------|------------------------------------------------------------------|
| 811            | 1.2                                                              | 829            | 13                                                               | 848            | 3.5                                                              |
| 812            | 2.1                                                              | 830            | 0.85                                                             | 849            | 0.68                                                             |
| 813            | 6.8                                                              | 831            | 3.1                                                              | 850            | 0.56                                                             |
| 814            | 1.8                                                              | 832            | 1.4                                                              | 851            | 0.92                                                             |
| 815            | >17                                                              | 833            | >12                                                              | 852            | 0.29                                                             |
| 816            | 9.3                                                              | 834            | 4.4                                                              | 853            | 1.3                                                              |
| 817            | 5.6                                                              | 835            | 20                                                               | 854            | Not tested                                                       |
| 818            | 3.8                                                              | 837            | 1.6                                                              | 855            | 0.44                                                             |
| 819            | >18                                                              | 838            | 7.6                                                              | 856            | 2.2                                                              |
| 820            | 4                                                                | 839            | 1.1                                                              | 857            | >33                                                              |
| 821            | 2                                                                | 840            | 2.6                                                              | 858            | >33                                                              |
| 822            | 1.7                                                              | 841            | 2.9                                                              | 859            | >33                                                              |
| 823            | 4.7                                                              | 842            | 1.1                                                              | 860            | 0.8                                                              |
| 824            | 1.9                                                              | 843            | 0.93                                                             | 861            | Not tested                                                       |
| 825            | 1.9                                                              | 844            | 0.78                                                             | 862            | Not tested                                                       |
| 826            | 1.4                                                              | 845            | 0.9                                                              | 863            | Not tested                                                       |
| 827            | 1                                                                | 846            | 0.27                                                             | 864            | Not tested                                                       |
| 828            | 9.5                                                              | 847            | 3.1                                                              |                |                                                                  |

b) Androgen Receptor – Ligand binding domain competitive binding assay

The ability of compounds to bind to isolated Androgen Receptor Ligand binding domain (AR-LBD) was assessed in competition assays using either a Fluorescence Polarisation (FP) or a Lanthascreen™ Time-Resolved Fluorescence Resonance Energy Transfer (TR-FRET) detection end-point.



For the FP test, an assay test kit was purchased from Invitrogen and used to measure compound binding to the isolated rat AR-LBD which shares 100% sequence identity to the human AR-LBD. The Invitrogen PolarScreen™ Androgen Receptor Competitor Assay Red (Product Code No. PV4293), is a fluorescence polarisation (FP) – based competition assay which measures if test compound can displace a fluorescently-labelled tracer compound. If the test compound binds to the AR-LBD it will prevent the formation of the receptor/tracer complex, which will result in a low polarisation value. If the test compound does not bind the receptor, it will have no effect on formation of the receptor/tracer complex, and the measured polarisation value of the tracer will remain high.

The assay was performed as essentially described in the Invitrogen method with the exception that the final assay volume was 12µl and this required an appropriate low volume black 384 well microtitre plate. Compounds were dosed directly from a compound source microplate containing serially diluted compound (4 wells containing 10mM, 0.1mM, 1µM and 10nM final compound respectively) to an assay microplate using the Labcyte Echo 550. The Echo 550 is a liquid handler that uses acoustic technology to perform direct microplate-to-microplate transfers of DMSO compound solutions and the system can be programmed to transfer multiple small nL volumes of compound from the different source plate wells to give the desired serial dilution of compound in the assay which is then back-filled to normalise the DMSO concentration across the dilution range.

FP dose response data obtained with each compound was exported into a suitable software package (such as Origin) to perform curve fitting analysis. Competitive AR binding was expressed as an IC<sub>50</sub> value. This was determined by calculation of the concentration of compound that was required to give a 50% reduction in tracer compound binding to AR-LBD.

The following table discloses various biological data for a representative selection of compounds of the present invention using the aforementioned FP ligand binding assay.

| Example Number | Androgen Receptor FP Ligand-Binding<br>Assay IC <sub>50</sub> /µM |
|----------------|-------------------------------------------------------------------|
| 4              | 20.18                                                             |
| 41             | 19.55                                                             |



| Example Number                                                                                                                   | Androgen Receptor FP Ligand-Binding Assay IC <sub>50</sub> /μM |
|----------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------|
| 166                                                                                                                              | 6.085                                                          |
| 174                                                                                                                              | 16.3                                                           |
| 183                                                                                                                              | 14.37                                                          |
| Other Examples within the range Example 1 - Example 215 show Androgen Receptor Ligand-Binding IC <sub>50</sub> greater than 20μM |                                                                |

For Lanthascreen™ TR-FRET, a suitable fluorophore (Product code PV4294) and rat GST-tagged AR-LBD were purchased from Invitrogen and used to measure compound binding. The assay principle is that AR-LBD is added to a fluorescent ligand to form a receptor/fluorophore complex. A terbium-labelled anti-GST antibody is used to indirectly label the receptor by binding to a GST tag, and competitive binding is detected by a test compounds' ability to displace the fluorescent ligand resulting in a loss of TR-FRET signal between the Tb-anti-GST antibody and the tracer. The assay was performed as follows with all reagent additions carried out using the Thermo Scientific Matrix PlateMate :-

1. Acoustic dispense 120nl of the test compound into a black low volume 384 well assay plates.
2. Dispense 6μl of the 2x Fluorophore reagent into each well of the assay plate
3. Dispense 6μl of the 2x AR-LBD/Tb-anti-GST Ab into each well of the assay plate
4. Cover the assay plate to protect the reagents from light and evaporation, and incubate at room temperature for 1 hour.
5. Excite at 340nm and measure the fluorescent emission signal of each well at 495nm and 570nm using the BMG PheraSTAR.

Compounds were dosed directly from a compound source microplate containing serially diluted compound (4 wells containing 10mM, 0.1mM, 1μM and 10nM final compound respectively) to an assay microplate using the Labcyte Echo 550. The Echo 550 is a liquid handler that uses acoustic technology to perform direct microplate-to-microplate transfers of DMSO compound solutions and the system can be programmed to transfer multiple small nL volumes of compound from the different source plate wells to give the desired serial dilution of compound in the assay which is then back-filled to normalise the



DMSO concentration across the dilution range. In total 120nL of compound plus DMSO is added to each well and compounds were tested in a 12-point concentration response format over a final compound concentration range of 100, 30, 10, 3, 1, 0.3, 0.1, 0.03, 0.01, 0.003, 0.001, 0.0001 $\mu$ M, respectively. TR-FRET dose response data obtained with each compound was exported into a suitable software package (such as Origin) to perform curve fitting analysis. Competitive AR binding was expressed as an IC<sub>50</sub> value. This was determined by calculation of the concentration of compound that was required to give a 50% reduction in tracer compound binding to AR-LBD.

Table of Results – LanthaScreen™ AR Binding Assay

|                             |            |           |
|-----------------------------|------------|-----------|
| Example Number              | 511        | 513       |
| IC <sub>50</sub> ( $\mu$ M) | >100 (n=2) | 1.3 (n=2) |

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of the Formula (I), or a pharmaceutically acceptable salt thereof, as defined hereinbefore in association with a pharmaceutically-acceptable diluent or carrier. The composition may be in a form suitable for oral administration, for example as a tablet or capsule; for parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion) as a sterile solution, suspension or emulsion; for topical administration as an ointment or cream; or for rectal administration as a suppository.

In general the above compositions may be prepared in a conventional manner using conventional excipients. For pre-clinical *in vivo* applications simple formulations and suspensions may be used. For example, 4-pyridin-3-yl-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol may be formulated as a simple aqueous suspensions in 1%w/v Polysorbate 80 or 0.67%w/v PVP (Polyvinylpyrrolidone)/0.33%w/v Aerosol AOT (sodium 1,2-bis(2-ethylhexoxycarbonyl)ethanesulphonate). Formulations of 6-[4-[4-[2-(1-methyl-1H-pyrazol-5-yl)ethoxy]phenyl]piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine and 6-[4-[4-[2-(1-methyl-1H-pyrazol-5-yl)ethoxy]phenyl]piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine may be prepared as suspensions with reduced particle size (mean particle size less than 1 micro-meter) as follows. The required amount of compound is vortexed and/or magnetically stirred in vehicle (water containing



1%w/v Pluronic F127) in order to break down any large aggregates, wet the compound and displace any air from the surface. The resultant slurry is transferred to a zirconia milling pot containing about one third of 0.6-0.8mm diameter zirconia milling beads. Additional zirconia milling beads are added to the pot until the level of slurry and beads is approximately equal and the top of the pot closed. The pot is then sealed with a teflon ring and zirconia lid and placed on a suitable mill, for example, a Fritsch P7 planetary micromill. The pot is rotated in the mill for 4 x 30 minute cycles at a rotation speed of 800rpm with 15 minutes cooling period between each cycle. At the end of the 4 cycles the pot is allowed to cool to room temperature. The milled suspension is removed from the pot using a suitable pipette and transferred to a suitable vessel. Finally the milled suspension is made to volume with vehicle (water containing 1%w/v Pluronic F127) to produce the suspension at the required concentration.

The compound of Formula (I) will normally be administered to a warm-blooded animal at a unit dose within the range 5-5000 mg/m<sup>2</sup> body area of the animal, i.e. approximately 0.1-100 mg/kg, and this normally provides a therapeutically-effective dose. A unit dose form such as a tablet or capsule will usually contain, for example 1-250 mg of active ingredient. Preferably a daily dose in the range of 1-50 mg/kg is employed. However the daily dose will necessarily be varied depending upon the host treated, the particular route of administration, and the severity of the illness being treated. Accordingly the optimum dosage may be determined by the practitioner who is treating any particular patient. For example, 4-pyridin-3-yl-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol could be administered to a human patient at a dose of 500 to 1500 mg BID (twice a day), more particularly about 1000 mg BID, and 6-[4-[4-[2-(1-methyl-1H-pyrazol-5-yl)ethoxy]phenyl]piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine could be administered to a human patient at a dose of 165 to 660 mg BID, more particularly about 430 mg BID. The predicted human doses for 4-pyridin-3-yl-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol and 6-[4-[4-[2-(1-methyl-1H-pyrazol-5-yl)ethoxy]phenyl]piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine are based on a standard human weighing 70 kg and BID doses are per dose (*i.e.* half the total daily dose).

For further information on Routes of Administration and Dosage Regimes the reader is referred to Chapter 25.3 in Volume 5 of Comprehensive Medicinal Chemistry



(Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

We have found that the compounds defined in the present invention, or a pharmaceutically acceptable salt thereof, or pharmaceutical compositions containing them, are effective modulators of the androgen-receptor.

5 Accordingly, the compounds of the present invention are expected to be potentially useful agents in the treatment of diseases or medical conditions mediated alone or in part by the androgen receptor. Compounds of the invention may induce down-regulation of the androgen receptor and/or be selective agonists, partial agonists, antagonists or partial antagonists of the androgen receptor.

10 The compound of the invention are useful in the treatment of androgen receptor-associated conditions. An "androgen receptor-associated condition," as used herein, denotes a condition or disorder which can be treated by modulating the function or activity of an androgen receptor in a subject, wherein treatment comprises prevention, partial alleviation or cure of the condition or disorder. Modulation may occur locally, for example,  
15 within certain tissues of the subject, or more extensively throughout a subject being treated for such a condition or disorder.

In one embodiment, compounds of the present invention can be administered to animals, for example humans, for the treatment of a variety of conditions and disorders, including, but not limited to the treatment of androgen-sensitive diseases or disorders  
20 whose progress or onset is aided by activation of the androgen receptor or androgen receptor modulators. Examples of particular androgen-sensitive diseases or disorders include, but are not limited to, androgen-sensitive cancers such as prostate cancer and other cancers composed of malignant tumor cells containing the androgen receptor, such as is the case for breast, brain, skin, ovarian, bladder, lymphatic, liver and kidney cancers; cancers  
25 of the skin, pancreas, endometrium, lung and colon; osteosarcoma; hypercalcemia of malignancy; metastatic bone disease; and androgen sensitive disorders such as benign prostatic hyperplasia and prostategaly, acne (acne vulgaris), seborrhoea, hirsutism (hypertrichosis), androgenic alopecia and male pattern baldness, precocious puberty, endometriosis, polycystic ovarian syndrome, treatment of spermatogenesis, coneracting  
30 preeclampsia, eclampsia of pregnancy and preterm labor, treatment of premenstrual syndrome, treatment of vaginal dryness, sexual perversion, virilisation, and the like. Compounds of the invention may also be used to improve ovulation in a domestic animal.



In another embodiment, compounds of the present invention can be administered to animals, for example humans, for the treatment of a variety of conditions and disorders, including, but not limited to maintenance of muscle strength and function (e.g., in the elderly); reversal or prevention of frailty or age-related functional decline ("ARFD") in the elderly (e.g., sarcopenia); treatment of catabolic side effects of glucocorticoids; prevention and/or treatment of reduced bone mass, density or growth (e.g., osteoporosis and osteopenia); treatment of chronic fatigue syndrome (CFS) ; chronic myalgia; treatment of acute fatigue syndrome and muscle loss following elective surgery (e.g., post-surgical rehabilitation); accelerating of wound healing; accelerating bone fracture repair (such as accelerating the recovery of hip fracture patients); accelerating healing of complicated fractures, e.g. distraction osteogenesis; in joint replacement; prevention of post-surgical adhesion formation; acceleration of tooth repair or growth; maintenance of sensory function (e.g., hearing, sight, olfaction and taste); treatment of periodontal disease; treatment of wasting secondary to fractures and wasting in connection with chronic obstructive pulmonary disease (COPD), chronic liver disease, AIDS, weightlessness, cancer cachexia, burn and trauma recovery, chronic catabolic state (e.g., coma), eating disorders (e.g., anorexia) and chemotherapy; treatment of cardiomyopathy; treatment of thrombocytopenia; treatment of growth retardation in connection with Crohn's disease; treatment of short bowel syndrome; treatment of irritable bowel syndrome; treatment of inflammatory bowel disease; treatment of Crohn's disease and ulcerative colitis; treatment of complications associated with transplantation; treatment of physiological short stature including growth hormone deficient children and short stature associated with chronic illness; treatment of obesity and growth retardation associated with obesity; treatment of anorexia (e.g., associated with cachexia or aging); treatment of hypercortisolism and Cushing's syndrome; Paget's disease; treatment of osteoarthritis; induction of pulsatile growth hormone release; treatment of osteochondrodysplasias; treatment of depression, nervousness, irritability and stress; treatment of reduced mental energy and low self-esteem (e.g., motivation/assertiveness); improvement of cognitive function (e.g., the treatment of dementia, including Alzheimer's disease and short term memory loss); treatment of catabolism in connection with pulmonary dysfunction and ventilator dependency; treatment of cardiac dysfunction (e.g., associated with valvular disease, myocardial infarction, cardiac hypertrophy or congestive heart failure); lowering blood pressure;



protection against ventricular-24 dysfunction or prevention of reperfusion events;  
treatment of adults in chronic dialysis; reversal or slowing of the catabolic state of aging;  
attenuation or reversal of protein catabolic responses following trauma (e.g., reversal of the  
catabolic state associated with surgery, congestive heart failure, cardiac myopathy, burns,  
5 cancer, COPD etc.); reducing cachexia and protein loss due to chronic illness such as  
cancer or AIDS; treatment of hyperinsulinemia including nesidioblastosis; treatment of  
immunosuppressed patients; treatment of wasting in connection with multiple sclerosis or  
other neurodegenerative disorders; promotion of myelin repair; maintenance of skin  
thickness; treatment of metabolic homeostasis and renal homeostasis (e.g., in the frail  
10 elderly); stimulation of osteoblasts, bone remodeling and cartilage growth; regulation of  
food intake; treatment of insulin resistance, including NIDDM, in mammals (e.g.,  
humans); treatment of insulin resistance in the heart; improvement of sleep quality and  
correction of the relative hyposomatotropism of senescence due to high increase in REM  
sleep and a decrease in REM latency; treatment of hypothermia; treatment of congestive  
15 heart failure; treatment of lipodystrophy (e.g., in patients taking HIV or AIDS therapies  
such as protease inhibitors); treatment of muscular atrophy (e.g., due to physical inactivity,  
bed rest or reduced weight-bearing conditions); treatment of musculoskeletal impairment  
(e.g., in the elderly); improvement of the overall pulmonary function; treatment of sleep  
disorders; and the treatment of the catabolic state of prolonged critical illness, ; age related  
20 decreased testosterone levels in men, male menopause, hypogonadism, male hormone  
replacement, male and female sexual dysfunction (e.g., erectile dysfunction, decreased sex  
drive, sexual well-being, decreased libido), urinary incontinence, male and female  
contraception, hair loss, and the enhancement of bone and muscle performance/strength.

The term treatment is also intended to include prophylactic treatment.

25 In addition, the conditions, diseases, and maladies collectively referenced to as  
"Syndrome X" or Metabolic Syndrome as detailed in Johannsson J. Clin. Endocrinol.  
Metab., 82, 727-34 (1997), may be treated employing the compounds of the invention.

In one embodiment the the androgen-receptor associated conditions include  
prostate cancer, benign prostatic hyperplasia and prostamegaly, acne (acne vulgaris),  
30 seborrhoea, hirsutism (hypertrichosis), androgenic alopecia and male pattern baldness,  
precocious puberty, polycystic ovarian syndrome, sexual perversion, virilisation, and the  
like. Compounds of the invention may also be used to improve ovulation in a domestic



animal.

Accordingly, the present invention relates to a method of treating any one of the  
aforementioned androgen-receptor associated condition in a warm-blooded animal, such as  
man, in need of such treatment which comprises administering to said animal an effective  
5 amount of a compound of the Formula (I), or a pharmaceutically acceptable salt thereof, as  
defined hereinbefore.

According to a further aspect the present invention relates to the use of compound  
of Formula (I), or a pharmaceutically acceptable salt thereof, as hereinbefore defined in the  
manufacture of a medicament for the treatment of any one of the aforementioned  
10 androgen-receptor associated condition.

According to another aspect of the present invention there is provided a compound  
of the Formula (I), or a pharmaceutically acceptable salt or pro-drug thereof, as defined  
hereinbefore for use in the treatment of any one of the aforementioned androgen-receptor  
associated condition.

15 According to another aspect of the present invention there is provided a compound  
of the Formula (Ia), or a pharmaceutically acceptable salt thereof, as defined hereinbefore  
for use in a method of treatment of the human or animal body by therapy.

According to a further aspect of the invention there is provided the use of a  
compound of the Formula (I), or a pharmaceutically acceptable salt or pro-drug thereof, as  
20 defined hereinbefore in the manufacture of a medicament for use in the production of an  
anti-androgenic effect in a warm-blooded animal such as man.

According to a further feature of this aspect of the invention there is provided a  
method for producing an anti-androgenic effect in a warm-blooded animal, such as man, in  
need of such treatment which comprises administering to said animal an effective amount  
25 of a compound of the Formula (I), or a pharmaceutically acceptable salt thereof, as defined  
hereinbefore.

The term “anti-androgenic effect” is used herein to mean the inhibition and/or down  
regulation of androgen receptors.

According to a further aspect of the invention there is provided the use of a  
30 compound of the Formula (I), or a pharmaceutically acceptable salt thereof, as defined  
hereinbefore in the manufacture of a medicament for use in the production of an  
anti-cell-proliferation effect in a warm-blooded animal such as man.



According to a further feature of this aspect of the invention there is provided a method for producing an anti-cell-proliferation effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of the Formula (I), or a pharmaceutically acceptable salt thereof, as defined hereinbefore.

According to an additional feature of this aspect of the invention there is provided a method of treating androgen-sensitive cancers in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of the Formula (I), or a pharmaceutically acceptable salt thereof, as defined hereinbefore.

According to a further feature of the invention there is provided a compound of the Formula (I), or a pharmaceutically acceptable salt thereof, as defined hereinbefore for use in the treatment of androgen-sensitive cancers.

According to a further feature of the invention there is provided the use of a compound of the Formula (I), or a pharmaceutically acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for use in the treatment of androgen-sensitive cancers.

According to an additional feature of this aspect of the invention there is provided a method of treating prostate cancer in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of the Formula (I), or a pharmaceutically acceptable salt thereof, as defined hereinbefore. In one embodiment of this aspect of the invention, the prostate cancer is hormone resistant.

According to a further feature of the invention there is provided a compound of the Formula (I), or a pharmaceutically acceptable salt thereof, as defined hereinbefore for use in the treatment of prostate cancer, more particularly hormone resistant prostate cancer.

According to a further feature of the invention there is provided the use of a compound of the Formula (I), or a pharmaceutically acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for use in the treatment of prostate cancer, more particularly hormone resistant prostate cancer.

Hormone resistant prostate cancer (HRPC) arises when the prostate cancer progresses to the hormone-independent stage of the disease.



According to an additional feature of this aspect of the invention there is provided a method of treating any one of the following conditions: benign prostatic hyperplasia, prostamegaly, acne (acne vulgaris), seborrhoea, hirsutism (hypertrichosis), androgenic alopecia and male pattern baldness, precocious puberty, polycystic ovarian syndrome, sexual perversion, or virilisation; in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of the Formula (I), or a pharmaceutically acceptable salt thereof, as defined hereinbefore.

According to a further feature of the invention there is provided a compound of the Formula (I), or a pharmaceutically acceptable salt thereof, as defined hereinbefore for use in the treatment of any one of the following conditions: benign prostatic hyperplasia, prostamegaly, acne (acne vulgaris), seborrhoea, hirsutism (hypertrichosis), androgenic alopecia and male pattern baldness, precocious puberty, polycystic ovarian syndrome, sexual perversion, or virilisation.

According to a further feature of the invention there is provided the use of a compound of the Formula (I), or a pharmaceutically acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for use in the treatment of any one of the following conditions: benign prostatic hyperplasia, prostamegaly, acne (acne vulgaris), seborrhoea, hirsutism (hypertrichosis), androgenic alopecia and male pattern baldness, precocious puberty, polycystic ovarian syndrome, sexual perversion, or virilisation.

As stated above the size of the dose required for the therapeutic or prophylactic treatment of a particular cell-proliferation disease will necessarily be varied depending on the host treated, the route of administration and the severity of the illness being treated. A unit dose in the range, for example, 1-100 mg/kg, preferably 1-50 mg/kg is envisaged.

The androgen receptor ligands of the present invention may be applied as a sole therapy or may involve, in addition to a compound of the invention, one or more other substances and/or treatments. Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate administration of the individual components of the treatment. In the field of medical oncology it is normal practice to use a combination of different forms of treatment to treat each patient with cancer. In medical oncology the other component(s) of such conjoint treatment, in addition to the androgen receptor ligand



treatment defined hereinbefore, may be: surgery, radiotherapy or chemotherapy. Such chemotherapy may include one or more of the following categories of anti-tumour agents:

- (i) other antiproliferative/antineoplastic drugs and combinations thereof, as used in medical oncology, such as alkylating agents (for example cis-platin, oxaliplatin, carboplatin, cyclophosphamide, nitrogen mustard, melphalan, chlorambucil, busulphan, temozolamide and nitrosoureas); antimetabolites (for example gemcitabine and antifolates such as fluoropyrimidines like 5-fluorouracil and tegafur, raltitrexed, methotrexate, cytosine arabinoside, and hydroxyurea); antitumour antibiotics (for example anthracyclines like adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin and mithramycin); antimitotic agents (for example vinca alkaloids like vincristine, vinblastine, vindesine and vinorelbine and taxoids like taxol and taxotere and polokine inhibitors); and topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, amsacrine, topotecan and camptothecin);
- (ii) cytostatic agents such as antioestrogens (for example tamoxifen, fulvestrant, toremifene, raloxifene, droloxifene and idoxifene), antiandrogens (for example bicalutamide, flutamide, nilutamide and cyproterone acetate), LHRH antagonists or LHRH agonists (for example goserelin, leuprorelin and buserelin), progestogens (for example megestrol acetate), aromatase inhibitors (for example anastrozole, letrozole, vorazole and exemestane) and inhibitors of 5 $\alpha$ -reductase such as finasteride;
- (iii) anti-invasion agents [for example c-Src kinase family inhibitors like 4-(6-chloro-2,3-methylenedioxyanilino)-7-[2-(4-methylpiperazin-1-yl)ethoxy]-5-tetrahydropyran-4-yloxyquinazoline (AZD0530; International Patent Application WO 01/94341), N-(2-chloro-6-methylphenyl)-2-{6-[4-(2-hydroxyethyl)piperazin-1-yl]-2-methylpyrimidin-4-ylamino}thiazole-5-carboxamide (dasatinib, BMS-354825; *J. Med. Chem.*, 2004, 47, 6658-6661) and bosutinib (SKI-606), and metalloproteinase inhibitors like marimastat, inhibitors of urokinase plasminogen activator receptor function or antibodies to Heparanase];
- (iv) inhibitors of growth factor function: for example such inhibitors include growth factor antibodies and growth factor receptor antibodies (for example the anti-erbB2 antibody trastuzumab [Herceptin<sup>TM</sup>], the anti-EGFR antibody panitumumab, the anti-erbB1 antibody cetuximab [Erbix, C225] and any growth factor or growth factor receptor antibodies disclosed by Stern *et al.* Critical reviews in oncology/haematology, 2005, Vol. 54, pp11-29); such inhibitors also include tyrosine kinase inhibitors, for example inhibitors



of the epidermal growth factor family (for example EGFR family tyrosine kinase inhibitors such as

*N*-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine (gefitinib, ZD1839), *N*-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine

(erlotinib, OSI-774) and 6-acrylamido-*N*-(3-chloro-4-fluorophenyl)-7-(3-

morpholinopropoxy)-quinazolin-4-amine (CI 1033), erbB2 tyrosine kinase inhibitors such

as lapatinib); inhibitors of the hepatocyte growth factor family; inhibitors of the insulin

growth factor family; inhibitors of the platelet-derived growth factor family such as

imatinib and/or nilotinib (AMN107); inhibitors of serine/threonine kinases (for example

Ras/Raf signalling inhibitors such as farnesyl transferase inhibitors, for example sorafenib

(BAY 43-9006), tipifarnib (R115777) and lonafarnib (SCH66336)), inhibitors of cell

signalling through MEK and/or AKT kinases, c-kit inhibitors, abl kinase inhibitors, PI3

kinase inhibitors, Plt3 kinase inhibitors, CSF-1R kinase inhibitors, IGF receptor (insulin-

like growth factor) kinase inhibitors; aurora kinase inhibitors (for example AZD1152,

PH739358, VX-680, MLN8054, R763, MP235, MP529, VX-528 AND AX39459) and

cyclin dependent kinase inhibitors such as CDK2 and/or CDK4 inhibitors;

(v) antiangiogenic agents such as those which inhibit the effects of vascular endothelial

growth factor, [for example the anti-vascular endothelial cell growth factor antibody

bevacizumab (Avastin™) and for example, a VEGF receptor tyrosine kinase inhibitor such

as vandetanib (ZD6474), vatalanib (PTK787), sunitinib (SU11248), axitinib (AG-013736),

pazopanib (GW 786034) and 4-(4-fluoro-2-methylindol-5-yloxy)-6-methoxy-7-(3-

pyrrolidin-1-ylpropoxy)quinazoline (AZD2171; Example 240 within WO 00/47212),

compounds such as those disclosed in International Patent Applications WO97/22596, WO

97/30035, WO 97/32856 and WO 98/13354 and compounds that work by other

mechanisms (for example linomide, inhibitors of integrin  $\alpha v \beta 3$  function and angiostatin)];

(vi) vascular damaging agents such as Combretastatin A4 and compounds disclosed in

International Patent Applications WO 99/02166, WO 00/40529, WO 00/41669,

WO 01/92224, WO 02/04434 and WO 02/08213;

(vii) an endothelin receptor antagonist, for example zibotentan (ZD4054) or atrasentan;

(viii) antisense therapies, for example those which are directed to the targets listed above,

such as ISIS 2503, an anti-ras antisense;



(ix) gene therapy approaches, including for example approaches to replace aberrant genes such as aberrant p53 or aberrant BRCA1 or BRCA2, GDEPT (gene-directed enzyme pro-drug therapy) approaches such as those using cytosine deaminase, thymidine kinase or a bacterial nitroreductase enzyme and approaches to increase patient tolerance to chemotherapy or radiotherapy such as multi-drug resistance gene therapy; and

(x) immunotherapy approaches, including for example ex-vivo and in-vivo approaches to increase the immunogenicity of patient tumour cells, such as transfection with cytokines such as interleukin 2, interleukin 4 or granulocyte-macrophage colony stimulating factor, approaches to decrease T-cell anergy, approaches using transfected immune cells such as cytokine-transfected dendritic cells, approaches using cytokine-transfected tumour cell lines and approaches using anti-idiotypic antibodies.

Herein, where the term “combination” is used it is to be understood that this refers to simultaneous, separate or sequential administration. In one aspect of the invention “combination” refers to simultaneous administration. In another aspect of the invention “combination” refers to separate administration. In a further aspect of the invention “combination” refers to sequential administration. Where the administration is sequential or separate, the delay in administering the second component should not be such as to lose the beneficial effect of the combination.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of Formula (I) or a pharmaceutically acceptable salt thereof in combination with an anti-tumour agent selected from one listed under (i) - (x) herein above, in association with a pharmaceutically acceptable diluent or carrier.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of Formula (I) or a pharmaceutically acceptable salt thereof in combination with an anti-tumour agent selected from one listed under (i) - (x) herein above, in association with a pharmaceutically acceptable diluent or carrier for use in the treatment of an androgen sensitive disorder.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of Formula (I) or a pharmaceutically acceptable salt thereof in combination with an anti-tumour agent selected from one listed under (i) - (x) herein above, in association with a pharmaceutically acceptable diluent or carrier for use in the treatment of cancer, such as prostate cancer.



According to another feature of the invention there is provided the use of a compound of the Formula (I) or a pharmaceutically acceptable salt thereof in combination with an anti-tumour agent selected from one listed under (i) – (x) herein above, in the manufacture of a medicament for use in the treatment of an androgen sensitive disorder in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound of the Formula (I) or a pharmaceutically acceptable salt thereof in combination with an anti-tumour agent selected from one listed under (i) – (x) herein above, in the manufacture of a medicament for use in the treatment of cancer, such as prostate cancer, in a warm-blooded animal, such as man.

According to another feature of the invention there is provided a compound of the Formula (I) or a pharmaceutically acceptable salt thereof in combination with an anti-tumour agent selected from one listed under (i) – (x) herein above for use in treatment of an androgen-sensitive disorder in a warm-blooded animal, such as man.

According to another feature of the invention there is provided a compound of the Formula (I) or a pharmaceutically acceptable salt thereof in combination with an anti-tumour agent selected from one listed under (i) – (x) herein above for use in treatment of cancer, such as prostate cancer in a warm-blooded animal, such as man.

Therefore in an additional feature of the invention, there is provided a method of treating an androgen-sensitive disorder in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof in combination with an anti-tumour agent selected from one listed under (i) – (x) herein above.

Therefore in an additional feature of the invention, there is provided a method of treating cancer, such as prostate cancer, in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof in combination with an anti-tumour agent selected from one listed under (i) – (x) herein above.

According to a further aspect of the present invention there is provided a kit comprising a compound of Formula (I) or a pharmaceutically acceptable salt thereof in combination with an anti-tumour agent selected from one listed under (i) – (x) herein above.



According to a further aspect of the present invention there is provided a kit comprising:

- a) a compound of Formula (I) or a pharmaceutically acceptable salt thereof in a first unit dosage form;
- 5 b) an anti-tumour agent selected from one listed under (i) – (ix) herein above; in a second unit dosage form; and
- c) container means for containing said first and second dosage forms.

In particular, the compounds of the invention may be used for the treatment of various hormone dependent cancers including without limitation prostate cancer in combination with one or more of the following agents: gonadotrophin agonists (GnRH) (LH-RH agonists); inhibitors of gonadotrophin secretion; 5-alpha reductase inhibitors; antiprogestins; antiestrogens; aromatase inhibitors; progestins; estrogens; cytostatic agents; cytotoxic agents; inhibitors of cell growth signalling pathways, including without limitation kinase inhibitors such as VEGF kinase inhibitors; antibodies including without limitation antibodies directed at cell-growth signalling factors such as EGF antibodies; 15 antisense oligonucleotides; immunological modifiers such as interferons, interleukins, growth hormones, and other cytokines; and other hormonal therapies.

The compounds of the invention may also be used for the treatment of various hormone dependent diseases and disorders, such as prostate cancer in combination with one or more of the following agents: antibiotics; anti-inflammatory agents; potassium 20 channel openers; synthetic thyroid hormone replacements; protein kinase C inhibitors (PKC inhibitors); and immunophilin inhibitors or antagonists.

According to this aspect of the invention there is provided a pharmaceutical composition comprising a compound of the Formula (I) as defined hereinbefore and an additional anti-tumour substance as defined hereinbefore for the conjoint treatment of 25 cancer.

In addition to their use in therapeutic medicine, the compounds of Formula (I) and their pharmaceutically acceptable salts thereof, are also useful as pharmacological tools in the development and standardisation of *in vitro* and *in vivo* test systems for the evaluation of the effects of inhibitors of cell cycle activity in laboratory animals such as cats, dogs, 30 rabbits, monkeys, rats and mice, as part of the search for new therapeutic agents.



The invention will now be illustrated in the following Examples in which, generally:

- (i) temperatures are given in degrees Celsius (°C); operations were carried out at room or ambient temperature, that is, at a temperature in the range of 18 to 25°C;
- 5 (ii) organic solutions were dried over anhydrous magnesium sulfate or anhydrous sodium sulfate; evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600 to 4000 Pascals; 4.5 to 30mmHg) with a bath temperature of up to 60°C;
- (iii) chromatography means flash chromatography on silica gel; thin layer chromatography (TLC) was carried out on silica gel plates;
- 10 (iv) in general, the course of reactions was followed by TLC and / or analytical LC-MS, and reaction times where given are for illustration only.
- (v) final products had satisfactory proton nuclear magnetic resonance (NMR) spectra and/or mass spectral data;
- (vi) yields are given for illustration only and are not necessarily those which can be
- 15 obtained by diligent process development; preparations were repeated if more material was required;
- (vii) when given, NMR data is in the form of delta values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard, determined at 500 MHz using perdeuterio dimethyl sulfoxide (DMSO-d<sub>6</sub>) as
- 20 solvent unless otherwise indicated; the following abbreviations have been used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; bs, broad singlet;
- (viii) chemical symbols have their usual meanings; SI units and symbols are used;
- (ix) Mass spectra (MS) and LC-MS data were generated on an LC-MS system where the HPLC component comprised generally either an Agilent 1100, Waters Alliance HT (2790
- 25 & 2795) equipment or an HP1100 pump and Diode Array with CTC autosampler and was run on a Phenomenex Gemini C18 5µm, 50 x 2 mm column (or similar) eluting with either acidic eluent (for example, using a gradient between 0 - 95% water / acetonitrile with 5% of a 1% formic acid in 50:50 water:acetonitrile (v/v) mixture), or basic eluent (for example, using a gradient between 0 - 95% water / acetonitrile with 5% of a 0.1% 880 Ammonia in
- 30 acetonitrile mixture); and the MS component comprised generally a Waters ZQ mass spectrometer scanning over an appropriate mass range. Chromatograms for Electrospray (ESI) positive and negative Base Peak Intensity, and UV Total Absorption Chromatogram



from 220-300nm, are generated and values for m/z are given; generally, only ions which indicate the parent mass are reported and unless otherwise stated the value quoted is the (M+H)+ for positive ion mode and (M-H)- for negative ion mod;

(x) unless stated otherwise compounds containing an asymmetrically substituted carbon and/or sulfur atom have not been resolved;

(xi) any microwave reactions were carried out in either a Biotage Optimizer EXP, or a CEM Explorer microwave;

(xii) preparative high performance liquid chromatography (HPLC) was performed on a Gilson instrument using the following conditions:-

Column: C18 reversed-phase silica, for example, Waters 'Xbridge', 5 µm silica, 19 x 100 mm, or 30 x 100 mm, using decreasingly polar solvent mixtures as eluent (decreasing ratio of Solvent A to Solvent B)

Solvent A: Water with 1% ammonium hydroxide

Solvent B: Acetonitrile

Flow rate: 28 ml / min or 61 ml / min

Gradient: Tailored to suit each compound – generally 7-10 min in length

Wavelength: 254 nm

(xiii) Strong cation exchange (SCX) chromatography was performed on pre-packed cartridges (for example, ISOLUTE SCX-2 propyl sulfonic acid-based cartridges supplied by International Sorbent Technology), using a basic eluent (for example, 2M ammonia in methanol);

(xiv) the following abbreviations have been used herein, where necessary:-

DMF            *N,N*-dimethylformamide

DCM            dichloromethane

DME            1,2-dimethoxyethane

DMSO          dimethylsulphoxide

THF            tetrahydrofuran

HATU           O-(7-Azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium  
hexafluorophosphate

EDCI           1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide

DCCI           1,3-Dicyclohexylcarbodiimide

PYBOP          Benzotriazole-1-yl-oxy-trispyrrolidinonophosphonium hexafluorophosphate



|          |                                |
|----------|--------------------------------|
| DEAD     | Diethyl azodicarboxylate       |
| DIAD     | Diisopropyl azodicarboxylate   |
| DTAD     | Di-tert-butyl azodicarboxylate |
| DIPEA    | N,N-Diisopropylethylamine      |
| 5 MeOH   | Methanol                       |
| TFA      | Trifluoroacetic acid           |
| m-CPBA   | m-Chloroperoxybenzoic acid     |
| AcOH     | Acetic acid                    |
| DMA      | N,N-Dimethylacetamide          |
| 10 EtOAc | Ethyl acetate                  |
| EtOH     | Ethanol                        |
| MeCN     | Acetonitrile                   |
| MTBE     | Methyl tert-butyl ether        |
| CAS      | Chemical Abstracts Service     |

#### 15 **X-Ray Powder Diffraction (XRPD)**

The X-ray powder diffraction patterns of the crystal forms were determined by mounting a sample of the crystalline material on Siemens single silicon crystal (SSC) wafer mounts and spreading out the sample into a thin layer with the aid of a microscope slide. The sample was spun at 30 revolutions per minute (to improve counting statistics) and irradiated with X-rays generated by a copper long-fine focus tube operated at 40 kV and 40 mA with a wavelength of 1.5418 Angstroms using a Bruker D5000 powder X-ray diffractometer (Bruker AXS, Banner Lane Coventry CV4 9GH). The collimated X-ray source was passed through an automatic variable divergence slit set at V20 and the reflected radiation directed through a 2 mm antiscatter slit and a 0.2 mm detector slit. The sample was exposed for 1 second per 0.02 degree 2-theta increment (continuous scan mode) over the range 2 degrees to 40 degrees 2-theta in continuous scan theta-theta mode. The instrument was equipped with a scintillation counter as detector. Control and data capture was by means of a Dell Optiplex 686 NT 4.0 Workstation operating with Diffrac+ software.

30 The skilled person is aware that an X-ray powder diffraction pattern may be obtained which has one or more measurement errors depending on measurement conditions (such as equipment, sample preparation or machine used). In particular, it is



generally known that intensities in an X-ray powder diffraction pattern may fluctuate depending on measurement conditions and sample preparation. For example, the skilled person will realize that the relative intensity of peaks can be affected by, for example, grains above 30 microns in size and non-unitary aspect ratios, which may affect analysis of samples. The skilled person will also realize that the position of reflections can be affected by the precise height at which the sample sits in the diffractometer and the zero calibration of the diffractometer. The surface planarity of the sample may also have a small effect. Hence a person skilled in the art will appreciate that the diffraction pattern data presented herein is not to be construed as absolute (for further information see Jenkins, R & Snyder, R.L. 'Introduction to X-Ray Powder Diffractometry' John Wiley & Sons, 1996).

Therefore, it shall be understood that the crystalline form is not limited to the crystals that provide X-ray powder diffraction patterns identical to the X-ray powder diffraction patterns shown in Figures A to D and any crystals providing X-ray powder diffraction patterns substantially the same as that shown in Figures A to D fall within the scope of the present invention. A person skilled in the art of X-ray powder diffraction is able to judge the substantial identity of X-ray powder diffraction patterns.

#### **Differential Scanning Calorimetry (DSC)**

DSC was recorded using a Thermal Analysis Q1000 system. Typically less than 5mg of material, contained in an aluminium pan fitted with a sealed lid, was heated over the temperature range 25°C to 300°C at a constant heating rate of 10°C per minute. A nitrogen purge gas was used with flow rate 50ml per minute.

#### **General Synthetic Method 1**

##### **General procedure for the reaction of a 6-chloro-3-(fluorinated-alkyl)-[1,2,4]-triazolo[4,3-b]pyridazine with a cyclic amine**

A solution of the cyclic amine (1.47 mmol; 3 equivalents ) in ethanol ( 1 mL) was added to the 6-chloro-3-(fluorinated-alkyl)-[1,2,4]-triazolo[4,3-b]pyridazine (0.49 mmol) (see below for preparation of novel starting materials) and the reaction was heated and shaken at 70°C overnight. The reaction mixture was evaporated to dryness and purified by hplc using an Waters X Bridge C18 column (5µ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 5% aqueous ammonia) and acetonitrile to give the corresponding 6-cyclicamino-3-(fluorinated-alkyl)-[1,2,4]-triazolo[4,3-b]pyridazine.



6-Chloro-3-difluoromethyl-[1,2,4]-triazolo[4,3-b]pyridazine used as starting material for General Synthetic Method 1 was prepared according to the following procedure:

**6-Chloro-3-difluoromethyl-[1,2,4]-triazolo[4,3-b]pyridazine**

5 A mixture of 3-chloropyridazin-6-yl hydrazine (5.0g, 34.72 mmol) and difluoroacetic acid (21.93 mL; ca. 347 mmol) was heated at 100 °C for 3 hours and then evaporated to dryness. The involatile residue was dissolved in ethyl acetate (200 mL) and washed sequentially with saturated aqueous sodium carbonate and then saturated brine. The organic phase was dried over MgSO<sub>4</sub>, filtered, and evaporated to give 6-chloro-3-difluoromethyl-[1,2,4]-triazolo[4,3-b]pyridazine (6.0 g, 84.7%) as a white solid that was used without further purification.

<sup>1</sup>H NMR (300.13 MHz, DMSO-d<sub>6</sub>) δ 7.68 (1H, t), 7.72 (1H, t, *J*<sub>HF</sub> = 51.2 Hz), 8.59 - 8.62 (1H, m); m/z 205.38 (M+1)<sup>+</sup>.

6-Chloro-3-(3,3,3-trifluoroethyl)-[1,2,4]-triazolo[4,3-b]pyridazine used as starting material for General Synthetic Method 1 was prepared according to the following procedure:

**6-Chloro-3-(3,3,3-trifluoroethyl)-[1,2,4]-triazolo[4,3-b]pyridazine**

A mixture of 3-chloropyridazin-6-yl hydrazine (5.0 g, 34.72 mmol) and trifluoropropionic acid (44.4 g, 347 mmol) was heated at 100 °C for 3 hours and then evaporated to dryness. The involatile residue was extracted with boiling ethyl acetate (200 mL), the hot ethyl acetate extract was filtered and allowed to cool to room temperature, and the product was isolated by filtration to give 6-chloro-3-(3,3,3-trifluoroethyl)-[1,2,4]-triazolo[4,3-b]pyridazine (2.0 g, 24 %) as an off-white solid that was used without further purification.

25 <sup>1</sup>H NMR (300.13 MHz, DMSO-d<sub>6</sub>) δ 4.37 - 4.40 (2H, m), 7.56 - 7.59 (1H, m), 8.51 - 8.54 (1H, m); m/z 237.42 (M+1)<sup>+</sup>.

6-Chloro-3-(2,2,3,3-tetrafluoroethyl)-[1,2,4]-triazolo[4,3-b]pyridazine used as starting material for General Synthetic Method 1 was prepared according to the following procedure:

30 **6-Chloro-3-(2,2,3,3-tetrafluoroethyl)-[1,2,4]-triazolo[4,3-b]pyridazine**

A mixture of 3-chloropyridazin-6-yl hydrazine (5.0 g, 34.72 mmol) and tetrafluoropropionic acid (32.5 mL; ca. 347 mmol) was heated at 100 °C for 3 hours and



then evaporated to dryness. The involatile residue was dissolved in ethyl acetate (200 mL) and washed sequentially with saturated aqueous sodium carbonate and then saturated brine. The organic phase was dried over  $\text{MgSO}_4$ , filtered, and evaporated to give 6-chloro-3-(2,2,3,3-tetrafluoroethyl)-[1,2,4]-triazolo[4,3-b]pyridazine (4.2 g, 48.8%) as a white solid that was used without further purification.

$^1\text{H}$  NMR (300.13 MHz,  $\text{DMSO-d}_6$ )  $\delta$  7.21 (1H, t), 7.73 - 7.77 (1H, m), 8.65 - 8.68 (1H, m);  $m/z$  255.28 ( $\text{M}+1$ ) $^+$ .

### **General Synthetic Method 2**

#### **General procedure for the reaction of a 6-chloro-3-(heteroatom)-[1,2,4]-triazolo[4,3-b]pyridazine with a cyclic amine**

A solution of the cyclic amine (1.10 mmol; 3 equivalents) in ethanol (2 mL) was added to the 6-chloro-3-(heteroatom)-[1,2,4]-triazolo[4,3-b]pyridazine (0.37 mmol) (see below for preparation of novel starting materials) and the reaction was heated and shaken at 70°C overnight. The reaction mixture was evaporated to dryness and purified by hplc using a Waters X Bridge C18 column (5 $\mu$  silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 5% aqueous ammonia) and acetonitrile to give the corresponding 6-(cyclicamino)-3-(heteroatom)-[1,2,4]-triazolo[4,3-b]pyridazine.

### **General Synthetic Method 3**

#### **General procedure for the reaction of a 6-chloro-3-trifluoromethyl-[1,2,4]-triazolo[4,3-b]pyridazine with a cyclic amine**

A solution of the cyclic amine (0.55 mmol) in ethanol (1 mL) was added to 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[3,4-f]pyridazine (0.050 g, 0.22 mmol) and the mixture was heated at 70°C for 16 hours or until analytical hplc-ms indicated that reaction was complete. The reaction mixture was evaporated to leave an involatile residue that was purified by preparative reverse phase chromatography to give the corresponding 6-(cyclicamino)-3-trifluoromethyl-[1,2,4]-triazolo[4,3-b]pyridazine.

### **General Synthetic Method 4**

#### **General procedure for the reaction of a 6-chloro-3-trifluoromethyl-[1,2,4]-triazolo[4,3-b]pyridazine with the acid salt of a cyclic amine**

A solution of the acid salt of a cyclic amine (0.55 mmol) in ethanol (1 mL) was added to 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[3,4-f]pyridazine (0.050 g, 0.22



mmol). The reaction mixture was treated with diisopropylethylamine (1 equivalent/acid salt) and the mixture was heated at 70°C for 16 hours or until analytical hplc-ms indicated that reaction was complete. The reaction mixture was evaporated to leave an involatile residue that was purified by preparative reverse phase chromatography to give the  
5 corresponding 6-(cyclicamino)-3-trifluoromethyl-[1,2,4]-triazolo[4,3-b]pyridazine.

### **General Synthetic Method 5**

#### **General procedure for the reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with an aldehyde**

(Polystyrylmethyl)trimethylammonium cyanoborohydride (4.1 mmol/g, 0.049 g,  
10 0.2 mmol) was added to the aldehyde (0.2 mmol) followed by a solution of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (0.05 g, 0.184 mmol) in a mixture of acetic acid and dichloromethane (1:9; 2 mL). The mixture was shaken for 40 hours and then filtered. The filtrate was evaporated and the involatile residue was purified by preparative reverse phase chromatography to yield the corresponding 6-(4-(substituted-  
15 methyl)-piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

The 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine used as starting material was prepared as follows:-

#### **Preparation of tert-butyl 4-(3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)piperazine-1-carboxylate**

20 A mixture of tert-butyl piperazine-1-carboxylate (8.29 g, 44.5 mmol) and ethanol (90 mL) was added to a mixture of diisopropylethylamine (9.16 mL, 52.6 mmol) and 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[3,4-f]pyridazine (9.0 g, 40.4 mmol) in ethanol (90 mL). The mixture was heated at 70°C for 11 hours and then allowed to cool to ambient temperature to give a precipitate. The precipitate was collected by filtration, washed with  
25 chilled ethanol and then with water, and dried under vacuum to afford tert-butyl 4-(3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)piperazine-1-carboxylate (13.64 g, 90.6%) as a white solid that was used without further purification.

<sup>1</sup>H NMR (300.132 MHz, DMSO) δ 1.43 (s, 9H), 3.48 (m, 4H), 3.62 (m, 4H), 7.58 (d, 1H), 8.28 (d, 1H); m/z 373 (M+H)<sup>+</sup>.

#### **30 Preparation of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

Trifluoroacetic acid (25 mL, 324.49 mmol) was added to a mixture of tert-butyl 4-(3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)piperazine-1-carboxylate (6.7 g,



17.99 mmol) and dichloromethane (100 mL) at ambient temperature and the resulting solution was stirred at ambient temperature for 1 hour. The reaction mixture was evaporated to give an involatile residue that was treated with saturated aqueous sodium bicarbonate solution (100 mL) and then extracted with dichloromethane (4 x 200mL). The organic phases were combined and dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and evaporated to give 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (4.78 g, 98 %) as a white solid that was used without further purification.

<sup>1</sup>H NMR (300.132 MHz, DMSO) δ 2.43 (s, 1H), 2.74 - 2.87 (m, 4H), 3.45 - 3.59 (m, 4H), 7.57 (d, 1H), 8.22 (d, 1H); m/z 273 (M+H)<sup>+</sup>.

#### **General Synthetic Method 6**

##### **General procedure for the reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with an aldehyde**

A solution of the aldehyde (0.2 mmol) in dichloromethane (0.5 mL) was added to a mixture of (polystyrylmethyl)trimethylammonium cyanoborohydride (4.1 mmol/g, 0.049 g, 0.2 mmol), 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (0.05 g, 0.184 mmol) and a mixture of acetic acid and dichloromethane (1:9; 2 mL). The reaction mixture was shaken for 16 hours and then filtered. The filtrate was evaporated and the involatile residue was purified by preparative reverse phase chromatography to yield the corresponding 6-(4-(substituted-methyl)-piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

#### **General Synthetic Method 7**

##### **General procedure for the reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with an aldehyde**

(Polystyrylmethyl)trimethylammonium cyanoborohydride (4.1 mmol/g, 0.061 g, 0.25 mmol) was added to the aldehyde (0.25 mmol) followed by a solution of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (0.05 g, 0.184 mmol) in a mixture of acetic acid and dichloromethane (1:9; 2 mL). The mixture was shaken for 4 days and then filtered. The filtrate was evaporated and the involatile residue was purified by preparative reverse phase chromatography to yield the corresponding 6-(4-(substituted-methyl)-piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.



**General Synthetic Method 8****General procedure for the reductive amination of 6-(1,4-diazepan-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with an aldehyde**

(Polystyrylmethyl)trimethylammonium cyanoborohydride (4.1 mmol/g, 0.049 g, 5 0.2 mmol) was added to the aldehyde (0.2 mmol) followed by a solution of 6-(1,4-diazepan-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[3,4-f]pyridazine (0.053 g, 0.184 mmol) in a mixture of acetic acid and dichloromethane (1:9; 2 mL). The mixture was shaken for 16 hours and then filtered. The filtrate was evaporated and the residue was purified by preparative reverse phase chromatography to yield the corresponding 6-(4-(substituted- 10 methyl)-1,4-diazepan-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

The 6-(1,4-diazepan-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[3,4-f]pyridazine used as starting material was prepared as follows:-

**Preparation of tert-butyl 4-[3-(trifluoromethyl)-[1,2,4]triazolo[3,4-f]pyridazin-6-yl]-1,4-diazepane-1-carboxylate**

15 tert-Butyl 1,4-diazepane -1-carboxylate (4.00 g, 20.0 mmol) was added to a mixture of diisopropylethylamine (4.11 mL, 23.7 mmol) and 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[3,4-f]pyridazine (4.0 g, 18.2 mmol) in ethanol (80 mL). The mixture was heated under reflux for 6 hours and then allowed to cool to ambient temperature to give a precipitate. The precipitate was collected by filtration, washed with ethanol, and dried 20 under vacuum to afford tert-butyl 4-[3-(trifluoromethyl)-[1,2,4]triazolo[3,4-f]pyridazin-6-yl]-1,4-diazepane-1-carboxylate (5.94 g, 85.4 %) as a white solid. <sup>1</sup>H NMR (300.132 MHz, DMSO)  $\delta$  1.15 (9H, d), 1.72 - 1.93 (2H, m), 3.27 - 3.39 (2H, m), 3.50 - 3.63 (2H, m), 3.66 - 3.75 (2H, m), 3.83 (2H, t), 7.46 - 7.56 (1H, m), 8.19 - 8.31 (1H, m); apparently as a mixture of rotamers; m/z 387 (M+H)<sup>+</sup>.

**25 Preparation of 6-(1,4-diazepan-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[3,4-f]pyridazine**

Trifluoroacetic acid (8 mL, 103.68 mmol) was added to a mixture of tert-butyl 4-[3-(trifluoromethyl)-[1,2,4]triazolo[3,4-f]pyridazin-6-yl]-1,4-diazepane-1-carboxylate (5.9 g, 15.3 mmol) and dichloromethane (80 mL) at ambient temperature and the resulting 30 solution was stirred at ambient temperature for 6 hours. The reaction mixture was evaporated to give an involatile residue that was treated with saturated aqueous sodium bicarbonate solution (100 mL) and then extracted with dichloromethane (4 x 200 mL). The



organic phases were combined and dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and evaporated to give 6-(1,4-diazepan-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[3,4-f]pyridazine (3.8 g, 86.9 %) as a white solid. <sup>1</sup>H NMR (300.132 MHz, DMSO) δ 1.68 - 1.84 (m, 2H), 2.69 (t, 2H), 2.88 (t, 2H), 3.60 - 3.79 (m, 4H), 7.46 (d, 1H), 8.19 (d, 1H); m/z. 287 (M+H)<sup>+</sup>.

## 5 **General Synthetic Method 9**

### **General procedure for the reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridine with an aldehyde**

(Polystyrylmethyl)trimethylammonium cyanoborohydride (4.1 mmol/g, 0.061 g, 0.25 mmol) was added to the aldehyde (0.25 mmol) followed by a solution of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridine (0.050 g, 0.184 mmol) in a mixture of acetic acid and dichloromethane (1:9; 2 mL). The mixture was shaken for 40 hours and then filtered. The filtrate was evaporated and the involatile residue was purified by preparative reverse phase chromatography yield the corresponding 6-(4-(substituted-methyl)-piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridine.

15 The 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridine used as starting material was prepared as follows:-

### **Preparation of 6-bromo-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridine**

A mixture of polyphosphoric acid (20 mL, 175 mmol) and N'-(5-bromopyridin-2-yl)-2,2,2-trifluoroacetohydrazide (1.9 g, 6.69 mmol) was stirred at 120 °C for 20 hours and then poured in to water. The mixture was then basified with saturated aqueous sodium bicarbonate solution and extracted with dichloromethane (3 x 250 mL). The organic phases were combined and washed with brine (1 x 100 mL), dried with MgSO<sub>4</sub> and evaporated to give an involatile residue. The residue was purified by flash chromatography on silica-gel using an increasing gradient of ethyl acetate in isohexane as eluant to give 6-bromo-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridine (1.39 g, 78 %) as a beige solid.

<sup>1</sup>H NMR (300.132 MHz, DMSO) δ 7.74 - 7.81 (m, 1H), 8.00 - 8.07 (m, 1H), 8.92 (s, 1H); m/z 266 and 268 (M+H<sup>+</sup>).

### **Preparation of tert-butyl 4-(3-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridin-6-yl)piperazine-1-carboxylate**

30 A solution of tert-butyl piperazine-1-carboxylate (1.30 g, 6.99 mmol), 6-bromo-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridine (0.93 g, 3.50 mmol),



bis(dibenzylideneacetone)palladium (0.101 g, 0.17 mmol), rac-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (0.163 g, 0.26 mmol) and sodium tert-butoxide (0.84g, 8.74 mmol) in xylenes (30 mL) was sealed into a microwave tube and degassed for 10 minutes. The reaction mixture was heated at 100 °C for 30 minutes and then cooled to ambient temperature. The reaction mixture was diluted with water (20 mL) and then extracted with ethyl acetate (2 x 40 mL). The organic phases were combined, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and evaporated to give an involatile residue. The residue was purified by flash chromatography on silica-gel using an increasing gradient of ethyl acetate in isohexane as eluant to give tert-butyl 4-(3-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridin-6-yl)piperazine-1-carboxylate (0.86 g, 66.2 %) as a yellow solid.

<sup>1</sup>H NMR (300.132 MHz, DMSO) δ 1.43 (s, 9H), 3.12 - 3.20 (m, 4H), 3.46 - 3.54 (m, 4H), 7.59 (s, 1H), 7.69 - 7.78 (m, 1H), 7.95 (d, 1H); m/z 372 (M+H<sup>+</sup>).

#### **Preparation of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridine**

Trifluoroacetic acid (5 mL, 64.90 mmol) was added to a mixture of tert-butyl 4-(3-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridin-6-yl)piperazine-1-carboxylate (0.86 g, 2.32 mmol) and dichloromethane (20 mL). The resulting solution was stirred at 20 °C for 90 minutes and then evaporated to leave an involatile residue. The residue was purified by ion-exchange chromatography on an SCX column using aqueous ammonia (7M) in methanol as eluant to give 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridine (0.540 g, 86 %) as a yellow solid that was used without further purification.

<sup>1</sup>H NMR (300.132 MHz, DMSO) δ 2.79 - 2.92 (m, 4H), 3.03 - 3.13 (m, 4H), 7.49 (s, 1H), 7.67 - 7.76 (m, 1H), 7.91 (d, 1H); m/z 272 (M+H<sup>+</sup>).

#### **General Synthetic Method 10**

#### **General procedure for the reductive amination of 6-(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with an aldehyde**

(Polystyrylmethyl)trimethylammonium cyanoborohydride (4.1 mmol/g, 0.061 g, 0.25 mmol) was added to the aldehyde (0.25 mmol) followed by a solution of 6-(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (0.055 g, 0.184 mmol) in a mixture of acetic acid and dichloromethane (1:9; 2 mL). The mixture was shaken for 16 hours and then filtered. The filtrate was evaporated and the involatile residue was purified by preparative reverse phase chromatography to



yield the corresponding 6-(2-(substitutedmethyl)-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-5-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

The 6-(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine used as starting material was prepared as follows:-

5 **Preparation of 6-(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

Trifluoroacetic acid (15 mL, 194.70 mmol) was added to a mixture of tert-butyl 5-(3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate (3 g, 7.53 mmol) and dichloromethane (60 mL). The resulting solution  
10 was stirred at ambient temperature for 1 hour and then evaporated to leave an involatile residue. The residue was purified by ion-exchange chromatography on an SCX column using aqueous ammonia (7M) in methanol as eluant to give 6-(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (2.200 g, 98 %) as a white solid that was used without further purification.  
15 <sup>1</sup>H NMR (300.132 MHz, DMSO)  $\delta$  2.61 - 2.74 (m, 2H), 2.82 - 2.96 (m, 4H), 3.27 - 3.38 (m under H<sub>2</sub>O, 2H), 3.67 - 3.80 (m, 2H), 7.27 (d, 1H), 8.20 (d, 1H); m/z 299 (M+H<sup>+</sup>).

**Example 1**

**Preparation of 6-(4-benzhydrylpiperazin-1-yl)-3-(1,1,2,2-tetrafluoroethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

20 A mixture of 1-benzhydrylpiperazine and 6-chloro-3-(2,2,3,3-tetrafluoroethyl)-1,2,4-triazolo[4,3-b]pyridazine was allowed to react by General Synthetic Method 1 to give 6-(4-benzhydrylpiperazin-1-yl)-3-(1,1,2,2-tetrafluoroethyl)-[1,2,4]triazolo[4,3-b]pyridazine.  
<sup>1</sup>H NMR (700.03 MHz, DMSO-d<sub>6</sub>)  $\delta$  2.46 (4H, t), 3.63 (4H, t), 4.39 (1H, s), 7.07 - 7.23 (3H, m), 7.33 (4H, t), 7.48 (4H, d), 7.51 - 7.52 (1H, m), 8.23 (1H, d); m/z = 471 [M+H]<sup>+</sup>.

25 **Example 2**

**Preparation of 6-(4-benzyl-1,4-diazepan-1-yl)-3-(1,1,2,2-tetrafluoroethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

A mixture of 1-benzyl-1,4-diazepane and 6-chloro-3-(2,2,3,3-tetrafluoroethyl)-1,2,4-triazolo[4,3-b]pyridazine was allowed to react by General Synthetic Method 1 to give 6-(4-benzyl-1,4-diazepan-1-yl)-3-(1,1,2,2-tetrafluoroethyl)-[1,2,4]triazolo[4,3-b]pyridazine.  
30



<sup>1</sup>H NMR (700.03 MHz, DMSO-d<sub>6</sub>) δ 1.85 - 1.90 (2H, m), 2.61 (2H, t), 2.72 - 2.76 (2H, m), 3.63 (2H, s), 3.73 (2H, t), 3.76 (2H, t), 7.05 - 7.21 (1H, m), 7.21 - 7.24 (1H, m), 7.24 - 7.27 (4H, m), 7.46 (1H, d), 8.19 (1H, d); m/z = 409 [M+H]<sup>+</sup>.

### **Example 3**

5 **Preparation of 6-piperidin-1-yl-3-(2,2,2-trifluoroethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

A mixture of piperidine and 6-chloro-3-(3,3,3-trifluoroethyl)-1,2,4-triazolo[4,3-b]pyridazine was allowed to react by General Synthetic Method 1 to give 6-piperidin-1-yl-3-(2,2,2-trifluoroethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

10 <sup>1</sup>H NMR (700.03 MHz, DMSO-d<sub>6</sub>) δ 1.59 - 1.62 (4H, m), 1.65 (2H, d), 3.60 (4H, t), 4.20 (2H, q), 7.43 (1H, d), 8.06 (1H, d); m/z = 286 [M+H]<sup>+</sup>.

### **Example 4**

**Preparation of 6-(4-benzhydrylpiperazin-1-yl)-3-(2,2,2-trifluoroethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

15 A mixture of 1-benzhydrylpiperazine and 6-chloro-3-(3,3,3-trifluoroethyl)-1,2,4-triazolo[4,3-b]pyridazine was allowed to react by General Synthetic Method 1 to give 6-(4-benzhydrylpiperazin-1-yl)-3-(2,2,2-trifluoroethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

<sup>1</sup>H NMR (700.03 MHz, DMSO-d<sub>6</sub>) δ 2.46 (4H, t), 3.62 (4H, t), 4.19 (2H, q), 4.39 (1H, s), 7.22 (2H, t), 7.33 (4H, t), 7.37 (1H, d), 7.48 (4H, d), 8.11 (1H, d); m/z = 453 [M+H]<sup>+</sup>.

20 **Example 5**

**Preparation of 6-(4-benzhydrylpiperazin-1-yl)-3-(difluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

A mixture of 1-benzhydrylpiperazine and 6-chloro-3-difluoromethyl-1,2,4-triazolo[4,3-b]pyridazine was allowed to react by General Synthetic Method 1 to give 6-(4-benzhydrylpiperazin-1-yl)-3-(difluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

25 <sup>1</sup>H NMR (700.03 MHz, DMSO-d<sub>6</sub>) δ 2.46 (4H, t), 3.63 (4H, t), 4.40 (1H, s), 7.21 - 7.23 (2H, m), 7.33 (4H, t), 7.28 - 7.57 (1H, m), 7.45 - 7.49 (5H, m), 8.18 - 8.19 (1H, m); m/z = 421 [M+H]<sup>+</sup>.

### **Example 6**

30 **Preparation of 6-(4-benzyl-1,4-diazepan-1-yl)-3-(difluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

A mixture of 1-benzyl-1,4-diazepane and 6-chloro-3-difluoromethyl-1,2,4-triazolo[4,3-



b]pyridazine was allowed to react by General Synthetic Method 1 to give 6-(4-benzyl-1,4-diazepan-1-yl)-3-(difluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

<sup>1</sup>H NMR (700.03 MHz, DMSO-d<sub>6</sub>) δ 1.86 - 1.90 (2H, m), 2.61 (2H, t), 2.74 (2H, t), 3.63 (2H, s), 3.73 (2H, t), 3.75 (2H, t), 7.21 - 7.24 (1H, m), 7.26 (4H, t), 7.41 (1H, d), 7.40 - 7.55 (1H, m), 8.14 (1H, d); m/z = 359 [M+H]<sup>+</sup>.

### **Example 7**

#### **Preparation of 6-piperidin-1-yl-[1,2,4]triazolo[4,3-b]pyridazin-3-amine**

A mixture of piperidine and 3-amino-6-chloro-1,2,4-triazolo[4,3-b]pyridazine was allowed to react by General Synthetic Method 2 to give 6-piperidin-1-yl-[1,2,4]triazolo[4,3-b]pyridazin-3-amine.

<sup>1</sup>H NMR (700.03 MHz, DMSO-d<sub>6</sub>) δ 1.58 - 1.63 (6H, m), 3.53 (4H, t), 6.00 (2H, s), 7.07 (1H, d), 7.72 (1H, d); m/z = 219 [M+H]<sup>+</sup>.

### **Example 8**

#### **Preparation of 6-(4-benzhydrylpiperazin-1-yl)-3-chloro-[1,2,4]triazolo[4,3-b]pyridazine**

A mixture of 1-benzhydrylpiperazine and 3,6-dichloro-1,2,4-triazolo[4,3-b]pyridazine was allowed to react by General Synthetic Method 2 to give 6-(4-benzhydrylpiperazin-1-yl)-3-chloro-[1,2,4]triazolo[4,3-b]pyridazine.

<sup>1</sup>H NMR (700.03 MHz, DMSO-d<sub>6</sub>) δ 2.46 (4H, t), 3.63 (4H, t), 4.40 (1H, s), 7.21 - 7.23 (2H, m), 7.33 (4H, t), 7.41 (1H, d), 7.47 (4H, d), 8.11 (1H, d); m/z = 405 [M+H]<sup>+</sup>.

### **Example 9**

#### **Preparation of 6-(4-benzhydrylpiperazin-1-yl)-3-methylsulfanyl-[1,2,4]triazolo[4,3-b]pyridazine**

A mixture of 1-benzhydrylpiperazine and 6-chloro-3-methylsulfanyl-1,2,4-triazolo[4,3-b]pyridazine was allowed to react by General Synthetic Method 2 to give 6-(4-benzhydrylpiperazin-1-yl)-3-methylsulfanyl-[1,2,4]triazolo[4,3-b]pyridazine.

<sup>1</sup>H NMR (700.03 MHz, DMSO-d<sub>6</sub>) δ 2.46 (4H, t), 2.68 (3H, s), 3.58 (4H, t), 4.39 (1H, s), 7.21 - 7.23 (2H, m), 7.31 (1H, d), 7.33 (4H, t), 7.47 (4H, d), 8.05 (1H, d); m/z = 417 [M+H]<sup>+</sup>.

### **Example 10**

#### **Preparation of 6-(4-benzyl-1,4-diazepan-1-yl)-3-methylsulfanyl-[1,2,4]triazolo[4,3-b]pyridazine**



A mixture of 1-benzyl-1,4-diazepane and 6-chloro-3-methylsulfanyl-1,2,4-triazolo[4,3-b]pyridazine was allowed to react by General Synthetic Method 2 to give 6-(4-benzyl-1,4-diazepan-1-yl)-3-methylsulfanyl-[1,2,4]triazolo[4,3-b]pyridazine.

<sup>1</sup>H NMR (700.03 MHz, DMSO-d<sub>6</sub>) δ 1.86 - 1.90 (2H, m), 2.60 (2H, t), 2.67 (3H, s), 2.74 (2H, t), 3.63 (2H, s), 3.72 (2H, t), 3.74 (2H, t), 7.22 - 7.24 (1H, m), 7.25 (1H, d), 7.26 - 7.28 (4H, m), 8.01 (1H, d); m/z = 355 [M+H]<sup>+</sup>.

### **Example 11**

#### **Preparation of 6-[4-(5-bromopyridin-2-yl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

A mixture of 1-(5-bromopyridin-2-yl)piperazine and 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine in ethanol (7 mL) was stirred at 80 °C for 20 hours. The reaction mixture was concentrated and partitioned between dichloromethane (50 mL) and saturated aqueous sodium bicarbonate solution (25 mL). The aqueous phase was extracted twice with dichloromethane (2 x 50 mL). The organic phases were combined, washed with water (100 mL), and concentrated to give a residue that was purified by flash chromatography on silica-gel using ethyl acetate as eluant to give 6-[4-(5-bromopyridin-2-yl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine 0.353 g, 73.4 %)

<sup>1</sup>H NMR (300.132 MHz, DMSO) δ 3.64 - 3.77 (8H, m), 6.90 (1H, d), 7.65 (1H, d), 7.71 - 7.76 (1H, m), 8.20 - 8.22 (1H, m), 8.29 (1H, d); m/z = 430 not assigned (Br).

### **Example 12**

Preparation of 4-((4-(8-Methyl-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)piperazin-1-yl)methyl)benzonitrile

A mixture of 1-(4-cyanobenzyl)-piperazine (0.158 g, 0.79 mmol) and 6-chloro-8-methyl-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine 0.062 g, 0.26 mmol) in ethanol (5 mL) was heated to 70 °C for 20 hours. The reaction mixture was allowed to cool and then concentrated to give an involatile residue that was purified by flash chromatography on silica-gel using an increasing gradient of ethyl acetate in dichloromethane to give 4-((4-(8-methyl-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)piperazin-1-yl)methyl)benzonitrile (0.0676 g, 64.3 %) as a white solid; <sup>1</sup>H NMR spectrum (CDCl<sub>3</sub>) δ 2.47 - 2.55 (4H, m), 2.61 (3H, d), 3.50 - 3.60 (6H, m), 6.72 - 6.76 (1H, m), 7.42 (2H, d), 7.57 (2H, d); m/z 402.69 (M+1)<sup>+</sup>.



The 6-chloro-8-methyl-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine used as starting material was prepared as follows

**Preparation of a mixture of 6-chloro-4-methylpyridazin-3-yl hydrazine and 6-chloro-5-methylpyridazin-3-yl hydrazine**

5 Hydrazine hydrate (1.79 mL, 36.81 mmol) was added to a stirred suspension of 3,6-dichloro-4-methylpyridazine (0.50 g, 3.07 mmol) in water (10 mL) and the reaction mixture was heated at 80 °C for 4 hours. The reaction mixture was allowed to cool and evaporated under reduced pressure to give a mixture of 3-chloro-6-hydrazinyl-4-methylpyridazine compound and 6-chloro-3-hydrazinyl-4-methylpyridazine (0.452 g) as an  
10 off-white solid that was used without further purification. m/z 159.41 (M+1)+.

**Preparation of 6-chloro-7-methyl-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine and 6-chloro-8-methyl-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

A suspension of a mixture of 3-chloro-6-hydrazinyl-4-methylpyridazine compound and 6-chloro-3-hydrazinyl-4-methylpyridazine (0.200 g) in trifluoroacetic acid (10 mL)  
15 was heated under reflux for 20 hours. The reaction mixture was allowed to cool and then concentrated to give an involatile residue that was purified by flash chromatography on silica-gel using dichloromethane as eluant to give pure fractions of:

6-chloro-8-methyl-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (0.0620 g) as a white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 2.74 (3H, d), 7.05 (1H, q); m/z 237.37 (M+1)+; and  
20 6-chloro-7-methyl-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (0.078 g) as a white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 2.49 (3H, d), 7.97 (1H, q); m/z 237.37 (M+1)+.

**Example 13**

**Preparation of 4-((4-(7-Methyl-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)piperazin-1-yl)methyl)benzonitrile**

25 The method of Example 12 was repeated using a mixture of 6-chloro-7-methyl-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (0.078 g, 0.33mmol) and 1-(4-cyanobenzyl)-piperazine (0.199 g, 0.99 mmol) to give 4-((4-(7-methyl-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)piperazin-1-yl)methyl)benzonitrile (0.099 g, 75%).  
<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 2.37 (3H, d), 2.53 - 2.63 (4H, m), 3.23 - 3.32 (4H, m), 3.57 (2H, s),  
30 7.42 (2H, d), 7.57 (2H, d), 7.73 - 7.76 (1H, m); m/z 402.71 (M+1)+.

The 6-chloro-7-methyl-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine used as starting material was prepared as described in Example 12.



**Example 14****Preparation of 6-[4-[(4-chlorophenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

A mixture of 1-[(4-chlorophenyl)methyl]piperazine and 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by General Synthetic Method 3. The crude product was purified by hplc using a Waters XTerra C18 column (5 $\mu$  silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(4-chlorophenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine. <sup>1</sup>H NMR (499.802 MHz, DMSO-d<sub>6</sub>)  $\delta$  2.48-2.51 (4H, m), 3.52 (2H, s), 3.56-3.62 (4H, m), 7.37 (4H, q), 7.57 (1H, d), 8.23 (1H, d) (Signal at 2.5 obscured by DMSO); m/z = 397 [M+H]<sup>+</sup>.

**Example 15****Preparation of 6-[4-[(4-methoxyphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

A mixture of 1-[(4-methoxyphenyl)methyl]piperazine and 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by General Synthetic Method 3. The crude product was purified by hplc using a Waters XTerra C18 column (5 $\mu$  silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(4-methoxyphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

<sup>1</sup>H NMR (499.802 MHz, DMSO-d<sub>6</sub>)  $\delta$  2.44-2.51 (4H, m), 3.47 (2H, s), 3.57-3.64 (4H, m), 3.75 (3H, s), 6.91 (2H, d), 7.25 (2H, d), 7.58 (1H, d), 8.24 (1H, d) (Signal at 2.5 partially obscured by DMSO); m/z = 393 [M+H]<sup>+</sup>.

**Example 16****Preparation of 6-[4-(2,6-dimethylphenyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

A mixture of 1-(2,6-dimethylphenyl)piperazine and 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by General Synthetic Method 3. The crude product was purified by hplc using a Waters XTerra C18 column (5 $\mu$  silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing



0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-(2,6-dimethylphenyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine. <sup>1</sup>H NMR (700.03 MHz, DMSO-d<sub>6</sub>) δ 2.31 (6H, s), 3.17 (4H, t), 3.73 (4H, t), 6.95 - 6.97 (1H, m), 7.00 (2H, d), 7.66 (1H, d), 8.27 (1H, d); m/z = 377 [M+H]<sup>+</sup>.

5 **Example 17**

**Preparation of 1-[4-[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]phenyl]ethanone**

A mixture of 1-(4-piperazin-1-ylphenyl)ethanone and 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by General Synthetic Method 3. The  
10 crude product was purified by hplc using a Waters XTerra C18 column (5μ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 1-[4-[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]phenyl]ethanone.

<sup>1</sup>H NMR (700.03 MHz, DMSO-d<sub>6</sub>) δ 2.47 (3H, s), 3.56 (4H, t), 3.79 (4H, t), 7.03 - 7.04  
15 (2H, m), 7.66 (1H, d), 7.84 - 7.86 (2H, m), 8.30 (1H, d); m/z = 391 [M+H]<sup>+</sup>.

**Example 18**

**Preparation of 6-[4-[4,4-bis(4-fluorophenyl)butyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

A mixture of 1-[4,4-bis(4-fluorophenyl)butyl]piperazine and 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by General Synthetic Method 3. The  
20 crude product was purified by hplc using a Waters XTerra C18 column (5μ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[4,4-bis(4-fluorophenyl)butyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.  
25 <sup>1</sup>H NMR (700.03 MHz, DMSO-d<sub>6</sub>) δ 1.34 - 1.38 (2H, m), 2.02 (2H, q), 2.34 (2H, t), 2.42 (4H, t), 3.57 (4H, t), 4.01 (1H, t), 7.09 - 7.13 (4H, m), 7.32 - 7.35 (4H, m), 7.58 (1H, d), 8.23 (1H, d); m/z = 517 [M+H]<sup>+</sup>.

**Example 19**

**Preparation of 6-[4-(3,5-dichloropyridin-4-yl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

30 A mixture of 1-(3,5-dichloropyridin-4-yl)piperazine and 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by General Synthetic Method 3. The



crude product was purified by hplc using a Waters XTerra C18 column (5 $\mu$  silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-(3,5-dichloropyridin-4-yl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

5 1H NMR (700.03 MHz, DMSO-d<sub>6</sub>)  $\delta$  3.45 - 3.46 (4H, m), 3.78 (4H, t), 7.67 (1H, d), 8.30 (1H, d), 8.50 (2H, s); m/z = 418 [M+H]<sup>+</sup>.

### **Example 20**

#### **Preparation of 1-phenyl-8-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]-1,3,8-triazaspiro[4.5]decan-4-one**

10 A mixture of 1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one and 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by General Synthetic Method 3. The crude product was purified by hplc using a Waters XTerra C18 column (5 $\mu$  silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 1-phenyl-8-[3-

15 (trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]-1,3,8-triazaspiro[4.5]decan-4-one. 1H NMR (700.03 MHz, DMSO-d<sub>6</sub>)  $\delta$  1.79 - 1.81 (2H, m), 2.55 (2H, d), 3.79 (2H, d), 4.19 - 4.22 (2H, m), 4.63 (2H, s), 6.67 (2H, d), 6.71 (1H, t), 7.07 - 7.09 (2H, m), 7.66 (1H, d), 8.29 (1H, d), 8.81 (1H, s); m/z = 418 [M+H]<sup>+</sup>.

### **Example 21**

#### **Preparation of 6-[4-(4-nitrophenyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

20 A mixture of 1-(4-nitrophenyl)piperazine and 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by General Synthetic Method 3. The crude product was purified by hplc using a Waters XTerra C18 column (5 $\mu$  silica, 19 mm

25 diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-(4-nitrophenyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine. 1H NMR (300.132 MHz, DMSO-d<sub>6</sub>)  $\delta$  3.66-3.74 (4H, m), 3.76-3.85 (4H, m), 7.06 (2H, d), 7.64 (1H, d), 8.10 (2H, d), 8.30 (1H, d); m/z = 394 [M+H]<sup>+</sup>.

### **Example 22**

#### **Preparation of 6-(4-benzhydrylpiperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**



A mixture of 1-benzhydrylpiperazine and 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by General Synthetic Method 3. The crude product was purified by hplc using a Phenomenex Luna C18 100A column (10 $\mu$  silica, 21mm diameter, 150mm length) eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-(4-benzhydrylpiperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

<sup>1</sup>H NMR (700.03 MHz, DMSO-d<sub>6</sub>)  $\delta$  2.46 (4H, t), 3.63 (4H, t), 4.40 (1H, s), 7.21 - 7.23 (2H, m), 7.32 - 7.34 (4H, m), 7.46 - 7.48 (4H, m), 7.54 (1H, d), 8.25 (1H, d); m/z = 439 [M+H]<sup>+</sup>.

### **Example 23**

#### **Preparation of 6-(4-phenethylpiperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

A mixture of 1-phenethylpiperazine and 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by General Synthetic Method 3. The crude product was purified by hplc using a Waters XTerra C18 column (5 $\mu$  silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-(4-phenethylpiperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

<sup>1</sup>H NMR (700.03 MHz, DMSO-d<sub>6</sub>)  $\delta$  2.58 - 2.60 (6H, m), 2.79 (2H, t), 3.62 (4H, t), 7.18 - 7.21 (1H, m), 7.25 - 7.26 (2H, m), 7.28 - 7.30 (2H, m), 7.61 (1H, d), 8.25 (1H, d); m/z = 377 [M+H]<sup>+</sup>.

### **Example 24**

#### **Preparation of 1-piperidin-1-yl-2-[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]ethanone**

A mixture of 2-piperazin-1-yl-1-piperidin-1-ylethanone and 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by General Synthetic Method 3. The crude product was purified by hplc using a Waters XTerra C18 column (5 $\mu$  silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 1-piperidin-1-yl-2-[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]ethanone.



<sup>1</sup>H NMR (700.03 MHz, DMSO-d<sub>6</sub>) δ 1.44 (2H, s), 1.53 (2H, d), 1.58 - 1.61 (2H, m), 2.58 (4H, t), 3.21 (2H, s), 3.42 (2H, t), 3.48 (2H, t), 3.61 (4H, t), 7.60 (1H, d), 8.26 (1H, d); m/z = 398 [M+H]<sup>+</sup>.

### **Example 25**

#### **Preparation of 6-[4-[(4-methoxyphenyl)-phenylmethyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

A mixture of 1-[(4-methoxyphenyl)-phenylmethyl]piperazine and 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by General Synthetic Method 3. The crude product was purified by hplc using a Waters XTerra C18 column (5μ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(4-methoxyphenyl)-phenylmethyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

<sup>1</sup>H NMR (700.03 MHz, DMSO-d<sub>6</sub>) δ 2.45 (4H, t), 3.62 (4H, t), 3.72 (3H, s), 4.34 (1H, s), 6.88 - 6.90 (2H, m), 7.20 - 7.24 (1H, m), 7.31 - 7.33 (2H, m), 7.35 - 7.37 (2H, m), 7.44 - 7.45 (2H, m), 7.54 (1H, d), 8.25 (1H, d); m/z = 469 [M+H]<sup>+</sup>.

### **Example 26**

#### **Preparation of 6-[4-[phenyl-[4-(trifluoromethyl)phenyl]methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

A mixture of 1-[phenyl-[4-(trifluoromethyl)phenyl]methyl]piperazine and 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by General Synthetic Method 3. The crude product was purified by hplc using a Waters XTerra C18 column (5μ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[phenyl-[4-(trifluoromethyl)phenyl]methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

<sup>1</sup>H NMR (700.03 MHz, DMSO-d<sub>6</sub>) δ 2.45 - 2.49 (4H, m), 3.64 (4H, t), 4.57 (1H, s), 7.24 - 7.26 (1H, m), 7.35 (2H, t), 7.47 - 7.48 (2H, m), 7.54 (1H, d), 7.69 - 7.73 (4H, m), 8.26 (1H, d); m/z = 507 [M+H]<sup>+</sup>.

### **Example 27**

#### **Preparation of 6-[4-(6-bromonaphthalen-2-yl)sulfonylpiperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**



A mixture of 1-(6-bromonaphthalen-2-yl)sulfonylpiperazine and 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by General Synthetic Method 3. The crude product was purified by hplc using a Waters XTerra C18 column (5 $\mu$  silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-(6-bromonaphthalen-2-yl)sulfonylpiperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

<sup>1</sup>H NMR (700.03 MHz, DMSO-d<sub>6</sub>)  $\delta$  3.16 (4H, t), 3.72 (4H, t), 7.49 (1H, d), 7.81 - 7.83 (1H, m), 7.84 - 7.86 (1H, m), 8.16 (1H, d), 8.19 (1H, d), 8.21 (1H, d), 8.39 (1H, d), 8.52 (1H, d); m/z = 543 not assigned (Br).

### **Example 28**

#### **Preparation of N-[[[(9aR)-2-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]-1,3,4,6,7,8,9,9a-octahydropyrido[1,6-a]pyrazin-7-yl]methyl]-2-methylquinolin-4-amine**

A mixture of N-[[[(9aR)-2,3,4,6,7,8,9,9a-octahydro-1H-pyrido[1,6-a]pyrazin-7-yl]methyl]-2-methylquinolin-4-amine and 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by General Synthetic Method 3. The crude product was purified by hplc using a Waters XTerra C18 column (5 $\mu$  silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give N-[[[(9aR)-2-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]-1,3,4,6,7,8,9,9a-octahydropyrido[1,6-a]pyrazin-7-yl]methyl]-2-methylquinolin-4-amine.

<sup>1</sup>H NMR (700.03 MHz, DMSO-d<sub>6</sub>)  $\delta$  1.06 - 1.10 (1H, m), 1.24 - 1.26 (1H, m), 1.69 - 1.71 (1H, m), 1.79 (1H, d), 1.91 - 1.94 (1H, m), 1.96 (1H, d), 2.09 - 2.12 (1H, m), 2.17 - 2.21 (1H, m), 2.47 (3H, s), 2.70 (1H, d), 2.85 - 2.87 (1H, m), 2.98 (1H, d), 3.02 - 3.06 (1H, m), 3.15 (2H, t), 4.13 (1H, d), 4.19 (1H, d), 6.37 (1H, s), 7.05 (1H, s), 7.33 - 7.36 (1H, m), 7.56 (1H, d), 7.62 (1H, d), 7.68 - 7.69 (1H, m), 8.19 (1H, d), 8.25 (1H, d); m/z = 497 [M+H]<sup>+</sup>.

### **Example 29**

#### **Preparation of 6-[4-(2,4-difluorophenyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

A mixture of 1-(2,4-difluorophenyl)piperazine and 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by General Synthetic Method 3. The



crude product was purified by hplc using a Waters XTerra C18 column (5 $\mu$  silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-(2,4-difluorophenyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

5 <sup>1</sup>H NMR (700.03 MHz, DMSO-d<sub>6</sub>)  $\delta$  3.13 (4H, t), 3.78 (4H, t), 7.01 - 7.04 (1H, m), 7.12 - 7.16 (1H, m), 7.22 - 7.25 (1H, m), 7.66 (1H, d), 8.29 (1H, d); m/z = 385 [M+H]<sup>+</sup>.

### **Example 30**

#### **Preparation of 6-[4-[3-chloro-5-(trifluoromethyl)pyridin-2-yl]-1,4-diazepan-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

10 A mixture of 1-[3-chloro-5-(trifluoromethyl)pyridin-2-yl]-1,4-diazepane and 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by General Synthetic Method 3. The crude product was purified by hplc using a Waters XTerra C18 column (5 $\mu$  silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give  
15 6-[4-[3-chloro-5-(trifluoromethyl)pyridin-2-yl]-1,4-diazepan-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

<sup>1</sup>H NMR (700.03 MHz, DMSO-d<sub>6</sub>)  $\delta$  2.04 (2H, d), 3.76 (2H, t), 3.80 (2H, t), 3.96 (2H, d), 4.02 (2H, s), 7.52 (1H, d), 7.96 (1H, s), 8.20 (1H, d), 8.29 (1H, d); m/z = 466 [M+H]<sup>+</sup>.

### **Example 31**

#### **Preparation of 6-[4-[4-(4-fluorophenyl)-5-(2-methoxypyrimidin-4-yl)imidazol-1-yl]piperidin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

A mixture of 4-[5-(4-fluorophenyl)-3-piperidin-4-ylimidazol-4-yl]-2-methoxypyrimidine and 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by General Synthetic Method 3. The crude product was purified by hplc using a Waters  
25 XTerra C18 column (5 $\mu$  silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[4-(4-fluorophenyl)-5-(2-methoxypyrimidin-4-yl)imidazol-1-yl]piperidin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

<sup>1</sup>H NMR (700.03 MHz, DMSO-d<sub>6</sub>)  $\delta$  2.07 - 2.13 (2H, m), 2.19 - 2.21 (2H, m), 3.13 (2H, d), 3.98 (3H, s), 4.43 - 4.45 (2H, m), 4.76 - 4.79 (1H, m), 6.96 (1H, d), 7.16 (2H, d), 7.42 -  
30 7.44 (2H, m), 7.67 (1H, d), 8.17 (1H, s), 8.29 (1H, d), 8.56 (1H, d); m/z = 540 [M+H]<sup>+</sup>.



**Example 32****Preparation of 6-[4-(2-methylphenyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

A mixture of 1-(2-methylphenyl)piperazine and 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by General Synthetic Method 3. The crude product was purified by hplc using a Waters XTerra C18 column (5 $\mu$  silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-(2-methylphenyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

<sup>1</sup>H NMR (700.03 MHz, DMSO-d<sub>6</sub>)  $\delta$  2.32 (3H, s), 3.00 (4H, t), 3.77 (4H, t), 6.99 - 7.01 (1H, m), 7.06 (1H, d), 7.16 - 7.18 (1H, m), 7.20 (1H, d), 7.66 (1H, d), 8.28 (1H, d); m/z = 363 [M+H]<sup>+</sup>.

**Example 33****Preparation of 6-[4-[(2-chlorophenyl)methyl]-1,4-diazepan-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

A mixture of 1-[(2-chlorophenyl)methyl]-1,4-diazepane and 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by General Synthetic Method 3. The crude product was purified by hplc using a Waters XTerra C18 column (5 $\mu$  silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(2-chlorophenyl)methyl]-1,4-diazepan-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

<sup>1</sup>H NMR (499.802 MHz, DMSO-d<sub>6</sub>)  $\delta$  1.81-1.92 (2H, m), 2.65-2.70 (2H, m), 2.77-2.83 (2H, m), 3.70 (2H, s), 3.71-3.76 (2H, m), 3.76-3.80 (2H, m), 7.18-7.27 (2H, m), 7.34 (1H, d), 7.41 (1H, d), 7.49 (1H, d), 8.21 (1H, d); m/z = 411 [M+H]<sup>+</sup>.

**Example 34****Preparation of 1-[2-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-5-yl]butan-1-one**

A mixture of 1-(2,3,3a,4,6,6a-hexahydro-1H-pyrrolo[3,4-c]pyrrol-5-yl)butan-1-one and 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by General Synthetic Method 3. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5 $\mu$  silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 0.2% aqueous ammonia) and acetonitrile



as eluents to give 1-[2-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-5-yl]butan-1-one.

<sup>1</sup>H NMR (300.132 MHz, DMSO-d<sub>6</sub>) δ 0.88 (3H, t), 1.51 (2H, sextet), 2.16-2.25 (2H, m), 2.94-3.19 (2H, m), 3.25-3.34 (1H, m), 3.35-3.50 (3H, m), 3.54-3.64 (1H, m), 3.66-3.83 (3H, m), 7.24 (1H, d), 8.22 (1H, d) (Signal at 3.3 partially obscured by water); m/z = 369 [M+H]<sup>+</sup>.

### **Example 35**

#### **Preparation of tert-butyl (1S,5R)-3-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate**

A mixture of tert-butyl (1S,5R)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate and 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by General Synthetic Method 3. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5μ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give tert-butyl (1S,5R)-3-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate.

<sup>1</sup>H NMR (300.132 MHz, DMSO-d<sub>6</sub>) δ 1.37 (9H, s), 1.59-1.69 (2H, m), 1.76-1.89 (2H, m), 3.00-3.10 (2H, m), 3.84-3.95 (2H, m), 4.18-4.25 (2H, m), 7.47 (1H, d), 8.20 (1H, d); m/z = 399 [M+H]<sup>+</sup>.

### **Example 36**

#### **Preparation of 6-[4-(3-methylphenyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

A mixture of 1-(3-methylphenyl)piperazine dihydrochloride and 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by General Synthetic Method 4. The crude product was purified by hplc using a Waters XTerra C18 column (5μ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-(3-methylphenyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine. <sup>1</sup>H NMR (700.03 MHz, DMSO-d<sub>6</sub>) δ 2.28 (3H, s), 3.76 (4H, t), 6.65 (1H, d), 6.80 - 6.81 (1H, m), 6.83 (1H, s), 7.13 (1H, t), 7.67 (1H, d), 8.29 (1H, d) (Some peaks obscured by solvent); m/z = 363 [M+H]<sup>+</sup>.



**Example 37****Preparation of 6-[4-(2-chlorophenyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

A mixture of 1-(2-chlorophenyl)piperazine hydrate hydrochloride and 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by General Synthetic Method 4. The crude product was purified by hplc using a Waters XTerra C18 column (5 $\mu$  silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-(2-chlorophenyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine. <sup>1</sup>H NMR (700.03 MHz, DMSO-d<sub>6</sub>)  $\delta$  3.15 (4H, t), 3.79 (4H, t), 7.08 - 7.11 (1H, m), 7.21 - 7.22 (1H, m), 7.32 - 7.35 (1H, m), 7.45 - 7.47 (1H, m), 7.67 (1H, d), 8.30 (1H, d); m/z = 383 [M+H]<sup>+</sup>.

**Example 38****Preparation of 6-[4-(6-chloronaphthalen-2-yl)sulfonylpiperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

A mixture of 1-(6-chloronaphthalen-2-yl)sulfonylpiperazine hydrochloride and 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by General Synthetic Method 4. The crude product was purified by hplc using a Waters XTerra C18 column (5 $\mu$  silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-(6-chloronaphthalen-2-yl)sulfonylpiperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

<sup>1</sup>H NMR (700.03 MHz, DMSO-d<sub>6</sub>)  $\delta$  3.16 (4H, t), 3.72 (4H, t), 7.49 (1H, d), 7.71 - 7.72 (1H, m), 7.85 - 7.86 (1H, m), 8.16 (1H, d), 8.21 (1H, d), 8.23 (1H, d), 8.27 (1H, d), 8.53 (1H, d); m/z = 497 [M+H]<sup>+</sup>.

**Example 39****Preparation of 1-[1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]-4H-3,1-benzoxazin-2-one**

A mixture of 1-piperidin-4-yl-4H-3,1-benzoxazin-2-one hydrochloride and 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by General Synthetic Method 4. The crude product was purified by hplc using a Waters XTerra C18 column (5 $\mu$  silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar



mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 1-[1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]-4H-3,1-benzoxazin-2-one.

<sup>5</sup> <sup>1</sup>H NMR (700.03 MHz, DMSO-d<sub>6</sub>) δ 1.95 - 1.97 (2H, m), 2.53 - 2.57 (2H, m), 3.22 (1H, d), 4.25 - 4.28 (1H, m), 4.41 - 4.43 (2H, m), 5.16 (2H, s), 7.12 - 7.15 (1H, m), 7.30 - 7.31 (1H, m), 7.37 (1H, d), 7.39 - 7.41 (1H, m), 7.67 (1H, d), 8.26 (1H, d) (Some peaks obscured by solvent); m/z = 419 [M+H]<sup>+</sup>.

#### **Example 40**

##### **Preparation of 1-[1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]-3,4-dihydroquinolin-2-one**

<sup>10</sup> A mixture of 1-piperidin-4-yl-3,4-dihydroquinolin-2-one hydrochloride and 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by General Synthetic Method 4. The crude product was purified by hplc using a Phenomenex Luna C18 100A column (10μ silica, 21mm diameter, 150mm length) eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 1-[1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]-3,4-dihydroquinolin-2-one.

<sup>15</sup> <sup>1</sup>H NMR (700.03 MHz, DMSO-d<sub>6</sub>) δ 1.83 - 1.85 (2H, m), 2.43 - 2.45 (2H, m), 2.61 - 2.67 (2H, m), 2.80 (2H, t), 3.15 - 3.18 (2H, m), 4.32 - 4.36 (1H, m), 4.39 - 4.41 (2H, m), 7.01 - 7.03 (1H, m), 7.23 - 7.26 (2H, m), 7.31 (1H, d), 7.66 (1H, d), 8.26 (1H, d); m/z = 417 [M+H]<sup>+</sup>.

#### **Example 41**

##### **Preparation of 6-(5-benzyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

<sup>25</sup> A mixture of (1R,4R)-6-benzyl-3,6-diazabicyclo[2.2.1]heptane dihydrobromide and 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by General Synthetic Method 4. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5μ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 0.2% aqueous ammonia) and acetonitrile as eluents to give 6-(5-benzyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

<sup>30</sup>



<sup>1</sup>H NMR (700.03 MHz, DMSO-d<sub>6</sub>) δ 1.83 - 1.84 (1H, m), 2.00 (1H, d), 2.88 (1H, d), 3.63 (2H, s), 3.73 (2H, s), 7.23 (1H, d), 7.29 - 7.31 (2H, m), 7.32 (3H, t), 8.21 (1H, d) (Some peaks obscured by solvent); m/z = 375 [M+H]<sup>+</sup>.

#### **Example 42**

5 **Preparation of 6-[4-(pyridin-2-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with pyridine-2-carbaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18  
10 OBD column, 5μ silica, 19 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-(pyridin-2-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

<sup>1</sup>H NMR (499.802 MHz, DMSO-d<sub>6</sub>) δ 2.55-2.62 (4H, m), 3.61-3.66 (4H, m), 3.68 (2H, s),  
15 7.26-7.32 (1H, m), 7.49 (1H, d), 7.59 (1H, d), 7.76-7.82 (1H, m), 8.25 (1H, d), 8.52 (1H, d); m/z = 364 [M+H]<sup>+</sup>.

#### **Example 43**

**Preparation of 3-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]benzonitrile**

20 Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 3-formylbenzonitrile was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5μ silica, 19 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 3-  
25 [[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]benzonitrile.

<sup>1</sup>H NMR (499.802 MHz, DMSO-d<sub>6</sub>) δ 2.51-2.57 (4H, m), 3.60-3.66 (6H, m), 7.54-7.62 (2H, m), 7.71 (1H, d), 7.76 (1H, d), 7.79 (1H, s), 8.26 (1H, d) (Signal at 2.5 partially obscured by DMSO); m/z = 388 [M+H]<sup>+</sup>.

30 **Example 44**

**Preparation of 4-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]benzonitrile**



Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 4-formylbenzonitrile was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5 $\mu$  silica, 19 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 4-  
5 [[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]benzonitrile.

<sup>1</sup>H NMR (499.802 MHz, DMSO-d<sub>6</sub>)  $\delta$  2.51-2.56 (4H, m), 3.59-3.68 (6H, m), 7.53-7.62 (3H, m), 7.82 (2H, d), 8.26 (1H, d) (Signal at 2.5 partially obscured by DMSO); m/z = 388  
10 [M+H]<sup>+</sup>.

#### **Example 45**

##### **Preparation of 6-[4-[(4-fluorophenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 4-fluorobenzaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5 $\mu$  silica, 19 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 6-  
15 [4-[(4-fluorophenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

<sup>1</sup>H NMR (499.802 MHz, DMSO-d<sub>6</sub>)  $\delta$  2.48-2.52 (4H, m), 3.53 (2H, s), 3.58-3.66 (4H, m), 7.17 (2H, t), 7.34-7.41 (2H, m), 7.58 (1H, d), 8.25 (1H, d) (Signal at 2.5 partially obscured by DMSO); m/z = 381 [M+H]<sup>+</sup>.

#### **Example 46**

##### **Preparation of 6-[4-[(2-methylphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 2-methylbenzaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5 $\mu$  silica, 19 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 6-  
30



[4-[(2-methylphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.802 MHz, DMSO-d<sub>6</sub>)  $\delta$  2.33 (3H, s), 2.49-2.53 (4H, m), 3.48 (2H, s), 3.56-3.61 (4H, m), 7.12-7.18 (3H, m), 7.25 (1H, d), 7.57 (1H, d), 8.23 (1H, d) (Signal at 2.5 partially obscured by DMSO); m/z = 377 [M+H]<sup>+</sup>.

#### **Example 47**

##### **Preparation of 6-[4-[(4-methylphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 4-methylbenzaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5 $\mu$  silica, 19 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(4-methylphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.802 MHz, DMSO-d<sub>6</sub>)  $\delta$  2.30 (3H, s), 2.45-2.51 (4H, m), 3.50 (2H, s), 3.56-3.65 (4H, m), 7.15 (2H, d), 7.22 (2H, d), 7.58 (1H, d), 8.24 (1H, d) (Signal at 2.5 partially obscured by DMSO); m/z = 377 [M+H]<sup>+</sup>.

#### **Example 48**

##### **Preparation of 6-[4-(1,3-benzothiazol-2-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 1,3-benzothiazole-2-carbaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5 $\mu$  silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-(1,3-benzothiazol-2-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.802 MHz, DMSO)  $\delta$  2.73 (4H, t), 3.66 (4H, t), 4.04 (2H, s), 7.40 - 7.43 (1H, m), 7.46 - 7.51 (1H, m), 7.60 (1H, d), 7.94 (1H, d), 8.06 (1H, d), 8.25 (1H, d); m/z = 420 [M+H]<sup>+</sup>.



**Example 49****Preparation of 6-[4-(1,3-benzoxazol-2-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 1,3-benzoxazole-2-carbaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5 $\mu$  silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-(1,3-benzoxazol-2-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

<sup>1</sup>H NMR (499.802 MHz, DMSO)  $\delta$  2.72 (4H, t), 3.65 (4H, t), 3.97 (2H, s), 7.36 - 7.44 (2H, m), 7.59 (1H, d), 7.72 - 7.77 (2H, m), 8.25 (1H, d); m/z = 404 [M+H]<sup>+</sup>.

**Example 50****Preparation of 4-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]quinoline**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with quinoline-4-carbaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5 $\mu$  silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 4-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]quinoline.

<sup>1</sup>H NMR (499.802 MHz, DMSO)  $\delta$  2.65 (4H, t), 3.64 (4H, t), 4.04 (2H, s), 7.56 1H, d), 7.60 (1H, d), 7.63 - 7.67 (1H, m), 7.75 - 7.80 (1H, m), 8.05 (1H, d), 8.26 (1H, d), 8.33 (1H, d), 8.88 (1H, d); m/z = 414 [M+H]<sup>+</sup>.

**Example 51****Preparation of 6-[4-(1,3-thiazol-2-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 1,3-thiazole-2-carbaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5 $\mu$  silica, 19 mm diameter, 100 mm length) eluted with decreasingly



polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-(1,3-thiazol-2-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.802 MHz, DMSO)  $\delta$  2.64 (4H, t), 3.63 (4H, t), 3.91 (2H, s), 7.58 (1H, d), 7.67 (1H, d), 7.73 (1H, d), 8.24 (1H, d); m/z = 370 [M+H]<sup>+</sup>.

### **Example 52**

#### **Preparation of 6-[4-(1-benzothiophen-2-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 1-benzothiophene-2-carbaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5 $\mu$  silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-(1-benzothiophen-2-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.802 MHz, DMSO)  $\delta$  2.62 (4H, t), 3.65 (4H, t), 3.88 (2H, s), 7.30 - 7.38 (3H, m), 7.60 (1H, d), 7.78 (1H, d), 7.91 (1H, d), 8.25 (1H, d); m/z = 419 [M+H]<sup>+</sup>.

### **Example 53**

#### **Preparation of 6-[4-(thiadiazol-4-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with thiadiazole-4-carbaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5 $\mu$  silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-(thiadiazol-4-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.802 MHz, DMSO)  $\delta$  2.62 (4H, t), 3.63 (4H, t), 4.13 (2H, s), 7.59 (1H, d), 8.25 (1H, d), 9.10 (1H, s); m/z = 371 [M+H]<sup>+</sup>.

### **Example 54**

#### **Preparation of 6-[4-[(1-methylbenzimidazol-2-yl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**



Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 1-methylbenzimidazole-2-carbaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5 $\mu$  silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(1-methylbenzimidazol-2-yl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

<sup>1</sup>H NMR (499.802 MHz, DMSO)  $\delta$  2.62 (4H, t), 3.62 (4H, t), 3.85 - 3.89 (5H, m), 7.16 - 7.22 (1H, m), 7.22 - 7.28 (1H, m), 7.54 (1H, d), 7.57 - 7.62 (2H, m), 8.25 (1H, d); m/z = 417 [M+H]<sup>+</sup>.

#### **Example 55**

##### **Preparation of 6-[4-(pyrazin-2-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with pyrazine-2-carbaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5 $\mu$  silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-(pyrazin-2-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

<sup>1</sup>H NMR (499.802 MHz, DMSO)  $\delta$  2.61 (4H, t), 3.64 (4H, t), 3.75 (2H, s), 7.60 (1H, d), 8.26 (1H, d), 8.57 (1H, d), 8.60 - 8.62 (1H, m), 8.74 (1H, d); m/z = 365 [M+H]<sup>+</sup>.

#### **Example 56**

##### **Preparation of 2-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]quinoline**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with quinoline-2-carbaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5 $\mu$  silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 2-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]quinoline.



<sup>1</sup>H NMR (499.802 MHz, DMSO)  $\delta$  2.61 (4H, t), 3.63 (4H, t), 3.83 (2H, s), 7.55 - 7.60 (2H, m), 7.67 (1H, d), 7.71 - 7.76 (1H, m), 7.96 (2H, t), 8.23 (1H, d), 8.34 (1H, d);  $m/z$  = 414 [M+H]<sup>+</sup>.

#### **Example 57**

5 **Preparation of 6-[4-[(2-methylsulfonylphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 2-methylsulfonylbenzaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep  
10 C18 OBD column (5 $\mu$  silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(2-methylsulfonylphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

<sup>1</sup>H NMR (499.802 MHz, DMSO)  $\delta$  2.60 (4H, t), 3.44 (3H, s), 3.62 (4H, t), 3.96 (2H, s),  
15 7.58 - 7.67 (3H, m), 7.70 - 7.75 (1H, m), 7.99 - 8.02 (1H, m), 8.27 (1H, d);  $m/z$  = 441 [M+H]<sup>+</sup>.

#### **Example 58**

**Preparation of 6-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]quinoxaline**

20 Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with quinoxaline-6-carbaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5 $\mu$  silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to  
25 give 6-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]quinoxaline.

<sup>1</sup>H NMR (499.802 MHz, DMSO)  $\delta$  2.59 (4H, t), 3.63 (4H, t), 3.81 (2H, s), 7.57 (1H, d), 7.86 - 7.89 (1H, m), 8.02 (1H, s), 8.07 (1H, d), 8.23 (1H, d), 8.91 (1H, d), 8.93 (1H, d);  $m/z$  = 415 [M+H]<sup>+</sup>.

30 **Example 59**

**Preparation of 2-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]benzonitrile**



Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 2-formylbenzonitrile was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5 $\mu$  silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 2-  
5 [[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]benzonitrile.

<sup>1</sup>H NMR (499.802 MHz, DMSO)  $\delta$  2.59 (4H, t), 3.63 (4H, t), 3.74 (2H, s), 7.50 (1H, t), 7.60 (1H, d), 7.64 (1H, d), 7.69 - 7.74 (1H, m), 7.84 (1H, d), 8.26 (1H, d); m/z = 388  
10 [M+H]<sup>+</sup>.

#### **Example 60**

##### **Preparation of 6-[4-(1-benzothiophen-3-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 1-benzothiophene-3-carbaldehyde was carried out according to General  
15 Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5 $\mu$  silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-(1-benzothiophen-3-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-  
20 [1,2,4]triazolo[4,3-b]pyridazine.

<sup>1</sup>H NMR (499.802 MHz, DMSO)  $\delta$  2.59 (4H, t), 3.62 (4H, t), 3.81 (2H, s), 7.36 - 7.44 (2H, m), 7.58 (1H, d), 7.63 (1H, s), 7.99 (1H, d), 8.03 (1H, d), 8.25 (1H, d); m/z = 419 [M+H]<sup>+</sup>.

#### **Example 61**

##### **Preparation of 6-[4-(1,3-thiazol-4-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 1,3-thiazole-4-carbaldehyde was carried out according to General  
25 Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5 $\mu$  silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to  
30 give 6-[4-(1,3-thiazol-4-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.



<sup>1</sup>H NMR (499.802 MHz, DMSO)  $\delta$  2.59 (4H, t), 3.62 (4H, t), 3.75 (2H, s), 7.56 - 7.61 (2H, m), 8.25 (1H, d), 9.06 (1H, d);  $m/z$  = 370 [M+H]<sup>+</sup>.

### **Example 62**

#### **Preparation of 6-[4-[(2-chlorophenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 2-chlorobenzaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5 $\mu$  silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(2-chlorophenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

<sup>1</sup>H NMR (499.802 MHz, DMSO)  $\delta$  2.59 (4H, t), 3.61 - 3.67 (6H, m), 7.30 - 7.34 (1H, m), 7.34 - 7.39 (1H, m), 7.44 - 7.47 (1H, m), 7.53 - 7.57 (1H, m), 7.60 (1H, d), 8.26 (1H, d);  $m/z$  = 397 [M+H]<sup>+</sup>.

### **Example 63**

#### **Preparation of 6-[4-(1H-indol-7-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 1H-indole-7-carbaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5 $\mu$  silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-(1H-indol-7-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

<sup>1</sup>H NMR (499.802 MHz, DMSO)  $\delta$  2.58 (4H, t), 3.64 (4H, t), 3.82 (2H, s), 6.44 - 6.46 (1H, m), 6.94 - 7.03 (2H, m), 7.33 (1H, t), 7.48 (1H, d), 7.58 (1H, d), 8.25 (1H, d), 10.84 (1H, s);  $m/z$  = 402 [M+H]<sup>+</sup>.

### **Example 64**

#### **Preparation of 3-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]quinoline**



Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with quinoline-3-carbaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5 $\mu$  silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 3-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]quinoline.

<sup>1</sup>H NMR (499.802 MHz, DMSO)  $\delta$  2.58 (4H, t), 3.63 (4H, t), 3.76 (2H, s), 7.55 - 7.62 (2H, m), 7.71 - 7.76 (1H, m), 7.97 (1H, d), 8.01 (1H, d), 8.21 - 8.26 (2H, m), 8.88 (1H, d); m/z = 414 [M+H]<sup>+</sup>.

#### **Example 65**

##### **Preparation of 5-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]isoquinoline**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with isoquinoline-5-carbaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5 $\mu$  silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 5-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]isoquinoline.

<sup>1</sup>H NMR (499.802 MHz, DMSO)  $\delta$  2.58 (4H, t), 3.58 (4H, t), 3.95 (2H, s), 7.56 (1H, d), 7.61 - 7.66 (1H, m), 7.74 (1H, d), 8.06 (1H, d), 8.13 (1H, d), 8.23 (1H, d), 8.53 (1H, d), 9.31 (1H, s); m/z = 414 [M+H]<sup>+</sup>.

#### **Example 66**

##### **Preparation of 6-[4-(naphthalen-1-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with naphthalene-1-carbaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5 $\mu$  silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to



give 6-[4-(naphthalen-1-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

<sup>1</sup>H NMR (499.802 MHz, DMSO)  $\delta$  2.58 (4H, t), 3.58 (4H, t), 3.94 (2H, s), 7.43 - 7.58 (5H, m), 7.83 - 7.88 (1H, m), 7.90 - 7.94 (1H, m), 8.23 (1H, d), 8.29 (1H, d); m/z = 413

5 [M+H]<sup>+</sup>.

### **Example 67**

#### **Preparation of 3-(trifluoromethyl)-6-[4-[[2-(trifluoromethyl)phenyl]methyl]piperazin-1-yl]-[1,2,4]triazolo[4,3-b]pyridazine**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 2-(trifluoromethyl)benzaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5 $\mu$  silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 3-(trifluoromethyl)-6-[4-[[2-(trifluoromethyl)phenyl]methyl]piperazin-1-yl]-[1,2,4]triazolo[4,3-b]pyridazine.

<sup>1</sup>H NMR (499.802 MHz, DMSO)  $\delta$  2.56 (4H, t), 3.64 (4H, t), 3.71 (2H, s), 7.50 (1H, t), 7.60 (1H, d), 7.67 - 7.75 (2H, m), 7.84 (1H, d), 8.26 (1H, d); m/z = 431 [M+H]<sup>+</sup>.

### **Example 68**

#### **Preparation of 6-[4-[(2,2-difluoro-1,3-benzodioxol-4-yl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 2,2-difluoro-1,3-benzodioxole-4-carbaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5 $\mu$  silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(2,2-difluoro-1,3-benzodioxol-4-yl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

<sup>1</sup>H NMR (499.802 MHz, DMSO)  $\delta$  2.56 (4H, t), 3.62 (4H, t), 3.67 (2H, s), 7.19 - 7.25 (2H, m), 7.32 - 7.35 (1H, m), 7.59 (1H, d), 8.25 (1H, d); m/z = 443 [M+H]<sup>+</sup>.

### **Example 69**

#### **Preparation of 6-[4-[(1-methylindol-2-yl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**



Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 1-methylindole-2-carbaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5 $\mu$  silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(1-methylindol-2-yl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

<sup>1</sup>H NMR (499.802 MHz, DMSO)  $\delta$  2.56 (4H, t), 3.59 (4H, t), 3.70 (2H, s), 3.78 (3H, s), 6.36 (1H, s), 6.99 (1H, t), 7.09 - 7.13 (1H, m), 7.40 (1H, d), 7.48 (1H, d), 7.57 (1H, d), 8.23 (1H, d); m/z = 416 [M+H]<sup>+</sup>.

#### **Example 70**

##### **Preparation of 6-[4-(thiophen-2-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with thiophene-2-carbaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5 $\mu$  silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-(thiophen-2-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

<sup>1</sup>H NMR (499.802 MHz, DMSO)  $\delta$  2.55 (4H, t), 3.62 (4H, t), 3.77 (2H, s), 6.98 - 7.02 (2H, m), 7.45 - 7.47 (1H, m), 7.59 (1H, d), 8.25 (1H, d); m/z = 369 [M+H]<sup>+</sup>.

#### **Example 71**

##### **Preparation of 6-[4-[(1-methylindol-3-yl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 1-methylindole-3-carbaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5 $\mu$  silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(1-methylindol-3-yl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.



<sup>1</sup>H NMR (499.802 MHz, DMSO)  $\delta$  2.55 (4H, t), 3.60 (4H, t), 3.70 (2H, s), 3.77 (3H, s), 7.04 (1H, t), 7.15 (1H, t), 7.26 (1H, s), 7.40 (1H, d), 7.56 (1H, d), 7.67 (1H, d), 8.23 (1H, d) (Signal at 2.55 partially under DMSO);  $m/z$  = 416 [M+H]<sup>+</sup>.

### **Example 72**

5 **Preparation of 6-[4-[(2-fluorophenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 2-fluorobenzaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18  
10 OBD column (5 $\mu$  silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(2-fluorophenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

<sup>1</sup>H NMR (499.802 MHz, DMSO)  $\delta$  2.55 (4H, t), 3.59 - 3.65 (6H, m), 7.16 - 7.23 (2H, m),  
15 7.32 - 7.38 (1H, m), 7.43 - 7.48 (1H, m), 7.58 (1H, d), 8.25 (1H, d) (Signal at 2.55 partially under DMSO);  $m/z$  = 381 [M+H]<sup>+</sup>.

### **Example 73**

**Preparation of 6-[4-(pyridin-4-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

20 Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with pyridine-4-carbaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5 $\mu$  silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 6-  
25 [4-(pyridin-4-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

<sup>1</sup>H NMR (499.802 MHz, DMSO)  $\delta$  2.54 (4H, t), 3.60 (2H, s), 3.64 (4H, t), 7.37 (2H, m), 7.59 (1H, d), 8.26 (1H, d), 8.52 - 8.55 (2H, m) (Signal at 2.54 partially obscured by DMSO);  $m/z$  = 364 [M+H]<sup>+</sup>.

30 **Example 74**

**Preparation of 6-[4-[(3-methylsulfonylphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**



Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 3-methylsulfonylbenzaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5 $\mu$  silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(3-methylsulfonylphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

<sup>1</sup>H NMR (499.802 MHz, DMSO)  $\delta$  2.53 (4H, t), 3.21 (3H, s), 3.62 (4H, t), 3.66 (2H, s), 7.57 (1H, d), 7.63 (1H, t), 7.69 (1H, d), 7.83 (1H, d), 7.88 (1H, s), 8.24 (1H, d); m/z = 441 [M+H]<sup>+</sup>.

#### **Example 75**

##### **Preparation of 6-[4-[(2-methoxyphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 2-methoxybenzaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5 $\mu$  silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(2-methoxyphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

<sup>1</sup>H NMR (499.802 MHz, DMSO)  $\delta$  2.52 (4H, t), 3.53 (2H, s), 3.60 (4H, t), 3.77 (3H, s), 6.90 - 6.95 (1H, m), 6.98 (1H, d), 7.21 - 7.26 (1H, m), 7.31 - 7.35 (1H, m), 7.56 (1H, d), 8.22 (1H, d); m/z = 393 [M+H]<sup>+</sup>.

#### **Example 76**

##### **Preparation of 6-[4-(2,3-dihydro-1,4-benzodioxin-5-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 2,3-dihydro-1,4-benzodioxine-5-carbaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5 $\mu$  silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as



eluent to give 6-[4-(2,3-dihydro-1,4-benzodioxin-5-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

<sup>1</sup>H NMR (499.802 MHz, DMSO) δ 2.52 (4H, t), 3.50 (2H, s), 3.59 (4H, t), 4.19 - 4.25 (4H, m), 6.73 - 6.80 (2H, m), 6.87 - 6.89 (1H, m), 7.56 (1H, d), 8.22 (1H, d); m/z = 421

5 [M+H]<sup>+</sup>.

### **Example 77**

#### **Preparation of 6-[4-(1H-indol-5-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 1H-indole-5-carbaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5μ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-(1H-indol-5-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

<sup>1</sup>H NMR (499.802 MHz, DMSO) δ 2.52 - 2.54 (4H, m), 3.58 - 3.63 (6H, m), 6.38 - 6.41 (1H, m), 7.06 - 7.10 (1H, m), 7.32 (1H, t), 7.35 (1H, d), 7.47 (1H, s), 7.58 (1H, d), 8.24 (1H, d), 11.02 (1H, s) (Signal at 2.52 under DMSO); m/z = 402 [M+H]<sup>+</sup>.

### **Example 78**

#### **Preparation of 6-[4-(1H-indol-6-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 1H-indole-6-carbaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5μ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-(1H-indol-6-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

<sup>1</sup>H NMR (499.802 MHz, DMSO) δ 2.51 - 2.55 (4H, m), 3.60 - 3.64 (6H, m), 6.38 - 6.41 (1H, m), 6.96 - 7.00 (1H, m), 7.31 (1H, t), 7.35 (1H, s), 7.49 (1H, d), 7.58 (1H, d), 8.24 (1H, d), 10.99 (1H, s) (Signal at 2.51 under DMSO); m/z = 402 [M+H]<sup>+</sup>.



**Example 79****Preparation of 6-[4-(furan-2-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with furan-2-carbaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5 $\mu$  silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-(furan-2-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine. <sup>5</sup> <sup>10</sup> <sup>1H</sup> NMR (499.802 MHz, DMSO)  $\delta$  2.51 - 2.55 (4H, m), 3.58 (2H, s), 3.61 (4H, t), 6.33 (1H, d), 6.40 - 6.44 (1H, m), 7.58 (1H, d), 7.60 - 7.62 (1H, m), 8.25 (1H, d) (Signal at 2.51 partially obscured by DMSO); m/z = 353 [M+H]<sup>+</sup>.

**Example 80****Preparation of 6-[4-(1H-pyrazol-3-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 1H-pyrazole-3-carbaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5 $\mu$  silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-(1H-pyrazol-3-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine. <sup>15</sup> <sup>20</sup>

<sup>1H</sup> NMR (499.802 MHz, DMSO)  $\delta$  2.51 - 2.54 (4H, m), 3.51 - 3.65 (6H, m), 6.18 (1H, s), 7.41 (0H, s), 7.55 - 7.70 (2H, m), 8.24 (1H, d) (Signal at 2.51 obscured by DMSO); m/z = <sup>25</sup> 353 [M+H]<sup>+</sup>.

**Example 81****Preparation of 6-[4-(pyridin-3-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with pyridine-3-carbaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5 $\mu$  silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar <sup>30</sup>



mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-(pyridin-3-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.802 MHz, DMSO)  $\delta$  2.50 - 2.53 (4H, m), 3.57 (2H, s), 3.60 (4H, t), 7.34 - 7.39 (1H, m), 7.57 (1H, d), 7.71 - 7.76 (1H, m), 8.23 (1H, d), 8.46 - 8.49 (1H, m), 8.52 (1H, d) (Signal at 2.5 obscured by DMSO peak); m/z = 364 [M+H]<sup>+</sup>.

### **Example 82**

#### **Preparation of 6-[4-[(3-methoxyphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

10 Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 3-methoxybenzaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5 $\mu$  silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(3-methoxyphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.802 MHz, DMSO)  $\delta$  2.49 - 2.51 (4H, m), 3.50 (2H, s), 3.60 (4H, t), 3.74 (3H, s), 6.81 - 6.84 (1H, m), 6.87 - 6.91 (2H, m), 7.24 (1H, t), 7.56 (1H, d), 8.23 (1H, d) (Signal at 2.49 obscured by DMSO); m/z = 393 [M+H]<sup>+</sup>.

### **Example 83**

#### **Preparation of 6-[4-(1H-pyrrol-2-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

25 Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 1H-pyrrole-2-carbaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5 $\mu$  silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-(1H-pyrrol-2-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

30 1H NMR (499.802 MHz, DMSO)  $\delta$  2.48 (4H, t), 3.48 (2H, s), 3.60 (4H, t), 5.89 - 5.92 (1H, m), 5.94 (1H, q), 6.64 - 6.67 (1H, m), 7.58 (1H, d), 8.24 (1H, d), 10.68 (1H, s) (Signal at 2.48 partially obscured by DMSO); m/z = 352 [M+H]<sup>+</sup>.



**Example 84****Preparation of 6-[4-(2,3-dihydro-1-benzofuran-5-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 2,3-dihydro-1-benzofuran-5-carbaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5 $\mu$  silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-(2,3-dihydro-1-benzofuran-5-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

<sup>1</sup>H NMR (499.802 MHz, DMSO)  $\delta$  2.47 - 2.51 (4H, m), 3.17 (2H, t), 3.45 (2H, s), 3.60 (4H, t), 4.51 (2H, t), 6.71 (1H, d), 7.02 (1H, d), 7.19 (1H, s), 7.58 (1H, d), 8.25 (1H, d) (Signal at 2.47 partially obscured by DMSO); m/z = 405 [M+H]<sup>+</sup>.

**Example 85****Preparation of 6-[4-(1,3-benzodioxol-5-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 1,3-benzodioxole-5-carbaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5 $\mu$  silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-(1,3-benzodioxol-5-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

<sup>1</sup>H NMR (499.802 MHz, DMSO)  $\delta$  2.47 - 2.50 (4H, m), 3.46 (2H, s), 3.61 (4H, t), 6.00 (2H, s), 6.77 - 6.80 (1H, m), 6.86 (1H, d), 6.90 (1H, d), 7.58 (1H, d), 8.25 (1H, d) (Signal at 2.47 partially obscured by DMSO); m/z = 407 [M+H]<sup>+</sup>.

**Example 86****Preparation of 6-[4-(thiophen-3-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with thiophene-3-carbaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep



C18 OBD column (5 $\mu$  silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-(thiophen-3-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.802 MHz, DMSO)  $\delta$  2.47 - 2.49 (4H, m), 3.54 (2H, s), 3.59 (4H, t), 7.05 - 7.08 (1H, m), 7.32 - 7.35 (1H, m), 7.47 - 7.50 (1H, m), 7.56 (1H, d), 8.23 (1H, d) (Signal at 2.47 partially under DMSO); m/z = 369 [M+H]<sup>+</sup>.

### **Example 87**

#### **Preparation of 6-[4-[(1-methylpyrrol-2-yl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 1-methylpyrrole-2-carbaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5 $\mu$  silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(1-methylpyrrol-2-yl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.802 MHz, DMSO)  $\delta$  2.46 (4H, t), 3.44 (2H, s), 3.57 (4H, t), 3.60 (3H, s), 5.86 - 5.90 (2H, m), 6.67 (1H, t), 7.56 (1H, d), 8.23 (1H, d) (Signal at 2.46 partially obscured by DMSO); m/z = 366 [M+H]<sup>+</sup>.

### **Example 88**

#### **Preparation of 6-[4-(2,3-dihydro-1,4-benzodioxin-6-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 2,3-dihydro-1,4-benzodioxine-6-carbaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5 $\mu$  silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-(2,3-dihydro-1,4-benzodioxin-6-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.



<sup>1</sup>H NMR (499.802 MHz, DMSO)  $\delta$  2.46 (4H, t), 3.40 (2H, s), 3.58 (4H, t), 4.21 (4H, s), 6.74 - 6.77 (1H, m), 6.78 (1H, s), 6.79 (1H, d), 7.56 (1H, d), 8.22 (1H, d) (Signal at 2.46 partially under DMSO);  $m/z$  = 421 [M+H]<sup>+</sup>.

#### **Example 89**

5 **Preparation of 6-[4-[(3-methylimidazol-4-yl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 3-methylimidazole-4-carbaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep  
10 C18 OBD column (5 $\mu$  silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(3-methylimidazol-4-yl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

<sup>1</sup>H NMR (499.802 MHz, DMSO)  $\delta$  2.46 - 2.50 (4H, m), 3.49 (2H, s), 3.58 (4H, t), 3.62  
15 (3H, s), 6.77 (1H, s), 7.55 (1H, s), 7.57 (1H, d), 8.23 (1H, d) (Signal at 2.46 under DMSO);  $m/z$  = 367 [M+H]<sup>+</sup>.

#### **Example 90**

**Preparation of 6-[4-(furan-3-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

20 Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with furan-3-carbaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5 $\mu$  silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 6-  
25 [4-(furan-3-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine. <sup>1</sup>H NMR (499.802 MHz, DMSO)  $\delta$  2.46 - 2.49 (4H, m), 3.39 (2H, s), 3.59 (4H, t), 6.43 - 6.45 (1H, m), 7.56 (1H, s), 7.57 - 7.59 (1H, m), 7.61 (1H, t), 8.23 (1H, d) (Signal at 2.46 obscured by DMSO);  $m/z$  = 353 [M+H]<sup>+</sup>.

#### **Example 91**

30 **Preparation of 6-[4-[(3-methylphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**



Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 3-methylbenzaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5 $\mu$  silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(3-methylphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

<sup>1</sup>H NMR (499.802 MHz, DMSO)  $\delta$  2.29 (3H, s), 2.47 (4H, t), 3.48 (2H, s), 3.59 (4H, t), 7.06 (1H, d), 7.10 (1H, d), 7.13 (1H, s), 7.21 (1H, t), 7.56 (1H, d), 8.22 (1H, d) (Signal at 2.29 obscured by DMSO); m/z = 377 [M+H]<sup>+</sup>.

### **Example 92**

#### **Preparation of 6-[4-(1H-benzimidazol-2-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 1H-benzimidazole-2-carbaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5 $\mu$  silica, 19 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-(1H-benzimidazol-2-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

<sup>1</sup>H NMR (300.132 MHz, DMSO-d<sub>6</sub>)  $\delta$  2.60-2.67 (4H, m), 3.61-3.69 (4H, m), 3.81 (2H, s), 7.09-7.21 (2H, m), 7.43-7.48 (1H, m), 7.53-7.62 (2H, m), 8.25 (1H, d), 12.33 (1H, s); m/z = 403 [M+H]<sup>+</sup>.

### **Example 93**

#### **Preparation of 6-[4-(1-benzofuran-2-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 1-benzofuran-2-carbaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5 $\mu$  silica, 19 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to



give 6-[4-(1-benzofuran-2-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

<sup>1</sup>H NMR (300.132 MHz, DMSO-d<sub>6</sub>) δ 2.58-2.67 (4H, m), 3.59-3.68 (4H, m), 3.76 (2H, s), 6.82 (1H, s), 7.18-7.32 (2H, m), 7.52-7.63 (3H, m), 8.24 (1H, d); m/z = 403 [M+H]<sup>+</sup>.

5 **Example 94**

**Preparation of 6-[4-(1H-indol-3-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 1H-indole-3-carbaldehyde was carried out according to General  
10 Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5μ silica, 19 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-(1H-indol-3-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

15 <sup>1</sup>H NMR (300.132 MHz, DMSO-d<sub>6</sub>) δ 2.51-2.59 (4H, m), 3.54-3.65 (4H, m), 3.71 (2H, s), 6.95-7.03 (1H, m), 7.04-7.12 (1H, m), 7.26 (1H, d), 7.36 (1H, d), 7.56 (1H, d), 7.66 (1H, d), 8.22 (1H, d), 10.94 (1H, s) (Signal at 2.5 partially obscured by DMSO); m/z = 402 [M+H]<sup>+</sup>.

**Example 95**

20 **Preparation of 3-(trifluoromethyl)-6-[4-[[3-(trifluoromethyl)phenyl]methyl]piperazin-1-yl]-[1,2,4]triazolo[4,3-b]pyridazine**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 3-(trifluoromethyl)benzaldehyde was carried out according to General  
25 Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5μ silica, 19 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 3-(trifluoromethyl)-6-[4-[[3-(trifluoromethyl)phenyl]methyl]piperazin-1-yl]-[1,2,4]triazolo[4,3-b]pyridazine.

30 <sup>1</sup>H NMR (300.132 MHz, DMSO-d<sub>6</sub>) δ 2.50-2.57 (4H, m), 3.57-3.69 (6H, m), 7.54-7.71 (5H, m), 8.25 (1H, d) (Signal at 2.5 partially obscured by DMSO); m/z = 431 [M+H]<sup>+</sup>.



**Example 96****Preparation of 6-[4-[(3-fluorophenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 3-fluorobenzaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5 $\mu$  silica, 21 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 0.05% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(3-fluorophenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

<sup>1</sup>H NMR (300.132 MHz, DMSO-d<sub>6</sub>)  $\delta$  2.50-2.56 (4H, m), 3.57 (2H, s), 3.59-3.66 (4H, m), 7.05-7.21 (3H, m), 7.34-7.44 (1H, m), 7.58 (1H, d), 8.25 (1H, d) (Signal at 2.5 partially obscured by DMSO); m/z = 381 [M+H]<sup>+</sup>.

**Example 97****Preparation of 6-[4-[(3-chlorophenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 3-chlorobenzaldehyde was carried out according to General Synthetic Method 5. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5 $\mu$  silica, 21 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.05% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(3-chlorophenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

<sup>1</sup>H NMR (300.132 MHz, DMSO-d<sub>6</sub>)  $\delta$  2.50-2.54 (4H, m), 3.56 (2H, s), 3.59-3.66 (4H, m), 7.27-7.43 (4H, m), 7.58 (1H, d), 8.25 (1H, d) (Signal at 2.5 partially obscured by DMSO); m/z = 397 [M+H]<sup>+</sup>.

**Example 98****Preparation of 6-[4-[(4,5-dimethylfuran-2-yl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 4,5-dimethylfuran-2-carbaldehyde was carried out according to General Synthetic Method 6. The crude product was purified by hplc using a Waters XBridge Prep



C18 OBD column (5 $\mu$  silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(4,5-dimethylfuran-2-yl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

5 <sup>1</sup>H NMR (700.03 MHz, DMSO-d<sub>6</sub>)  $\delta$  1.88 (3H, s), 2.15 (3H, s), 3.45 (2H, s), 3.60 (4H, t), 6.07 (1H, s), 7.58 (1H, d), 8.24 (1H, d) (Some peaks obscured by solvent); m/z = 381 [M+H]<sup>+</sup>.

### **Example 99**

#### **Preparation of 6-[4-(cyclohexylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

10 Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with cyclohexanecarbaldehyde was carried out according to General Synthetic Method 6. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5 $\mu$  silica, 19 mm diameter, 100 mm length) eluted with decreasingly  
15 polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-(cyclohexylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

<sup>1</sup>H NMR (700.03 MHz, DMSO-d<sub>6</sub>)  $\delta$  0.84 - 0.89 (2H, m), 1.15 - 1.18 (1H, m), 1.20 - 1.26 (2H, m), 1.51 - 1.54 (1H, m), 1.63 - 1.69 (3H, m), 1.76 (2H, d), 2.14 (2H, d), 2.46 (4H, t),  
20 3.60 (4H, t), 7.59 (1H, d), 8.24 (1H, d); m/z = 369 [M+H]<sup>+</sup>.

### **Example 100**

#### **Preparation of 6-[4-[(2,2-difluoro-1,3-benzodioxol-5-yl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 2,2-difluoro-1,3-benzodioxole-5-carbaldehyde was carried out according  
25 to General Synthetic Method 7. The crude product was purified by hplc using a Phenomenex Luna C18 100A, 10m silica, 21mm diameter, 150mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(2,2-difluoro-1,3-benzodioxol-5-yl)methyl]piperazin-1-yl]-3-  
30 (trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.



<sup>1</sup>H NMR (300.132 MHz, DMSO-d<sub>6</sub>) δ 2.50-2.55 (4H, m), 3.56 (2H, s), 3.58-3.65 (4H, m), 7.14-7.20 (1H, m), 7.33-7.40 (2H, m), 7.58 (1H, d), 8.25 (1H, d) (Signal at 2.5 obscured by DMSO); m/z = 443 [M+H]<sup>+</sup>.

#### **Example 101**

5 **Preparation of 6-[4-(1H-indol-2-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 1H-indole-2-carbaldehyde was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep  
10 C18 OBD column, 5μ silica, 21 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.05% aqueous ammonia) and acetonitrile as eluents to give 6-[4-(1H-indol-2-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

<sup>1</sup>H NMR (500.133 MHz, DMSO-d<sub>6</sub>) δ 2.52-2.58 (4H, m), 3.58-3.65 (4H, m), 3.68 (2H, s),  
15 6.29 (1H, s), 6.93 (1H, t), 7.02 (1H, t), 7.31 (1H, d), 7.44 (1H, d), 7.57 (1H, d), 8.22 (1H, d), 11.00 (1H, s); m/z = 402 [M+H]<sup>+</sup>.

#### **Example 102**

**Preparation of 6-[4-(1,3-benzodioxol-4-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

20 Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 1,3-benzodioxole-4-carbaldehyde was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5μ silica, 21 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.05% aqueous ammonia) and acetonitrile as eluents to  
25 give 6-[4-(1,3-benzodioxol-4-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

<sup>1</sup>H NMR (500.133 MHz, DMSO-d<sub>6</sub>) δ 2.49-2.54 (4H, m), 3.51 (2H, s), 3.57-3.61 (4H, m), 5.98 (2H, s), 6.79-6.86 (3H, m), 7.56 (1H, d), 8.22 (1H, d) (Signal at 2.5 partially obscured by DMSO); m/z = 407 [M+H]<sup>+</sup>.

30 **Example 103**

**Preparation of 5-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]quinoxaline**



Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with quinoxaline-5-carbaldehyde was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5 $\mu$  silica, 21 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.05% aqueous ammonia) and acetonitrile as eluents to give 5-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]quinoxaline.

<sup>1</sup>H NMR (500.133 MHz, DMSO-d<sub>6</sub>)  $\delta$  2.60-2.66 (4H, m), 3.60-3.66 (4H, m), 4.24 (2H, s), 7.57 (1H, d), 7.85-7.90 (1H, m), 7.95 (1H, d), 8.03 (1H, s), 8.23 (1H, d), 8.96 (2H, s); m/z = 415 [M+H]<sup>+</sup>.

#### **Example 104**

##### **Preparation of 6-[4-(1H-pyrrol-3-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 1H-pyrrole-3-carbaldehyde was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5 $\mu$  silica, 21 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.05% aqueous ammonia) and acetonitrile as eluents to give 6-[4-(1H-pyrrol-3-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

<sup>1</sup>H NMR (500.133 MHz, DMSO-d<sub>6</sub>)  $\delta$  2.43-2.48 (4H, m), 3.36 (2H, s), 3.54-3.60 (4H, m), 5.96 (1H, s), 6.63 (1H, s), 6.65-6.68 (1H, m), 7.56 (1H, d), 8.21 (1H, d), 10.57 (1H, s); m/z = 352 [M+H]<sup>+</sup>.

#### **Example 105**

##### **Preparation of 6-[4-[[3-(4-methylphenoxy)phenyl]methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 3-(4-methylphenoxy)benzaldehyde was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5 $\mu$  silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to



give 6-[4-[[3-(4-methylphenoxy)phenyl]methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.8 MHz, DMSO-d<sub>6</sub>)  $\delta$  2.30 (3H, s), 2.49 – 2.52 (4H, m), 3.53 (2H, s), 3.60 (4H, t), 6.86 - 6.88 (1H, m), 6.92 - 6.94 (2H, m), 6.96 (1H, s), 7.08 (1H, d), 7.21 (2H, d),  
5 7.34 (1H, t), 7.58 (1H, d), 8.25 (1H, d) (Signal at 2.5 partially obscured by DMSO); m/z = 469 [M+H]<sup>+</sup>.

#### **Example 106**

##### **Preparation of N,N-dimethyl-4-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]aniline**

10 Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 4-dimethylaminobenzaldehyde was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5 $\mu$  silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to  
15 give N,N-dimethyl-4-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]aniline.

1H NMR (499.8 MHz, DMSO-d<sub>6</sub>)  $\delta$  2.45 - 2.49 (4H, t), 2.88 (6H, s), 3.31 (2H, s), 3.60 (4H, t), 6.70 (2H, d), 7.13 (2H, d), 7.58 (1H, d), 8.24 (1H, d) (Benzyl signal obscured by water); m/z = 406 [M+H]<sup>+</sup>.

#### **Example 107**

##### **Preparation of N-[4-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]phenyl]acetamide**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with N-(4-formylphenyl)acetamide was carried out according to General  
25 Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5 $\mu$  silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give N-[4-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]phenyl]acetamide.

30 1H NMR (499.8 MHz, DMSO-d<sub>6</sub>)  $\delta$  2.04 (3H, s), 2.50 (4H, t), 3.48 (2H, s), 3.61 (4H, t), 7.24 (2H, d), 7.54 (2H, d), 7.58 (1H, d), 8.25 (1H, d), 9.90 (1H, s) (Signal at 2.5 partially obscured by DMSO); m/z = 420 [M+H]<sup>+</sup>.



**Example 108****Preparation of 6-[4-[(4-ethoxyphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 4-ethoxybenzaldehyde was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5 $\mu$  silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(4-ethoxyphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

<sup>1</sup>H NMR (499.8 MHz, DMSO-d<sub>6</sub>)  $\delta$  1.33 (3H, t), 2.48 (4H, t), 3.47 (2H, s), 3.60 (4H, t), 4.02 (2H, q), 6.89 (2H, d), 7.23 (2H, d), 7.58 (1H, d), 8.24 (1H, d); m/z = 407 [M+H]<sup>+</sup>.

**Example 109****Preparation of 6-[4-[(4-butoxyphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 4-butoxybenzaldehyde was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5 $\mu$  silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(4-butoxyphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

<sup>1</sup>H NMR (499.8 MHz, DMSO-d<sub>6</sub>)  $\delta$  0.94 (3H, t), 1.41 - 1.48 (2H, m), 1.67 - 1.73 (2H, m), 2.48 (4H, t), 3.47 (2H, s), 3.60 (4H, t), 3.96 (2H, t), 6.89 (2H, d), 7.22 (2H, d), 7.58 (1H, d), 8.24 (1H, d); m/z = 435 [M+H]<sup>+</sup>.

**Example 110****Preparation of 6-[4-[(3-nitrophenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 3-nitrobenzaldehyde was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5 $\mu$  silica, 30 mm diameter, 100 mm length eluted with decreasingly polar



mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(3-nitrophenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.8 MHz, DMSO-d<sub>6</sub>)  $\delta$  2.57 (4H, t), 3.62 (4H, t), 3.71 (2H, s), 7.57 (1H, d), 7.64 (1H, t), 7.80 (1H, d), 8.12 - 8.15 (1H, m), 8.21 (1H, s), 8.24 (1H, d); m/z = 408 [M+H]<sup>+</sup>.

#### **Example 111**

##### **Preparation of 6-[4-[(4-nitrophenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 4-nitrobenzaldehyde was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5 $\mu$  silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(4-nitrophenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.8 MHz, DMSO-d<sub>6</sub>)  $\delta$  2.56 (4H, t), 3.64 (4H, t), 3.71 (2H, s), 7.60 (1H, d), 7.65 (2H, d), 8.23 (2H, d), 8.26 (1H, d); m/z = 408 [M+H]<sup>+</sup>.

#### **Example 112**

##### **Preparation of N,N-dimethyl-3-[4-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]phenoxy]propan-1-amine**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 4-(3-dimethylaminopropoxy)benzaldehyde was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5 $\mu$  silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give N,N-dimethyl-3-[4-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]phenoxy]propan-1-amine.

1H NMR (499.8 MHz, DMSO-d<sub>6</sub>)  $\delta$  1.81 - 1.87 (2H, m), 2.15 (6H, s), 2.36 (2H, t), 2.49 (4H, t), 3.47 (2H, s), 3.60 (4H, t), 3.98 (2H, t), 6.89 (2H, d), 7.23 (2H, d), 7.58 (1H, d), 8.25 (1H, d) (Signal at 2.49 partially obscured by DMSO); m/z = 464 [M+H]<sup>+</sup>.



**Example 113****Preparation of 6-[4-[(4-pyrrolidin-1-yl)phenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 4-pyrrolidin-1-ylbenzaldehyde was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Phenomenex Luna C18 100A, 10m silica, 21mm diameter, 150mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(4-pyrrolidin-1-yl)phenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

<sup>1</sup>H NMR (300.13 MHz, DMSO-d<sub>6</sub>) δ 1.92 - 1.97 (4H, m), 2.46 (4H, t), 3.21 (4H, t), 3.40 (2H, s), 3.59 (4H, t), 6.50 (2H, d), 7.10 (2H, d), 7.57 (1H, d), 8.23 (1H, d); m/z = 432 [M+H]<sup>+</sup>.

**Example 114****Preparation of 6-[4-[[4-[(2-methylpropan-2-yl)oxy]phenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 4-[(2-methylpropan-2-yl)oxy]benzaldehyde was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5μ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[[4-[(2-methylpropan-2-yl)oxy]phenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

<sup>1</sup>H NMR (499.8 MHz, DMSO-d<sub>6</sub>) δ 1.30 (9H, s), 2.48 - 2.52 (4H, m), 3.50 (2H, s), 3.61 (4H, t), 6.94 (2H, d), 7.24 (2H, d), 7.58 (1H, d), 8.25 (1H, d) (Signal at 2.50 partially obscured by DMSO); m/z = 435 [M+H]<sup>+</sup>.

**Example 115****Preparation of 6-[4-[(4-propan-2-yloxy)phenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 4-propan-2-yloxybenzaldehyde was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep



C18 OBD column, 5 $\mu$  silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(4-propan-2-yloxyphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

5 <sup>1</sup>H NMR (499.8 MHz, DMSO-d<sub>6</sub>)  $\delta$  1.27 (6H, d), 2.49 (4H, t), 3.46 (2H, s), 3.61 (4H, t), 4.56 - 4.61 (1H, m), 6.88 (2H, d), 7.22 (2H, d), 7.58 (1H, d), 8.25 (1H, d) (Signal at 2.49 partially obscured by DMSO); m/z = 421 [M+H]<sup>+</sup>.

### **Example 116**

#### **Preparation of 3-(trifluoromethyl)-6-[4-[[3-**

10 **(trifluoromethylsulfanyl)phenyl]methyl]piperazin-1-yl]-[1,2,4]triazolo[4,3-b]pyridazine**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 3-(trifluoromethylsulfanyl)benzaldehyde was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters  
15 XBridge Prep C18 OBD column, 5 $\mu$  silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 3-(trifluoromethyl)-6-[4-[[3-(trifluoromethylsulfanyl)phenyl]methyl]piperazin-1-yl]-[1,2,4]triazolo[4,3-b]pyridazine.  
1H NMR (499.8 MHz, DMSO-d<sub>6</sub>)  $\delta$  2.52 - 2.55 (4H, m), 3.63 (6H, d), 7.54 (1H, t), 7.59  
20 (2H, d), 7.64 (1H, d), 7.70 (1H, s), 8.26 (1H, d) (Signal at 2.54 partially obscured by DMSO); m/z = 463 [M+H]<sup>+</sup>.

### **Example 117**

#### **Preparation of 6-[4-[(4-pyridin-3-ylphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

25 Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 4-pyridin-3-ylbenzaldehyde was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5 $\mu$  silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to  
30 give 6-[4-[(4-pyridin-3-ylphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.



<sup>1</sup>H NMR (499.8 MHz, DMSO-d<sub>6</sub>) δ 2.56 (4H, t), 3.62 (2H, s), 3.64 (4H, t), 7.48 - 7.51 (3H, m), 7.59 (1H, d), 7.72 (2H, d), 8.07 - 8.10 (1H, m), 8.26 (1H, d), 8.57 - 8.58 (1H, m), 8.91 (1H, d); m/z = 440 [M+H]<sup>+</sup>.

#### **Example 118**

5 **Preparation of 6-[4-[(3-bromophenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 3-bromobenzaldehyde was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18  
10 OBD column, 5μ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(3-bromophenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

<sup>1</sup>H NMR (499.8 MHz, DMSO-d<sub>6</sub>) δ 2.50 - 2.54 (4H, m), 3.56 (2H, s), 3.63 (4H, t), 7.32 (1H, t), 7.35 - 7.37 (1H, m), 7.47 - 7.49 (1H, m), 7.55 (1H, s), 7.59 (1H, d), 8.25 (1H, d)  
15 (Signal at 2.52 partially obscured by DMSO); m/z = 441 not assigned (Br).

#### **Example 119**

**Preparation of 6-[4-[[3-(4-chlorophenoxy)phenyl]methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

20 Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 3-(4-chlorophenoxy)benzaldehyde was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5μ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to  
25 give 6-[4-[[3-(4-chlorophenoxy)phenyl]methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

<sup>1</sup>H NMR (499.8 MHz, DMSO-d<sub>6</sub>) δ 2.51 - 2.53 (4H, m), 3.56 (2H, s), 3.61 (4H, t), 6.94 - 6.96 (1H, m), 7.03 - 7.06 (3H, m), 7.15 (1H, d), 7.38 (1H, d), 7.43 - 7.46 (2H, m), 7.59 (1H, d), 8.25 (1H, d) (Signal at 2.52 partially obscured by DMSO); m/z = 489 [M+H]<sup>+</sup>.

30 **Example 120**

**Preparation of 6-[4-[[3-(4-methoxyphenoxy)phenyl]methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**



Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 3-(4-methoxyphenoxy)benzaldehyde was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5 $\mu$  silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[[3-(4-methoxyphenoxy)phenyl]methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

<sup>1</sup>H NMR (499.8 MHz, DMSO-d<sub>6</sub>)  $\delta$  2.49 - 2.51 (4H, m), 3.52 (2H, s), 3.60 (4H, t), 3.76 (3H, s), 6.81 - 6.83 (1H, m), 6.93 (1H, s), 6.96 - 6.98 (2H, m), 7.01 - 7.02 (2H, m), 7.05 (1H, d), 7.31 (1H, t), 7.58 (1H, d), 8.25 (1H, d) (Signal at 2.50 partially obscured by DMSO); m/z = 485 [M+H]<sup>+</sup>.

#### **Example 121**

##### **Preparation of methyl 4-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]benzoate**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with methyl 4-formylbenzoate was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5 $\mu$  silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give methyl 4-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]benzoate.

<sup>1</sup>H NMR (499.8 MHz, DMSO-d<sub>6</sub>)  $\delta$  2.53 (4H, t), 3.62 - 3.64 (6H, m), 3.86 (3H, s), 7.51 (2H, d), 7.59 (1H, d), 7.95 (2H, d), 8.25 (1H, d) (Signal at 2.53 partially obscured by DMSO); m/z = 421 [M+H]<sup>+</sup>.

#### **Example 122**

##### **Preparation of 6-[4-[(4-tert-butylphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 4-tert-butylbenzaldehyde was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5 $\mu$  silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give



6-[4-[(4-tert-butylphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.8 MHz, DMSO-d<sub>6</sub>) δ 1.29 (9H, s), 2.49 - 2.51 (4H, m), 3.51 (2H, s), 3.61 (4H, t), 7.26 (2H, d), 7.37 (2H, d), 7.58 (1H, d), 8.25 (1H, d) (Signal at 2.50 partially obscured by DMSO); m/z = 419 [M+H]<sup>+</sup>.

### **Example 123**

#### **Preparation of 6-[4-[[4-(2-methylpropyl)phenyl]methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 4-(2-methylpropyl)benzaldehyde was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5μ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[[4-(2-methylpropyl)phenyl]methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.8 MHz, DMSO-d<sub>6</sub>) δ 0.87 (6H, d), 1.81 - 1.86 (1H, m), 2.44 (2H, d), 2.48 - 2.51 (4H, m), 3.51 (2H, s), 3.61 (4H, t), 7.13 (2H, d), 7.24 (2H, d), 7.58 (1H, d), 8.25 (1H, d) (Signal at 2.49 partially obscured by DMSO); m/z = 419 [M+H]<sup>+</sup>.

### **Example 124**

#### **Preparation of 6-[4-[[6-(4-methylphenyl)sulfanylpiperidin-3-yl]methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 6-(4-methylphenyl)sulfanylpiperidine-3-carbaldehyde was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5μ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[[6-(4-methylphenyl)sulfanylpiperidin-3-yl]methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.8 MHz, DMSO-d<sub>6</sub>) δ 2.38 (3H, s), 2.48 - 2.51 (4H, m), 3.51 (2H, s), 3.60 (4H, t), 6.89 (1H, d), 7.32 (2H, d), 7.48 (2H, d), 7.59 (2H, d), 8.25 (1H, d), 8.34 - 8.34 (1H, m) (Signal at 2.50 partially obscured by DMSO); m/z = 486 [M+H]<sup>+</sup>.



**Example 125****Preparation of 6-[4-[[3-(4-fluorophenyl)phenyl]methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 3-(4-fluorophenyl)benzaldehyde was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5 $\mu$  silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[[3-(4-fluorophenyl)phenyl]methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

<sup>1</sup>H NMR (499.8 MHz, DMSO-d<sub>6</sub>)  $\delta$  2.56 (4H, t), 3.63 - 3.64 (6H, m), 7.28 - 7.32 (2H, m), 7.35 (1H, d), 7.45 (1H, t), 7.57 (3H, d), 7.70 - 7.73 (2H, m), 8.25 (1H, d); m/z = 457 [M+H]<sup>+</sup>.

**Example 126****Preparation of 6-[4-[[4-(4-fluorophenoxy)phenyl]methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 4-(4-fluorophenoxy)benzaldehyde was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5 $\mu$  silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[[4-(4-fluorophenoxy)phenyl]methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

<sup>1</sup>H NMR (499.8 MHz, DMSO-d<sub>6</sub>)  $\delta$  2.51 - 2.53 (4H, m), 3.52 (2H, s), 3.62 (4H, t), 6.97 (2H, d), 7.05 - 7.09 (2H, m), 7.21 - 7.26 (2H, m), 7.34 (2H, d), 7.59 (1H, d), 8.26 (1H, d) (Signal at 2.51 partially obscured by DMSO); m/z = 473 [M+H]<sup>+</sup>.

**Example 127****Preparation of 6-[4-[(4-bromophenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 4-bromobenzaldehyde was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18



OBD column, 5 $\mu$  silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(4-bromophenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

5 <sup>1</sup>H NMR (499.8 MHz, DMSO-d<sub>6</sub>)  $\delta$  2.49 - 2.52 (4H, m), 3.53 (2H, s), 3.62 (4H, t), 7.31 (2H, d), 7.54 (2H, d), 7.58 (1H, d), 8.25 (1H, d) (Signal at 2.50 partially obscured by DMSO); m/z = 443 not assigned (Br).

### **Example 128**

#### **Preparation of N,N-diethyl-4-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]aniline**

10 Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 4-diethylaminobenzaldehyde was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5 $\mu$  silica, 30 mm diameter, 100 mm length eluted with decreasingly  
15 polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give N,N-diethyl-4-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]aniline.

<sup>1</sup>H NMR (499.8 MHz, DMSO-d<sub>6</sub>)  $\delta$  1.09 (6H, t), 2.47 (4H, t), 3.39 (2H, s), 3.60 (4H, t), 6.62 (2H, d), 7.09 (2H, d), 7.58 (1H, d), 8.24 (1H, d) (Aminomethylene signals obscured  
20 by water); m/z = 434 [M+H]<sup>+</sup>.

### **Example 129**

#### **Preparation of 6-[4-[(4-methylsulfanylphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 4-methylsulfanylbenzaldehyde was carried out according to General  
25 Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5 $\mu$  silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(4-methylsulfanylphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-  
30 [1,2,4]triazolo[4,3-b]pyridazine.

<sup>1</sup>H NMR (499.8 MHz, DMSO-d<sub>6</sub>)  $\delta$  2.48 (3H, s), 2.49 - 2.51 (4H, m), 3.51 (2H, s), 3.61 (4H, t), 7.25 (2H, d), 7.29 (2H, d), 7.58 (1H, d), 8.25 (1H, d) (Signal at 2.50 partially



obscured by DMSO);  $m/z = 409 [M+H]^+$ .

### **Example 130**

#### **Preparation of 6-[4-[(4-propan-2-ylphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

5 Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 4-propan-2-ylbenzaldehyde was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5 $\mu$  silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to  
10 give 6-[4-[(4-propan-2-ylphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

$^1\text{H}$  NMR (499.8 MHz, DMSO- $d_6$ )  $\delta$  1.21 (6H, d), 2.48 - 2.51 (4H, m), 2.86 - 2.91 (1H, m), 3.50 (2H, s), 3.61 (4H, t), 7.21 (2H, d), 7.25 (2H, d), 7.58 (1H, d), 8.25 (1H, d) (Signal at 2.49 partially obscured by DMSO);  $m/z = 405 [M+H]^+$ .

### **Example 131**

#### **Preparation of 6-[4-[[4-(trifluoromethoxy)phenyl]methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 4-(trifluoromethoxy)benzaldehyde was carried out according to General  
20 Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5 $\mu$  silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[[4-(trifluoromethoxy)phenyl]methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

25  $^1\text{H}$  NMR (499.8 MHz, DMSO- $d_6$ )  $\delta$  2.51 - 2.54 (4H, m), 3.58 (2H, s), 3.62 (4H, t), 7.34 (2H, d), 7.48 (2H, d), 7.59 (1H, d), 8.26 (1H, d) (Signal at 2.52 partially obscured by DMSO);  $m/z = 447 [M+H]^+$ .

### **Example 132**

#### **Preparation of 6-[4-[[4-(4-chlorophenoxy)phenyl]methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

30 Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 4-(4-chlorophenoxy)benzaldehyde was carried out according to General



Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5 $\mu$  silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[[4-(4-chlorophenoxy)phenyl]methyl]piperazin-1-yl]-3-(trifluoromethyl)-

[1,2,4]triazolo[4,3-b]pyridazine.

<sup>1</sup>H NMR (499.8 MHz, DMSO-d<sub>6</sub>)  $\delta$  2.51 - 2.54 (4H, m), 3.54 (2H, s), 3.62 (4H, t), 7.01 - 7.04 (4H, m), 7.36 - 7.38 (2H, m), 7.42 - 7.45 (2H, m), 7.59 (1H, d), 8.26 (1H, d) (Signal at 2.52 partially obscured by DMSO); m/z = 489 [M+H]<sup>+</sup>.

### **Example 133**

#### **Preparation of 6-[4-[(4-ethynylphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 4-ethynylbenzaldehyde was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5 $\mu$  silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(4-ethynylphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

<sup>1</sup>H NMR (499.8 MHz, DMSO-d<sub>6</sub>)  $\delta$  2.50 - 2.53 (4H, m), 3.57 (2H, s), 3.62 (4H, t), 7.36 (2H, d), 7.46 (2H, d), 7.59 (1H, d), 8.25 (1H, d) (Signal at 2.52 obscured by DMSO); m/z = 387 [M+H]<sup>+</sup>.

### **Example 134**

#### **Preparation of 6-[4-[(4-pyridin-2-ylphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 4-pyridin-2-ylbenzaldehyde was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5 $\mu$  silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(4-pyridin-2-ylphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.



<sup>1</sup>H NMR (499.8 MHz, DMSO-d<sub>6</sub>) δ 2.56 (4H, t), 3.62 (2H, s), 3.64 (4H, t), 7.34 - 7.37 (1H, m), 7.47 (2H, d), 7.60 (1H, d), 7.87 - 7.91 (1H, m), 7.96 (1H, d), 8.07 (2H, d), 8.25 (1H, d), 8.67 - 8.68 (1H, m); m/z = 440 [M+H]<sup>+</sup>.

### **Example 135**

#### **Preparation of 6-[4-[(4-ethylsulfonylphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 4-ethylsulfonylbenzaldehyde was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5μ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(4-ethylsulfonylphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

<sup>1</sup>H NMR (499.8 MHz, DMSO-d<sub>6</sub>) δ 1.12 (3H, t), 2.55 (4H, t), 3.24 - 3.29 (2H, m), 3.64 (4H, t), 3.68 (2H, s), 7.59 (1H, d), 7.64 (2H, d), 7.87 (2H, d), 8.26 (1H, d) (Signal at 3.27 partially obscured water); m/z = 455 [M+H]<sup>+</sup>.

### **Example 136**

#### **Preparation of 6-[4-[(3-prop-2-enoxyphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 3-prop-2-enoxybenzaldehyde was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5μ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(3-prop-2-enoxyphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

<sup>1</sup>H NMR (499.8 MHz, DMSO-d<sub>6</sub>) δ 2.50 - 2.53 (4H, m), 3.52 (2H, s), 3.62 (4H, t), 4.56 - 4.58 (2H, m), 5.25 - 5.28 (1H, m), 5.38 - 5.43 (1H, m), 6.02 - 6.09 (1H, m), 6.85 - 6.87 (1H, m), 6.92 (2H, d), 7.25 (1H, t), 7.59 (1H, d), 8.25 (1H, d) (Signal at 2.51 obscured by DMSO); m/z = 419 [M+H]<sup>+</sup>.

### **Example 137**

#### **Preparation of 6-[4-[(6-chloropyridin-3-yl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-**



**[1,2,4]triazolo[4,3-b]pyridazine**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 6-chloropyridine-3-carbaldehyde was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5 $\mu$  silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(6-chloropyridin-3-yl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

<sup>1</sup>H NMR (499.8 MHz, DMSO-d<sub>6</sub>)  $\delta$  2.52 - 2.55 (4H, m), 3.60 (2H, s), 3.62 (4H, t), 7.51 (1H, d), 7.59 (1H, d), 7.82 - 7.84 (1H, m), 8.25 (1H, d), 8.37 (1H, d) (Signal at 2.53 partially obscured by DMSO); m/z = 398 [M+H]<sup>+</sup>.

**Example 138****Preparation of N-[3-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]phenyl]acetamide**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with N-(3-formylphenyl)acetamide was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5 $\mu$  silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give N-[3-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]phenyl]acetamide.

<sup>1</sup>H NMR (499.8 MHz, DMSO-d<sub>6</sub>)  $\delta$  2.04 (3H, s), 2.50 - 2.53 (4H, m), 3.51 (2H, s), 3.62 (4H, t), 7.00 (1H, d), 7.25 (1H, t), 7.51 (1H, d), 7.56 - 7.61 (2H, m), 8.25 (1H, d), 9.90 (1H, s) (Signal at 2.51 obscured by DMSO); m/z = 420 [M+H]<sup>+</sup>.

**Example 139****Preparation of 6-[4-[(4-prop-2-enoxyphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 4-prop-2-enoxybenzaldehyde was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5 $\mu$  silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to



give 6-[4-[(4-prop-2-enoxyphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

<sup>1</sup>H NMR (499.8 MHz, DMSO-d<sub>6</sub>) δ 2.49 (4H, t), 3.47 (2H, s), 3.61 (4H, t), 4.55 - 4.57 (2H, m), 5.25 - 5.28 (1H, m), 5.38 - 5.42 (1H, m), 6.02 - 6.09 (1H, m), 6.92 (2H, d), 7.24 (2H, d), 7.58 (1H, d), 8.25 (1H, d); m/z = 419 [M+H]<sup>+</sup>.

#### **Example 140**

##### **Preparation of N,N-dimethyl-2-[4-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]phenoxy]ethanamine**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 4-(2-dimethylaminoethoxy)benzaldehyde was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5μ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give N,N-dimethyl-2-[4-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]phenoxy]ethanamine.

<sup>1</sup>H NMR (499.8 MHz, DMSO-d<sub>6</sub>) δ 2.22 (6H, s), 2.47 - 2.51 (4H, m), 2.62 (2H, t), 3.47 (2H, s), 3.61 (4H, t), 4.04 (2H, t), 6.91 (2H, d), 7.23 (2H, d), 7.58 (1H, d), 8.25 (1H, d); m/z = 450 [M+H]<sup>+</sup>.

#### **Example 141**

##### **Preparation of N,N-dimethyl-4-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]benzamide**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 4-formyl-N,N-dimethylbenzamide was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5μ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give N,N-dimethyl-4-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]benzamide.

<sup>1</sup>H NMR (499.8 MHz, DMSO-d<sub>6</sub>) δ 2.52 - 2.55 (4H, m), 2.90 - 3.02 (6H, m), 3.59 (2H, s), 3.63 (4H, t), 7.37 - 7.41 (4H, m), 7.59 (1H, d), 8.25 (1H, d) (Signal at 2.53 partially obscured by DMSO); m/z = 434 [M+H]<sup>+</sup>.



**Example 142****Preparation of 6-[4-[(6-methoxypyridin-3-yl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 6-methoxypyridine-3-carbaldehyde was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5 $\mu$  silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(6-methoxypyridin-3-yl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

<sup>1</sup>H NMR (499.8 MHz, DMSO-d<sub>6</sub>)  $\delta$  2.49 - 2.52 (4H, m), 3.50 (2H, s), 3.61 (4H, t), 3.85 (3H, s), 6.81 (1H, d), 7.59 (1H, d), 7.66 - 7.68 (1H, m), 8.09 (1H, d), 8.25 (1H, d) (Signal at 2.50 partially obscured by DMSO); m/z = 394 [M+H]<sup>+</sup>.

**Example 143****Preparation of 6-[4-[(6-morpholin-4-yl)pyridin-3-yl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 6-morpholin-4-ylpyridine-3-carbaldehyde was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5 $\mu$  silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(6-morpholin-4-yl)pyridin-3-yl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

<sup>1</sup>H NMR (499.8 MHz, DMSO-d<sub>6</sub>)  $\delta$  2.47 - 2.51 (4H, m), 3.41 - 3.45 (6H, m), 3.60 (4H, t), 3.70 (4H, t), 6.83 (1H, d), 7.51 - 7.54 (1H, m), 7.58 (1H, d), 8.05 (1H, d), 8.25 (1H, d) (Signal at 2.49 partially obscured by DMSO. Some signals distorted by water); m/z = 449 [M+H]<sup>+</sup>.

**Example 144****Preparation of 6-[4-[(6-phenoxy)pyridin-3-yl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 6-phenoxy)pyridine-3-carbaldehyde was carried out according to General



Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5 $\mu$  silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(6-phenoxy pyridin-3-yl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-

[1,2,4]triazolo[4,3-b]pyridazine.

<sup>1</sup>H NMR (499.8 MHz, DMSO-d<sub>6</sub>)  $\delta$  2.51 - 2.54 (4H, m), 3.54 (2H, s), 3.62 (4H, t), 7.02 (1H, d), 7.12 - 7.14 (2H, m), 7.20 - 7.23 (1H, m), 7.41 - 7.44 (2H, m), 7.59 (1H, d), 7.81 - 7.83 (1H, m), 8.09 (1H, d), 8.25 (1H, d) (Signal at 2.52 partially obscured by DMSO); m/z = 456 [M+H]<sup>+</sup>.

#### **Example 145**

##### **Preparation of 6-[4-[(3-ethynylphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 3-ethynylbenzaldehyde was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5 $\mu$  silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(3-ethynylphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

<sup>1</sup>H NMR (499.8 MHz, DMSO-d<sub>6</sub>)  $\delta$  2.50 - 2.53 (4H, m), 3.55 (2H, s), 3.62 (4H, t), 4.17 (1H, s), 7.37 - 7.41 (3H, m), 7.45 (1H, s), 7.58 (1H, d), 8.25 (1H, d) (Signal at 2.52 partially obscured by DMSO.); m/z = 387 [M+H]<sup>+</sup>.

#### **Example 146**

##### **Preparation of tert-butyl N-[4-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]phenyl]carbamate**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with tert-butyl N-(4-formylphenyl)carbamate was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5 $\mu$  silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give tert-butyl N-[4-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]phenyl]carbamate.



<sup>1</sup>H NMR (499.8 MHz, DMSO-d<sub>6</sub>) δ 1.48 (9H, s), 2.48 (4H, t), 3.46 (2H, s), 3.61 (4H, t), 7.20 (2H, d), 7.42 (2H, d), 7.58 (1H, d), 8.24 (1H, d), 9.29 (1H, s); m/z = 478 [M+H]<sup>+</sup>.

#### **Example 147**

##### **Preparation of 6-[4-[(6-ethoxypyridin-3-yl)methyl]piperazin-1-yl]-3-**

##### **(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 6-ethoxypyridine-3-carbaldehyde was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5μ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(6-ethoxypyridin-3-yl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

<sup>1</sup>H NMR (499.8 MHz, DMSO-d<sub>6</sub>) δ 1.32 (3H, t), 2.48 - 2.51 (4H, m), 3.49 (2H, s), 3.61 (4H, t), 4.30 (2H, q), 6.78 (1H, d), 7.59 (1H, d), 7.64 - 7.67 (1H, m), 8.06 (1H, d), 8.25 (1H, d) (Signal at 2.49 partially obscured by DMSO); m/z = 408 [M+H]<sup>+</sup>.

#### **Example 148**

##### **Preparation of 6-[4-[(6-propan-2-yloxy)pyridin-3-yl)methyl]piperazin-1-yl]-3-**

##### **(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 6-propan-2-yloxy)pyridine-3-carbaldehyde was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5μ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(6-propan-2-yloxy)pyridin-3-yl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

<sup>1</sup>H NMR (499.8 MHz, DMSO-d<sub>6</sub>) δ 1.29 (6H, d), 2.49 - 2.52 (4H, m), 3.48 (2H, s), 3.61 (4H, t), 5.21 - 5.26 (1H, m), 6.72 (1H, d), 7.59 (1H, d), 7.62 - 7.65 (1H, m), 8.06 (1H, d), 8.25 (1H, d) (Signal at 2.50 partially obscured by DMSO); m/z = 422 [M+H]<sup>+</sup>.

#### **Example 149**

##### **Preparation of [3-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl)methyl]phenyl]methanol**



Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 3-(hydroxymethyl)benzaldehyde was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5 $\mu$  silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give [3-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]phenyl]methanol.

<sup>1</sup>H NMR (499.8 MHz, DMSO-d<sub>6</sub>)  $\delta$  2.50 - 2.53 (4H, m), 3.54 (2H, s), 3.62 (4H, t), 4.51 (2H, d), 5.15 (1H, t), 7.21 (2H, t), 7.28 - 7.32 (2H, m), 7.59 (1H, d), 8.25 (1H, d) (Signal at 2.51 partially obscured by DMSO); m/z = 393 [M+H]<sup>+</sup>.

#### **Example 150**

##### **Preparation of N-[3-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]phenyl]methanesulfonamide**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with N-(3-formylphenyl)methanesulfonamide was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5 $\mu$  silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give N-[3-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]phenyl]methanesulfonamide.

<sup>1</sup>H NMR (499.8 MHz, DMSO-d<sub>6</sub>)  $\delta$  2.51 - 2.54 (4H, m), 2.99 (3H, s), 3.53 (2H, s), 3.62 (4H, t), 7.08 (1H, d), 7.13 (1H, d), 7.22 (1H, s), 7.31 (1H, t), 7.59 (1H, d), 8.25 (1H, d), 9.69 (1H, s) (Signal at 2.52 partially obscured by DMSO); m/z = 456 [M+H]<sup>+</sup>.

#### **Example 151**

##### **Preparation of [3-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]phenyl] methanesulfonate**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with (3-formylphenyl) methanesulfonate was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5 $\mu$  silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to



give [3-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]phenyl] methanesulfonate.

<sup>1</sup>H NMR (499.8 MHz, DMSO-d<sub>6</sub>) δ 2.52 - 2.56 (4H, m), 3.36 (3H, s), 3.61 - 3.64 (6H, m), 7.26 - 7.28 (1H, m), 7.34 (1H, s), 7.37 (1H, d), 7.47 (1H, t), 7.59 (1H, d), 8.25 (1H, d) (Signal at 2.54 partially obscured by DMSO. Methyl signal distorted by water); m/z = 457 [M+H]<sup>+</sup>.

### **Example 152**

#### **Preparation of [4-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]phenyl] methanesulfonate**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with (4-formylphenyl) methanesulfonate was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5μ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give [4-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]phenyl] methanesulfonate.

<sup>1</sup>H NMR (499.8 MHz, DMSO-d<sub>6</sub>) δ 2.51 - 2.55 (4H, m), 3.38 (3H, s), 3.58 (2H, s), 3.63 (4H, t), 7.32 - 7.34 (2H, m), 7.46 (2H, d), 7.59 (1H, d), 8.26 (1H, d) (Signal at 2.53 partially obscured by DMSO); m/z = 457 [M+H]<sup>+</sup>.

### **Example 153**

#### **Preparation of 2-[4-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]phenoxy]acetamide**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 2-(4-formylphenoxy)acetamide was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5μ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 2-[4-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]phenoxy]acetamide.

<sup>1</sup>H NMR (499.8 MHz, DMSO-d<sub>6</sub>) δ 2.48 - 2.51 (4H, m), 3.48 (2H, s), 3.61 (4H, t), 4.42 (2H, s), 6.93 (2H, d), 7.26 (2H, d), 7.36 (1H, s), 7.49 (1H, s), 7.58 (1H, d), 8.25 (1H, d) (Signal at 2.50 partially obscured by DMSO); m/z = 436 [M+H]<sup>+</sup>.



**Example 154****Preparation of 2-[4-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]phenoxy]acetonitrile**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 2-(4-formylphenoxy)acetonitrile was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5 $\mu$  silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 2-[4-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]phenoxy]acetonitrile.

<sup>1</sup>H NMR (499.8 MHz, DMSO-d<sub>6</sub>)  $\delta$  2.49 - 2.52 (4H, m), 3.51 (2H, s), 3.61 (4H, t), 5.16 (2H, s), 7.05 (2H, d), 7.33 (2H, d), 7.58 (1H, d), 8.25 (1H, d) (Signal at 2.51 partially obscured by DMSO); m/z = 418 [M+H]<sup>+</sup>.

**Example 155****Preparation of 6-[4-[[4-(4-methylpiperazin-1-yl)phenyl]methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 4-(4-methylpiperazin-1-yl)benzaldehyde was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Phenomenex Luna C18 100A, 10m silica, 21mm diameter, 150mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[[4-(4-methylpiperazin-1-yl)phenyl]methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

<sup>1</sup>H NMR (300.13 MHz, DMSO-d<sub>6</sub>)  $\delta$  2.23 (3H, s), 2.43 - 2.51 (8H, m), 3.12 (4H, t), 3.43 (2H, s), 3.56 - 3.62 (4H, m), 6.89 (2H, d), 7.15 (2H, d), 7.57 (1H, d), 8.24 (1H, d) (Signal at 2.46 partially obscured by DMSO); m/z = 461 [M+H]<sup>+</sup>.

**Example 156****Preparation of N,N-dimethyl-3-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]benzamide**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 3-formyl-N,N-dimethylbenzamide was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep



C18 OBD column, 5 $\mu$  silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give N,N-dimethyl-3-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]benzamide.

5 1H NMR (499.8 MHz, DMSO-d<sub>6</sub>)  $\delta$  2.51 - 2.55 (4H, m), 2.90 - 3.01 (6H, m), 3.59 (2H, s), 3.63 (4H, t), 7.29 - 7.32 (1H, m), 7.36 (1H, s), 7.39 - 7.43 (2H, m), 7.59 (1H, d), 8.25 (1H, d) (Signal at 2.53 partially obscured by DMSO); m/z = 434 [M+H]<sup>+</sup>.

### **Example 157**

#### **Preparation of 6-[4-[(3-butoxyphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

10 Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 3-butoxybenzaldehyde was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5 $\mu$  silica, 30 mm diameter, 100 mm length eluted with decreasingly polar  
15 mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(3-butoxyphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.8 MHz, DMSO-d<sub>6</sub>)  $\delta$  0.94 (3H, t), 1.41 - 1.49 (2H, m), 1.67 - 1.73 (2H, m), 2.50 - 2.53 (4H, m), 3.52 (2H, s), 3.62 (4H, t), 3.97 (2H, t), 6.82 - 6.84 (1H, m), 6.90 (2H,  
20 t), 7.25 (1H, t), 7.59 (1H, d), 8.25 (1H, d) (Signal at 2.52 obscured by DMSO); m/z = 435 [M+H]<sup>+</sup>.

### **Example 158**

#### **Preparation of 6-[4-[(4-propylphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

25 Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 4-propylbenzaldehyde was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5 $\mu$  silica, 30 mm diameter, 100 mm length eluted with decreasingly polar  
30 mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(4-propylphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.



<sup>1</sup>H NMR (499.8 MHz, DMSO-d<sub>6</sub>) δ 0.90 (3H, t), 1.56 - 1.63 (2H, m), 2.48 - 2.51 (4H, m), 2.55 (2H, t), 3.51 (2H, s), 3.61 (4H, t), 7.16 (2H, d), 7.24 (2H, d), 7.58 (1H, d), 8.25 (1H, d) (Signal at 2.49 partially obscured by DMSO); m/z = 405 [M+H]<sup>+</sup>.

#### **Example 159**

5 **Preparation of 6-[4-[(4-ethylphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 4-ethylbenzaldehyde was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18  
10 OBD column, 5μ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(4-ethylphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

<sup>1</sup>H NMR (499.8 MHz, DMSO-d<sub>6</sub>) δ 1.19 (3H, t), 2.48 - 2.51 (4H, m), 2.60 (2H, q), 3.50  
15 (2H, s), 3.61 (4H, t), 7.18 (2H, d), 7.24 (2H, d), 7.58 (1H, d), 8.25 (1H, d) (Signal at 2.49 partially obscured by DMSO); m/z = 391 [M+H]<sup>+</sup>.

#### **Example 160**

**Preparation of 6-[4-[(4-morpholin-4-ylphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

20 Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 4-morpholin-4-ylbenzaldehyde was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5μ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to  
25 give 6-[4-[(4-morpholin-4-ylphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

<sup>1</sup>H NMR (499.8 MHz, DMSO-d<sub>6</sub>) δ 2.48 (4H, t), 3.09 (4H, t), 3.45 (2H, s), 3.60 (4H, t), 3.74 (4H, t), 6.91 (2H, d), 7.18 (2H, d), 7.58 (1H, d), 8.24 (1H, d); m/z = 448 [M+H]<sup>+</sup>.

#### **Example 161**

30 **Preparation of 6-[4-[[4-(difluoromethoxy)phenyl]methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**



Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 4-(difluoromethoxy)benzaldehyde was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5 $\mu$  silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[[4-(difluoromethoxy)phenyl]methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

<sup>1</sup>H NMR (499.8 MHz, DMSO-d<sub>6</sub>)  $\delta$  2.49 - 2.52 (4H, m), 3.54 (2H, s), 3.62 (4H, t), 7.16 (2H, d), 7.22 (1H, t), 7.39 (2H, d), 7.58 (1H, d), 8.25 (1H, d) (Signal at 2.49 partially obscured by DMSO); m/z = 429 [M+H]<sup>+</sup>.

### **Example 162**

#### **Preparation of 6-[4-[[3-(difluoromethoxy)phenyl]methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 3-(difluoromethoxy)benzaldehyde was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5 $\mu$  silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[[3-(difluoromethoxy)phenyl]methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

<sup>1</sup>H NMR (499.8 MHz, DMSO-d<sub>6</sub>)  $\delta$  2.51 - 2.55 (4H, m), 3.58 (2H, s), 3.63 (4H, t), 7.07 - 7.11 (1H, m), 7.16 (1H, s), 7.23 (1H, d), 7.24 (1H, t), 7.41 (1H, t), 7.59 (1H, d), 8.26 (1H, d) (Signal at 2.49 partially obscured by DMSO); m/z = 429 [M+H]<sup>+</sup>.

### **Example 163**

#### **Preparation of ethyl (E)-3-[4-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]phenyl]prop-2-enoate**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with ethyl (E)-3-(4-formylphenyl)prop-2-enoate was carried out according to General Synthetic Method 7. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5 $\mu$  silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile



as eluents to give ethyl (*E*)-3-[4-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]piperazin-1-yl]methyl]phenyl]prop-2-enoate.

<sup>1</sup>H NMR (499.8 MHz, DMSO-*d*<sub>6</sub>) δ 1.27 (3H, t), 2.51 - 2.54 (4H, m), 3.59 (2H, s), 3.63 (4H, t), 4.21 (2H, q), 6.62 (1H, d), 7.40 (2H, d), 7.59 (1H, d), 7.64 - 7.67 (1H, m), 7.70 (2H, d), 8.25 (1H, d) (Signal at 2.52 partially obscured by DMSO); *m/z* = 461 [M+H]<sup>+</sup>.

#### **Example 164**

##### **Preparation of 6-[4-[(2-methylsulfonylphenyl)methyl]-1,4-diazepan-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine**

Reductive amination of 6-(1,4-diazepan-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine with 2-methylsulfonylbenzaldehyde was carried out according to General Synthetic Method 8. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5μ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 0.05% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(2-methylsulfonylphenyl)methyl]-1,4-diazepan-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine.

<sup>1</sup>H NMR (499.8 MHz, DMSO-*d*<sub>6</sub>) δ 1.86 - 1.92 (2H, m), 2.67 (2H, t), 2.79 - 2.83 (2H, m), 3.27 (3H, s), 3.74 (2H, t), 3.78 (2H, t), 4.03 (2H, s), 7.51 (1H, d), 7.55 - 7.60 (3H, m), 7.95 (1H, d), 8.23 (1H, d); *m/z* = 455 [M+H]<sup>+</sup>.

#### **Example 165**

##### **Preparation of 6-[4-[(3-methylsulfonylphenyl)methyl]-1,4-diazepan-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine**

Reductive amination of 6-(1,4-diazepan-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine with 3-methylsulfonylbenzaldehyde was carried out according to General Synthetic Method 8. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5μ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 0.05% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(3-methylsulfonylphenyl)methyl]-1,4-diazepan-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-*b*]pyridazine.

<sup>1</sup>H NMR (499.8 MHz, DMSO-*d*<sub>6</sub>) δ 1.86 - 1.92 (2H, m), 2.64 (2H, t), 2.77 - 2.81 (2H, m), 3.18 (3H, s), 3.73 - 3.78 (6H, m), 7.50 (1H, d), 7.53 (1H, d), 7.61 (1H, d), 7.80 (1H, d), 7.84 (1H, s), 8.22 (1H, d); *m/z* = 455 [M+H]<sup>+</sup>.



**Example 166****Preparation of 6-[4-[(4-methylsulfonylphenyl)methyl]-1,4-diazepan-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

Reductive amination of 6-(1,4-diazepan-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 4-methylsulfonylbenzaldehyde was carried out according to General Synthetic Method 8. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5 $\mu$  silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 0.05% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(4-methylsulfonylphenyl)methyl]-1,4-diazepan-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

<sup>1</sup>H NMR (499.8 MHz, DMSO-d<sub>6</sub>)  $\delta$  1.86 - 1.92 (2H, m), 2.64 (2H, t), 2.77 (2H, t), 3.19 (4H, s), 3.73 - 3.78 (6H, m), 7.50 (1H, d), 7.53 (2H, d), 7.81 (2H, d), 8.23 (1H, d); m/z = 455 [M+H]<sup>+</sup>.

**Example 167****Preparation of 6-[4-[(2-methoxyphenyl)methyl]-1,4-diazepan-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

Reductive amination of 6-(1,4-diazepan-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 2-methoxybenzaldehyde was carried out according to General Synthetic Method 8. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5 $\mu$  silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 0.05% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(2-methoxyphenyl)methyl]-1,4-diazepan-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

<sup>1</sup>H NMR (499.8 MHz, DMSO-d<sub>6</sub>)  $\delta$  1.85 - 1.92 (2H, m), 2.63 (2H, t), 2.76 (2H, t), 3.61 (2H, s), 3.70 - 3.74 (5H, m), 3.76 (2H, t), 6.83 (1H, t), 6.94 (1H, d), 7.19 (1H, t), 7.26 (1H, d), 7.49 (1H, d), 8.21 (1H, d); m/z = 407 [M+H]<sup>+</sup>.

**Example 168****Preparation of 3-(trifluoromethyl)-6-[4-[[4-(trifluoromethyl)phenyl]methyl]-1,4-diazepan-1-yl]-[1,2,4]triazolo[4,3-b]pyridazine**

Reductive amination of 6-(1,4-diazepan-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 4-(trifluoromethyl)benzaldehyde was carried out according to General Synthetic Method 8. The crude product was purified by hplc using a Waters XBridge Prep



C18 OBD column (5 $\mu$  silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 0.05% aqueous ammonia) and acetonitrile as eluents to give 3-(trifluoromethyl)-6-[4-[[4-(trifluoromethyl)phenyl]methyl]-1,4-diazepan-1-yl]-[1,2,4]triazolo[4,3-b]pyridazine.

5 <sup>1</sup>H NMR (499.8 MHz, DMSO-d<sub>6</sub>)  $\delta$  1.85 - 1.91 (2H, sm, 2.65 (2H, t), 2.75 (2H, t), 3.73 - 3.77 (6H, m), 7.46 (2H, d), 7.50 (1H, d), 7.58 (2H, d), 8.23 (1H, d); m/z = 445 [M+H]<sup>+</sup>.

#### **Example 169**

#### **Preparation of 6-[4-[(2-fluorophenyl)methyl]-1,4-diazepan-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

10 Reductive amination of 6-(1,4-diazepan-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 2-fluorobenzaldehyde was carried out according to General Synthetic Method 8. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5 $\mu$  silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 0.05% aqueous ammonia) and acetonitrile as eluents to give  
15 6-[4-[(2-fluorophenyl)methyl]-1,4-diazepan-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

<sup>1</sup>H NMR (499.8 MHz, DMSO-d<sub>6</sub>)  $\delta$  1.85 - 1.91 (2H, m), 2.64 (2H, t), 2.76 (2H, t), 3.68 (2H, s), 3.71 (2H, t), 3.76 (2H, t), 7.06 - 7.11 (2H, m), 7.25 - 7.28 (1H, m), 7.36 (1H, t), 7.48 (1H, d), 8.21 (1H, d); m/z = 395 [M+H]<sup>+</sup>.

#### **Example 170**

#### **Preparation of 4-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]-1,4-diazepan-1-yl]methyl]benzonitrile**

Reductive amination of 6-(1,4-diazepan-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 4-formylbenzonitrile was carried out according to General Synthetic  
25 Method 8. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5 $\mu$  silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 0.05% aqueous ammonia) and acetonitrile as eluents to give 4-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]-1,4-diazepan-1-yl]methyl]benzonitrile.

30 <sup>1</sup>H NMR (499.8 MHz, DMSO-d<sub>6</sub>)  $\delta$  1.84 - 1.91 (2H, m), 2.63 (2H, t), 2.75 (2H, t), 3.72 (2H, s), 3.73 - 3.79 (4H, m), 7.45 (2H, d), 7.49 (1H, d), 7.69 (2H, d), 8.23 (1H, d); m/z = 402 [M+H]<sup>+</sup>.



**Example 171****Preparation of 3-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]-1,4-diazepan-1-yl]methyl]benzonitrile**

Reductive amination of 6-(1,4-diazepan-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 3-formylbenzonitrile was carried out according to General Synthetic Method 8. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5 $\mu$  silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 0.05% aqueous ammonia) and acetonitrile as eluents to give 3-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]-1,4-diazepan-1-yl]methyl]benzonitrile.

<sup>1</sup>H NMR (499.8 MHz, DMSO-d<sub>6</sub>)  $\delta$  1.84 - 1.91 (2H, m), 2.63 (2H, t), 2.75 (2H, t), 3.69 (2H, s), 3.72 - 3.77 (4H, m), 7.45 (1H, t), 7.50 (1H, d), 7.59 (1H, d), 7.69 (2H, d), 8.22 (1H, d); m/z = 402 [M+H]<sup>+</sup>.

**Example 172****Preparation of 6-[4-[(3-fluorophenyl)methyl]-1,4-diazepan-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

Reductive amination of 6-(1,4-diazepan-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 3-fluorobenzaldehyde was carried out according to General Synthetic Method 8. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5 $\mu$  silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 0.05% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(3-fluorophenyl)methyl]-1,4-diazepan-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

<sup>1</sup>H NMR (499.8 MHz, DMSO-d<sub>6</sub>)  $\delta$  1.84 - 1.90 (2H, m), 2.63 (2H, t), 2.75 (2H, t), 3.65 (2H, s), 3.73 (2H, t), 3.76 (2H, t), 7.01 - 7.04 (2H, m), 7.08 (1H, d), 7.26 - 7.30 (1H, m), 7.49 (1H, d), 8.22 (1H, d); m/z = 395 [M+H]<sup>+</sup>.

**Example 173****Preparation of 6-[4-[(3-methoxyphenyl)methyl]-1,4-diazepan-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

Reductive amination of 6-(1,4-diazepan-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 3-methoxybenzaldehyde was carried out according to General Synthetic Method 8. The crude product was purified by hplc using a Waters XBridge Prep C18



OBD column (5 $\mu$  silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 0.05% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(3-methoxyphenyl)methyl]-1,4-diazepan-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

5 <sup>1</sup>H NMR (499.8 MHz, DMSO-d<sub>6</sub>)  $\delta$  1.84 - 1.90 (2H, m), 2.61 (2H, t), 2.74 (2H, t), 3.60 (2H, s), 3.67 (3H, s), 3.73 - 3.77 (4H, m), 6.77 - 6.82 (3H, m), 7.16 (1H, t), 7.49 (1H, d), 8.21 (1H, d); m/z = 407 [M+H]<sup>+</sup>.

#### **Example 174**

##### **Preparation of 3-(trifluoromethyl)-6-[4-[[2-(trifluoromethyl)phenyl]methyl]-1,4-diazepan-1-yl]-[1,2,4]triazolo[4,3-b]pyridazine**

10 Reductive amination of 6-(1,4-diazepan-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 2-(trifluoromethyl)benzaldehyde was carried out according to General Synthetic Method 8. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5 $\mu$  silica, 19 mm diameter, 100 mm length) eluted with decreasingly  
15 polar mixtures of water (containing 0.05% aqueous ammonia) and acetonitrile as eluents to give 3-(trifluoromethyl)-6-[4-[[2-(trifluoromethyl)phenyl]methyl]-1,4-diazepan-1-yl]-[1,2,4]triazolo[4,3-b]pyridazine.

<sup>1</sup>H NMR (499.8 MHz, DMSO-d<sub>6</sub>)  $\delta$  1.83 - 1.90 (2H, m), 2.65 (2H, t), 2.77 (2H, t), 3.76 (6H, d), 7.42 (1H, t), 7.45 - 7.52 (2H, m), 7.65 (2H, t), 8.22 (1H, d); m/z = 445 [M+H]<sup>+</sup>.

#### **Example 175**

##### **Preparation of 6-[4-[(3-chlorophenyl)methyl]-1,4-diazepan-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

Reductive amination of 6-(1,4-diazepan-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 3-chlorobenzaldehyde was carried out according to General Synthetic  
25 Method 8. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5 $\mu$  silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 0.05% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(3-chlorophenyl)methyl]-1,4-diazepan-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

30 <sup>1</sup>H NMR (499.8 MHz, DMSO-d<sub>6</sub>)  $\delta$  1.83 - 1.90 (2H, m), 2.64 (2H, t), 2.75 (2H, t), 3.64 (2H, s), 3.73 (2H, t), 3.76 (2H, t), 7.19 - 7.21 (1H, m), 7.24 - 7.28 (3H, m), 7.49 (1H, d), 8.22 (1H, d); m/z = 411 [M+H]<sup>+</sup>.



**Example 176****Preparation of 6-[4-[(4-chlorophenyl)methyl]-1,4-diazepan-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

Reductive amination of 6-(1,4-diazepan-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 4-chlorobenzaldehyde was carried out according to General Synthetic Method 8. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5 $\mu$  silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 0.05% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(4-chlorophenyl)methyl]-1,4-diazepan-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

<sup>1</sup>H NMR (499.8 MHz, DMSO-d<sub>6</sub>)  $\delta$  1.83 - 1.90 (2H, m), 2.61 (2H, t), 2.73 (2H, t), 3.62 (2H, s), 3.71 - 3.76 (4H, m), 7.25 - 7.30 (4H, m), 7.49 (1H, d), 8.22 (1H, d); m/z = 411 [M+H]<sup>+</sup>.

**Example 177****Preparation of 6-[4-[(4-fluorophenyl)methyl]-1,4-diazepan-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

Reductive amination of 6-(1,4-diazepan-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 4-fluorobenzaldehyde was carried out according to General Synthetic Method 8. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5 $\mu$  silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 0.05% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(4-fluorophenyl)methyl]-1,4-diazepan-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

<sup>1</sup>H NMR (499.8 MHz, DMSO-d<sub>6</sub>)  $\delta$  1.83 - 1.90 (2H, m), 2.61 (2H, t), 2.72 (2H, t), 3.61 (2H, s), 3.71 - 3.75 (4H, m), 7.05 (2H, t), 7.26 - 7.29 (2H, m), 7.49 (1H, d), 8.22 (1H, d); m/z = 395 [M+H]<sup>+</sup>.

**Example 178****Preparation of 6-[4-[(3-methylphenyl)methyl]-1,4-diazepan-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

Reductive amination of 6-(1,4-diazepan-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 3-methylbenzaldehyde was carried out according to General Synthetic Method 8. The crude product was purified by hplc using a Waters XBridge Prep C18



OBD column (5 $\mu$  silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 0.05% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(3-methylphenyl)methyl]-1,4-diazepan-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

5 <sup>1</sup>H NMR (499.8 MHz, DMSO-d<sub>6</sub>)  $\delta$  1.83 - 1.90 (2H, m), 2.22 (3H, s), 2.61 (2H, t), 2.73 (2H, t), 3.58 (2H, s), 3.70 - 3.77 (4H, m), 7.03 (3H, d), 7.13 (1H, t), 7.49 (1H, d), 8.22 (1H, d); m/z = 391 [M+H]<sup>+</sup>.

### **Example 179**

#### **Preparation of 3-(trifluoromethyl)-6-[4-[[3-(trifluoromethyl)phenyl]methyl]-1,4-diazepan-1-yl]-[1,2,4]triazolo[4,3-b]pyridazine**

10 Reductive amination of 6-(1,4-diazepan-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 3-(trifluoromethyl)benzaldehyde was carried out according to General Synthetic Method 8. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5 $\mu$  silica, 19 mm diameter, 100 mm length) eluted with decreasingly  
15 polar mixtures of water (containing 0.05% aqueous ammonia) and acetonitrile as eluents to give 3-(trifluoromethyl)-6-[4-[[3-(trifluoromethyl)phenyl]methyl]-1,4-diazepan-1-yl]-[1,2,4]triazolo[4,3-b]pyridazine.

<sup>1</sup>H NMR (499.8 MHz, DMSO-d<sub>6</sub>)  $\delta$  1.83 - 1.89 (2H, m), 2.65 (2H, t), 2.77 (2H, t), 3.71 - 3.79 (6H, m), 7.45 - 7.51 (2H, m), 7.53 - 7.59 (3H, m), 8.22 (1H, d); m/z = 445 [M+H]<sup>+</sup>.

### **Example 180**

#### **Preparation of 2-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]-1,4-diazepan-1-yl]methyl]benzonitrile**

Reductive amination of 6-(1,4-diazepan-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 2-formylbenzonitrile was carried out according to General Synthetic  
25 Method 8. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5 $\mu$  silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 0.05% aqueous ammonia) and acetonitrile as eluents to give 2-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]-1,4-diazepan-1-yl]methyl]benzonitrile.

30 <sup>1</sup>H NMR (499.8 MHz, DMSO-d<sub>6</sub>)  $\delta$  1.82 - 1.89 (2H, m), 2.69 (2H, t), 2.80 (2H, t), 3.71 - 3.78 (6H, m), 7.42 (1H, t), 7.46 - 7.51 (2H, m), 7.57 (1H, t), 7.70 (1H, d), 8.20 (1H, d); m/z = 402 [M+H]<sup>+</sup>.



**Example 181****Preparation of 6-[4-[(4-methoxyphenyl)methyl]-1,4-diazepan-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

Reductive amination of 6-(1,4-diazepan-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 4-methoxybenzaldehyde was carried out according to General Synthetic Method 8. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5 $\mu$  silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 0.05% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(4-methoxyphenyl)methyl]-1,4-diazepan-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

<sup>1</sup>H NMR (499.8 MHz, DMSO-d<sub>6</sub>)  $\delta$  1.82 - 1.89 (2H, m), 2.59 (2H, t), 2.71 (2H, t), 3.54 (2H, s), 3.70 - 3.74 (7H, m), 6.79 (2H, d), 7.14 (2H, d), 7.48 (1H, d), 8.21 (1H, d); m/z = 407 [M+H]<sup>+</sup>.

**Example 182****Preparation of 6-[4-[(4-methylphenyl)methyl]-1,4-diazepan-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

Reductive amination of 6-(1,4-diazepan-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 4-methylbenzaldehyde was carried out according to General Synthetic Method 8. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5 $\mu$  silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 0.05% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(4-methylphenyl)methyl]-1,4-diazepan-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

<sup>1</sup>H NMR (499.8 MHz, DMSO-d<sub>6</sub>)  $\delta$  1.82 - 1.89 (2H, m), 2.26 (3H, s), 2.60 (2H, t), 2.71 (2H, t), 3.57 (2H, s), 3.70 - 3.74 (4H, m), 7.03 (2H, d), 7.11 (2H, d), 7.48 (1H, d), 8.21 (1H, d); m/z = 391 [M+H]<sup>+</sup>.

**Example 183****Preparation of 6-[4-[(2-methylphenyl)methyl]-1,4-diazepan-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

Reductive amination of 6-(1,4-diazepan-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 2-methylbenzaldehyde was carried out according to General Synthetic Method 8. The crude product was purified by hplc using a Waters XBridge Prep C18



OBD column (5 $\mu$  silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 0.05% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(2-methylphenyl)methyl]-1,4-diazepan-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

5 <sup>1</sup>H NMR (499.8 MHz, DMSO-d<sub>6</sub>)  $\delta$  1.78 - 1.85 (2H, m), 2.15 (3H, s), 2.61 (2H, t), 2.71 - 2.77 (2H, m), 3.55 (2H, s), 3.71 (2H, t), 3.75 (2H, t), 7.04 - 7.09 (2H, m), 7.08 - 7.15 (1H, m), 7.16 - 7.18 (1H, m), 7.48 (1H, d), 8.20 (1H, d); m/z = 391 [M+H]<sup>+</sup>.

#### **Example 184**

##### **Preparation of 3-(trifluoromethyl)-6-[4-[[6-(trifluoromethyl)pyridin-3-yl]methyl]piperazin-1-yl]-[1,2,4]triazolo[4,3-a]pyridine**

10 Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridine with 6-(trifluoromethyl)pyridine-3-carbaldehyde was carried out according to General Synthetic Method 9. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5 $\mu$  silica, 30 mm diameter, 100 mm length eluted with  
15 decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 3-(trifluoromethyl)-6-[4-[[6-(trifluoromethyl)pyridin-3-yl]methyl]piperazin-1-yl]-[1,2,4]triazolo[4,3-a]pyridine.

<sup>1</sup>H NMR (499.8 MHz, DMSO-d<sub>6</sub>)  $\delta$  2.60 (4H, t), 3.22 (4H, t), 3.73 (2H, s), 7.54 (1H, s), 7.72 - 7.75 (1H, m), 7.90 - 7.94 (2H, m), 8.05 - 8.07 (1H, m), 8.75 (1H, s); m/z =  
20 431 [M+H]<sup>+</sup>.

#### **Example 185**

##### **Preparation of 3-(trifluoromethyl)-6-[4-[[3-(trifluoromethyl)phenyl]methyl]piperazin-1-yl]-[1,2,4]triazolo[4,3-a]pyridine**

25 Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridine with 3-(trifluoromethyl)benzaldehyde was carried out according to General Synthetic Method 9. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5 $\mu$  silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 3-(trifluoromethyl)-6-[4-[[3-(trifluoromethyl)phenyl]methyl]piperazin-1-yl]-  
30 [1,2,4]triazolo[4,3-a]pyridine.



<sup>1</sup>H NMR (499.8 MHz, DMSO-d<sub>6</sub>) δ 2.58 (4H, t), 3.22 (4H, t), 3.68 (2H, s), 7.54 (1H, s), 7.60 (1H, t), 7.66 (2H, d), 7.70 (1H, s), 7.72 - 7.74 (1H, m), 7.93 (1H, d); m/z = 430 [M+H]<sup>+</sup>.

#### **Example 186**

5 **Preparation of 3-(trifluoromethyl)-6-[4-[[4-(trifluoromethyl)phenyl]methyl]piperazin-1-yl]-[1,2,4]triazolo[4,3-a]pyridine**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridine with 4-(trifluoromethyl)benzaldehyde was carried out according to General Synthetic Method 9. The crude product was purified by hplc using a Waters XBridge Prep  
10 C18 OBD column, 5μ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 3-(trifluoromethyl)-6-[4-[[4-(trifluoromethyl)phenyl]methyl]piperazin-1-yl]-[1,2,4]triazolo[4,3-a]pyridine.

<sup>1</sup>H NMR (499.8 MHz, DMSO-d<sub>6</sub>) δ 2.58 (4H, t), 3.22 (4H, t), 3.67 (3H, s), 7.54 (1H, s),  
15 7.58 - 7.60 (2H, m), 7.71 - 7.74 (3H, m), 7.92 - 7.94 (1H, m); m/z = 430 [M+H]<sup>+</sup>.

#### **Example 187**

**Preparation of 4-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridin-6-yl]piperazin-1-yl]methyl]benzonitrile**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridine with 4-formylbenzonitrile was carried out according to General Synthetic  
20 Method 9. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5μ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 4-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridin-6-yl]piperazin-1-yl]methyl]benzonitrile.  
25

<sup>1</sup>H NMR (499.8 MHz, DMSO-d<sub>6</sub>) δ 2.58 (4H, t), 3.22 (4H, t), 3.67 (2H, s), 7.54 (1H, s), 7.57 (2H, d), 7.72 - 7.74 (1H, m), 7.83 (2H, d), 7.93 (1H, d); m/z = 387 [M+H]<sup>+</sup>.

#### **Example 188**

30 **Preparation of 3-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridin-6-yl]piperazin-1-yl]methyl]benzonitrile**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridine with 3-formylbenzonitrile was carried out according to General Synthetic



Method 9. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5 $\mu$  silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 3-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridin-6-yl]piperazin-1-yl]methyl]benzonitrile.

<sup>1</sup>H NMR (499.8 MHz, DMSO-d<sub>6</sub>)  $\delta$  2.57 (4H, t), 3.22 (4H, t), 3.64 (2H, s), 7.54 (1H, s), 7.58 (1H, t), 7.72 - 7.74 (2H, m), 7.75 - 7.77 (1H, m), 7.80 (1H, s), 7.93 (1H, d); m/z = 387 [M+H]<sup>+</sup>.

### **Example 189**

#### **Preparation of 6-[4-[(3-fluorophenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridine**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridine with 3-fluorobenzaldehyde was carried out according to General Synthetic Method 9. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5 $\mu$  silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(3-fluorophenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridine.

<sup>1</sup>H NMR (499.8 MHz, DMSO-d<sub>6</sub>)  $\delta$  2.57 (4H, t), 3.21 (4H, t), 3.60 (2H, s), 7.08 - 7.12 (1H, m), 7.16 - 7.21 (2H, m), 7.38 - 7.42 (1H, m), 7.54 (1H, s), 7.72 - 7.74 (1H, m), 7.93 (1H, d); m/z = 380 [M+H]<sup>+</sup>.

### **Example 190**

#### **Preparation of 6-[4-[(4-chlorophenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridine**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridine with 4-chlorobenzaldehyde was carried out according to General Synthetic Method 9. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5 $\mu$  silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(4-chlorophenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridine.



<sup>1</sup>H NMR (499.8 MHz, DMSO-d<sub>6</sub>) δ 2.55 (4H, t), 3.20 (4H, t), 3.56 (2H, s), 7.39 (4H, d), 7.53 (1H, s), 7.71 - 7.74 (1H, m), 7.93 (1H, d); m/z = 396 [M+H]<sup>+</sup>.

#### **Example 191**

##### **Preparation of 6-[4-[(4-fluorophenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridine**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridine with 4-fluorobenzaldehyde was carried out according to General Synthetic Method 9. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5μ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(4-fluorophenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridine.

<sup>1</sup>H NMR (499.8 MHz, DMSO-d<sub>6</sub>) δ 2.55 (4H, t), 3.20 (4H, t), 3.55 (2H, s), 7.18 (2H, t), 7.37 - 7.40 (2H, m), 7.53 (1H, s), 7.71 - 7.74 (1H, m), 7.93 (1H, d); m/z = 380 [M+H]<sup>+</sup>.

#### **Example 192**

##### **Preparation of 6-[4-[(4-methoxyphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridine**

Reductive amination of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridine with 4-methoxybenzaldehyde was carried out according to General Synthetic Method 9. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5μ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[4-[(4-methoxyphenyl)methyl]piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridine.

<sup>1</sup>H NMR (499.8 MHz, DMSO-d<sub>6</sub>) δ 2.53 (4H, t), 3.19 (4H, t), 3.49 (2H, s), 3.76 (3H, s), 6.88 - 6.92 (2H, m), 7.25 (2H, d), 7.53 (1H, s), 7.71 - 7.73 (1H, m), 7.92 (1H, d); m/z = 392 [M+H]<sup>+</sup>.

#### **Example 193**

##### **Preparation of 6-[2-(pyridin-4-ylmethyl)-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-5-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

Reductive amination of 6-(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with pyridine-4-carbaldehyde was carried out according to



General Synthetic Method 10. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5 $\mu$  silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[2-(pyridin-4-ylmethyl)-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-5-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

<sup>1</sup>H NMR (499.8 MHz, DMSO-d<sub>6</sub>)  $\delta$  2.98 (2H, s), 3.42 (1H, d), 3.62 (2H, s), 3.75 - 3.78 (2H, m), 7.30 - 7.33 (3H, m), 8.23 (1H, d), 8.48 (2H, q) (Some peaks obscured by solvent); m/z = 390 [M+H]<sup>+</sup>.

#### **Example 194**

##### **Preparation of 6-[2-[(3-methoxyphenyl)methyl]-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-5-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

Reductive amination of 6-(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 3-methoxybenzaldehyde was carried out according to General Synthetic Method 10. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5 $\mu$  silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[2-[(3-methoxyphenyl)methyl]-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-5-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

<sup>1</sup>H NMR (499.8 MHz, DMSO-d<sub>6</sub>)  $\delta$  2.96 (2H, s), 3.55 (2H, s), 3.70 (3H, s), 3.72 - 3.76 (2H, m), 6.79 - 6.81 (1H, m), 6.85 - 6.86 (2H, m), 7.21 (1H, t), 7.31 (1H, d), 8.22 (1H, d) (Some peaks obscured by solvent); m/z = 419 [M+H]<sup>+</sup>.

#### **Example 195**

##### **Preparation of 6-[2-[(4-methoxyphenyl)methyl]-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-5-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

Reductive amination of 6-(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 4-methoxybenzaldehyde was carried out according to General Synthetic Method 10. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5 $\mu$  silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[2-[(4-methoxyphenyl)methyl]-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-5-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.



<sup>1</sup>H NMR (499.8 MHz, DMSO-d<sub>6</sub>) δ 2.94 - 2.95 (2H, m), 3.40 (2H, s), 3.50 (2H, s), 3.73 (5H, s), 6.85 (2H, d), 7.19 (2H, d), 7.30 (1H, d), 8.22 (1H, d) (Some peaks obscured by solvent); m/z = 419 [M+H]<sup>+</sup>.

### **Example 196**

5 **Preparation of 3-(trifluoromethyl)-6-[2-[[3-(trifluoromethyl)phenyl]methyl]-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-5-yl]-[1,2,4]triazolo[4,3-b]pyridazine**

Reductive amination of 6-(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 3-(trifluoromethyl)benzaldehyde was carried out according to General Synthetic Method 10. The crude product was purified by hplc using  
10 a Waters XBridge Prep C18 OBD column, 5μ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 3-(trifluoromethyl)-6-[2-[[3-(trifluoromethyl)phenyl]methyl]-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-5-yl]-[1,2,4]triazolo[4,3-b]pyridazine.

15 <sup>1</sup>H NMR (499.8 MHz, DMSO-d<sub>6</sub>) δ 2.61 - 2.64 (2H, m), 2.97 - 2.98 (2H, m), 3.34 (1H, s), 3.68 (2H, s), 3.72 - 3.75 (2H, m), 7.31 (1H, d), 7.54 (1H, t), 7.59 - 7.67 (3H, m), 8.22 (1H, d) (Some peaks obscured by solvent); m/z = 457 [M+H]<sup>+</sup>.

### **Example 197**

20 **Preparation of 3-[[5-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-2-yl]methyl]benzonitrile**

Reductive amination of 6-(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 3-formylbenzonitrile was carried out according to General Synthetic Method 10. The crude product was purified by hplc using a Waters  
25 XBridge Prep C18 OBD column, 5μ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 3-[[5-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-2-yl]methyl]benzonitrile.

<sup>1</sup>H NMR (499.8 MHz, DMSO-d<sub>6</sub>) δ 2.60 - 2.63 (2H, m), 2.97 - 2.98 (2H, m), 3.64 (2H, s), 3.73 - 3.77 (2H, m), 7.31 (1H, d), 7.53 (1H, t), 7.65 (1H, d), 7.71 (2H, d), 8.22 (1H, d)  
30 (Some peaks obscured by solvent); m/z = 414 [M+H]<sup>+</sup>.

### **Example 198**

**Preparation of 6-[2-[(3-chlorophenyl)methyl]-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-**



**c]pyrrol-5-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

Reductive amination of 6-(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 3-chlorobenzaldehyde was carried out according to General Synthetic Method 10. The crude product was purified by hplc using a Waters  
5 XBridge Prep C18 OBD column, 5 $\mu$  silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[2-[(3-chlorophenyl)methyl]-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-5-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.8 MHz, DMSO-d<sub>6</sub>)  $\delta$  2.59 - 2.62 (2H, m), 2.97 (2H, d), 3.32 - 3.35 (245H, m), 3.59 (2H, s), 3.72 - 3.76 (2H, m), 7.25 - 7.35 (5H, m), 8.22 (1H, d) (Some peaks  
10 obscured by solvent); m/z = 423 [M+H]<sup>+</sup>.

**Example 199****Preparation of 3-(trifluoromethyl)-6-[2-[[4-(trifluoromethyl)phenyl]methyl]-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-5-yl]-[1,2,4]triazolo[4,3-b]pyridazine**

15 Reductive amination of 6-(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 4-(trifluoromethyl)benzaldehyde was carried out according to General Synthetic Method 10. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5 $\mu$  silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and  
20 acetonitrile as eluents to give 3-(trifluoromethyl)-6-[2-[[4-(trifluoromethyl)phenyl]methyl]-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-5-yl]-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (499.8 MHz, DMSO-d<sub>6</sub>)  $\delta$  2.59 - 2.62 (1H, m), 2.97 - 3.01 (2H, m), 3.67 (2H, s), 3.74 - 3.77 (2H, m), 7.31 (1H, d), 7.52 (2H, d), 7.66 (2H, d), 8.22 (1H, d) (Some  
25 peaks obscured by solvent); m/z = 457 [M+H]<sup>+</sup>.

**Example 200****Preparation of 6-[2-[(3-fluorophenyl)methyl]-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-5-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

Reductive amination of 6-(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3-(trifluoromethyl)-  
30 [1,2,4]triazolo[4,3-b]pyridazine with 3-fluorobenzaldehyde was carried out according to General Synthetic Method 10. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5 $\mu$  silica, 30 mm diameter, 100 mm length eluted with



decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[2-[(3-fluorophenyl)methyl]-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-5-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

<sup>1</sup>H NMR (499.8 MHz, DMSO-d<sub>6</sub>) δ 2.58 - 2.65 (1H, m), 2.97 (2H, d), 3.60 (2H, s), 3.73 - 3.77 (2H, m), 7.03 - 7.07 (1H, m), 7.11 (1H, d), 7.13 (1H, d), 7.30 (1H, t), 7.33 - 7.36 (1H, m), 8.22 (1H, d) (Some peaks obscured by solvent); m/z = 407 [M+H]<sup>+</sup>.

### **Example 201**

#### **Preparation of 3-(trifluoromethyl)-6-[2-[[6-(trifluoromethyl)pyridin-3-yl]methyl]-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-5-yl]-[1,2,4]triazolo[4,3-b]pyridazine**

Reductive amination of 6-(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 6-(trifluoromethyl)pyridine-3-carbaldehyde was carried out according to General Synthetic Method 10. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5μ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 3-(trifluoromethyl)-6-[2-[[6-(trifluoromethyl)pyridin-3-yl]methyl]-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-5-yl]-[1,2,4]triazolo[4,3-b]pyridazine.

<sup>1</sup>H NMR (499.8 MHz, DMSO-d<sub>6</sub>) δ 2.58 - 2.64 (4H, m), 2.98 - 3.02 (2H, m), 3.34 (1H, s), 3.73 - 3.75 (4H, m), 3.77 (1H, s), 7.31 (1H, d), 7.84 (1H, d), 7.99 (1H, d), 8.22 (1H, d), 8.69 (1H, s) (Some peaks obscured by solvent); m/z = 458 [M+H]<sup>+</sup>.

### **Example 202**

#### **Preparation of 4-[[5-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-2-yl]methyl]-1H-pyridin-2-one**

Reductive amination of 6-(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 2-hydroxypyridine-4-carbaldehyde was carried out according to General Synthetic Method 10. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5μ silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 4-[[5-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-2-yl]methyl]-1H-pyridin-2-one.

<sup>1</sup>H NMR (499.8 MHz, DMSO-d<sub>6</sub>) δ 2.58 - 2.59 (2H, m), 2.98 - 2.99 (2H, m), 3.78 (2H, t), 6.11 (1H, d), 6.21 (1H, s), 7.25 (1H, d), 7.32 (1H, d), 8.22 (1H, d) (Some peaks obscured



by solvent);  $m/z = 406$   $[M+H]^+$ .

### **Example 203**

#### **Preparation of 6-[2-[(4-fluorophenyl)methyl]-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-5-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

Reductive amination of 6-(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 4-fluorobenzaldehyde was carried out according to General Synthetic Method 10. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5 $\mu$  silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[2-[(4-fluorophenyl)methyl]-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-5-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

$^1\text{H}$  NMR (499.8 MHz, DMSO- $d_6$ )  $\delta$  2.56 – 2.59 (2H, m), 2.96 (2H, s), 3.56 (2H, s), 3.73 – 3.76 (2H, m), 7.11 (2H, t), 7.31 (1H, d), 7.32 (2H, t), 8.22 (1H, d) (Some peaks obscured by solvent);  $m/z = 407$   $[M+H]^+$ .

### **Example 204**

#### **Preparation of 6-[2-[(4-chlorophenyl)methyl]-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-5-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

Reductive amination of 6-(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with 4-chlorobenzaldehyde was carried out according to General Synthetic Method 10. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5 $\mu$  silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[2-[(4-chlorophenyl)methyl]-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-5-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

$^1\text{H}$  NMR (499.8 MHz, DMSO- $d_6$ )  $\delta$  2.56 - 2.59 (2H, m), 2.96 (2H, s), 3.57 (2H, s), 3.74 (1H, d), 3.77 (1H, s), 7.29 - 7.36 (5H, m), 8.21 - 8.23 (1H, m) (Some peaks obscured by solvent);  $m/z = 423$   $[M+H]^+$ .

### **Example 205**

#### **Preparation of 4-[[5-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-2-yl]methyl]benzonitrile**

Reductive amination of 6-(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3-(trifluoromethyl)-



[1,2,4]triazolo[4,3-b]pyridazine with 4-formylbenzonitrile was carried out according to General Synthetic Method 10. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5 $\mu$  silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 4-[[5-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-2-yl]methyl]benzonitrile.

<sup>1</sup>H NMR (499.8 MHz, DMSO-d<sub>6</sub>)  $\delta$  2.54 – 2.62 (4H, m), 2.97 – 2.98 (2H, m), 3.67 (2H, s), 3.78 – 3.74 (2H, m), 7.31 (1H, d), 7.50 (2H, d), 8.22 (1H, d) (Some peaks obscured by solvent); m/z = 414 [M+H]<sup>+</sup>.

#### **Example 206**

##### **Preparation of 6-[2-(pyridin-3-ylmethyl)-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-5-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

Reductive amination of 6-(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine with pyridine-3-carbaldehyde was carried out according to General Synthetic Method 10. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column, 5 $\mu$  silica, 30 mm diameter, 100 mm length eluted with decreasingly polar mixtures of water (containing 0.1% aqueous ammonia) and acetonitrile as eluents to give 6-[2-(pyridin-3-ylmethyl)-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-5-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

<sup>1</sup>H NMR (499.8 MHz, DMSO-d<sub>6</sub>)  $\delta$  2.53 - 2.56 (2H, m), 2.59 - 2.62 (2H, m), 2.93 - 3.01 (2H, m), 3.61 (2H, s), 3.72 - 3.76 (2H, m), 7.28 - 7.31 (1H, m), 7.33 (1H, d), 7.68 - 7.70 (1H, m), 8.22 (1H, d), 8.45 - 8.46 (1H, m), 8.49 (1H, d) (Some peaks obscured by solvent); m/z = 390 [M+H]<sup>+</sup>.

#### **Example 207**

##### **Preparation of (3-methoxyphenyl)-[2-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-5-yl]methanone**

The amine 6-(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine was acylated with 3-methoxybenzoyl chloride by General Synthetic Method 11. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5 $\mu$  silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as



eluent to give (3-methoxyphenyl)-[2-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-5-yl]methanone.

<sup>1</sup>H NMR (300.132 MHz, DMSO-d<sub>6</sub>) δ 2.96-3.17 (2H, m), 3.34-3.60 (4H, m), 3.62-3.90 (7H, m), 6.98-7.11 (3H, m), 7.23 (1H, d), 7.34 (1H, t), 8.23 (1H, d); m/z = 433 [M+H]<sup>+</sup>.

5 **Example 208**

**Preparation of 2-methyl-1-[2-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-5-yl]propan-1-one**

The amine 6-(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine was acylated with 2-methylpropanoyl chloride by General  
10 Synthetic Method 11. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5μ silica, 19 mm diameter, 100 mm length) eluted with decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 2-methyl-1-[2-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-5-yl]propan-1-one.

15 <sup>1</sup>H NMR (300.132 MHz, DMSO-d<sub>6</sub>) δ 0.94-1.05 (6H, m), 2.59-2.70 (1H, m), 2.95-3.19 (2H, m), 3.24-3.29 (1H, m), 3.35-3.54 (3H, m), 3.55-3.64 (1H, m), 3.71-3.83 (3H, m), 7.24 (1H, d), 8.22 (1H, d) (Signal at 3.3 partially obscured by water); m/z = 369 [M+H]<sup>+</sup>.

**Example 209**

20 **Preparation of 3-methyl-1-[2-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-5-yl]butan-1-one**

The amine 6-(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine was acylated with 3-methylbutanoyl chloride by General  
Synthetic Method 11. The crude product was purified by hplc using a Waters XBridge Prep C18 OBD column (5μ silica, 19 mm diameter, 100 mm length) eluted with  
25 decreasingly polar mixtures of water (containing 1% aqueous ammonia) and acetonitrile as eluents to give 3-methyl-1-[2-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-5-yl]butan-1-one.

<sup>1</sup>H NMR (300.132 MHz, DMSO-d<sub>6</sub>) δ 0.84-0.94 (6H, m), 1.92-2.06 (1H, m), 2.09-2.15 (2H, m), 2.92-3.18 (2H, m), 3.24-3.35 (1H, m), 3.35-3.48 (3H, m), 3.54-3.64 (1H, m),  
30 3.67-3.82 (3H, m), 7.24 (1H, d), 8.22 (1H, d) (Signal at 3.3 partially obscured by water); m/z = 383 [M+H]<sup>+</sup>.



**Example 210****Preparation of 6-(5-benzyl-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-2-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[3,4-f]pyridazine**

2-Benzyl-3,3a,4,5,6,6a-hexahydro-1H-pyrrolo[3,4-c]pyrrole hydrochloride (0.129 g, 0.54 mmol) and then diisopropylethylamine (0.070 g, 0.54 mmol) were added sequentially to a solution of 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[3,4-f]pyridazine (0.080 g, 0.36 mmol) in ethanol (2mL). The reaction mixture was heated at 70°C for 4 hours and then evaporated to leave an involatile residue. The residue was purified by preparative hplc using a Phenomenex Luna C18 100A column (10 $\mu$  silica, 21mm diameter, 150mm length) eluted with decreasingly polar mixtures of water (containing 0.1% trifluoroacetic acid) and acetonitrile as eluents to give a partially purified product that was further purified by ion exchange chromatography an SCX column eluted with 7M aqueous ammonia in methanol as eluents to give 6-(5-benzyl-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-2-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[3,4-f]pyridazine (0.116 g, 83%) as a white solid.

<sup>1</sup>H NMR (300.132 MHz, CDCl<sub>3</sub>) 2.57-2.71 (4H, m), 2.96-3.09 (2H, m), 3.39-3.49 (2H, m), 3.61 (2H, s), 3.74-3.86 (2H, m), 6.87 (1H, d), 7.20-7.34 (5H, m), 7.89 (1H, d); m/z =389 [M+H]<sup>+</sup>.

**Example 211****Preparation of tert-butyl 5-(3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate**

tert-Butyl hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate (3.15 g, 14.83 mmol) was added to a mixture of 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (3 g, 13.48 mmol) and diisopropylethylamine (4.66 mL, 26.96 mmol) and ethanol (50 mL). The mixture was warmed to 70°C over a period of 10 minutes, stirred at 70 °C for 1 hour, and then allowed to cool to ambient temperature to give a precipitate. The precipitate was collected by filtration, washed with ethanol (50 mL), and and dried under vacuum to afford tert-butyl 5-(3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate (3.00 g, 55.9 %) as a white solid.

<sup>1</sup>H NMR (300.132 MHz, DMSO)  $\delta$  1.39 (s, 9H), 2.96 - 3.09 (m, 2H), 3.16 - 3.26 (m, 2H), 3.35 - 3.47 (m, 2H), 3.48 - 3.60 (m, 2H), 3.67 - 3.80 (m, 2H), 7.23 (d, 1H), 8.22 (d, 1H); m/z 399 (M+H<sup>+</sup>).



**Example 212****Preparation of 4-((4-(3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)piperazin-1-yl)methyl)aniline**

A mixture of trifluoroacetic acid (0.5 mL, 0.15 mmol) and tert-butyl 4-((4-(3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)piperazin-1-yl)methyl)phenylcarbamate (0.072 g, 0.15 mmol) in dichloromethane (2 mL) was stirred at ambient temperature for 2 hours and then evaporated to give an involatile residue. The residue was purified by hplc using a Phenomenex Luna C18 100A column (10 $\mu$  silica, 21mm diameter, 150mm length) eluted with decreasingly polar mixtures of water (containing 0.1% TFA) and acetonitrile as eluents to give a partially purified product that was further purified by ion exchange chromatography using an SCX column eluted 7M aqueous ammonia in methanol to give 4-((4-(3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)piperazin-1-yl)methyl)aniline (0.032 g, 56.2 %) as a white solid. <sup>1</sup>H NMR (300.132 MHz, DMSO-d<sub>6</sub>)  $\delta$  2.24-2.32 (4H, m), 3.18 (2H, s), 3.35-3.49 (4H, m), 4.79 (2H, s), 6.36 (2H, d), 6.79 (2H, d), 7.41 (1H, d), 8.07 (1H, d); m/z = 378 [M+H]<sup>+</sup>.

The tert-butyl 4-((4-(3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)piperazin-1-yl)methyl)phenylcarbamate used as starting material was prepared as follows:-

**Preparation of tert-butyl 4-((4-(3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)piperazin-1-yl)methyl)phenylcarbamate**

A solution of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (0.079 g, 0.29 mmol) in a mixture of acetic acid and dichloromethane (1:9; 3 mL) was added to a mixture of (polystyrylmethyl)trimethylammonium cyanoborohydride (4.1 mmol/g, 0.097 g, 0.4 mmol) and N-(4-formylphenyl)carbamic acid tert-butyl ester (0.088.4 g, 0.4 mmol). The reaction mixture was shaken for 4 days and then filtered. The filtrate was evaporated and the and the involatile residue was purified by hplc using a Waters XBridge Prep C18 OBD column (5 $\mu$  silica, 21mm diameter, 100mm length) eluted with decreasingly polar mixtures of water (containing 0.05% aqueous ammonia) and acetonitrile as eluents to give tert-butyl 4-((4-(3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)piperazin-1-yl)methyl)phenylcarbamate (0.0722 g, 52 %) as a white solid, which was used without further purification.



**Example 213****N-(4-fluorophenyl)-2-[3-(trifluoromethyl)-[1,2,4]triazolo[3,4-f]pyridazin-6-yl]-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrole-5-carboxamide**

1-Fluoro-4-isocyanatobenzene (0.026 g, 0.19 mmol) was added to a suspension of 6-(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (0.05 g, 0.17 mmol) in toluene (1.5 mL). The reaction mixture was heated at 70°C for 1 hour and evaporated to give an involatile residue. The residue was purified by hplc using a Phenomenex Luna C18 100A column (10 $\mu$  silica, 21mm diameter, 150mm length) eluted with decreasingly polar mixtures of water (containing 0.1% trifluoroacetic acid) and acetonitrile as eluents to give N-(4-fluorophenyl)-2-[3-(trifluoromethyl)-[1,2,4]triazolo[3,4-f]pyridazin-6-yl]-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrole-5-carboxamide (0.0309 g, 42 %) as a white solid.

**Example 214****N,N-dimethyl-2-[3-(trifluoromethyl)-[1,2,4]triazolo[3,4-f]pyridazin-6-yl]-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrole-5-sulfonamide**

N,N-Dimethylsulfamoyl chloride (0.027 g, 0.19 mmol) and then dichloromethane were added sequentially to a mixture of diisopropylethylamine (0.044 g, 0.34 mmol) and 6-(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (0.05 g, 0.17 mmol) in toluene (1.5 mL). The reaction mixture was stirred for 1 hour and evaporated to give an involatile residue. The residue was purified by preparative hplc using a Phenomenex Luna C18 100A column (10 $\mu$  silica, 21mm diameter, 150mm length) eluted with decreasingly polar mixtures of water (containing 0.1% trifluoroacetic acid) and acetonitrile as eluents to give N,N-dimethyl-2-[3-(trifluoromethyl)-[1,2,4]triazolo[3,4-f]pyridazin-6-yl]-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrole-5-sulfonamide (0.0206 g, 30 %) as a white solid.

<sup>1</sup>H NMR (300.132 MHz, DMSO-d<sub>6</sub>)  $\delta$  2.75 (6H, s), 3.05-3.15 (2H, m), 3.17-3.24 (2H, m), 3.40-3.55 (4H, m), 3.72-3.81 (2H, m), 7.27 (1H, d), 8.23 (1H, d); m/z = 406 [M+H]<sup>+</sup>.

**Example 215****6-(5-ethylsulfonyl-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-2-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[3,4-f]pyridazine**

Ethanesulfonyl chloride (0.024 g, 0.19 mmol) and then dichloromethane (0.5 mL) were added sequentially to a mixture of diisopropylethylamine (0.044 g, 0.34 mmol) and 6-



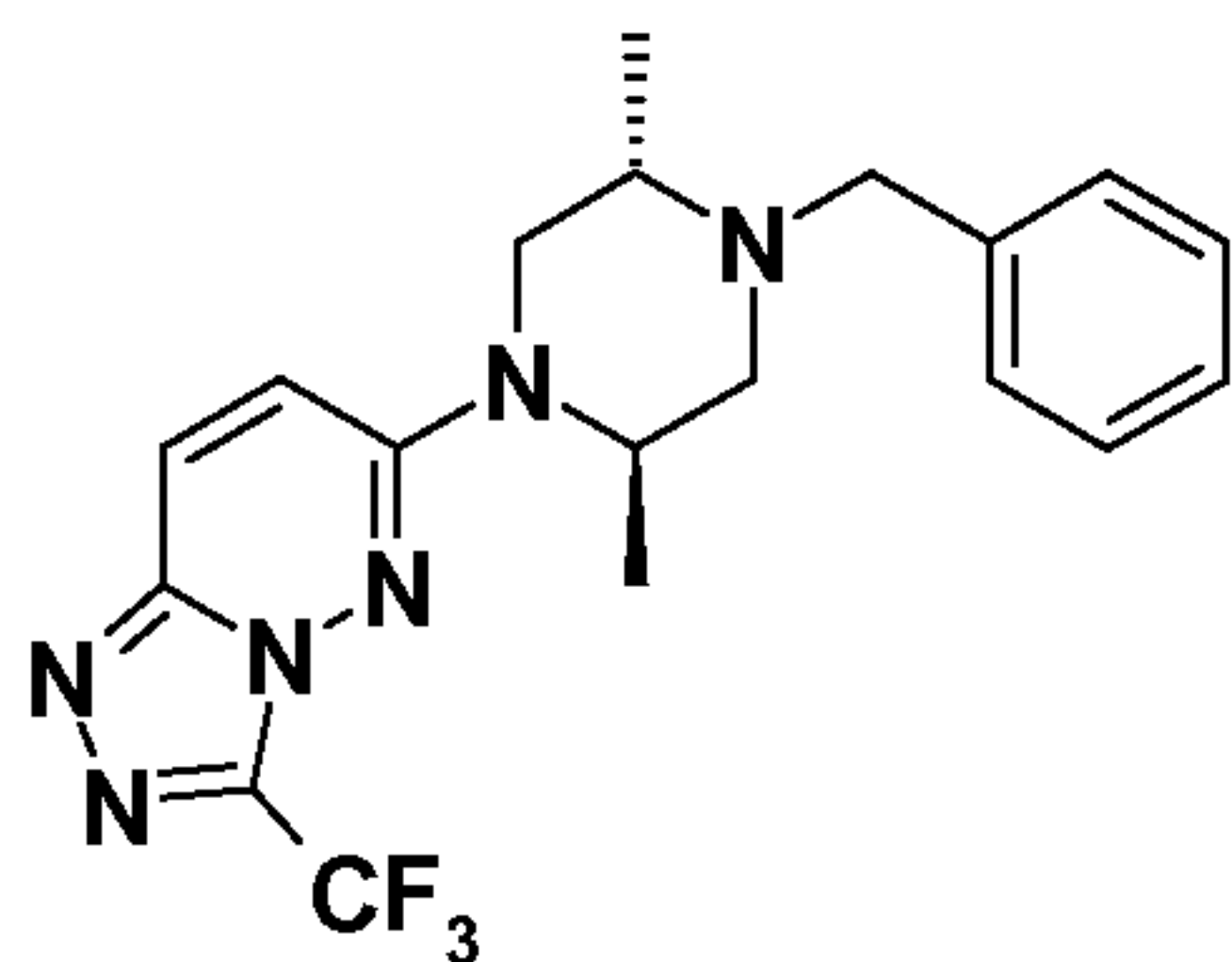
(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (0.050 g, 0.17 mmol) in toluene (1.5 mL). The reaction mixture was stirred for 1 hour at ambient temperature and then for 1.5 hours at 50°C and then evaporated to give an involatile residue. The residue was purified by preparative hplc using a

5 Phenomenex Luna C18 100A column (10 $\mu$  silica, 21mm diameter, 150mm length) eluted with decreasingly polar mixtures of water (containing 0.1% trifluoroacetic acid) and acetonitrile as eluents to give 6-(5-ethylsulfonyl-1,3,3a,4,6,6a-hexahydropyrrolo[3,4-c]pyrrol-2-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[3,4-f]pyridazine (0.0143 g, 22 %) as a white solid.

10 <sup>1</sup>H NMR (300.132 MHz, DMSO-d<sub>6</sub>)  $\delta$  2.75 (6H, s), 3.05-3.15 (2H, m), 3.17-3.24 (2H, m), 3.40-3.55 (4H, m), 3.72-3.81 (2H, m), 7.27 (1H, d), 8.23 (1H, d); m/z = 406 [M+H]<sup>+</sup>.

### **Example 216**

#### **Preparation of 6-[(2R,5S)-4-benzyl-2,5-dimethylpiperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine**



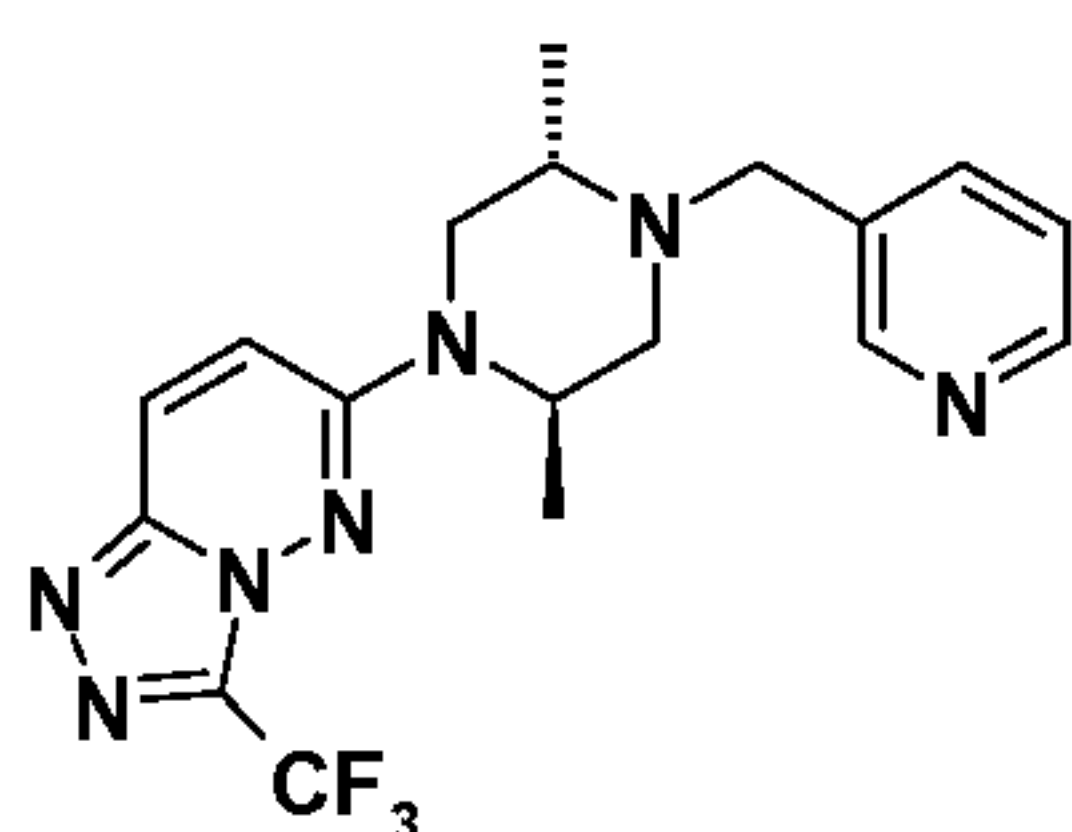
15

A stirred solution of 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (4.45 g, 20 mmol), (2S,5R)-1-benzyl-2,5-dimethylpiperazine (4.90 g, 24.00 mmol) and DIPEA (5.14 mL, 30.00 mmol) in DMF (40 mL) was heated at 125°C for 2 hours. The reaction mixture was evaporated to dryness, redissolved in DCM and washed sequentially with 1M

20 aqueous K<sub>2</sub>CO<sub>3</sub>, water and saturated brine. The organic layer was dried over MgSO<sub>4</sub>, filtered and evaporated. The crude product was purified by MPLC silica chromatography, eluting with 75% EtOAc / isohexane. Pure fractions were evaporated to dryness to afford 6-[(2R,5S)-4-benzyl-2,5-dimethylpiperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine (6.16 g, 79%) as a tan gum.

25 <sup>1</sup>H NMR (399.9 MHz, DMSO-d<sub>6</sub>)  $\delta$  1.01 - 1.03 (3H, m), 1.26 (3H, d), 2.34 - 2.37 (1H, m), 2.80 - 2.84 (1H, m), 3.11 (1H, t), 3.44 - 3.48 (1H, m), 3.53 (1H, d), 3.66 (1H, d), 3.93 (1H, d), 4.42 (1H, s), 7.24 - 7.30 (1H, m), 7.31 - 7.41 (4H, m), 7.56 - 7.59 (1H, m), 8.22 - 8.26 (1H, m); m/z = 391 [M+H]<sup>+</sup>.



**Example 217****Preparation of 6-[(2R,5S)-2,5-dimethyl-4-(pyridin-3-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine**

5 A mixture of pyridine-3-carboxaldehyde and 6-[(2R,5S)-2,5-dimethylpiperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by General Synthetic Method 5 to give 6-[(2R,5S)-2,5-dimethyl-4-(3-pyridylmethyl)piperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine in 84% yield.

1H NMR (399.9 MHz, CDCl<sub>3</sub>) δ 1.09 - 1.11 (3H, m), 1.33 (3H, d), 2.36 - 2.40 (1H, m),  
 10 2.88 - 2.95 (1H, m), 3.15 - 3.18 (1H, m), 3.53 - 3.59 (2H, m), 3.69 (1H, d), 3.84 (1H, d), 4.31 (1H, s), 7.03 (1H, d), 7.28 - 7.30 (1H, m), 7.71 - 7.74 (1H, m), 7.91 (1H, d), 8.52 - 8.54 (1H, m), 8.60 (1H, d); m/z = 392 [M+H]<sup>+</sup>.

The 6-[(2R,5S)-2,5-dimethylpiperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine used as starting material was prepared as follows:-

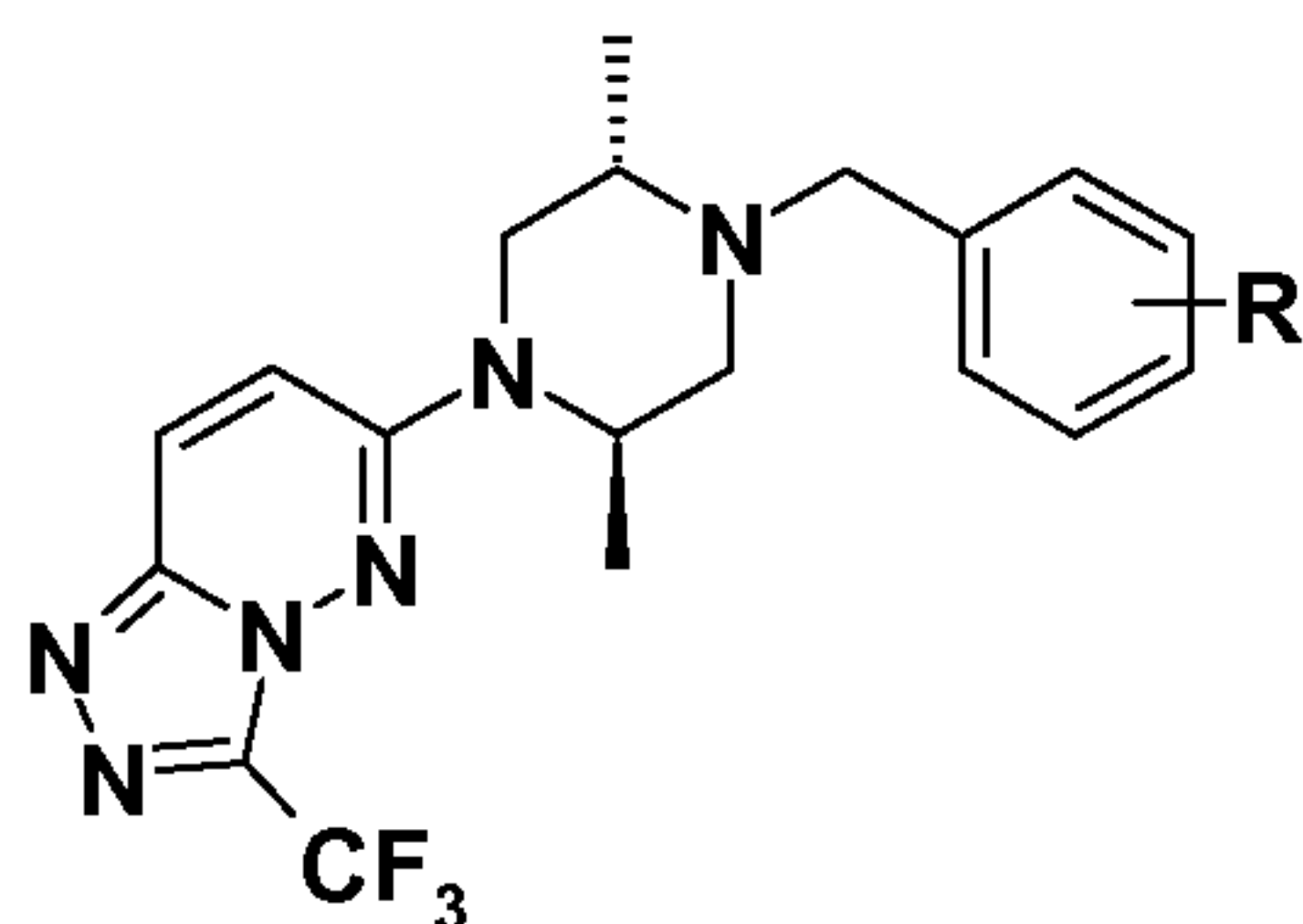
15 A solution of 6-[(2R,5S)-4-benzyl-2,5-dimethylpiperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine (6.1 g, 15.62 mmol) in ethanol (150 mL) and 5M hydrochloric acid (9.37 mL, 46.87 mmol) was hydrogenated over 10% palladium on charcoal (1 g, 9.40 mmol) under hydrogen at 1 atmosphere for 3 days. The catalyst was filtered off and the filtrate was evaporated. The residue was taken into DCM and washed  
 20 with 2M aqueous K<sub>2</sub>CO<sub>3</sub>. The organic phase was dried over MgSO<sub>4</sub> and evaporated. The crude product was purified by MPLC silica chromatography, elution gradient 2 to 5% methanolic ammonia in DCM. Product fractions were evaporated to near dryness and crystallised from ether to afford 6-[(2R,5S)-2,5-dimethylpiperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (1.430 g, 30.5%) as a white crystalline  
 25 solid.

1H NMR (400.1 MHz, CDCl<sub>3</sub>) δ 1.23 - 1.25 (3H, m), 1.33 (3H, d), 2.71 - 2.75 (1H, m), 3.32 - 3.39 (2H, m), 3.47 (1H, d), 3.59 - 3.64 (1H, m), 4.15 - 4.19 (1H, m), 7.04 (1H, d), 7.92 (1H, d); m/z = 301 [M+H]<sup>+</sup>



**Examples 218-222**

The following compounds were prepared in 73-82% yield by General Synthetic Method 5, starting from 6-[(2R,5S)-2,5-dimethylpiperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine and the appropriate aldehyde:-

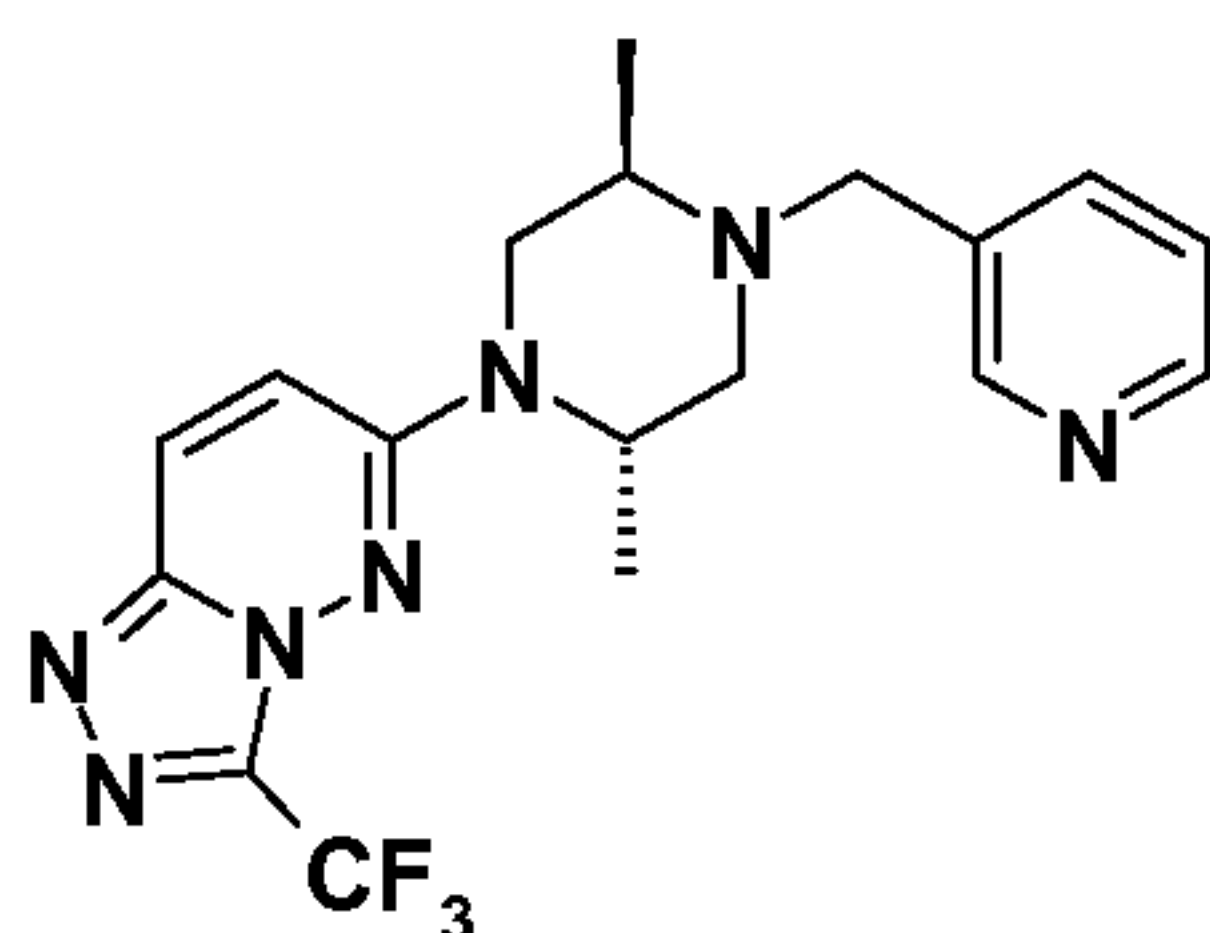


5

| Ex. | R         | <sup>1</sup> H NMR (399.9 MHz, CDCl <sub>3</sub> )                                                                                                                                                                                      | m/z [M+H] <sup>+</sup> |
|-----|-----------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|
| 218 | 4-CN      | δ 1.09 - 1.10 (3H, m), 1.35 (3H, d), 2.33 - 2.36 (1H, m), 2.90 - 2.94 (1H, m), 3.16 (1H, d), 3.58 (2H, d), 3.72 - 3.75 (1H, m), 3.85 (1H, d), 4.32 (1H, s), 7.03 (1H, d), 7.51 (2H, d), 7.63 (2H, d), 7.92 (1H, d)                      | 416                    |
| 219 | 3,4-di-F  | δ 1.07 (3H, d), 1.33 - 1.35 (3H, m), 2.35 - 2.38 (1H, m), 2.87 - 2.91 (1H, m), 3.13 - 3.16 (1H, m), 3.50 (1H, d), 3.53 - 3.57 (1H, m), 3.62 (1H, d), 3.84 (1H, d), 4.31 (1H, s), 7.02 - 7.15 (3H, m), 7.21 - 7.30 (1H, m), 7.91 (1H, d) | 427                    |
| 220 | 3,5-di-F  | δ 1.07 - 1.09 (3H, m), 1.36 (3H, d), 2.36 - 2.40 (1H, m), 2.89 - 2.93 (1H, m), 3.14 - 3.17 (1H, m), 3.51 - 3.59 (2H, m), 3.66 (1H, d), 3.85 (1H, d), 4.32 (1H, d), 6.68 - 6.74 (1H, m), 6.91 - 6.95 (2H, m), 7.04 (1H, d), 7.92 (1H, d) | 427                    |
| 221 | 4-F       | δ 1.07 (3H, d), 1.32 (3H, d), 2.35 - 2.39 (1H, m), 2.86 - 2.90 (1H, m), 3.13 - 3.16 (1H, m), 3.50 - 3.56 (2H, m), 3.63 (1H, d), 3.83 (1H, d), 4.30 (1H, t), 7.00 - 7.05 (3H, m), 7.32 - 7.35 (2H, m), 7.89 - 7.91 (1H, m)               | 409                    |
| 222 | 3-CN, 4-F | δ 1.09 (3H, d), 1.34 (3H, d), 2.31 - 2.35 (1H, m), 2.89 - 2.93 (1H, m), 3.12 - 3.16 (1H, m), 3.52 - 3.58 (2H, m)                                                                                                                        | 434                    |



|  |  |                                                                                                                           |  |
|--|--|---------------------------------------------------------------------------------------------------------------------------|--|
|  |  | m), 3.65 - 3.69 (1H, m), 3.84 - 3.87 (1H, m), 4.33 (1H, s), 7.04 (1H, d), 7.20 (1H, t), 7.60 - 7.67 (2H, m), 7.92 (1H, d) |  |
|--|--|---------------------------------------------------------------------------------------------------------------------------|--|

**Example 223****Preparation of 6-[(2S,5R)-2,5-dimethyl-4-(pyridin-3-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine**

5 A mixture of pyridine-3-carboxaldehyde and 6-[(2S,5R)-2,5-dimethylpiperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by General Synthetic Method 5 to give 6-[(2S,5R)-2,5-dimethyl-4-(pyridin-3-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine in 84% yield.

1H NMR (399.9 MHz, CDCl<sub>3</sub>)  $\delta$  1.09 - 1.11 (3H, m), 1.33 (3H, d), 2.36 - 2.40 (1H, m),  
 10 2.88 - 2.95 (1H, m), 3.15 - 3.18 (1H, m), 3.53 - 3.59 (2H, m), 3.69 (1H, d), 3.84 (1H, d), 4.31 (1H, s), 7.03 (1H, d), 7.28 - 7.30 (1H, m), 7.71 - 7.74 (1H, m), 7.91 (1H, d), 8.52 - 8.54 (1H, m), 8.60 (1H, d);  $m/z = 392$  [M+H]<sup>+</sup>.

The 6-[(2S,5R)-2,5-dimethylpiperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine used as starting material was prepared as follows:-

15 **Preparation of (2R,5S)-tert-butyl 2,5-dimethyl-4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazine-1-carboxylate**

A stirred solution of 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (4.45 g, 20 mmol), (2R,5S)-tert-butyl 2,5-dimethylpiperazine-1-carboxylate (5.14, 24 mmol) and DIPEA (5.14 mL, 30.00 mmol) in DMF (40.0 mL) was heated at 125°C for 2.5  
 20 hours. The reaction mixture was evaporated to dryness, redissolved in DCM and washed sequentially with 1M aqueous K<sub>2</sub>CO<sub>3</sub>, water and saturated brine. The organic layer was dried over MgSO<sub>4</sub>, filtered and evaporated. The crude product was purified by MPLC silica chromatography, eluting with EtOAc. Product fractions were evaporated and triturated with ether. The solid was collected by filtration, washed with ether and dried  
 25 under vacuum to afford (2R,5S)-tert-butyl 2,5-dimethyl-4-[3-(trifluoromethyl)-



[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazine-1-carboxylate (6.09 g, 76%) as a white crystalline solid.

<sup>1</sup>H NMR (399.9 MHz, DMSO-d<sub>6</sub>) δ 1.14 - 1.21 (6H, m), 1.44 (9H, s), 3.36 - 3.42 (2H, m), 3.71 (1H, d), 3.88 (1H, d), 4.25 - 4.35 (1H, m), 4.47 (1H, s), 7.59 (1H, d), 8.28 (1H, d); m/z = 401 [M+H]<sup>+</sup>.

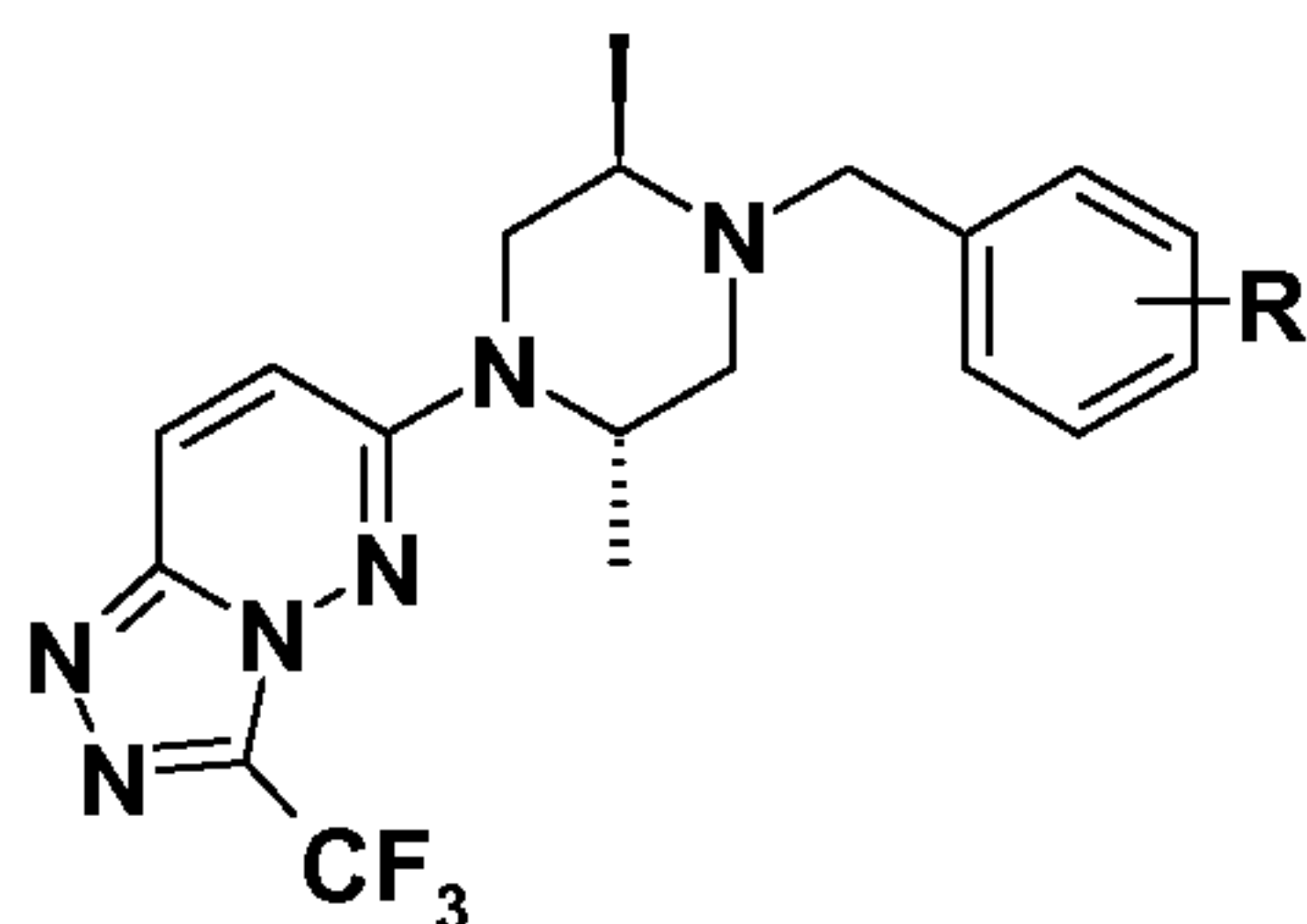
#### Preparation of 6-[(2S,5R)-2,5-dimethylpiperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine

(2R,5S)-tert-Butyl 2,5-dimethyl-4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazine-1-carboxylate (6.01 g, 15 mmol) was added in portions to stirred TFA (25 mL) over 5 minutes. There was a moderate exotherm and the reaction mixture was allowed to stir for a further 15 minutes. The bulk of the TFA was evaporated and the residue was basified with 1M aqueous K<sub>2</sub>CO<sub>3</sub>. It was extracted thoroughly with DCM (4 x 200 mL) and the combined organic phase was dried over MgSO<sub>4</sub> and evaporated to give an oil which rapidly crystallised. The solid was collected by filtration and dried under vacuum to give 6-[(2S,5R)-2,5-dimethylpiperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (3.52 g, 78%) as a white crystalline solid.

<sup>1</sup>H NMR (400.1 MHz, CDCl<sub>3</sub>) δ 1.23 - 1.25 (3H, m), 1.33 (3H, d), 2.71 - 2.75 (1H, m), 3.32 - 3.39 (2H, m), 3.47 (1H, d), 3.59 - 3.64 (1H, m), 4.15 - 4.19 (1H, m), 7.04 (1H, d), 7.92 (1H, d); m/z = 301 [M+H]<sup>+</sup>.

#### Examples 224-228

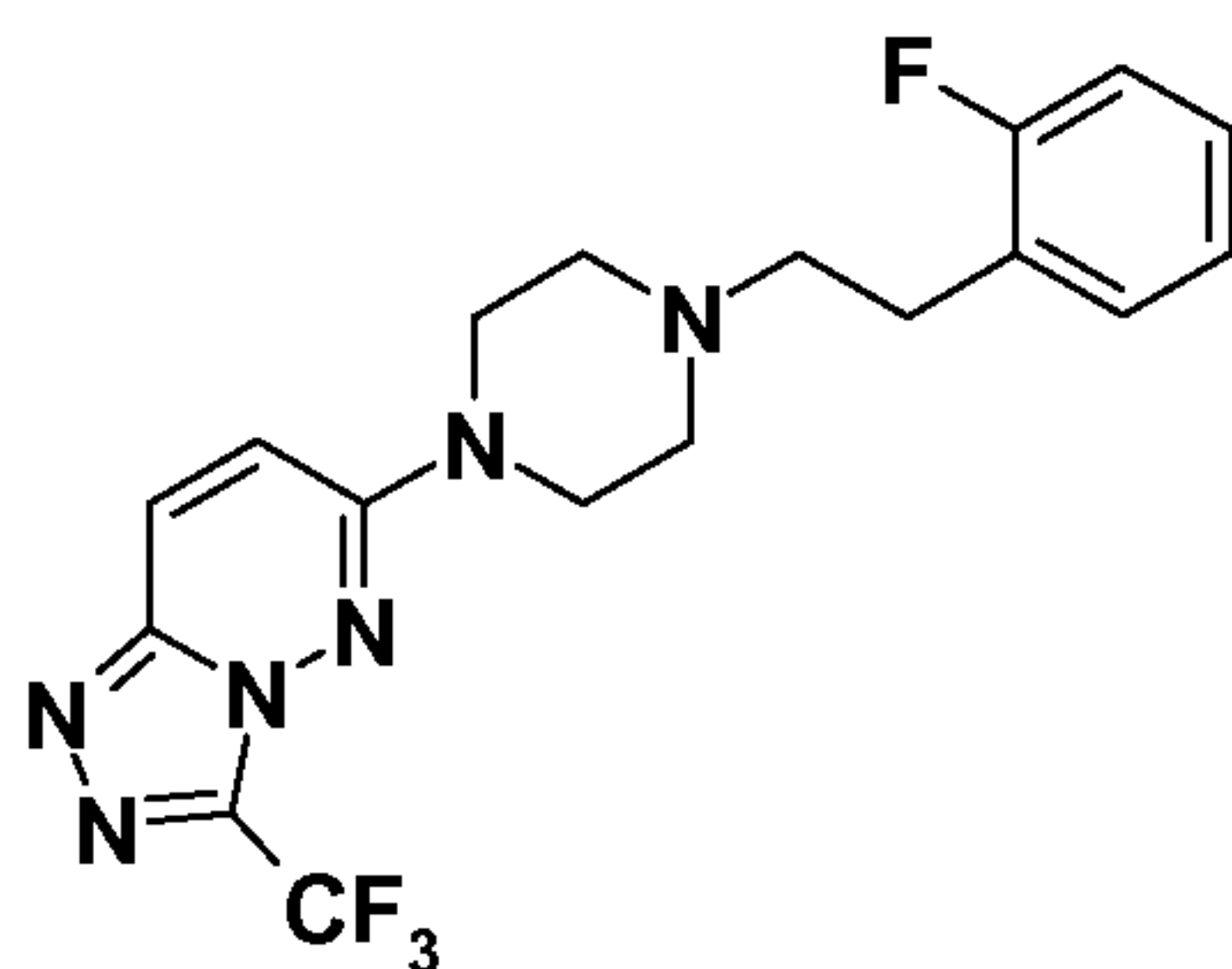
The following compounds were prepared in 63-84% yield by General Synthetic Method 5, starting from 6-[(2S,5R)-2,5-dimethylpiperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine and the appropriate aldehyde:-



| Ex. | R        | <sup>1</sup> H NMR (399.9 MHz, CDCl <sub>3</sub> )                                                       | m/z [M+H] <sup>+</sup> |
|-----|----------|----------------------------------------------------------------------------------------------------------|------------------------|
| 224 | 3,4-di-F | δ 1.07 (3H, d), 1.33 - 1.35 (3H, m), 2.35 - 2.38 (1H, m), 2.87 - 2.91 (1H, m), 3.13 - 3.16 (1H, m), 3.50 | 427                    |



|     |           |                                                                                                                                                                                                                                                 |     |
|-----|-----------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
|     |           | (1H, d), 3.53 - 3.57 (1H, m), 3.62 (1H, d), 3.84 (1H, d), 4.31 (1H, s), 7.02 - 7.15 (3H, m), 7.21 - 7.30 (1H, m), 7.91 (1H, d)                                                                                                                  |     |
| 225 | 3,5-di-F  | $\delta$ 1.07 - 1.09 (3H, m), 1.36 (3H, d), 2.36 - 2.40 (1H, m), 2.89 - 2.93 (1H, m), 3.14 - 3.17 (1H, m), 3.51 - 3.59 (2H, m), 3.66 (1H, d), 3.85 (1H, d), 4.32 (1H, d), 6.68 - 6.74 (1H, m), 6.91 - 6.95 (2H, m), 7.04 (1H, d), 7.92 (1H, d)  | 426 |
| 226 | 4-F       | $\delta$ 1.07 (3H, d), 1.32 (3H, d), 2.35 - 2.39 (1H, m), 2.86 - 2.90 (1H, m), 3.13 - 3.16 (1H, m), 3.50 - 3.56 (2H, m), 3.63 (1H, d), 3.83 (1H, d), 4.30 (1H, t), 7.00 - 7.05 (3H, m), 7.32 - 7.35 (2H, m), 7.89 - 7.91 (1H, m)                | 408 |
| 227 | 3-CN, 4-F | $\delta$ 1.09 (3H, d), 1.34 (3H, d), 2.31 - 2.35 (1H, m), 2.89 - 2.93 (1H, m), 3.12 - 3.16 (1H, m), 3.52 - 3.58 (2H, m), 3.65 - 3.69 (1H, m), 3.84 - 3.87 (1H, m), 4.33 (1H, s), 7.04 (1H, d), 7.20 (1H, t), 7.60 - 7.67 (2H, m), 7.92 (1H, d)  | 434 |
| 228 | 4-CN      | $\delta$ 1.10 (3H, d), 1.35 (3H, d), 2.33 - 2.36 (1H, m), 2.90 - 2.94 (1H, m), 3.14 - 3.17 (1H, m), 3.54 - 3.62 (2H, m), 3.72 - 3.75 (1H, m), 3.85 (1H, s), 4.33 (1H, d), 7.04 (1H, d), 7.50 - 7.52 (2H, m), 7.63 - 7.65 (2H, m), 7.92 (1H, d). | 416 |

**Example 229****Preparation of 6-[4-[2-(2-fluorophenyl)ethyl]piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine**

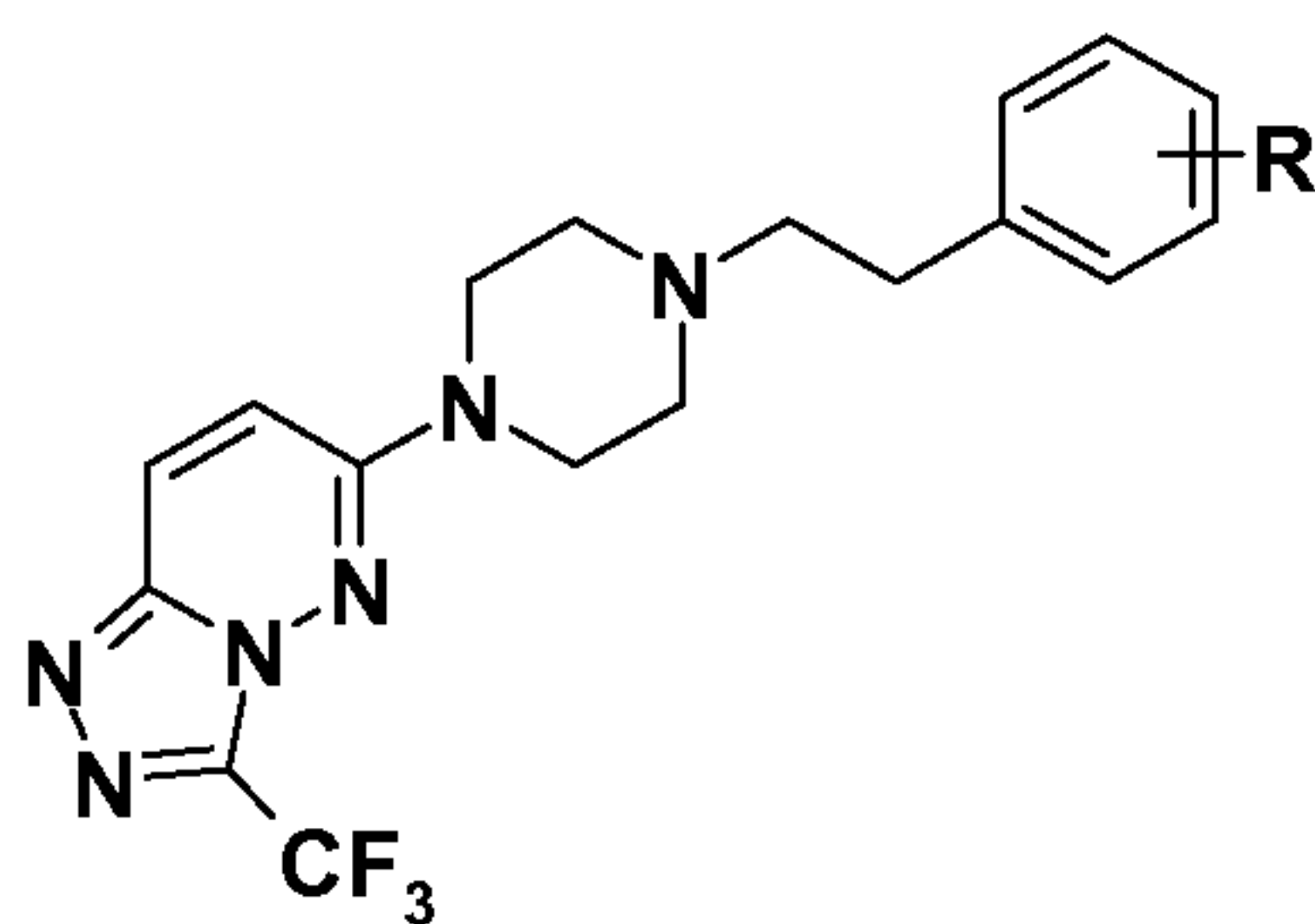


A stirred solution of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine dihydrochloride (0.173 g, 0.5 mmol), DIPEA (0.300 mL, 1.75 mmol) and 2-fluorophenethyl bromide (0.084 mL, 0.60 mmol) in DMF (2 mL) was heated at 100°C for 2.5 hours. The reaction was incomplete and further DIPEA (0.300 mL, 1.75 mmol) and 2-fluorophenethyl bromide (0.084 mL, 0.60 mmol) were added. The solution was stirred at 100°C for a further 90 minutes. The crude product was purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5 $\mu$  silica, 19 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 1% ammonia) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford 6-[4-[2-(2-fluorophenyl)ethyl]piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine (0.131 g, 66.4%) as a crisp foam.

<sup>1</sup>H NMR (399.9 MHz, DMSO-d<sub>6</sub>)  $\delta$  2.53 - 2.61 (6H, m), 2.81 - 2.85 (2H, m), 3.61 (4H, t), 7.12 - 7.17 (2H, m), 7.23 - 7.27 (1H, m), 7.34 - 7.39 (1H, m), 7.61 (1H, d), 8.25 (1H, d); m/z = 395 [M+H]<sup>+</sup>.

### **Examples 230-235**

The following compounds were prepared in 24-64% yield by an analogous method to Example 229, starting from 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine and the appropriate phenethyl bromide:-



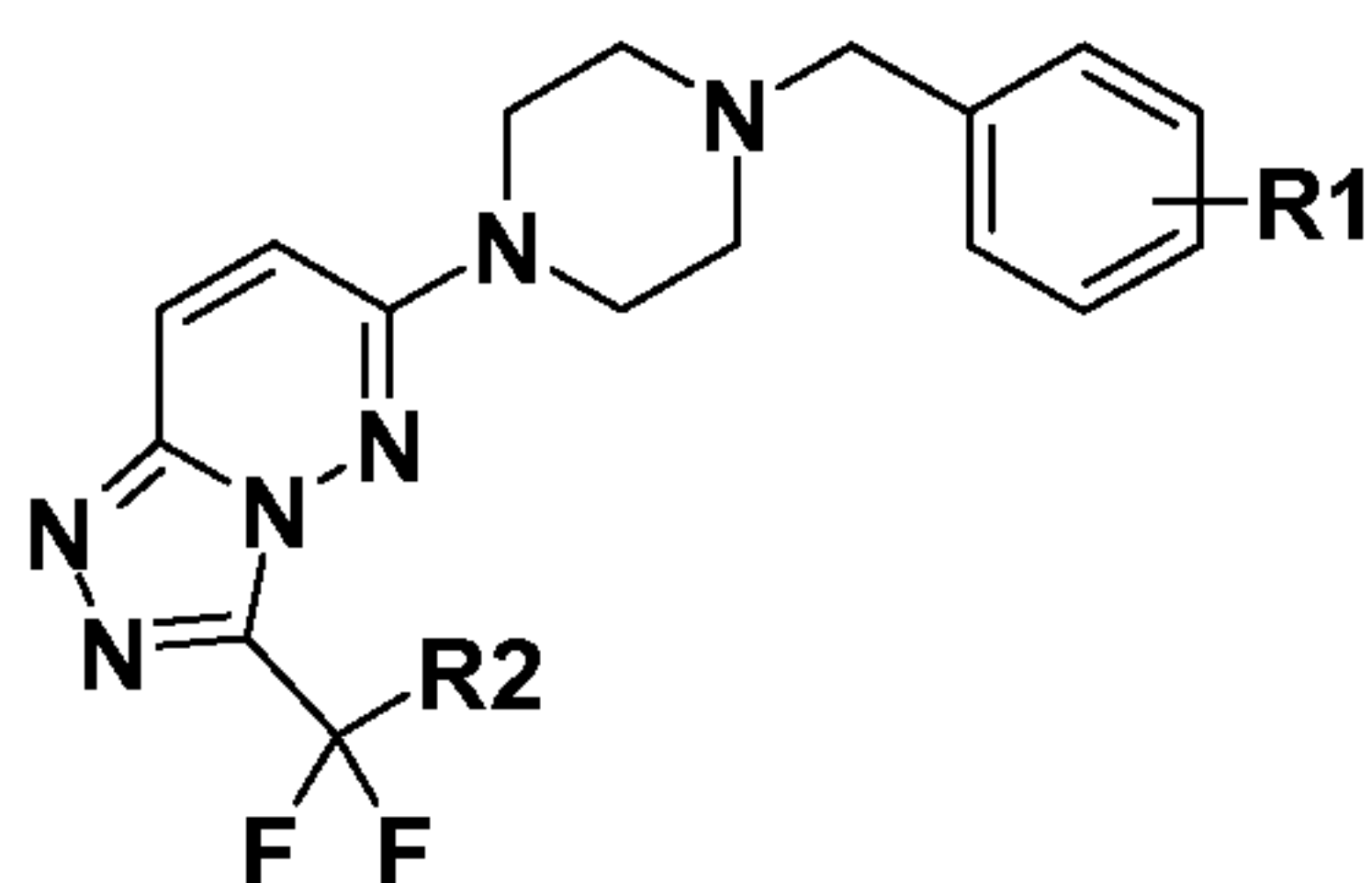
| Ex. | R    | <sup>1</sup> H NMR (399.9 MHz, CDCl <sub>3</sub> )                                                                                    | m/z<br>[M+H] <sup>+</sup> |
|-----|------|---------------------------------------------------------------------------------------------------------------------------------------|---------------------------|
| 230 | 4-F  | $\delta$ 2.63 - 2.67 (6H, m), 2.79 - 2.83 (2H, m), 3.65 (4H, t), 6.96 - 7.01 (2H, m), 7.07 (1H, d), 7.15 - 7.19 (2H, m), 7.93 (1H, d) | 395                       |
| 231 | 4-Cl | $\delta$ 2.63 - 2.67 (6H, m), 2.79 - 2.82 (2H, m), 3.64 (4H, t), 7.06 (1H, d), 7.13 - 7.16 (2H, m), 7.25 - 7.28 (2H, m), 7.93 (1H, d) | 411                       |



|     |      |                                                                                                                                                     |     |
|-----|------|-----------------------------------------------------------------------------------------------------------------------------------------------------|-----|
| 232 | 2-Cl | $\delta$ 2.66 - 2.71 (6H, m), 2.95 - 2.99 (2H, m), 3.66 (4H, t), 7.07 (1H, d), 7.14 - 7.22 (2H, m), 7.25 (1H, d), 7.34 - 7.36 (1H, m), 7.93 (1H, d) | 411 |
| 233 | 3-Cl | $\delta$ 2.64 - 2.68 (6H, m), 2.79 - 2.83 (2H, m), 3.65 (4H, t), 7.05 - 7.11 (2H, m), 7.18 - 7.25 (3H, m), 7.93 (1H, s)                             | 411 |
| 234 | 3-F  | $\delta$ 2.64 - 2.70 (6H, m), 2.82 - 2.86 (2H, m), 3.65 (4H, t), 6.88 - 6.95 (2H, m), 6.99 (1H, s), 7.07 (1H, d), 7.23 - 7.28 (1H, m), 7.93 (1H, d) | 395 |
| 235 | 4-CN | $\delta$ 2.64 - 2.70 (6H, m), 2.87 - 2.91 (2H, m), 3.64 (4H, t), 7.06 (1H, d), 7.32 - 7.34 (2H, m), 7.58 - 7.61 (2H, m), 7.93 (1H, d)               | 402 |

**Examples 236-247**

The following compounds were prepared in 33-89% yield by an analogous method to Example 216, starting from the appropriate 3-substituted 6-chloro-[1,2,4]triazolo[4,3-b]pyridazine (obtained as described in the corresponding footnote) and the appropriate benzyl piperazine:-



| Ex. | Note | R1   | R2 | <sup>1</sup> H NMR (399.9 MHz, CDCl <sub>3</sub> )                                                                                           | m/z<br>[M+H] <sup>+</sup> |
|-----|------|------|----|----------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|
| 236 | [1]  | 4-F  | H  | $\delta$ 2.57 (4H, t), 3.54 (2H, s), 3.61 (4H, t), 6.99 - 7.05 (3H, m), 7.12 (1H, t), 7.25 - 7.33 (2H, m), 7.88 - 7.91 (1H, m)               | 363                       |
| 237 | [1]  | 4-CN | H  | $\delta$ 2.59 (4H, t), 3.62 - 3.64 (6H, m), 7.02 (1H, d), 7.12 (1H, t), 7.49 (2H, d), 7.62 - 7.65 (2H, m), 7.91 (1H, d)                      | 370                       |
| 238 | [1]  | 3-CN | H  | $\delta$ 2.59 (4H, t), 3.60 (2H, s), 3.63 (4H, t), 7.03 (1H, d), 7.12 (1H, t), 7.45 (1H, t), 7.57 - 7.60 (2H, m), 7.69 (1H, t), 7.91 (1H, d) | 370                       |



|     |     |      |    |                                                                                                                                                                                 |     |
|-----|-----|------|----|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
| 239 | [1] | 3-F  | H  | $\delta$ 2.59 (4H, t), 3.57 (2H, s), 3.63 (4H, t), 6.95 - 6.99 (1H, m), 7.02 (1H, d), 7.08 - 7.12 (2H, m), 7.12 (1H, t), 7.25 - 7.32 (1H, m), 7.90 (1H, d)                      | 363 |
| 240 | [2] | 4-F  | Me | $\delta$ 2.30 (3H, t), 2.57 (4H, t), 3.53 (2H, s), 3.60 (4H, t), 6.98 - 7.01 (1H, m), 7.00 - 7.05 (2H, m), 7.29 - 7.32 (2H, m), 7.88 (1H, d)                                    | 377 |
| 241 | [2] | 4-CN | Me | $\delta$ 2.30 (3H, t), 2.59 (4H, t), 3.61 - 3.63 (6H, m), 7.00 (1H, d), 7.48 (2H, d), 7.62 - 7.65 (2H, m), 7.90 (1H, d)                                                         | 384 |
| 242 | [2] | 3-CN | Me | $\delta$ 2.30 (3H, t), 2.59 (4H, t), 3.60 (2H, s), 3.63 (4H, t), 7.00 (1H, d), 7.45 (1H, t), 7.56 - 7.60 (2H, m), 7.69 - 7.69 (1H, m), 7.90 (1H, d)                             | 384 |
| 243 | [2] | 3-F  | Me | $\delta$ 2.30 (3H, t), 2.59 (4H, t), 3.56 (2H, s), 3.62 (4H, t), 6.94 - 6.99 (1H, m), 7.00 (1H, d), 7.08 - 7.11 (2H, m), 7.26 - 7.32 (1H, m), 7.89 (1H, d)                      | 377 |
| 244 | [3] | 4-F  | Et | $\delta$ 1.18 (3H, t), 2.56 - 2.70 (6H, m), 3.53 (2H, s), 3.60 (4H, t), 6.98 - 7.01 (1H, m), 6.99 - 7.05 (2H, m), 7.28 - 7.32 (2H, m), 7.87 - 7.89 (1H, m)                      | 391 |
| 245 | [3] | 4-CN | Et | $\delta$ 1.18 (3H, t), 2.60 (4H, q), 2.56 - 2.70 (2H, m), 3.57 - 3.62 (4H, m), 3.60 - 3.63 (2H, m), 7.00 (1H, d), 7.48 (2H, d), 7.62 - 7.65 (2H, m), 7.90 (1H, d)               | 398 |
| 246 | [3] | 3-CN | Et | $\delta$ 1.18 (3H, t), 2.59 - 2.61 (2H, m), 2.56 - 2.70 (4H, m), 3.60 (2H, s), 3.62 (4H, t), 7.00 (1H, d), 7.45 (1H, t), 7.57 - 7.60 (2H, m), 7.68 - 7.69 (1H, m), 7.90 (1H, d) | 398 |
| 247 | [3] | 3-F  | Et | $\delta$ 1.18 (3H, t), 2.56 - 2.70 (6H, m), 3.56 (2H, s), 3.61 (4H, t), 6.94 - 7.00 (1H, m), 7.00 (1H,                                                                          | 391 |



|  |  |  |  |                                                               |  |
|--|--|--|--|---------------------------------------------------------------|--|
|  |  |  |  | d), 7.08 - 7.11 (2H, m), 7.27 - 7.32 (1H, m),<br>7.89 (1H, d) |  |
|--|--|--|--|---------------------------------------------------------------|--|

[1] Starting from 6-chloro-3-difluoromethyl-[1,2,4]-triazolo[4,3-b]pyridazine, obtained as described in General Synthetic Method 1, preparation of starting materials.

[2] Starting from 6-chloro-3-(1,1-difluoroethyl)-[1,2,4]-triazolo[4,3-b]pyridazine, obtained  
5 in 66% yield by an analogous method to General Synthetic Method 1, preparation of starting materials, starting from 3-chloropyridazin-6-yl hydrazine and 2,2-difluoropropanoic acid.

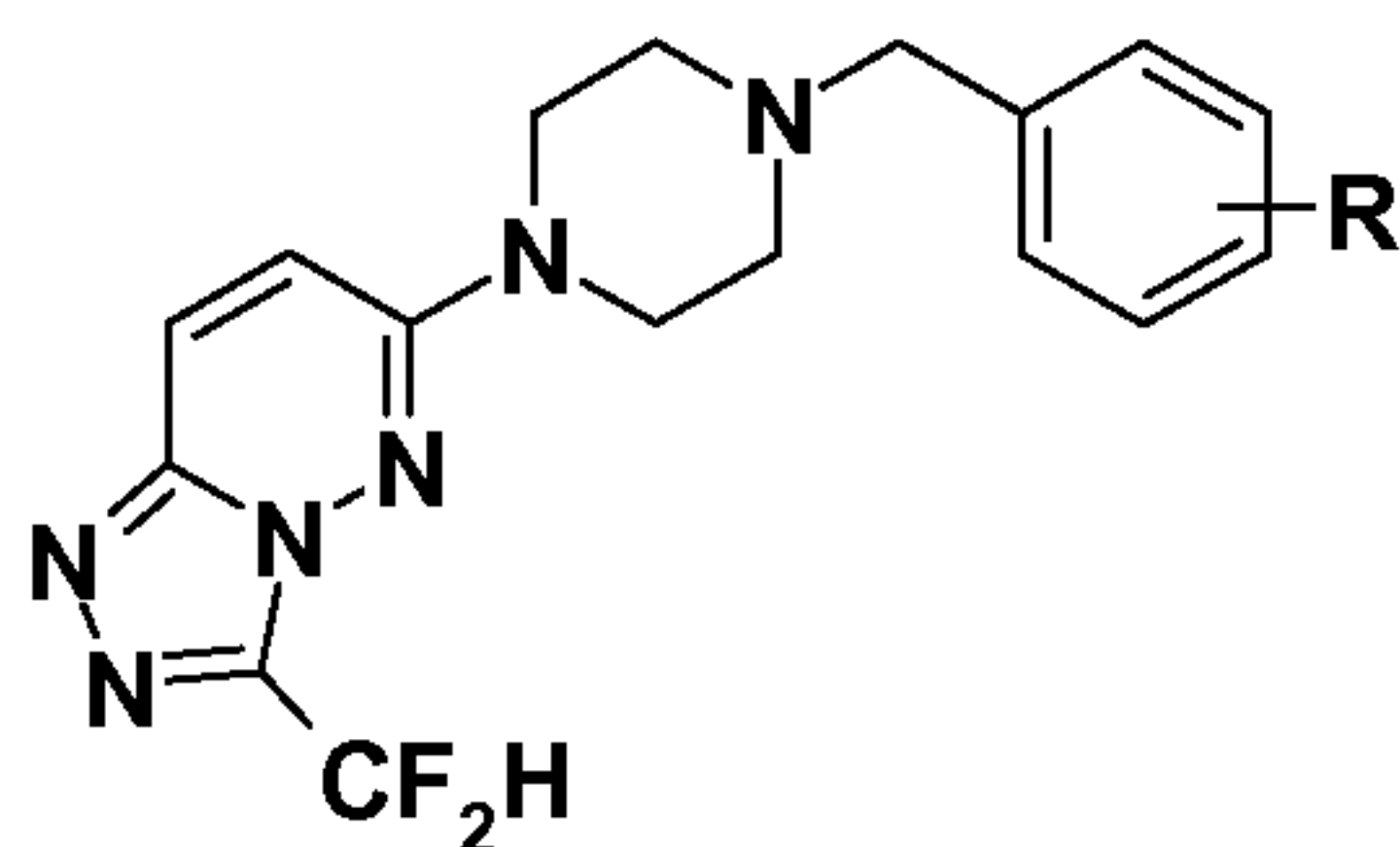
<sup>1</sup>H NMR (399.9 MHz, CDCl<sub>3</sub>) δ 2.37 (3H, t), 7.25 (1H, d), 8.15 (1H, d); m/z = 219 [M+H]<sup>+</sup>.

10 [3] Starting from 6-chloro-3-(1,1-difluoropropyl)-[1,2,4]-triazolo[4,3-b]pyridazine, obtained in 52% yield by an analogous method to General Synthetic Method 1, preparation of starting materials, starting from 3-chloropyridazin-6-yl hydrazine and 2,2-difluorobutanoic acid.

15 <sup>1</sup>H NMR (399.9 MHz, CDCl<sub>3</sub>) δ 1.23 (3H, t), 2.60 - 2.74 (2H, m), 7.24 (1H, d), 8.15 (1H, d); m/z = 274 [M+H]<sup>+</sup>.

### **Examples 248-263**

The following compounds were prepared in 35-83% yield by General Synthetic Method 5, starting from 3-(difluoromethyl)-6-(piperazin-1-yl)-[1,2,4]triazolo[4,3-b]pyridazine and the appropriate aldehyde:-



20

| Ex. | R        | <sup>1</sup> H NMR (399.9 MHz, CDCl <sub>3</sub> )                                                                             | m/z [M+H] <sup>+</sup> |
|-----|----------|--------------------------------------------------------------------------------------------------------------------------------|------------------------|
| 248 | 3-Cl     | δ 2.60 (4H, d), 3.55 (2H, s), 3.63 (4H, t), 7.02 (1H, d), 6.99 - 7.25 (1H, m), 7.22 - 7.31 (3H, m), 7.37 (1H, s), 7.90 (1H, d) | 379                    |
| 249 | 2,4-di-F | δ 2.63 (4H, s), 3.62 (3H, s), 3.63 (3H, s), 6.79 - 6.84 (1H, m), 6.85 - 6.90 (1H, m), 7.02 (1H,                                | 381                    |



|     |                   |                                                                                                                                                                                 |     |
|-----|-------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
|     |                   | d), 7.12 (1H, t), 7.38 (1H, q), 7.90 (1H, d)                                                                                                                                    |     |
| 250 | 3,4-di-F          | $\delta$ 2.59 (4H, s), 3.53 (2H, s), 3.63 (4H, t), 7.02 (1H, d), 7.06 - 7.13 (2H, m), 6.99 - 7.25 (1H, m), 7.15 - 7.24 (1H, m), 7.90 (1H, d)                                    | 381 |
| 251 | 3,5-di-F          | $\delta$ 2.60 (4H, s), 3.55 (2H, s), 3.64 (4H, s), 6.70 - 6.75 (1H, m), 6.90 - 6.92 (2H, m), 7.03 (1H, d), 7.12 (1H, t), 7.91 (1H, d)                                           | 381 |
| 252 | 2,6-di-F          | $\delta$ 2.66 (4H, s), 3.62 (4H, t), 3.79 (2H, s), 6.89 - 6.94 (2H, m), 6.99 (1H, t), 6.98 - 7.24 (1H, m), 7.23 - 7.31 (1H, m), 7.88 (1H, s)                                    | 381 |
| 253 | 2-F, 4-OMe        | $\delta$ 2.61 - 2.62 (4H, m), 3.60 - 3.63 (6H, m), 3.80 (3H, s), 6.60 - 6.64 (1H, m), 6.68 - 6.70 (1H, m), 7.01 (1H, d), 6.99 - 7.25 (1H, m), 7.24 - 7.28 (1H, m), 7.89 (1H, d) | 393 |
| 254 | 3-Br              | $\delta$ 2.59 (4H, s), 3.55 (2H, s), 3.63 (4H, s), 7.02 (1H, d), 7.12 (1H, t), 7.19 - 7.23 (1H, m), 7.28 - 7.31 (1H, m), 7.42 (1H, d), 7.52 - 7.53 (1H, m), 7.90 (1H, d)        | 423 |
| 255 | 3-CF <sub>3</sub> | $\delta$ 2.61 (4H, s), 3.63 (6H, s), 7.02 (1H, d), 7.12 (1H, t), 7.46 (1H, t), 7.55 (2H, d), 7.63 (1H, s), 7.89 - 7.92 (1H, m)                                                  | 413 |
| 256 | 2,3-di-F          | $\delta$ 2.64 (4H, t), 3.63 (4H, t), 3.68 (2H, s), 7.02 (1H, d), 7.06 - 7.16 (3H, m), 7.12 (1H, t), 7.90 (1H, d)                                                                | 381 |
| 257 | 3-OMe, 4-F        | $\delta$ 2.58 (4H, t), 3.51 (2H, d), 3.62 (4H, t), 3.91 (3H, s), 6.82 - 6.86 (1H, m), 6.99 - 7.05 (3H, m), 7.12 (1H, t), 7.89 - 7.91 (1H, m)                                    | 393 |
| 258 | 2-F, 5-OMe        | $\delta$ 2.64 (4H, t), 3.63 (4H, s), 3.64 (2H, s), 3.80 (3H, s), 6.75 - 6.79 (1H, m), 6.93 - 6.96 (1H, m), 6.97 - 6.99 (1H, m), 7.02 (1H, d), 6.99 - 7.25 (1H, m), 7.89 (1H, d) | 393 |



|     |                |                                                                                                                                                     |     |
|-----|----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------|-----|
| 259 | 2,5-di-F       | $\delta$ 2.65 (4H, s), 3.63 (6H, s), 6.92 - 6.99 (1H, m), 7.01 - 7.04 (2H, m), 7.25 (1H, t), 7.12 - 7.18 (1H, m), 7.90 (1H, s)                      | 381 |
| 260 | 3-CN, 4-F      | $\delta$ 2.59 (4H, t), 3.56 (2H, s), 3.63 (4H, t), 7.03 (1H, d), 7.12 (1H, t), 7.20 (1H, t), 7.58 - 7.62 (1H, m), 7.64 - 7.66 (1H, m), 7.91 (1H, d) | 388 |
| 261 | 3-F, 4-OMe     | $\delta$ 2.57 (4H, t), 3.50 (2H, s), 3.62 (4H, t), 3.89 (3H, s), 6.92 (1H, t), 7.02 (2H, d), 7.10 - 7.13 (1H, m), 7.12 (1H, t), 7.89 (1H, d)        | 393 |
| 262 | 2-F, 4-CN      | $\delta$ 2.64 (4H, t), 3.63 (4H, t), 3.69 (2H, s), 7.02 (1H, d), 7.12 (1H, t), 7.35 - 7.38 (1H, m), 7.46 - 7.48 (1H, m), 7.61 (1H, t), 7.91 (1H, d) | 388 |
| 263 | 2,6-di-F, 4-CN | $\delta$ 2.65 (4H, t), 3.60 - 3.62 (4H, m), 3.78 (2H, t), 7.00 (1H, t), 7.12 (1H, t), 7.24 - 7.25 (2H, m), 7.89 (1H, d)                             | 406 |

The 3-(difluoromethyl)-6-(piperazin-1-yl)-[1,2,4]triazolo[4,3-b]pyridazine used as starting material was prepared as follows:-

**Preparation of tert-butyl 4-[3-(difluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazine-1-carboxylate**

5 A stirred solution of 6-chloro-3-(difluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (3.07 g, 15 mmol), tert-butyl piperazine-1-carboxylate (3.35 g, 18.00 mmol) and DIPEA (3.85 mL, 22.50 mmol) in DMF (25 mL) was heated at 100°C for 1 hour. The reaction mixture was evaporated to dryness, redissolved in DCM and washed sequentially with 1M aqueous K<sub>2</sub>CO<sub>3</sub>, water and saturated brine. The organic layer was dried over MgSO<sub>4</sub>,  
 10 filtered and evaporated. The crude product was triturated with ether and the solid was collected by filtration, washed with ether and dried under vacuum to afford tert-butyl 4-[3-(difluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazine-1-carboxylate (5.05 g, 95%) as a white crystalline solid.

1H NMR (399.9 MHz, CDCl<sub>3</sub>)  $\delta$  1.49 (9H, s), 3.60 (8H, s), 7.04 (1H, d), 7.13 (1H, t), 7.94  
 15 (1H, d) ; m/z = 355 [M+H]<sup>+</sup>.



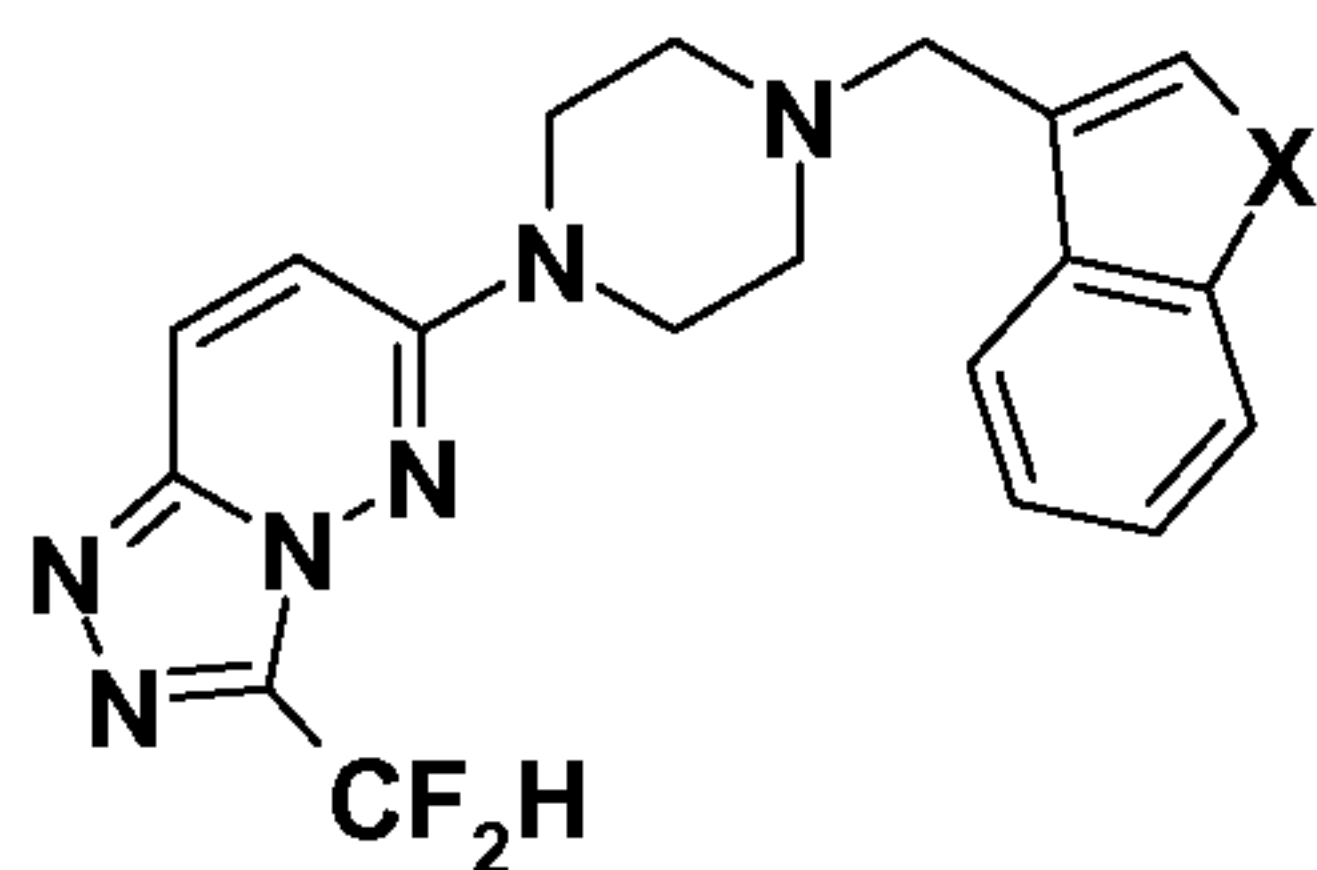
**Preparation of 3-(difluoromethyl)-6-(piperazin-1-yl)-[1,2,4]triazolo[4,3-b]pyridazine**

4M Hydrogen chloride in dioxan (10.58 mL, 42.33 mmol) was added to a stirred partial solution of tert-butyl 4-[3-(difluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazine-1-carboxylate (5.0 g, 14.11 mmol) in 1,4-dioxan (14.11 mL) at ambient temperature and the mixture was stirred for 1 hour. During this time it gave a clear solution that precipitated a gum, which crystallised on further stirring. The precipitate was collected by filtration, washed with ether and dried giving the dihydrochloride salt. This was dissolved in MeOH and adsorbed onto a SCX cartridge, then eluted with 2M ammonia in methanol. The product crystallised on evaporation and was triturated with ether. The solid was collected by filtration, washed with ether and dried under vacuum to afford 3-(difluoromethyl)-6-(piperazin-1-yl)-[1,2,4]triazolo[4,3-b]pyridazine (3.28 g, 91%) as a white crystalline solid.

<sup>1</sup>H NMR (399.9 MHz, CDCl<sub>3</sub>) δ 3.01 - 3.03 (4H, m), 3.59 (4H, t), 7.02 - 7.05 (1H, m), 7.13 (1H, t), 7.90 (1H, d) ; m/z = 255 [M+H]<sup>+</sup>.

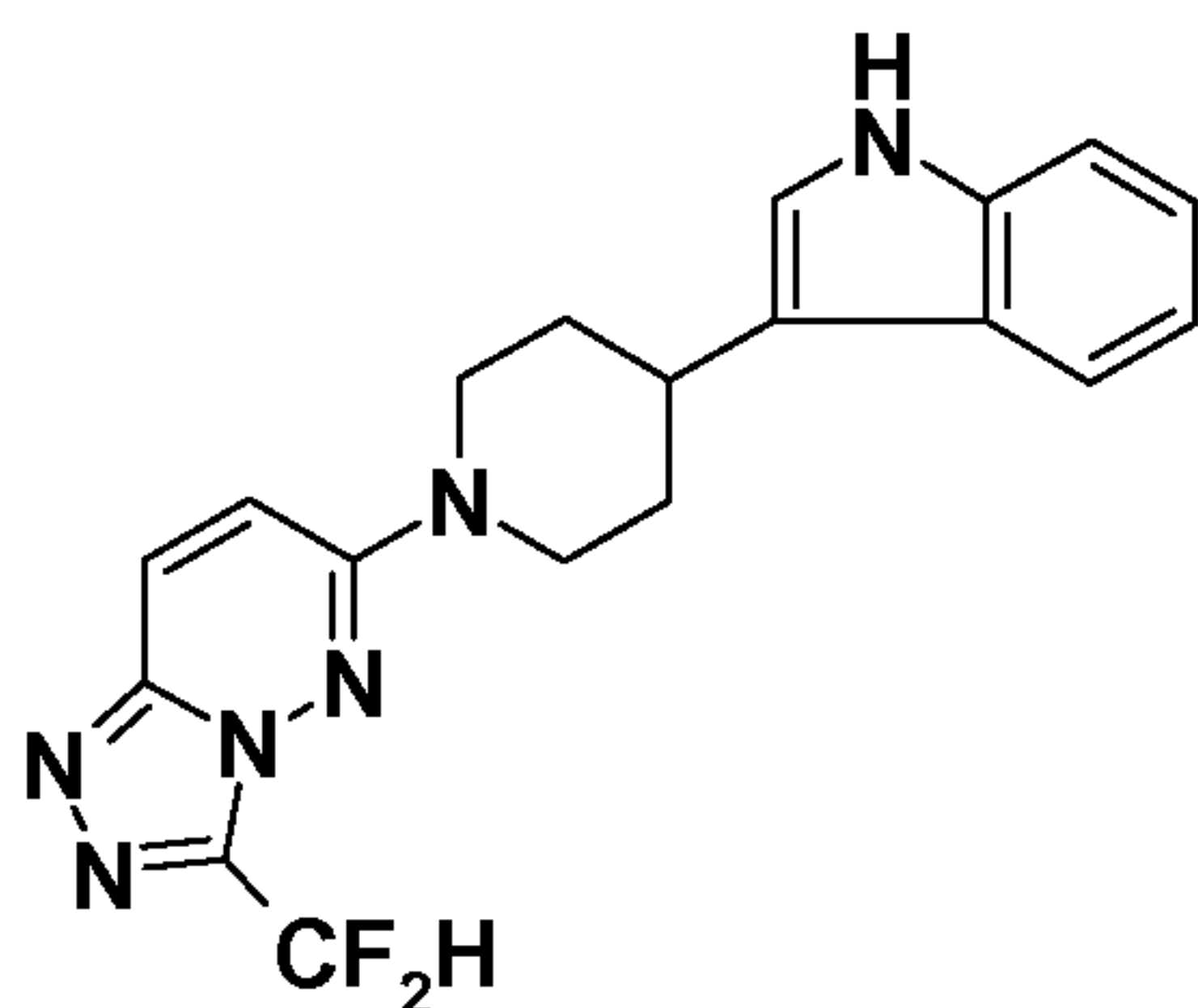
**Examples 264-265**

The following compounds were both prepared in 78% yield by General Synthetic Method 5, starting from 3-(difluoromethyl)-6-(piperazin-1-yl)-[1,2,4]triazolo[4,3-b]pyridazine (obtained as described in Examples 248-263, preparation of starting materials) and the appropriate aldehyde:-



| Ex. | X  | <sup>1</sup> H NMR (399.9 MHz, CDCl <sub>3</sub> )                                                                                                                                            | m/z [M+H] <sup>+</sup> |
|-----|----|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|
| 264 | S  | δ 2.65 (4H, t), 3.62 (4H, t), 3.83 (2H, s), 7.00 - 7.03 (1H, m), 7.25 (1H, t), 7.32 (1H, d), 7.35 - 7.41 (2H, m), 7.85 - 7.91 (2H, m), 7.98 - 8.02 (1H, m)                                    | 401                    |
| 265 | NH | δ 2.64 (4H, t), 3.61 (4H, t), 3.79 (2H, d), 7.00 (1H, d), 6.98 - 7.25 (1H, m), 7.12 - 7.16 (2H, m), 7.20 - 7.24 (1H, m), 7.37 - 7.40 (1H, m), 7.75 - 7.78 (1H, m), 7.87 (1H, d), 8.13 (1H, s) | 384                    |



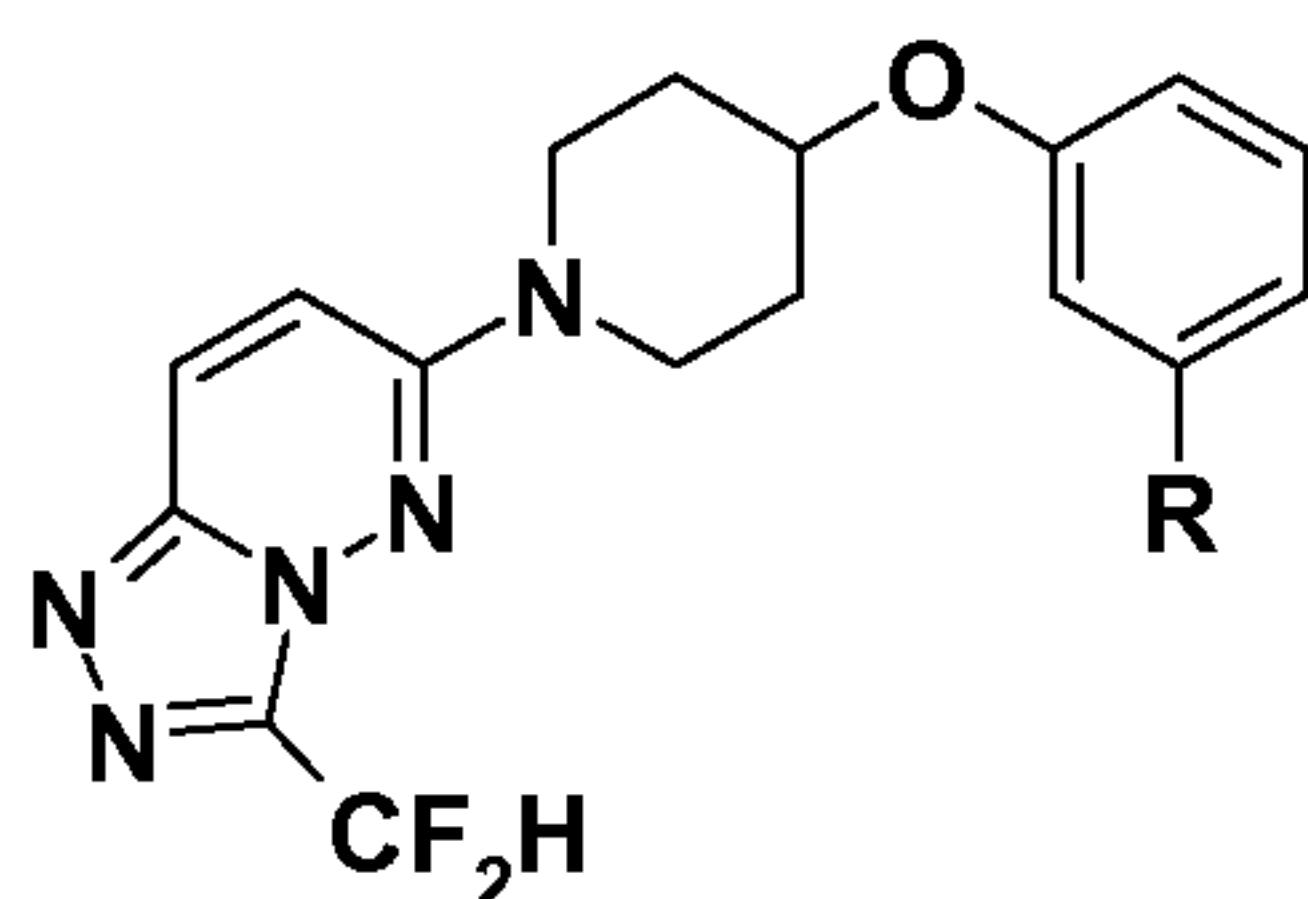
**Example 266****Preparation of 3-(difluoromethyl)-6-[4-(1H-indol-3-yl)piperidin-1-yl][1,2,4]triazolo[4,3-b]pyridazine**

- 5 A mixture of 3-(piperidin-4-yl)-1H-indole and 3-(difluoromethyl)-6-(piperazin-1-yl)-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by an analogous method to Example 216 to give 3-(difluoromethyl)-6-[4-(1H-indol-3-yl)piperidin-1-yl][1,2,4]triazolo[4,3-b]pyridazine in 85% yield.

1H NMR (399.9 MHz, CDCl<sub>3</sub>)  $\delta$  1.81 - 1.92 (2H, m), 2.23 - 2.26 (2H, m), 3.17 (1H, t),  
 10 3.18 - 3.25 (2H, m), 4.36 (2H, s), 6.99 - 6.99 (1H, m), 7.09 - 7.15 (2H, m), 7.15 (1H, t),  
 7.19 - 7.23 (1H, m), 7.38 - 7.40 (1H, m), 7.65 (1H, s), 7.90 (1H, s), 8.04 (1H, s); m/z = 369 [M+H]<sup>+</sup>.

**Examples 267-268**

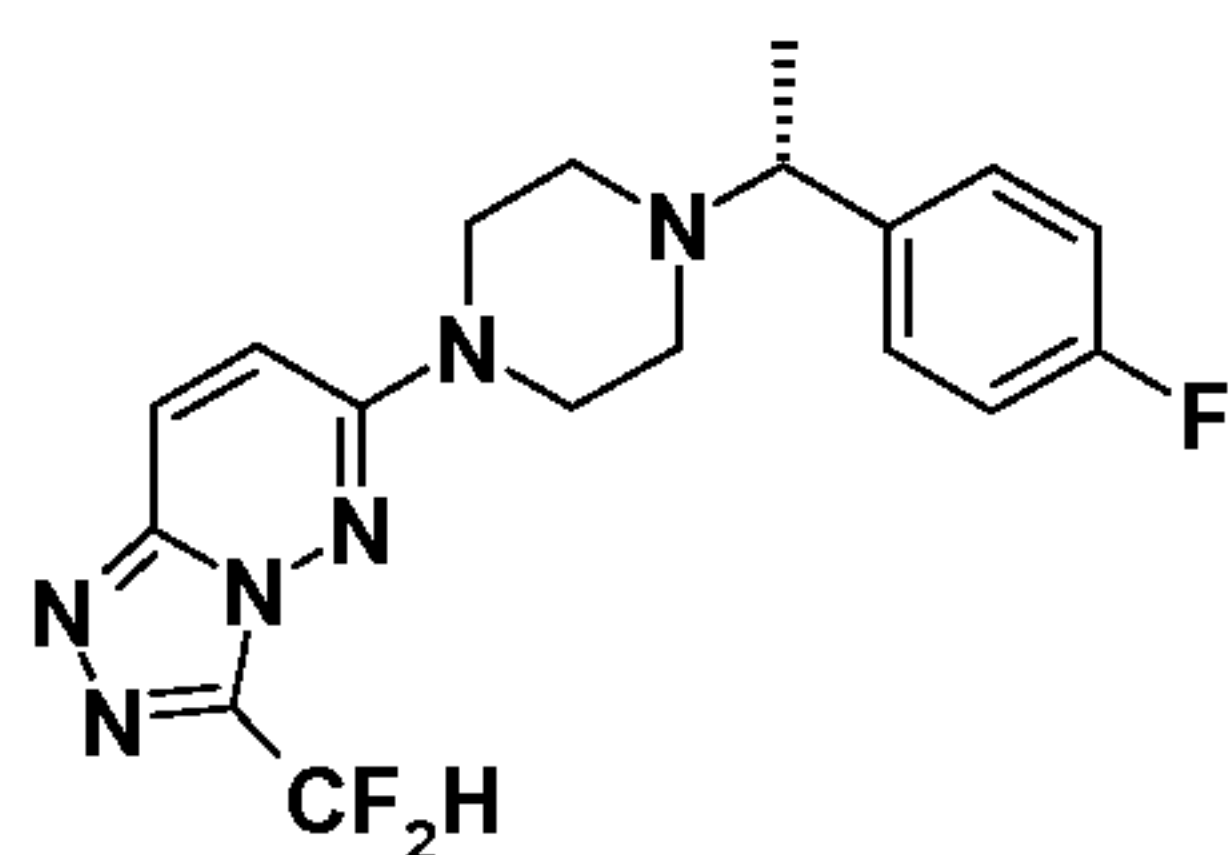
- The following compounds were prepared in 83-89% yield by an analogous method to  
 15 Example 216, starting from 3-(difluoromethyl)-6-(piperazin-1-yl)-[1,2,4]triazolo[4,3-b]pyridazine and the appropriate 4-aryloxy piperidine:-



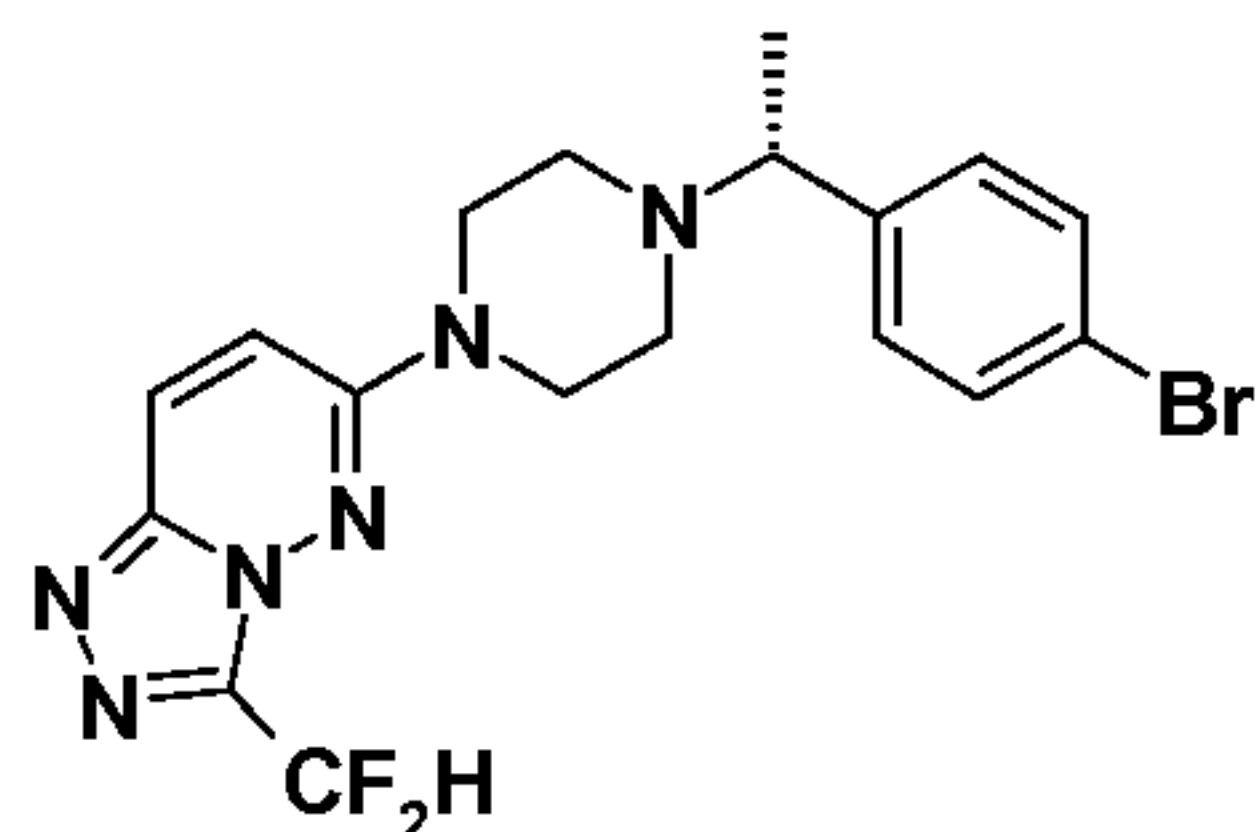
| Ex. | R   | <sup>1</sup> H NMR (399.9 MHz, CDCl <sub>3</sub> )                                                                                                                                               | m/z [M+H] <sup>+</sup> |
|-----|-----|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|
| 267 | OMe | $\delta$ 1.94 - 2.10 (4H, m), 3.62 - 3.68 (2H, m), 3.80 (3H, s),<br>3.82 - 3.86 (2H, m), 4.58 - 4.62 (1H, m), 6.49 - 6.56 (3H, m), 7.07 (1H, d), 7.00 - 7.26 (1H, m), 7.20 (1H, t), 7.91 (1H, d) | 376                    |
| 268 | F   | $\delta$ 1.94 - 2.11 (4H, m), 3.63 - 3.69 (2H, m), 3.79 - 3.85 (2H, m), 7.00 - 7.26 (1H, m), 7.20 (1H, t), 7.91 (1H, d)                                                                          | 364                    |



|  |  |                                                                                                         |  |
|--|--|---------------------------------------------------------------------------------------------------------|--|
|  |  | m), 4.58 - 4.62 (1H, m), 6.63 - 6.73 (3H, m), 7.08 (1H, d),<br>7.13 (1H, t), 7.24 (1H, q), 7.91 (1H, d) |  |
|--|--|---------------------------------------------------------------------------------------------------------|--|

**Example 269****Preparation of 3-(difluoromethyl)-6-[4-[(1R)-1-(4-fluorophenyl)ethyl]piperazin-1-yl][1,2,4]triazolo[4,3-b]pyridazine**

- 5 A stirred solution of 6-chloro-3-(difluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (103 mg, 0.5 mmol), (R)-1-[1-(4-fluorophenyl)ethyl]piperazine (125 mg, 0.6 mmol) (prepared as described in J. Med. Chem. 2007, 50, 3528) and DIPEA (97 mg, 0.75 mmol, 129  $\mu$ l) in DMF (2 mL) was heated at 100°C for 2 hours. The crude product was purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5 $\mu$  silica, 19 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 1% ammonia) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford 3-(difluoromethyl)-6-[4-[(1R)-1-(4-fluorophenyl)ethyl]piperazin-1-yl][1,2,4]triazolo[4,3-b]pyridazine (158 mg, 84%) as a crisp foam.
- 1H NMR (399.9 MHz, CDCl<sub>3</sub>)  $\delta$  1.38 (3H, d), 2.48 - 2.54 (2H, m), 2.59 - 2.64 (2H, m), 3.43 (1H, q), 3.54 - 3.62 (4H, m), 6.99 - 7.05 (3H, m), 7.12 (1H, t), 7.28 - 7.31 (2H, m), 7.88 (1H, d); m/z = 377 [M+H]<sup>+</sup>.

**Example 270****Preparation of 6-[4-[(1R)-1-(4-bromophenyl)ethyl]piperazin-1-yl]-3-(difluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

20

A mixture of (R)-1-[1-(4-bromophenyl)ethyl]piperazine and 6-chloro-3-difluoromethyl-[1,2,4]-triazolo[4,3-b]pyridazine was allowed to react by an analogous method to Example



269 to give 6-[4-[(1R)-1-(4-bromophenyl)ethyl]piperazin-1-yl]-3-(difluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine in 75% yield.

<sup>1</sup>H NMR (399.9 MHz, CDCl<sub>3</sub>) δ 1.37 (3H, d), 2.49 - 2.54 (2H, m), 2.60 - 2.65 (2H, m), 3.41 (1H, q), 3.53 - 3.62 (4H, m), 6.99 (1H, d), 7.12 (1H, t), 7.20 - 7.24 (2H, m), 7.44 -  
5 7.48 (2H, m), 7.88 (1H, d); m/z = 437 [M+H]<sup>+</sup>.

The (R)-1-[1-(4-bromophenyl)ethyl]piperazine used as starting material was prepared as follows:-

#### **Preparation of (R)-1-[1-(4-bromophenyl)ethyl]-4-tosylpiperazine**

N,N-Bis(2-chloroethyl)-4-methylbenzenesulfonamide (4.0 g, 13.50 mmol) and (R)-  
10 1-(4-bromophenyl)ethanamine (2.57 g, 12.83 mmol) in DIPEA (5 mL) were stirred and heated at 125°C for 32 hours. The resulting dark mixture was cooled to 80°C then a mixture of EtOH / water (70/30, 20 mL) added slowly to give a brown precipitate. The precipitate was collected by filtration, washed with EtOH / water (70/30) and iso-hexane and air dried to afford (R)-1-[1-(4-bromophenyl)ethyl]-4-tosylpiperazine (4.45 g, 78%) as  
15 a brown solid, which was used without further purification.

<sup>1</sup>H NMR (399.9 MHz, CDCl<sub>3</sub>) δ 1.27 (3H, d), 2.40 - 2.45 (5H, m), 2.52 - 2.57 (2H, m), 2.97 (4H, m), 3.32 (1H, q), 7.10 (2H, d), 7.32 (2H, d), 7.40 (2H, d), 7.62 (2H, d); m/z = 423/425 [M+H]<sup>+</sup>.

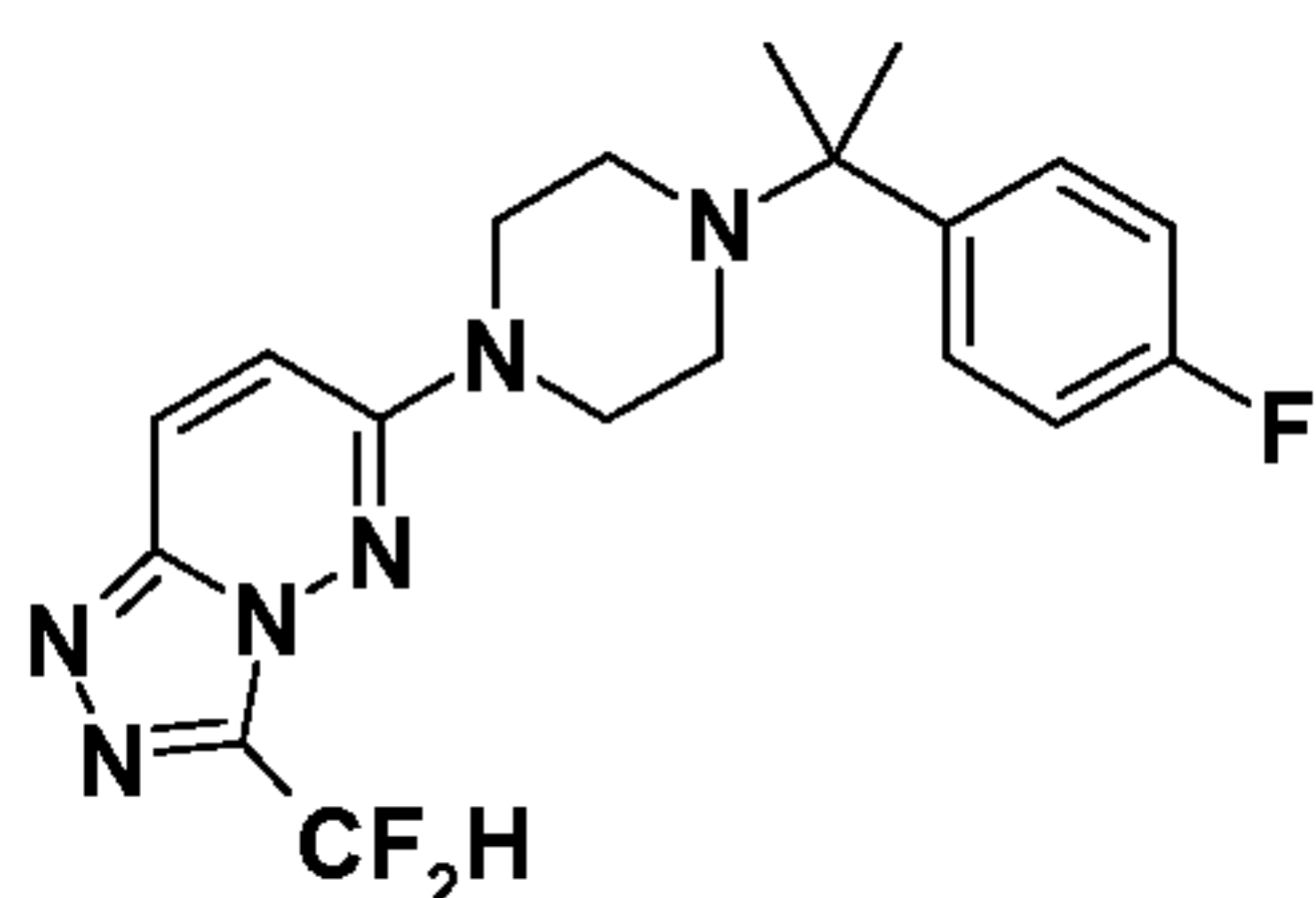
#### **Preparation of (R)-1-[1-(4-bromophenyl)ethyl]piperazine**

(R)-1-(1-(4-Bromophenyl)ethyl)-4-tosylpiperazine (4.44 g, 10.49 mmol) and 4-  
20 hydroxybenzoic acid (4.35 g, 31.46 mmol) in hydrobromic acid (33% in AcOH, 40 mL,) were stirred at room temperature for 48 hours. Water (40 mL) was then added to the dark mixture and stirring continued for a further 2 hours to give a beige solid, which was filtered off and washed with water (10 mL). The combined filtrate and washings were  
25 washed with toluene (3 x 50 mL) then cooled to 5°C and basified to pH >10 with 40% NaOH. The resulting mixture was extracted with tert butyl methyl ether (2 x 50 mL) and the combined extracts washed with saturated brine, dried over MgSO<sub>4</sub> and evaporated to give (R)-1-[1-(4-bromophenyl)ethyl]piperazine (2.69 g, 95%) as an orange, viscous oil.  
30 <sup>1</sup>H NMR (399.9 MHz, CDCl<sub>3</sub>) δ 1.31 (3H, d), 2.29 - 2.35 (2H, m), 2.37 - 2.48 (2H, m), 2.85 (4H, t), 3.30 (1H, q), 7.19 (2H, d), 7.42 (2H, d); m/z = 269/271 [M+H]<sup>+</sup>.

#### **Example 271**

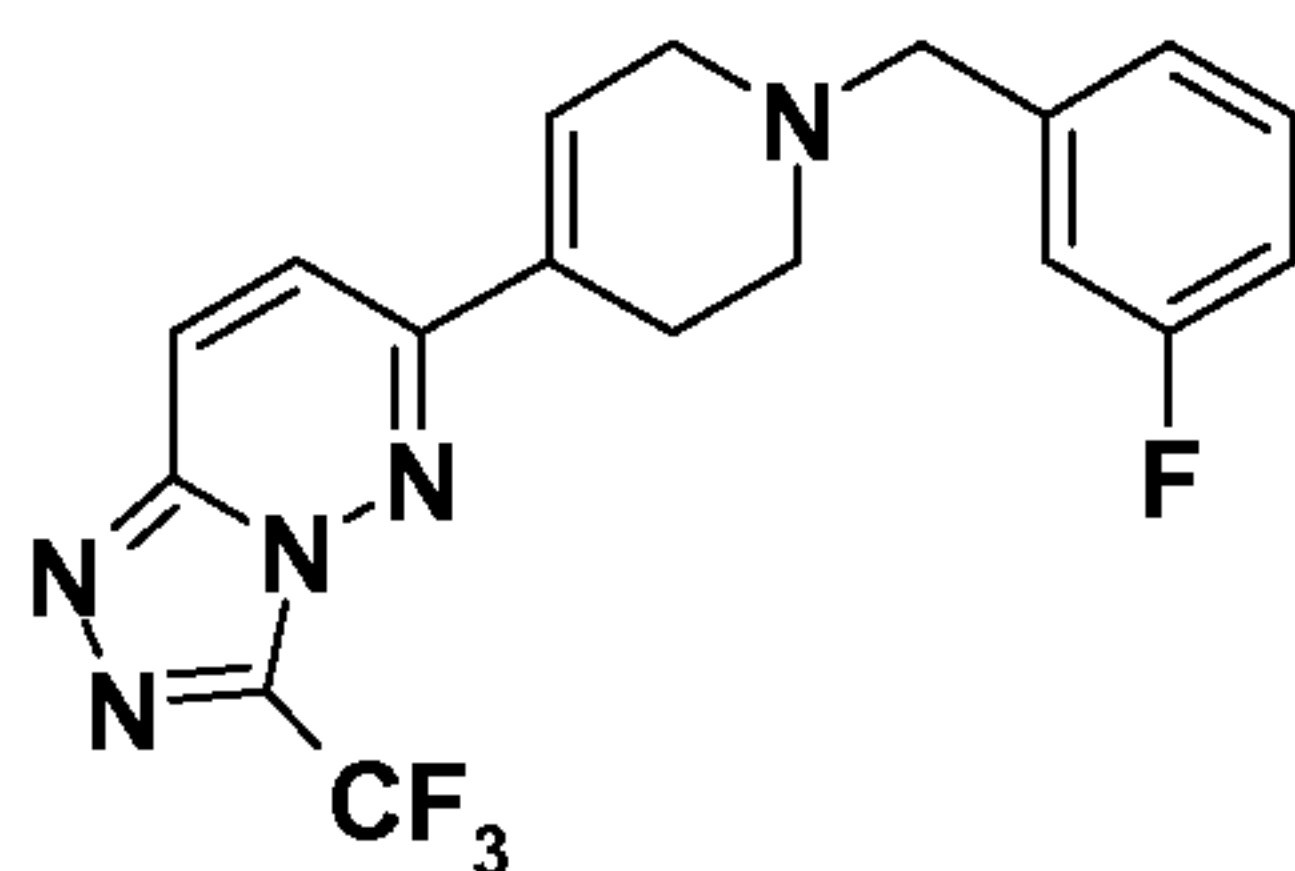
#### **Preparation of 3-(difluoromethyl)-6-[4-[1-(4-fluorophenyl)-1-methylethyl]piperazin-**



**1-yl][1,2,4]triazolo[4,3-b]pyridazine**

A mixture of 1-[1-(4-fluorophenyl)-1-methyl-ethyl]piperazine (obtained as described in J. Med. Chem. 2007, 50, 3528) and 6-chloro-3-(difluoromethyl)-[1,2,4]-triazolo[4,3-b]pyridazine was allowed to react by an analogous method to Example 269 to give 3-(difluoromethyl)-6-[4-[1-(4-fluorophenyl)-1-methylethyl]piperazin-1-yl][1,2,4]triazolo[4,3-b]pyridazine in 62% yield.

<sup>1</sup>H NMR (399.9 MHz, CDCl<sub>3</sub>) δ 1.37 (6H, s), 2.61 (4H, t), 3.56 (4H, t), 6.98 - 7.02 (3H, m), 6.98 - 7.24 (1H, m), 7.49 - 7.53 (2H, m), 7.86 - 7.89 (1H, m); m/z = 391 [M+H]<sup>+</sup>.

**Example 272****Preparation of 6-[1-(3-fluorobenzyl)-1,2,3,6-tetrahydropyridin-4-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine**

A mixture of 3-fluorobenzaldehyde and 6-(3,6-dihydro-2H-pyridin-4-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by General Synthetic Method 5 to give 6-[1-(3-fluorobenzyl)-1,2,3,6-tetrahydropyridin-4-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine in 46% yield.

<sup>1</sup>H NMR (399.9 MHz, CDCl<sub>3</sub>) δ 2.76 (4H, s), 3.29 (2H, d), 3.67 (2H, s), 6.72 (1H, t), 6.95 - 7.00 (1H, m), 7.10 - 7.15 (2H, m), 7.27 - 7.33 (1H, m), 7.54 (1H, d), 8.11 (1H, d); m/z = 376 [M-H]<sup>-</sup>.

The 6-(3,6-dihydro-2H-pyridin-4-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine used as starting material was prepared as follows:-

**Preparation of tert-butyl 4-(6-chloropyridazin-3-yl)-5,6-dihydropyridine-1(2H)-carboxylate**



Saturated aqueous NaHCO<sub>3</sub> solution (10 mL) was added to a stirred solution of 3,6-dichloropyridazine (0.968 g, 6.5 mmol), tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydropyridine-1(2H)-carboxylate (2.010 g, 6.50 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.376 g, 0.33 mmol) in DME (20 mL). The vessel was flushed with nitrogen and the initial suspension was heated at 80°C for 9 hours. The reaction mixture was diluted with DCM and washed with water. The organic phase was dried over MgSO<sub>4</sub> and evaporated. The crude product was purified by MPLC silica chromatography, elution gradient 35 to 45% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford tert-butyl 4-(6-chloropyridazin-3-yl)-5,6-dihydropyridine-1(2H)-carboxylate (0.929 g, 48.3%) as a colourless crystalline solid. <sup>1</sup>H NMR (399.9 MHz, CDCl<sub>3</sub>) δ 1.50 (9H, s), 2.77 - 2.78 (2H, m), 3.67 (2H, t), 4.18 (2H, q), 6.62 (1H, s), 7.45 (1H, d), 7.55 (1H, d); m/z = 240 [M+H-butylene]<sup>+</sup>.

**Preparation of tert-butyl 4-(6-hydrazinylpyridazin-3-yl)-5,6-dihydropyridine-1(2H)-carboxylate**

A stirred mixture of tert-butyl 4-(6-chloropyridazin-3-yl)-5,6-dihydropyridine-1(2H)-carboxylate (870 mg, 2.94 mmol) and hydrazine hydrate (4.29 mL, 88.25 mmol) in acetonitrile (15 mL) was heated at 80°C for 4 hours. The mixture was partially evaporated (removing MeCN) and diluted with water (10 mL). The reaction mixture was extracted with DCM (3 x 50 mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated to afford crude product as a gum, which crystallised on trituration with ether. The precipitate was collected by filtration, washed with ether and dried under vacuum to afford tert-butyl 4-(6-hydrazinylpyridazin-3-yl)-5,6-dihydropyridine-1(2H)-carboxylate (503 mg, 58.7%) as a cream crystalline solid.

<sup>1</sup>H NMR (399.9 MHz, CDCl<sub>3</sub>) δ 1.49 (9H, s), 2.76 - 2.79 (2H, m), 3.65 (2H, t), 4.00 (2H, s), 4.13 (2H, q), 6.07 (1H, s), 6.33 - 6.35 (1H, m), 6.95 (1H, d), 7.43 (1H, d); m/z = 292 [M+H]<sup>+</sup>.

**Preparation of 6-(1,2,3,6-tetrahydropyridin-4-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

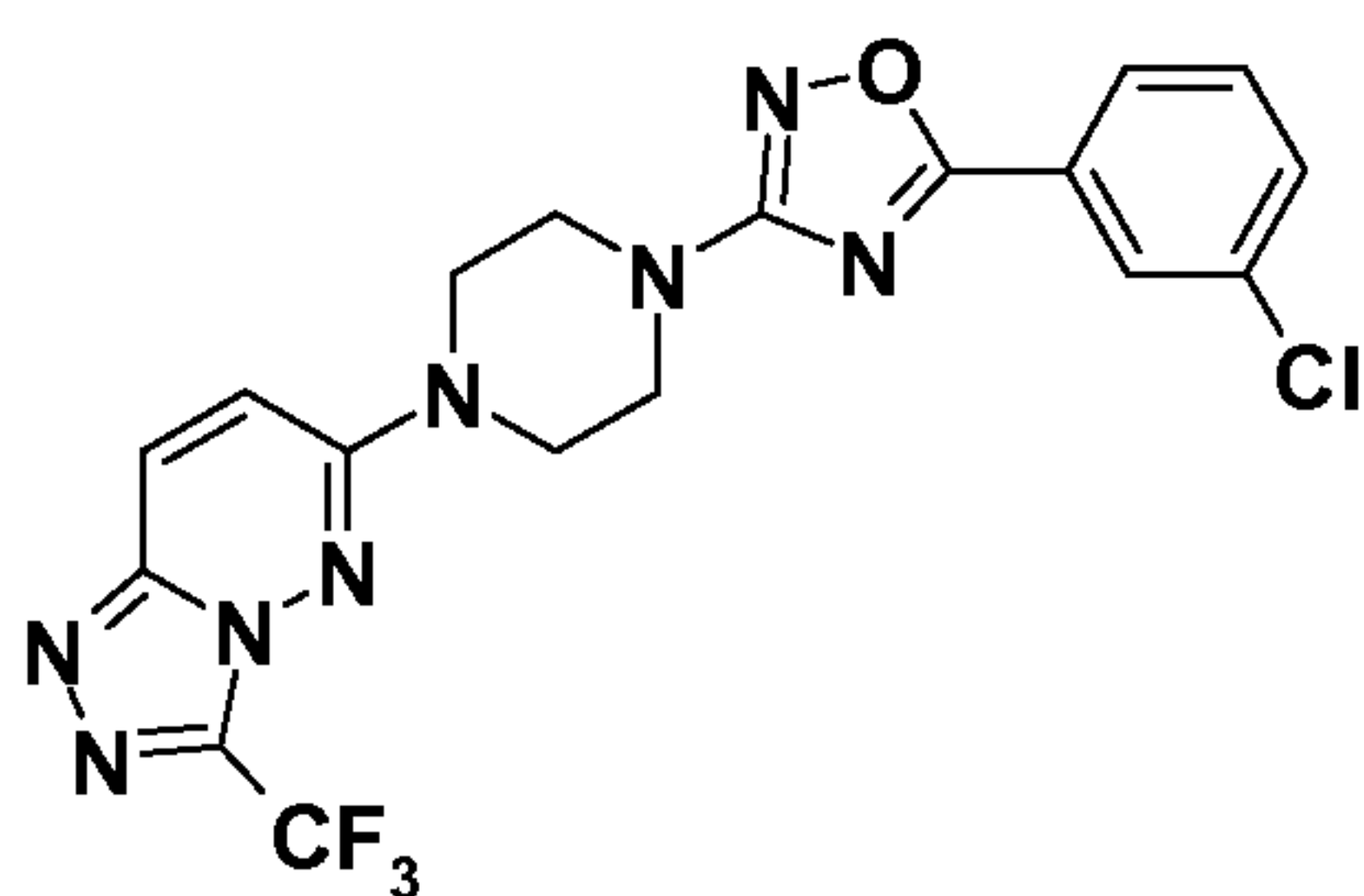
TFA (2 mL) was added in one portion to tert-butyl 4-(6-hydrazinylpyridazin-3-yl)-5,6-dihydropyridine-1(2H)-carboxylate (480 mg, 1.65 mmol) which dissolved with a vigorous effervescence. The solution was stirred for 24 hours at 70°C. The solution was evaporated and the residue was dissolved in methanol. It was run on an SCX cartridge,



eluting with 2M ammonia in methanol. Product containing fractions were evaporated to dryness and triturated with ether to afford 6-(1,2,3,6-tetrahydropyridin-4-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (90 mg, 20.29%) as a cream solid. 1H NMR (399.9 MHz, DMSO-d<sub>6</sub>)  $\delta$  2.79 (2H, s), 3.37 (2H, t), 3.91 (2H, s), 6.99 (1H, s), 7.96 (1H, d), 8.49 (1H, d), NH not observed; m/z = 270 [M+H]<sup>+</sup>.

### **Example 273**

#### **Preparation of 6-[4-[5-(3-chlorophenyl)-1,2,4-oxadiazol-3-yl]piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine**



- 3-Chlorobenzoyl chloride (92 mg, 0.53 mmol) was added to a stirred partial solution of N-hydroxy-4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazine-1-carboximidamide (165 mg, 0.5 mmol) and DIPEA (97 mg, 0.75 mmol) in THF (3 mL). The reaction mixture became a clear solution over 30 minutes and LCMS after 1 hour showed complete initial acylation. The reaction mixture was heated at 150°C for 15 minutes by microwave after which LCMS showed complete cyclisation to the desired product. The reaction mixture was evaporated and the residue was boiled briefly with ethanol, cooled and filtered off to give 6-[4-[5-(3-chlorophenyl)-1,2,4-oxadiazol-3-yl]piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine (104 mg, 46%) as a crystalline powder.
- 1H NMR (399.9 MHz, DMSO-d<sub>6</sub>)  $\delta$  3.60 - 3.63 (4H, m), 3.78 - 3.81 (4H, m), 7.65 - 7.69 (2H, m), 7.77 - 7.80 (1H, m), 8.01 - 8.06 (2H, m), 8.32 (1H, d); m/z = 451 [M+H]<sup>+</sup>.

The N-hydroxy-4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazine-1-carboximidamide used as starting material was prepared in as follows:-

#### **Preparation of 4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazine-1-carbonitrile**

A stirred solution of 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (3.48 g, 15.65 mmol), piperazine-1-carbonitrile (2 g, 17.99 mmol) and DIPEA (3.54 mL, 20.34 mmol) in DMF (20 mL) was heated at 70°C for 1 hour. The solution was evaporated



and partitioned between DCM and 1M aqueous  $K_2CO_3$ . The organic phase was washed with brine, dried over  $MgSO_4$ , evaporated and triturated with ether. The precipitate was collected by filtration, washed with ether and dried under vacuum to afford 4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazine-1-carbonitrile (4.29 g, 92%) as a cream crystalline solid.

$^1H$  NMR (399.9 MHz,  $CDCl_3$ )  $\delta$  3.41 - 3.43 (4H, m), 3.75 (4H, t), 7.05 (1H, d), 8.02 (1H, d);  $m/z$  = 298  $[M+H]^+$ .

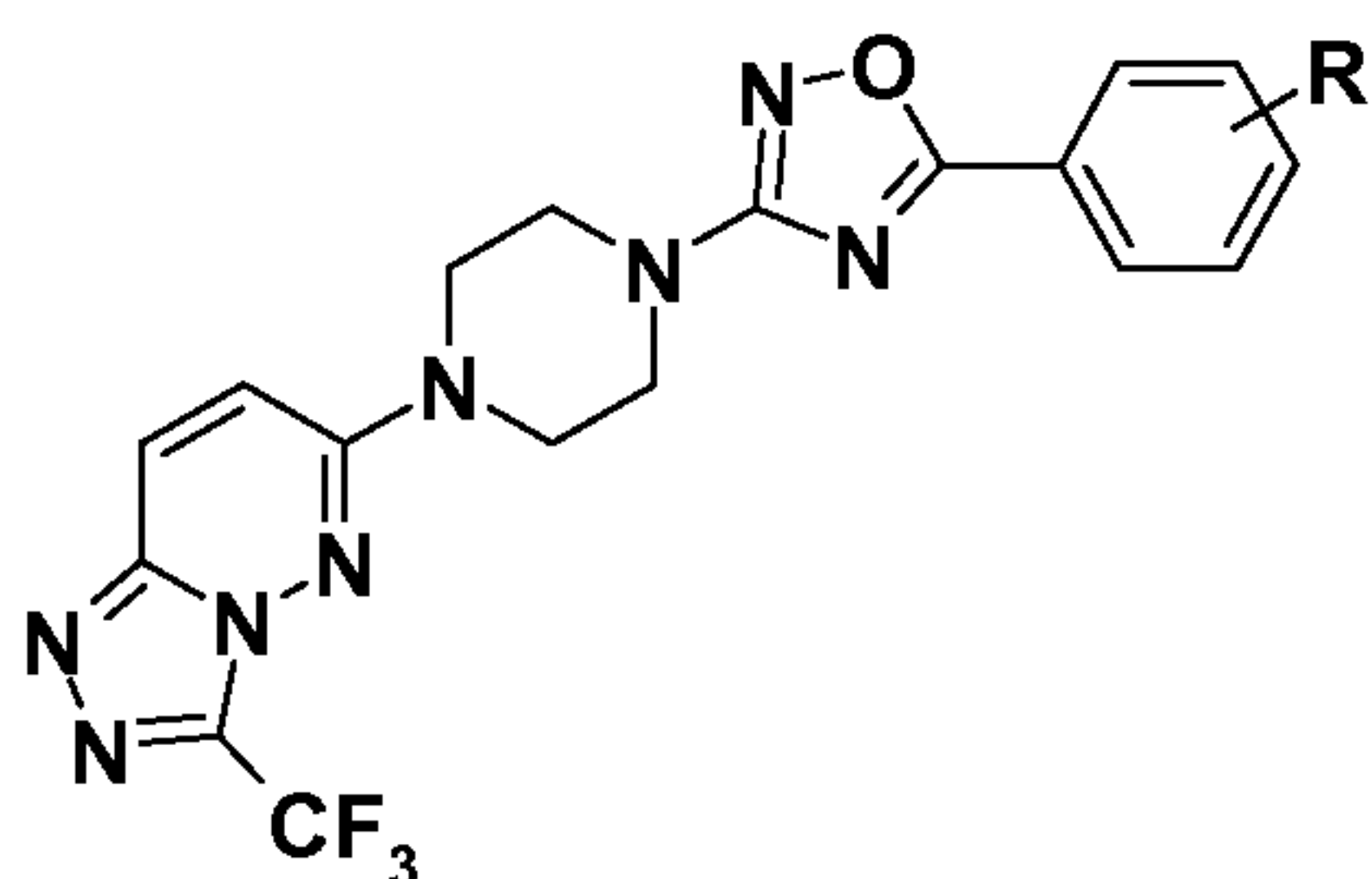
### Preparation of N-hydroxy-4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazine-1-carboximidamide

Hydroxylamine (50% w/v aqueous solution) (0.667 mL, 10.09 mmol) was added to a stirred suspension of 4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazine-1-carbonitrile (2.5 g, 8.41 mmol) in ethanol (16.82 mL) and the suspension was stirred at ambient temperature. Over 20 minutes the starting material largely dissolved and the product began to crystallise. The mixture was stirred for 2 hours and the precipitate was collected by filtration, washed with EtOH followed by ether and dried under vacuum to afford N-hydroxy-4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazine-1-carboximidamide (2.410 g, 87%) as a colourless crystalline solid.

$^1H$  NMR (399.9 MHz,  $DMSO-d_6$ )  $\delta$  3.15 (3H, t), 3.44 - 3.47 (1H, m), 3.58 - 3.63 (4H, m), 5.24 - 5.26 (1H, m), 6.09 & 8.37 (1H, 2S), 7.63 (1H, d), 8.26 - 8.29 (1H, m), 8.38 (1H, s), one exchangeable not observed);  $m/z$  = 331  $[M+H]^+$ .

### Examples 274-277

The following compounds were prepared in 43-55% yield by an analogous method to Example 273, starting from N-hydroxy-4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazine-1-carboximidamide and the appropriate benzoyl chloride:-



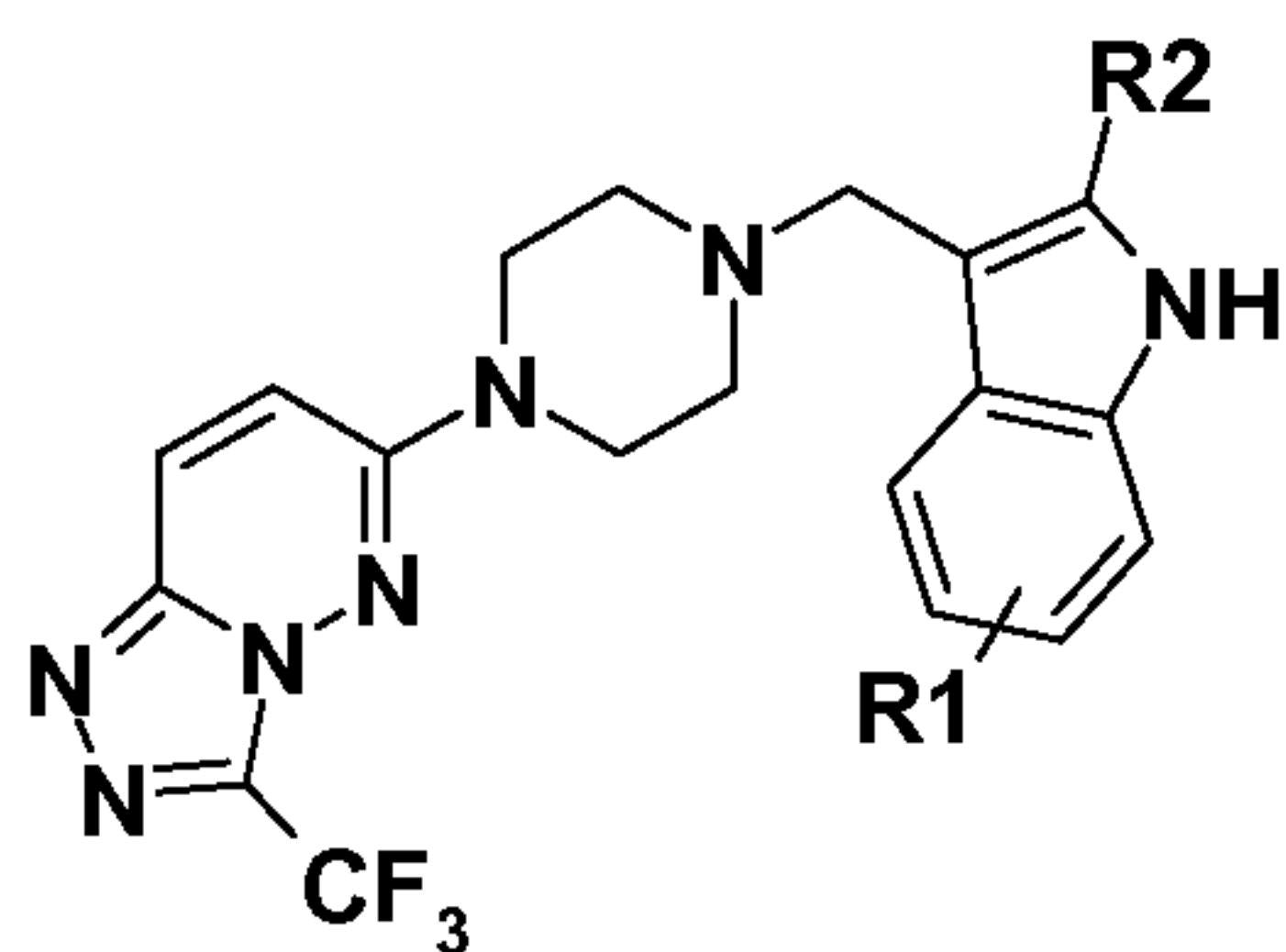
| Ex. | R   | $^1H$ NMR (399.9 MHz, $DMSO-d_6$ )                             | $m/z$ $[M+H]^+$ |
|-----|-----|----------------------------------------------------------------|-----------------|
| 274 | 4-F | $\delta$ 3.59 - 3.62 (4H, m), 3.78 - 3.81 (4H, m), 7.45 - 7.50 | 433             |



|     |      |                                                                                                                                              |        |
|-----|------|----------------------------------------------------------------------------------------------------------------------------------------------|--------|
|     |      | (2H, m), 7.66 (1H, d), 8.11 - 8.15 (2H, m), 8.32 (1H, d)                                                                                     | [M-H]- |
| 275 | H    | 3.60 - 3.63 (4H, m), 3.78 - 3.81 (4H, m), 7.61 - 7.73 (4H, m), 8.05 - 8.08 (2H, m), 8.31 - 8.34 (1H, m)                                      | 417    |
| 276 | 3-F  | $\delta$ 3.60 - 3.63 (4H, m), 3.79 - 3.81 (4H, m), 7.58 (1H, d), 7.65 - 7.70 (2H, m), 7.82 - 7.85 (1H, m), 7.91 - 7.93 (1H, m), 8.33 (1H, s) | 435    |
| 277 | 4-CN | $\delta$ 3.61 - 3.64 (4H, m), 3.79 - 3.81 (4H, m), 7.67 (1H, d), 8.09 - 8.12 (2H, m), 8.21 - 8.24 (2H, m), 8.33 (1H, d)                      | 442    |

**Examples 278-284**

The following compounds were prepared in 9-71% yield by General Synthetic Method 5, starting from 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine and the appropriate indole-3-carboxaldehyde:-



5

| Ex. | R1   | R2 | <sup>1</sup> H NMR (399.9 MHz, DMSO-d <sub>6</sub> )                                                                                                                      | m/z [M+H] <sup>+</sup> |
|-----|------|----|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|
| 278 | 5-CN | H  | $\delta$ 2.55 (4H, t), 3.61 (4H, t), 3.75 (2H, s), 7.42 - 7.45 (1H, m), 7.50 (1H, s), 7.53 - 7.55 (1H, m), 7.57 (1H, d), 8.20 - 8.20 (1H, m), 8.23 (1H, d), 11.55 (1H, s) | 427                    |
| 279 | H    | Me | [1] $\delta$ 2.44 (3H, s), 2.62 (4H, t), 3.60 (4H, t), 3.71 (2H, s), 7.04 (1H, d), 7.08 - 7.16 (2H, m), 7.28 - 7.31 (1H, m), 7.65 (1H, d), 7.89 (2H, m)                   | 416                    |
| 280 | 5-Cl | H  | $\delta$ 2.53 - 2.57 (4H, m), 3.60 (4H, t), 3.69 (2H, s), 7.07 - 7.10 (1H, m), 7.35 - 7.40 (2H, m), 7.57 (1H, d), 7.69 (1H, d), 8.23 (1H, d), 11.16 (1H, s)               | 436                    |
| 281 | 5-Br | H  | $\delta$ 2.53 - 2.57 (4H, m), 3.60 (4H, t), 3.68 (2H, s), 7.18 - 7.21 (1H, m), 7.34 - 7.36 (2H, m), 7.58 (1H, d), 7.83 (1H, d), 8.23 (1H, d), 11.17 (1H, s)               | 480                    |
| 282 | 4-Cl | H  | $\delta$ 2.56 - 2.61 (4H, m), 3.60 (4H, s), 3.86 (2H, s),                                                                                                                 | 436                    |

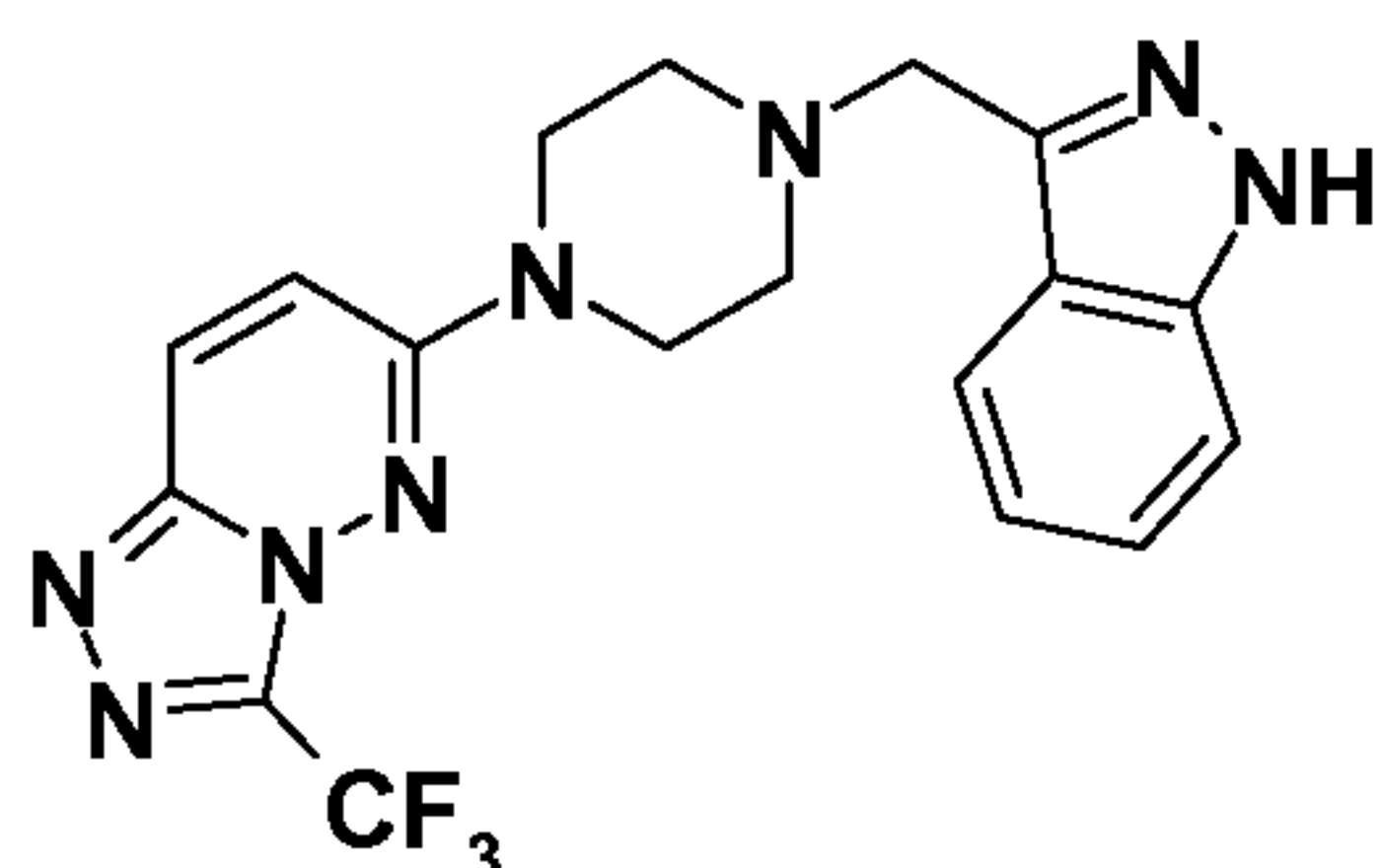


|     |     |   |                                                                                                                                                                                  |     |
|-----|-----|---|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
|     |     |   | 7.00 - 7.07 (2H, m), 7.34 - 7.37 (2H, m), 7.59 (1H, d), 8.24 (1H, d), 11.33 (1H, s)                                                                                              |     |
| 283 | 5-F | H | $\delta$ 2.54 - 2.57 (4H, m), 3.60 (4H, t), 3.68 (2H, s), 6.90 - 6.95 (1H, m), 7.34 - 7.41 (3H, m), 7.57 (1H, d), 8.23 (1H, d), 11.05 (1H, s)                                    | 420 |
| 284 | 6-F | H | $\delta$ 2.54 - 2.57 (4H, m), 3.60 (4H, t), 3.69 (2H, s), 6.83 - 6.89 (1H, m), 7.12 - 7.15 (1H, m), 7.27 (1H, d), 7.57 (1H, d), 7.64 - 7.68 (1H, m), 8.23 (1H, d), 11.01 (1H, s) | 420 |

[1] Spectrum recorded in CDCl<sub>3</sub>

### **Example 285**

#### **Preparation of 6-[4-(1H-indazol-3-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine**



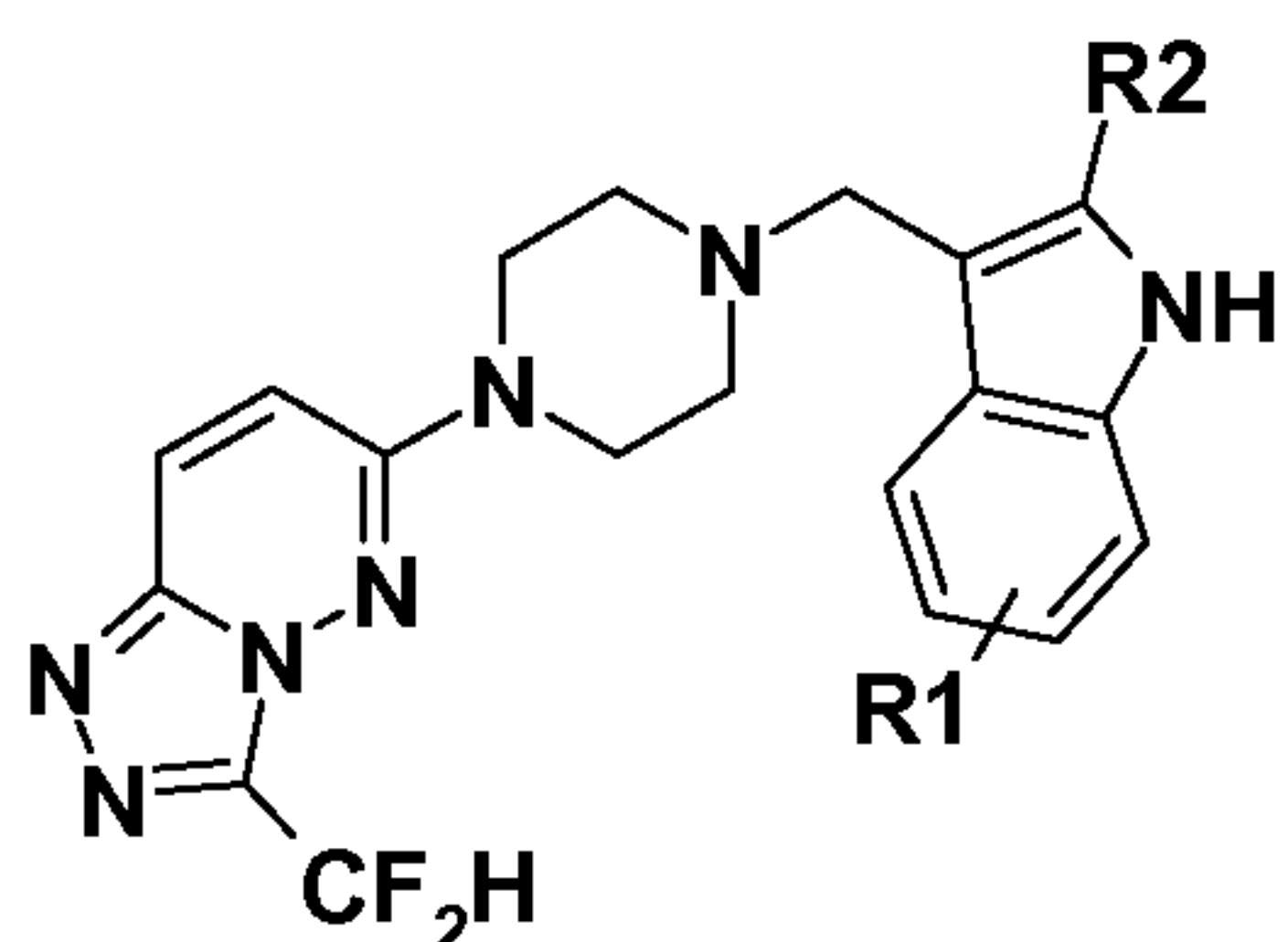
1H-Indazole-3-carboxaldehyde (75 mg, 0.51 mmol) and (polystyrylmethyl)trimethylammonium cyanoborohydride (125 mg, 0.51 mmol) were added to a solution of 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (100 mg, 0.37 mmol) in DCM (2 mL) / acetic acid (0.2 mL). The mixture was stirred at ambient temperature for 18 hours. The resin was filtered off and the filtrate was evaporated. The crude product was purified by preparative HPLC (Waters XTerra C18 column, 5 $\mu$  silica, 19 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 1% ammonia) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford 6-[4-(1H-indazol-3-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine (89 mg, 60%) as a white solid.

<sup>1</sup>H NMR (399.9 MHz, DMSO-d<sub>6</sub>)  $\delta$  2.60 (4H, t), 3.61 (4H, t), 3.92 (2H, s), 7.09 - 7.13 (1H, m), 7.33 - 7.36 (1H, m), 7.50 (1H, d), 7.57 (1H, d), 7.90 (1H, d), 8.23 (1H, d), 12.85 (1H, s); m/z = 403 [M+H]<sup>+</sup>.



**Examples 286-292**

The following compounds were prepared in 57-74% yield by by General Synthetic Method 5, starting from 3-(difluoromethyl)-6-(piperazin-1-yl)-[1,2,4]triazolo[4,3-b]pyridazine and the appropriate indole-3-carboxaldehyde:-

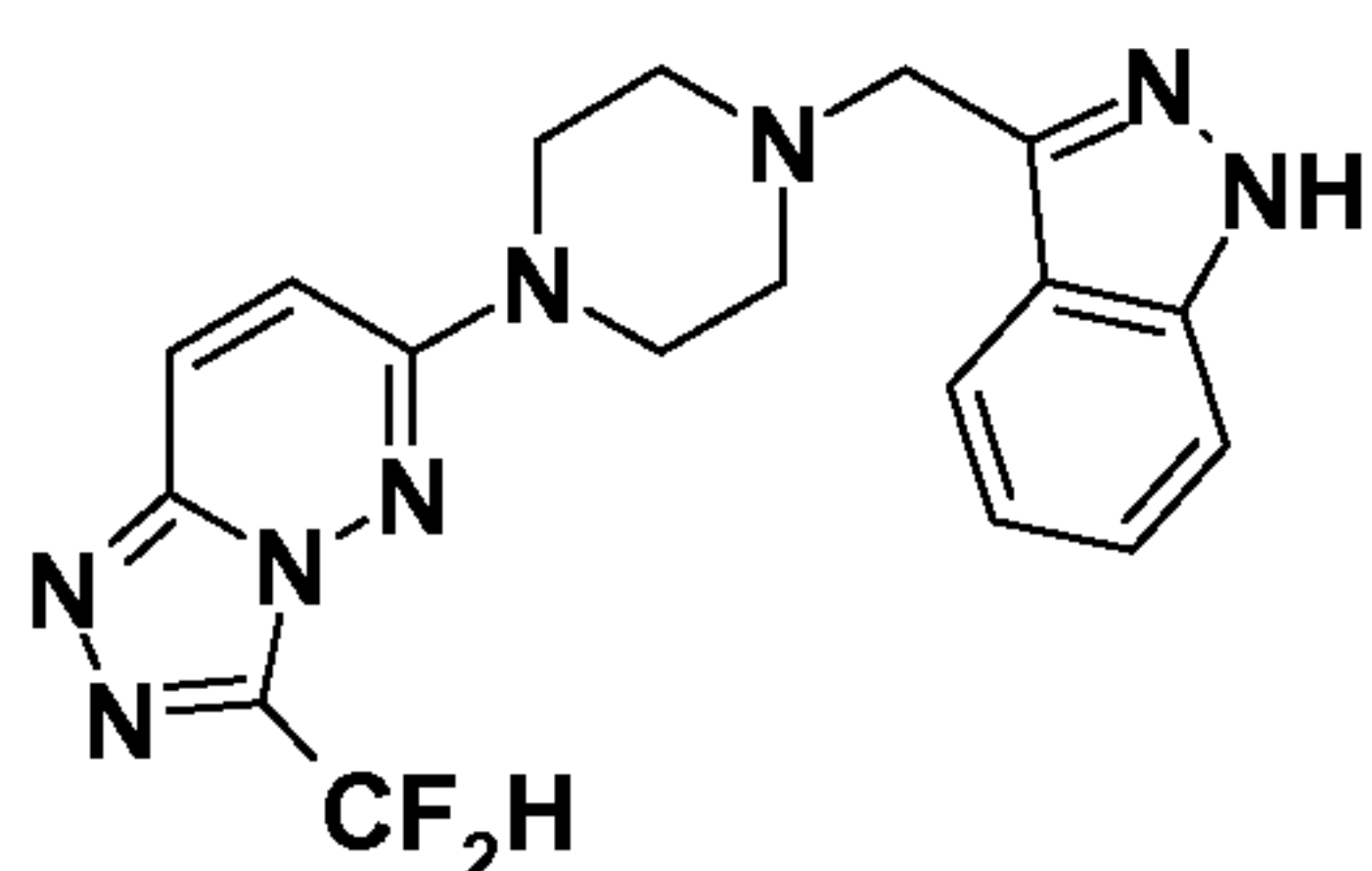


5

| Ex. | R1   | R2 | <sup>1</sup> H NMR (399.9 MHz, DMSO-d <sub>6</sub> )                                                                                                                       | m/z [M+H] <sup>+</sup> |
|-----|------|----|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|
| 286 | 5-CN | H  | δ 2.53 - 2.56 (4H, m), 3.61 (4H, t), 3.75 (2H, s), 7.43 - 7.45 (1H, m), 7.49 - 7.65 (4H, m), 8.15 - 8.21 (2H, m), 11.55 (1H, s)                                            | 409                    |
| 287 | 5-Cl | H  | δ 2.53 - 2.57 (4H, m), 3.60 (4H, t), 3.69 (2H, s), 7.07 - 7.10 (1H, m), 7.37 (2H, t), 7.49 - 7.51 (1H, m), 7.52 (1H, t), 7.70 (1H, d), 8.15 - 8.18 (1H, m), 11.17 (1H, s). | 418                    |
| 288 | 5-Br | H  | δ 2.53 - 2.57 (4H, m), 3.60 (4H, t), 3.69 (2H, s), 7.18 - 7.21 (1H, m), 7.34 (2H, s), 7.52 (1H, t), 7.52 (1H, d), 7.84 (1H, d), 8.15 - 8.18 (1H, m), 11.17 (1H, s).        | 462                    |
| 289 | 4-Cl | H  | δ 2.61 (4H, t), 3.60 (4H, t), 3.86 (2H, s), 7.00 - 7.08 (2H, m), 7.34 - 7.37 (2H, m), 7.50 - 7.53 (1H, m), 7.53 (1H, t), 8.17 (1H, d), 11.17 (1H, s).                      | 418                    |
| 290 | 5-F  | H  | δ 2.53 - 2.57 (4H, m), 3.60 (4H, t), 3.69 (2H, s), 6.92 (1H, d), 7.34 - 7.42 (3H, m), 7.50 (1H, d), 7.52 (1H, t), 8.15 - 8.18 (1H, m), 11.05 (1H, s)                       | 402                    |
| 291 | H    | Cl | δ 2.56 (4H, t), 3.60 (4H, t), 3.69 (2H, s), 7.07 (1H, s), 7.13 - 7.14 (1H, m), 7.29 - 7.31 (1H, m), 7.48 - 7.51 (1H, m), 7.52 (1H, t), 7.66 (1H, s), 8.15 -                | 418                    |

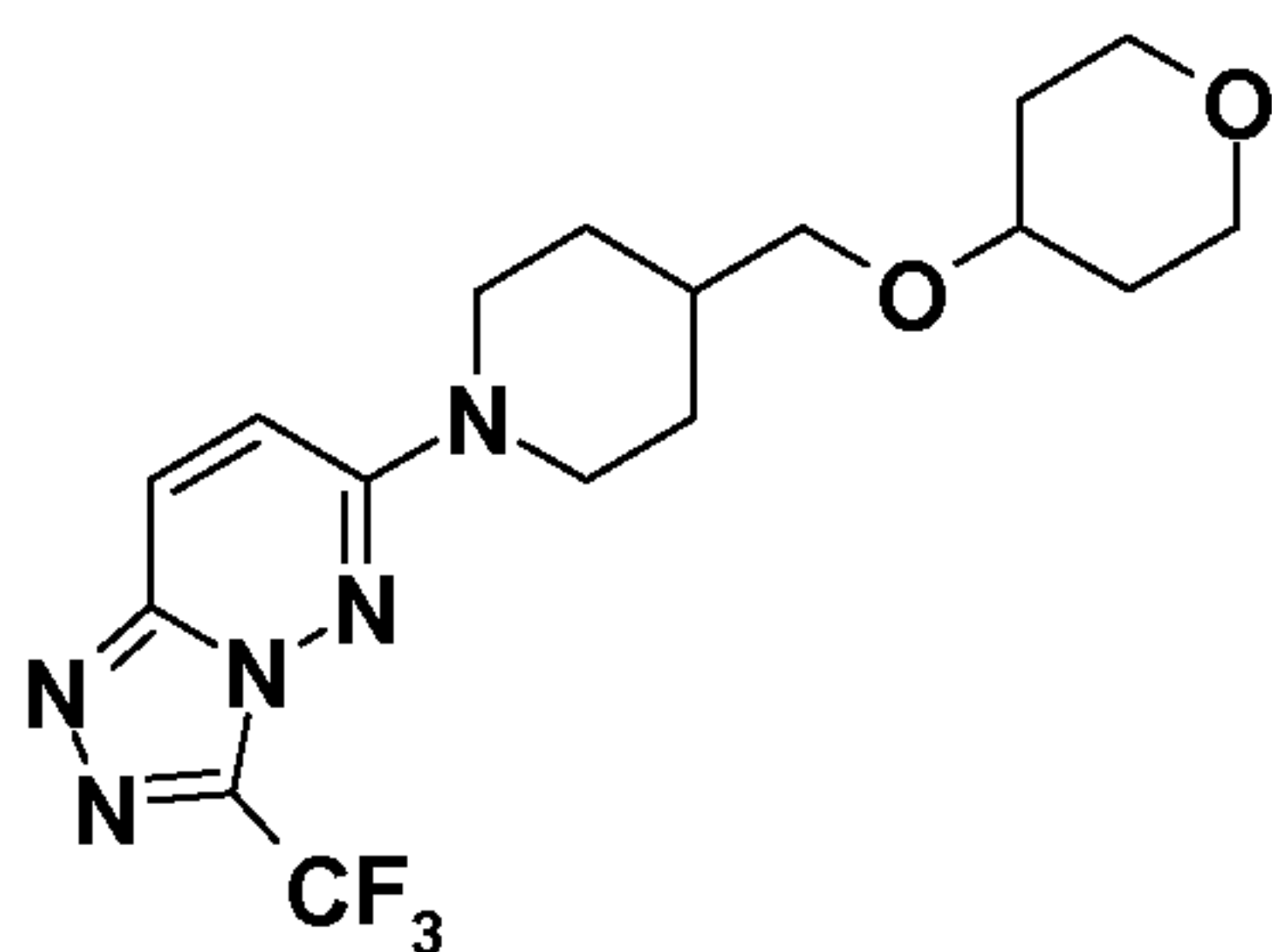


|     |     |   |                                                                                                                                                                                                |     |
|-----|-----|---|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
|     |     |   | 8.17 (1H, m), 11.79 (1H, s)                                                                                                                                                                    |     |
| 292 | 6-F | H | $\delta$ 2.52 (4H, t), 3.59 (4H, s), 3.69 (2H, s), 6.83 - 6.89 (1H, m), 7.12 - 7.15 (1H, m), 7.27 (1H, s), 7.50 (1H, d), 7.39 - 7.64 (1H, m), 7.66 - 7.68 (1H, m), 8.17 (1H, d), 11.01 (1H, s) | 402 |

**Example 293****Preparation of 3-(difluoromethyl)-6-[4-(1H-indazol-3-ylmethyl)piperazin-1-yl][1,2,4]triazolo[4,3-b]pyridazine**

- 5 A mixture of indazole-3-carboxaldehyde and 3-(difluoromethyl)-6-(piperazin-1-yl)-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by General Synthetic Method 5 to give 3-(difluoromethyl)-6-[4-(1H-indazol-3-ylmethyl)piperazin-1-yl][1,2,4]triazolo[4,3-b]pyridazine in 65% yield.

1H NMR (399.9 MHz, DMSO-d<sub>6</sub>)  $\delta$  2.57 - 2.61 (4H, m), 3.61 (4H, t), 3.92 (2H, s), 7.11  
 10 (1H, t), 7.33 - 7.37 (1H, m), 7.48 - 7.52 (2H, m), 7.52 (1H, t), 7.91 (1H, s), 8.17 (1H, d), 12.85 (1H, s); m/z = 385 [M+H]<sup>+</sup>.

**Example 294****Preparation of 6-[4-[(tetrahydro-2H-pyran-4-yloxy)methyl]piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine**

15

Sodium hydride (60% dispersion in oil, 42 mg, 1.05 mmol) was added to stirred tetrahydro-4H-pyran-4-ol (1 g). 6-[4-(Methanesulfonyloxymethyl)piperidin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (133 mg, 0.35 mmol) was added and the mixture was stirred at 80°C for 3 hours. The reaction mixture was diluted with MeOH and



run down a 20 g SCX cartridge, eluting with 2M ammonia in methanol. The solution was evaporated and the crude product was purified by preparative HPLC (Waters XTerra C18 column, 5 $\mu$  silica, 19 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 1% ammonia) and MeCN as eluents. Fractions containing the desired  
5 compound were evaporated to dryness to afford 66-[4-[(tetrahydro-2H-pyran-4-yloxy)methyl]piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine (43 mg, 32%) as a white solid.

<sup>1</sup>H NMR (399.9 MHz, CDCl<sub>3</sub>)  $\delta$  1.25 - 1.33 (2H, m), 1.46 - 1.55 (2H, m), 1.78 - 1.87 (5H, m), 2.93 - 3.00 (2H, m), 3.27 - 3.28 (2H, m), 3.34 - 3.42 (3H, m), 3.83 - 3.88 (2H, m), 4.16  
10 - 4.20 (2H, m), 7.01 (1H, d), 7.83 (1H, d); m/z = 386 [M+H]<sup>+</sup>.

The 6-[4-(methanesulfonyloxymethyl)piperidin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine used as starting material was prepared as follows:-

**Preparation of [1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]methanol**

15 A stirred solution of 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (5.56 g, 25 mmol), piperidin-4-ylmethanol (3.17 g, 27.50 mmol) and DIPEA (5.66 mL, 32.50 mmol) in DMF (50 mL) was heated at 70°C for 1 hour. The solution was evaporated and partitioned between DCM and 1M aqueous K<sub>2</sub>CO<sub>3</sub>. The organic phase was washed with brine, dried over MgSO<sub>4</sub>, evaporated and triturated with ether. The precipitate was  
20 collected by filtration, washed with ether and dried under vacuum to afford [1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]methanol (6.68 g, 89%) as a cream crystalline solid.

<sup>1</sup>H NMR (399.9 MHz, CDCl<sub>3</sub>)  $\delta$  1.31 - 1.41 (2H, m), 1.80 - 1.93 (3H, m), 3.00 - 3.07 (2H, m), 3.57 (2H, t), 4.25 - 4.29 (2H, m), 7.09 (1H, d), 7.90 (1H, d), OH not observed; m/z =  
25 302 [M+H]<sup>+</sup>.

**Preparation of 6-[4-(methanesulfonyloxymethyl)piperidin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

Methanesulfonyl chloride (2.83 mL, 36.51 mmol) in DCM (30 mL) was added dropwise to a stirred partial solution of [1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-  
30 b]pyridazin-6-yl]piperidin-4-yl]methanol (10 g, 33.19 mmol) and triethylamine (5.09 mL, 36.51 mmol) in DCM (140 mL). The reaction was stirred for 20 minutes, quenched with water (100 mL) and extracted with DCM (2 x 75 mL). The organic layer was dried over

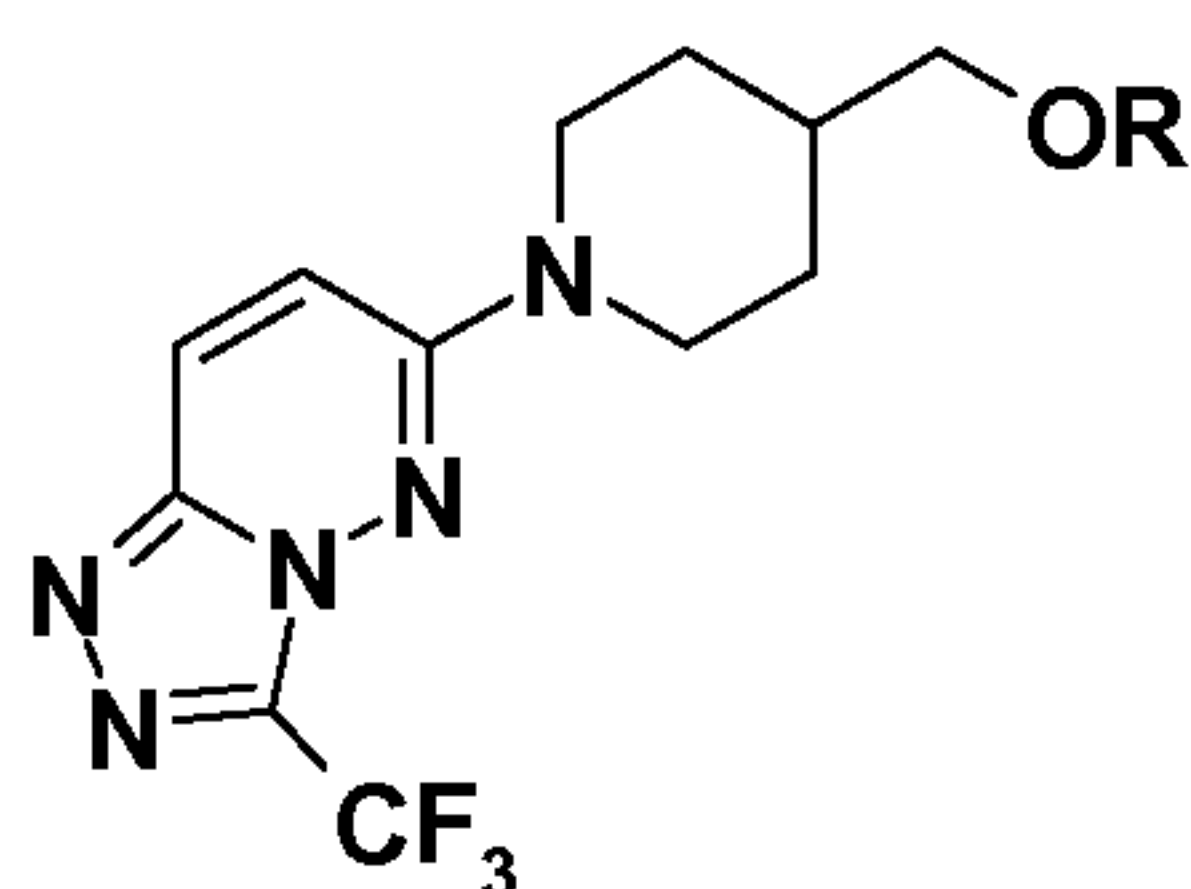


MgSO<sub>4</sub>, filtered and evaporated to afford a yellow solid. The crude solid was triturated with ether to give a solid which was collected by filtration and dried under vacuum to give 6-[4-(methanesulfonyloxymethyl)piperidin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (7.60 g, 60.4%) as a white solid.

5 1H NMR (400.1 MHz, DMSO)  $\delta$  1.32 (2H, ddd), 1.82 (2H, d), 2.09 - 2.02 (1H, m), 3.05 (2H, t), 3.18 (3H, s), 4.11 (2H, d), 4.30 (2H, d), 7.61 (1H, d), 8.22 (1H, d); m/z = 380 [M+H]<sup>+</sup>.

### **Examples 295-298**

The following compounds were prepared in 17-71% yield by an analogous method to  
10 Example 294, starting from 6-[4-(methanesulfonyloxymethyl)piperidin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine and the appropriate alcohol:-



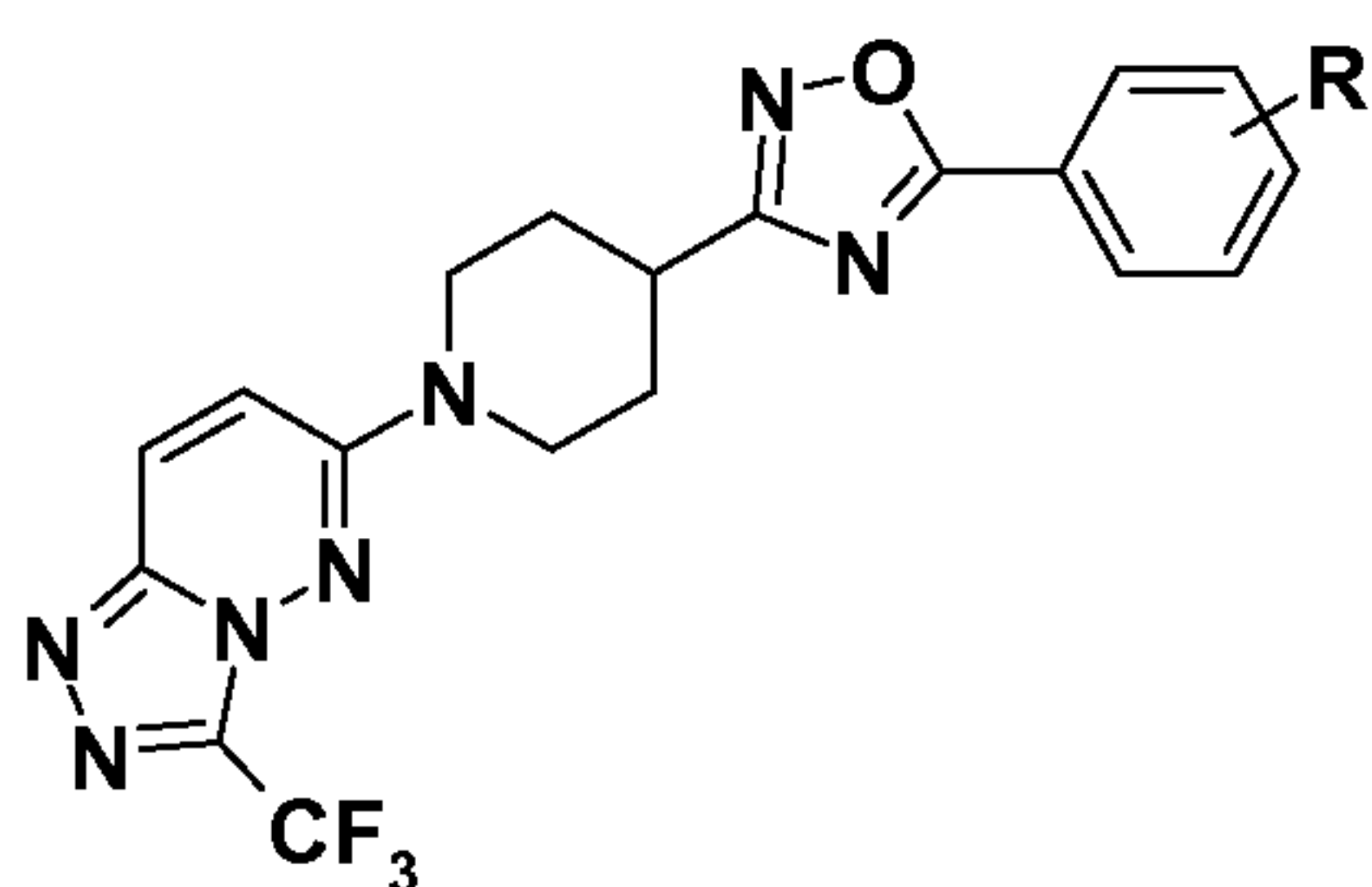
| Ex. | R                 | 1H NMR (399.9 MHz, CDCl <sub>3</sub> )                                                                                                                                                                                    | m/z [M+H] <sup>+</sup> |
|-----|-------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|
| 295 | cyclopropylmethyl | $\delta$ 0.12 - 0.15 (2H, m), 0.45 - 0.49 (2H, m), 0.95 - 1.01 (1H, m), 1.22 - 1.32 (2H, m), 1.84 - 1.90 (3H, m), 2.92 - 2.99 (2H, m), 3.20 - 3.21 (2H, m), 3.26 (2H, d), 4.15 - 4.20 (2H, m), 7.01 (1H, d), 7.83 (1H, d) | 356                    |
| 296 | 2-methoxyethyl    | $\delta$ 1.21 - 1.31 (2H, m), 1.83 - 1.93 (3H, m), 2.91 - 2.98 (2H, m), 3.28 - 3.30 (2H, m), 3.32 (3H, s), 3.46 - 3.49 (2H, m), 3.49 - 3.54 (2H, m), 4.14 - 4.19 (2H, m), 7.01 (1H, d), 7.83 (1H, d)                      | 360                    |
| 297 | 2-morpholinoethyl | $\delta$ 1.21 - 1.31 (2H, m), 1.80 - 1.89 (3H, m), 2.49 - 2.56 (6H, m), 2.91 - 2.98 (2H, m), 3.25 - 3.27 (2H, m), 3.54 (2H, s), 3.69 (4H, s), 4.15 - 4.19 (2H, m), 7.01 (1H, d), 7.83 (1H, d)                             | 415                    |



|     |          |                                                                                                                                                                          |     |
|-----|----------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
| 298 | 2-propyl | $\delta$ 1.08 (6H, d), 1.20 - 1.30 (2H, m), 1.78 - 1.86 (3H, m), 2.92 - 2.99 (2H, m), 3.22 (2H, d), 3.44 - 3.50 (1H, m), 4.15 - 4.19 (2H, m), 7.01 (1H, d), 7.83 (1H, d) | 344 |
|-----|----------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|

**Examples 299-303**

The following compounds were prepared in 1-84% yield by an analogous method to Example 273, starting from N-hydroxy-1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidine-4-carboximidamide and the appropriate benzoyl chloride.



5

| Ex. | R    | <sup>1</sup> H NMR (399.9 MHz, CDCl <sub>3</sub> )                                                                                                                                                                 | m/z [M+H] <sup>+</sup> |
|-----|------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|
| 299 | 3-Cl | $\delta$ 2.01 - 2.10 (2H, m), 2.23 - 2.27 (2H, m), 3.20 - 3.27 (1H, m), 3.28 - 3.35 (2H, m), 4.24 - 4.29 (2H, m), 7.13 (1H, d), 7.47 (1H, t), 7.56 - 7.59 (1H, m), 7.95 (1H, d), 7.99 - 8.02 (1H, m), 8.12 (1H, t) | 450                    |
| 300 | 4-F  | $\delta$ 2.00 - 2.10 (2H, m), 2.22 - 2.27 (2H, m), 3.18 - 3.26 (1H, m), 3.28 - 3.35 (2H, m), 4.23 - 4.29 (2H, m), 7.13 (1H, d), 7.19 - 7.25 (2H, m), 7.95 (1H, d), 8.11 - 8.16 (2H, m)                             | 434                    |
| 301 | H    | $\delta$ 2.00 - 2.12 (2H, m), 2.23 - 2.28 (2H, m), 3.20 - 3.27 (1H, m), 3.28 - 3.35 (2H, m), 4.24 - 4.29 (2H, m), 7.13 (1H, d), 7.51 - 7.55 (2H, m), 7.58 - 7.62 (1H, m), 7.95 (1H, d), 8.11 - 8.14 (2H, m)        | 416                    |
| 302 | 3-F  | $\delta$ 2.01 - 2.11 (2H, m), 2.23 - 2.28 (2H, m), 3.20 - 3.27 (1H, m), 3.28 - 3.35 (2H, m), 4.24 - 4.29 (2H, m), 7.13 (1H, d), 7.28 - 7.33 (1H, m), 7.49 - 7.54 (1H, m), 7.80 - 7.84 (1H, m), 7.91 - 7.96 (2H, m) | 434                    |
| 303 | 3-CN | $\delta$ 2.00 - 2.10 (2H, m), 2.24 - 2.29 (2H, m), 3.21 - 3.28                                                                                                                                                     | 441                    |



|  |  |                                                                                                                                                                         |  |
|--|--|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|
|  |  | (1H, m), 3.28 - 3.35 (2H, m), 4.24 - 4.30 (2H, m), 7.13<br>(1H, d), 7.67 - 7.71 (1H, m), 7.87 - 7.89 (1H, m), 7.96<br>(1H, d), 8.34 - 8.36 (1H, m), 8.42 - 8.43 (1H, m) |  |
|--|--|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|

The N-hydroxy-1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidine-4-carboximidamide used as starting material was prepared as follows:-

**Preparation of 1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidine-4-carbonitrile**

5 A stirred solution of 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (5.56 g, 25 mmol), piperidine-4-carbonitrile (3.03 g, 27.50 mmol) and DIPEA (5.66 mL, 32.50 mmol) in DMF (50 mL) was heated at 70°C for 1 hour. The solution was evaporated and partitioned between DCM and 1M aqueous K<sub>2</sub>CO<sub>3</sub>. The organic phase was washed with brine, dried over MgSO<sub>4</sub>, evaporated and the residue was triturated with ether. The  
10 solid was collected by filtration, washed with ether and dried under vacuum to afford 1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidine-4-carbonitrile (6.86 g, 93%) as a cream crystalline solid.

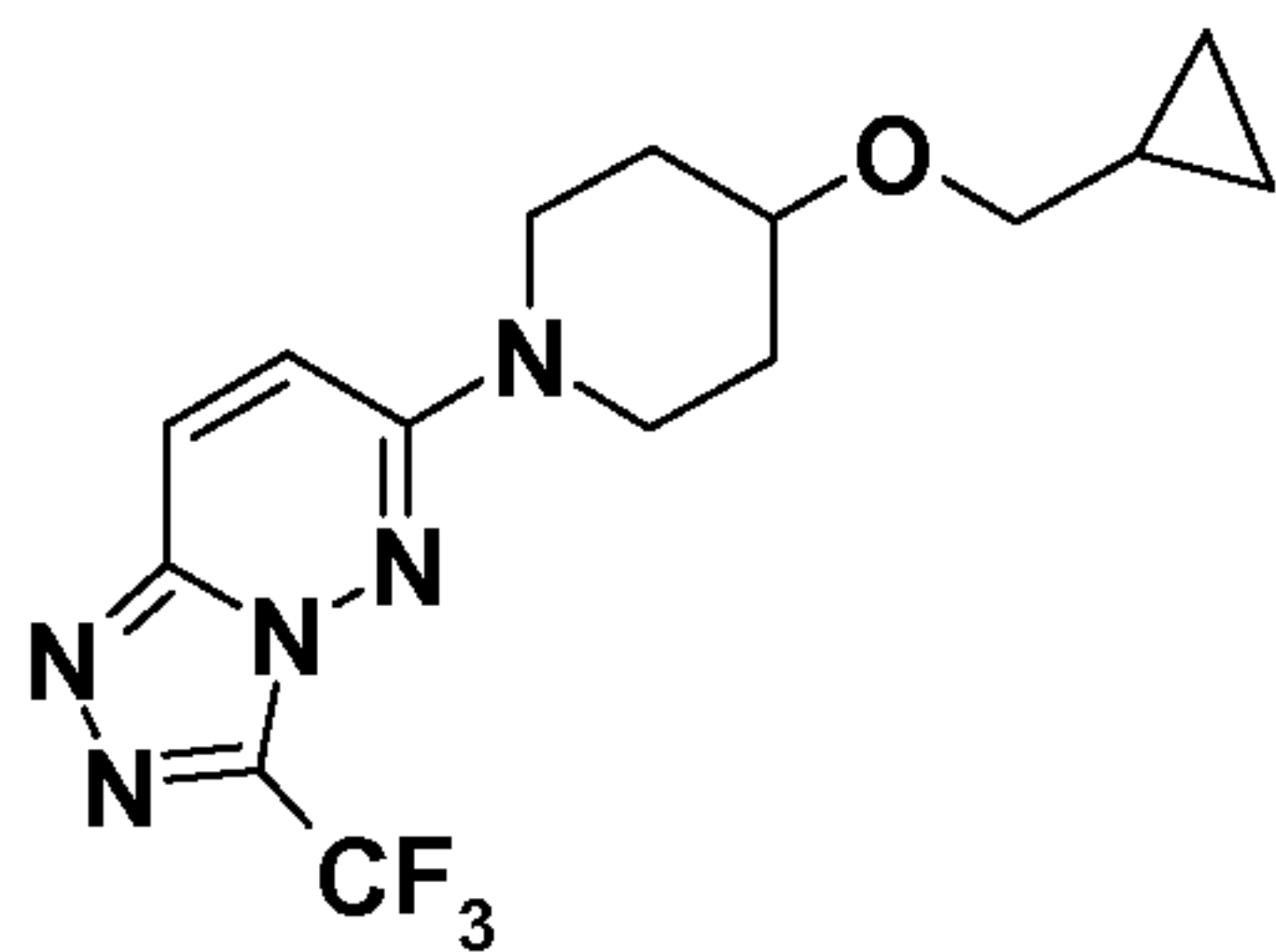
<sup>1</sup>H NMR (399.9 MHz, CDCl<sub>3</sub>) δ 1.97 - 2.12 (4H, m), 2.95 - 3.01 (1H, m), 3.62 - 3.68 (2H, m), 3.80 - 3.86 (2H, m), 7.08 (1H, d), 7.97 (1H, d); m/z = 297 [M+H]<sup>+</sup>.

15 **Preparation of N-hydroxy-1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidine-4-carboximidamide**

Hydroxylamine (50% w/v aqueous solution) (0.669 mL, 10.13 mmol) was added to a stirred suspension of 1-(3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)piperidine-4-carbonitrile (2.5 g, 8.44 mmol) in ethanol (16.88 mL) and the suspension  
20 was stirred at ambient temperature. Additional hydroxylamine (50% w/v aqueous solution) (3 mL) was added and stirring was continued for 18 hours. The mixture was then heated for 1 hour. The precipitate was collected by filtration, washed with EtOH and ether and dried under vacuum to afford N-hydroxy-1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidine-4-carboximidamide (2.380 g, 86%) as a colourless crystalline  
25 solid.

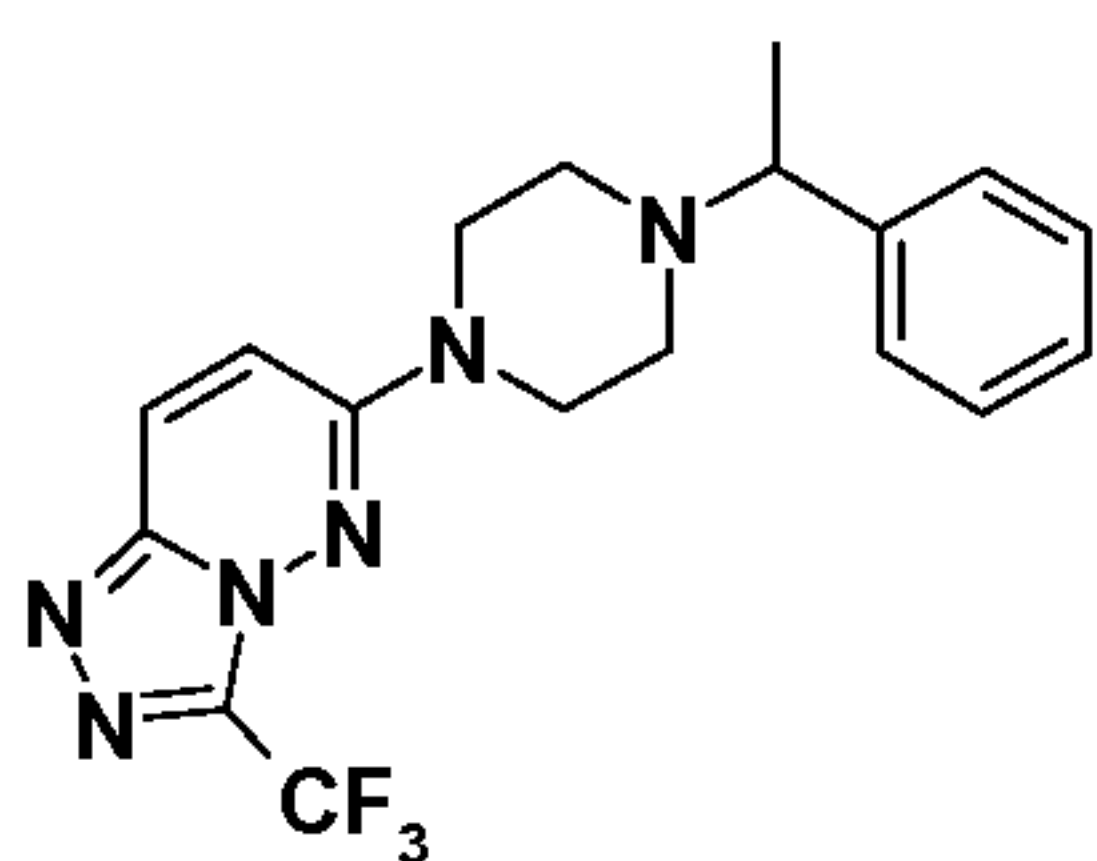
<sup>1</sup>H NMR (399.9 MHz, DMSO-d<sub>6</sub>) δ 1.61 - 1.71 (2H, m), 1.81 - 1.86 (2H, m), 2.32 - 2.38 (1H, m), 3.01 - 3.08 (2H, m), 4.29 (2H, d), 5.32 - 5.34 (2H, m), 7.62 (1H, d), 8.23 (1H, d), 8.81 (1H, s); m/z = 330 [M+H]<sup>+</sup>.



**Example 304****Preparation of 6-[4-(cyclopropylmethoxy)piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine**

5 A mixture of 4-(cyclopropylmethoxy)piperidine and 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by an analogous method to Example 216 to give 6-[4-(cyclopropylmethoxy)piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine in 69% yield.

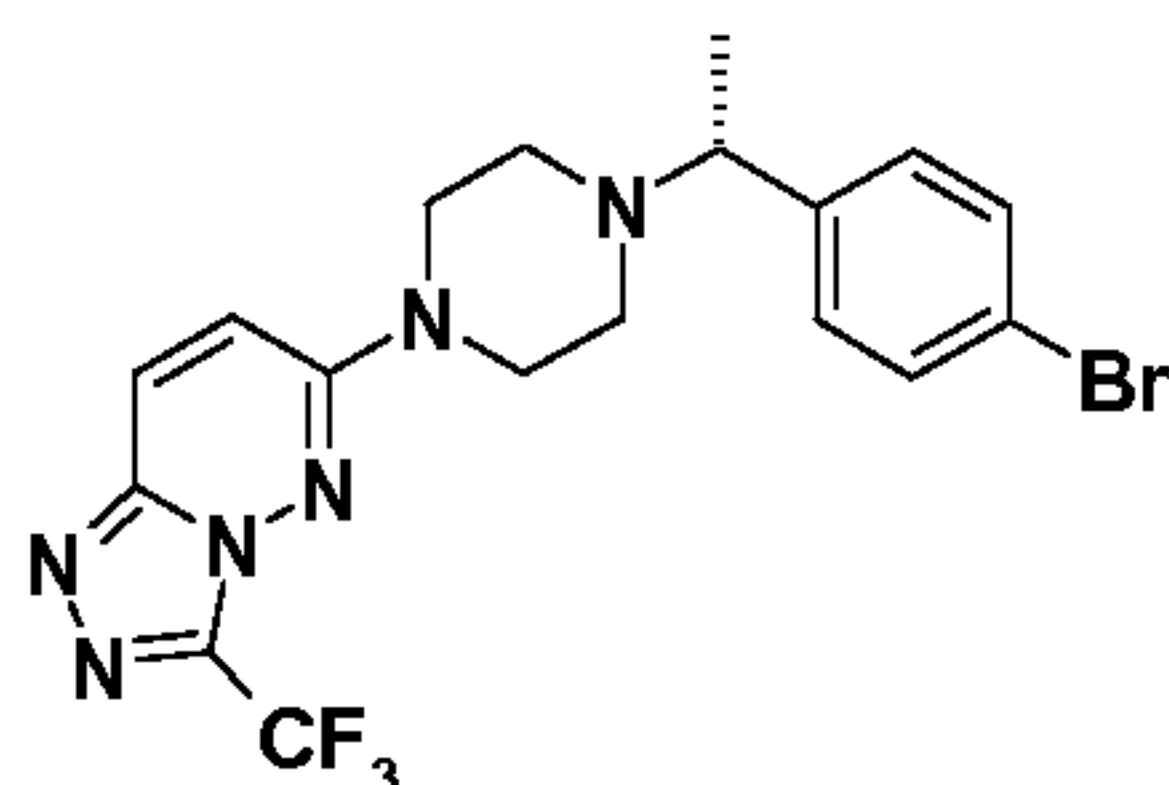
1H NMR (399.9 MHz, CDCl<sub>3</sub>)  $\delta$  0.20 - 0.24 (2H, m), 0.54 - 0.59 (2H, m), 1.02 - 1.12 (1H, m), 1.70 - 1.79 (2H, m), 1.94 - 2.00 (2H, m), 3.34 (2H, d), 3.40 - 3.44 (2H, m), 3.61 - 3.66 (1H, m), 3.87 - 3.93 (2H, m), 7.10 (1H, d), 7.91 (1H, d); m/z = 342 [M+H]<sup>+</sup>.

**Example 305****Preparation of 6-[4-(1-phenylethyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine**

15 6-Chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (400 mg, 1.80 mmol), 1-(1-phenylethyl)piperazine (342 mg, 1.80 mmol) and DIPEA (0.34 mL, 1.98 mmol) in DMF (4 mL) were stirred and heated at 80°C for 30 minutes. The mixture was cooled to ambient temperature then applied to an SCX column and eluted with methanol followed by 2M ammonia in methanol. Fractions containing pure product were evaporated to give a solid which was recrystallised from MTBE / isohexane to give 6-[4-(1-phenylethyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine (516 mg, 76%).

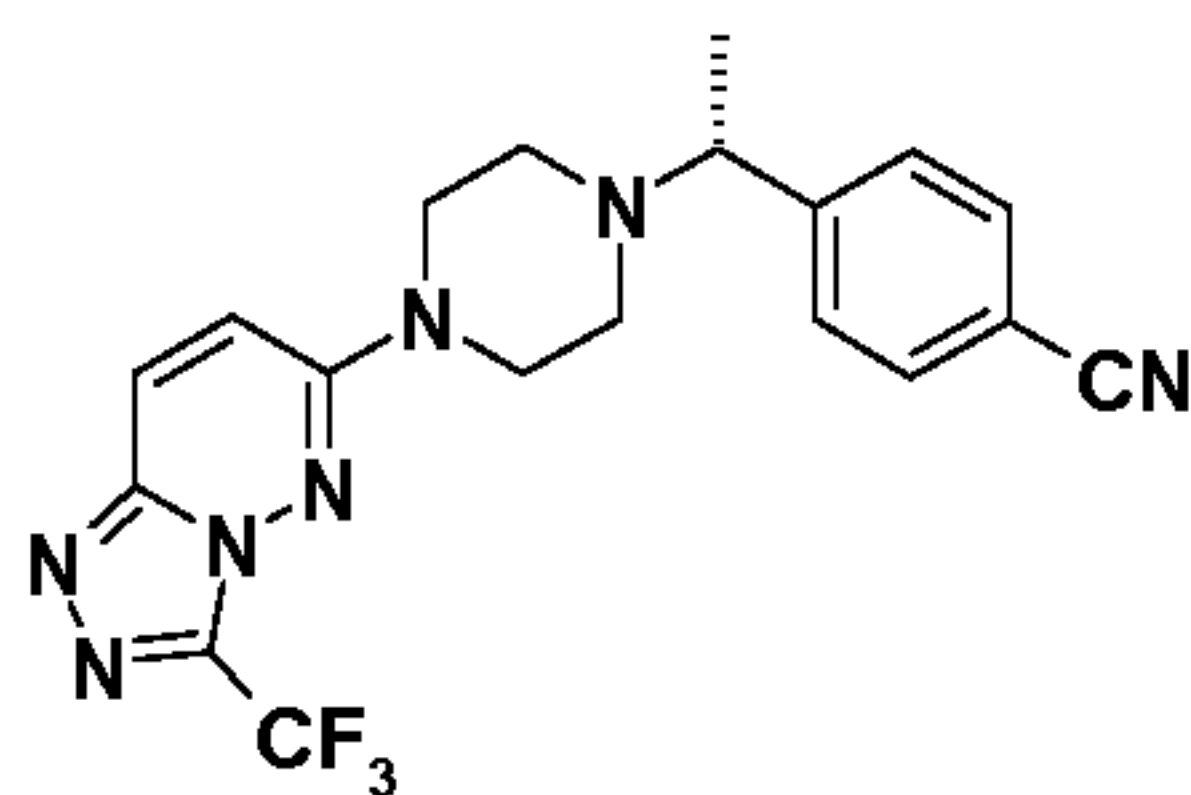
20 1H NMR (399.9 MHz, CDCl<sub>3</sub>)  $\delta$  1.41 (3H, d), 2.50 - 2.56 (2H, m), 2.60 - 2.66 (2H, m), 3.44 (1H, q), 3.55 - 3.64 (4H, m), 7.03 (1H, d), 7.24 - 7.35 (5H, m), 7.89 (1H, d); m/z = 377 [M+H]<sup>+</sup>.



**Example 306****Preparation of 6-[4-[(1R)-1-(4-bromophenyl)ethyl]piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine**

5 6-Chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (251 mg, 1.13 mmol), (R)-1-[1-(4-bromophenyl)ethyl]piperazine (obtained as described in Example 270, preparation of starting materials, 304 mg, 1.13 mmol) and DIPEA (0.20 mL, 1.13 mmol) in DMF (3 mL) were stirred and heated at 80°C for 1 hour. The resulting solution was cooled to ambient temperature then quenched with water (10 mL) to give a pale brown precipitate. The  
10 precipitate was collected by filtration, washed sequentially with water, acetonitrile and ether and dried under vacuum to afford 6-[4-[(1R)-1-(4-bromophenyl)ethyl]piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine (437 mg, 85%) as a pale brown solid.

1H NMR (399.9 MHz, CDCl<sub>3</sub>)  $\delta$  1.37 (3H, d), 2.48 - 2.54 (2H, m), 2.59 - 2.65 (2H, m),  
15 3.40 (1H, q), 3.54 - 3.64 (4H, m), 7.03 (1H, d), 7.21 (2H, d), 7.46 (2H, d), 7.90 (1H, d);  
m/z = 455/457 [M+H]<sup>+</sup>.

**Example 307****Preparation of 4-[(1R)-1-[4-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]ethyl]benzonitrile**

20 6-[4-[(1R)-1-(4-Bromophenyl)ethyl]piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine (obtained as described in Example 306) (250 mg, 0.55 mmol), zinc cyanide (38.7 mg, 0.33 mmol), tris(dibenzylideneacetone)dipalladium(0) (5.0 mg, 5.49  $\mu$ mol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (6.3 mg, 10.98  $\mu$ mol) and N,N,N',N'-  
25 tetramethylethylenediamine (0.017 mL, 0.11 mmol) were suspended in DMF (2.5 mL) and sealed into a microwave tube. The reaction was heated to 160°C for 5 minutes in a



microwave reactor and cooled to ambient temperature. The resulting mixture was applied to an SCX column and eluted with methanol followed by 2M ammonia in methanol.

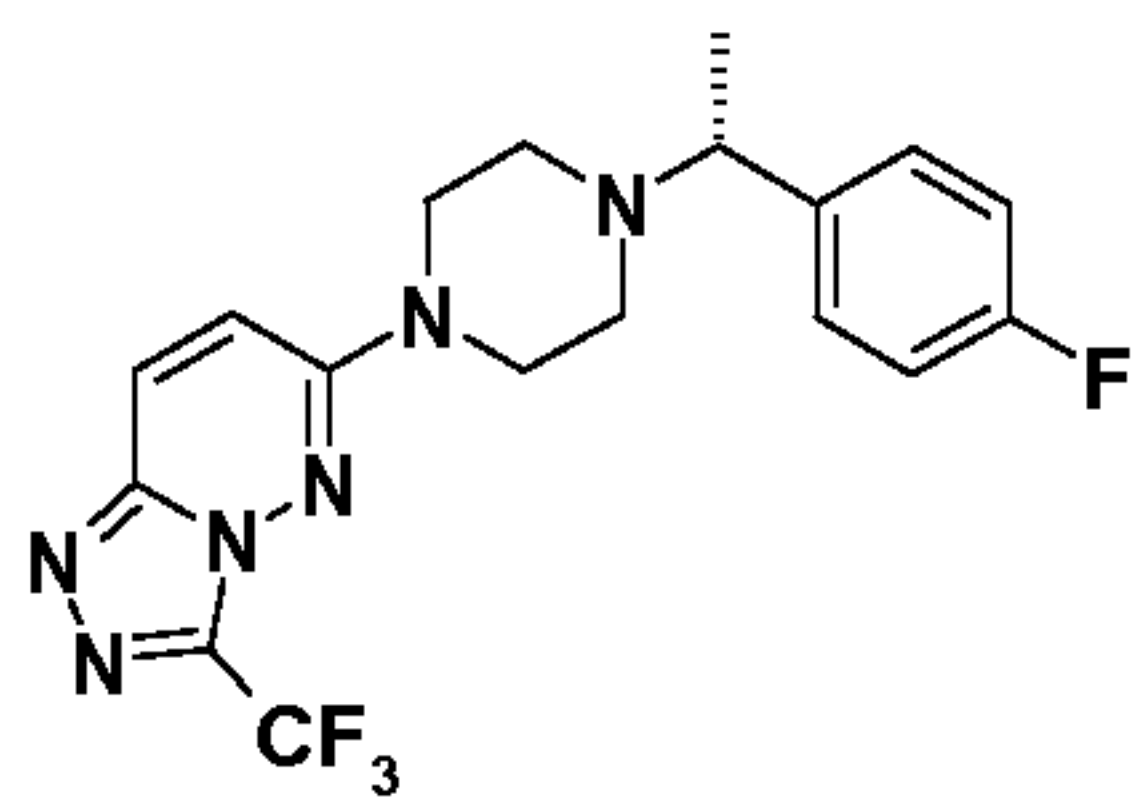
Fractions containing product were combined and evaporated then purified by preparative HPLC (Waters XTerra C18 column, 5 $\mu$  silica, 19 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 1% ammonia) and MeCN as eluents.

Fractions containing the desired compound were evaporated to dryness to afford 4-[(1R)-1-[4-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]ethyl]benzonitrile (168 mg, 76%) as a colourless solid.

<sup>1</sup>H NMR (399.9 MHz, CDCl<sub>3</sub>)  $\delta$  1.39 (3H, d), 2.48 - 2.53 (2H, m), 2.63 - 2.68 (2H, m), 3.49 (1H, q), 3.55 - 3.65 (4H, m), 7.04 (1H, d), 7.48 (2H, d), 7.64 (2H, d), 7.92 (1H, d); m/z = 402 [M+H]<sup>+</sup>.

### **Example 308**

#### **Preparation of 6-[4-[(1R)-1-(4-fluorophenyl)ethyl]piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine**



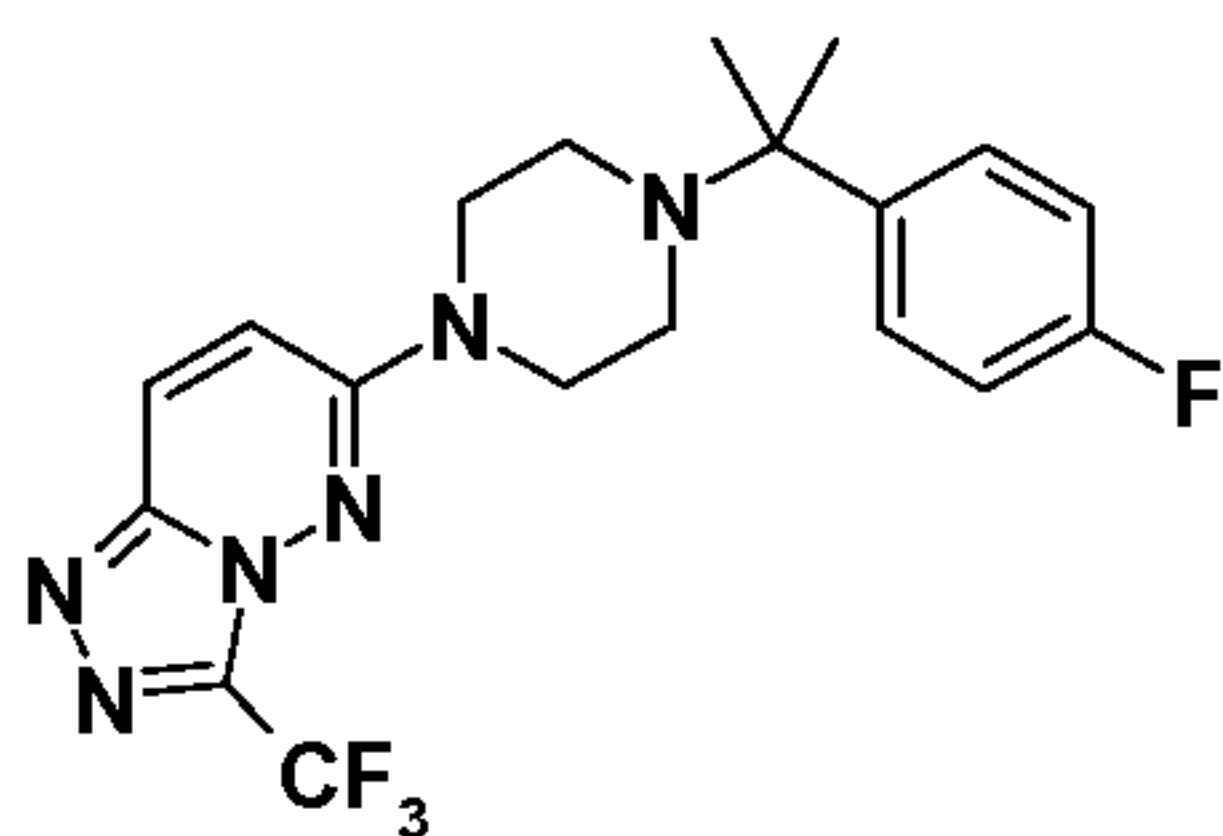
A mixture of (R)-1-[1-(4-fluorophenyl)ethyl]piperazine (obtained as described in J. Med. Chem. 2007, 50, 3528) and 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by the method described in Example 306 to give 6-[4-[(1R)-1-(4-fluorophenyl)ethyl]piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine in 87% yield.

<sup>1</sup>H NMR (399.9 MHz, CDCl<sub>3</sub>)  $\delta$  1.38 (3H, d), 2.49 - 2.54 (2H, m), 2.59 - 2.65 (2H, m), 3.43 (1H, q), 3.54 - 3.64 (4H, m), 6.99 - 7.04 (3H, m), 7.29 (2H, dd), 7.90 (1H, d); m/z = 395 [M+H]<sup>+</sup>.

### **Example 309**

#### **Preparation of 6-[4-[1-(4-fluorophenyl)-1-methylethyl]piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine**

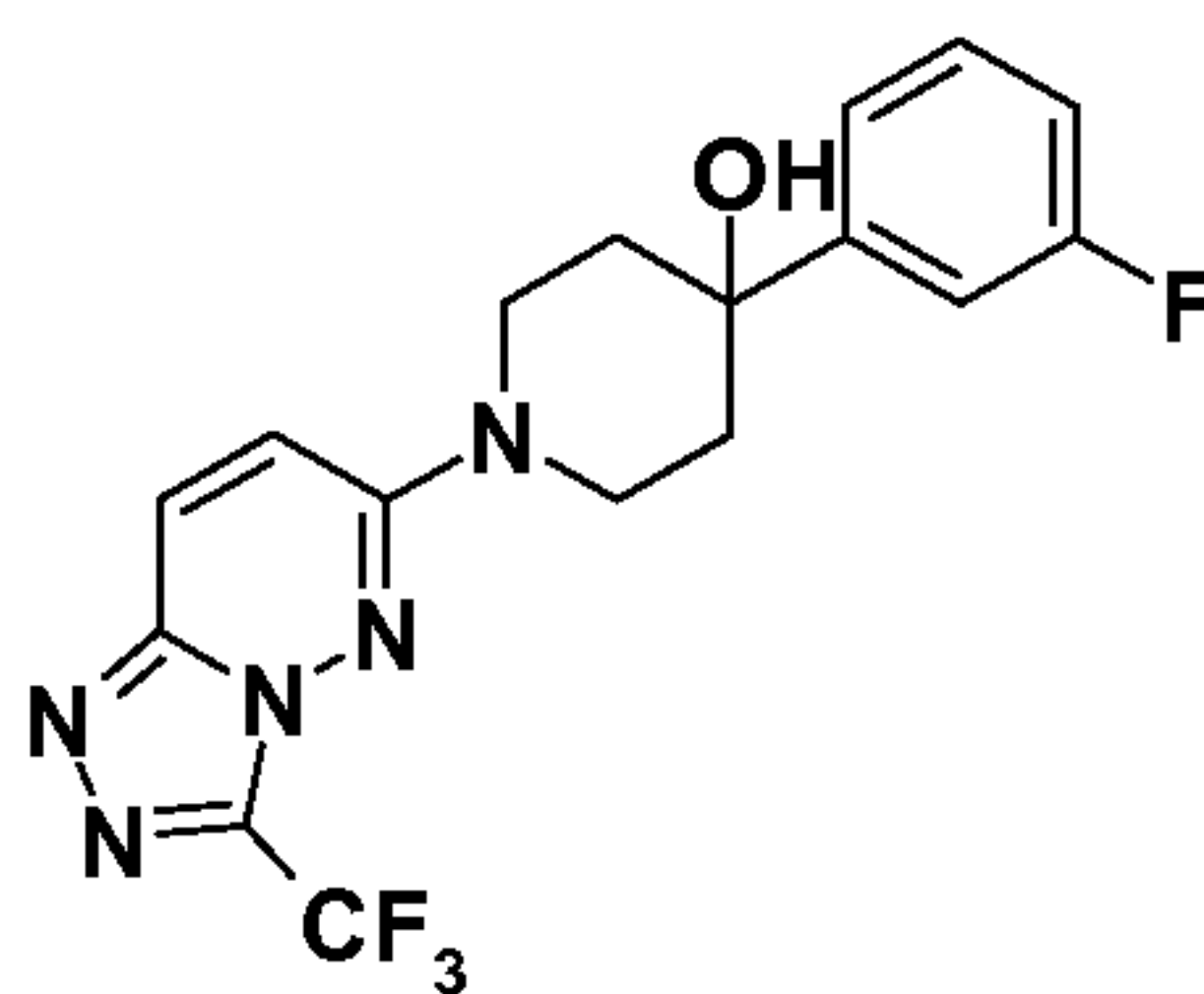




6-Chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (120 mg, 0.54 mmol), DIPEA (0.094 mL, 0.54 mmol) and 1-[2-(4-fluorophenyl)propan-2-yl]piperazine (obtained as described in J. Med. Chem. 2007, 50, 3528) (120 mg, 0.54 mmol) in DMF (1.5 mL) were stirred and heated at 80°C for 1 hour. The resulting solution was cooled to room temperature then applied to an SCX column and eluted with MeOH followed by 2M ammonia in methanol. Fractions containing product were combined and evaporated, then purified by preparative HPLC (Waters XTerra C18 column, 5 $\mu$  silica, 19 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 1% ammonia) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford 6-[4-[1-(4-fluorophenyl)-1-methylethyl]piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine (155 mg, 70%) as a colourless solid. <sup>1</sup>H NMR (399.9 MHz, CDCl<sub>3</sub>)  $\delta$  1.37 (6H, s), 2.62 (4H, t), 3.57 (4H, t), 6.99 (2H, d), 7.04 (1H, d), 7.51 (2H, dd), 7.90 (1H, d); m/z = 409 [M+H]<sup>+</sup>.

### **Example 310**

#### **Preparation of 4-(3-fluorophenyl)-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol**



3-Fluorophenylmagnesium bromide (1.0M in THF, 1.68 mL, 1.68 mmol) was added dropwise to 1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-one (400 mg, 1.40 mmol) in THF (10 mL) cooled to 0°C over a period of 10 minutes. The resulting mixture was stirred at 0°C for 20 minutes, then quenched with saturated ammonium chloride solution (20 mL) and extracted with ethyl acetate. The extract was washed with saturated brine, dried over MgSO<sub>4</sub> and evaporated to a pale orange oil which was triturated with DCM to give a beige solid. The solid was filtered, washed with DCM



and dried, then purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5 $\mu$  silica, 19 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 1% ammonia) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford 4-(3-fluorophenyl)-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol (96 mg, 18%) as a colourless solid.

<sup>1</sup>H NMR (399.9 MHz, DMSO-d<sub>6</sub>)  $\delta$  1.71 - 1.74 (2H, m), 2.00 - 2.08 (2H, m), 3.40 - 3.46 (2H, m), 4.20 - 4.24 (2H, m), 5.37 (1H, s), 7.02 - 7.08 (1H, m), 7.31 - 7.40 (3H, m), 7.66 (1H, d), 8.24 (1H, d).; m/z = 382 [M+H]<sup>+</sup>.

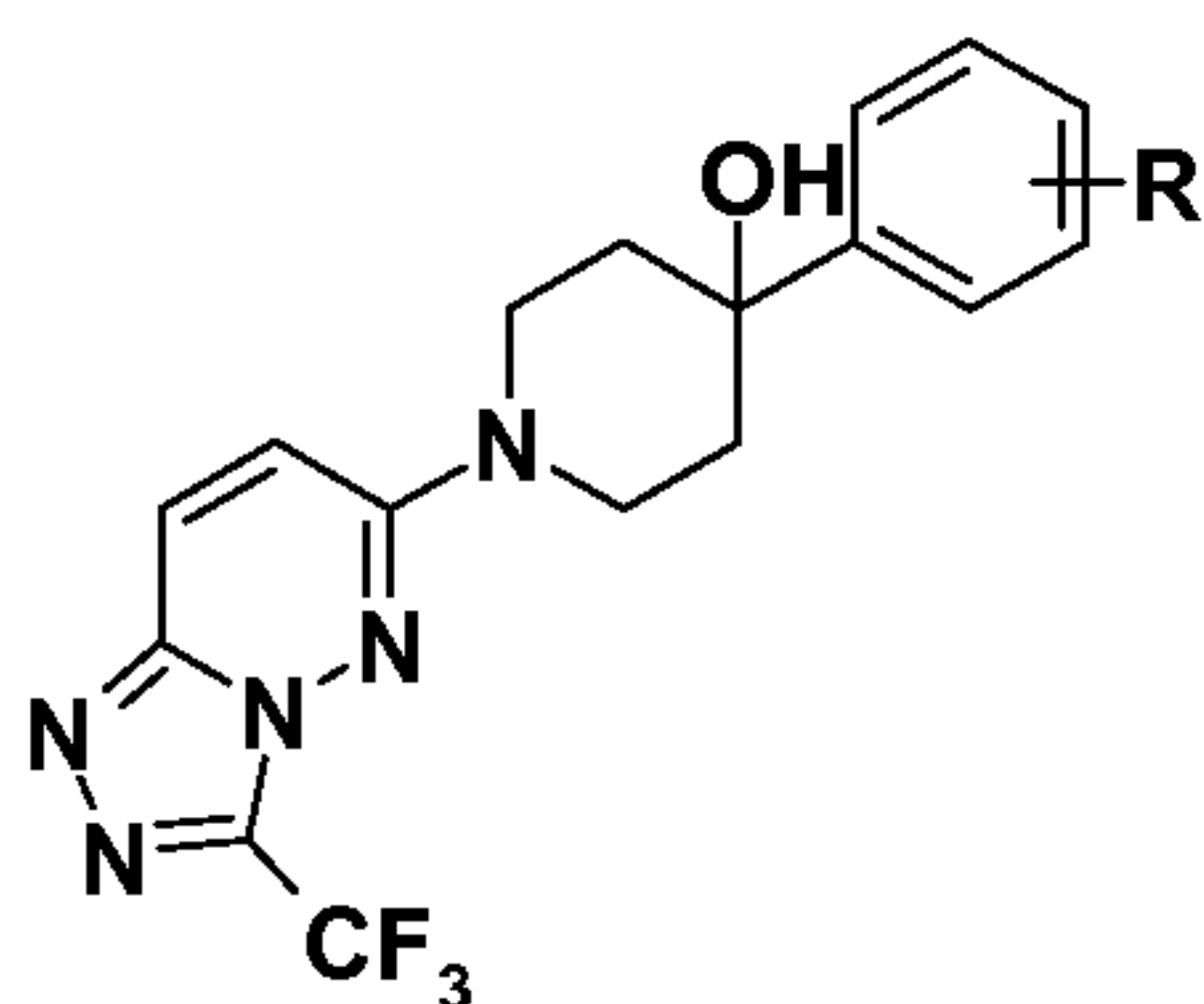
The 1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-one used as starting material was prepared as follows:-

6-Chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (10.0 g, 44.93 mmol), 4-piperidone monohydrate hydrochloride (8.48 g, 49.43 mmol) and DIPEA (16.3 mL, 98.85 mmol) in DMF (100 mL) were stirred and heated at 90°C for 1 hour. The DMF was then evaporated *in vacuo* and the residue purified by flash silica chromatography, eluting with 2% MeOH in DCM. Pure fractions were concentrated to give a pale yellow precipitate. The precipitate was collected by filtration, washed with ether and air dried to afford 1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-one (10.61 g, 83%) as a pale yellow solid.

<sup>1</sup>H NMR (399.9 MHz, CDCl<sub>3</sub>)  $\delta$  2.65 (4H, t), 3.98 (4H, t), 7.15 (1H, d), 8.02 (1H, d); m/z = 286 [M+H]<sup>+</sup>.

### **Examples 311-314**

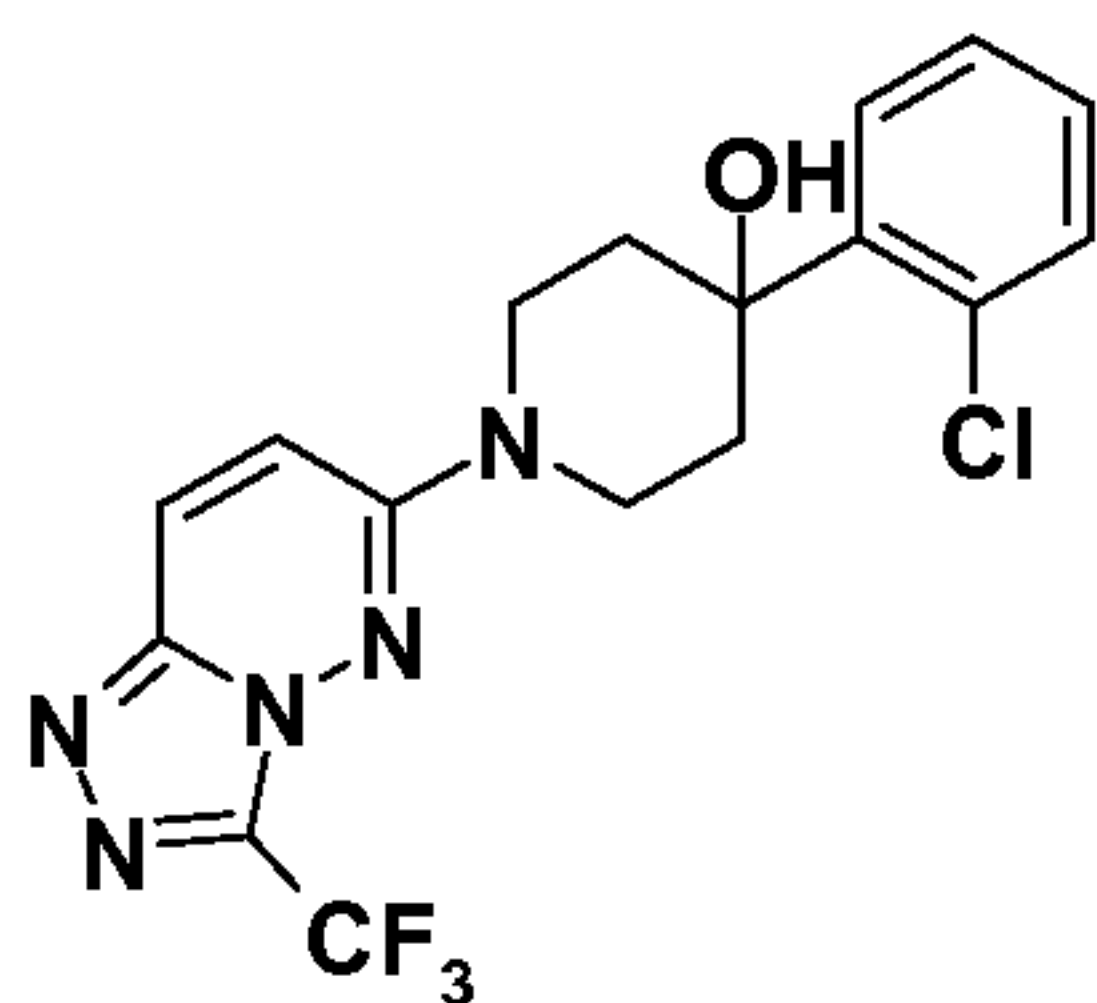
The following compounds were prepared in 27-37% yield by an analogous method to Example 310, starting from 1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-one and the appropriate aryl magnesium bromide:-



| Ex. | R     | <sup>1</sup> H NMR (399.9 MHz, DMSO-d <sub>6</sub> )           | m/z [M+H] <sup>+</sup> |
|-----|-------|----------------------------------------------------------------|------------------------|
| 311 | 4-OMe | $\delta$ 1.71 - 1.74 (2H, m), 1.95 - 2.03 (2H, m), 3.40 - 3.46 | 394                    |



|     |       |                                                                                                                                                                                                              |     |
|-----|-------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
|     |       | (2H, m), 3.74 (3H, s), 4.17 - 4.20 (2H, m), 5.12 (1H, s), 6.88 (2H, d), 7.41 (2H, d), 7.65 (1H, d), 8.23 (1H, d).                                                                                            |     |
| 312 | 3-OMe | $\delta$ 1.71 - 1.74 (2H, m), 1.99 - 2.06 (2H, m), 3.40 - 3.46 (2H, m), 3.76 (3H, s), 4.19 - 4.22 (2H, m), 5.22 (1H, s), 6.80 (1H, dd), 7.05 - 7.09 (2H, m), 7.24 (1H, t), 7.66 (1H, d), 8.24 (1H, d).       | 394 |
| 313 | 3-Cl  | $\delta$ 1.70 - 1.73 (2H, m), 2.00 - 2.08 (2H, m), 3.40 - 3.46 (2H, m), 4.21 - 4.24 (2H, m), 5.39 (1H, s), 7.29 (1H, d), 7.36 (1H, t), 7.46 (1H, d), 7.57 (1H, m), 7.66 (1H, d), 8.24 (1H, d).               | 398 |
| 314 | 2-OMe | $\delta$ 1.55 - 1.58 (2H, m), 2.52 - 2.58 (2H, m), 3.40 - 3.48 (2H, m), 3.63 (3H, s), 4.14 - 4.17 (2H, m), 5.10 (1H, s), 6.94 - 6.98 (2H, m), 7.21 - 7.25 (1H, m), 7.61 (1H, m), 7.67 (1H, d), 8.25 (1H, d). | 394 |

**Example 315****Preparation of 4-(2-chlorophenyl)-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol**

5

Isopropylmagnesium chloride-lithium chloride complex (1.0M in THF, 10 mL, 10.00 mmol) was added dropwise to 1-bromo-2-chlorobenzene (1.91 g, 9.98 mmol) in THF (2.0 mL) cooled to 0°C over a period of 10 minutes. The resulting solution was stirred at 0°C for 1 hour then a 2.0 mL aliquot was added dropwise to 1-[3-(trifluoromethyl)-

10 [1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-one (400 mg, 1.40 mmol) in THF (10 mL) cooled to 0°C over a period of 10 minutes. The resulting solution was stirred at 0°C for 10 minutes then allowed to warm slowly to room temperature and stirred for a further hour. The reaction mixture was then quenched with saturated ammonium chloride (30 mL) and

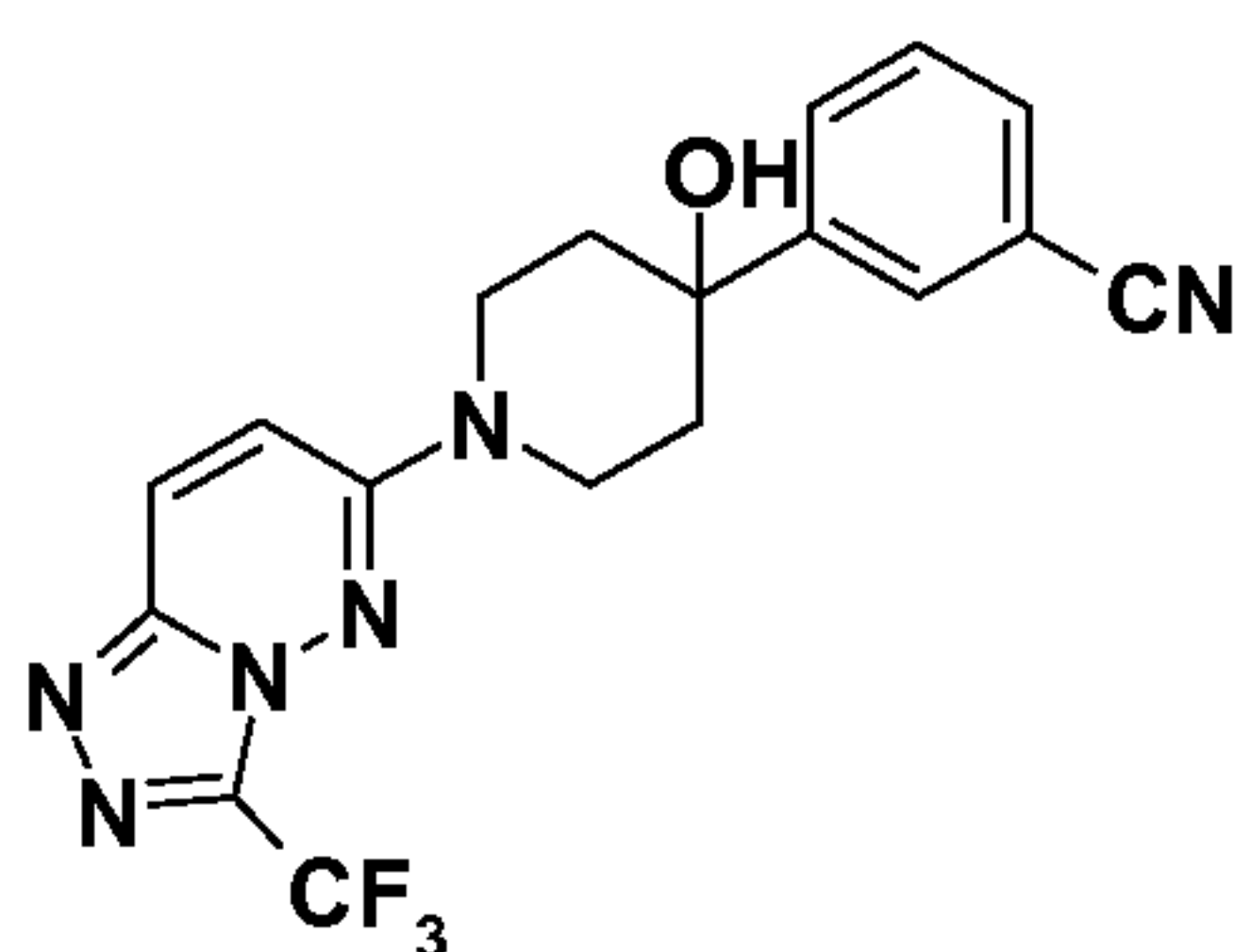


extracted with EtOAc. The extract was washed with saturated brine, dried over  $\text{MgSO}_4$  and concentrated by evaporation, then purified by flash silica chromatography, eluting with EtOAc. Pure fractions were evaporated to dryness to afford 4-(2-chlorophenyl)-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol (230 mg, 41%) as a colourless solid.

$^1\text{H}$  NMR (399.9 MHz,  $\text{DMSO-d}_6$ )  $\delta$  1.68 - 1.71 (2H, m), 2.61 - 2.69 (2H, m), 3.44 - 3.51 (2H, m), 4.20 - 4.24 (2H, m), 5.47 (1H, s), 7.26 - 7.30 (1H, m), 7.36 - 7.40 (2H, m), 7.69 (1H, d), 7.84 - 7.86 (1H, m), 8.26 (1H, d);  $m/z = 398$   $[\text{M}+\text{H}]^+$ .

### **Example 316**

#### **Preparation of 3-[4-hydroxy-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]benzonitrile**

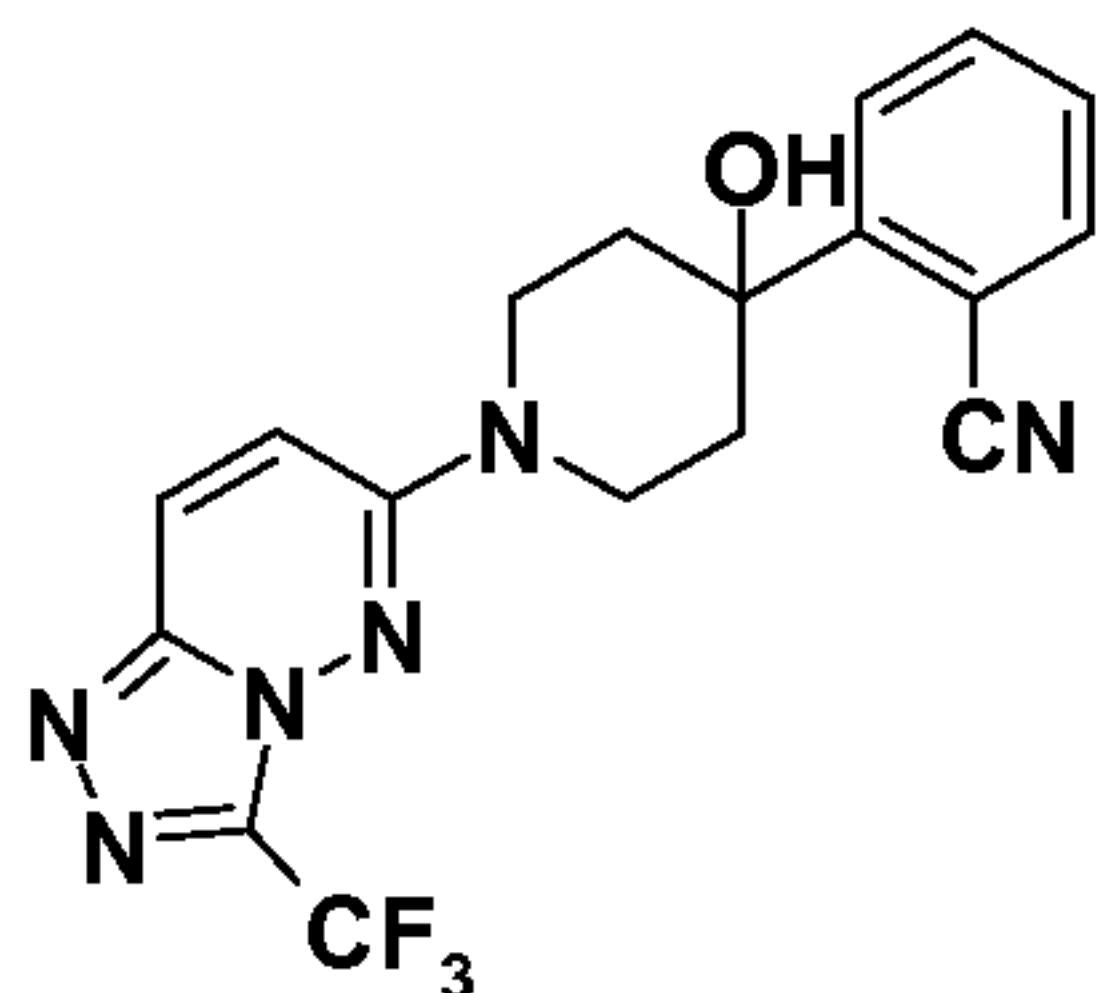


A mixture of 1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-one and 3-bromobenzonitrile was allowed to react by the method of Example 315 to give 3-[4-hydroxy-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]benzonitrile in 26% yield.

$^1\text{H}$  NMR (399.9 MHz,  $\text{DMSO-d}_6$ )  $\delta$  1.70 - 1.73 (2H, m), 2.04 - 2.11 (2H, m), 3.41 - 3.47 (2H, m), 4.22 - 4.25 (2H, m), 5.49 (1H, s), 7.55 (1H, t), 7.67 (1H, d), 7.71 (1H, m), 7.87 (1H, m), 7.95 (1H, m), 8.25 (1H, d);  $m/z = 389$   $[\text{M}+\text{H}]^+$ .

### **Example 317**

#### **Preparation of 2-[4-hydroxy-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]benzonitrile**



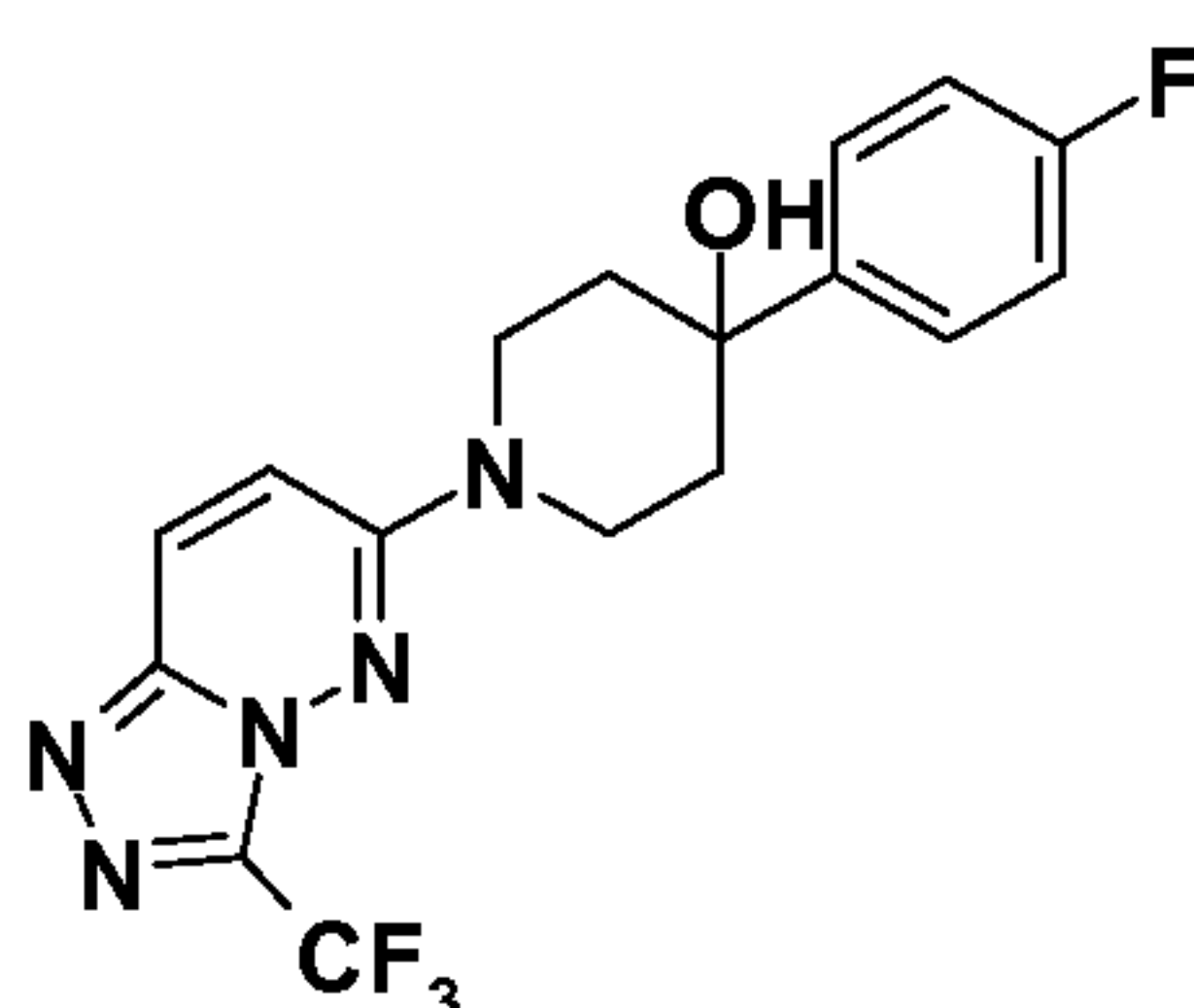


A mixture of 1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-one and 2-bromobenzonitrile was allowed to react by the method of Example 315 to give 2-[4-hydroxy-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]benzonitrile in 24% yield.

- 5 <sup>1</sup>H NMR (399.9 MHz, DMSO-d<sub>6</sub>) δ 1.72 - 1.75 (2H, m), 2.23 - 2.30 (2H, m), 3.39 - 3.45 (2H, m), 4.39 - 4.43 (2H, m), 7.51 - 7.63 (4H, m), 7.72 (1H, d), 8.30 (1H, d), 8.04 (s) & 8.71 (s)(1H); m/z = 389 [M+H]<sup>+</sup>.

### **Example 318**

#### **Preparation of 4-(4-fluorophenyl)-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol**

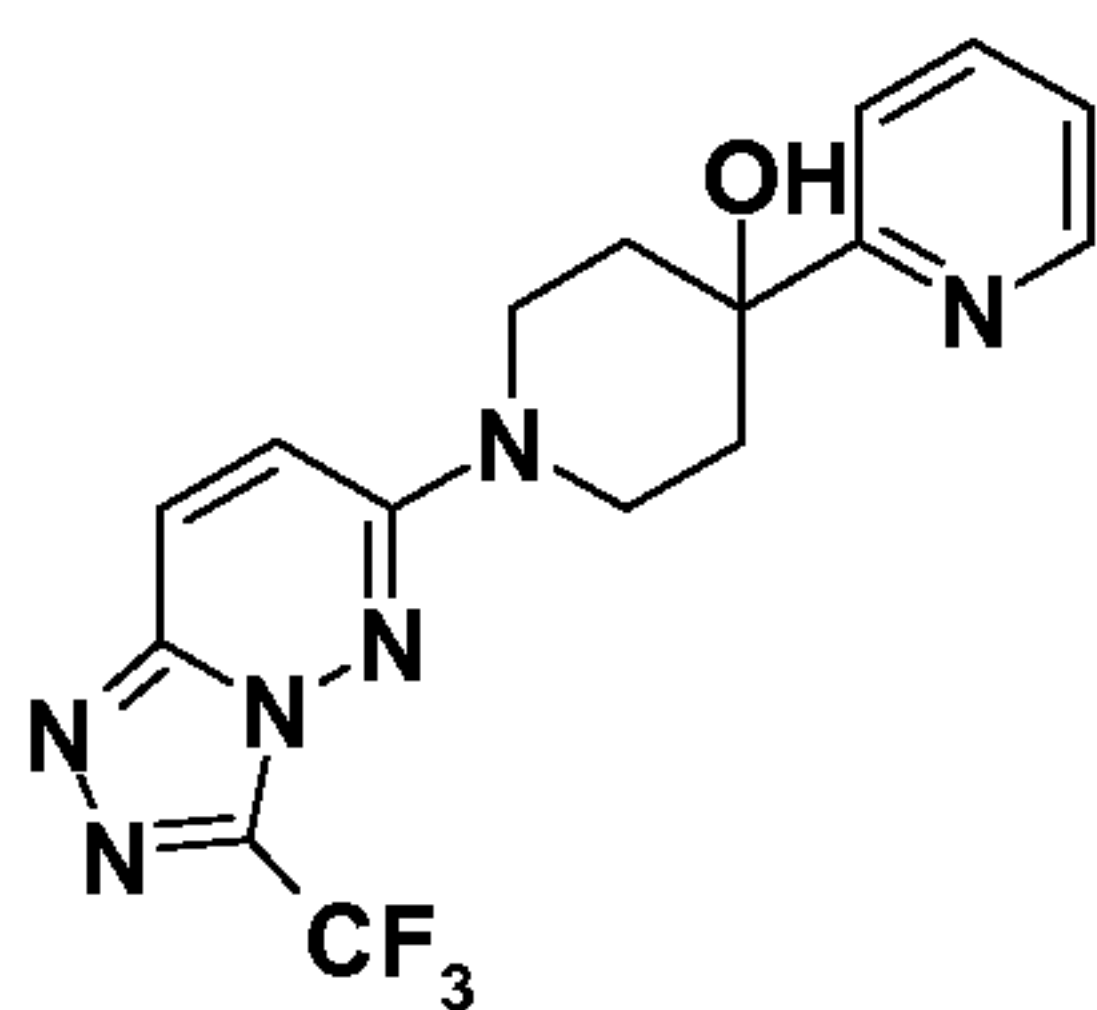


A mixture of 4-(4-fluorophenyl)piperidin-4-ol and 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by the method of Example 306 to give 4-(4-fluorophenyl)-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol in 74% yield.

15 <sup>1</sup>H NMR (399.9 MHz, DMSO-d<sub>6</sub>) δ 1.71 - 1.75 (2H, m), 1.98 - 2.06 (2H, m), 3.40 - 3.46 (2H, m), 4.19 - 4.22 (2H, m), 5.28 (1H, s), 7.14 (2H, t), 7.54 (2H, dd), 7.66 (1H, d), 8.24 (1H, d); m/z = 382 [M+H]<sup>+</sup>.

### **Example 319**

#### **Preparation of 4-pyridin-2-yl-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol**



A mixture of 4-(pyridin-2-yl)piperidin-4-ol and 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by the method of Example 306 to

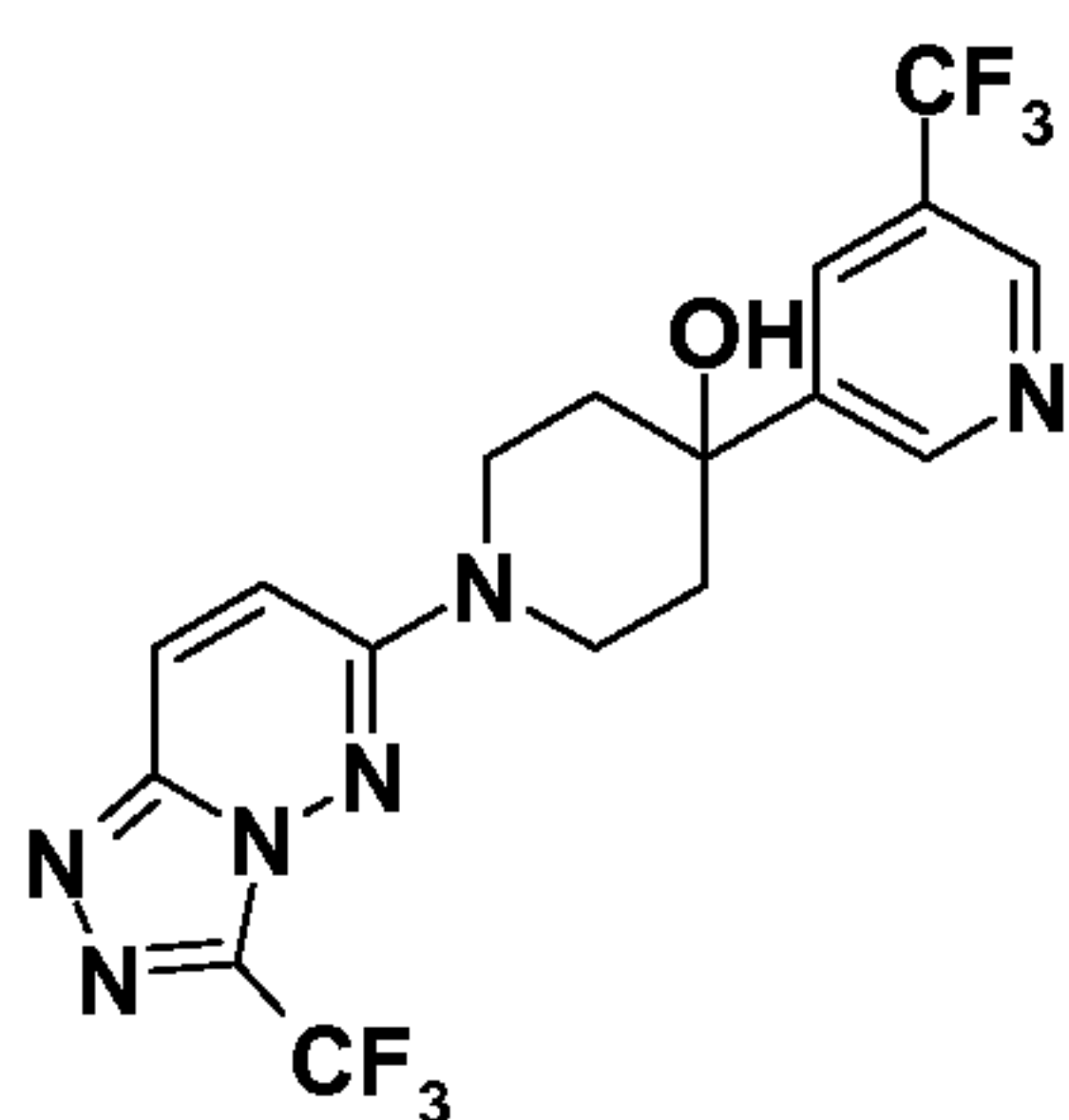


give 4-pyridin-2-yl-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol in 77% yield.

<sup>1</sup>H NMR (399.9 MHz, DMSO-d<sub>6</sub>) δ 1.66 - 1.69 (2H, m), 2.18 - 2.25 (2H, m), 3.44 - 3.50 (2H, m), 4.20 - 4.23 (2H, m), 5.47 (1H, s), 7.24 - 7.27 (1H, m), 7.67 (1H, d), 7.72 (1H, d),  
 5 7.82 (1H, td), 8.25 (1H, d), 8.49 (1H, d); m/z = 365 [M+H]<sup>+</sup>.

### **Example 320**

#### **Preparation of 4-[5-(trifluoromethyl)pyridin-3-yl]-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol**



10 A mixture of 4-[5-(trifluoromethyl)pyridin-3-yl]piperidin-4-ol and 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by the method of Example 306 to give 4-[5-(trifluoromethyl)pyridin-3-yl]-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol in 75% yield.

<sup>1</sup>H NMR (399.9 MHz, DMSO-d<sub>6</sub>) δ 1.77 - 1.80 (2H, m), 2.12 - 2.20 (2H, m), 3.43  
 15 - 3.49 (2H, m), 4.25 - 4.28 (2H, m), 5.69 (1H, s), 7.68 (1H, d), 8.26 (2H, m), 8.87 (1H, d), 9.05 (1H, d); m/z = 433 [M+H]<sup>+</sup>.

The 4-[5-(trifluoromethyl)pyridin-3-yl]piperidin-4-ol used as starting material was prepared as follows:-

#### **Preparation of benzyl 4-hydroxy-4-[5-(trifluoromethyl)pyridin-3-yl]piperidine-1-carboxylate**

Isopropylmagnesium chloride-lithium chloride complex (1.0M in THF) (5.31 mL, 5.31 mmol) was added dropwise to 3-bromo-5-(trifluoromethyl)pyridine (1.20 g, 5.31 mmol) in THF (10 mL) cooled to 0 °C over a period of 10 minutes. The resulting solution was stirred at 0°C for 1 hour then benzyl 4-oxo-1-piperidinecarboxylate (1.24 g, 5.31  
 25 mmol) in THF (5 mL) was added dropwise. The mixture was allowed to warm slowly to room temperature and stirred for a further 1 hour before quenching with aqueous ammonium chloride (25 mL). The mixture was then extracted with tert butyl methyl ether.



The extract was washed with water followed by saturated brine, dried over  $\text{MgSO}_4$ , concentrated by evaporation then purified by flash silica chromatography, elution gradient 20 to 50% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford benzyl 4-hydroxy-4-[5-(trifluoromethyl)pyridin-3-yl]piperidine-1-carboxylate (1.32 g, 65%) as a pale yellow oil.

$^1\text{H}$  NMR (399.9 MHz,  $\text{CDCl}_3$ )  $\delta$  1.76 - 1.79 (2H, m), 1.94 - 2.08 (2H, m), 3.26 - 3.37 (2H, m), 4.12 - 4.27 (2H, m), 5.16 (2H, s), 5.17 (1H, s), 7.32 - 7.38 (5H, m), 8.05 (1H, m), 8.79 (1H, d), 8.90 (1H, d);  $m/z$  = 381  $[\text{M}+\text{H}]^+$ .

### Preparation of 4-[5-(trifluoromethyl)pyridin-3-yl]piperidin-4-ol

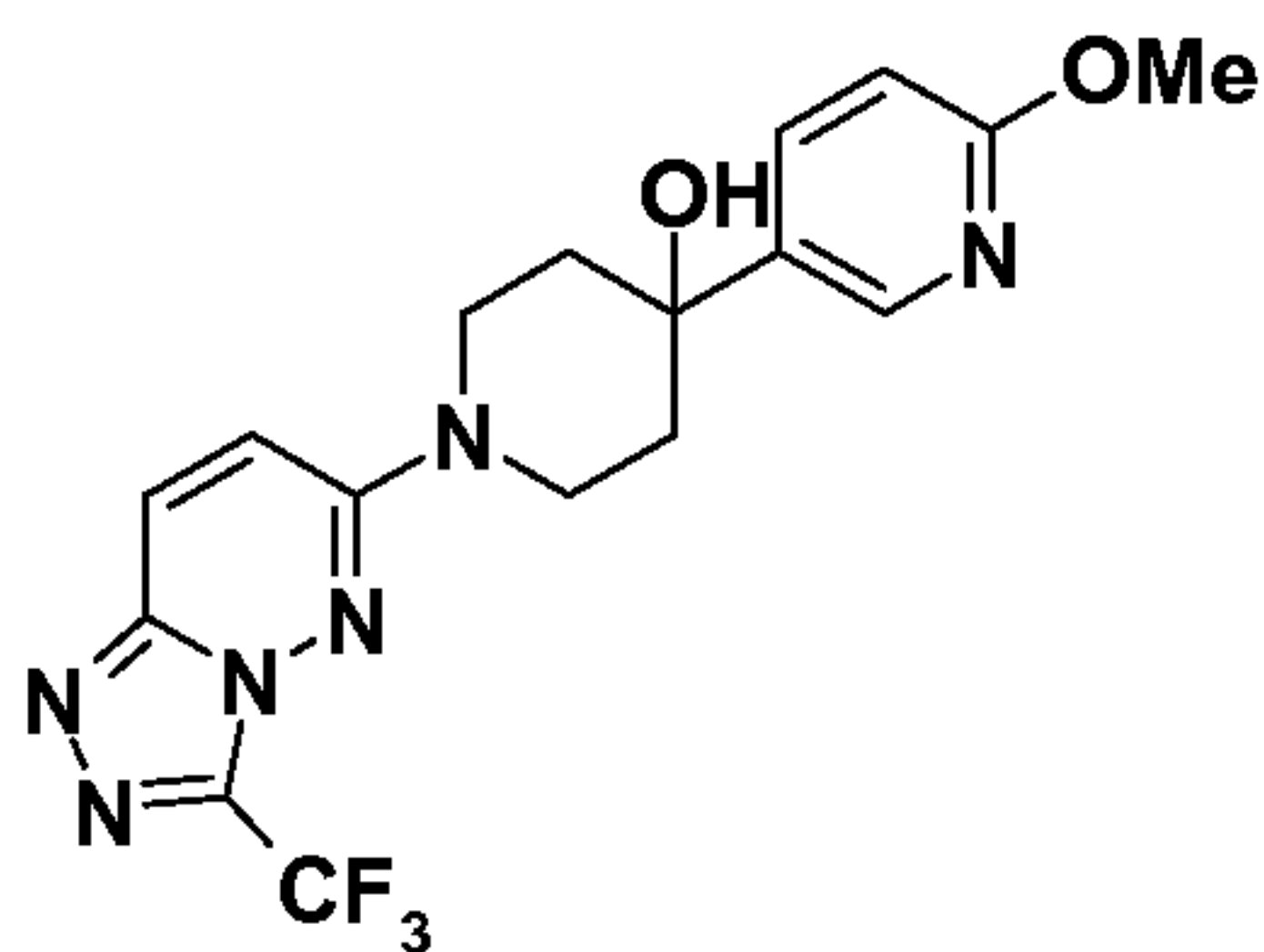
Benzyl 4-hydroxy-4-[5-(trifluoromethyl)pyridin-3-yl]piperidine-1-carboxylate (1.30 g, 3.42 mmol), 5% palladium on activated carbon (50 mg) and ammonium formate (2.0 g) in ethanol (20 mL) were stirred and heated under reflux for 1 hour then cooled to ambient temperature and filtered through diatomaceous earth. The filtrate was applied to an SCX column and eluted with methanol followed by 2M ammonia in methanol.

Fractions containing product were combined and evaporated then purified by flash silica chromatography, elution gradient 10 to 20% 2M ammonia in methanol in DCM. Pure fractions were evaporated to dryness to afford 4-[5-(trifluoromethyl)pyridin-3-yl]piperidin-4-ol (0.417 g, 50%) as a pale yellow solid.

$^1\text{H}$  NMR (399.9 MHz,  $\text{DMSO}-d_6$ )  $\delta$  1.56 - 1.59 (2H, m), 1.86 - 1.93 (2H, m), 2.77 - 2.80 (2H, m), 2.92 - 2.98 (2H, m), 5.27 (1H, s), 8.17 (1H, s), 8.85 (1H, s), 8.98 (1H, s);  $m/z$  = 247  $[\text{M}+\text{H}]^+$ .

### Example 321

#### Preparation of 4-(6-methoxypyridin-3-yl)-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol



A mixture of 4-(6-methoxypyridin-3-yl)piperidin-4-ol and 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by the method of Example 306 to



give 4-(6-methoxypyridin-3-yl)-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol in 58% yield.

<sup>1</sup>H NMR (399.9 MHz, DMSO-d<sub>6</sub>) δ 1.75 - 1.78 (2H, m), 1.99 - 2.04 (2H, m), 3.41 - 3.47 (2H, m), 3.84 (3H, s), 4.18 - 4.21 (2H, m), 5.30 (1H, s), 6.77 (1H, d), 7.66 (1H, d), 7.81 (1H, d), 8.24 (1H, d), 8.28 (1H, s); m/z = 395 [M+H]<sup>+</sup>.

The 4-(6-methoxypyridin-3-yl)piperidin-4-ol used as starting material was prepared as follows:-

**Preparation of benzyl 4-hydroxy-4-(6-methoxypyridin-3-yl)piperidine-1-carboxylate**

n-Butyllithium (1.6M in hexanes, 6.65 mL, 10.64 mmol) was added dropwise to 5-bromo-2-methoxypyridine (2.0 g, 10.64 mmol) in ether (30 mL) cooled to -78 °C over a period of 15 minutes. The resulting solution was stirred at -78°C for 40 minutes then a solution of benzyl 4-oxo-1-piperidinecarboxylate (2.48 g, 10.64 mmol) in ether (10 mL) was added dropwise. The reaction was allowed to warm slowly to room temperature then quenched with ammonium chloride solution (50 mL) and extracted with EtOAc. The extract was washed sequentially with water and saturated brine, dried over MgSO<sub>4</sub> and concentrated by evaporation then purified by flash silica chromatography, elution gradient 50 to 80% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford benzyl 4-hydroxy-4-(6-methoxypyridin-3-yl)piperidine-1-carboxylate (1.90 g, 52%) as a pale orange oil.

<sup>1</sup>H NMR (399.9 MHz, CDCl<sub>3</sub>) δ 1.75 - 1.79 (2H, m), 1.88 - 2.02 (2H, m), 3.29 - 3.35 (2H, m), 3.92 (3H, s), 4.03 - 4.16 (2H, m), 5.14 (2H, s), 6.72 (1H, d), 7.36 (5H, m), 7.66 (1H, dd), 8.24 (1H, d); m/z = 343 [M+H]<sup>+</sup>.

**Preparation of 4-(6-methoxypyridin-3-yl)piperidin-4-ol**

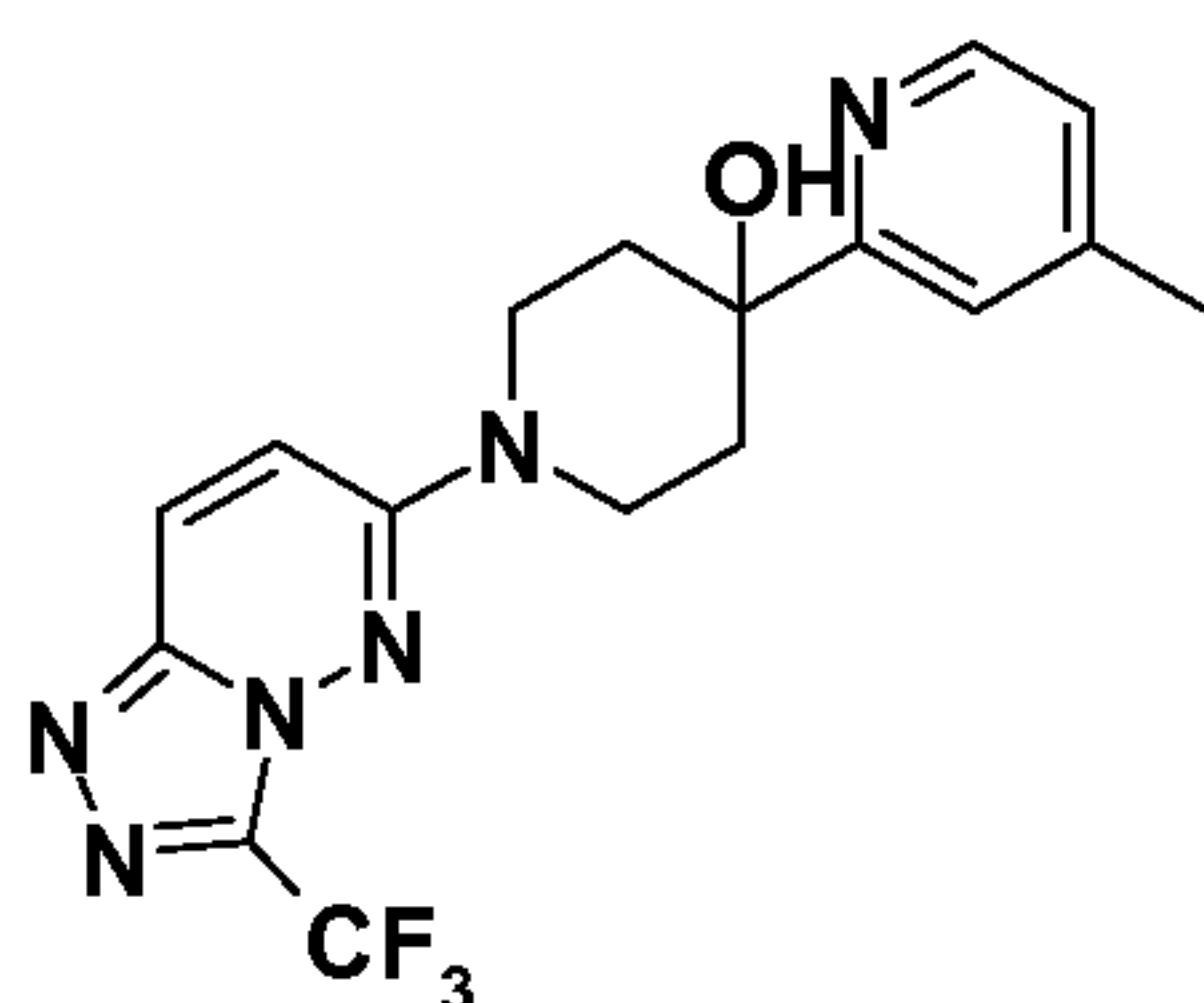
Obtained in 39% yield by an analogous method to Example 320, preparation of starting materials, starting from benzyl 4-hydroxy-4-(6-methoxypyridin-3-yl)piperidine-1-carboxylate.

<sup>1</sup>H NMR (399.9 MHz, DMSO-d<sub>6</sub>) δ 1.65 - 1.68 (2H, m), 1.92 - 1.99 (2H, m), 2.92 - 2.95 (2H, m), 3.01 - 3.07 (2H, m), 3.84 (3H, s), 5.13 (1H, br s), 6.79 (1H, d), 7.76 (1H, dd), 8.23 (1H, d); m/z = 209 [M+H]<sup>+</sup>.

**Example 322**

**Preparation of 4-(4-methylpyridin-2-yl)-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol**





A mixture of 4-(4-methylpyridin-2-yl)piperidin-4-ol and 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by the method of Example 306 to give 4-(4-methylpyridin-2-yl)-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol in 81% yield.

<sup>1</sup>H NMR (399.9 MHz, DMSO-d<sub>6</sub>) δ 1.64 - 1.67 (2H, m), 2.20 (2H, td), 2.35 (3H, s), 3.42 - 3.49 (2H, m), 4.19 - 4.22 (2H, m), 5.43 (1H, s), 7.09 (1H, d), 7.55 (1H, s), 7.66 (1H, d), 8.24 (1H, d), 8.34 (1H, d); m/z = 379 [M+H]<sup>+</sup>.

The 4-(4-methylpyridin-2-yl)piperidin-4-ol used as starting material was prepared as follows:-

#### **Preparation of benzyl 4-hydroxy-4-(4-methylpyridin-2-yl)piperidine-1-carboxylate**

Obtained in 56% yield by an analogous method to Example 321, preparation of starting materials, starting from benzyl 4-oxo-1-piperidinecarboxylate and 2-bromo-4-methylpyridine.

<sup>1</sup>H NMR (399.9 MHz, CDCl<sub>3</sub>) δ 1.58 - 1.61 (2H, m), 1.87 - 2.00 (2H, m), 3.21 (3H, s), 3.29 - 3.45 (2H, m), 4.09 - 4.29 (2H, m), 5.17 (2H, s), 5.32 (1H, s), 7.03 (1H, d), 7.10 (1H, s), 7.30 - 7.41 (5H, m), 8.37 (1H, d); m/z = 327 [M+H]<sup>+</sup>.

#### **Preparation of 4-(4-methylpyridin-2-yl)piperidin-4-ol**

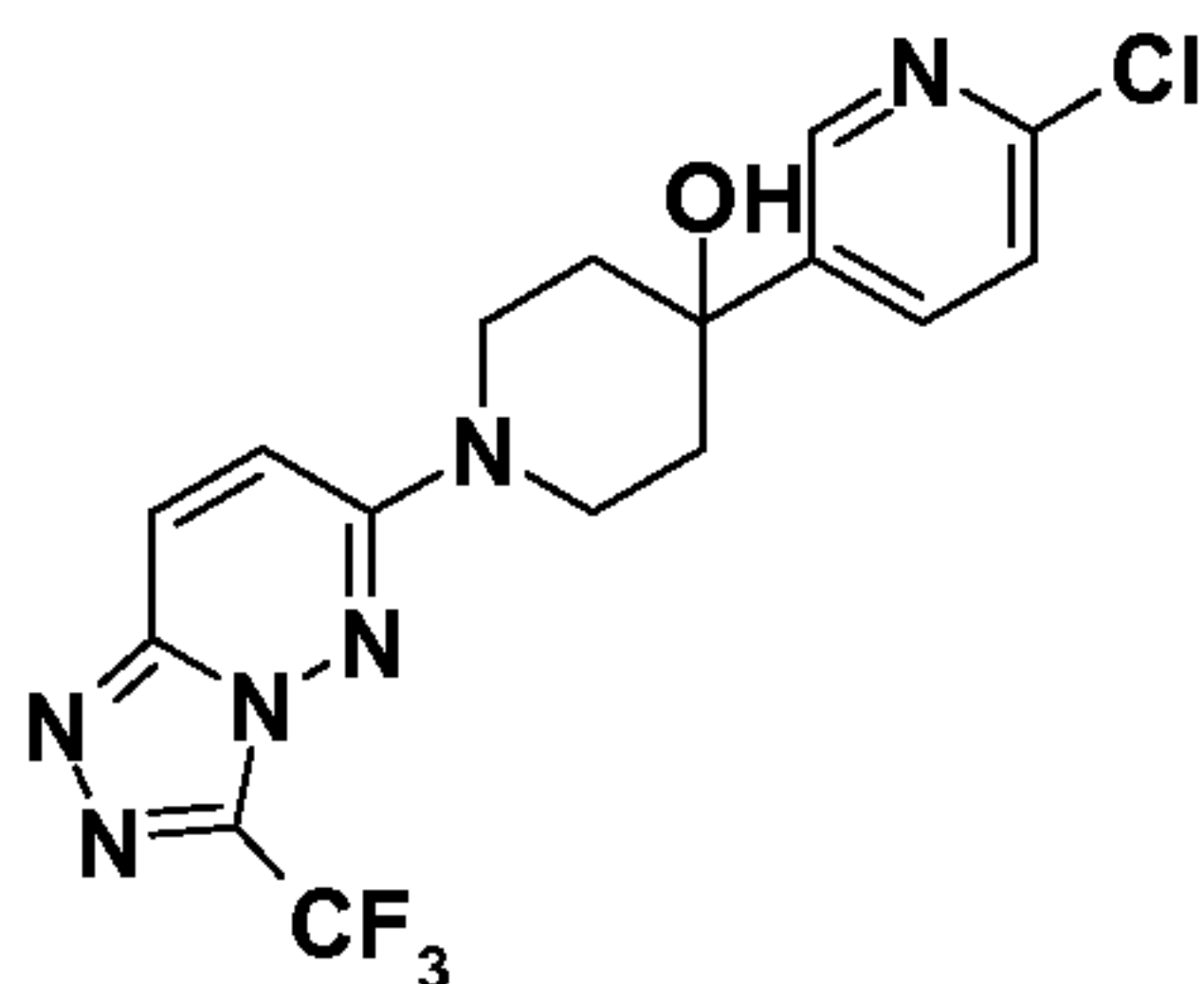
Obtained in 56% yield by an analogous method to Example 321, preparation of starting materials, starting from benzyl 4-hydroxy-4-(4-methylpyridin-2-yl)piperidine-1-carboxylate.

<sup>1</sup>H NMR (399.9 MHz, DMSO-d<sub>6</sub>) δ 1.39 - 1.42 (2H, m), 2.01 (2H, td), 2.33 (3H, s), 2.73 - 2.76 (2H, m), 2.88 - 2.94 (2H, m), 4.96 (1H, s), 7.06 (1H, d), 7.47 (1H, s), 8.36 (1H, d); m/z = 193 [M+H]<sup>+</sup>.

#### **Example 323**

#### **Preparation of 4-(6-chloropyridin-3-yl)-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol**





A mixture of 4-(6-chloropyridin-3-yl)piperidin-4-ol and 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by the method of Example 306 to give 4-(6-chloropyridin-3-yl)-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol in 80% yield.

<sup>1</sup>H NMR (399.9 MHz, DMSO-d<sub>6</sub>) δ 1.74 - 1.78 (2H, m), 2.06 (2H, td), 3.44 (2H, t), 4.21 - 4.25 (2H, m), 5.54 (1H, s), 7.47 (1H, d), 7.67 (1H, d), 7.96 (1H, dd), 8.25 (1H, d), 8.55 (1H, d); m/z = 399 [M+H]<sup>+</sup>.

The 4-(6-chloropyridin-3-yl)piperidin-4-ol used as starting material was prepared as follows:-

#### **Preparation of tert-butyl 4-hydroxy-4-(6-chloropyridin-3-yl)piperidine-1-carboxylate**

n-Butyl lithium (1.6M in hexanes, 6.50 mL, 10.39 mmol) was added dropwise to 5-bromo-2-chloropyridine (2.0 g, 10.39 mmol) in ether (30 mL) cooled to -78 °C over a period of 15 minutes. The resulting solution was stirred at -78°C for 45 minutes then a solution of tert-butyl 4-oxo-1-piperidinecarboxylate (1.66 g, 8.31 mmol) in ether (10 mL) was added dropwise. The reaction was allowed to warm slowly to room temperature then quenched with ammonium chloride solution (50 mL) and extracted with EtOAc. The extract was washed sequentially with water and saturated brine, dried over MgSO<sub>4</sub> and concentrated by evaporation, then purified by flash silica chromatography, elution gradient 20 to 50% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford tert-butyl 4-(6-chloropyridin-3-yl)-4-hydroxypiperidine-1-carboxylate (1.33 g, 41%) as a cream solid.

<sup>1</sup>H NMR (399.9 MHz, CDCl<sub>3</sub>) δ 1.48 (9H, s), 1.72 - 1.76 (2H, m), 1.90 - 2.01 (2H, m), 3.16 - 3.27 (2H, m), 3.99 - 4.13 (2H, m), 7.31 (1H, d), 7.76 (1H, dd), 8.50 (1H, d); m/z = 313 [M+H]<sup>+</sup>.

#### **Preparation of 4-(6-chloropyridin-3-yl)piperidin-4-ol**

HCl (4M in dioxan, 4.22 mL, 16.88 mmol) was added in one portion to a stirred suspension of tert-butyl 4-(6-chloropyridin-3-yl)-4-hydroxypiperidine-1-carboxylate (1.32

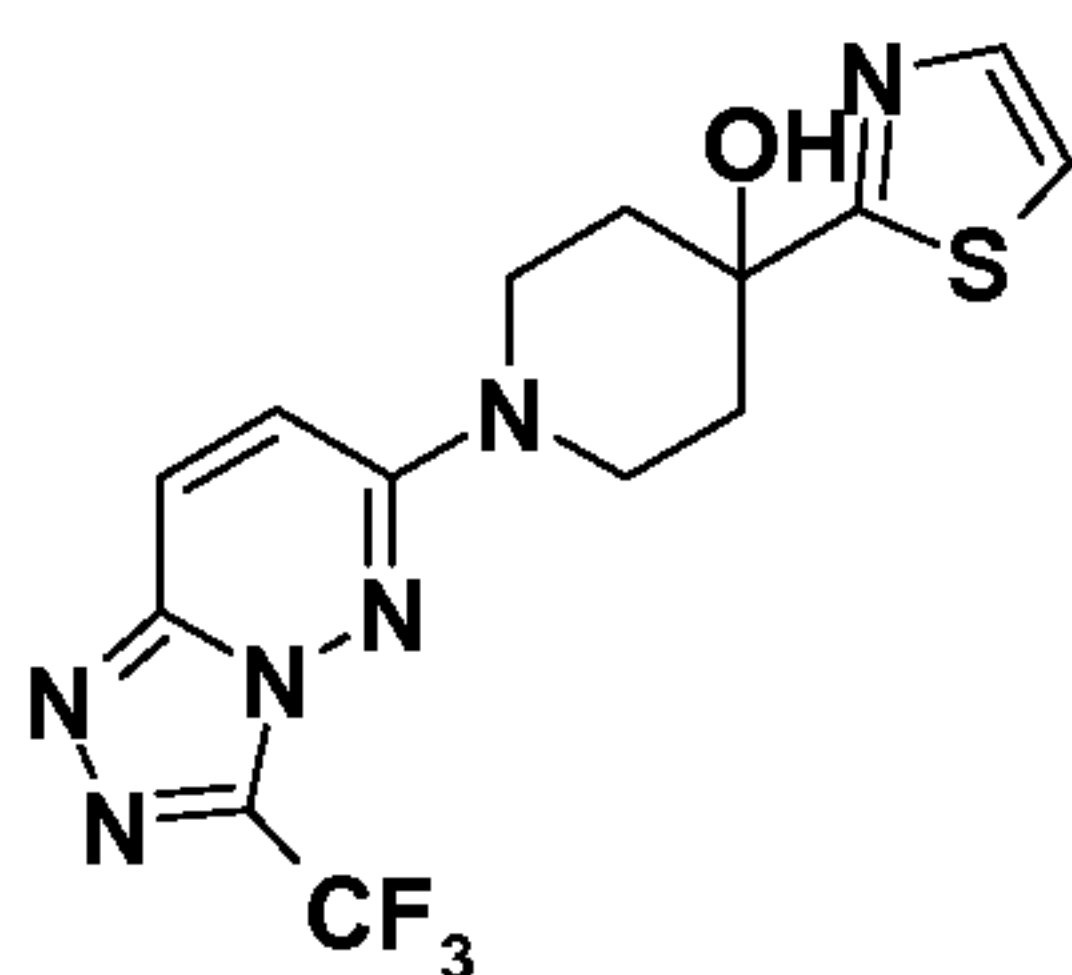


g, 4.22 mmol) in ethyl acetate (20 mL) at ambient temperature. The resulting mixture was stirred at 50°C for 90 minutes then cooled to room temperature, diluted with ether (20 mL) and filtered. The filtered solid was washed with ether and dried then taken up in methanol, applied to an SCX column and eluted with methanol followed by 2M ammonia in  
 5 methanol. Product-containing fractions were combined and evaporated then purified by flash silica chromatography, elution gradient 10 to 20% 2M ammonia in methanol in DCM. Pure fractions were evaporated to dryness to afford 4-(6-chloropyridin-3-yl)piperidin-4-ol (0.43 g, 48%) as a pale orange solid.

<sup>1</sup>H NMR (399.9 MHz, DMSO-d<sub>6</sub>) δ 1.53 - 1.56 (2H, m), 1.80 (2H, td), 2.72 - 2.75 (2H, m), 2.89 - 2.96 (2H, m), 5.09 (1H, s), 7.46 (1H, d), 7.90 (1H, dd), 8.49 (1H, d); m/z = 213 [M+H]<sup>+</sup>.

### **Example 324**

#### **Preparation of 4-(1,3-thiazol-2-yl)-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol**



A mixture of 4-(1,3-thiazol-2-yl)piperidin-4-ol and 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by the method of Example 306 to give 4-(1,3-thiazol-2-yl)-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol in 65% yield.

<sup>1</sup>H NMR (399.9 MHz, DMSO-d<sub>6</sub>) δ 1.86 - 1.89 (2H, m), 2.15 (2H, td), 3.44 - 3.51 (2H, m), 4.16 - 4.19 (2H, m), 6.28 (1H, s), 7.62 (1H, d), 7.66 (1H, d), 7.72 (1H, d), 8.26 (1H, d); m/z = 371 [M+H]<sup>+</sup>.

The 4-(1,3-thiazol-2-yl)piperidin-4-ol used as starting material was prepared as follows:-

#### **Preparation of tert-butyl 4-hydroxy-4-(1,3-thiazol-2-yl)piperidine-1-carboxylate**

Obtained in 80% yield by an analogous method to Example 323, preparation of starting materials, starting from tert-butyl 4-oxo-1-piperidinecarboxylate and 2-bromothiazole.



<sup>1</sup>H NMR (399.9 MHz, CDCl<sub>3</sub>) δ 1.47 (9H, s), 1.85 - 1.88 (2H, m), 2.11 (2H, td), 3.24 - 3.35 (2H, m), 3.92 - 4.08 (2H, m), 7.30 (1H, d), 7.71 (1H, d); m/z = 285 [M+H]<sup>+</sup>.

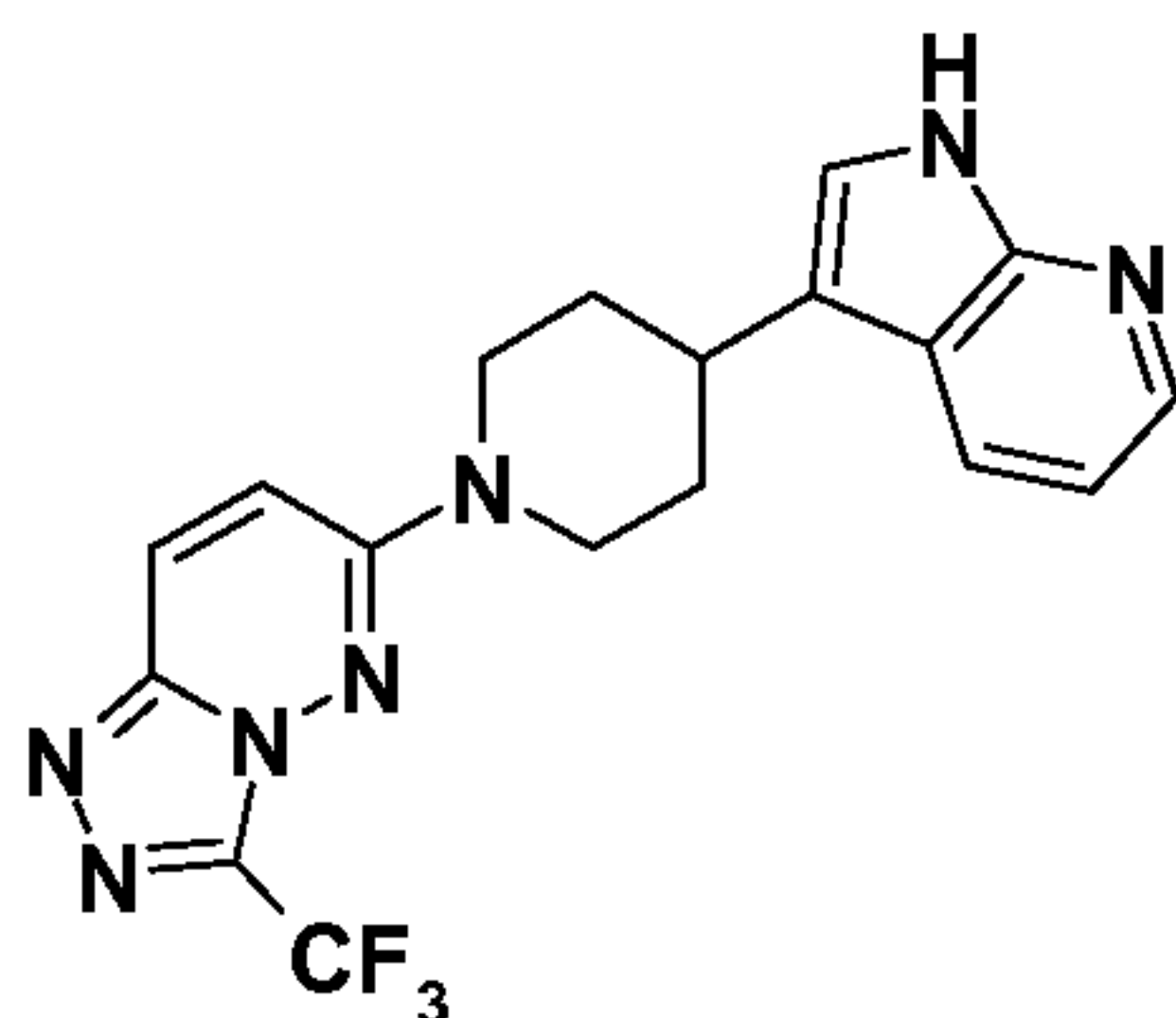
### Preparation of 4-(1,3-thiazol-2-yl)piperidin-4-ol

Obtained in 82% yield by an analogous method to Example 323, preparation of starting materials, starting from tert-butyl 4-hydroxy-4-(2-thiazolyl)piperidine-1-carboxylate.

<sup>1</sup>H NMR (399.9 MHz, DMSO-d<sub>6</sub>) δ 1.77 - 1.80 (2H, m), 2.14 (2H, td), 3.02 - 3.04 (4H, m), 6.17 (1H, br s), 7.61 (1H, d), 7.74 (1H, d); m/z = 185 [M+H]<sup>+</sup>.

### Example 325

#### Preparation of 6-[4-(1H-pyrrolo[2,3-b]pyridin-3-yl)piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine



6-Chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (160 mg, 0.72 mmol), 3-(piperidin-4-yl)-1H-pyrrolo[2,3-b]pyridine (145 mg, 0.72 mmol) and DIPEA (0.14 mL, 0.79 mmol) in DMF (2.0 mL) were stirred and heated at 80°C for 1 hour. The resulting mixture was then cooled to ambient temperature and quenched in water (10 mL) to give a beige solid. The solid was collected by filtration, washed sequentially with water, acetonitrile and ether, and air dried to give 6-[4-(1H-pyrrolo[2,3-b]pyridin-3-yl)piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine (217 mg, 78%) as a colourless solid.

<sup>1</sup>H NMR (399.9 MHz, DMSO-d<sub>6</sub>) δ 1.70 - 1.81 (2H, m), 2.09 - 2.12 (2H, m), 3.12 - 3.26 (3H, m), 4.40 - 4.43 (2H, m), 7.03 (1H, dd), 7.25 (1H, d), 7.67 (1H, d), 8.04 (1H, d), 8.19 (1H, dd), 8.24 (1H, d), 11.34 (1H, s); m/z = 388 [M+H]<sup>+</sup>.

The 4-(1H-pyrrolo[5,4-b]pyridin-3-yl)piperidine used as starting material was prepared as follows:-

### Preparation of tert-butyl 4-(1H-pyrrolo[2,3-b]pyridin-3-yl)-5,6-dihydropyridine-1(2H)-carboxylate



Potassium hydroxide (1.90 g, 33.86 mmol) was added to 1H-pyrrolo[2,3-b]pyridine (1.0 g, 8.46 mmol) and tert-butyl 4-oxopiperidine-1-carboxylate (3.37 g, 16.93 mmol) in methanol (25 mL) at ambient temperature, then the resulting solution was stirred at 65°C for 18 hours. The mixture was cooled to ambient temperature, quenched in dilute aqueous ammonium chloride (80 mL) and extracted with ethyl acetate. The extract was washed sequentially with water and saturated brine, dried over MgSO<sub>4</sub>, concentrated by evaporation and purified by flash silica chromatography, using 5% MeOH in DCM eluent. Pure fractions were combined and concentrated by evaporation, then triturated with ether to give a colourless precipitate. The precipitate was collected by filtration, washed with ether and air dried to afford tert-butyl 4-(1H-pyrrolo[2,3-b]pyridin-3-yl)-5,6-dihydropyridine-1(2H)-carboxylate (1.37 g, 54%) as a colourless solid.

<sup>1</sup>H NMR (399.9 MHz, CDCl<sub>3</sub>) δ 1.51 (9H, s), 2.57 (2H, m), 3.68 (2H, m), 4.14 (2H, m), 6.15 (1H, m), 7.13 (1H, dd), 7.33 (1H, s), 8.20 (1H, d), 8.34 (1H, d), 10.29 (1H, s); m/z = 300 [M+H]<sup>+</sup>.

#### **Preparation of tert-butyl 4-(1H-pyrrolo[2,3-b]pyridin-3-yl)piperidine-1-carboxylate**

tert-Butyl 4-(1H-pyrrolo[2,3-b]pyridin-3-yl)-5,6-dihydropyridine-1(2H)-carboxylate (1.35 g, 4.51 mmol), ammonium formate (1.42 g, 22.55 mmol) and 5% palladium on activated carbon (50 mg) in ethanol (25 mL) were stirred and refluxed for 1 hour. The resulting mixture was cooled to room temperature and filtered through diatomaceous earth. The filtrate was concentrated by evaporation then treated with dilute aqueous ammonium chloride (50 mL) and extracted with DCM. The extract was washed with water, dried over MgSO<sub>4</sub> and evaporated to a colourless solid. The solid was triturated with ether then collected by filtration and dried under vacuum to give tert-butyl 4-(1H-pyrrolo[2,3-b]pyridin-3-yl)piperidine-1-carboxylate (1.088 g, 80%) as a colourless solid.

<sup>1</sup>H NMR (399.9 MHz, CDCl<sub>3</sub>) δ 1.49 (9H, s), 1.64 - 1.74 (2H, m), 2.00 - 2.03 (2H, m), 2.86 - 3.00 (3H, m), 4.16 - 4.34 (2H, m), 7.06 - 7.10 (2H, m), 7.96 (1H, d), 8.31 (1H, s), 9.73 (1H, s); m/z = 302 [M+H]<sup>+</sup>.

#### **Preparation of 4-(1H-pyrrolo[5,4-b]pyridin-3-yl)piperidine**

TFA (5.0 mL, 3.58 mmol) was added in one portion at ambient temperature to a stirred suspension of tert-butyl 4-(1H-pyrrolo[2,3-b]pyridin-3-yl)piperidine-1-carboxylate (1.08 g, 3.58 mmol) in DCM (8 mL). The resulting solution was stirred for 30 minutes then



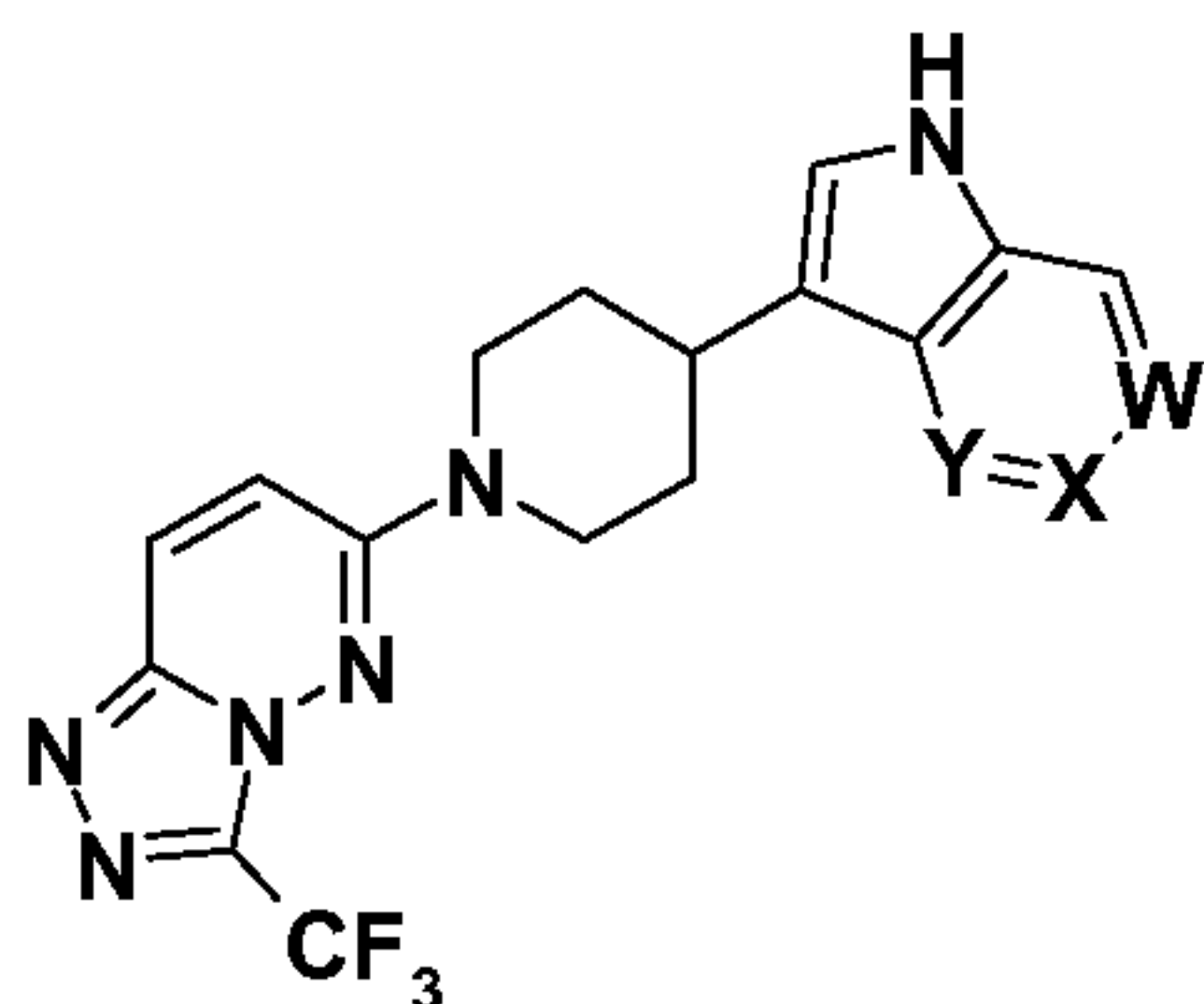
applied to an SCX column and eluted with MeOH followed by 2M ammonia in methanol. Pure fractions were combined and concentrated by evaporation, then triturated with ether to give a solid which was collected by filtration and air-dried to give 3-(piperidin-4-yl)-1H-pyrrolo[2,3-b]pyridine (0.64 g, 88%) as a colourless solid.

1H NMR (399.9 MHz, DMSO-d6)  $\delta$  1.54 - 1.63 (2H, m), 1.86 - 1.89 (2H, m), 2.62 - 2.68 (2H, m), 2.81 - 2.87 (1H, m), 3.02 - 3.05 (2H, m), 7.01 (1H, dd), 7.18 (1H, s), 7.98 (1H, d), 8.17 (1H, d), 11.28 (1H, s); m/z = 202 [M+H]<sup>+</sup>.

### Examples 326-328

The following compounds were prepared in 40-60% yield by an analogous method to

10 Example 325, starting from 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine  
and the appropriate 4-(1H-pyrrolopyridin-3-yl)piperidine:-



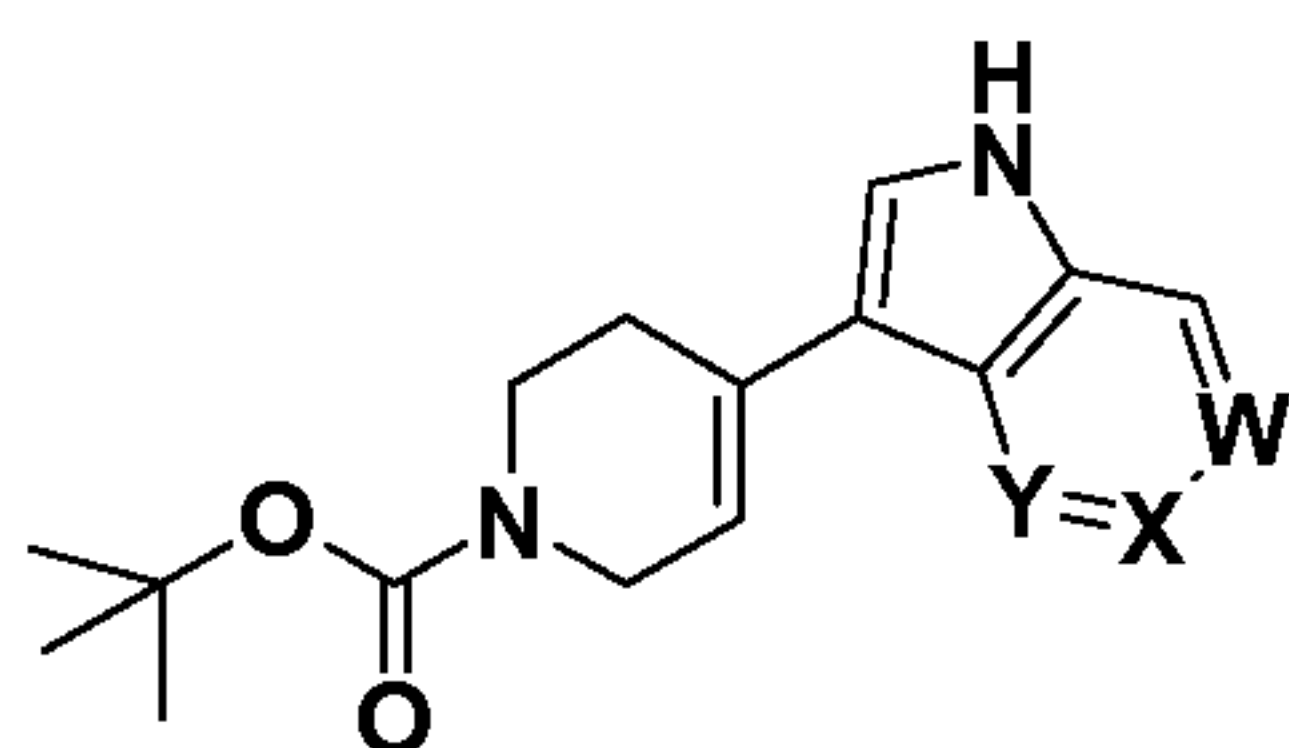
| Ex. | W  | X  | Y  | <sup>1</sup> H NMR (399.9 MHz, DMSO-d <sub>6</sub> )                                                                                                                                      | m/z [M+H] <sup>+</sup> |
|-----|----|----|----|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|
| 326 | CH | N  | CH | δ 1.72 - 1.82 (2H, m), 2.13 - 2.16 (2H, m), 3.18 - 3.27 (3H, m), 4.40 - 4.43 (2H, m), 7.22 (1H, dd), 7.32 (1H, d), 7.68 (1H, d), 8.14 (1H, d), 8.24 (1H, d), 8.93 (1H, s), 11.23 (1H, s). | 388                    |
| 327 | N  | CH | CH | δ 1.71 - 1.81 (2H, m), 2.09 - 2.12 (2H, m), 3.12 - 3.27 (3H, m), 4.40 - 4.43 (2H, m), 7.40 (1H, d), 7.60 (1H, d), 7.68 (1H, d), 8.07 (1H, d), 8.25 (1H, d), 8.70 (1H, d), 11.33 (1H, s).  | 388                    |
| 328 | CH | CH | N  | δ 1.81 - 1.92 (2H, m), 2.17 - 2.20 (2H, m), 3.18 - 3.30 (3H, m), 4.40 (2H, d), 7.08 (1H, dd), 7.42 (1H, d), 7.67 (1H, d), 7.71 (1H, dd), 8.24 (1H, d), 8.29 (1H, dd), 11.02 (1H, s).      | 388                    |



The isomeric 4-(1H-pyrrolopyridin-3-yl)piperidines used as starting materials in Examples 326-328 were prepared in 3 steps as follows:-

**Preparation of tert-butyl 4-(1H-pyrrolopyridin-3-yl)-3,6-dihydro-2H-pyridine-1-carboxylates**

- 5 Obtained in 49-54% yield by an analogous procedure to Example 325, preparation of starting materials, starting from tert-butyl 4-oxopiperidine-1-carboxylate and the appropriate 1H-pyrrolopyridine.

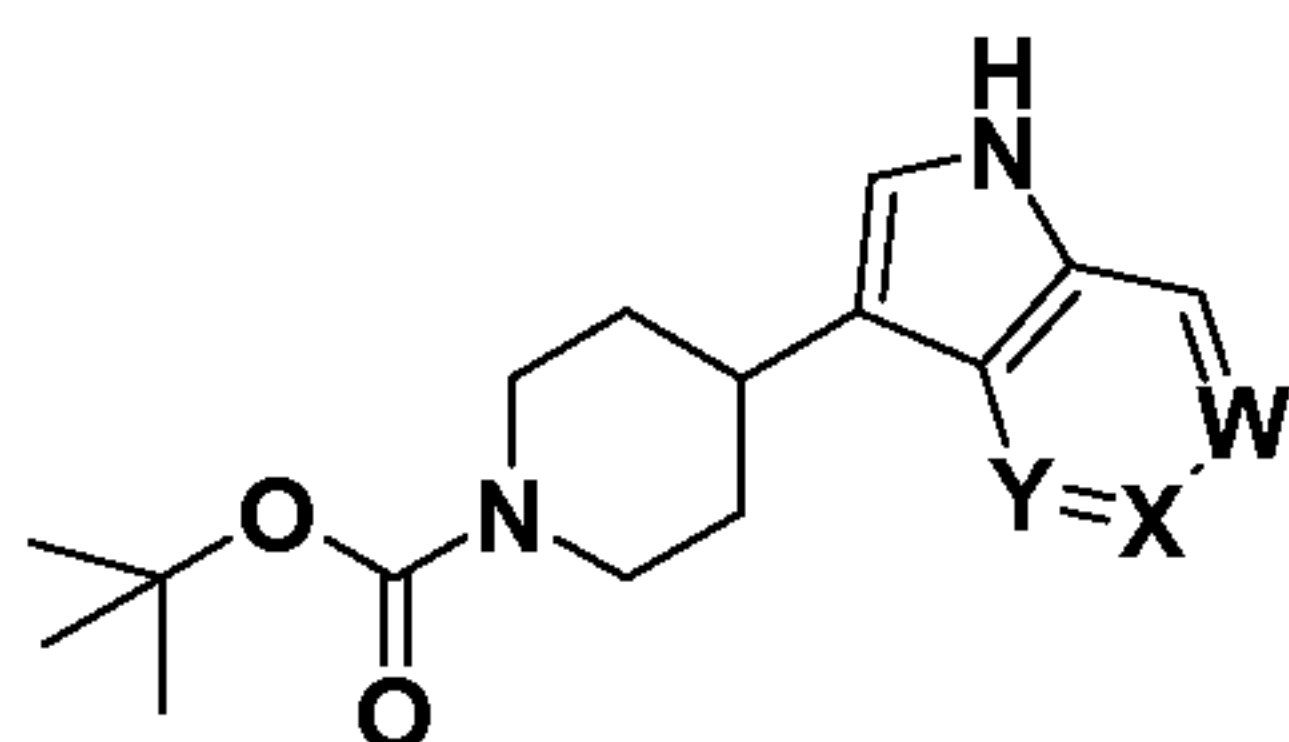


| Precursor to Ex. | W  | X  | Y  | <sup>1</sup> H NMR (399.9 MHz, CDCl <sub>3</sub> )                                                                                                                    | m/z<br>[M+H] <sup>+</sup> |
|------------------|----|----|----|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|
| 326              | CH | N  | CH | δ 1.51 (9H, s), 2.55 - 2.61 (2H, m), 3.69 (2H, t), 4.16 (2H, m), 6.23 (1H, m), 7.22 (1H, s), 7.31 (1H, d), 8.33 (1H, d), 9.20 (2H, m).                                | 300                       |
| 327              | N  | CH | CH | δ 1.51 (9H, s), 2.54 - 2.62 (2H, m), 3.68 - 3.71 (2H, m), 4.12 - 4.19 (2H, m), 6.16 (1H, m), 7.38 (1H, s), 7.77 (1H, d), 8.29 (1H, d), 8.83 (1H, s), 9.63 (1H, br s). | 300                       |
| 328              | CH | CH | N  | δ 1.49 (9H, s), 2.57 - 2.60 (2H, m), 3.68 - 3.71 (2H, m), 4.17 - 4.19 (2H, m), 7.13 (1H, dd), 7.20 (1H, m), 7.36 (1H, d), 7.65 (1H, dd), 8.36 (1H, s), 8.53 (1H, dd). | 300                       |



**Preparation of tert-butyl 4-(1H-pyrrolopyridin-3-yl)piperidine-1-carboxylates**

Obtained in 75-81% yield by an analogous procedure to Example 325, preparation of starting materials, starting from the appropriate tert-butyl 4-(1H-pyrrolopyridin-3-yl)-3,6-dihydro-2H-pyridine-1-carboxylate.



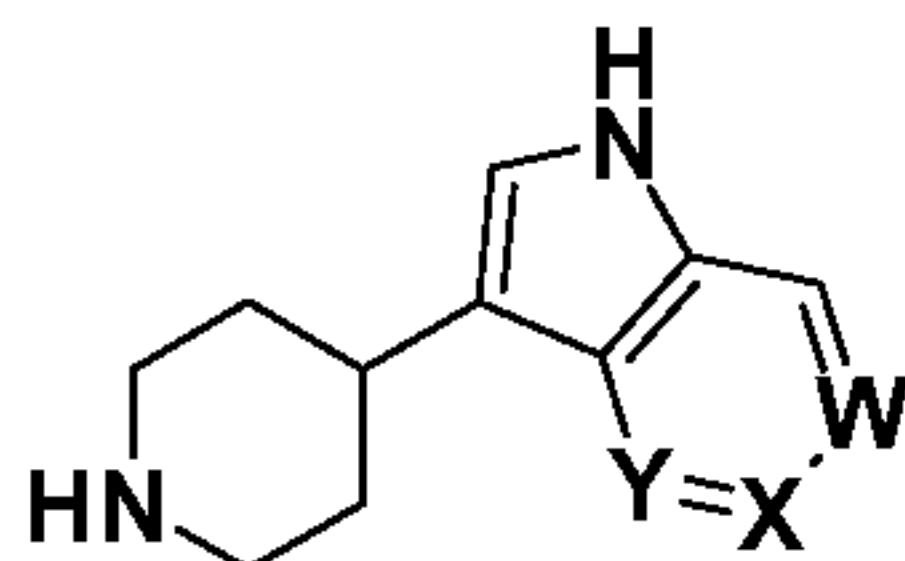
5

| Precursor to Ex. | W  | X  | Y  | <sup>1</sup> H NMR (399.9 MHz, CDCl <sub>3</sub> )                                                                                                                                                 | m/z [M+H] <sup>+</sup> |
|------------------|----|----|----|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|
| 326              | CH | N  | CH | δ 1.49 (9H, s), 1.63 - 1.74 (2H, m), 2.04 - 2.07 (2H, m), 2.88 - 2.95 (2H, m), 3.00 - 3.08 (1H, m), 4.16 - 4.34 (2H, m), 7.03 (1H, s), 7.31 (1H, dd), 8.29 (1H, d), 8.96 (1H, d), 9.04 (1H, br s). | 302                    |
| 327              | N  | CH | CH | δ 1.49 (9H, s), 1.64 - 1.74 (2H, m), 1.98 - 2.02 (2H, m), 2.86 - 2.92 (2H, m), 2.97 - 3.05 (1H, m), 4.16 - 4.37 (2H, m), 6.25 (1H, br s), 7.58 (1H, s), 7.76 (1H, d), 8.11 (1H, d), 9.26 (1H, s).  | 302                    |
| 328              | CH | CH | N  | δ 1.48 (9H, s), 1.60 - 1.70 (2H, m), 2.14 - 2.17 (2H, m), 2.90 - 2.96 (2H, m), 3.22 - 3.30 (1H, m), 4.21 (2H, m), 7.11 (1H, dd), 7.18 (1H, d), 7.64 (1H, dd), 8.31 (1H, s), 8.47 (1H, dd).         | 302                    |



**Preparation of 4-(1H-pyrrolopyridin-3-yl)piperidines**

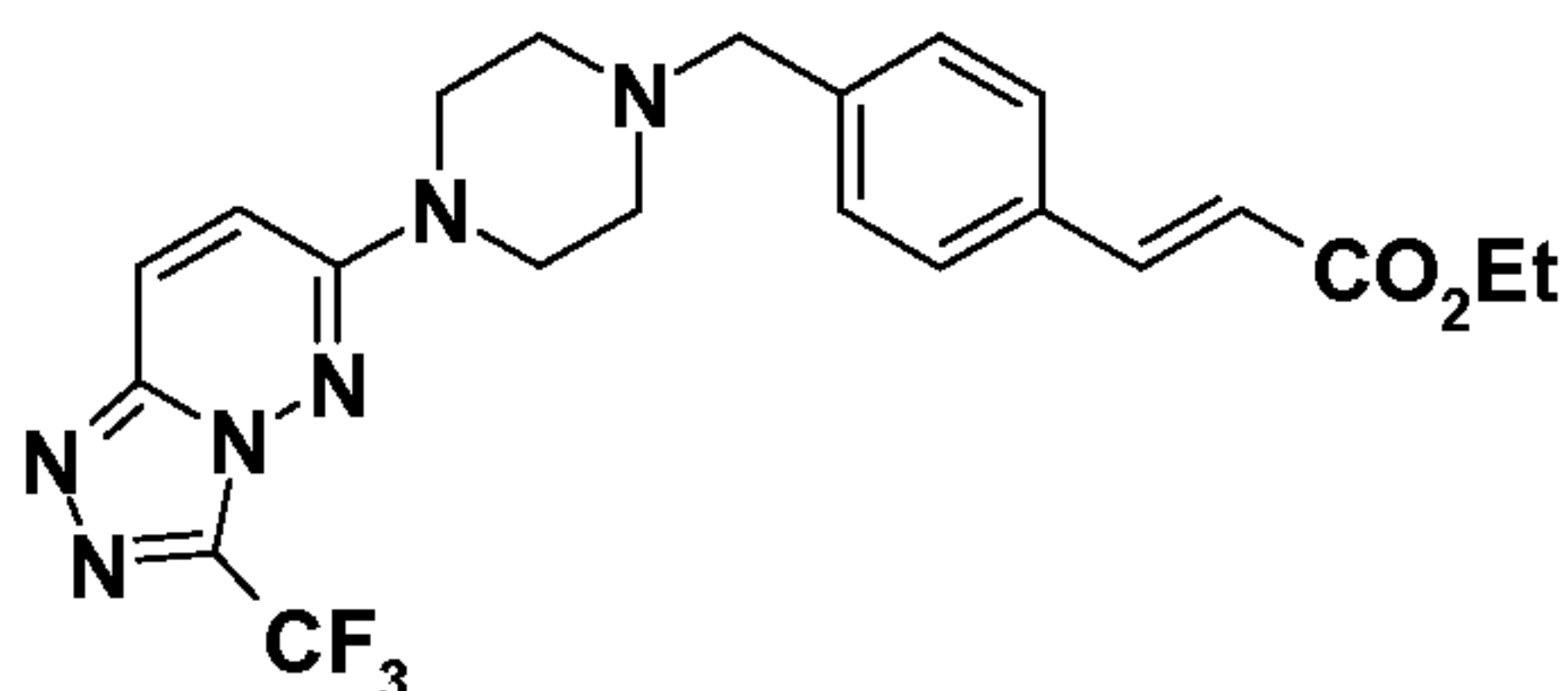
Obtained in 72-100% yield by an analogous procedure to Example 325, preparation of starting materials, starting from the appropriate tert-butyl 4-(1H-pyrrolopyridin-3-yl)piperidine-1-carboxylates.



5

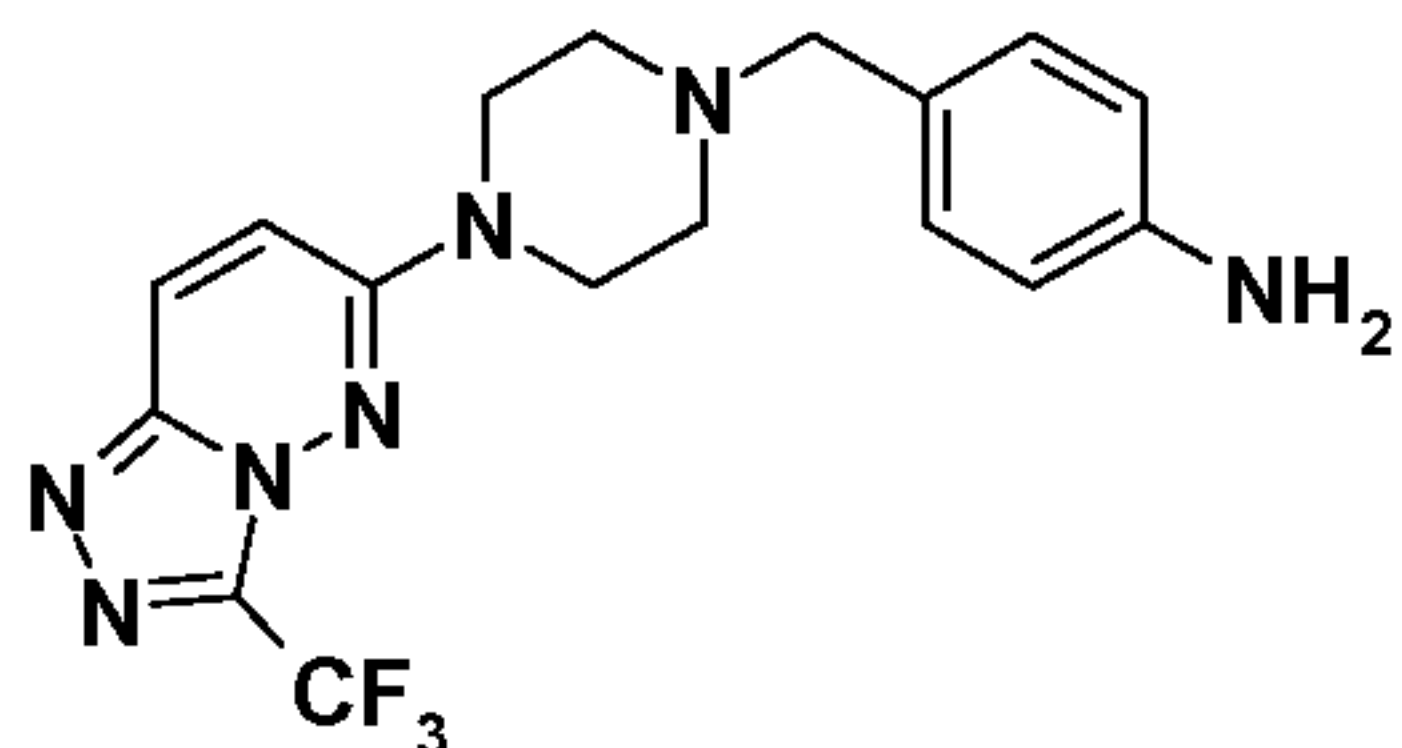
| Precursor to Ex. | W  | X  | Y  | <sup>1</sup> H NMR (399.9 MHz, DMSO-d <sub>6</sub> )                                                                                                                              | m/z [M+H] <sup>+</sup> |
|------------------|----|----|----|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|
| 326              | CH | N  | CH | δ 1.60 - 1.70 (2H, m), 1.92 - 1.95 (2H, m), 2.69 - 2.75 (2H, m), 2.91 - 2.99 (1H, m), 3.07 - 3.10 (2H, m), 7.17 (1H, s), 7.32 (1H, d), 8.13 (1H, d), 8.89 (1H, s), 11.20 (1H, s). | 202                    |
| 327              | N  | CH | CH | δ 1.53 - 1.64 (2H, m), 1.85 - 1.88 (2H, m), 2.63 - 2.68 (2H, m), 2.82 - 2.88 (1H, m), 3.02 - 3.05 (2H, m), 7.33 (1H, s), 7.55 (1H, d), 8.05 (1H, d), 8.69 (1H, s), 11.27 (1H, s). | 202                    |
| 328              | CH | CH | N  | δ 1.59 - 1.69 (2H, m), 1.96 - 2.00 (2H, m), 2.63 - 2.70 (2H, m), 2.96 - 3.06 (3H, m), 7.06 (1H, dd), 7.35 (1H, d), 7.69 (1H, dd), 8.28 (1H, dd), 10.96 (1H, s).                   | 202                    |



**Example 329****Preparation of ethyl (2E)-3-[4-([4-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl)methyl]phenyl]prop-2-enoate**

5 A mixture of ethyl (E)-3-(4-formylphenyl)prop-2-enoate and 6-(piperazin-1-yl)-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by General Synthetic Method 7 to give ethyl (2E)-3-[4-([4-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl)methyl]phenyl]prop-2-enoate in 59% yield.

1H NMR (300.1 MHz, DMSO-d<sub>6</sub>) δ 1.27 (3H, t), 2.49 - 2.51 (4H, m), 3.58 (2H, s), 3.62  
 10 (4H, t), 4.20 (2H, q), 6.61 (1H, d), 7.39 (2H, d), 7.54 - 7.73 (4H, m), 8.24 (1H, d); m/z = 461 [M+H]<sup>+</sup>.

**Example 330****Preparation of 4-[[4-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl)methyl]aniline**

15 TFA (0.5 mL, 0.15 mmol) was added to tert-butyl N-[4-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl)methyl]phenyl]carbamate (obtained as described in Example 146, 72 mg, 0.15 mmol) in DCM (2 mL). The resulting solution was stirred at ambient temperature for 2 hours and then evaporated to dryness. The crude  
 20 product was purified by preparative HPLC using decreasingly polar mixtures of water (containing 0.1% TFA) and MeCN as eluents. Fractions containing the desired compound were evaporated and further purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 7M ammonia in methanol and pure fractions were evaporated to dryness to afford 4-[[4-[3-  
 25 (trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl)methyl]aniline (32 mg, 56%).

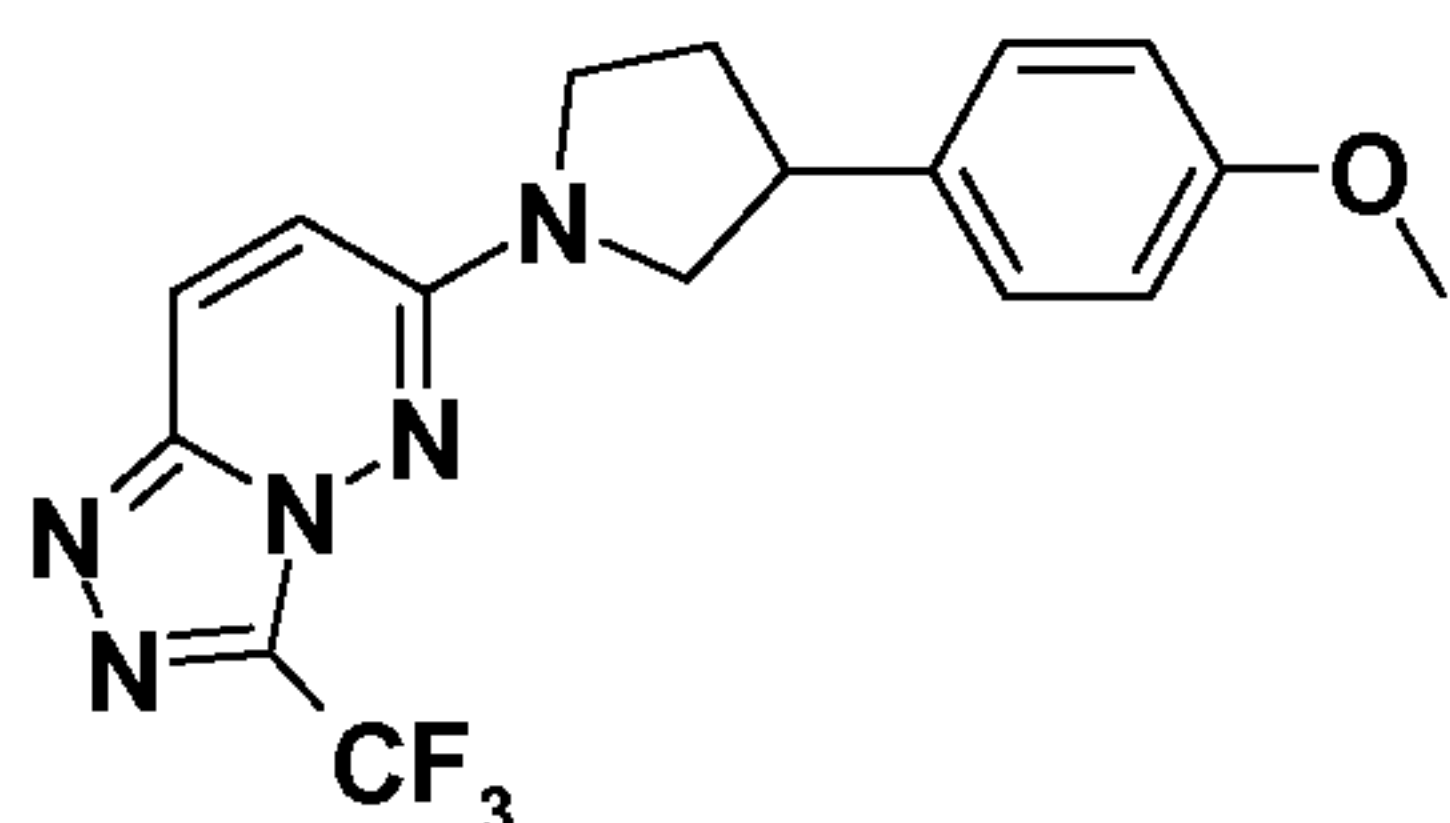


<sup>1</sup>H NMR (300.1 MHz, DMSO-d<sub>6</sub>) δ 2.29 (4H, t), 3.18 (2H, s), 3.42 (4H, t), 4.79 (2H, s), 6.36 (2H, d), 6.79 (2H, d), 7.41 (1H, d), 8.07 (1H, d); m/z = 378 [M+H]<sup>+</sup>.

### **Example 331**

#### **Preparation of 6-[3-(4-methoxyphenyl)pyrrolidin-1-yl]-3-**

#### **(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine**

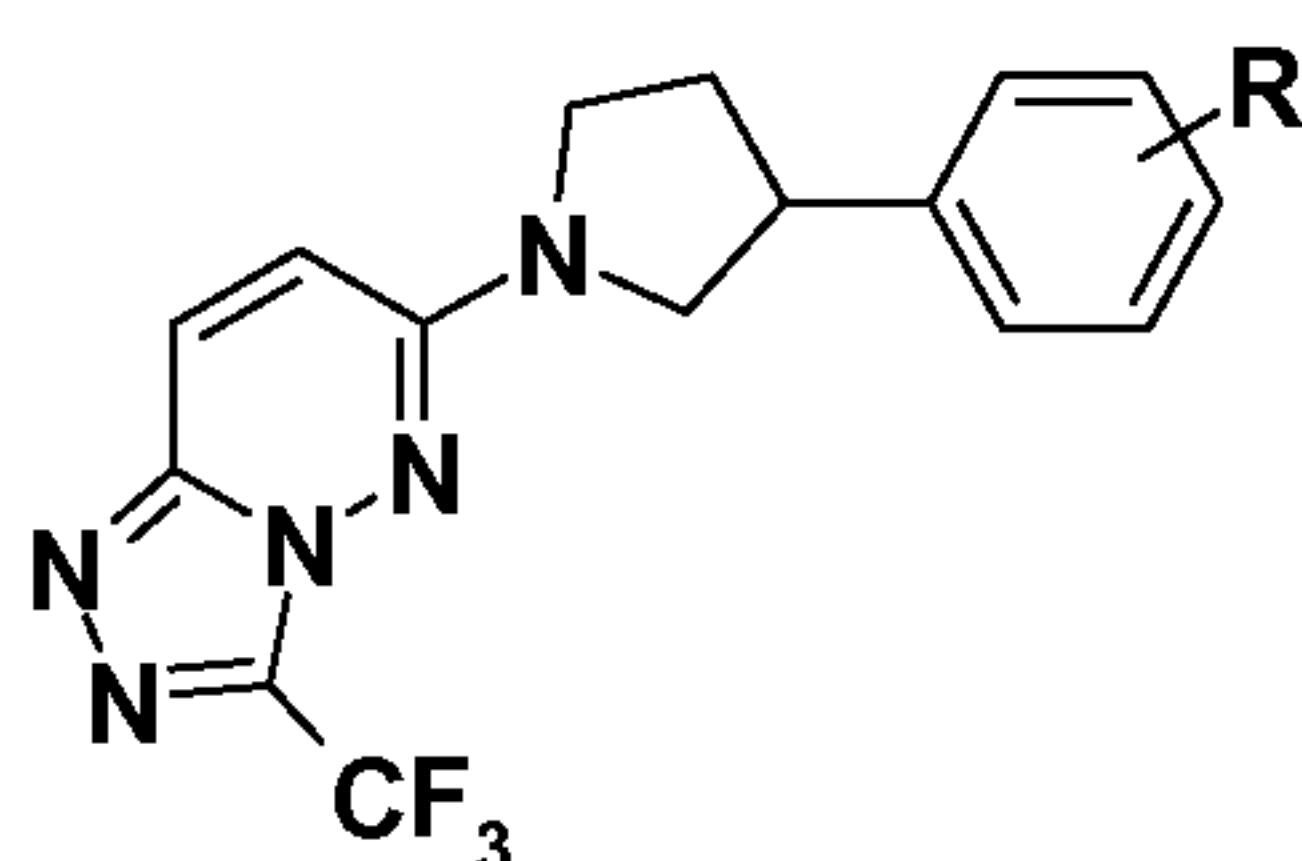


A solution of 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (50 mg, 0.22 mmol) in ethanol (1 mL) was added to 3-(4-methoxyphenyl)pyrrolidine hydrochloride (71 mg, 0.33 mmol). The reaction mixture was treated with DIPEA (86 mg, 0.66 mmol) and the mixture was heated at 70°C for 16 hours. The reaction mixture was evaporated to leave an involatile residue that was purified by preparative reverse phase chromatography to give 6-[3-(4-methoxyphenyl)pyrrolidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine (45 mg, 55%).

<sup>1</sup>H NMR (300.1 MHz, DMSO-d<sub>6</sub>) δ 2.00 - 2.18 (1H, m), 2.30 - 2.42 (1H, m), 3.33 - 3.66 (3H, m), 3.68 - 3.83 (4H, m), 3.89 - 4.06 (1H, m), 6.88 - 6.96 (2H, m), 7.24 - 7.34 (3H, m), 8.23 (1H, d); m/z = 364 [M+H]<sup>+</sup>.

### **Examples 332-334**

The following compounds were prepared in 64-77% yield by an analogous method to Example 331, starting from 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine and the appropriate aryl pyrrolidine hydrochloride:-



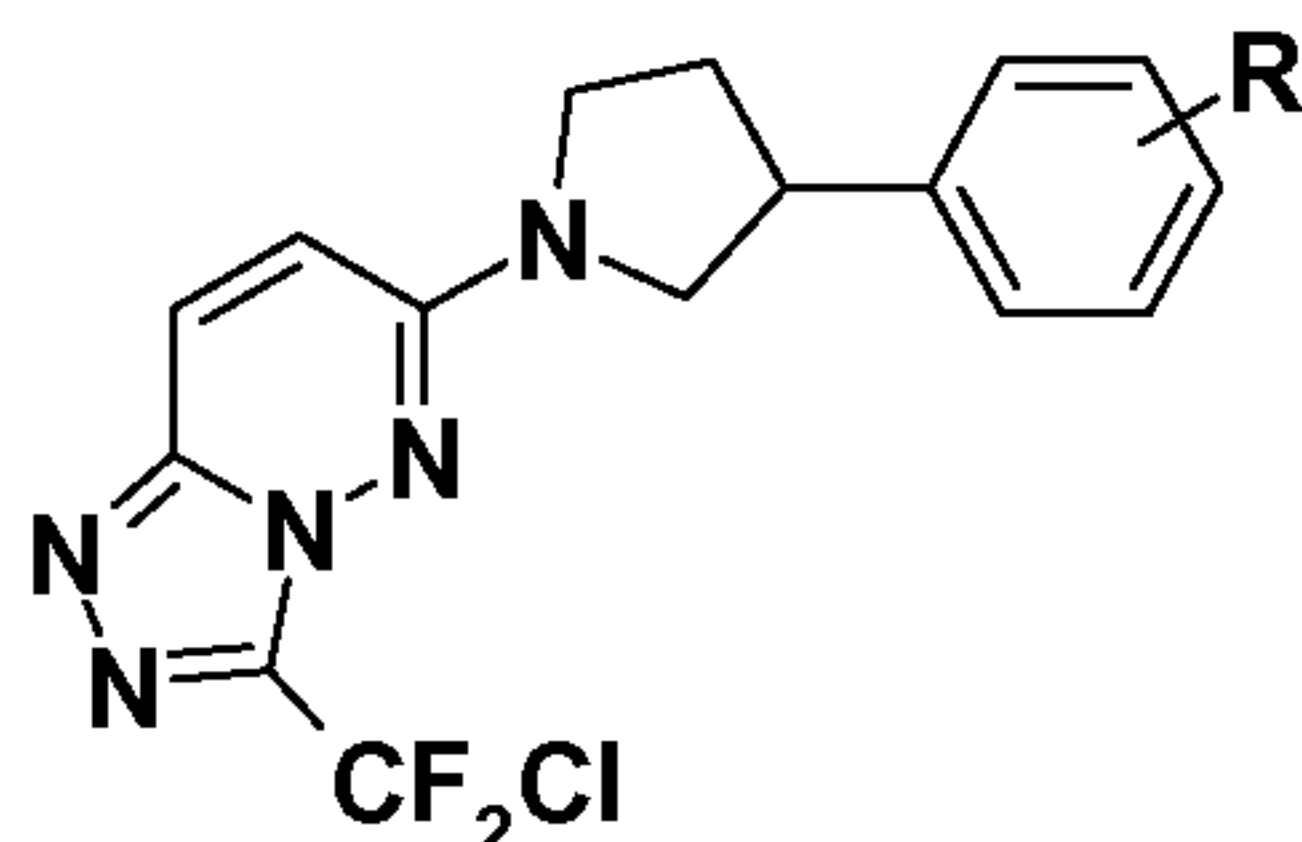
| Ex. | R    | <sup>1</sup> H NMR (300.1 MHz, DMSO-d <sub>6</sub> )                                                                                                           | m/z [M+H] <sup>+</sup> |
|-----|------|----------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|
| 332 | 3-CN | 6-cδ 2.08 - 2.25 (1H, m), 2.37 - 2.48 (1H, m), 3.41 - 3.71 (3H, m), 3.72 - 3.86 (1H, m), 3.98 - 4.11 (1H, m), 7.31 (1H, d), 7.58 (1H, t), 7.72 - 7.77 (2H, m), | 359                    |



|     |                      |                                                                                                                                                                                                                              |     |
|-----|----------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
|     |                      | 7.88 (1H, t), 8.26 (1H, d)                                                                                                                                                                                                   |     |
| 333 | 2-CO <sub>2</sub> Me | 6-cδ 2.14 - 2.30 (1H, m), 2.31 - 2.44 (1H, m), 3.41 - 3.68 (2H, m), 3.71 - 3.83 (1H, m), 3.86 (3H, s), 3.97 (1H, t), 4.10 - 4.23 (1H, m), 7.31 (1H, d), 7.36 - 7.43 (1H, m), 7.55 - 7.61 (2H, m), 7.77 (1H, d), 8.24 (1H, d) | 392 |
| 334 | 3-CO <sub>2</sub> Me | 6-cδ 2.15 - 2.33 (1H, m), 2.47 - 2.58 (1H, m), 3.47 - 3.81 (3H, m), 3.82 - 3.92 (1H, m), 3.94 (3H, s), 4.06 - 4.21 (1H, m), 7.41 (1H, d), 7.60 (1H, t), 7.73 - 7.79 (1H, m), 7.92 - 7.98 (1H, m), 8.03 (1H, t), 8.32 (1H, d) | 392 |

**Examples 335-338**

The following compounds were prepared in 52-74% yield by an analogous method to Example 331, starting from 6-chloro-3-[chloro(difluoro)methyl]-[1,2,4]triazolo[4,3-b]pyridazine and the appropriate aryl pyrrolidine hydrochloride:-



5

| Ex. | R                 | <sup>1</sup> H NMR (300.1 MHz, CDCl <sub>3</sub> )                                                                                                                              | m/z [M+H] <sup>+</sup> |
|-----|-------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|
| 335 | 4-CF <sub>3</sub> | δ 2.17 - 2.32 (1H, m), 2.49 - 2.61 (1H, m), 3.54 - 3.75 (3H, m), 3.81 - 3.91 (1H, m), 4.03 - 4.11 (1H, m), 6.89 (1H, d), 7.42 (2H, d), 7.64 (2H, d), 7.95 (1H, d)               | 418                    |
| 336 | 3-CF <sub>3</sub> | δ 2.18 - 2.34 (1H, m), 2.49 - 2.61 (1H, m), 3.52 - 3.75 (3H, m), 3.83 - 3.93 (1H, m), 4.04 - 4.13 (1H, m), 6.89 (1H, d), 7.47 - 7.53 (2H, m), 7.53 - 7.60 (2H, m), 7.95 (1H, d) | 418                    |
| 337 | H (S-enantiomer)  | δ 2.16 - 2.32 (1H, m), 2.45 - 2.56 (1H, m), 3.52 - 3.72 (3H, m), 3.80 - 3.91 (1H, m), 3.98 - 4.11 (1H, m), 6.89 (1H, d), 7.27 - 7.33 (3H,                                       | 350                    |



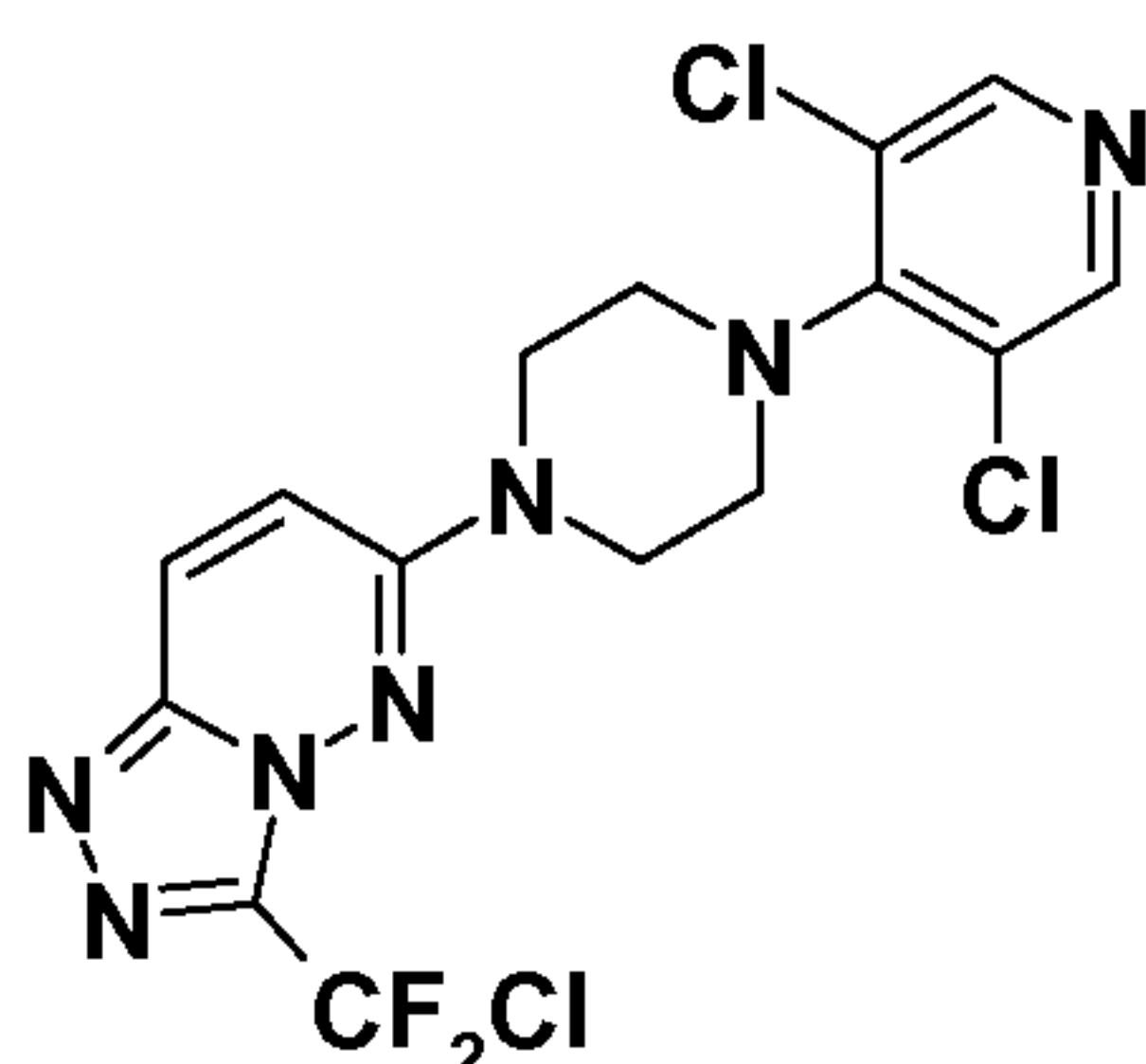
|     |                  |                                                                                                                                                                                        |     |
|-----|------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
|     |                  | m), 7.34 - 7.42 (2H, m), 7.93 (1H, d)                                                                                                                                                  |     |
| 338 | H (R-enantiomer) | $\delta$ 2.16 - 2.31 (1H, m), 2.45 - 2.56 (1H, m), 3.51 - 3.72 (3H, m), 3.79 - 3.90 (1H, m), 3.98 - 4.10 (1H, m), 6.89 (1H, d), 7.27 - 7.33 (3H, m), 7.34 - 7.42 (2H, m), 7.92 (1H, d) | 350 |

The 6-chloro-3-[chloro(difluoro)methyl]-[1,2,4]triazolo[4,3-b]pyridazine used as starting material was obtained in 70% yield by an analogous method to General Synthetic Method 1, preparation of starting materials, starting from 3-chloropyridazin-6-yl hydrazine and chlorodifluoroacetic acid.

5 <sup>1</sup>H NMR (300.1 MHz, DMSO)  $\delta$  7.77 (d, 1H), 8.68 (d, 1H); m/z = 239 [M+H]<sup>+</sup>.

### **Example 339**

#### **Preparation of 3-[chloro(difluoro)methyl]-6-[4-(3,5-dichloropyridin-4-yl)piperazin-1-yl][1,2,4]triazolo[4,3-b]pyridazine**



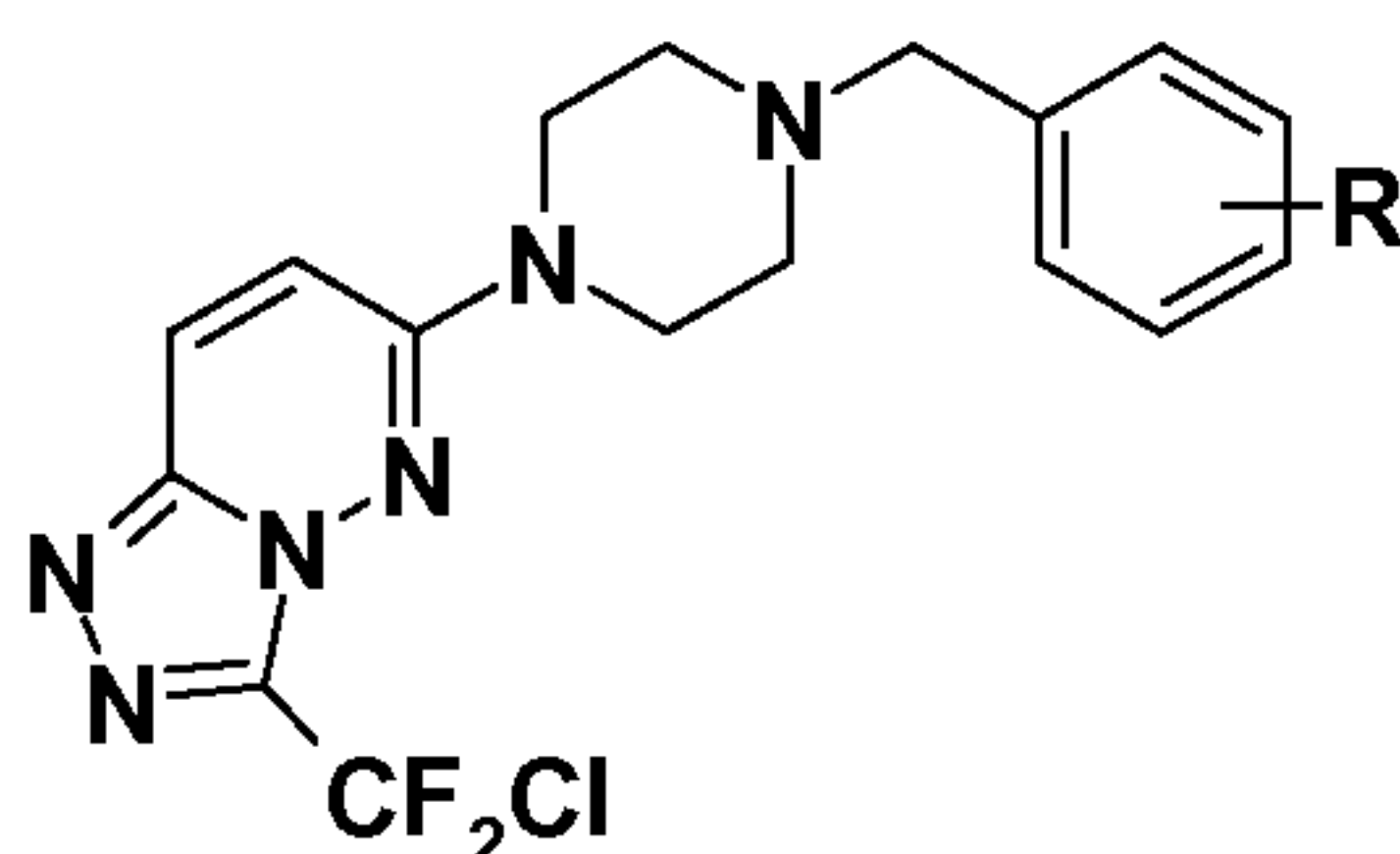
10 A solution of 6-chloro-3-[chloro(difluoro)methyl]-[1,2,4]triazolo[4,3-b]pyridazine (obtained as described in Examples 335-338, preparation of starting materials) (53 mg, 0.22 mmol) in ethanol (1 mL) was added to 1-(3,5-dichloropyridin-4-yl)piperazine (77 mg, 0.33 mmol). The reaction mixture was treated with DIPEA (43 mg, 0.33 mmol) and the mixture was heated at 70°C for 4 hours. The reaction mixture was evaporated to leave an  
 15 involatile residue that was purified by preparative reverse phase chromatography to give 3-[chloro(difluoro)methyl]-6-[4-(3,5-dichloropyridin-4-yl)piperazin-1-yl][1,2,4]triazolo[4,3-b]pyridazine (28 mg, 29%).

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>)  $\delta$  3.48 - 3.54 (4H, m), 3.78 - 3.84 (4H, m), 7.13 (1H, d), 7.99 (1H, d), 8.41 (2H, s); m/z = 434 [M+H]<sup>+</sup>.

### **Examples 340-343**

The following compounds were prepared in 50-73% yield by an analogous method to Example 339, starting from 6-chloro-3-[chloro(difluoro)methyl]-[1,2,4]triazolo[4,3-b]pyridazine and the appropriate benzyl piperazine:-

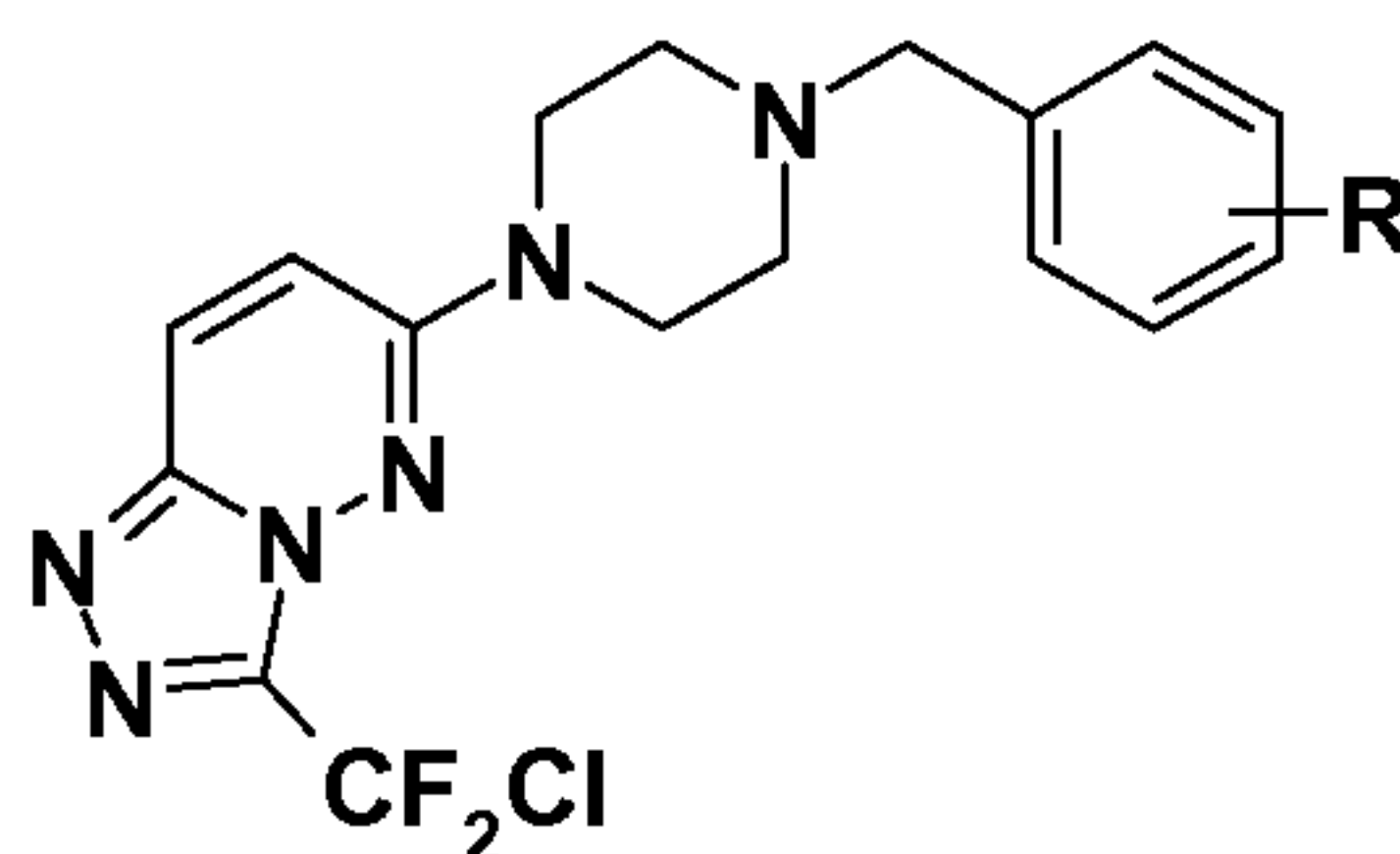




| Ex. | R    | <sup>1</sup> H NMR (300.1 MHz, CDCl <sub>3</sub> )                                                                      | m/z [M+H] <sup>+</sup> |
|-----|------|-------------------------------------------------------------------------------------------------------------------------|------------------------|
| 340 | H    | δ 2.60 (4H, t), 3.58 (2H, s), 3.64 (4H, t), 7.06 (1H, d), 7.27 - 7.37 (5H, m), 7.92 (1H, d)                             | 379                    |
| 341 | 4-F  | δ 2.58 (4H, t), 3.54 (2H, s), 3.63 (4H, t), 6.98 - 7.09 (3H, m), 7.27 - 7.35 (2H, m), 7.92 (1H, d)                      | 397                    |
| 342 | 4-CN | δ 2.60 (4H, t), 3.60 - 3.69 (6H, m), 7.07 (1H, d), 7.49 (2H, d), 7.64 (2H, d), 7.94 (1H, d)                             | 404                    |
| 343 | 3-CN | δ 2.60 (4H, t), 3.60 (2H, s), 3.66 (4H, t), 7.07 (1H, d), 7.46 (1H, t), 7.56 - 7.62 (2H, m), 7.70 (1H, s), 7.94 (1H, d) | 404                    |

#### **Examples 344-348**

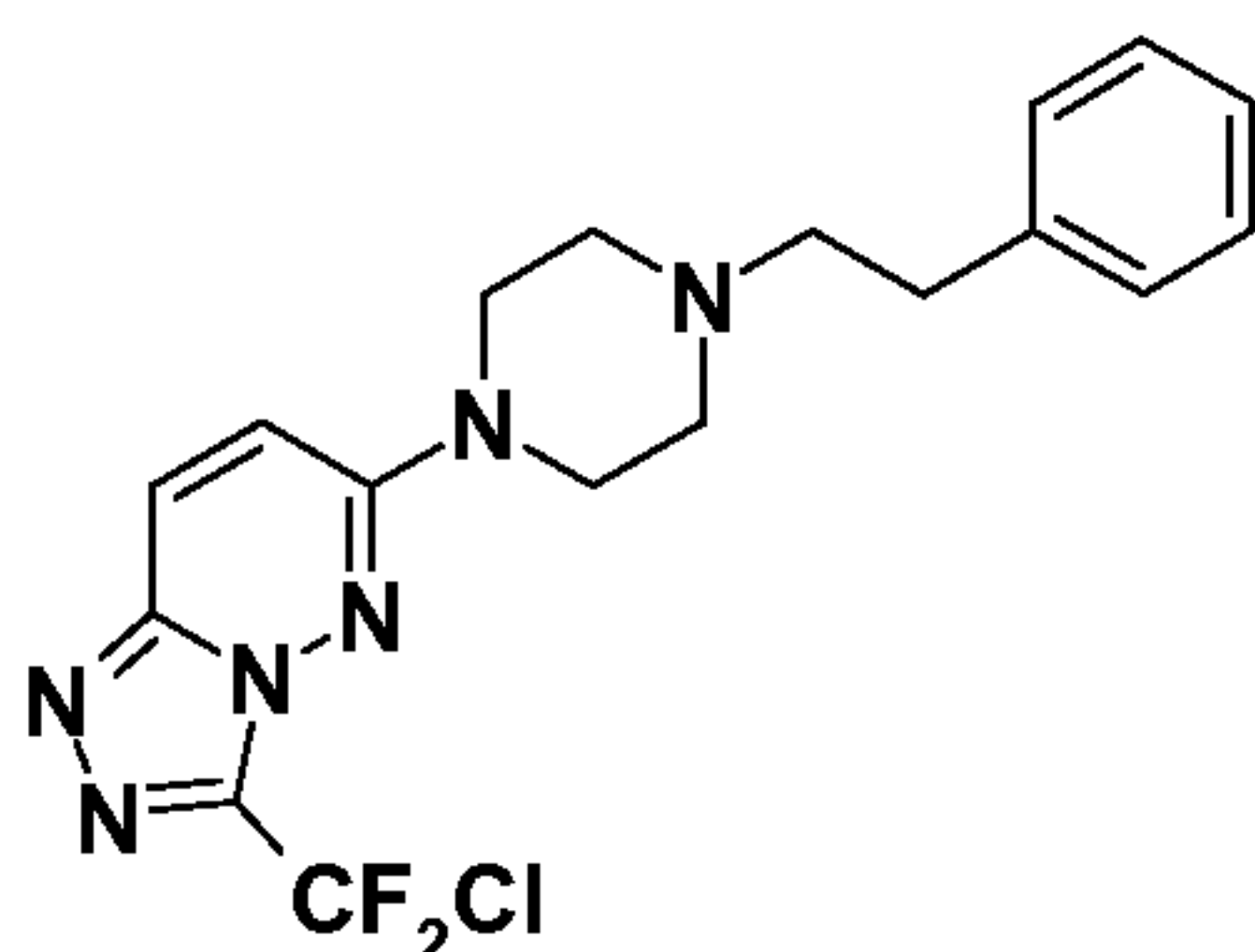
The following compounds were prepared in 24-76% yield by an analogous method to Example 339, starting from 6-chloro-3-[chloro(difluoro)methyl]-[1,2,4]triazolo[4,3-b]pyridazine and the appropriate benzyl piperazine:-



| Ex. | R                 | <sup>1</sup> H NMR (300.1 MHz, DMSO-d <sub>6</sub> )                                                                                         | m/z [M+H] <sup>+</sup> |
|-----|-------------------|----------------------------------------------------------------------------------------------------------------------------------------------|------------------------|
| 344 | 3-Br              | δ 2.49 - 2.52 (4H, m), 3.56 (2H, s), 3.63 (4H, t), 7.28 - 7.38 (2H, m), 7.45 - 7.50 (1H, m), 7.53 - 7.55 (1H, m), 7.58 (1H, d), 8.24 (1H, d) | 459                    |
| 345 | 3-F               | δ 2.50 - 2.55 (4H, m), 3.57 (2H, s), 3.64 (4H, t), 7.05 - 7.21 (3H, m), 7.34 - 7.44 (1H, m), 7.58 (1H, d), 8.24 (1H, d)                      | 397                    |
| 346 | 4-CF <sub>3</sub> | δ 2.50 - 2.57 (4H, m), 3.60 - 3.69 (6H, m), 7.55 - 7.62 (3H, m), 7.68 - 7.75 (2H, m), 8.25 (1H, d)                                           | 447                    |

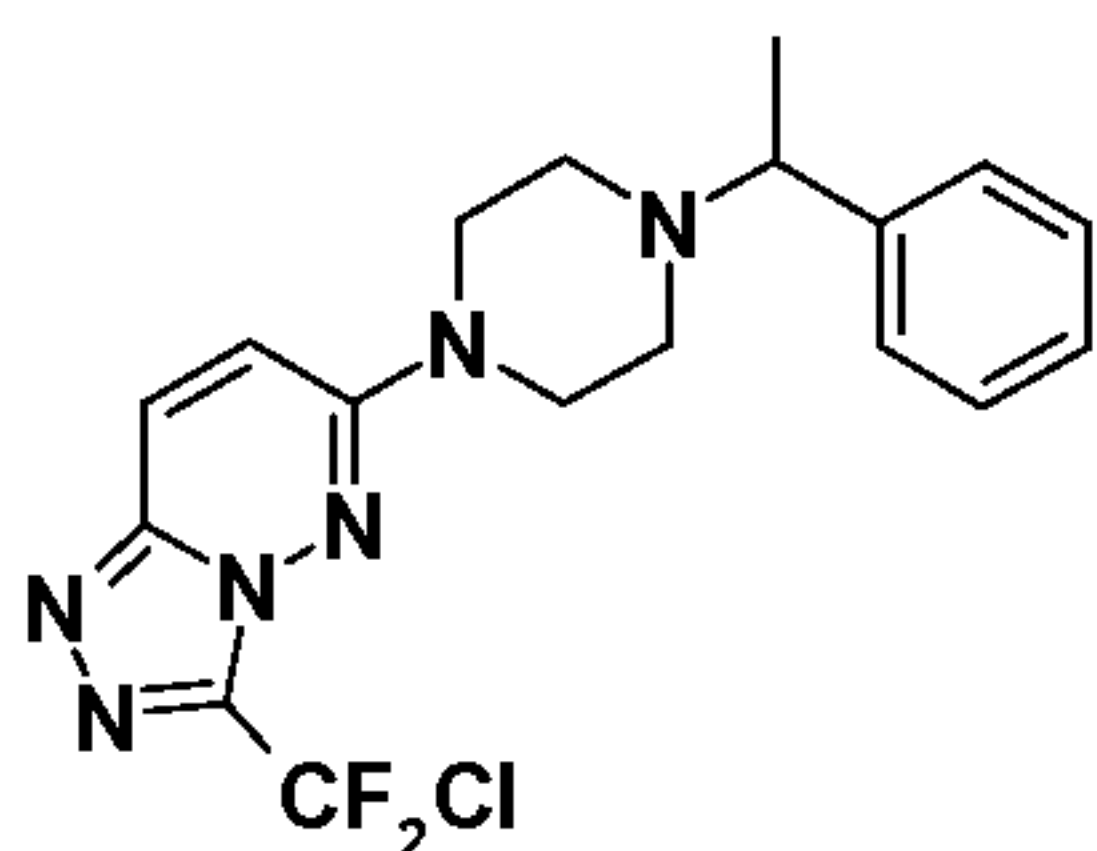


|     |                   |                                                                                                           |     |
|-----|-------------------|-----------------------------------------------------------------------------------------------------------|-----|
| 347 | 3-CF <sub>3</sub> | $\delta$ 2.50 - 2.53 (4H, m), 3.60 - 3.68 (6H, m), 7.55 - 7.70 (5H, m), 8.24 (1H, d)                      | 447 |
| 348 | 4-Br              | $\delta$ 2.49 - 2.52 (4H, m), 3.52 (2H, s), 3.62 (4H, t), 7.31 (2H, d), 7.50 - 7.61 (3H, m), 8.24 (1H, d) | 459 |

**Example 349****Preparation of 3-[chloro(difluoro)methyl]-6-[4-(2-phenylethyl)piperazin-1-yl][1,2,4]triazolo[4,3-b]pyridazine**

- 5 A mixture of 1-phenethylpiperazine and 6-chloro-3-[chloro(difluoro)methyl]-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by an analogous method to Example 339 to give 3-[chloro(difluoro)methyl]-6-[4-(2-phenylethyl)piperazin-1-yl][1,2,4]triazolo[4,3-b]pyridazine in 71% yield.

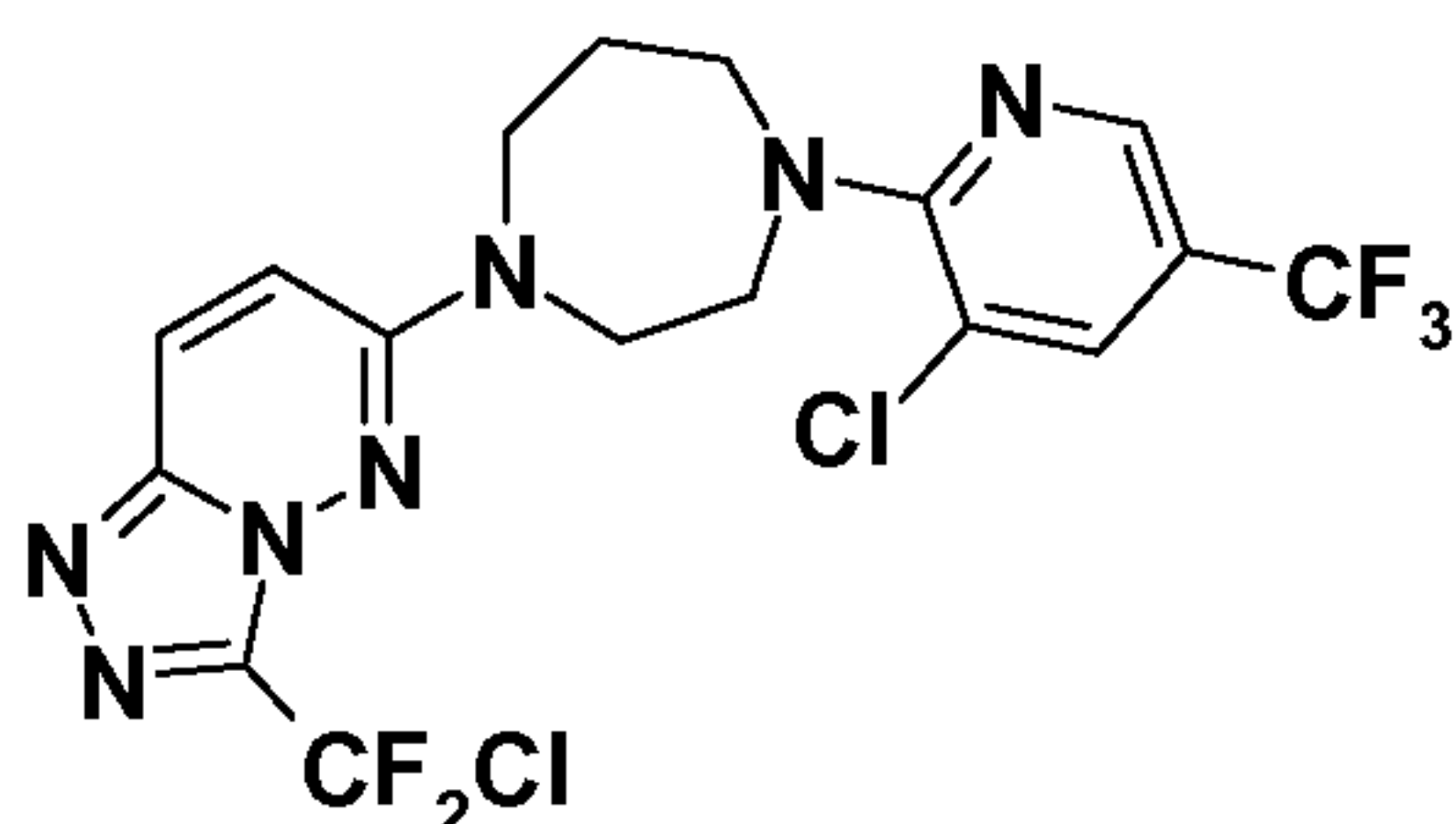
1H NMR (300.1 MHz, CDCl<sub>3</sub>)  $\delta$  2.64 - 2.73 (6H, m), 2.81 - 2.89 (2H, m), 3.67 (4H, t),  
 10 7.08 (1H, d), 7.19 - 7.34 (5H, m), 7.93 (1H, d); m/z = 393 [M+H]<sup>+</sup>.

**Example 350****Preparation of 3-[chloro(difluoro)methyl]-6-[4-(1-phenylethyl)piperazin-1-yl][1,2,4]triazolo[4,3-b]pyridazine**

- 15 A mixture of 1-(1-phenylethyl)piperazine and 6-chloro-3-[chloro(difluoro)methyl]-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by an analogous method to Example 339 to give 3-[chloro(difluoro)methyl]-6-[4-(1-phenylethyl)piperazin-1-yl][1,2,4]triazolo[4,3-b]pyridazine in 64% yield.

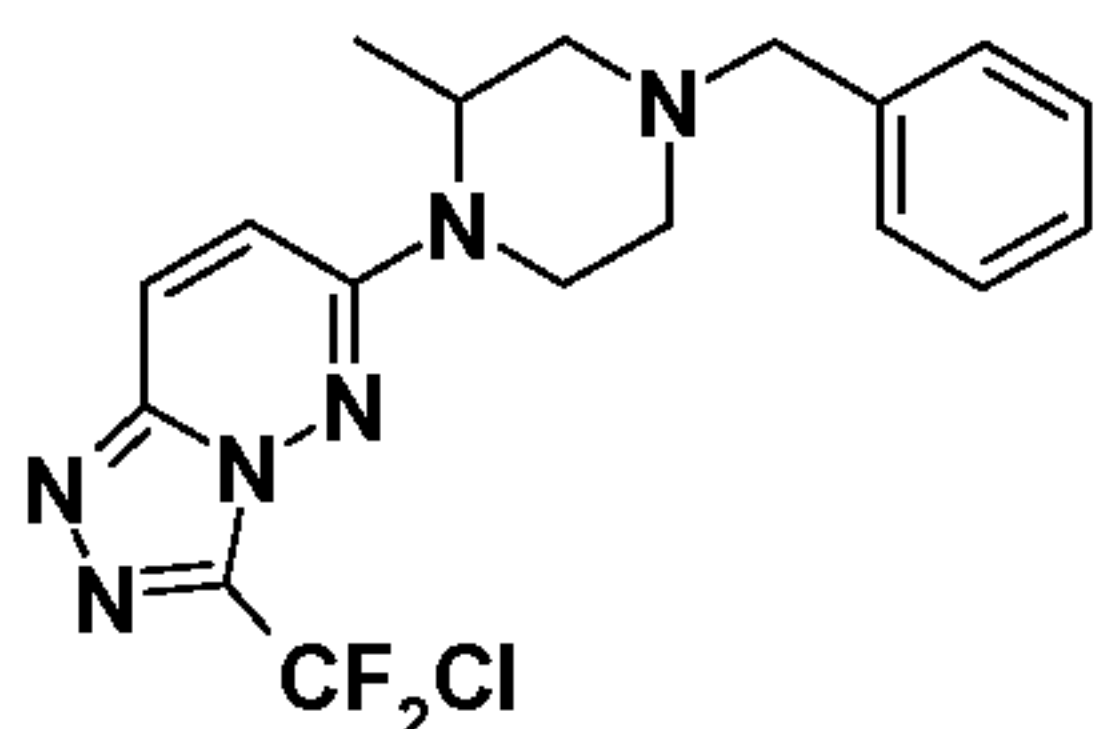
1H NMR (499.8 MHz, DMSO-d<sub>6</sub>)  $\delta$  1.32 (3H, d), 2.39 - 2.57 (4H, m), 3.47 (1H, q), 3.58  
 20 (4H, t), 7.22 - 7.27 (1H, m), 7.30 - 7.35 (4H, m), 7.53 (1H, d), 8.20 (1H, d); m/z = 393 [M+H]<sup>+</sup>.



**Example 351****Preparation of 3-[chloro(difluoro)methyl]-6-[4-[3-chloro-5-(trifluoromethyl)pyridin-2-yl]-1,4-diazepan-1-yl][1,2,4]triazolo[4,3-b]pyridazine**

5 A mixture of 1-(3-chloro-5-trifluoromethyl-2-pyridyl)-1,4-diazepane and 6-chloro-3-[chloro(difluoro)methyl]-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by an analogous method to Example 339 to give 3-[chloro(difluoro)methyl]-6-[4-[3-chloro-5-(trifluoromethyl)pyridin-2-yl]-1,4-diazepan-1-yl][1,2,4]triazolo[4,3-b]pyridazine in 62% yield.

10 <sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>) δ 2.09 - 2.19 (2H, m), 3.75 (2H, t), 3.81 (2H, t), 4.01 (4H, s), 7.04 (1H, d), 7.70 - 7.72 (1H, m), 7.94 (1H, d), 8.29 - 8.31 (1H, m); m/z = 482 [M+H]<sup>+</sup>.

**Example 352****Preparation of 6-(4-benzyl-2-methylpiperazin-1-yl)-3-[chloro(difluoro)methyl][1,2,4]triazolo[4,3-b]pyridazine**

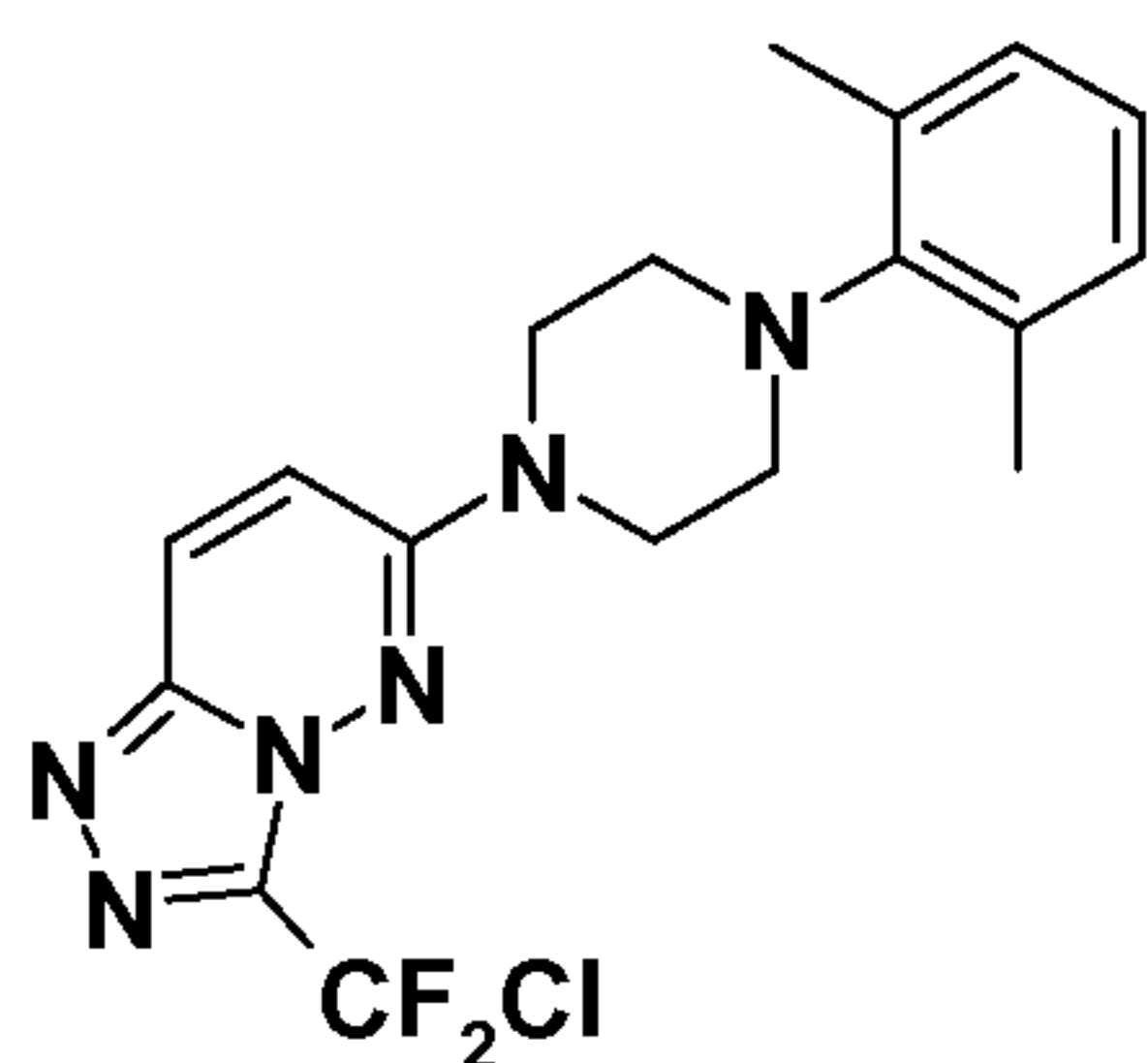
15 A mixture of 1-benzyl-3-methyl-piperazine and 6-chloro-3-[chloro(difluoro)methyl]-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by an analogous method to Example 339 to give 6-(4-benzyl-2-methylpiperazin-1-yl)-3-[chloro(difluoro)methyl][1,2,4]triazolo[4,3-b]pyridazine in 41% yield.

20 <sup>1</sup>H NMR (300.1 MHz, DMSO-d<sub>6</sub>) δ 1.26 (3H, d), 2.06 - 2.19 (1H, m), 2.22 - 2.30 (1H, m), 2.75 (1H, d), 2.94 (1H, d), 3.14 - 3.27 (1H, m), 3.53 (2H, q), 4.04 (1H, d), 4.41 - 4.53 (1H, m), 7.23 - 7.39 (5H, m), 7.56 (1H, d), 8.24 (1H, d); m/z = 393 [M+H]<sup>+</sup>.

**Example 353****Preparation of 3-[chloro(difluoro)methyl]-6-[4-(2,6-dimethylphenyl)piperazin-1-yl][1,2,4]triazolo[4,3-b]pyridazine**

25





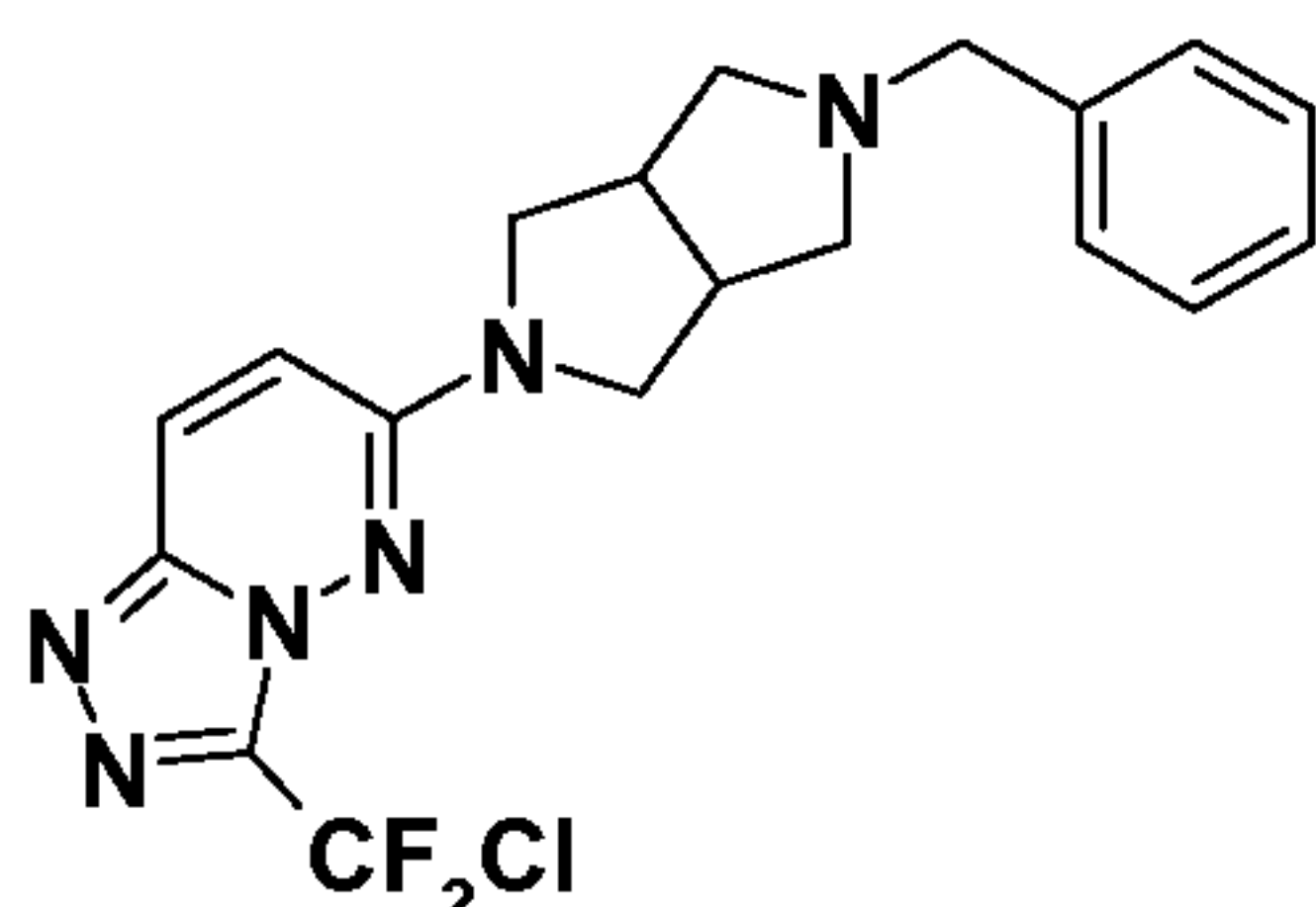
A mixture of 1-(2,6-dimethylphenyl)piperazine and 6-chloro-3-[chloro(difluoro)methyl]-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by an analogous method to Example 339 to give 3-[chloro(difluoro)methyl]-6-[4-(2,6-dimethylphenyl)piperazin-1-yl][1,2,4]triazolo[4,3-b]pyridazine in 64% yield.

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>) δ 2.35 (6H, s), 3.26 (4H, t), 3.74 (4H, t), 7.00 - 7.05 (3H, m), 7.14 (1H, d), 7.95 (1H, d); m/z = 393 [M+H]<sup>+</sup>.

#### **Example 354**

#### **Preparation of 6-(5-benzylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3-**

#### **[chloro(difluoro)methyl][1,2,4]triazolo[4,3-b]pyridazine**



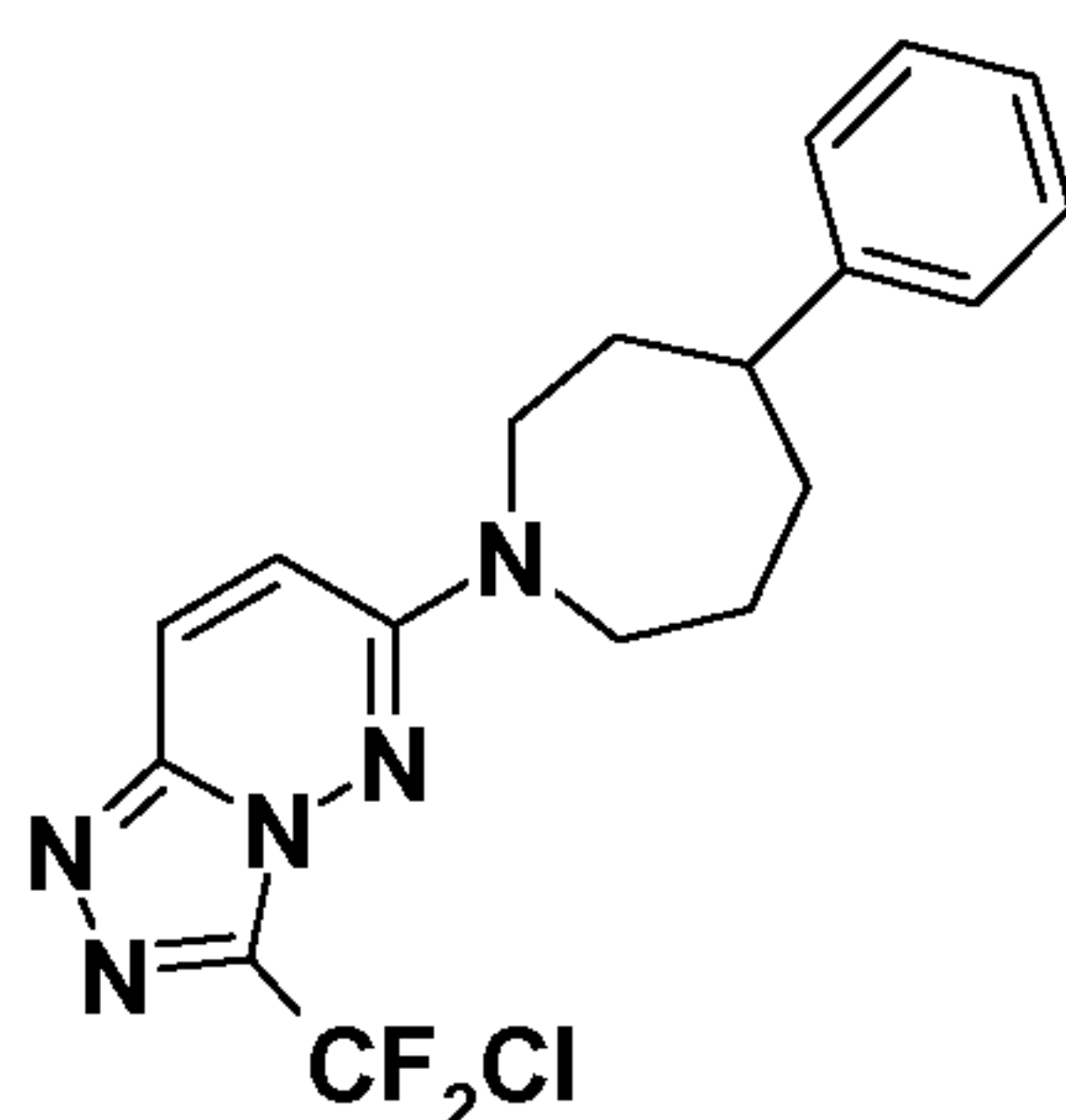
A mixture of 2-benzylhexahydropyrrolo[3,4-c]pyrrole hydrochloride and 6-chloro-3-[chloro(difluoro)methyl]-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by an analogous method to Example 331 to give 6-(5-benzylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3-[chloro(difluoro)methyl][1,2,4]triazolo[4,3-b]pyridazine in 66% yield.

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>) δ 2.58 - 2.75 (4H, m), 3.04 (2H, s), 3.41 - 3.50 (2H, m), 3.63 (2H, s), 3.76 - 3.85 (2H, m), 6.88 (1H, d), 7.22 - 7.33 (5H, m), 7.90 (1H, d); m/z = 405 [M+H]<sup>+</sup>.

#### **Example 355**

#### **Preparation of 3-[chloro(difluoro)methyl]-6-(4-phenylazepan-1-yl)[1,2,4]triazolo[4,3-b]pyridazine**



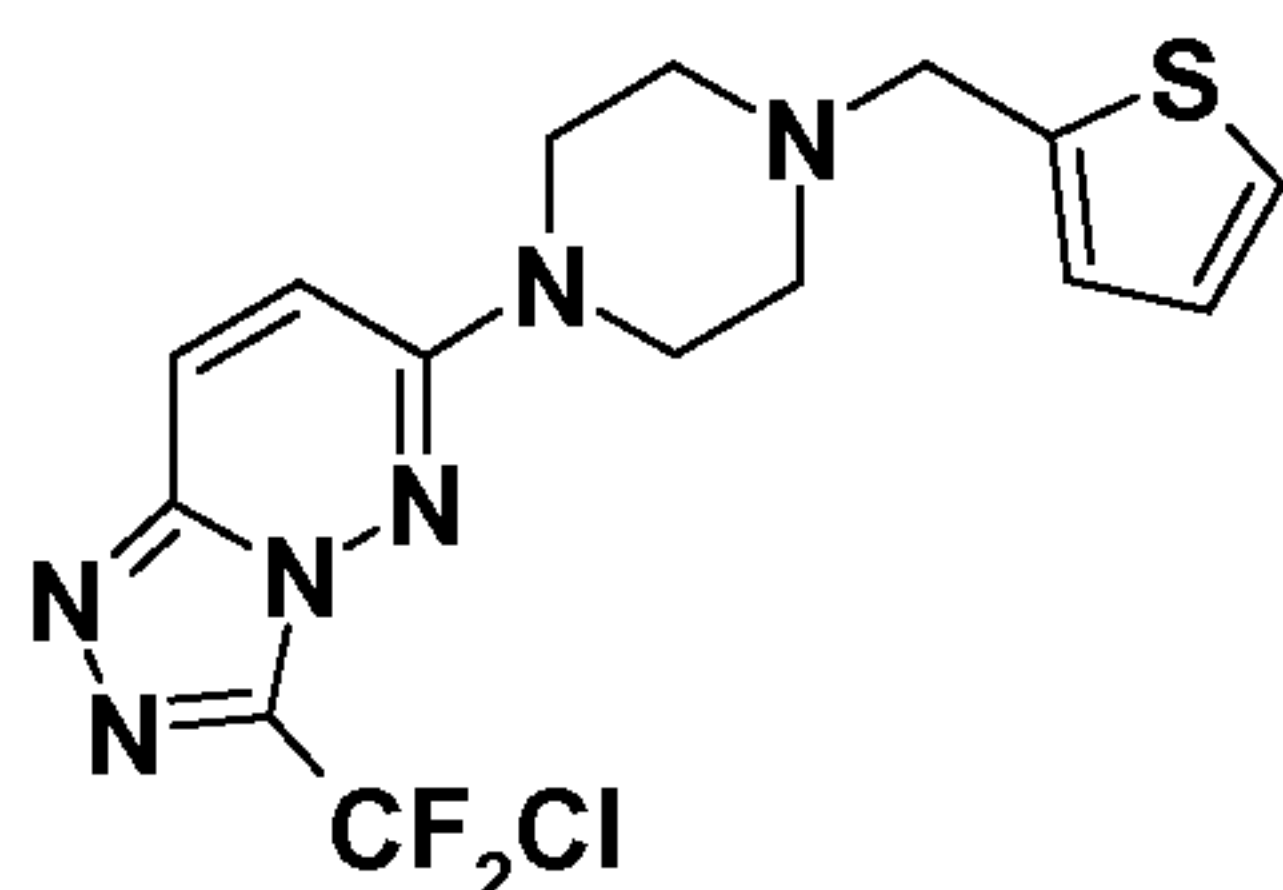


A mixture of 4-phenylazepane hydrochloride and 6-chloro-3-[chloro(difluoro)methyl]-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by an analogous method to Example 331 to give 3-[chloro(difluoro)methyl]-6-(4-phenylazepan-1-yl)[1,2,4]triazolo[4,3-b]pyridazine in 69% yield.

<sup>1</sup>H NMR (499.8 MHz, DMSO-d<sub>6</sub>) δ 1.64 - 1.90 (4H, m), 1.98 - 2.09 (2H, m), 2.68 (1H, t), 3.59 - 3.75 (2H, m), 3.76 - 3.86 (1H, m), 3.87 - 3.96 (1H, m), 7.10 - 7.20 (3H, m), 7.24 (2H, t), 7.49 (1H, d), 8.20 (1H, d); m/z = 378 [M+H]<sup>+</sup>.

#### **Example 356**

#### **Preparation of 3-[chloro(difluoro)methyl]-6-[4-(thiophen-2-ylmethyl)piperazin-1-yl][1,2,4]triazolo[4,3-b]pyridazine**



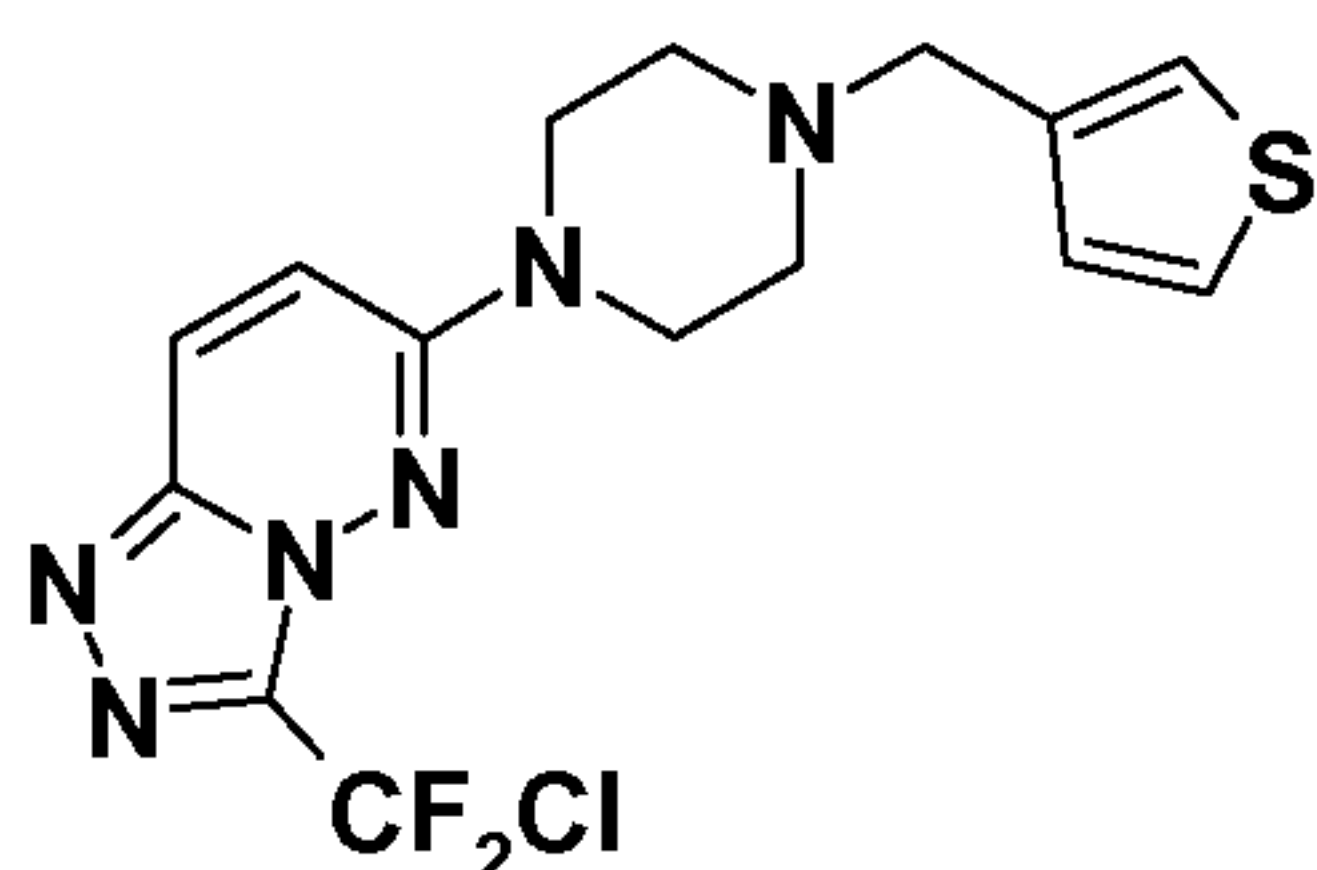
A mixture of 1-(thiophen-2-ylmethyl)piperazine and 6-chloro-3-[chloro(difluoro)methyl]-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by an analogous method to Example 339 to give 3-[chloro(difluoro)methyl]-6-[4-(thiophen-2-ylmethyl)piperazin-1-yl][1,2,4]triazolo[4,3-b]pyridazine in 74% yield.

<sup>1</sup>H NMR (300.1 MHz, DMSO-d<sub>6</sub>) δ 2.52 - 2.59 (4H, m), 3.63 (4H, t), 3.77 (2H, s), 6.97 - 7.01 (2H, m), 7.44 - 7.48 (1H, m), 7.58 (1H, d), 8.24 (1H, d); m/z = 385 [M+H]<sup>+</sup>.

#### **Example 357**

#### **Preparation of 3-[chloro(difluoro)methyl]-6-[4-(thiophen-3-ylmethyl)piperazin-1-yl][1,2,4]triazolo[4,3-b]pyridazine**



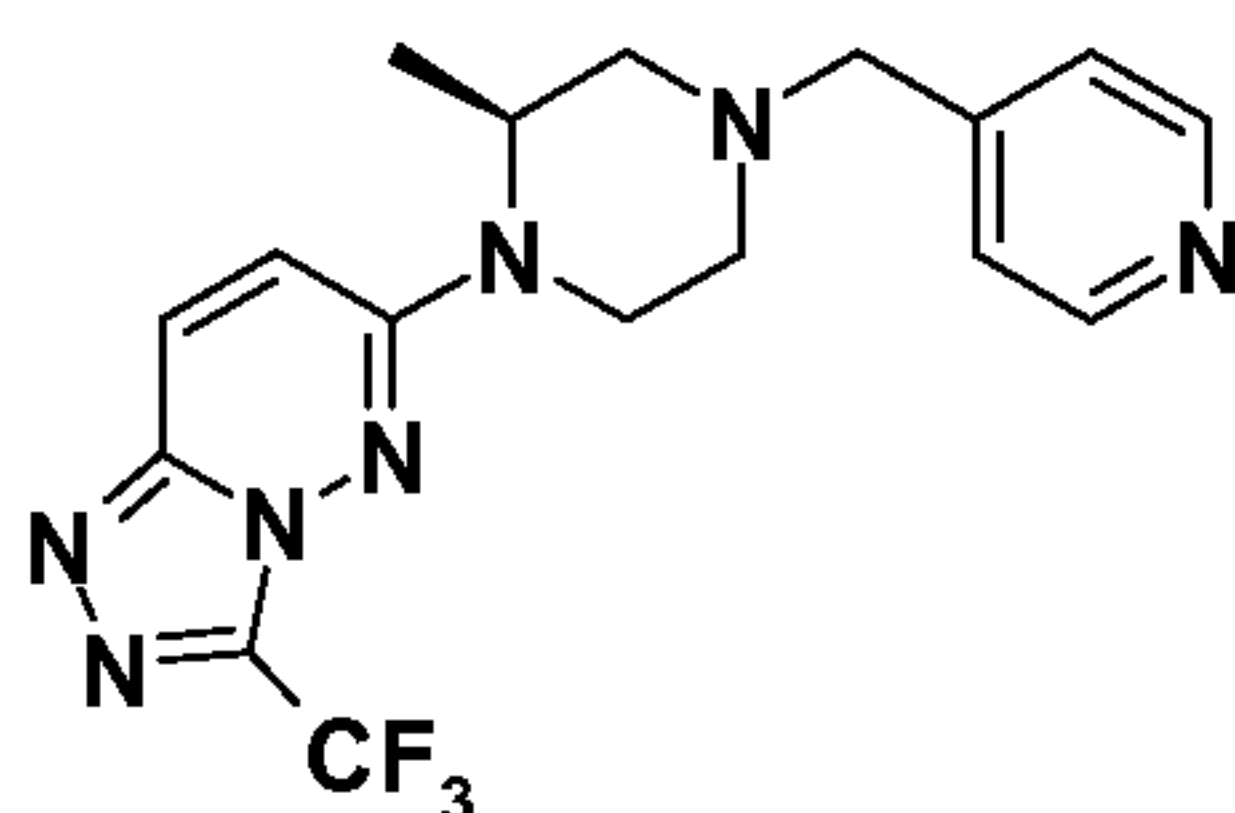


A mixture of 1-(thiophen-3-ylmethyl)piperazine and 6-chloro-3-[chloro(difluoro)methyl]-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by an analogous method to Example 339 to give 3-[chloro(difluoro)methyl]-6-[4-(thiophen-3-ylmethyl)piperazin-1-yl][1,2,4]triazolo[4,3-b]pyridazine in 70% yield.

<sup>1</sup>H NMR (300.1 MHz, DMSO-d<sub>6</sub>) δ 2.49 - 2.52 (4H, m), 3.56 (2H, s), 3.62 (4H, t), 7.06 - 7.10 (1H, m), 7.33 - 7.37 (1H, m), 7.49 - 7.52 (1H, m), 7.58 (1H, d), 8.24 (1H, d); m/z = 385 [M+H]<sup>+</sup>.

### **Example 358**

#### **Preparation of 6-[(2S)-2-methyl-4-(pyridin-4-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine**



A mixture of pyridine-4-carboxaldehyde and 6-[(2S)-2-methylpiperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by General Synthetic Method 5 to give 6-[(2S)-2-methyl-4-(pyridin-4-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine in 53% yield.

<sup>1</sup>H NMR (399.9 MHz, DMSO-d<sub>6</sub>) δ 1.29 (3H, d), 2.15 - 2.21 (1H, m), 2.30 - 2.34 (1H, m), 2.74 (1H, d), 2.94 (1H, d), 3.22 - 3.28 (1H, m), 3.52 (1H, d), 3.63 (1H, d), 4.04 (1H, d), 4.48 (1H, s), 7.39 (2H, d), 7.39 (1H, s), 7.58 (1H, d), 8.26 (1H, d), 8.54 - 8.55 (2H, m); m/z = 378 [M+H]<sup>+</sup>.

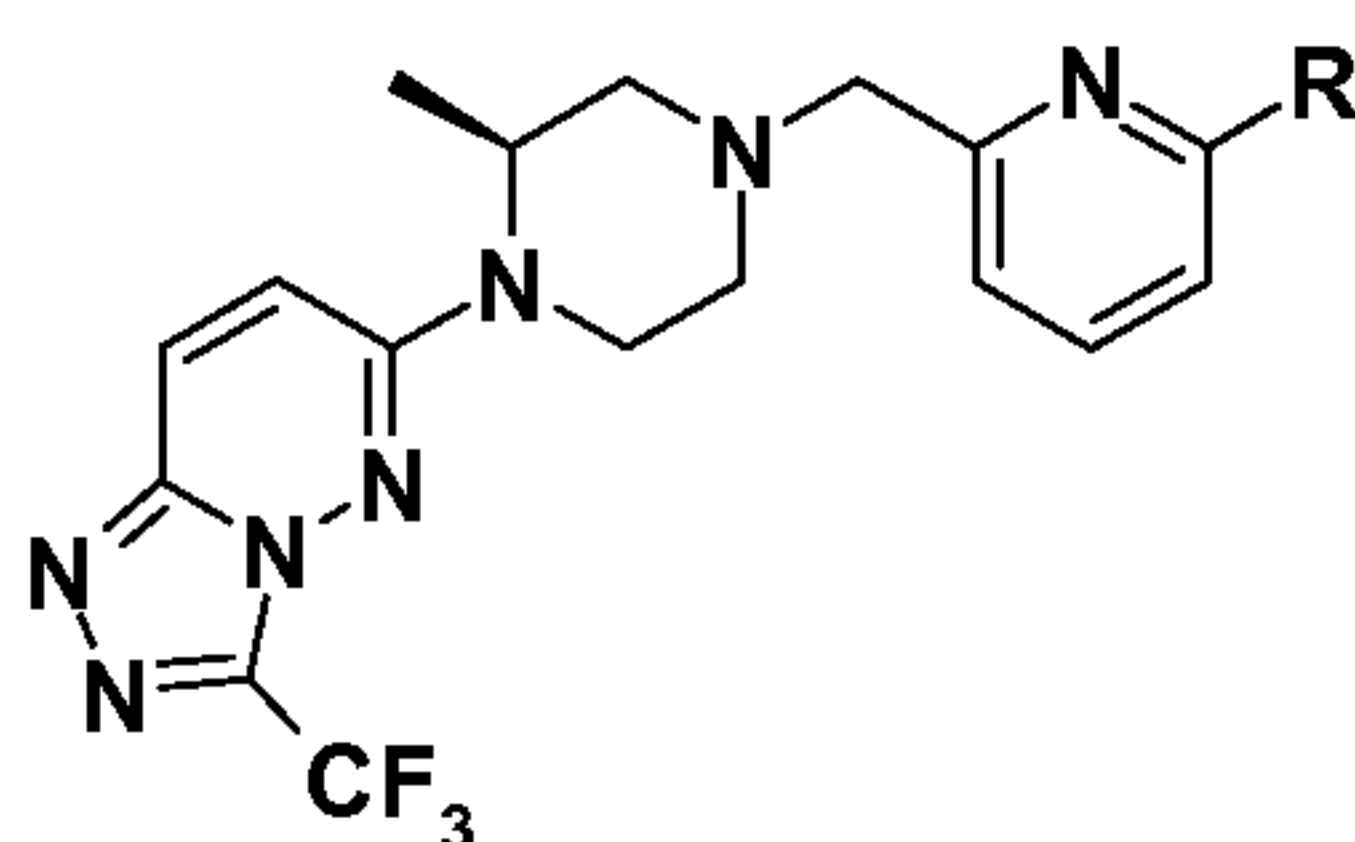
The 6-[(2S)-2-methylpiperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine used as starting material was prepared in 2 steps in 64% overall yield by an analogous method to Example 223, preparation of starting materials, starting from 6-chloro-3-(trifluoromethyl)-[1,2,4]-triazolo[4,3-b]pyridazine and (3S)-tert-butyl 3-methylpiperazine-1-carboxylate.



<sup>1</sup>H NMR (399.9 MHz, DMSO-d<sub>6</sub>) δ 1.23 (3H, d), 2.42 (1H, m), 2.65 (1H, m), 2.85 (2H, m), 3.04 (2H, m), 3.91 (1H, m), 4.35 (1H, m), 7.56 (1H, d), 8.23 (1H, d); m/z = 387 [M+H]<sup>+</sup>.

### Examples 359-360

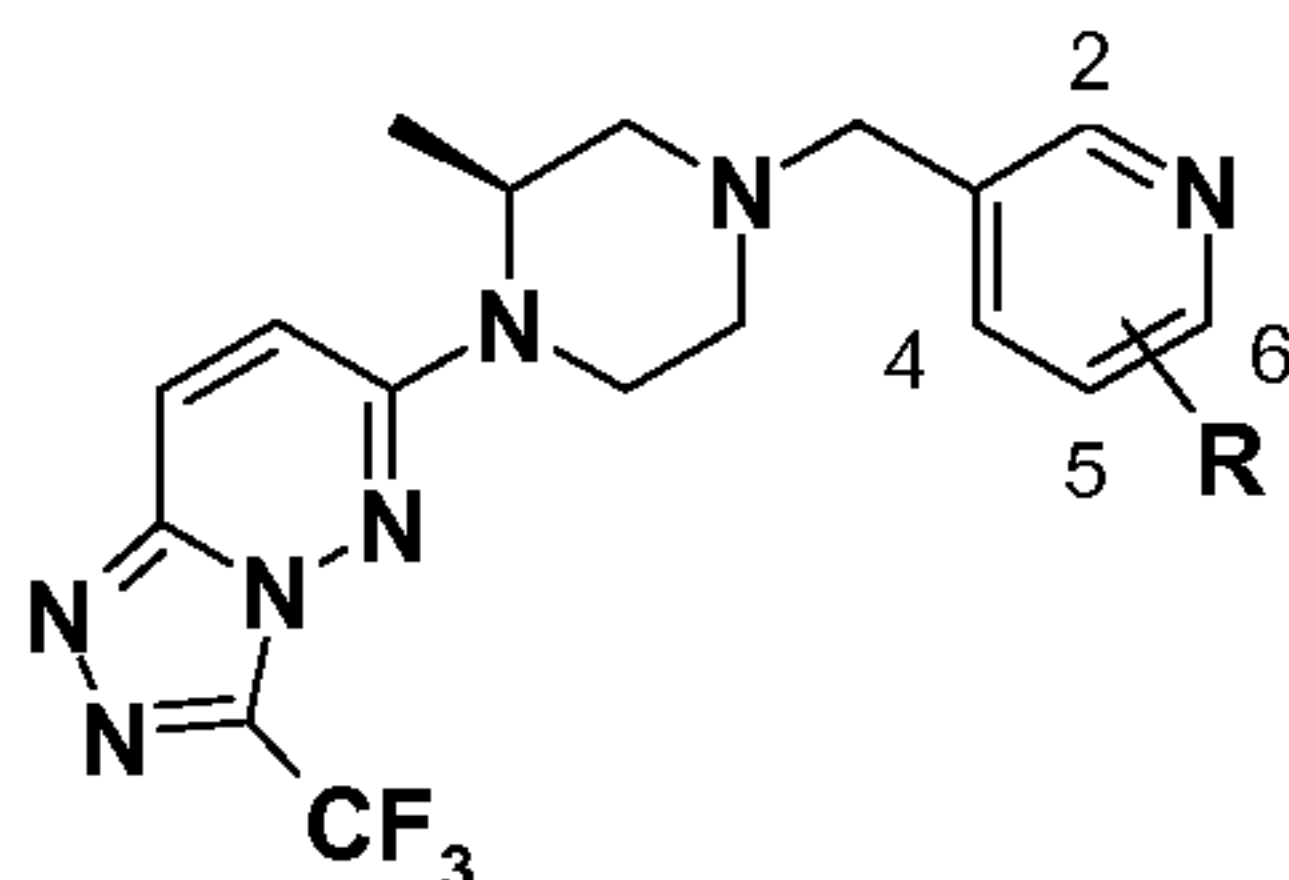
- 5 The following compounds were prepared in 31 - 84% yield by General Synthetic Method 5, starting from 6-[(2S)-2-methylpiperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (obtained as described in Example 358, preparation of starting materials) and the appropriate aldehyde:-



| Ex. | R  | <sup>1</sup> H NMR (399.9 MHz, DMSO-d <sub>6</sub> )                                                                                                                                                                                                                                                   | m/z [M+H] <sup>+</sup> |
|-----|----|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|
| 359 | H  | δ 1.27 - 1.29 (3H, m), 2.18 - 2.25 (1H, m), 2.35 - 2.39 (1H, m), 2.79 (1H, d), 2.96 - 2.99 (1H, m), 3.21 - 3.27 (1H, m), 3.62 (1H, d), 3.70 (1H, d), 4.03 (1H, d), 4.48 (1H, s), 7.27 - 7.31 (1H, m), 7.52 (1H, s), 7.54 (1H, s), 7.58 (1H, d), 7.79 - 7.83 (1H, m), 8.26 (1H, d), 8.51 - 8.53 (1H, m) | 378                    |
| 360 | Br | δ 1.28 - 1.30 (3H, m), 2.20 - 2.27 (1H, m), 2.37 - 2.41 (1H, m), 2.79 (1H, d), 2.97 (1H, d), 3.22 - 3.27 (1H, m), 3.61 (1H, d), 3.69 (1H, d), 4.04 (1H, d), 4.49 (1H, s), 7.56 (2H, t), 7.58 (1H, d), 7.79 (1H, t), 8.26 (1H, d)                                                                       | 456                    |

### Examples 361-366

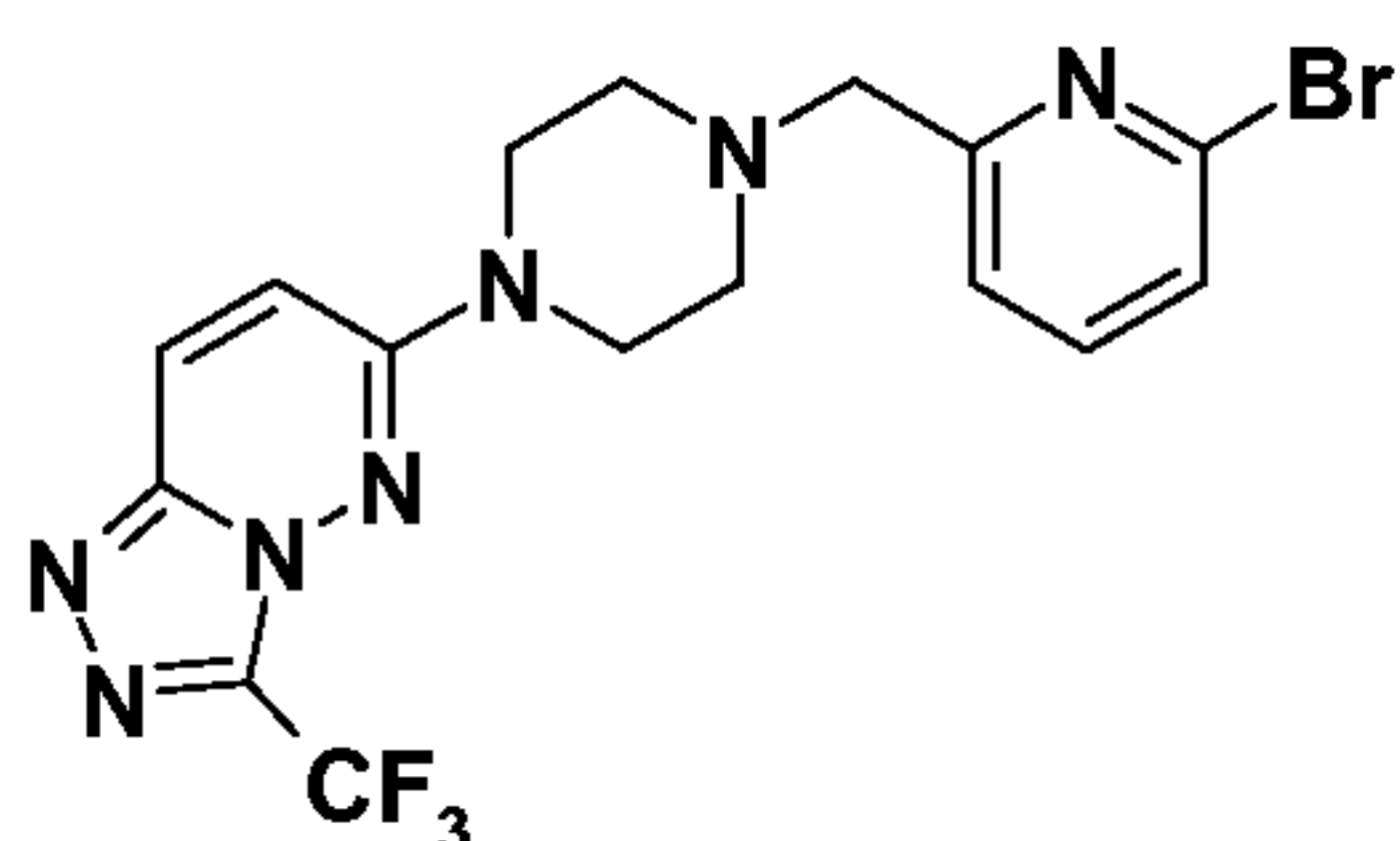
10 The following compounds were prepared in 32 - 84% yield by General Synthetic Method 5, starting from 6-[(2S)-2-methylpiperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine and the appropriate aldehyde:-





| Ex. | R                 | <sup>1</sup> H NMR (399.9 MHz, DMSO-d <sub>6</sub> )                                                                                                                                                                                                  | m/z [M+H] <sup>+</sup> |
|-----|-------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|
| 361 | 6-CF <sub>3</sub> | δ 1.27 - 1.28 (3H, m), 2.16 - 2.23 (1H, m), 2.33 - 2.37 (1H, m), 2.77 (1H, d), 2.95 (1H, d), 3.20 - 3.27 (1H, m), 3.66 (1H, d), 3.74 (1H, d), 4.03 (1H, d), 4.49 (1H, d), 7.58 (1H, d), 7.91 (1H, d), 8.06 - 8.08 (1H, m), 8.26 (1H, d), 8.76 (1H, d) | 446                    |
| 362 | 2-Cl              | δ 1.28 - 1.29 (3H, m), 2.22 - 2.29 (1H, m), 2.42 - 2.46 (1H, m), 2.80 (1H, d), 2.95 (1H, d), 3.20 - 3.27 (1H, m), 3.62 (2H, s), 4.04 (1H, d), 4.50 (1H, t), 7.46 - 7.49 (1H, m), 7.59 (1H, d), 7.99 - 8.01 (1H, m), 8.26 (1H, d), 8.34 - 8.36 (1H, m) | 421                    |
| 363 | 2-Cl, 5-F         | δ 1.29 - 1.31 (3H, m), 2.24 - 2.31 (1H, m), 2.46 - 2.49 (1H, m), 2.82 (1H, d), 2.97 (1H, d), 3.24 - 3.28 (1H, m), 3.63 (2H, s), 4.03 (1H, d), 4.50 (1H, t), 7.60 (1H, d), 7.91 - 7.94 (1H, m), 8.27 (1H, d), 8.41 (1H, d)                             | 430                    |
| 364 | 6-OMe             | δ 1.23 (3H, d), 2.24 - 2.27 (1H, m), 2.74 (1H, d), 3.43 (1H, d), 3.53 (1H, d), 3.86 (2H, s), 4.02 (1H, d), 4.47 (1H, d), 6.81 - 6.83 (1H, m), 7.57 (1H, d), 7.67 - 7.70 (1H, m), 8.10 (1H, d), 8.25 (1H, d)                                           | 409                    |
| 365 | 5-Br, 2-F         | δ 1.25 - 1.27 (3H, m), 2.18 - 2.24 (1H, m), 2.36 - 2.40 (1H, m), 2.79 (1H, d), 2.96 (1H, d), 3.22 - 3.27 (1H, m), 3.56 - 3.64 (2H, m), 4.01 - 4.05 (1H, m), 4.49 (1H, d), 7.58 (1H, d), 8.20 (1H, d), 8.26 (1H, d), 8.32 - 8.33 (1H, m)               | 476                    |
| 366 | 5-F               | δ 1.26 - 1.27 (3H, m), 2.14 - 2.21 (1H, m), 2.31 - 2.35 (1H, m), 2.76 (1H, d), 2.95 (1H, d), 3.20 - 3.27 (1H, m), 3.59 (1H, d), 3.67 (1H, d), 4.03 (1H, d), 4.48 (1H, s), 7.58 (1H, d), 7.67 - 7.71 (1H, m), 8.26 (1H, d), 8.45 (1H, t), 8.50 (1H, d) | 396                    |



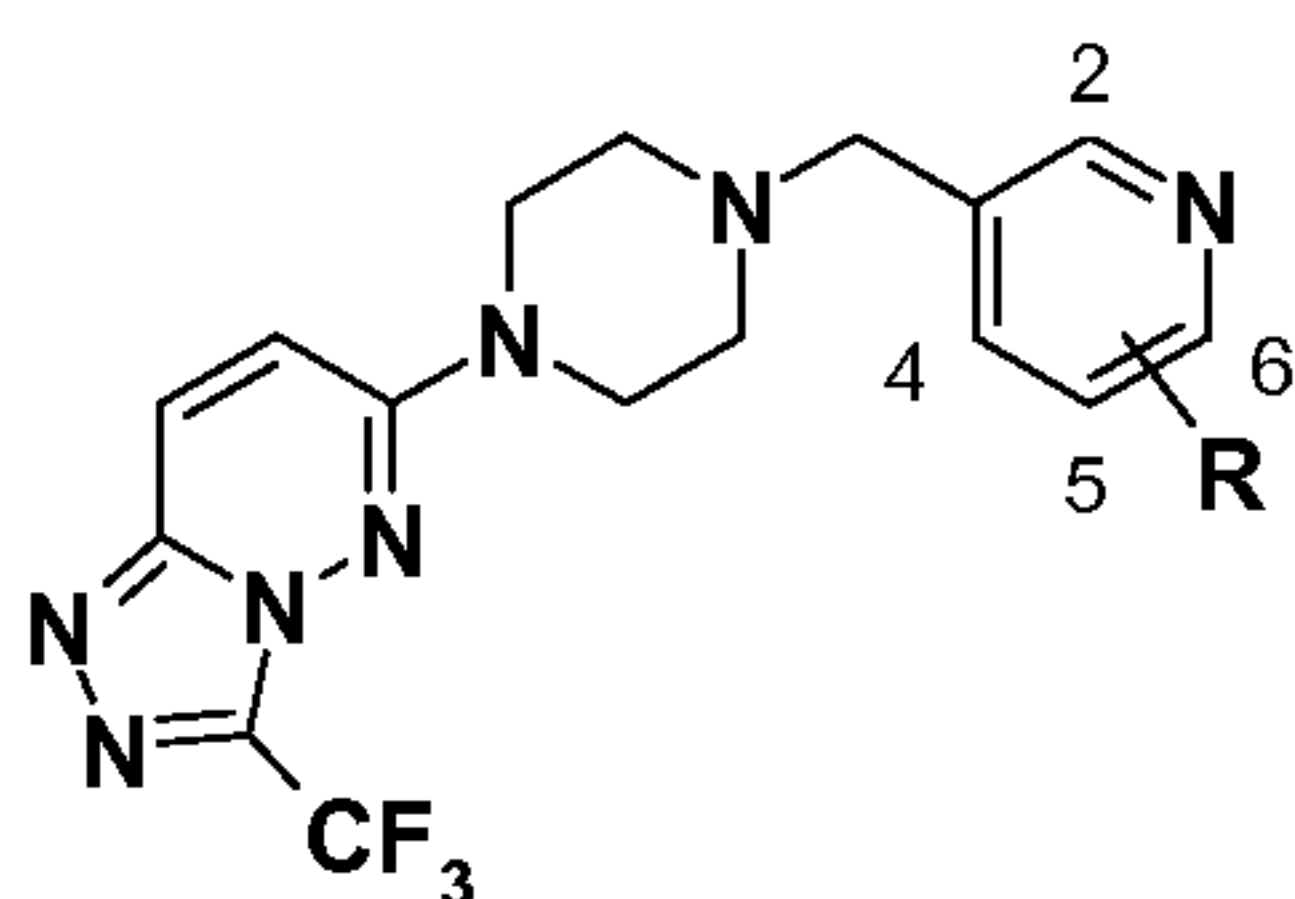
**Example 367****Preparation of 6-[4-[(6-bromopyridin-2-yl)methyl]piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine**

5 A mixture of 6-bromopyridine-2-carboxaldehyde and 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by General Synthetic Method 5 to give 6-[4-[(6-bromopyridin-2-yl)methyl]piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine in 66% yield.

1H NMR (399.9 MHz, DMSO-d<sub>6</sub>)  $\delta$  2.56 - 2.61 (4H, m), 3.64 (4H, t), 3.66 (2H, s), 7.53 - 7.54 (1H, m), 7.55 - 7.56 (1H, m), 7.60 (1H, d), 7.77 (1H, t), 8.26 (1H, d); m/z = 444 [M+H]<sup>+</sup>.

**Examples 368-377**

The following compounds were prepared in 20 - 79% yield by General Synthetic Method 5, starting from 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine and the appropriate aldehyde:-



| Ex. | R                 | <sup>1</sup> H NMR (399.9 MHz, DMSO-d <sub>6</sub> )                                                                           | m/z [M+H] <sup>+</sup> |
|-----|-------------------|--------------------------------------------------------------------------------------------------------------------------------|------------------------|
| 368 | 6-CF <sub>3</sub> | $\delta$ 2.56 (4H, t), 3.64 (4H, t), 3.71 (2H, s), 7.60 (1H, d), 7.90 (1H, d), 8.04 - 8.07 (1H, m), 8.26 (1H, d), 8.74 (1H, d) | 474 [1]                |
| 369 | 2-Cl              | $\delta$ 2.61 (4H, t), 3.66 (6H, s), 7.45 - 7.48 (1H, m), 7.61 (1H, d), 7.97 - 7.99 (1H, m), 8.27 (1H, d), 8.34 - 8.35 (1H, m) | 398                    |
| 370 | 2-Cl, 5-F         | $\delta$ 2.64 (4H, t), 3.66 - 3.67 (6H, m), 7.62 (1H, d), 7.90 - 7.93 (1H, m), 8.27 (1H, d), 8.40 (1H, d)                      | 416                    |

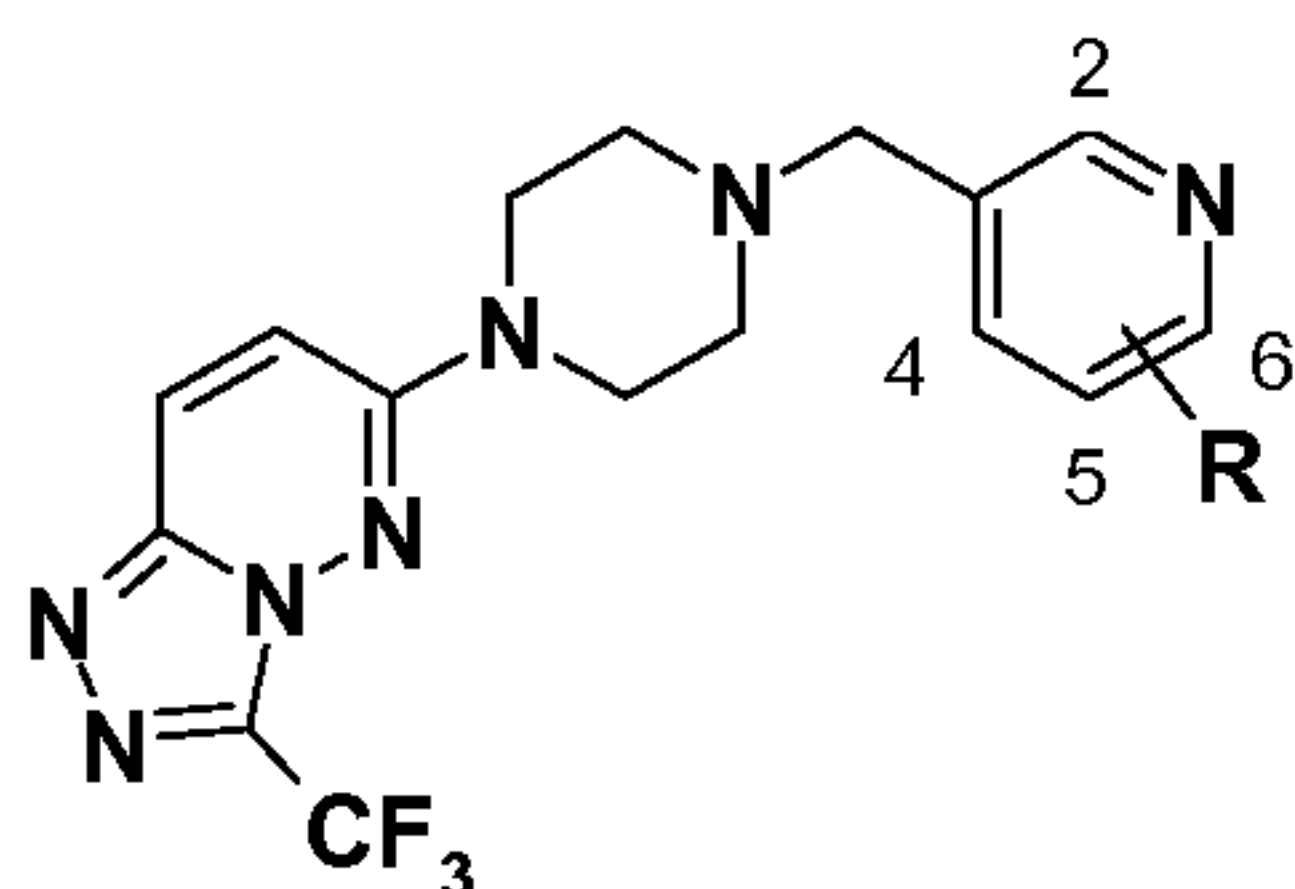


|     |           |                                                                                                                                                                   |         |
|-----|-----------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|
| 371 | 5-F       | $\delta$ 2.55 (4H, t), 3.63 (6H, t), 7.60 (1H, d), 7.67 - 7.71 (1H, m), 8.26 (1H, d), 8.44 (1H, t), 8.50 (1H, d)                                                  | 424 [1] |
| 372 | 5-Br, 2-F | $\delta$ 2.58 (4H, t), 3.62 (2H, s), 3.64 (4H, t), 7.59 (1H, d), 8.20 (1H, d), 8.26 (1H, d), 8.32 - 8.33 (1H, m)                                                  | 462     |
| 373 | 4-OMe     | $\delta$ 2.56 (4H, t), 3.53 (2H, s), 3.63 (4H, t), 3.88 (3H, s), 6.99 - 7.02 (1H, m), 7.59 (1H, d), 7.72 - 7.75 (1H, m), 8.08 - 8.10 (1H, m), 8.25 (1H, d)        | 394     |
| 374 | 6-Br      | $\delta$ 2.54 (4H, s), 3.57 - 3.61 (2H, m), 3.62 - 3.63 (4H, m), 7.59 (1H, d), 7.64 (1H, d), 7.72 - 7.74 (1H, m), 8.26 (1H, d), 8.36 (1H, d)                      | 444     |
| 375 | 5-OMe     | $\delta$ 2.53 - 2.56 (4H, m), 3.59 - 3.62 (2H, m), 3.63 (4H, d), 3.84 (3H, s), 7.33 (1H, q), 7.58 (1H, d), 8.14 (1H, d), 8.21 - 8.22 (1H, m), 8.23 - 8.25 (1H, m) | 394     |
| 376 | 2-Br      | $\delta$ 2.53 - 2.57 (4H, m), 3.60 - 3.64 (6H, m), 7.59 (1H, d), 8.02 (1H, t), 8.26 (1H, d), 8.54 (1H, d), 8.63 (1H, d)                                           | 444     |
| 377 | 4-Br      | $\delta$ 2.59 - 2.63 (4H, m), 3.62 - 3.66 (4H, m), 3.68 (2H, s), 7.61 (1H, d), 7.72 (1H, d), 8.27 (1H, d), 8.36 (1H, d), 8.62 (1H, s)                             | 444     |

[1] Detected as adduct with acetonitrile used as solvent for mass spectral determination

### **Examples 378-379**

The following compounds were prepared in 33 - 54% yield by an analogous method to Example 307, starting from the appropriate bromopyridine (obtained as described in the corresponding footnote):-



| Ex. | R    | Note | H NMR (399.9 MHz, DMSO-d6)                              | m/z [M+H] <sup>+</sup> |
|-----|------|------|---------------------------------------------------------|------------------------|
| 378 | 2-CN | [1]  | $\delta$ 2.61 (4H, t), 3.63 (4H, t), 3.78 (2H, s), 7.61 | 389                    |



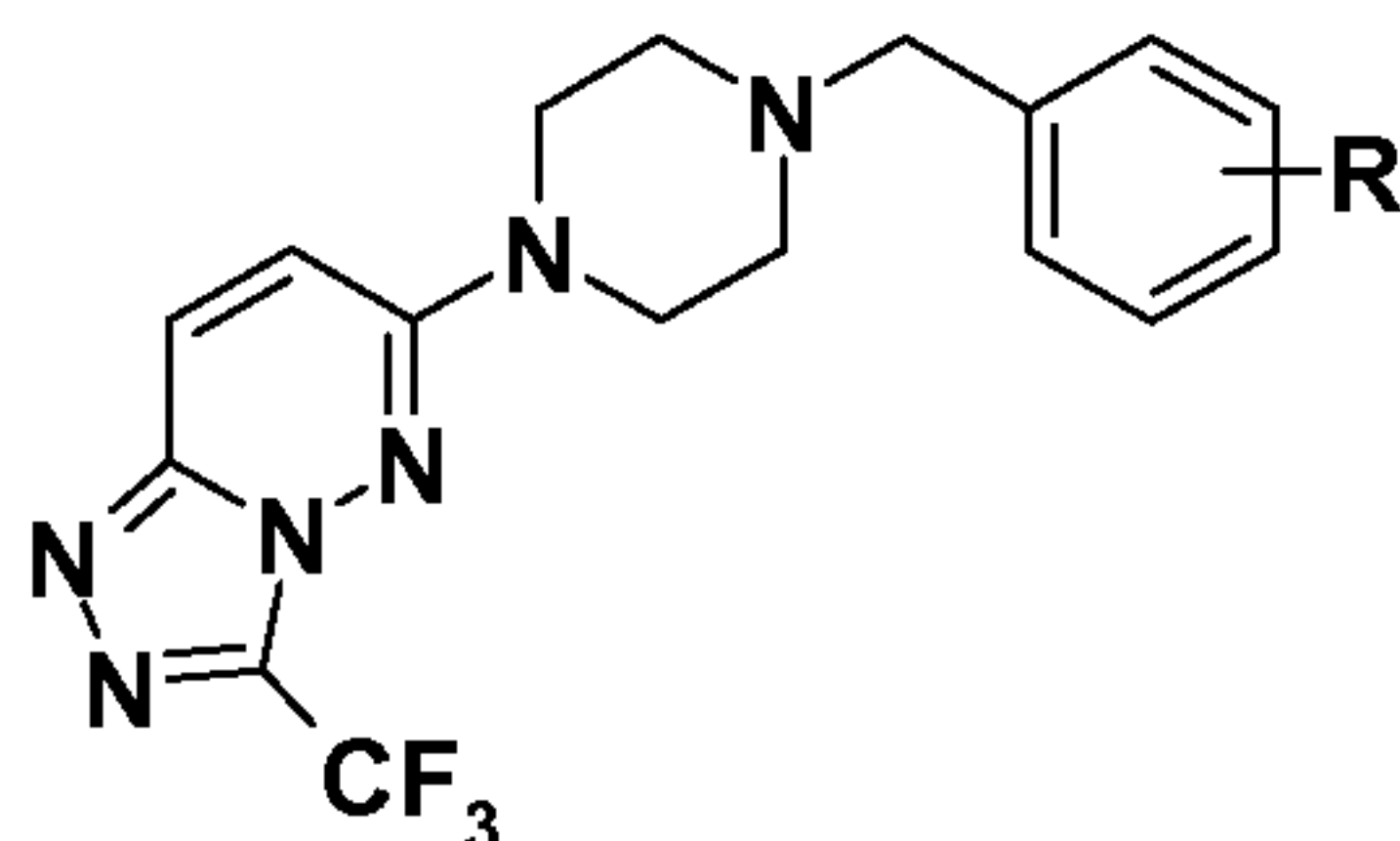
|     |      |     |                                                                                                                               |     |
|-----|------|-----|-------------------------------------------------------------------------------------------------------------------------------|-----|
|     |      |     | (1H, d), 7.74 - 7.77 (1H, m), 8.08 - 8.10 (1H, m),<br>8.27 (1H, d), 8.68 - 8.70 (1H, m)                                       |     |
| 379 | 4-CN | [2] | $\delta$ 2.61 (4H, s), 3.63 (4H, s), 3.76 (2H, s), 7.60<br>(1H, d), 7.88 (1H, s), 8.26 (1H, d), 8.75 (1H, s),<br>8.85 (1H, s) | 389 |

[1] Starting from 6-[4-[(2-bromopyridin-3-yl)methyl]piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine, obtained as described in Example 376.

[2] Starting from 6-[4-[(4-bromopyridin-3-yl)methyl]piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine, obtained as described in Example 377.

### **Examples 380-393**

The following compounds were prepared in 23 - 93% yield by General Synthetic Method 5, starting from 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine and the appropriate aldehyde:-



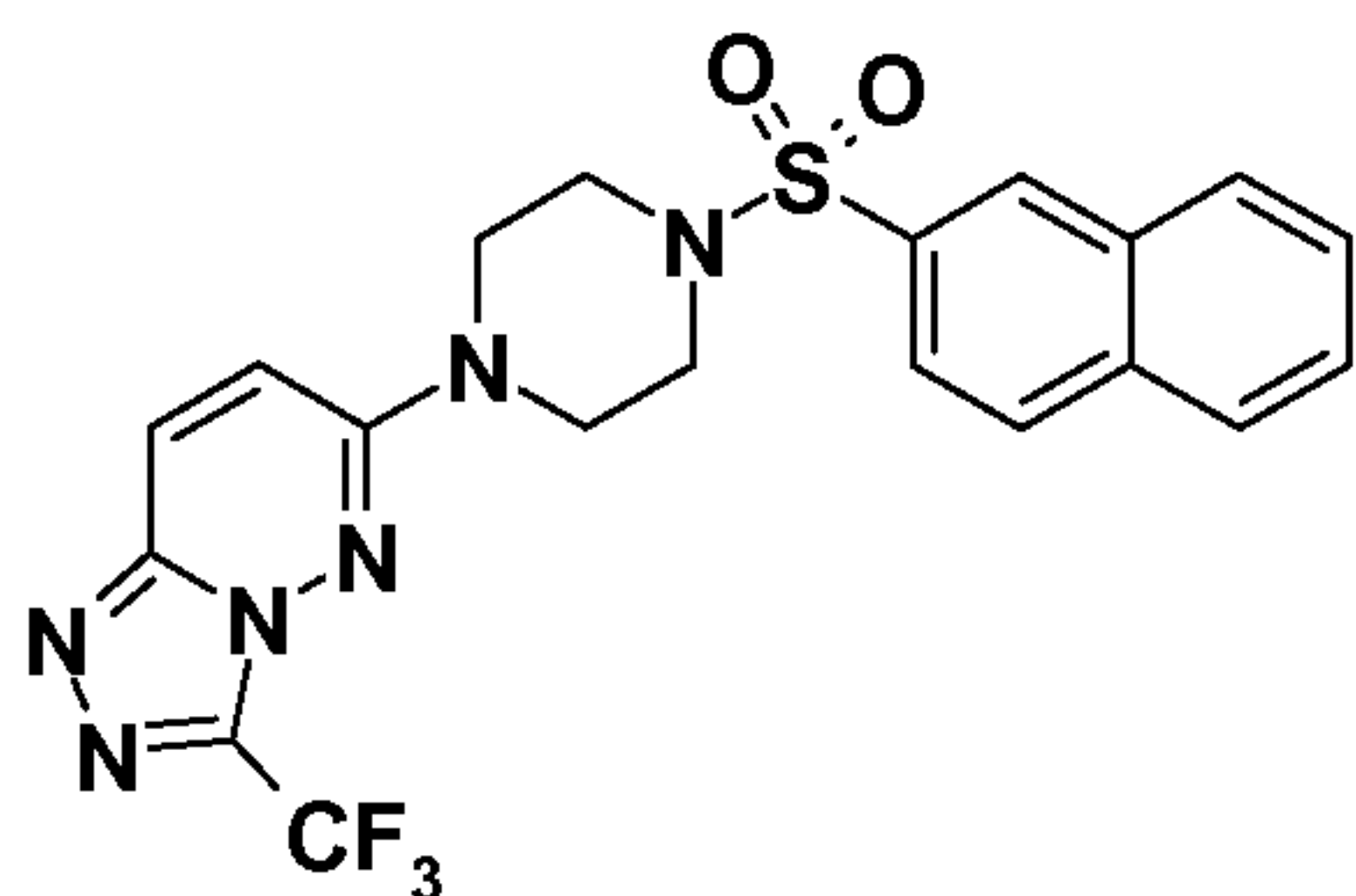
10

| Ex. | R              | <sup>1</sup> H NMR (399.9 MHz, DMSO-d <sub>6</sub> )                                                                                                                                  | m/z [M+H] <sup>+</sup> |
|-----|----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|
| 380 | 2,6-di-F, 4-CN | $\delta$ 2.65 (4H, m), 3.62 (4H, m), 3.78 (2H, s),<br>7.03 (1H, d), 7.25 (2H, m), 7.92 (1H, d)                                                                                        | 424                    |
| 381 | 2,3-di-F       | $\delta$ 2.64 (4H, m), 3.63 (4H, m), 3.69 (2H, s),<br>7.13 (4H, m), 7.92 (1H, d)                                                                                                      | 399                    |
| 382 | 2,4-di-F       | <sup>1</sup> H NMR (399.9 MHz, DMSO-d <sub>6</sub> ) $\delta$ 2.52 (4H,<br>m), 3.30 (2H, s), 3.61 (4H, m), 7.09 (1H, m),<br>7.22 (1H, m), 7.50 (1H, m), 7.58 (1H, d), 8.25<br>(1H, d) | 399                    |
| 383 | 3,4-di-F       | <sup>1</sup> H NMR (399.9 MHz, DMSO-d <sub>6</sub> ) $\delta$ 3.29 (4H,<br>m), 3.55 (2H, s), 3.62 (4H, m), 7.19 (1H, m),<br>7.40 (2H, m), 7.59 (1H, d), 8.26 (1H, d)                  | 399                    |
| 384 | 2,6-di-F       | $\delta$ 2.76 (4H, m), 3.67 (4H, m), 3.85 (2H, s),                                                                                                                                    | 399                    |



|     |            |                                                                                                                                                                                            |     |
|-----|------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
|     |            | 7.08 (2H, m), 7.44 (2H, m), 8.15 (1H, d)                                                                                                                                                   |     |
| 385 | 2-F, 4-OMe | $\delta$ 2.91 (4H, s), 3.74 (4H, s), 3.81 (3H, s), 3.91 (2H, s), 6.82 (2H, m), 7.40 (1H, m), 7.49 (1H, d), 8.18 (1H, d)                                                                    | 411 |
| 386 | 2,5-di-F   | $\delta$ 2.78 (4H, m), 3.70 (4H, m), 3.80 (2H, s), 7.16 (1H, m), 7.22 (1H, m), 7.31 (1H, m), 7.49 (1H, d), 8.16 (1H, d)                                                                    | 399 |
| 387 | 3-CN, 4-F  | <sup>1</sup> H NMR (399.9 MHz, DMSO-d <sub>6</sub> ) $\delta$ 3.29 (4H, m), 3.60 (2H, s), 3.63 (4H, m), 7.52 (1H, m), 7.60 (1H, d), 7.77 (1H, m), 7.87 (1H, m), 8.26 (1H, d)               | 406 |
| 388 | 3-F, 4-OMe | <sup>1</sup> H NMR (399.9 MHz, DMSO-d <sub>6</sub> ) $\delta$ 3.30 (4H, m), 3.49 (2H, s), 3.62 (4H, m), 3.84 (3H, s), 7.14 (3H, m), 7.59 (1H, d), 8.25 (1H, d)                             | 411 |
| 389 | 2-F, 4-CN  | <sup>1</sup> H NMR (399.9 MHz, DMSO-d <sub>6</sub> ) $\delta$ 2.57 (4H, m), 3.30 (2H, s), 3.63 (4H, m), 7.60 (1H, d), 7.70 (2H, m), 7.85 (1H, m), 8.26 (1H, d)                             | 406 |
| 390 | 2-F, 5-OMe | <sup>1</sup> H NMR (399.9 MHz, DMSO-d <sub>6</sub> ) $\delta$ 2.55 (4H, m), 3.30 (3H, s), 3.62 (4H, m), 3.76 (2H, s), 6.88 (1H, m), 6.98 (1H, m), 7.12 (1H, m), 7.59 (1H, d), 8.25 (1H, d) | 411 |
| 391 | 3,5-di-F   | <sup>1</sup> H NMR (399.9 MHz, DMSO-d <sub>6</sub> ) $\delta$ 3.30 (4H, m), 3.59 (2H, s), 3.64 (4H, m), 7.11 (3H, m), 7.60 (1H, d), 8.26 (1H, d)                                           | 399 |
| 392 | 3-OMe, 4-F | <sup>1</sup> H NMR (399.9 MHz, DMSO-d <sub>6</sub> ) $\delta$ 2.52 (4H, m), 3.52 (2H, s), 3.63 (4H, m), 3.85 (3H, s), 6.90 (1H, m), 7.15 (2H, m), 7.59 (1H, d), 8.26 (1H, d)               | 411 |
| 393 | 3-F, 4-CN  | $\delta$ 2.55 (4H, m), 3.65 (4H, m), 3.67 (2H, s), 7.42 (1H, m), 7.51 (1H, m), 7.60 (1H, d), 7.91 (1H, m), 8.26 (1H, d)                                                                    | 406 |

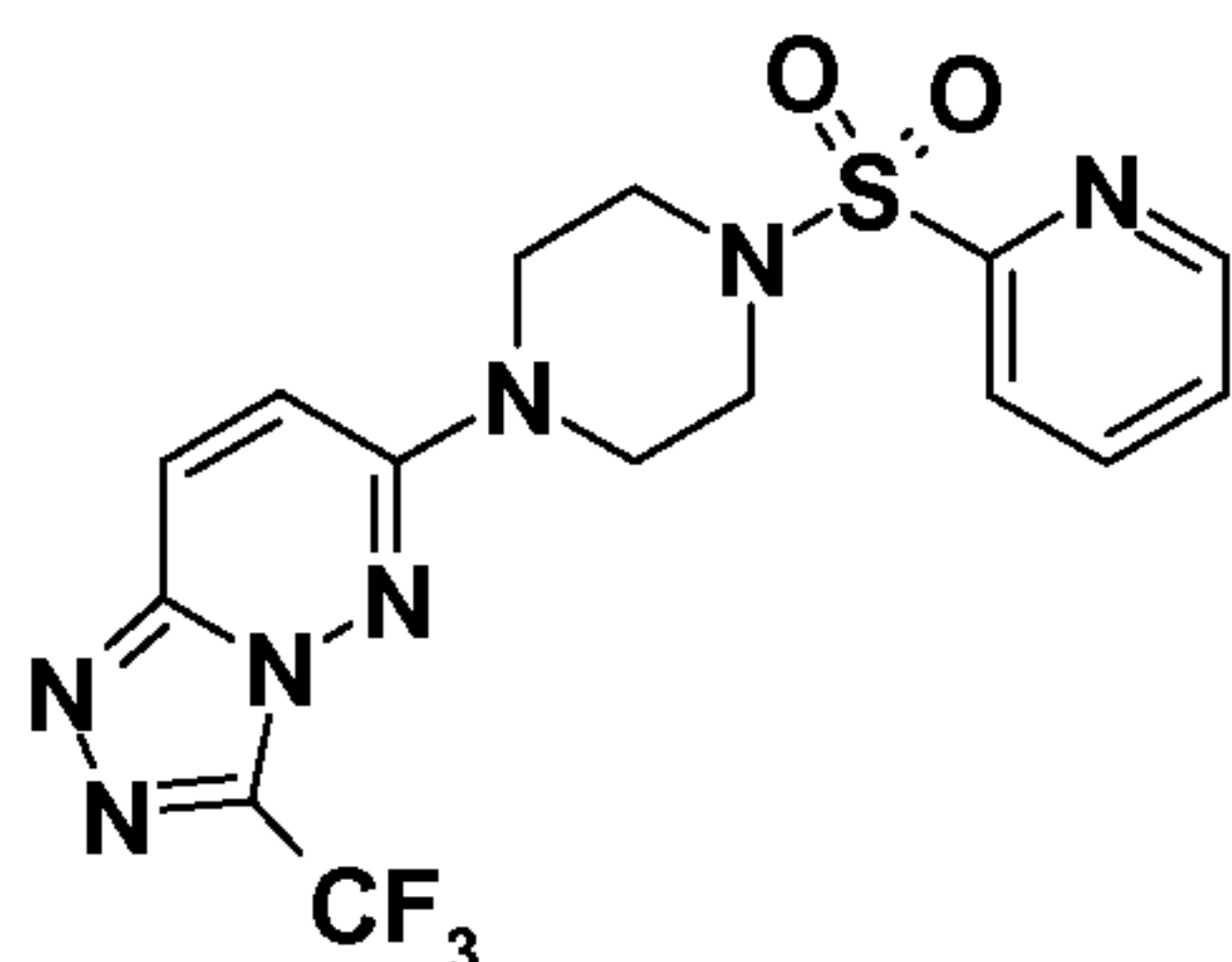


**Example 394****Preparation of 6-[4-(naphthalen-2-ylsulfonyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine**

- 5 Naphthalene-2-sulfonyl chloride (175 mg, 0.77 mmol) was added to 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (150 mg, 0.55 mmol) in pyridine (2 mL). The resulting solution was stirred at room temperature for 18 hours. The reaction mixture was evaporated to remove the pyridine. The crude product was purified by preparative HPLC (Phenomenex Gemini C18 110A (axia) column, 5 $\mu$  silica, 19 mm diameter, 100 mm
- 10 length), using decreasingly polar mixtures of water (containing 1% ammonia) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford 6-[4-(naphthalen-2-ylsulfonyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine (168 mg, 66%) as a solid.

1H NMR (399.9 MHz, DMSO-d<sub>6</sub>)  $\delta$  3.15 (4H, m), 3.72 (4H, m), 7.49 (1H, d), 7.74 (3H, m), 8.07 (1H, d), 8.19 (3H, m), 8.49 (1H, s); m/z = 463 [M+H]<sup>+</sup>.

15

**Example 395****Preparation of 6-[4-(pyridin-2-ylsulfonyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine**

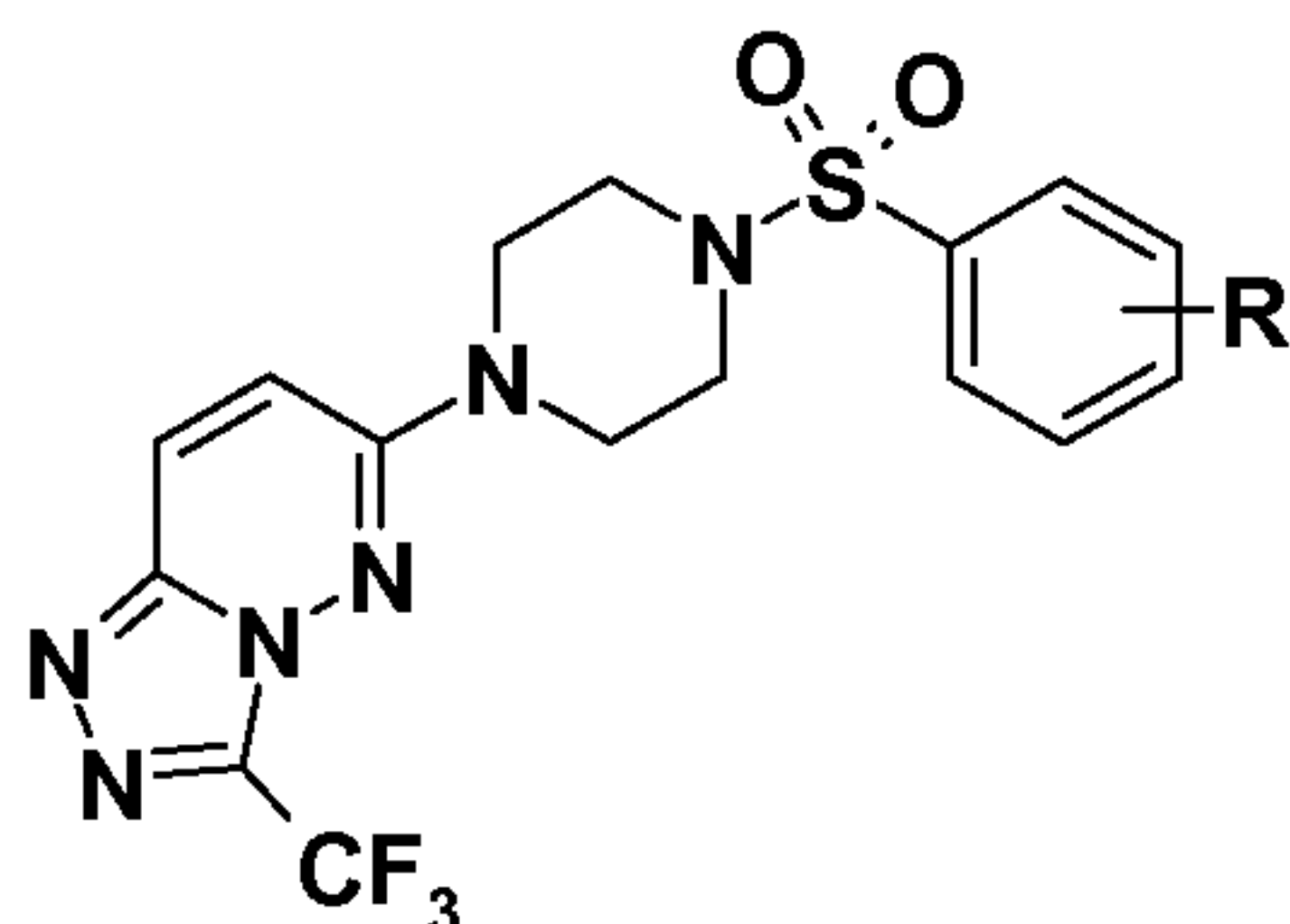
- 20 Obtained in 32% yield by an analogous method to Example 394, starting from pyridine-2-sulfonyl chloride and 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

1H NMR (399.9 MHz, DMSO-d<sub>6</sub>)  $\delta$  3.28 (4H, m), 3.63 (4H, m), 7.47 (1H, d), 7.64 (1H, m), 7.90 (1H, m), 8.06 (1H, m), 8.20 (1H, d), 8.68 (1H, m); m/z = 414 [M+H]<sup>+</sup>.



**Examples 396-405**

The following compounds were prepared in 7 - 90% yield by an analogous method to Example 394, starting from 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine and the appropriate sulfonyl chloride:-

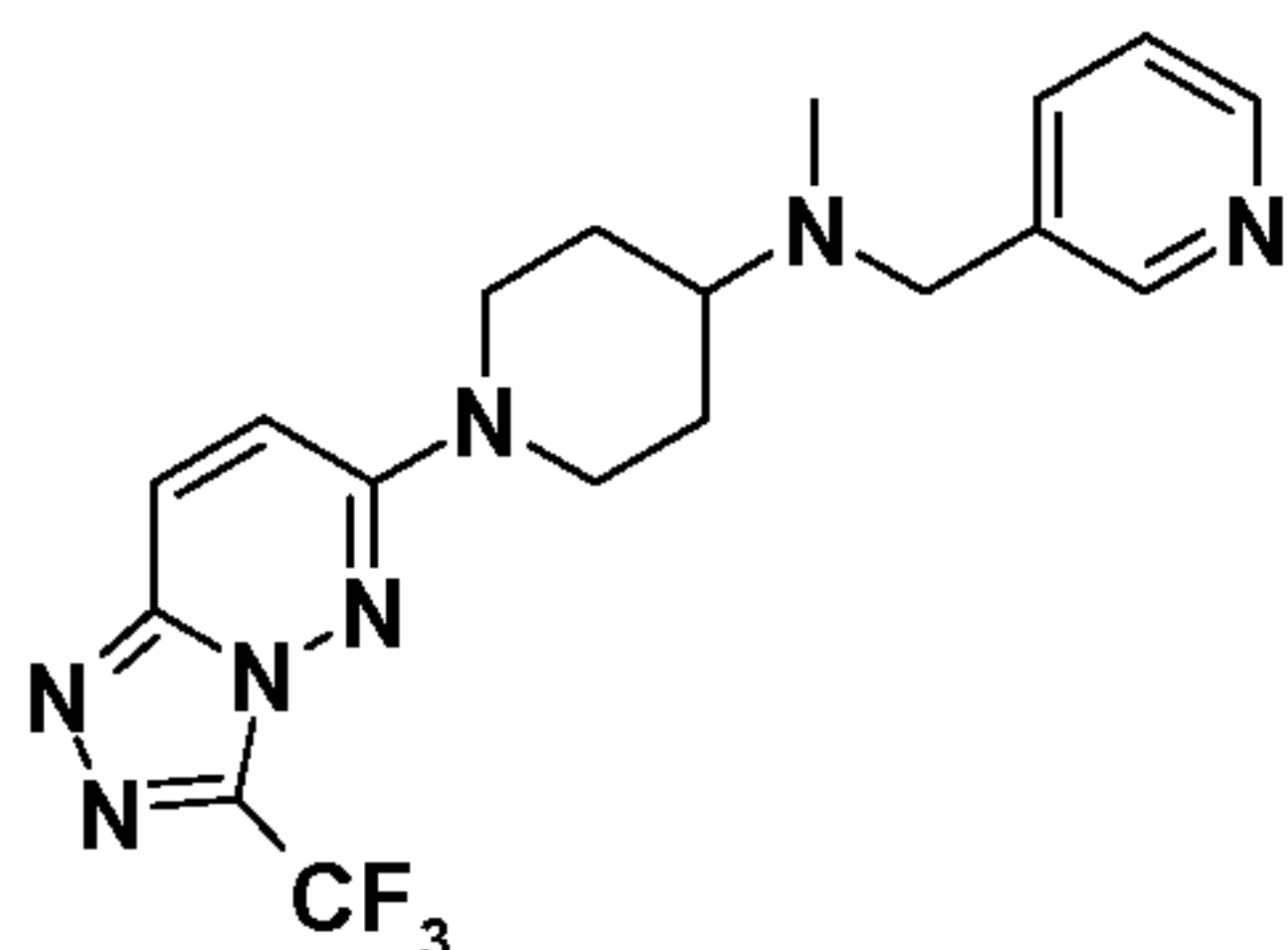


5

| Ex. | R          | <sup>1</sup> H NMR (399.9 MHz, DMSO-d <sub>6</sub> )                                                                           | m/z [M+H] <sup>+</sup> |
|-----|------------|--------------------------------------------------------------------------------------------------------------------------------|------------------------|
| 396 | 3-OMe      | δ 3.09 (4H, m), 3.71 (4H, m), 3.85 (3H, s), 7.23 (1H, m), 7.32 (2H, m), 7.56 (2H, m), 8.25 (1H, d)                             | 443                    |
| 397 | 2-OMe      | δ 3.27 (4H, m), 3.67 (4H, m), 3.89 (3H, s), 7.12 (1H, m), 7.26 (1H, m), 7.56 (1H, d), 7.65 (1H, m), 7.78 (1H, m), 8.28 (1H, d) | 443                    |
| 398 | 4-OMe      | δ 2.96 (4H, m), 3.63 (4H, m), 3.76 (3H, s), 7.09 (2H, m), 7.44 (1H, d), 7.63 (2H, m), 8.17 (1H, d)                             | 443                    |
| 399 | 2,5-di-OMe | δ 3.20 (4H, m), 3.59 (4H, m), 3.70 (3H, s), 3.76 (3H, s), 7.16 (3H, m), 7.48 (1H, d), 8.20 (1H, d)                             | 473                    |
| 400 | 2-F        | δ 3.16 (4H, m), 3.64 (4H, m), 7.42 (3H, m), 7.72 (2H, m), 8.19 (1H, d)                                                         | 431                    |
| 401 | 3-F        | δ 3.14 (4H, m), 3.72 (4H, m), 7.63 (5H, m), 8.26 (1H, d)                                                                       | 431                    |
| 402 | 3,4-di-OMe | δ 3.06 (4H, m), 3.71 (4H, m), 3.85 (6H, m), 7.18 (2H, m), 7.36 (1H, m), 7.53 (1H, d), 8.26 (1H, d)                             | 473                    |
| 403 | 2-CN       | δ 3.29 (4H, m), 3.74 (4H, m), 7.57 (1H, d), 7.94 (2H, m), 8.07 (1H, m), 8.18 (1H, m), 8.28 (1H, d)                             | 438                    |
| 404 | 2,4-di-OMe | δ 3.21 (4H, m), 3.67 (4H, m), 3.85 (3H, s), 3.87 (3H, s), 6.68 (1H, m), 6.73 (1H, m), 7.56 (1H, d), 7.69 (1H, d), 8.27 (1H, d) | 473                    |
| 405 | 4-F        | δ 3.09 (4H, m), 3.72 (4H, m), 7.51 (3H, m), 7.86                                                                               | 431                    |



|  |  |                       |  |
|--|--|-----------------------|--|
|  |  | (2H, m), 8.26 (1H, d) |  |
|--|--|-----------------------|--|

**Example 406****Preparation of N-methyl-N-(pyridin-3-ylmethyl)-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-amine**

- 5 DIPEA (0.174 mL, 1.00 mmol) was added to N-methyl-1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-amine (100 mg, 0.34 mmol) and 3-(bromomethyl)pyridine hydrobromide (127 mg, 0.50 mmol) in DMA (2 mL) and the mixture was sealed into a microwave tube. The reaction was heated to 150°C for 15 minutes in the microwave reactor and cooled to ambient temperature. The crude product
- 10 was purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5μ silica, 30 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 1% ammonia) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford N-methyl-N-(pyridin-3-ylmethyl)-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-amine (113 mg, 78%) as a
- 15 solid.

<sup>1</sup>H NMR (399.9 MHz, DMSO-d<sub>6</sub>) δ 1.59 (2H, m), 1.91 (2H, m), 2.12 (2H, s), 2.75 (1H, m), 3.03 (2H, m), 3.61 (3H, s), 4.34 (2H, m), 7.35 (1H, m), 7.63 (1H, d), 7.70 (1H, m), 8.23 (1H, d), 8.48 (2H, m); m/z = 392 [M+H]<sup>+</sup>.

- The N-methyl-1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-amine used as starting material was prepared as follows:-
- 20

**Preparation of tert-butyl methyl[1-(3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)piperidin-4-yl]carbamate**

- DIPEA (1.355 mL, 7.78 mmol) was added to 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (0.865 g, 3.89 mmol) and tert-butyl methyl(piperidin-4-yl)carbamate (1 g, 4.67 mmol) in DMA (15 mL). The resulting solution was stirred at 50°C
- 25 for 2 hours. The reaction mixture was evaporated and diluted with DCM (100 mL), and washed sequentially with water (100 mL) and saturated brine (100 mL). The organic layer



was dried over MgSO<sub>4</sub>, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 10% MeOH in DCM.

Pure fractions were evaporated to dryness to afford tert-butyl methyl[1-(3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)piperidin-4-yl]carbamate (1.500 g, 96%) as a solid.

<sup>1</sup>H NMR (399.9 MHz, DMSO-d<sub>6</sub>) δ 1.40 (9H, s), 1.71 (4H, m), 2.67 (3H, s), 3.05 (2H, m), 4.06 (1H, s), 4.38 (2H, m), 7.63 (1H, d), 8.24 (1H, d); m/z = 401 [M+H]<sup>+</sup>.

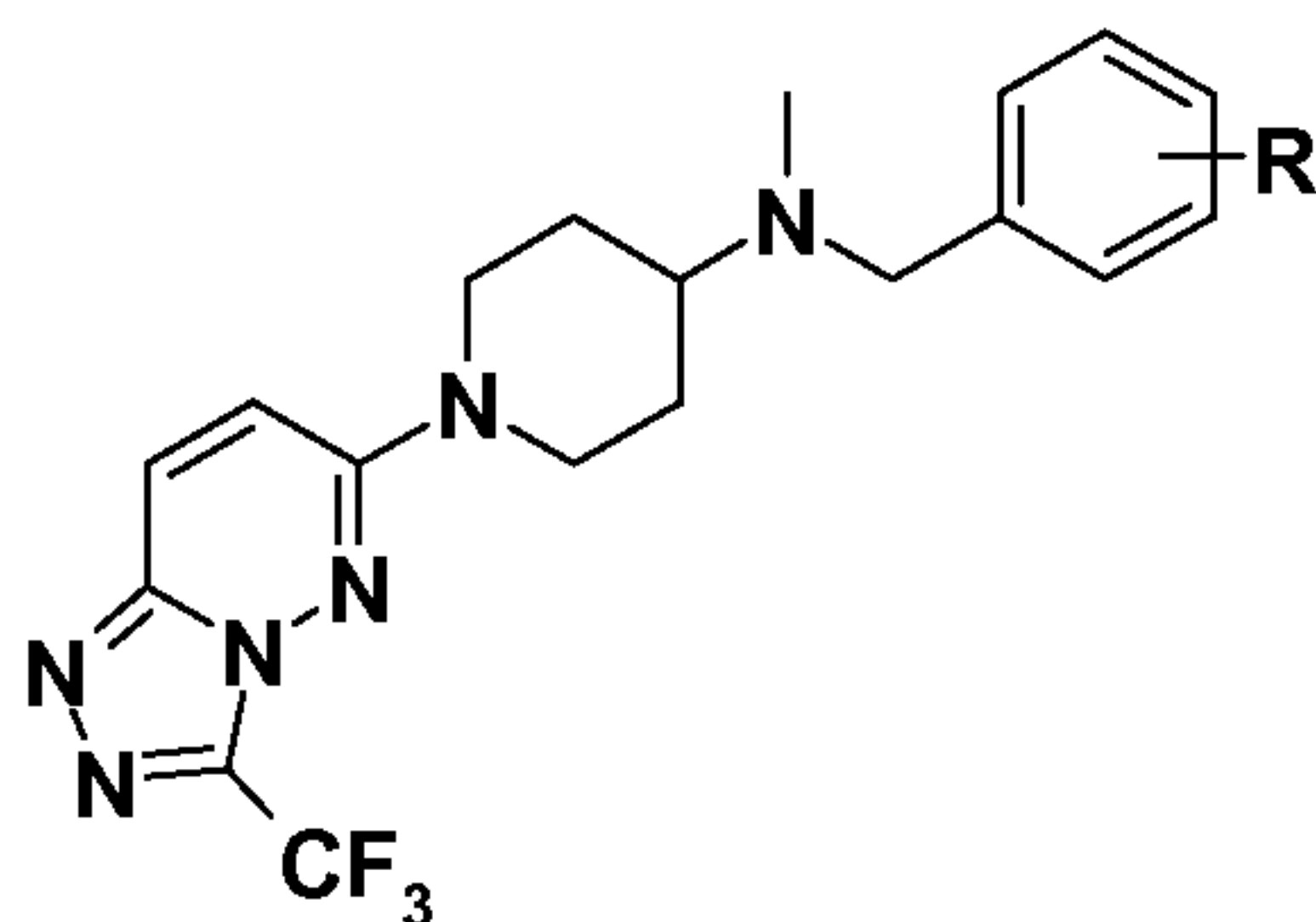
#### Preparation of N-methyl-1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-amine

tert-Butyl methyl[1-(3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)piperidin-4-yl]carbamate (1.5 g, 3.75 mmol) was dissolved in TFA (5 mL) and DCM (5 mL). The resulting solution was stirred at ambient temperature for 2 hours. The crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 2M ammonia in methanol and pure fractions were evaporated to dryness to afford N-methyl-1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-amine (1.090 g, 97%) as a solid.

<sup>1</sup>H NMR (399.9 MHz, DMSO-d<sub>6</sub>) δ 1.30 (2H, m), 1.91 (2H, m), 2.59 (1H, m), 3.16 (2H, m), 3.30 (3H, s), 4.11 (2H, m), 7.61 (1H, d), 8.22 (1H, d); m/z = 301 [M+H]<sup>+</sup>.

#### Examples 407-411

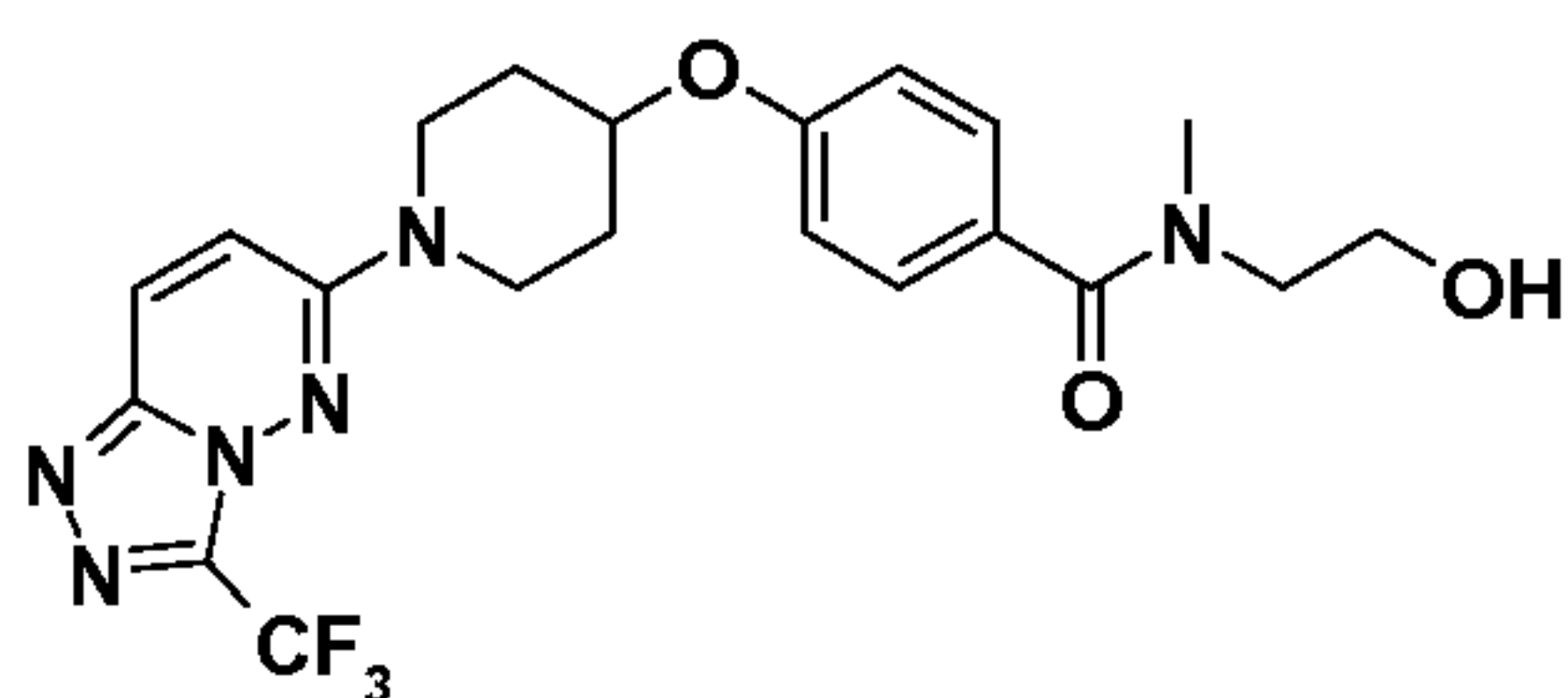
The following compounds were prepared in 39 - 78% yield by an analogous method to Example 406, starting from N-methyl-1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-amine and the appropriate benzyl bromide:-



| Ex. | R   | <sup>1</sup> H NMR (399.9 MHz, DMSO-d <sub>6</sub> )                                                                                                       | m/z [M+H] <sup>+</sup> |
|-----|-----|------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|
| 407 | 4-F | δ 1.58 (2H, m), 1.90 (2H, m), 2.11 (2H, s), 2.73 (1H, m), 3.02 (2H, m), 3.56 (3H, s), 4.32 (2H, m), 7.13 (2H, m), 7.34 (2H, m), 7.62 (1H, d), 8.23 (1H, d) | 409                    |



|     |           |                                                                                                                                                                                 |     |
|-----|-----------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
| 408 | 3,4-di-F  | $\delta$ 1.57 (2H, m), 1.89 (2H, m), 2.13 (2H, s), 2.73 (1H, m), 3.02 (2H, m), 3.56 (3H, s), 4.33 (2H, m), 7.16 (1H, m), 7.35 (2H, m), 7.63 (1H, d), 8.23 (1H, d)               | 427 |
| 409 | 4-CN      | $\delta$ 1.59 (2H, m), 1.90 (2H, m), 2.13 (2H, s), 2.65 (1H, m), 3.05 (2H, m), 3.66 (3H, s), 4.34 (2H, m), 7.65 (4H, m), 7.98 (1H, m), 8.27 (1H, m)                             | 416 |
| 410 | 3,5-di-F  | $\delta$ 1.57 (2H, m), 1.89 (2H, m), 2.15 (2H, s), 2.73 (1H, m), 3.02 (2H, m), 3.61 (3H, s), 4.33 (2H, m), 7.06 (3H, m), 7.63 (1H, d), 8.23 (1H, d)                             | 427 |
| 411 | 3-CN, 4-F | $\delta$ 1.58 (2H, m), 1.89 (2H, m), 2.13 (2H, s), 2.74 (1H, m), 3.04 (2H, m), 3.60 (3H, s), 4.33 (2H, m), 7.48 (1H, m), 7.63 (1H, d), 7.73 (1H, m), 7.82 (1H, m), 8.23 (1H, d) | 434 |

**Example 412****Preparation of N-(2-hydroxyethyl)-N-methyl-4-[[1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]oxy]benzamide**

DIPEA (0.087 mL, 0.5 mmol) was added to 4-[[1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]oxy]benzoic acid (100 mg, 0.25 mmol), 2-(methylamino)ethanol (20.28 mg, 0.27 mmol) and HATU (114 mg, 0.3 mmol) in DMF (2 mL). The resulting solution was stirred at room temperature for 24 hours. The crude product was purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5  $\mu$  silica, 21 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 1% ammonia) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford N-(2-hydroxyethyl)-N-methyl-4-[[1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]oxy]benzamide (64 mg, 55%).

<sup>1</sup>H NMR (399.9 MHz, DMSO-d<sub>6</sub>)  $\delta$  1.75 (2H, m), 2.10 (2H, m), 2.98 (3H, s), 3.56 (6H, m), 3.99 (2H, m), 4.76 (1H, m), 7.04 (2H, d), 7.39 (2H, d), 7.65 (1H, d), 8.27 (1H, d);



$m/z = 465 [M+H]^+$ .

The 4-[[1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]oxy]benzoic acid used as starting material was prepared as follows:-

**Preparation of 1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol**

4-Hydroxypiperidine (10.91 g, 107.84 mmol) was added to 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (20 g, 89.87 mmol) and DIPEA (23.48 mL, 134.80 mmol) in DMF (200 mL). The resulting solution was stirred at 125°C for 2 hours. The reaction mixture was evaporated to dryness, redissolved in DCM and purified by flash silica chromatography, elution gradient 0 to 5% MeOH in DCM. Pure fractions were evaporated to dryness to give a beige solid which was stirred with ether then filtered to afford 1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol (22.64 g, 88%) as a solid.

$^1\text{H}$  NMR (399.9 MHz, DMSO- $d_6$ )  $\delta$  1.46 (2H, m), 1.85 (2H, m), 3.32 (2H, m), 3.78 (1H, m), 3.96 (2H, m), 4.78 (1H, d), 7.61 (1H, d), 8.22 (1H, d);  $m/z = 288 [M+H]^+$ .

**Preparation of ethyl 4-[[1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]oxy]benzoate**

DIAD (2.262 mL, 11.49 mmol) was added to 1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol (3 g, 10.44 mmol), ethyl 4-hydroxybenzoate (1.909 g, 11.49 mmol) and triphenylphosphine (3.01 g, 11.49 mmol) in THF (50 mL) under nitrogen. The resulting solution was stirred at ambient temperature for 4 hours. The crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 2M ammonia in methanol. The crude solid was triturated with MeOH to give a solid which was collected by filtration and dried under vacuum to give ethyl 4-[[1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]oxy]benzoate (2.220 g, 49%) as a solid.

$^1\text{H}$  NMR (399.9 MHz, DMSO- $d_6$ )  $\delta$  1.33 (3H, t), 1.76 (2H, m), 2.11 (2H, m), 3.55 (2H, m), 3.98 (2H, m), 4.29 (2H, q), 4.83 (1H, m), 7.13 (2H, m), 7.66 (1H, d), 7.92 (2H, m), 8.27 (1H, d);  $m/z = 436 [M+H]^+$ .

**Preparation of 4-[[1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]oxy]benzoic acid**

Lithium hydroxide monohydrate (0.488 g, 20.40 mmol) was added to ethyl 4-[[1-

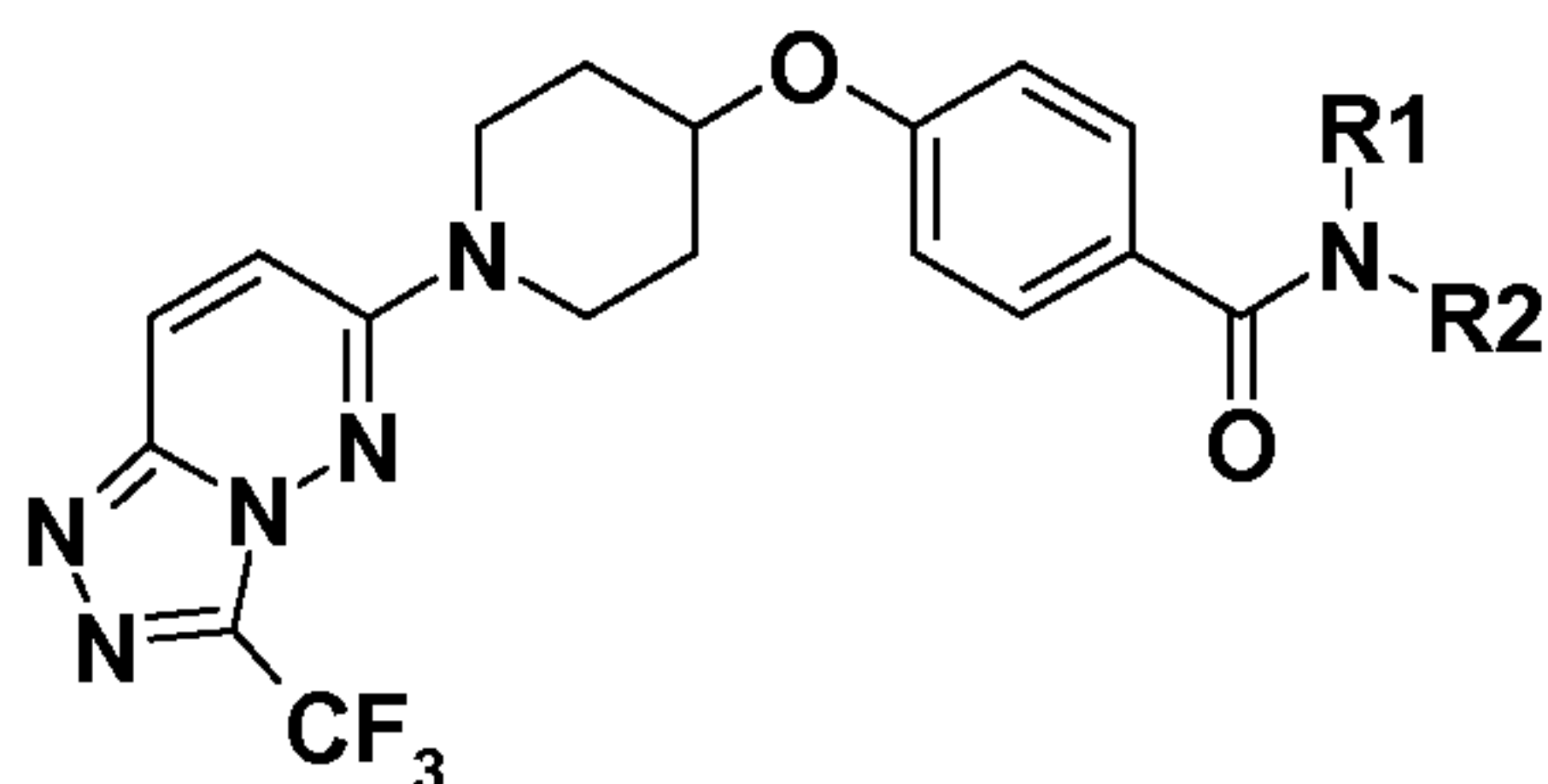


[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]oxy]benzoate (2.22 g, 5.10 mmol) in MeOH (80 mL) and water (40.0 mL). The resulting suspension was stirred at 50°C for 2 days. The reaction was cooled to room temperature, the methanol was evaporated and the aqueous residues treated with citric acid until precipitation ceased. The precipitate was collected by filtration, washed with water and dried to afford 4-[[1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]oxy]benzoic acid (2.020 g, 97%) as a solid.

<sup>1</sup>H NMR (399.9 MHz, DMSO-d<sub>6</sub>) δ 1.76 (2H, m), 2.12 (2H, m), 3.54 (2H, m), 3.99 (2H, m), 4.82 (1H, m), 7.10 (2H, m), 7.66 (1H, d), 7.90 (2H, m), 8.26 (1H, d), 12.60 (1H, s);  
m/z = 408 [M+H]<sup>+</sup>.

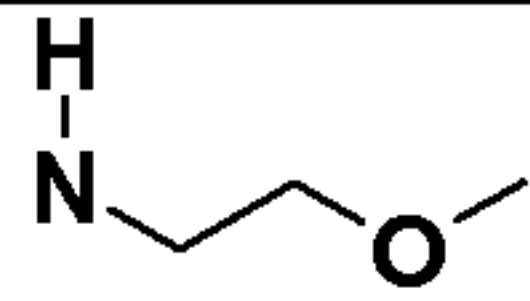
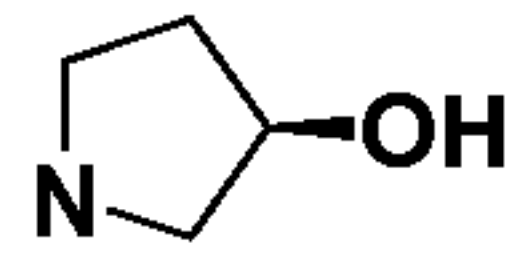
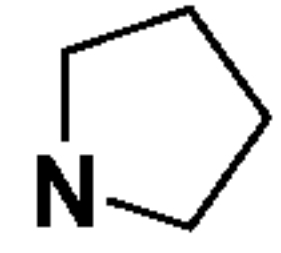
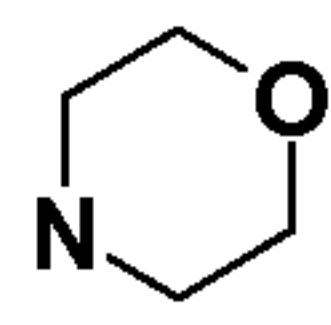
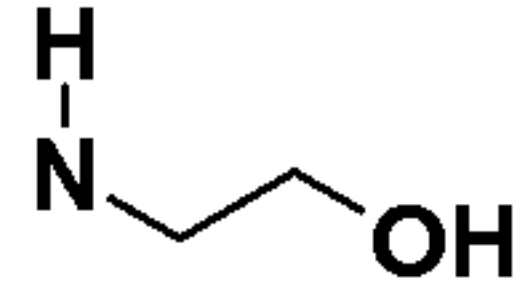
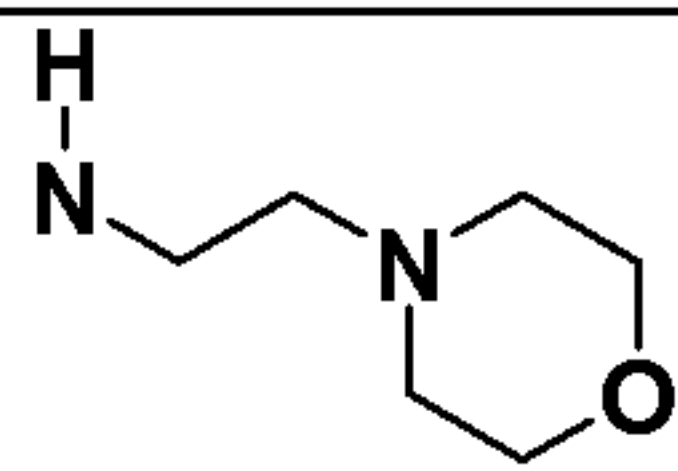
### Examples 413-429

The following compounds were prepared in 9 - 62% yield by an analogous method to Example 412, starting from 4-[[1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]oxy]benzoic acid and the appropriate amine:-

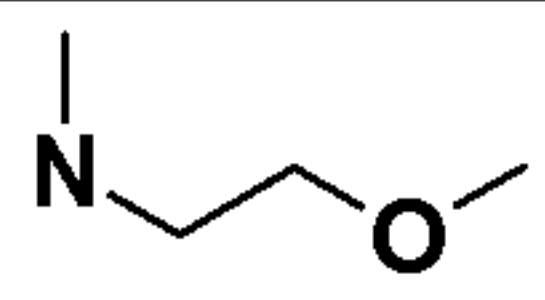
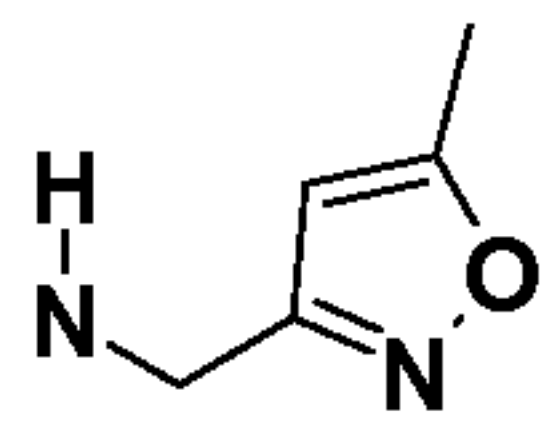
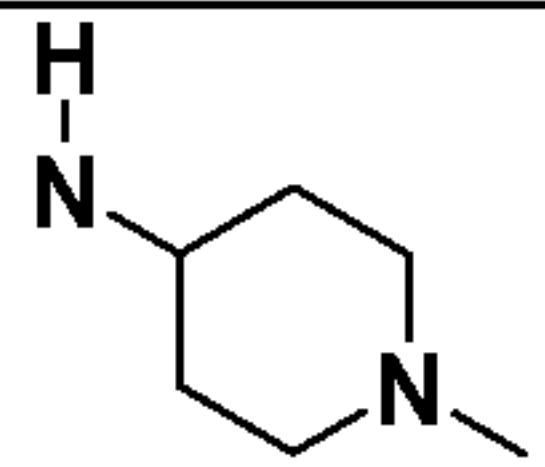
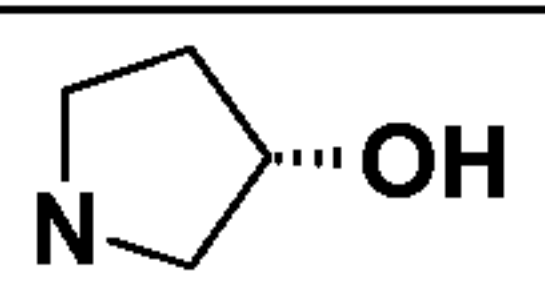
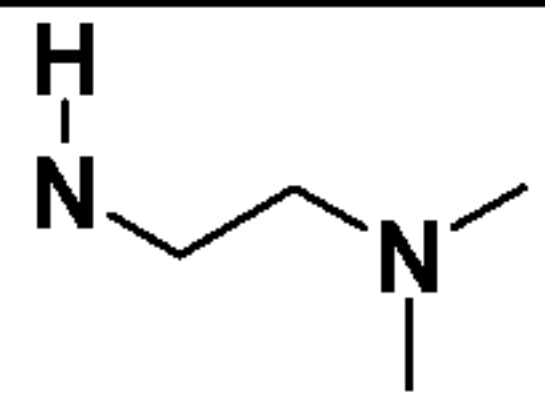


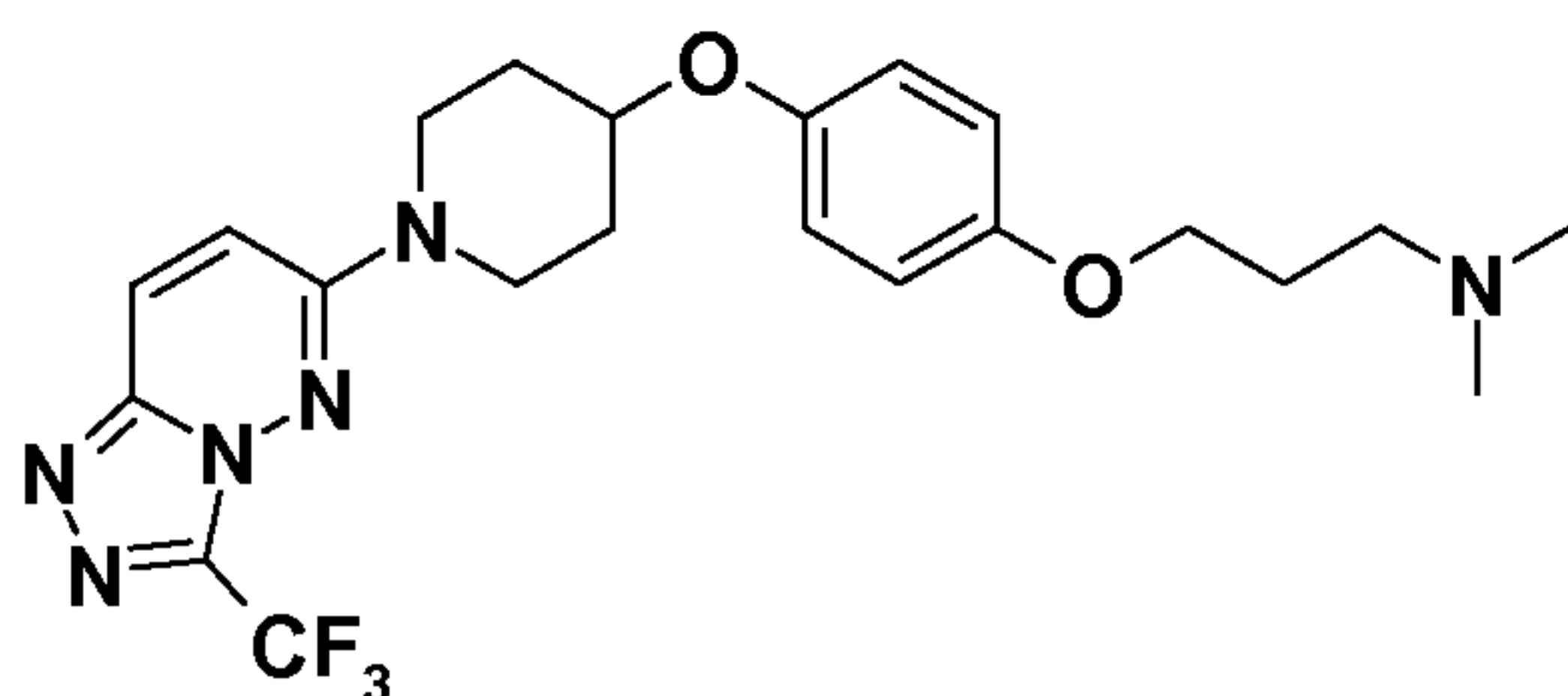
| Ex. | NR <sub>1</sub> R <sub>2</sub> | <sup>1</sup> H NMR (399.9 MHz, DMSO-d <sub>6</sub> )                                                                                                                     | m/z [M+H] <sup>+</sup> |
|-----|--------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|
| 413 |                                | δ 1.72 (6H, m), 2.10 (2H, m), 2.49 (4H, m), 2.57 (2H, m), 3.37 (2H, m), 3.55 (2H, m), 3.99 (2H, m), 4.79 (1H, m), 7.07 (2H, d), 7.65 (1H, d), 7.82 (2H, d), 8.26 (2H, m) | 504                    |
| 414 |                                | δ 1.75 (2H, m), 2.10 (2H, m), 2.20 (3H, s), 2.32 (4H, m), 3.50 (6H, m), 3.98 (2H, m), 4.76 (1H, m), 7.06 (2H, d), 7.35 (2H, d), 7.65 (1H, d), 8.26 (1H, d)               | 490                    |
| 415 |                                | δ 1.75 (2H, m), 2.10 (2H, m), 2.68 (4H, m), 3.41 (4H, m), 3.54 (2H, m), 3.98 (2H, m), 4.75 (1H, m), 7.05 (2H, m), 7.34 (2H, m), 7.65 (1H, d), 8.26 (1H, d)               | 476                    |



|     |                                                                                     |                                                                                                                                                                                                                              |     |
|-----|-------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
| 416 |    | $^1\text{H}$ NMR (499.803 MHz, DMSO- $d_6$ ) $\delta$ 1.72 (2H, m), 2.08 (2H, m), 3.26 (3H, s), 3.41 (4H, m), 3.51 (2H, m), 3.96 (2H, m), 4.77 (1H, m), 7.05 (2H, d), 7.63 (1H, d), 7.82 (2H, d), 8.24 (1H, d), 8.33 (1H, m) | 465 |
| 417 | NMe <sub>2</sub>                                                                    | $\delta$ 1.76 (2H, m), 2.11 (2H, m), 2.97 (6H, s), 3.53 (2H, m), 3.99 (2H, m), 4.76 (1H, m), 7.05 (2H, d), 7.38 (2H, d), 7.65 (1H, d), 8.26 (1H, d)                                                                          | 435 |
| 418 |   | $\delta$ 1.76 (3H, m), 1.94 (1H, m), 2.10 (2H, m), 3.53 (5H, m), 3.98 (2H, m), 4.28 (1H, m), 4.77 (1H, m), 4.94 (1H, m), 7.05 (2H, d), 7.51 (2H, d), 7.66 (1H, d), 8.26 (1H, d)                                              | 477 |
| 419 |  | $\delta$ 1.80 (6H, m), 2.10 (2H, m), 3.50 (6H, m), 3.98 (2H, m), 4.76 (1H, m), 7.04 (2H, d), 7.51 (2H, d), 7.65 (1H, d), 8.26 (1H, d)                                                                                        | 461 |
| 420 |  | $\delta$ 1.75 (2H, m), 2.10 (2H, m), 3.56 (10H, m), 3.98 (2H, m), 4.77 (1H, m), 7.07 (2H, m), 7.39 (2H, m), 7.65 (1H, d), 8.26 (1H, d)                                                                                       | 477 |
| 421 | NHMe                                                                                | $\delta$ 1.75 (2H, m), 2.10 (2H, m), 2.77 (3H, m), 3.53 (2H, m), 3.98 (2H, m), 4.79 (1H, m), 7.06 (2H, d), 7.65 (1H, m), 7.81 (2H, d), 8.27 (2H, m)                                                                          | 421 |
| 422 | NHEt                                                                                | $\delta$ 1.12 (3H, t), 1.75 (2H, m), 2.10 (2H, m), 3.30 (2H, m), 3.54 (2H, m), 3.98 (2H, m), 4.79 (1H, m), 7.06 (2H, d), 7.66 (1H, d), 7.82 (2H, d), 8.27 (2H, m)                                                            | 435 |
| 423 |  | $\delta$ 1.75 (2H, m), 2.11 (2H, m), 3.34 (2H, m), 3.53 (4H, m), 3.98 (2H, m), 4.69 (1H, t), 4.79 (1H, m), 7.07 (2H, d), 7.66 (1H, d), 7.84 (2H, d), 8.27 (2H, m)                                                            | 451 |
| 424 |  | $\delta$ 1.75 (2H, m), 2.10 (2H, m), 2.42 (4H, m), 2.57 (2H, m), 3.38 (2H, m), 3.55 (6H, m), 3.98 (2H, m)                                                                                                                    | 520 |



|     |                                                                                     |                                                                                                                                                                                                                                           |     |
|-----|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
|     |                                                                                     | m), 4.79 (1H, m), 7.07 (2H, d), 7.65 (1H, d), 7.81 (2H, d), 8.25 (2H, m)                                                                                                                                                                  |     |
| 425 |    | $\delta$ 1.74 (2H, m), 2.11 (2H, m), 2.98 (3H, s), 3.25 (3H, m), 3.52 (6H, m), 3.99 (2H, m), 4.75 (1H, m), 7.05 (2H, d), 7.36 (2H, d), 7.65 (1H, d), 8.26 (1H, d)                                                                         | 479 |
| 426 |    | $\delta$ 1.75 (2H, m), 2.11 (2H, m), 2.37 (3H, s), 3.54 (2H, m), 3.99 (2H, m), 4.45 (2H, d), 4.80 (1H, m), 6.14 (1H, s), 7.09 (2H, d), 7.66 (1H, d), 7.87 (2H, d), 8.26 (1H, d), 8.90 (1H, m)                                             | 502 |
| 427 |  | $\delta$ 1.63 (2H, m), 1.80 (4H, m), 1.99 (2H, m), 2.14 (2H, m), 2.22 (3H, s), 2.82 (2H, m), 3.60 (2H, m), 3.77 (1H, m), 4.02 (2H, m), 4.84 (1H, m), 7.11 (2H, d), 7.70 (1H, d), 7.88 (2H, d), 8.10 (1H, d), 8.31 (1H, d)                 | 504 |
| 428 |  | $\delta$ 1.76 (3H, m), 1.93 (1H, m), 2.10 (2H, m), 3.55 (5H, m), 3.98 (2H, m), 4.29 (1H, m), 4.77 (1H, m), 4.94 (1H, m), 7.05 (2H, d), 7.50 (2H, d), 7.65 (1H, d), 8.26 (1H, d)                                                           | 477 |
| 429 |  | $^1\text{H}$ NMR (500.13 MHz, DMSO- $d_6$ ) $\delta$ 1.72 (2H, m), 2.08 (2H, m), 2.16 (6H, s), 2.37 (2H, m), 3.32 (2H, m), 3.51 (2H, m), 3.95 (2H, m), 4.77 (1H, m), 7.04 (2H, d), 7.63 (1H, d), 7.80 (2H, d), 8.19 (1H, m), 8.24 (1H, m) | 478 |

**Example 430****Preparation of N,N-dimethyl-3-[4-[[1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]oxy]phenoxy]propan-1-amine**



DIAD (0.05 mL, 0.29 mmol) was added to 4-[[1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]oxy]phenol, 3-dimethylamino-1-propanol (100 mg, 0.26 mmol (33 mg, 0.32 mmol) and triphenylphosphine (76 mg, 0.29 mmol) in THF (2 mL). The resulting solution was stirred at ambient temperature for 4 hours. The crude product  
5 was purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5 $\mu$  silica, 19 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 1% ammonia) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford the product (19.1 mg, 16%) as a gum.

<sup>1</sup>H NMR (399.9 MHz, DMSO-d<sub>6</sub>)  $\delta$  1.74 (2H, m), 1.86 (2H, m), 2.08 (2H, m), 2.19 (6H, s), 2.39 (2H, m), 3.57 (2H, m), 3.99 (4H, m), 4.58 (1H, m), 6.94 (4H, m), 7.69 (1H, d),  
10 8.30 (1H, d); m/z = 465 [M+H]<sup>+</sup>.

The 4-[[1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]oxy]phenol used as starting material was prepared as follows:-

**Preparation of 6-[4-[4-(benzyloxy)phenoxy]piperidin-1-yl]-3-(trifluoromethyl)-  
15 [1,2,4]triazolo[4,3-b]pyridazine**

DIAD (2.262 mL, 11.49 mmol) was added to 1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol (3 g, 10.44 mmol), 4-(benzyloxy)phenol (2.300 g, 11.49 mmol) and triphenylphosphine (3.01 g, 11.49 mmol) in THF (50 mL) under nitrogen. The resulting solution was stirred at ambient temperature for 4 hours. The  
20 crude oil was triturated with MeOH to give a solid which was collected by filtration and dried under vacuum to give 6-[4-[4-(benzyloxy)phenoxy]piperidin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (2.53 g, 52%) as a solid.

<sup>1</sup>H NMR (399.9 MHz, DMSO-d<sub>6</sub>)  $\delta$  1.75 (2H, m), 2.08 (2H, m), 3.56 (2H, m), 3.99 (2H, m), 4.60 (1H, m), 5.10 (2H, s), 7.00 (4H, m), 7.44 (5H, m), 7.69 (1H, d), 8.30 (1H, d); m/z  
25 = 470 [M+H]<sup>+</sup>.

**Preparation of 4-[[1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]oxy]phenol**

10% Palladium on carbon (0.574 g, 0.54 mmol) was added to 6-[4-[4-(benzyloxy)phenoxy]piperidin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine  
30 (2.53 g, 5.39 mmol) in MeOH (30 mL) under an atmosphere of hydrogen. The resulting suspension was stirred at ambient temperature for 24 hours. The reaction mixture was evaporated. The crude product was purified by flash silica chromatography, elution

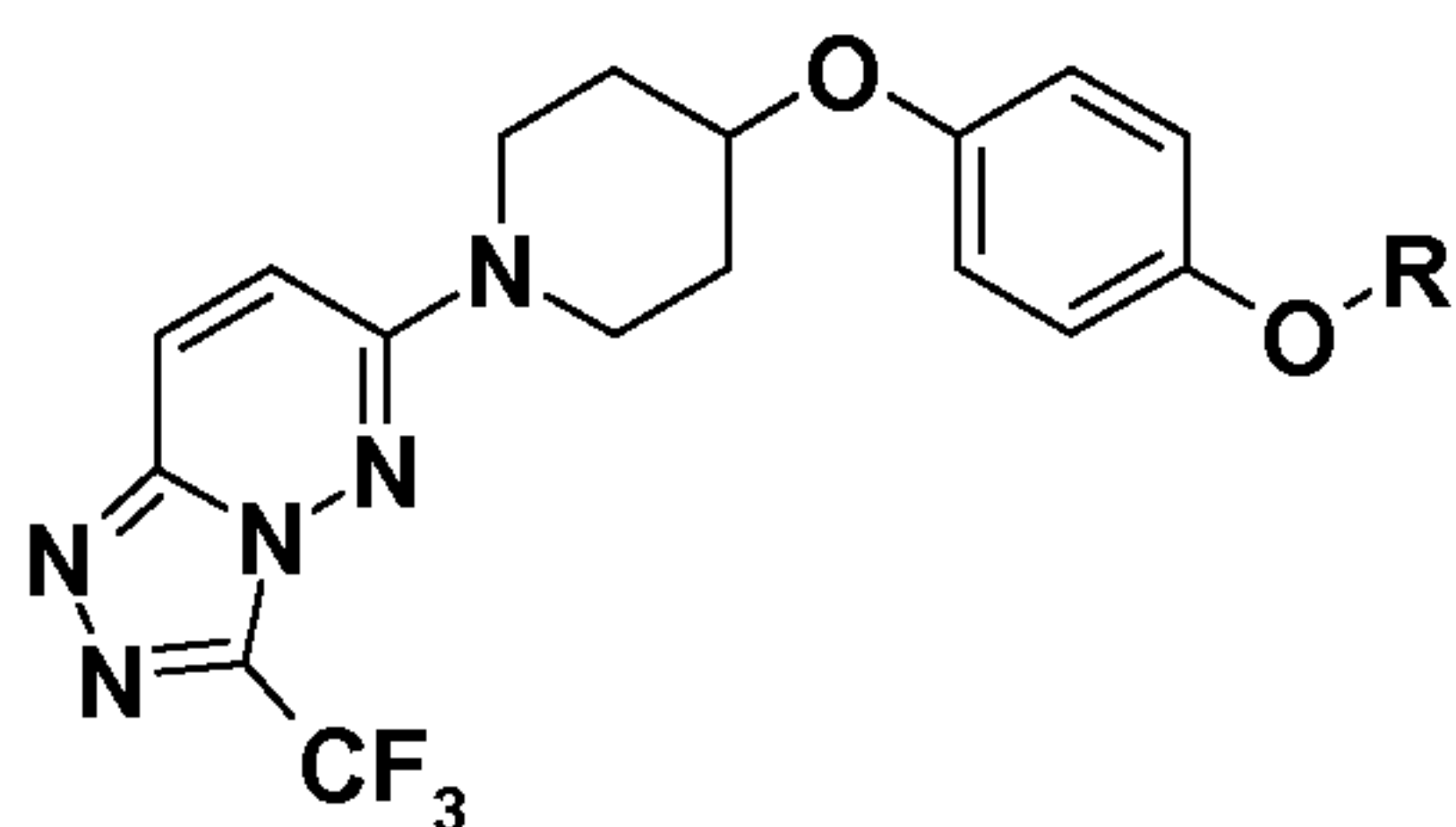


gradient 0 to 3% MeOH in DCM. Pure fractions were evaporated to dryness to afford 4-[[1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]oxy]phenol (1.760 g, 86%) as a gum which crystallised on standing.

<sup>1</sup>H NMR (399.9 MHz, DMSO-d<sub>6</sub>) δ 1.69 (2H, m), 2.01 (2H, m), 3.51 (2H, m), 3.94 (2H, m), 4.46 (1H, m), 6.69 (2H, m), 6.83 (2H, m), 7.64 (1H, d), 8.25 (1H, d), 8.94 (1H, s); m/z = 380 [M+H]<sup>+</sup>.

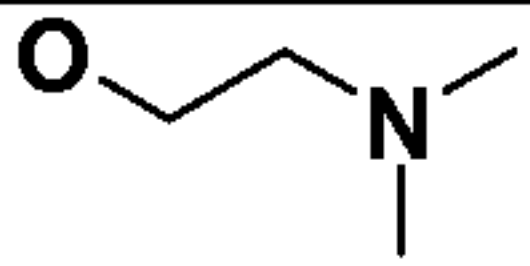
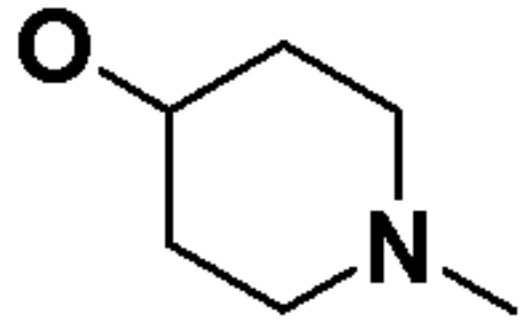
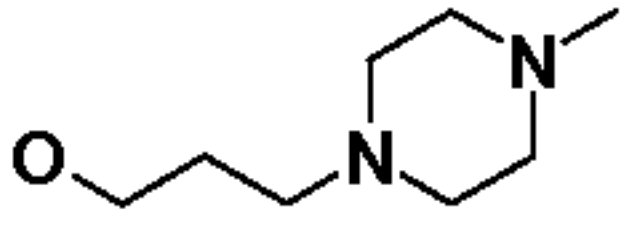
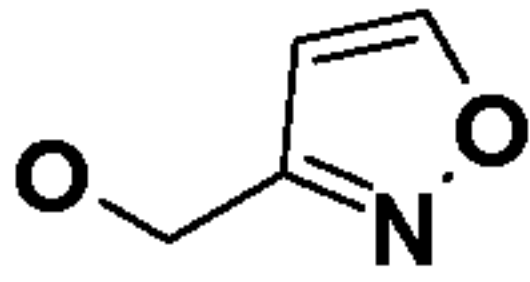
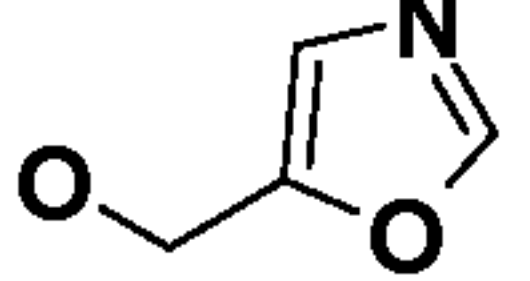
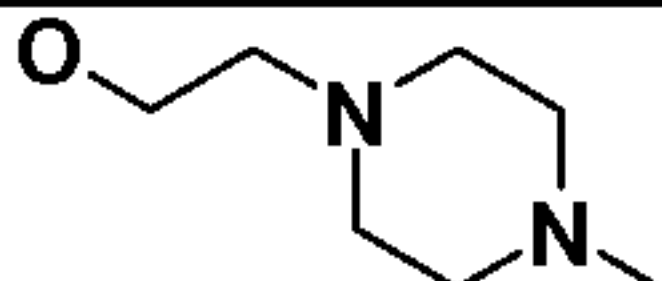
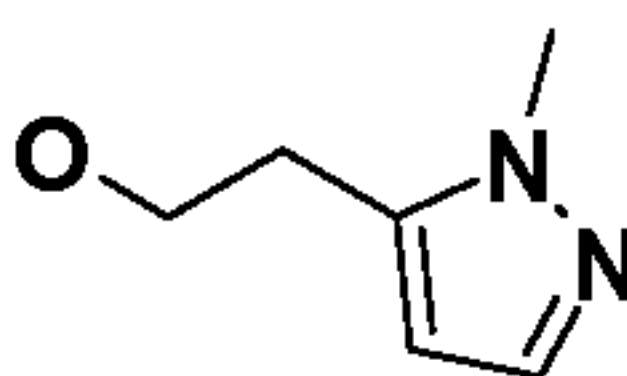
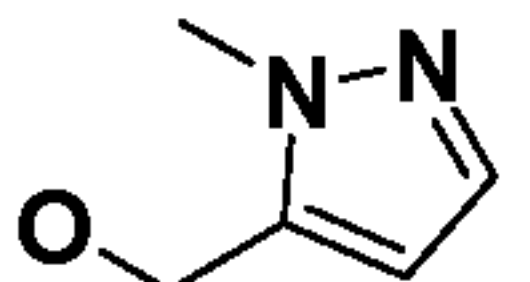
### **Examples 431-442**

The following compounds were prepared in 8 - 43% yield by an analogous method to Example 430, starting from 4-[[1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]oxy]phenol and the appropriate alcohol:-



| Ex. | OR | <sup>1</sup> H NMR (399.9 MHz, DMSO-d <sub>6</sub> )                                                                                                                                   | m/z [M+H] <sup>+</sup> |
|-----|----|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|
| 431 |    | δ 1.70 (6H, m), 2.03 (2H, m), 2.52 (4H, m), 2.76 (2H, m), 3.52 (2H, m), 3.97 (4H, m), 4.54 (1H, m), 6.91 (4H, m), 7.64 (1H, d), 8.25 (1H, d)                                           | 477                    |
| 432 |    | δ 1.74 (2H, m), 2.08 (2H, m), 2.44 (2H, m), 2.67 (4H, m), 2.74 (4H, m), 3.23 (2H, m), 3.55 (2H, m), 4.05 (2H, m), 4.59 (1H, m), 6.74 (1H, m), 6.94 (4H, m), 7.69 (1H, d), 8.30 (1H, d) | 492                    |
| 433 |    | δ 1.68 (2H, m), 1.81 (2H, m), 2.01 (2H, m), 2.27 (4H, m), 2.35 (2H, m), 2.66 (4H, m), 3.49 (2H, m), 3.92 (4H, m), 4.52 (1H, m), 6.84 (2H, m), 6.91 (2H, m), 7.62 (1H, d), 8.23 (1H, d) | 506                    |
| 434 |    | δ 1.75 (2H, m), 2.08 (2H, m), 2.47 (3H, s), 3.57 (2H, m), 4.00 (2H, m), 4.61 (1H, m), 5.13 (2H, m), 6.37 (1H, m), 7.01 (4H, m), 7.69 (1H, d), 8.30 (1H, d)                             | 475                    |

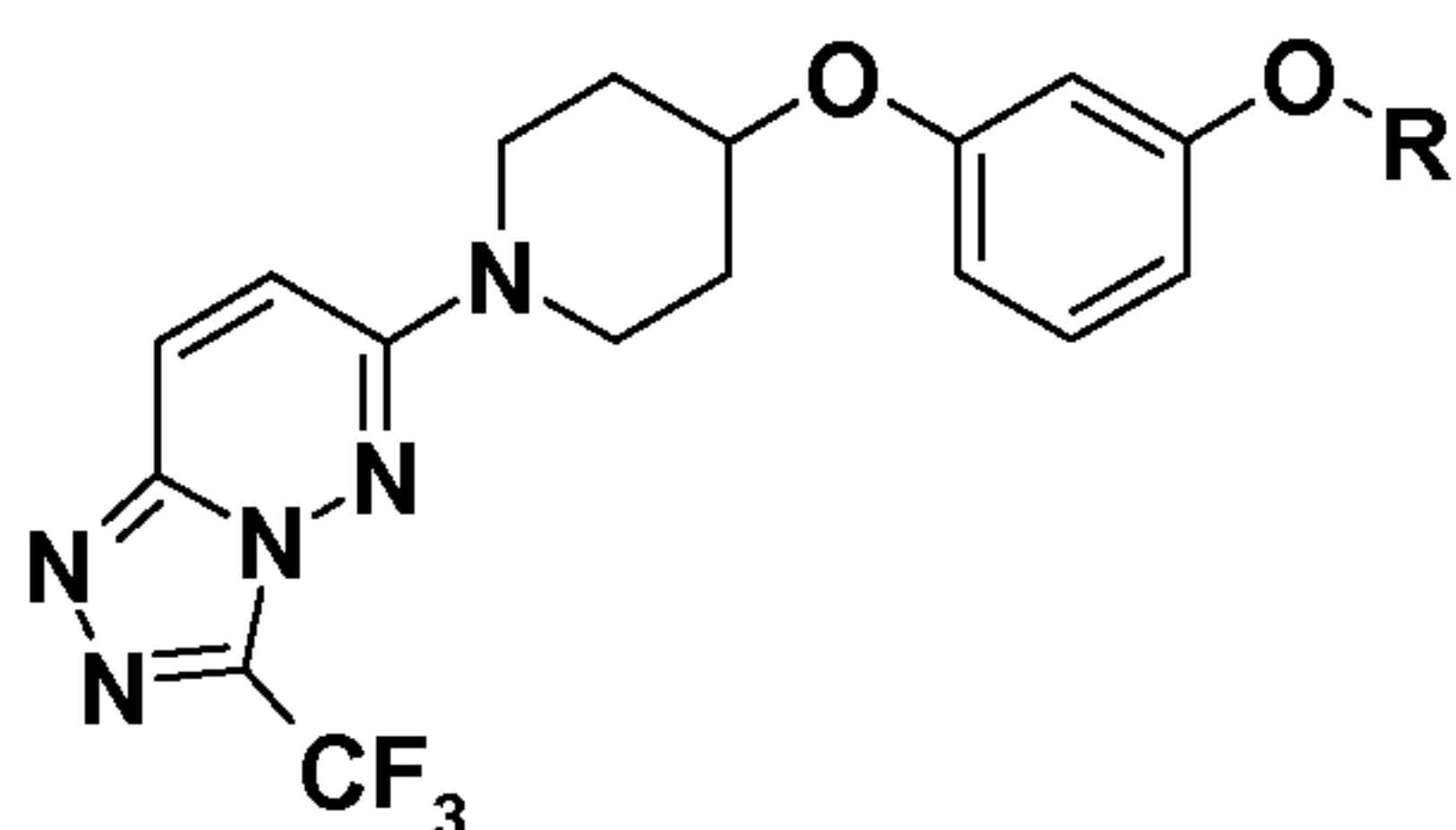


|     |                                                                                     |                                                                                                                                                                                               |     |
|-----|-------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
| 435 |    | $\delta$ 1.70 (2H, m), 2.03 (2H, m), 2.22 (6H, s), 2.61 (2H, m), 3.52 (2H, m), 3.96 (4H, m), 4.54 (1H, m), 6.91 (4H, m), 7.64 (1H, d), 8.25 (1H, d)                                           | 451 |
| 436 |    | $\delta$ 1.68 (4H, m), 1.94 (2H, m), 2.08 (2H, m), 2.19 (3H, m), 2.64 (4H, m), 3.56 (2H, m), 3.99 (2H, m), 4.26 (1H, m), 4.59 (1H, m), 6.95 (4H, m), 7.69 (1H, d), 8.30 (1H, d)               | 477 |
| 437 |    | $\delta$ 1.70 (2H, m), 1.84 (2H, m), 2.03 (2H, m), 2.15 (3H, s), 2.34 (10H, m), 3.52 (2H, m), 3.94 (4H, m), 4.53 (1H, m), 6.86 (2H, m), 6.94 (2H, m), 7.64 (1H, d), 8.25 (1H, d)              | 520 |
| 438 |  | $\delta$ 1.68 (2H, m), 2.01 (2H, m), 3.49 (2H, m), 3.93 (2H, m), 4.54 (1H, m), 5.15 (2H, s), 6.67 (1H, d), 6.95 (4H, m), 7.62 (1H, d), 8.23 (1H, d), 8.92 (1H, d)                             | 461 |
| 439 |  | $\delta$ 1.70 (2H, m), 2.04 (2H, m), 3.52 (2H, m), 3.95 (2H, m), 4.56 (1H, m), 5.12 (2H, s), 6.97 (4H, m), 7.31 (1H, s), 7.64 (1H, d), 8.25 (1H, d), 8.41 (1H, s)                             | 461 |
| 440 |  | $\delta$ 1.70 (2H, m), 2.03 (2H, m), 2.15 (3H, s), 2.39 (8H, m), 2.66 (2H, m), 3.51 (2H, m), 3.97 (4H, m), 4.54 (1H, m), 6.91 (4H, m), 7.64 (1H, d), 8.25 (1H, d)                             | 506 |
| 441 |  | $\delta$ 1.70 (2H, m), 2.03 (2H, m), 2.82 (2H, t), 3.52 (2H, m), 3.79 (3H, s), 3.95 (2H, m), 4.03 (2H, t), 4.54 (1H, m), 6.91 (4H, m), 7.56 (1H, s), 7.56 (1H, s), 7.64 (1H, d), 8.25 (1H, d) | 488 |
| 442 |  | $\delta$ 1.71 (2H, m), 2.04 (2H, m), 3.53 (2H, m), 3.84 (3H, s), 3.95 (2H, m), 4.58 (1H, m), 5.11 (2H, s), 6.35 (1H, m), 6.98 (4H, m), 7.38 (1H, m), 7.64 (1H, d), 8.25 (1H, d)               | 474 |



**Examples 443-446**

The following compounds were prepared in 7 - 33% yield by an analogous method to Example 430, starting from 3-[[1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]oxy]phenol and the appropriate alcohol:-



5

| Ex. | OR | <sup>1</sup> H NMR (399.9 MHz, DMSO-d <sub>6</sub> )                                                                                                                                   | m/z [M+H] <sup>+</sup> |
|-----|----|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|
| 443 |    | δ 1.72 (2H, m), 1.84 (2H, m), 2.06 (2H, m), 2.15 (6H, s), 2.35 (2H, m), 3.54 (2H, m), 3.97 (4H, m), 4.69 (1H, m), 6.55 (3H, m), 7.18 (1H, m), 7.64 (1H, d), 8.26 (1H, d)               | 465                    |
| 444 |    | δ 1.73 (2H, m), 2.06 (2H, m), 2.40 (4H, m), 2.66 (6H, m), 3.53 (2H, m), 3.96 (2H, m), 4.06 (2H, m), 4.69 (1H, m), 6.56 (3H, m), 7.18 (1H, m), 7.64 (1H, d), 8.25 (1H, d)               | 492                    |
| 445 |    | δ 1.69 (2H, m), 1.83 (2H, m), 2.04 (2H, m), 2.29 (4H, m), 2.36 (2H, m), 2.70 (4H, m), 3.51 (2H, m), 3.94 (4H, m), 4.66 (1H, m), 6.53 (3H, m), 7.16 (1H, m), 7.63 (1H, d), 8.24 (1H, d) | 506                    |
| 446 |    | δ 1.72 (2H, m), 2.07 (2H, m), 2.42 (3H, s), 3.52 (2H, m), 3.97 (2H, m), 4.69 (1H, m), 5.13 (2H, s), 6.33 (1H, s), 6.64 (3H, m), 7.21 (1H, m), 7.65 (1H, d), 8.26 (1H, d)               | 475                    |

The 3-[[1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]oxy]phenol used as starting material was prepared as follows:-

**Preparation of 6-[4-[3-(benzyloxy)phenoxy]piperidin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

10

Obtained in 40% yield by an analogous procedure to Example 430, preparation of



starting materials, starting from 3-(benzyloxy)phenol and 1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol.

<sup>1</sup>H NMR (399.9 MHz, DMSO-d<sub>6</sub>) δ 1.71 (2H, m), 2.05 (2H, m), 3.51 (2H, m), 3.96 (2H, m), 4.67 (1H, m), 5.10 (2H, s), 6.63 (3H, m), 7.19 (1H, m), 7.40 (5H, m), 7.64 (1H, d), 8.26 (1H, d); m/z = 470 [M+H]<sup>+</sup>.

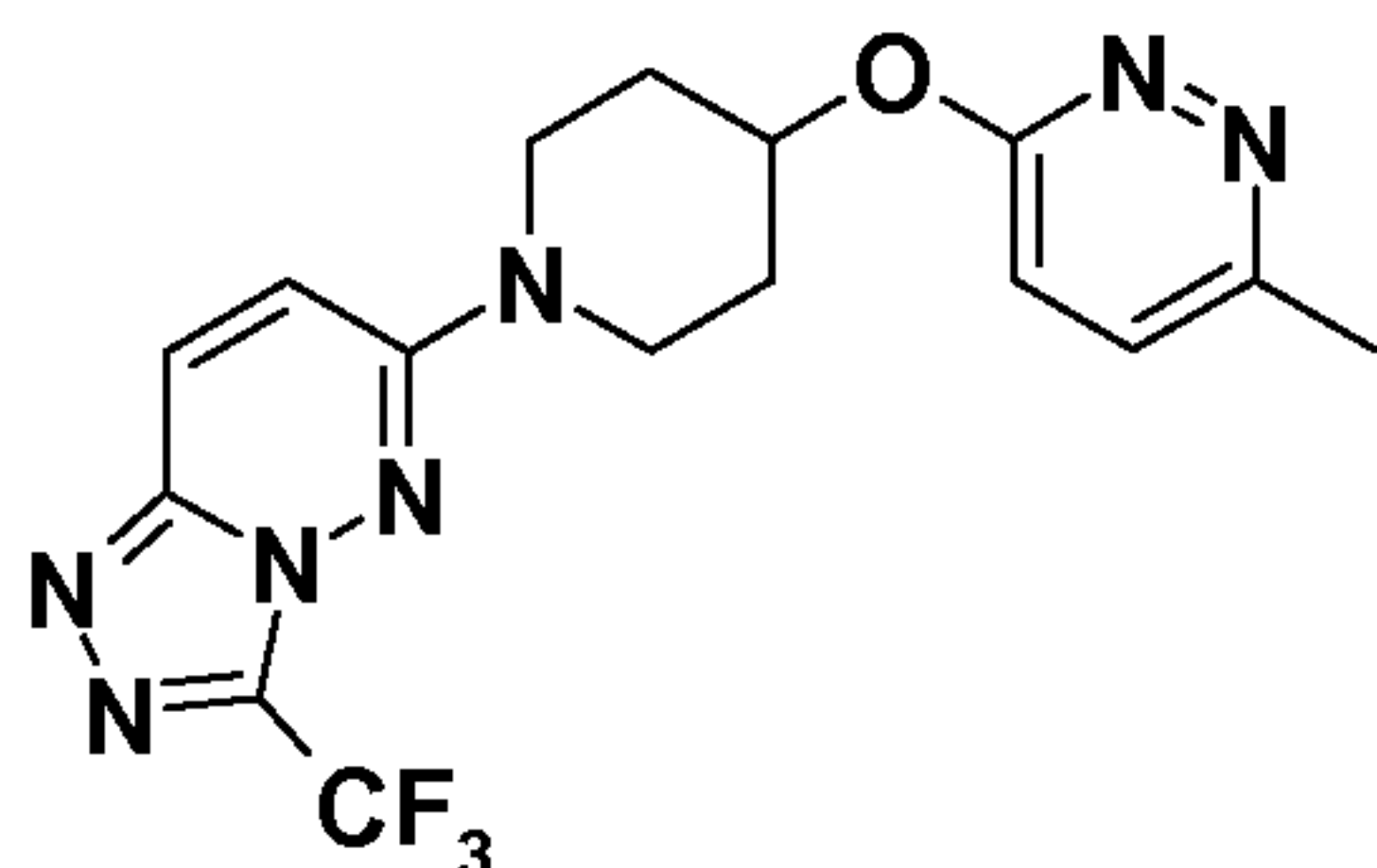
**Preparation of 3-[[1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]oxy]phenol**

Obtained in 80% yield by an analogous procedure to Example 430, preparation of starting materials, starting from 6-[4-[3-(benzyloxy)phenoxy]piperidin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine.

<sup>1</sup>H NMR (399.9 MHz, DMSO-d<sub>6</sub>) δ 1.71 (2H, m), 2.06 (2H, m), 3.53 (2H, m), 3.95 (2H, m), 4.60 (1H, m), 6.40 (3H, m), 7.07 (1H, m), 7.64 (1H, d), 8.25 (1H, d), 9.36 (1H, s); m/z = 380 [M+H]<sup>+</sup>.

**Example 447**

**Preparation of 6-[4-[(6-methylpyridazin-3-yl)oxy]piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine**



DIAD (0.102 mL, 0.52 mmol) was added to 1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol (obtained as described in Example 310, preparation of starting materials) (135 mg, 0.47 mmol), 6-methylpyridazin-3(2H)-one (56.9 mg, 0.52 mmol) and triphenylphosphine (136 mg, 0.52 mmol) in THF (5 mL). The resulting solution was stirred at ambient temperature for 3 days. The crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 2M ammonia in methanol and evaporated to give crude product. The crude product was purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5 μ silica, 19 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 1% ammonia) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford 6-[4-[(6-methylpyridazin-3-



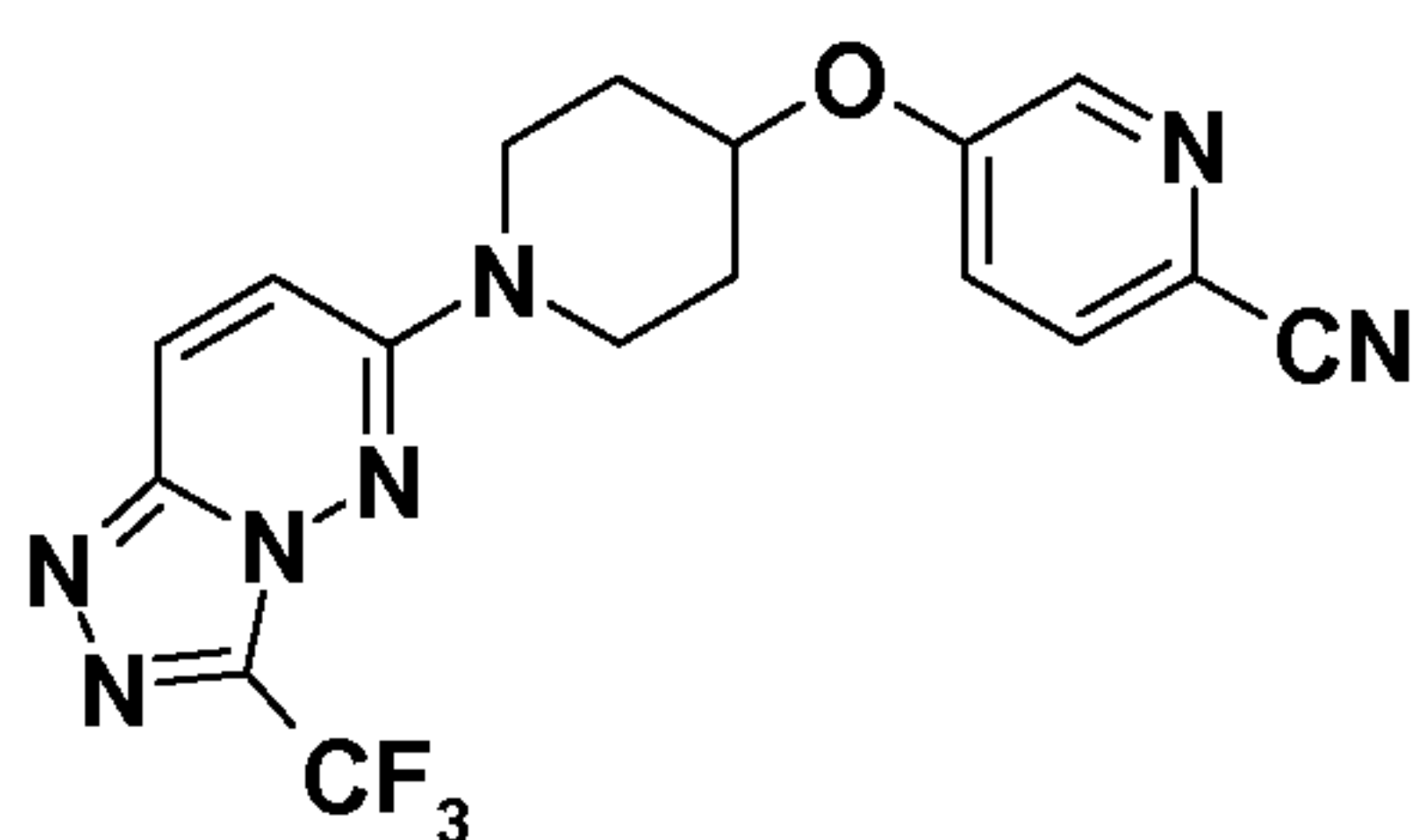
yl)oxy]piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine (22.00 mg, 12%) as a solid.

<sup>1</sup>H NMR (399.9 MHz, DMSO-d<sub>6</sub>) δ 1.91 (4H, m), 2.25 (3H, s), 3.22 (2H, m), 4.42 (2H, m), 5.10 (1H, m), 6.89 (1H, d), 7.32 (1H, d), 7.66 (1H, d), 8.27 (1H, d); m/z = 380

5 [M+H]<sup>+</sup>.

### **Example 448**

#### **Preparation of 5-[[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]oxy]pyridine-2-carbonitrile**



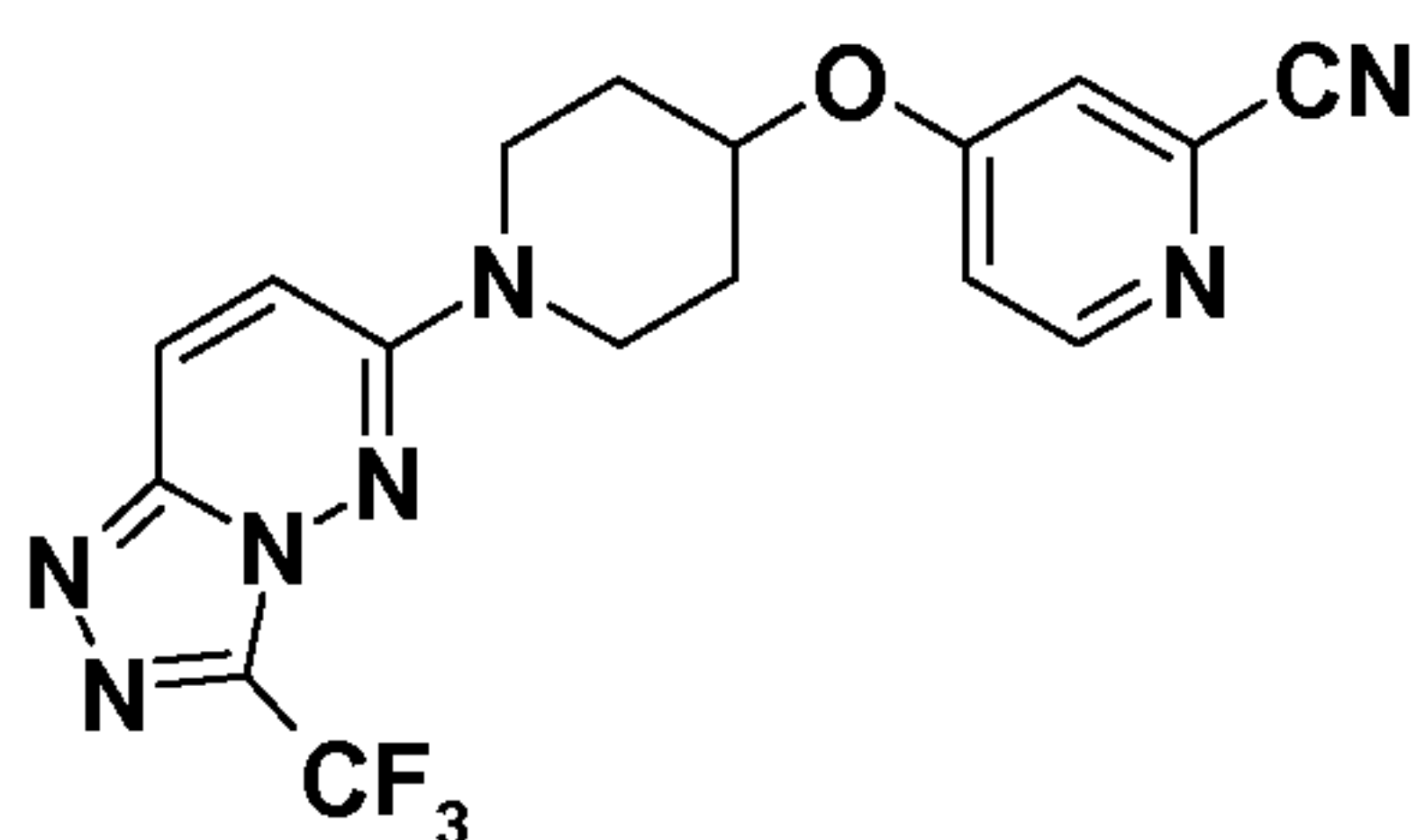
10 A solution of 1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol (150 mg, 0.52 mmol) and sodium hydride (60% dispersion in oil, 22.98 mg, 0.57 mmol) in DMF (5 mL) was stirred for 30 minutes at ambient temperature under nitrogen. 5-Chloropicolinonitrile (80 mg, 0.57 mmol) was added to the reaction mixture. The resulting solution was stirred at 50°C for 18 hours. The reaction mixture was diluted with a few  
15 drops of MeOH. The crude product was purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5 μ silica, 19 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 1% ammonia) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford 5-[[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]oxy]pyridine-2-carbonitrile (55.0 mg, 27%) as a solid.  
20

<sup>1</sup>H NMR (399.9 MHz, DMSO-d<sub>6</sub>) δ 1.78 (2H, m), 2.13 (2H, m), 3.53 (2H, m), 3.99 (2H, m), 4.95 (1H, m), 7.69 (2H, m), 8.02 (1H, d), 8.27 (1H, d), 8.50 (1H, m); m/z = 390 [M+H]<sup>+</sup>.

### **Example 449**

25 **Preparation of 4-[[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]oxy]pyridine-2-carbonitrile**



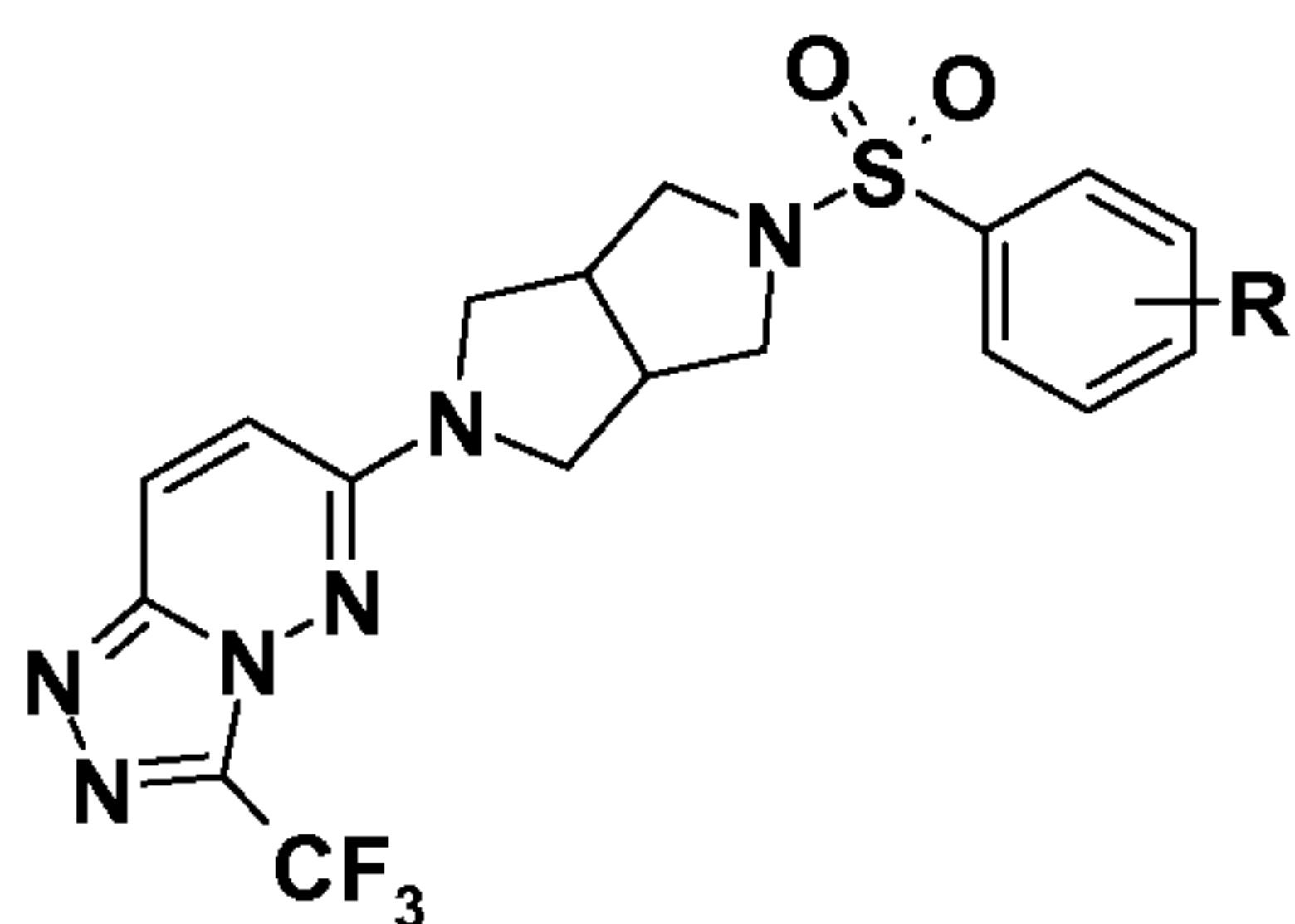


Obtained in 62% yield by an analogous procedure to Example 448, starting from 4-chloro-2-cyanopyridine and 1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol.

- 5 <sup>1</sup>H NMR (399.9 MHz, DMSO-d<sub>6</sub>)  $\delta$  1.76 (2H, m), 2.14 (2H, m), 3.51 (2H, m), 4.01 (2H, m), 4.95 (1H, m), 7.37 (1H, m), 7.66 (1H, d), 7.81 (1H, m), 8.27 (1H, d), 8.55 (1H, m); m/z = 390 [M+H]<sup>+</sup>.

### Examples 450-455

- The following compounds were prepared in 16 - 83% yield by an analogous method to  
 10 Example 394, starting from 6-(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (obtained as described in General Synthetic Method 10, preparation of starting materials) and the appropriate sulfonyl chloride:-



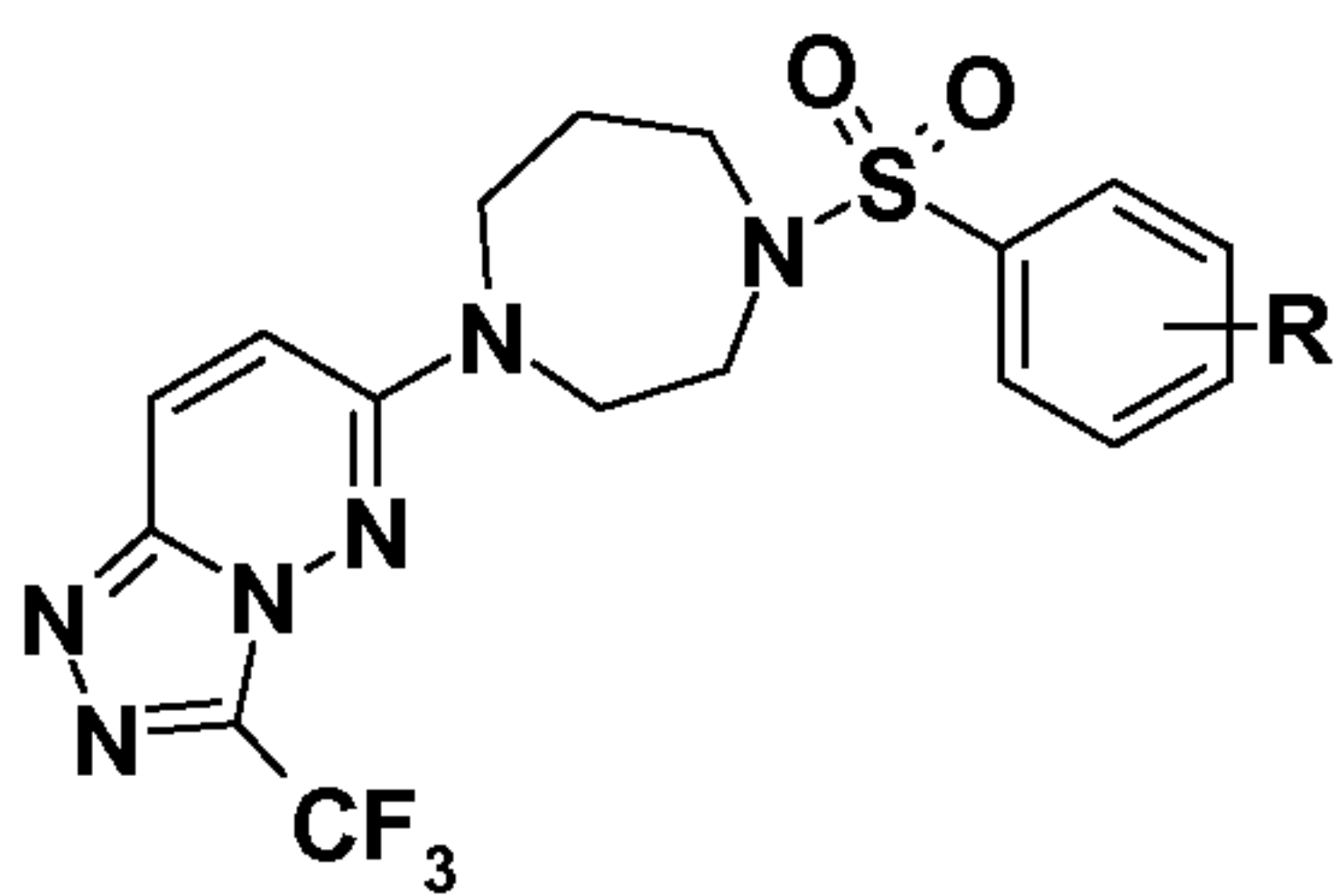
| Ex. | R     | <sup>1</sup> H NMR (399.9 MHz, CDCl <sub>3</sub> )                                                                                                                                                          | m/z [M+H] <sup>+</sup> |
|-----|-------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|
| 450 | 3-F   | $\delta$ 3.04 - 3.10 (2H, m), 3.28 - 3.32 (2H, m), 3.35 - 3.39 (2H, m), 3.46 - 3.50 (2H, m), 3.75 - 3.79 (2H, m), 6.79 (1H, d), 7.29 - 7.35 (1H, m), 7.51 - 7.57 (2H, m), 7.62 - 7.64 (1H, m), 7.93 (1H, d) | 457                    |
| 451 | 2-OMe | $\delta$ 3.06 - 3.11 (2H, m), 3.38 - 3.44 (4H, m), 3.67 - 3.72 (2H, m), 3.76 - 3.80 (2H, m), 3.90 (3H, s), 6.81 (1H, d), 6.99 - 7.07 (2H, m), 7.50 - 7.54 (1H, m), 7.90 - 7.94 (2H, m)                      | 469                    |
| 452 | 2-F   | $\delta$ 3.09 - 3.13 (2H, m), 3.38 - 3.46 (4H, m), 3.66 (2H,                                                                                                                                                | 457                    |



|     |       |                                                                                                                                                                                                                    |     |
|-----|-------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
|     |       | q), 3.79 (2H, q), 6.81 (1H, d), 7.18 - 7.31 (2H, m), 7.55 - 7.61 (1H, m), 7.89 - 7.95 (2H, m)                                                                                                                      |     |
| 453 | 4-F   | $\delta$ 3.03 - 3.10 (2H, m), 3.27 - 3.30 (2H, m), 3.36 - 3.46 (4H, m), 3.78 (2H, q), 6.78 (1H, d), 7.21 - 7.25 (2H, m), 7.83 - 7.87 (2H, m), 7.93 (1H, d)                                                         | 457 |
| 454 | 3-OMe | $\delta$ 3.01 - 3.06 (2H, m), 3.27 - 3.30 (2H, m), 3.34 - 3.38 (2H, m), 3.45 - 3.49 (2H, m), 3.73 - 3.77 (2H, m), 3.84 (3H, s), 6.77 (1H, d), 7.11 - 7.14 (1H, m), 7.33 (1H, t), 7.38 - 7.47 (2H, m), 7.92 (1H, d) | 469 |
| 455 | 4-OMe | $\delta$ 3.00 - 3.05 (2H, m), 3.23 - 3.27 (2H, m), 3.35 - 3.44 (4H, m), 3.73 - 3.77 (2H, m), 3.86 (3H, s), 6.77 (1H, d), 6.98 - 7.01 (2H, m), 7.75 - 7.79 (2H, m), 7.92 (1H, d)                                    | 469 |

**Examples 456-461**

The following compounds were prepared in 54 - 96% yield by an analogous method to Example 394, starting from 6-(1,4-diazepan-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (obtained as described in General Synthetic Method 8, preparation of starting materials) and the appropriate sulfonyl chloride:-



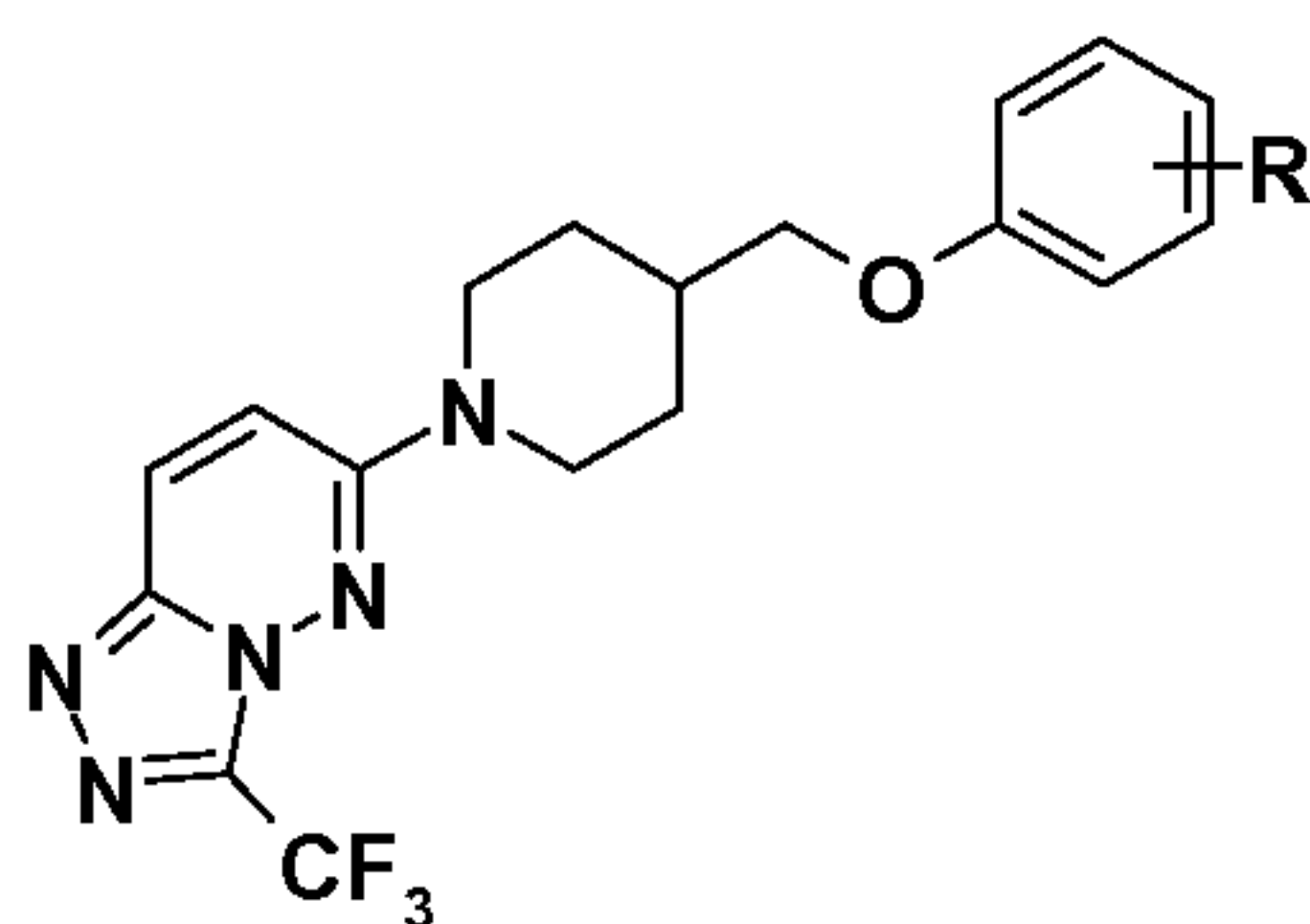
| Ex. | R     | <sup>1</sup> H NMR (399.9 MHz, CDCl <sub>3</sub> )                                                                                                                                                   | m/z [M+H] <sup>+</sup> |
|-----|-------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|
| 456 | 3-F   | $\delta$ 2.05 - 2.11 (2H, m), 3.36 (2H, t), 3.54 (2H, t), 3.82 (2H, t), 3.90 (2H, t), 6.94 (1H, d), 7.14 - 7.19 (1H, m), 7.36 - 7.41 (1H, m), 7.43 - 7.46 (1H, m), 7.52 - 7.55 (1H, m), 7.93 (1H, d) | 445                    |
| 457 | 4-F   | $\delta$ 2.06 - 2.12 (2H, m), 3.29 (2H, t), 3.51 (2H, t), 3.83 (2H, t), 3.90 (2H, t), 6.95 (1H, d), 7.09 - 7.15 (2H, m), 7.75 - 7.80 (2H, m), 7.94 (1H, d)                                           | 445                    |
| 458 | 3-OMe | $\delta$ 2.03 - 2.09 (2H, m), 3.37 (2H, t), 3.54 (2H, t), 3.78 -                                                                                                                                     | 457                    |



|     |       |                                                                                                                                                                                                      |     |
|-----|-------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
|     |       | 3.81 (5H, m), 3.88 (2H, t), 6.90 - 6.95 (2H, m), 7.22 - 7.23 (1H, m), 7.28 - 7.31 (2H, m), 7.90 (1H, d)                                                                                              |     |
| 459 | 2-OMe | $\delta$ 2.07 - 2.13 (2H, m), 3.31 (2H, t), 3.56 - 3.58 (2H, m), 3.87 - 3.91 (7H, m), 6.94 - 7.04 (3H, m), 7.46 - 7.50 (1H, m), 7.90 - 7.94 (2H, m)                                                  | 457 |
| 460 | 2-F   | $\delta$ 2.06 - 2.12 (2H, m), 3.41 (2H, t), 3.60 (2H, t), 3.85 (2H, t), 3.90 (2H, t), 6.98 (1H, d), 7.03 - 7.08 (1H, m), 7.19 - 7.23 (1H, m), 7.44 - 7.50 (1H, m), 7.85 - 7.89 (1H, m), 7.94 (1H, d) | 445 |
| 461 | 4-OMe | $\delta$ 2.02 - 2.08 (2H, m), 3.34 (2H, t), 3.50 (2H, t), 3.78 - 3.81 (5H, m), 3.87 (2H, t), 6.81 - 6.84 (2H, m), 6.91 (1H, d), 7.64 - 7.67 (2H, m), 7.90 (1H, d)                                    | 457 |

**Examples 462-476**

The following compounds were prepared in 15 - 70% yield by an analogous method to Example 447, starting from [1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]methanol (obtained as described in Example 294, preparation of starting materials) and the appropriate phenol:-



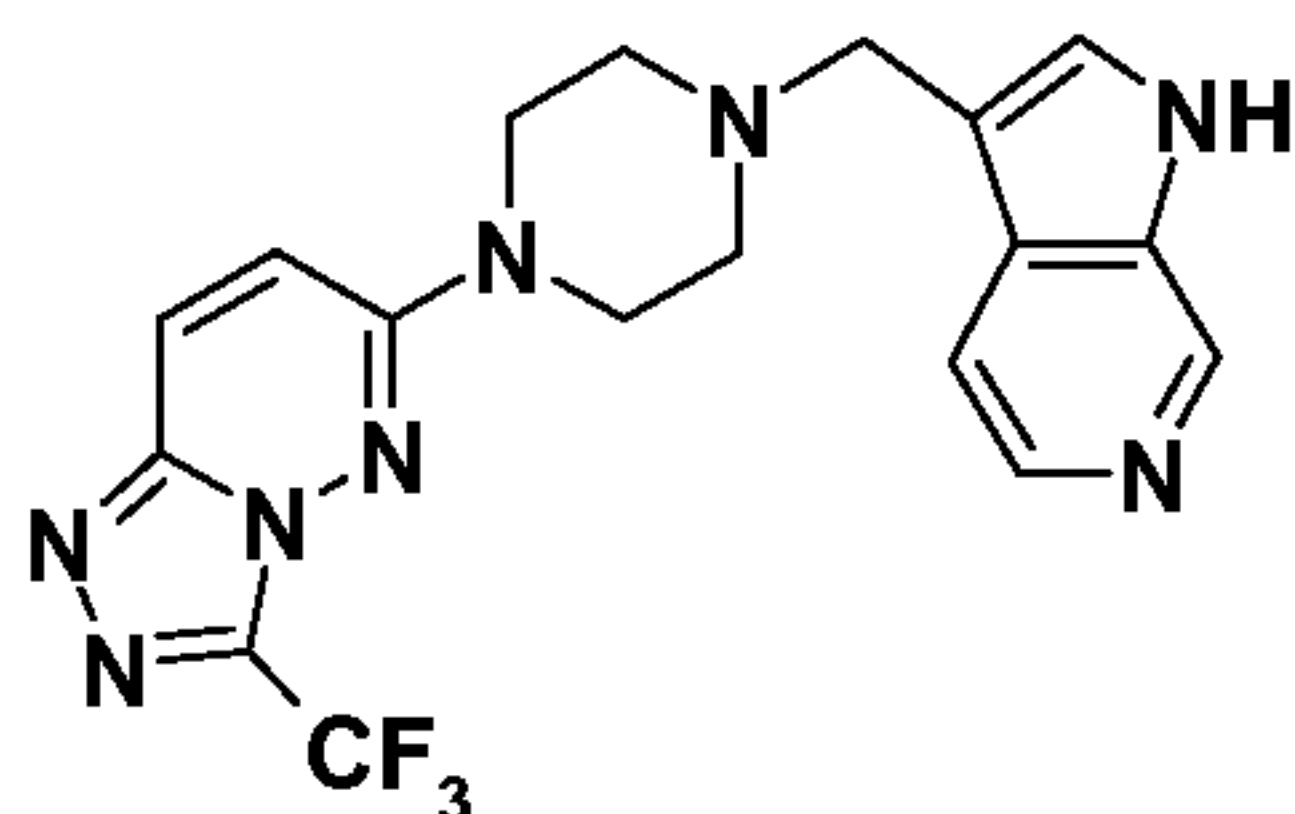
| Ex. | R     | <sup>1</sup> H NMR (399.9 MHz, DMSO-d <sub>6</sub> )                                                                                                                                                               | m/z [M+H] <sup>+</sup> |
|-----|-------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|
| 462 | 2-OMe | $\delta$ 1.32 - 1.43 (2H, m), 1.90 - 1.94 (2H, m), 2.09 - 2.15 (1H, m), 3.05 - 3.12 (2H, m), 3.76 (3H, s), 3.85 (2H, d), 4.30 - 4.34 (2H, m), 6.85 - 6.92 (2H, m), 6.95 - 6.98 (2H, m), 7.63 (1H, d), 8.23 (1H, d) | 408                    |
| 463 | 4-F   | $\delta$ 1.33 - 1.42 (2H, m), 1.89 - 1.92 (2H, m), 2.07 - 2.13 (1H, m), 3.03 - 3.11 (2H, m), 3.85 (2H, d), 4.30 - 4.34 (2H, m), 6.94 - 6.97 (2H, m), 7.09 - 7.13 (2H, m), 7.63 (1H, d), 8.23 (1H, d)               | 396                    |
| 464 | 3-F   | $\delta$ 1.33 - 1.43 (2H, m), 1.88 - 1.92 (2H, m), 2.07 - 2.14                                                                                                                                                     | 396                    |



|     |                   |                                                                                                                                                                                                                           |     |
|-----|-------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
|     |                   | (1H, m), 3.04 - 3.11 (2H, m), 3.90 (2H, d), 4.30 - 4.34 (2H, m), 6.73 - 6.84 (3H, m), 7.28 - 7.34 (1H, m), 7.63 (1H, d), 8.23 (1H, d)                                                                                     |     |
| 465 | 4-OMe             | $\delta$ 1.31 - 1.41 (2H, m), 1.88 - 1.92 (2H, m), 2.05 - 2.11 (1H, m), 3.03 - 3.10 (2H, m), 3.70 (3H, s), 3.81 (2H, d), 4.30 - 4.34 (2H, m), 6.84 - 6.89 (4H, m), 7.63 (1H, d), 8.23 (1H, d)                             | 408 |
| 466 | 3-OMe             | $\delta$ 1.32 - 1.42 (2H, m), 1.89 - 1.93 (2H, m), 2.05 - 2.14 (1H, m), 3.04 - 3.11 (2H, m), 3.73 (3H, s), 3.86 (2H, d), 4.30 - 4.34 (2H, m), 6.49 - 6.54 (3H, m), 7.17 (1H, t), 7.63 (1H, d), 8.23 (1H, d)               | 408 |
| 467 | 2-F               | $\delta$ 1.34 - 1.44 (2H, m), 1.89 - 1.93 (2H, m), 2.11 - 2.18 (1H, m), 3.05 - 3.12 (2H, m), 3.96 (2H, d), 4.30 - 4.34 (2H, m), 6.91 - 6.97 (1H, m), 7.10 - 7.23 (3H, m), 7.63 (1H, d), 8.23 (1H, d)                      | 396 |
| 468 | 4-CF <sub>3</sub> | $\delta$ 1.34 - 1.44 (2H, m), 1.89 - 1.94 (2H, m), 2.10 - 2.19 (1H, m), 3.05 - 3.12 (2H, m), 3.97 (2H, d), 4.31 - 4.34 (2H, m), 7.13 (2H, d), 7.62 - 7.66 (3H, m), 8.24 (1H, d)                                           | 446 |
| 469 | 2-CN              | $\delta$ 1.39 - 1.49 (2H, m), 1.91 - 1.94 (2H, m), 2.15 - 2.22 (1H, m), 3.07 - 3.14 (2H, m), 4.06 (2H, d), 4.32 - 4.36 (2H, m), 7.08 - 7.12 (1H, m), 7.26 (1H, d), 7.63 - 7.68 (2H, m), 7.71 - 7.73 (1H, m), 8.24 (1H, d) | 403 |
| 470 | 4-Cl              | $\delta$ 1.32 - 1.42 (2H, m), 1.88 - 1.92 (2H, m), 2.05 - 2.14 (1H, m), 3.03 - 3.10 (2H, m), 3.87 (2H, d), 4.29 - 4.33 (2H, m), 6.95 - 6.99 (2H, m), 7.29 - 7.34 (2H, m), 7.62 (1H, d), 8.23 (1H, d)                      | 412 |
| 471 | 2-CF <sub>3</sub> | $\delta$ 1.39 - 1.49 (2H, m), 1.88 - 1.91 (2H, m), 2.12 - 2.19 (1H, m), 3.06 - 3.13 (2H, m), 4.02 (2H, d), 4.31 - 4.35 (2H, m), 7.09 (1H, t), 7.25 (1H, d), 7.60 - 7.65 (3H, m), 8.24 (1H, d)                             | 446 |



|     |                   |                                                                                                                                                                                                                                                |     |
|-----|-------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
| 472 | 3-CF <sub>3</sub> | $\delta$ 1.35 - 1.45 (2H, m), 1.91 - 1.94 (2H, m), 2.09 - 2.18 (1H, m), 3.05 - 3.12 (2H, m), 3.97 (2H, d), 4.31 - 4.34 (2H, m), 7.24 - 7.30 (3H, m), 7.53 (1H, t), 7.64 (1H, d), 8.24 (1H, d)                                                  | 446 |
| 473 | 3-Cl              | $\delta$ 1.32 - 1.42 (2H, m), 1.87 - 1.92 (2H, m), 2.07 - 2.15 (1H, m), 3.04 - 3.11 (2H, m), 3.91 (2H, d), 4.30 - 4.33 (2H, m), 6.92 - 6.94 (1H, m), 6.98 - 7.00 (1H, m), 7.03 (1H, t), 7.31 (1H, t), 7.63 (1H, d), 8.23 (1H, d)               | 412 |
| 474 | 4-CN              | $\delta$ 1.33 - 1.44 (2H, m), 1.87 - 1.92 (2H, m), 2.08 - 2.17 (1H, m), 3.05 - 3.11 (2H, m), 3.99 (2H, d), 4.30 - 4.34 (2H, m), 7.11 - 7.14 (2H, m), 7.63 (1H, d), 7.75 - 7.78 (2H, m), 8.23 (1H, d)                                           | 403 |
| 475 | 2-Cl              | $\delta$ 1.37 - 1.48 (2H, m), 1.92 - 1.96 (2H, m), 2.12 - 2.19 (1H, m), 3.06 - 3.13 (2H, m), 3.98 (2H, d), 4.31 - 4.35 (2H, m), 6.93 - 6.97 (1H, m), 7.14 - 7.16 (1H, d), 7.28 - 7.32 (1H, m), 7.41 - 7.43 (1H, m), 7.64 (1H, d), 8.24 (1H, d) | 412 |
| 476 | 3-CN              | $\delta$ 1.34 - 1.43 (2H, m), 1.88 - 1.92 (2H, m), 2.10 - 2.16 (1H, m), 3.05 - 3.12 (2H, m), 3.96 (2H, d), 4.30 - 4.34 (2H, d), 7.29 - 7.32 (1H, m), 7.39 - 7.41 (1H, m), 7.43 - 7.44 (1H, m), 7.47 - 7.51 (1H, m), 7.63 (1H, d), 8.24 (1H, d) | 403 |

**Example 477****Preparation of 6-[4-(1H-pyrrolo[2,3-c]pyridin-3-yl)piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine**

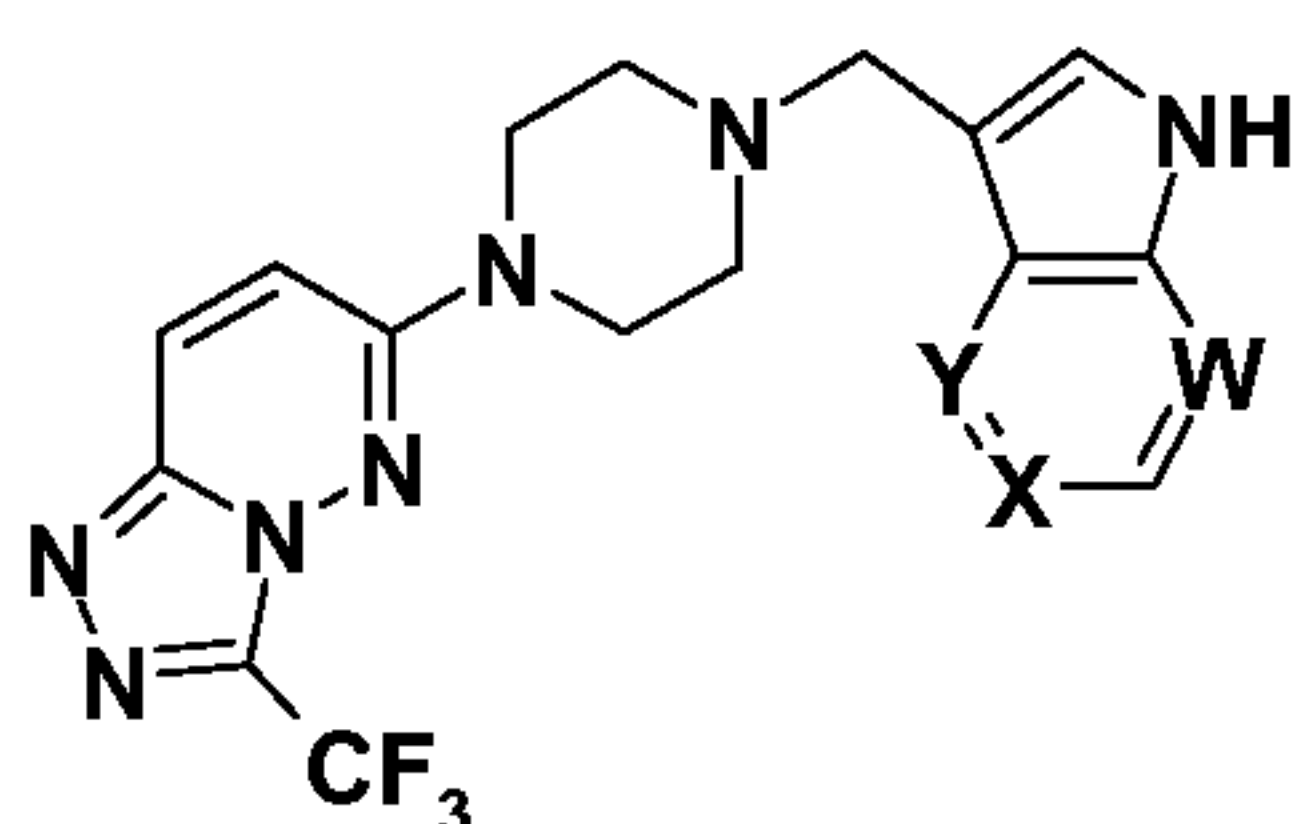
- 5 Obtained in 68% yield by General Synthetic Method 5, starting from 6-(piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine and 1H-pyrrolo[2,3-c]pyridine-3-carboxaldehyde (obtained as described in J. Chem. Soc. (C) 1970, 498).



<sup>1</sup>H NMR (399.9 MHz, DMSO-d<sub>6</sub>) δ 2.25 (4H, t), 3.60 (4H, t), 3.73 (2H, s), 7.53 (1H, s), 7.57 (1H, d), 7.63 - 7.65 (1H, m), 8.10 (1H, d), 8.23 (1H, d), 8.72 (1H, d), 11.47 (1H, s); m/z = 403 [M+H]<sup>+</sup>.

### Examples 478-480

- 5 The following compounds were prepared in 61-82% yield by General Synthetic Method 5, starting from 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine and the appropriate 1H-pyrrolopyridine-3-carboxaldehyde (obtained as described in the corresponding footnote):-



| Ex. | W  | X  | Y  | Note | <sup>1</sup> H NMR (399.9 MHz, DMSO-d <sub>6</sub> )                                                                                                        | m/z [M+H] <sup>+</sup> |
|-----|----|----|----|------|-------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|
| 478 | N  | CH | CH | [1]  | δ 2.55 (4H, s), 3.60 (4H, s), 3.71 (2H, s), 7.04 - 7.07 (1H, m), 7.39 (1H, s), 7.57 (1H, d), 8.07 (1H, d), 8.20 - 8.24 (2H, m), 11.48 (1H, s)               | 403                    |
| 479 | CH | CH | N  | [2]  | δ 2.59 (4H, t), 3.60 (4H, t), 3.81 (2H, s), 7.08 - 7.11 (1H, m), 7.55 - 7.58 (2H, m), 7.73 - 7.75 (1H, m), 8.22 (1H, d), 8.32 - 8.34 (1H, m), 11.21 (1H, s) | 403                    |
| 480 | CH | N  | CH | [3]  | δ 2.56 (4H, t), 3.62 (4H, t), 3.77 (2H, s), 7.34 - 7.35 (1H, m), 7.36 (1H, d), 7.58 (1H, d), 8.16 (1H, d), 8.23 (1H, d), 8.97 (1H, d), 11.34 (1H, s)        | 403                    |

10

Obtained from 1H-pyrrolo[2,3-b]pyridine-3-carboxaldehyde, prepared as described in Bioorg. Med. Chem. 2004, 12, 5505.

[2] Obtained from 1H-pyrrolo[3,2-b]pyridine-3-carboxaldehyde, prepared as described in US Pat Appl. 2007/0123535, page 35.

15

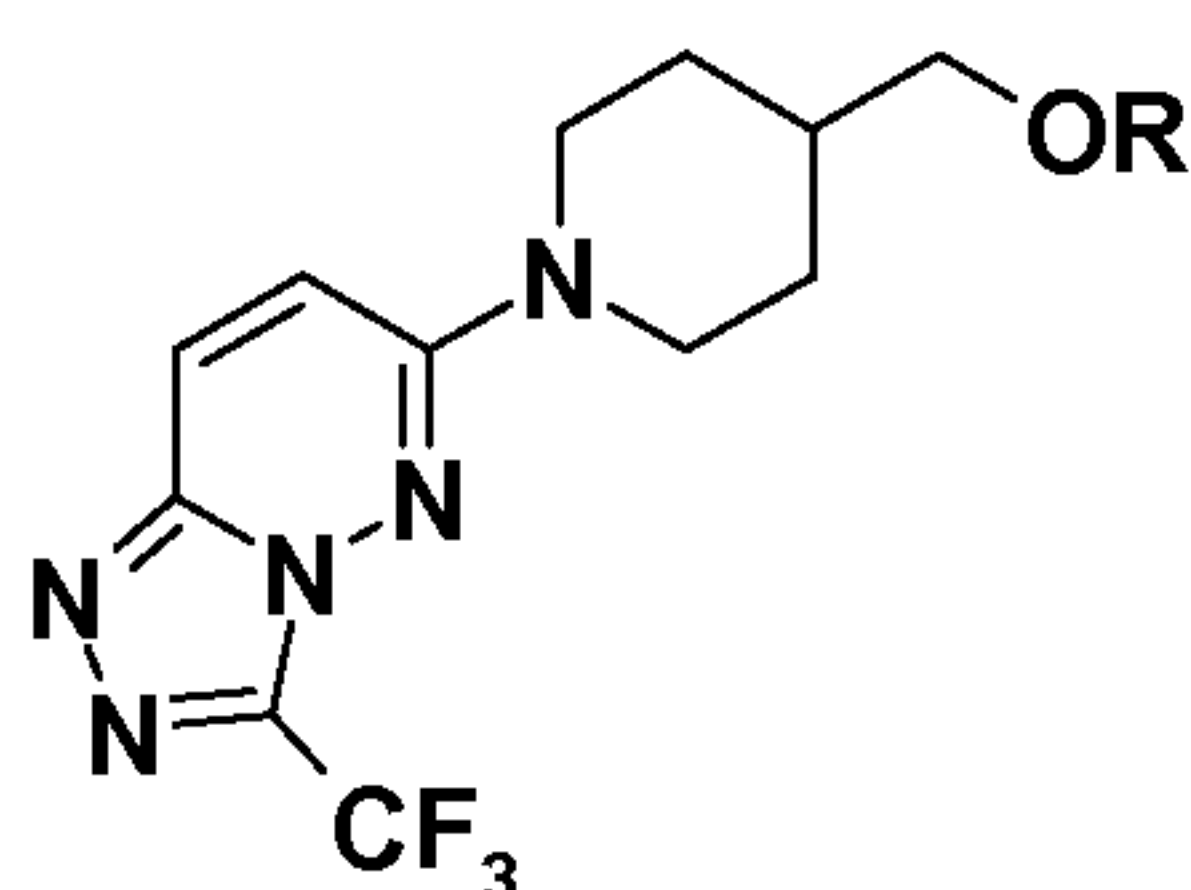
[3] Obtained from 1H-pyrrolo[3,2-c]pyridine-3-carboxaldehyde, prepared as follows:-



A solution of 1H-pyrrolo[3,2-c]pyridine (2.95 g, 25 mmol) and hexamethylenetetramine (5.26 g, 37.50 mmol) in acetic acid (25 mL) and water (50 mL) was heated under reflux for 4 hours. The reaction mixture was evaporated and the residue was purified by MPLC silica chromatography, elution gradient 5 to 10% ammonia-methanol in DCM. Product  
 5 containing fractions were evaporated to dryness and triturated with MeCN to afford 1H-pyrrolo[3,2-c]pyridine-3-carbaldehyde (0.170 g, 4.65%) as a white crystalline solid. 1H NMR (399.9 MHz, DMSO-d<sub>6</sub>)  $\delta$  7.52 - 7.54 (1H, m), 8.36 (1H, d), 8.42 (1H, s), 9.30 (1H, d), 10.01 (1H, s), 12.41 (1H, s); m/z = 188 [M+H]<sup>+</sup> (detected as adduct with acetonitrile used in mass spectral determination).

### 10 Examples 481-482

The following compounds were prepared in 10-48% yield by an analogous method to Example 294, starting from 6-[4-(methanesulfonyloxymethyl)piperidin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine and the appropriate alcohol:-

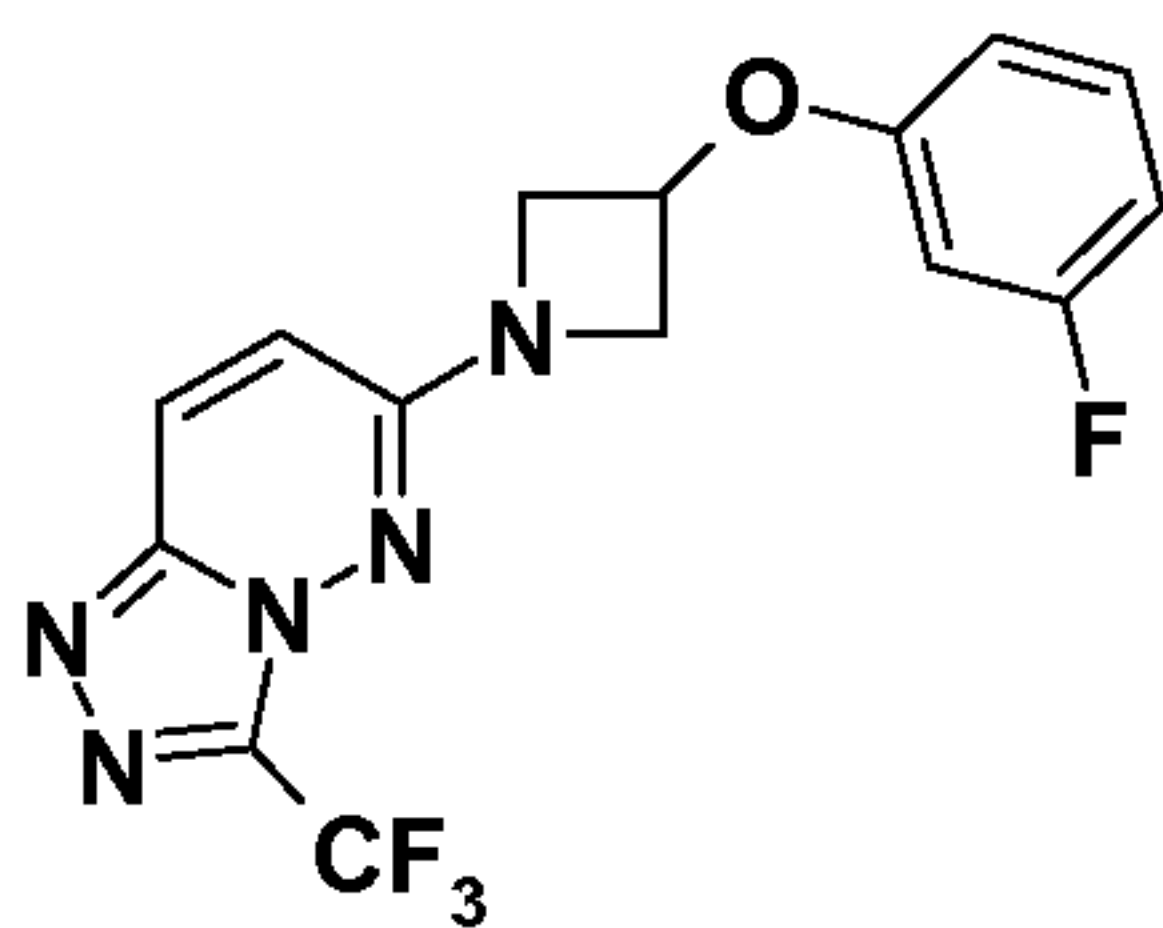


| Ex. | R                    | 1H NMR (399.9 MHz, CDCl <sub>3</sub> )                                                                                                                                                               | m/z [M+H] <sup>+</sup> |
|-----|----------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|
| 481 | oxetan-3-yl          | $\delta$ 1.31 - 1.42 (2H, m), 1.86 - 1.97 (3H, m), 3.00 - 3.07 (2H, m), 3.24 (2H, d), 4.23 - 4.28 (2H, m), 4.50 - 4.55 (1H, m), 4.57 - 4.60 (2H, m), 4.75 - 4.78 (2H, m), 7.09 (1H, d), 7.90 (1H, d) | 358                    |
| 482 | 2,2,2-trifluoroethyl | $\delta$ 1.35 - 1.39 (2H, m), 1.90 - 1.99 (3H, m), 2.99 - 3.06 (2H, m), 3.50 - 3.52 (2H, m), 3.83 (2H, q), 4.24 - 4.28 (2H, m), 7.09 (1H, d), 7.91 (1H, d)                                           | 384                    |

### Example 483

#### Preparation of 6-[3-(3-fluorophenoxy)azetidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine





A stirred partial solution of 6-[3-(methanesulfonyloxy)azetidin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (169 mg, 0.5 mmol), 3-fluorophenol (112 mg, 1.5 mmol) and potassium carbonate (207 mg, 1.5 mmol) in DMF (3 mL) was heated at 100°C for 24 hours. The reaction mixture was filtered and the product was isolated by preparative HPLC (Waters XBridge Prep C18 OBD column, 5 $\mu$  silica, 19 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 1% ammonia) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to give 6-[3-(3-fluorophenoxy)azetidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine (58 mg, 33%) as a solid.

<sup>1</sup>H NMR (399.9 MHz, CDCl<sub>3</sub>)  $\delta$  4.17 - 4.21 (2H, m), 4.50 - 4.54 (2H, m), 5.05 - 5.10 (1H, m), 6.44 - 6.47 (1H, m), 6.50 - 6.52 (1H, m), 6.60 (1H, d), 6.66 - 6.71 (1H, m), 7.18 - 7.24 (1H, m), 7.88 (1H, d); m/z = 354 [M+H]<sup>+</sup>.

The starting 6-[3-(methanesulfonyloxy)azetidin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine was prepared as follows:-

#### **Preparation of 1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]azetidin-3-ol**

A stirred solution of 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (5.56 g, 25 mmol), azetidin-3-ol hydrochloride (3.01 g, 27.50 mmol) and DIPEA (10.89 mL, 62.50 mmol) in DMF (50 mL) was heated at 70°C for 1 hour. The solution was slowly diluted with water and the product crystallised. The precipitate was collected by filtration, washed with water, drained well and washed with ether. It was dried under vacuum to afford 1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]azetidin-3-ol (5.30 g, 82%) as a white crystalline solid.

<sup>1</sup>H NMR (399.9 MHz, DMSO-d<sub>6</sub>)  $\delta$  3.88 (2H, q), 4.32 - 4.36 (2H, m), 4.61 - 4.65 (1H, m), 5.82 - 5.83 (1H, m), 7.04 (1H, d), 8.22 (1H, d); m/z = 260 [M+H]<sup>+</sup>.

#### **Preparation of 6-[3-(methanesulfonyloxy)azetidin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

Methanesulfonyl chloride (0.929 mL, 12 mmol) was added dropwise to a stirred



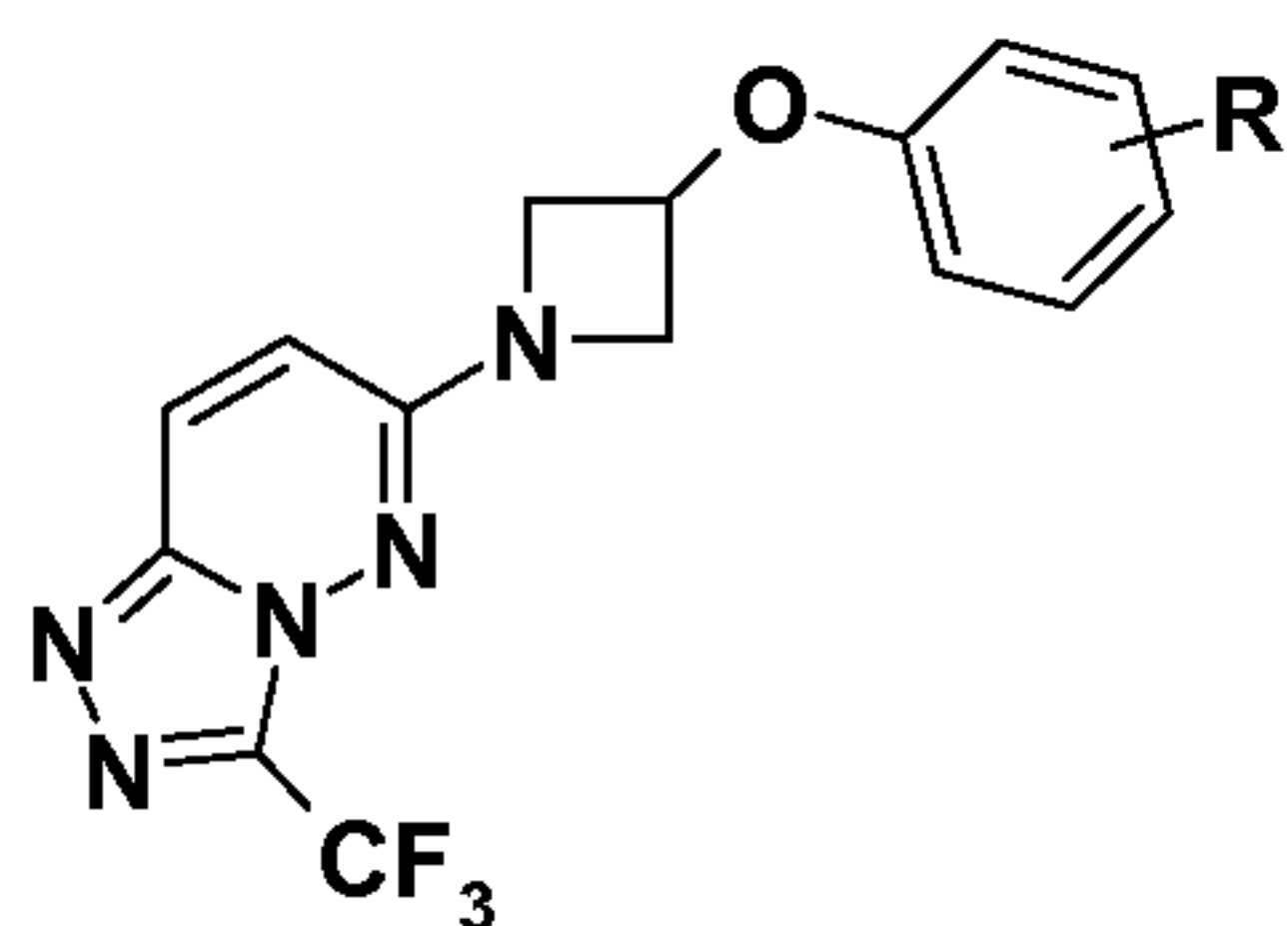
partial solution of 1-(3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)azetidin-3-ol (2.59 g, 10 mmol) and triethylamine (1.951 mL, 14 mmol) in DCM (17 mL) at 0°C. The solution was allowed to warm to ambient temperature and stirred for 30 minutes. The precipitate was collected by filtration, washed with a little DCM, a little ethanol and ether.

5 It was dried under vacuum to afford 6-[3-(methanesulfonyloxy)azetidin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (2.400 g, 71.2%) as a white crystalline solid.

<sup>1</sup>H NMR (399.9 MHz, DMSO-d<sub>6</sub>) δ 3.32 (3H, s), 4.25 - 4.29 (2H, m), 4.54 - 4.59 (2H, m), 5.45 - 5.50 (1H, m), 7.11 (1H, d), 8.29 (1H, d); m/z = 338 [M+H]<sup>+</sup>.

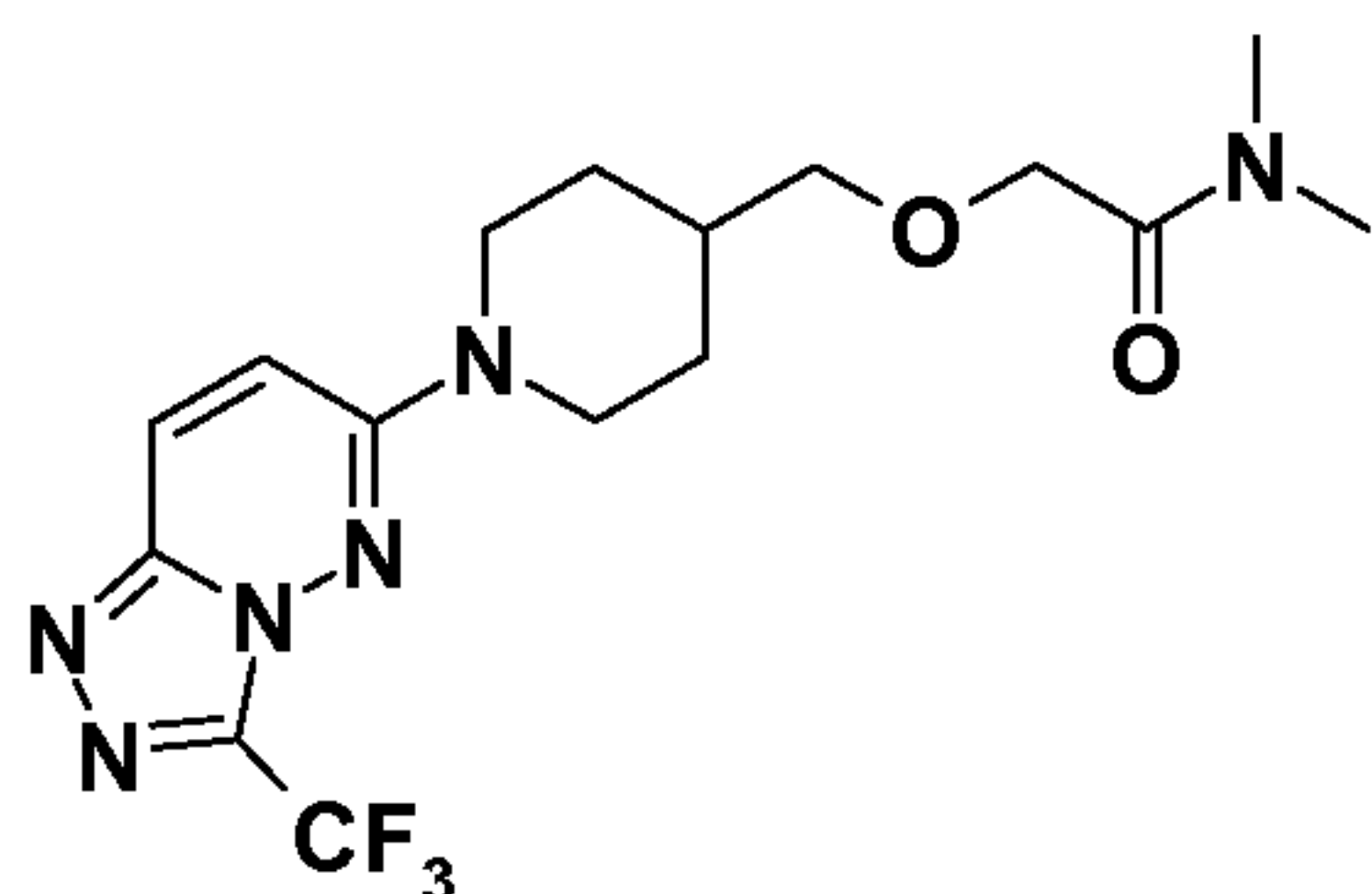
#### 10 Examples 484-486

The following compounds were prepared in 49-56% yield by an analogous method to Example 483, starting from 6-[3-(methanesulfonyloxy)azetidin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine and the appropriate phenol:-



| Ex. | R     | <sup>1</sup> H NMR (399.9 MHz, CDCl <sub>3</sub> )                                                                                                                       | m/z [M+H] <sup>+</sup> |
|-----|-------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|
| 484 | 4-F   | δ 4.16 - 4.20 (2H, m), 4.48 - 4.52 (2H, m), 5.02 - 5.07 (1H, m), 6.60 (1H, d), 6.66 - 6.70 (2H, m), 6.92 - 6.98 (2H, m), 7.88 (1H, d)                                    | 354                    |
| 485 | 3-OMe | δ 3.74 (3H, s), 4.16 - 4.20 (2H, m), 4.48 - 4.53 (2H, m), 5.05 - 5.10 (1H, m), 6.29 - 6.32 (2H, m), 6.51 - 6.54 (1H, m), 6.60 (1H, d), 7.13 - 7.18 (1H, m), 7.88 (1H, d) | 366                    |
| 486 | 4-OMe | δ 3.72 (3H, s), 4.15 - 4.19 (2H, m), 4.46 - 4.50 (2H, m), 5.00 - 5.05 (1H, m), 6.60 (1H, d), 6.65 - 6.69 (2H, m), 6.77 - 6.82 (2H, m), 7.88 (1H, d)                      | 366                    |



**Example 487****Preparation of N,N-dimethyl-2-[[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]methoxy]acetamide**

5 A stirred solution of methyl 2-[[1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]methoxy]acetate (95 mg, 0.25 mmol) in 2M dimethylamine in methanol (2.0 mL, 4.00 mmol) was heated at 120°C in a microwave reactor for 1 hour. The reaction mixture was evaporated and the crude product was purified by preparative LCMS (Waters XBridge Prep C18 OBD column, 5 $\mu$  silica, 19 mm diameter, 100 mm length), using  
 10 decreasingly polar mixtures of water (containing 1% ammonia) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford N,N-dimethyl-2-[[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]methoxy]acetamide (48.0 mg, 48.8%) as a white solid.

1H NMR (399.9 MHz, CDCl<sub>3</sub>)  $\delta$  1.32 - 1.43 (2H, m), 1.93 (2H, d), 1.98 - 2.02 (1H, m),  
 15 2.96 (3H, s), 3.00 (3H, s), 3.03 - 3.07 (2H, m), 3.41 - 3.43 (2H, m), 4.15 (2H, s), 4.25 (2H, d), 7.09 (1H, d), 7.90 (1H, d); m/z = 387 [M+H]<sup>+</sup>.

The methyl 2-[[1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]methoxy]acetate used as starting material was prepared as follows:-

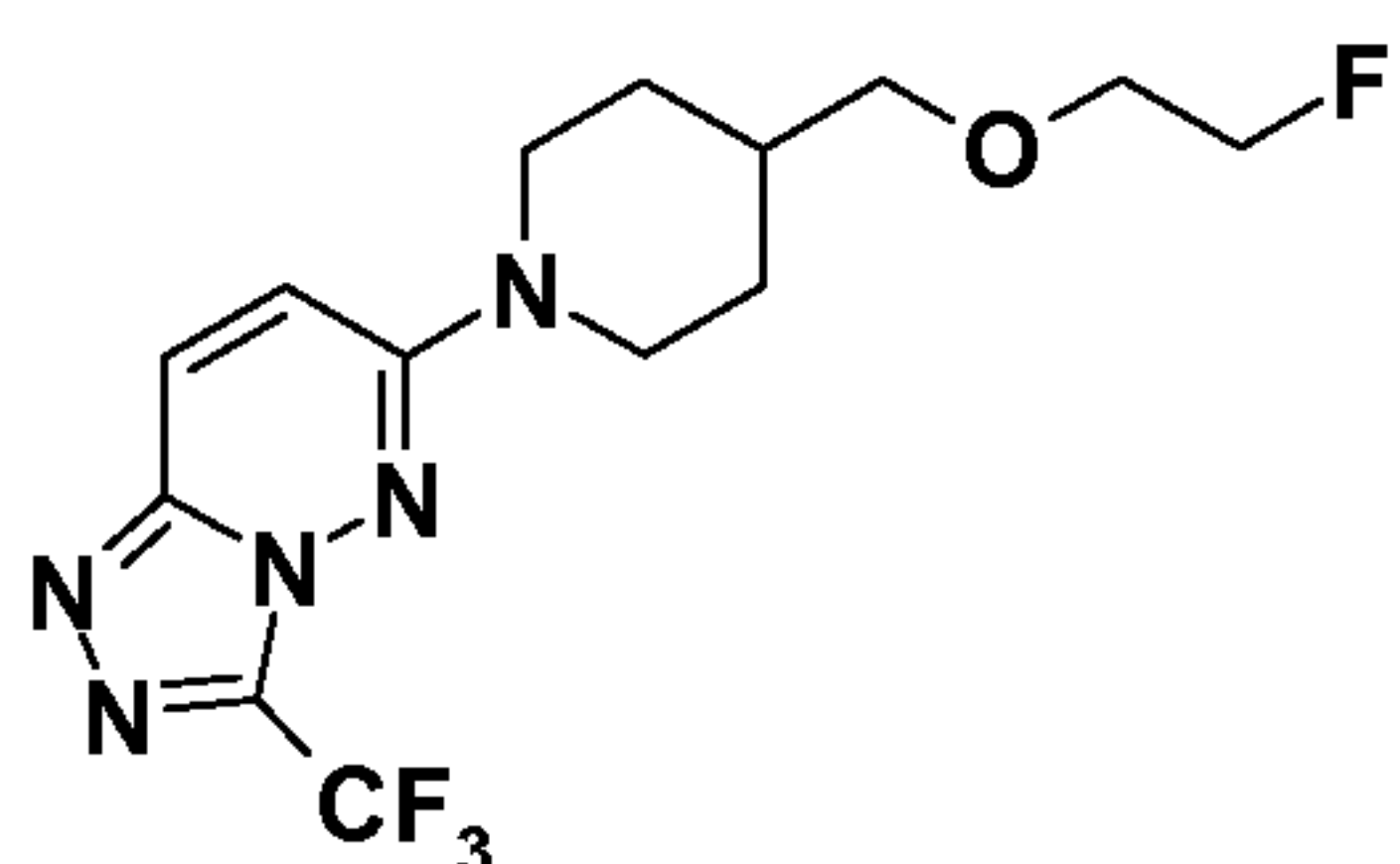
Sodium hydride (60% dispersion in oil, 0.120 g, 3.0 mmol) was added to neat  
 20 methyl glycolate (1.544 mL, 20.0 mmol). When the effervescence had subsided 6-[4-(methanesulfonyloxymethyl)piperidin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (0.759 g, 2.0 mmol) was added and the mixture was heated at 100°C for 40 minutes. The reaction mixture was partitioned between DCM and water. The organic phase was washed with water and brine, dried over MgSO<sub>4</sub> and evaporated. The product was  
 25 isolated by MPLC silica chromatography, eluting with ethyl acetate. The product containing fractions were evaporated to an oil which crystallised from ether, giving methyl 2-[[1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]methoxy]acetate (0.130 g, 17%).



<sup>1</sup>H NMR (399.9 MHz, CDCl<sub>3</sub>) δ 1.33 - 1.43 (2H, m), 1.92 - 2.02 (3H, m), 3.00 - 3.07 (2H, m), 3.42 - 3.44 (2H, m), 3.76 (3H, s), 4.09 (2H, s), 4.23 - 4.26 (2H, m), 7.08 (1H, d), 7.90 (1H, d); m/z = 374 [M+H]<sup>+</sup>.

### **Example 488**

#### **Preparation of 6-[4-[(2-fluoroethoxy)methyl]piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine**



(Diethylamino)sulfur trifluoride (0.059 mL, 0.45 mmol) was added dropwise to a stirred solution of 2-[[1-(3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl)methoxy]ethanol (104 mg, 0.3 mmol) in DCM (3 mL) at -70°C. The solution was allowed to warm to ambient temperature and stir for 18 hours. The solution was diluted with DCM and washed with 2M aqueous K<sub>2</sub>CO<sub>3</sub>. The organic phase was dried over MgSO<sub>4</sub> and evaporated. The crude product was purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5μ silica, 19 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 1% ammonia) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford 6-[4-[(2-fluoroethoxy)methyl]piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine (22.0 mg, 21%) as a white solid.

<sup>1</sup>H NMR (399.9 MHz, CDCl<sub>3</sub>) δ 1.30 - 1.40 (2H, m), 1.90 - 2.01 (3H, m), 2.99 - 3.06 (2H, m), 3.40 (2H, d), 3.65 - 3.74 (2H, m), 4.23 - 4.27 (2H, m), 4.49 - 4.63 (2H, m), 7.09 (1H, d), 7.90 (1H, d); m/z = 348 [M+H]<sup>+</sup>.

The starting 2-[[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]methoxy]ethanol was prepared as follows:-

Sodium hydride (60% dispersion in oil, 0.180 g, 4.5 mmol) was added to neat tetrahydropyranylene glycol (3 g, 20.5 mmol). When the effervescence had subsided 6-[4-(methanesulfonyloxymethyl)piperidin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (obtained as described in Example 294, preparation of starting materials) (1.138 g, 3 mmol) was added and the mixture was heated at 100°C for 40 minutes. The reaction mixture was partitioned between DCM and water. The organic phase was washed



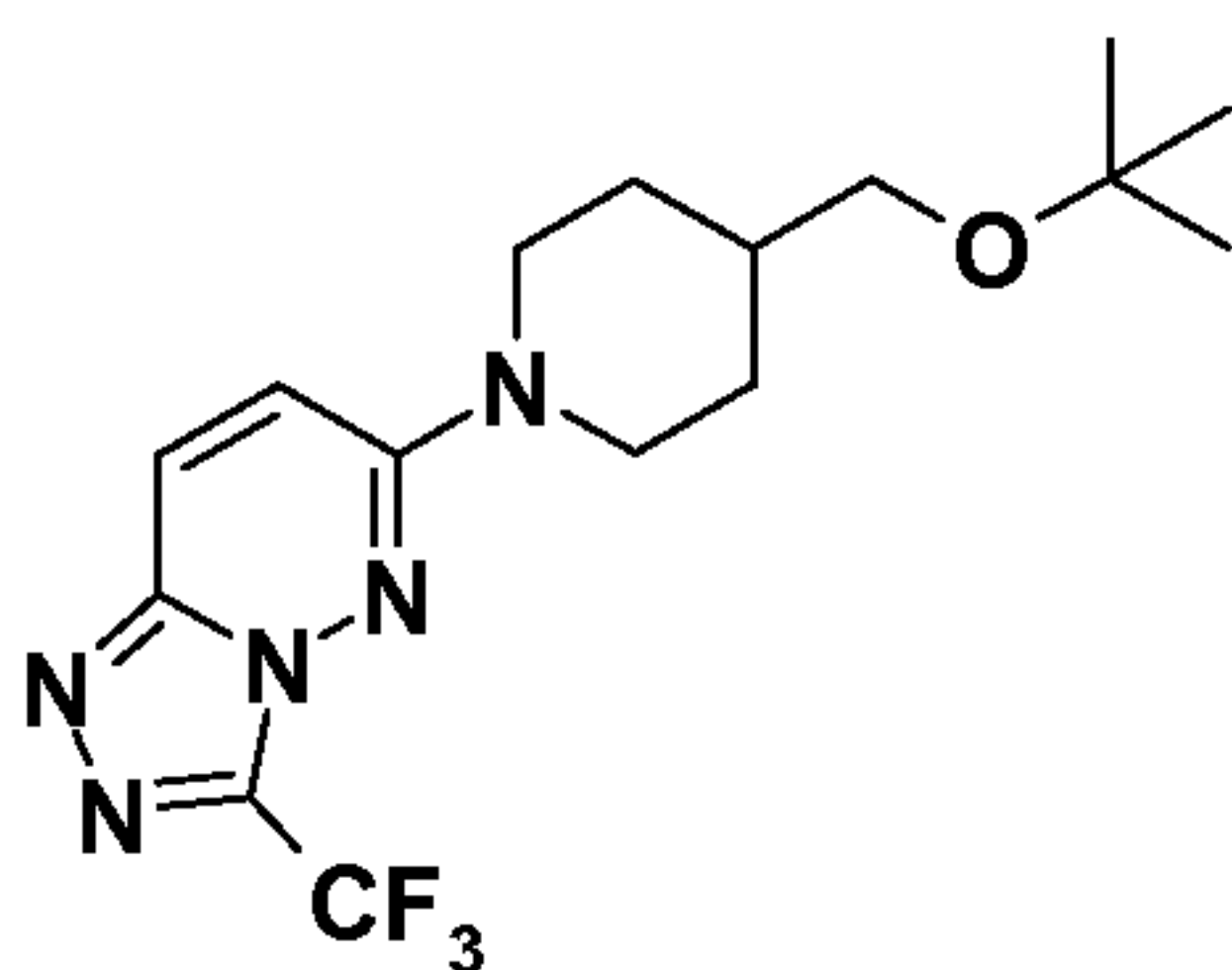
with water and brine, dried over  $\text{MgSO}_4$  and evaporated. The crude intermediate was dissolved in methanol (20 mL) and p-toluenesulfonic acid monohydrate (0.855 g, 4.5 mmol) was added. The solution was stirred for 1 hour and then evaporated. The reaction mixture was partitioned between DCM and water and the organic phase was washed with water and  
 5 brine, dried over  $\text{MgSO}_4$  and evaporated. The product was isolated by MPLC silica chromatography, eluting with 5% methanol / DCM. The product containing fractions were evaporated giving a crystalline solid which was triturated with ether, giving 2-[[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]methoxy]ethanol (0.563 g, 54%)

10  $^1\text{H}$  NMR (399.9 MHz,  $\text{CDCl}_3$ )  $\delta$  1.31 - 1.41 (2H, m), 1.89 - 2.00 (3H, m), 2.99 - 3.06 (2H, m), 3.38 - 3.39 (2H, m), 3.55 - 3.57 (2H, m), 3.74 - 3.76 (2H, m), 4.23 - 4.27 (2H, m), 7.08 (1H, d), 7.90 (1H, d), OH not observed;  $m/z = 346$   $[\text{M}+\text{H}]^+$ .

### **Example 489**

#### **Preparation of 6-[4-(tert-butoxymethyl)piperidin-1-yl]-3-**

15 **(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine**



A stirred solution of [1-(3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)piperidin-4-yl]methanol (obtained as described in Example 294, preparation of starting materials) (151 mg, 0.5 mmol) and p-toluenesulfonic acid monohydrate (190 mg, 1.0 mmol) in DCM  
 20 (2 mL) was cooled to  $-70^\circ\text{C}$  and 2-methylpropene (1 mL, 10.48 mmol) was condensed in from a cylinder. The mixture was stirred for 2 days at ambient temperature in a sealed tube. The tube was re-cooled to open then allowed to warm to ambient temperature with stirring. The solution was diluted with DCM and washed with 2M aqueous  $\text{K}_2\text{CO}_3$ . The organic phase was dried over  $\text{MgSO}_4$  and evaporated. The crude product was purified by  
 25 preparative HPLC (Waters XBridge Prep C18 OBD column,  $5\mu$  silica, 19 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 1% ammonia) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness



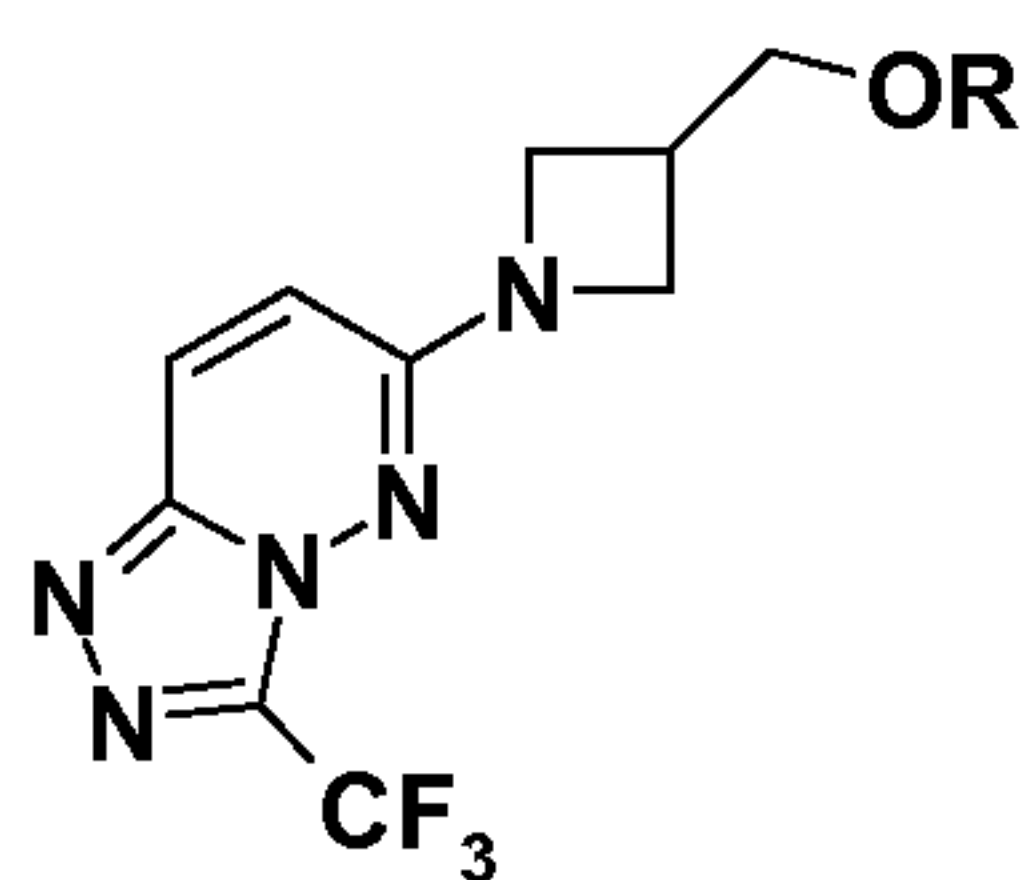
to afford 6-(4-(tert-butoxymethyl)piperidin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (98 mg, 54%) as a white solid.

<sup>1</sup>H NMR (399.9 MHz, CDCl<sub>3</sub>) δ 1.18 (9H, s), 1.24 - 1.35 (2H, m), 1.79 - 1.84 (1H, m), 1.92 (2H, d), 2.98 - 3.05 (2H, m), 3.23 (2H, d), 4.25 (2H, d), 7.09 (1H, d), 7.89 (1H, d);  
 5 m/z = 358 [M+H]<sup>+</sup>.

### **Examples 490-493**

The following compounds were prepared in 43-63% yield by an analogous method to Example 447, starting from [1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]azetidin-3-yl]methanol and the appropriate phenol:-

10



| Ex. | R              | <sup>1</sup> H NMR (399.9 MHz, CDCl <sub>3</sub> )                                                                                                         | m/z [M+H] <sup>+</sup> |
|-----|----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|
| 490 | 3-fluorophenyl | δ 3.26 - 3.33 (1H, m), 4.08 - 4.11 (2H, m), 4.18 (2H, d), 4.34 (2H, t), 6.61 - 6.66 (2H, m), 6.68 - 6.73 (2H, m), 7.21 - 7.27 (1H, m), 7.92 (1H, s)        | 368                    |
| 491 | 3-fluorophenyl | δ 3.25 - 3.32 (1H, m), 4.08 - 4.11 (2H, m), 4.15 (2H, d), 4.34 (2H, t), 6.64 (1H, d), 6.84 - 6.87 (2H, m), 6.96 - 7.02 (2H, m), 7.91 (1H, d)               | 368                    |
| 492 | pyridin-3-yl   | δ 3.30 - 3.37 (1H, m), 4.10 - 4.13 (2H, m), 4.26 (2H, d), 4.37 (2H, t), 6.65 (1H, d), 7.20 - 7.26 (2H, m), 7.93 (1H, d), 8.27 - 8.28 (1H, m), 8.34 (1H, q) | 351                    |
| 493 | pyrimidin-2-yl | δ 3.32 - 3.40 (1H, m), 4.10 - 4.13 (2H, m), 4.34 (2H, t), 4.61 - 4.63 (2H, m), 6.64 (1H, d), 7.00 (1H, t), 7.90 (1H, d), 8.54 (2H, d)                      | 352                    |

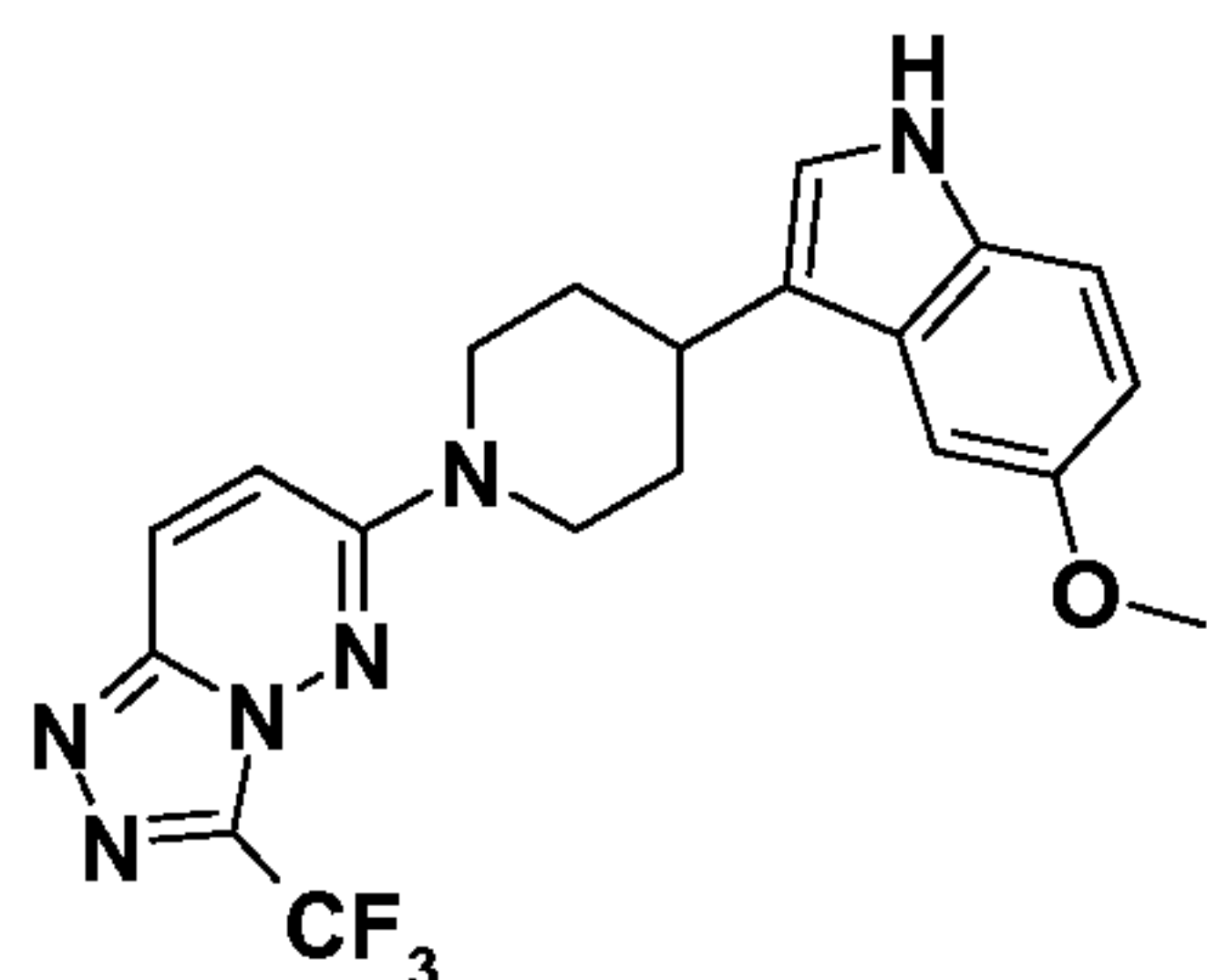


The starting [1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]azetidin-3-yl]methanol was prepared as follows:-

A stirred solution of 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (4.44 g, 20.0 mmol), azetidin-3-ylmethanol (2.25 g, 22.0 mmol) and DIPEA (5.21 mL, 30.0 mmol) in DMF (40 mL) was heated at 70°C for 1 hour. The solution was evaporated and partitioned between water and 2M aqueous K<sub>2</sub>CO<sub>3</sub>. The organic phase was washed with water and brine and dried over MgSO<sub>4</sub>. The crude product was purified by MPLC silica chromatography, eluting with 5% MeOH in DCM. Pure fractions were evaporated to dryness and triturated with ether, giving [1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]azetidin-3-yl]methanol (1.65 g, 30%) as a cream crystalline solid. <sup>1</sup>H NMR (399.9 MHz, DMSO-d<sub>6</sub>) δ 2.87 (1H, t), 3.59 (2H, t), 3.86 - 3.89 (2H, m), 4.14 (2H, t), 4.88 (1H, t), 7.03 (1H, d), 8.21 (1H, d); m/z = 274 [M+H]<sup>+</sup>.

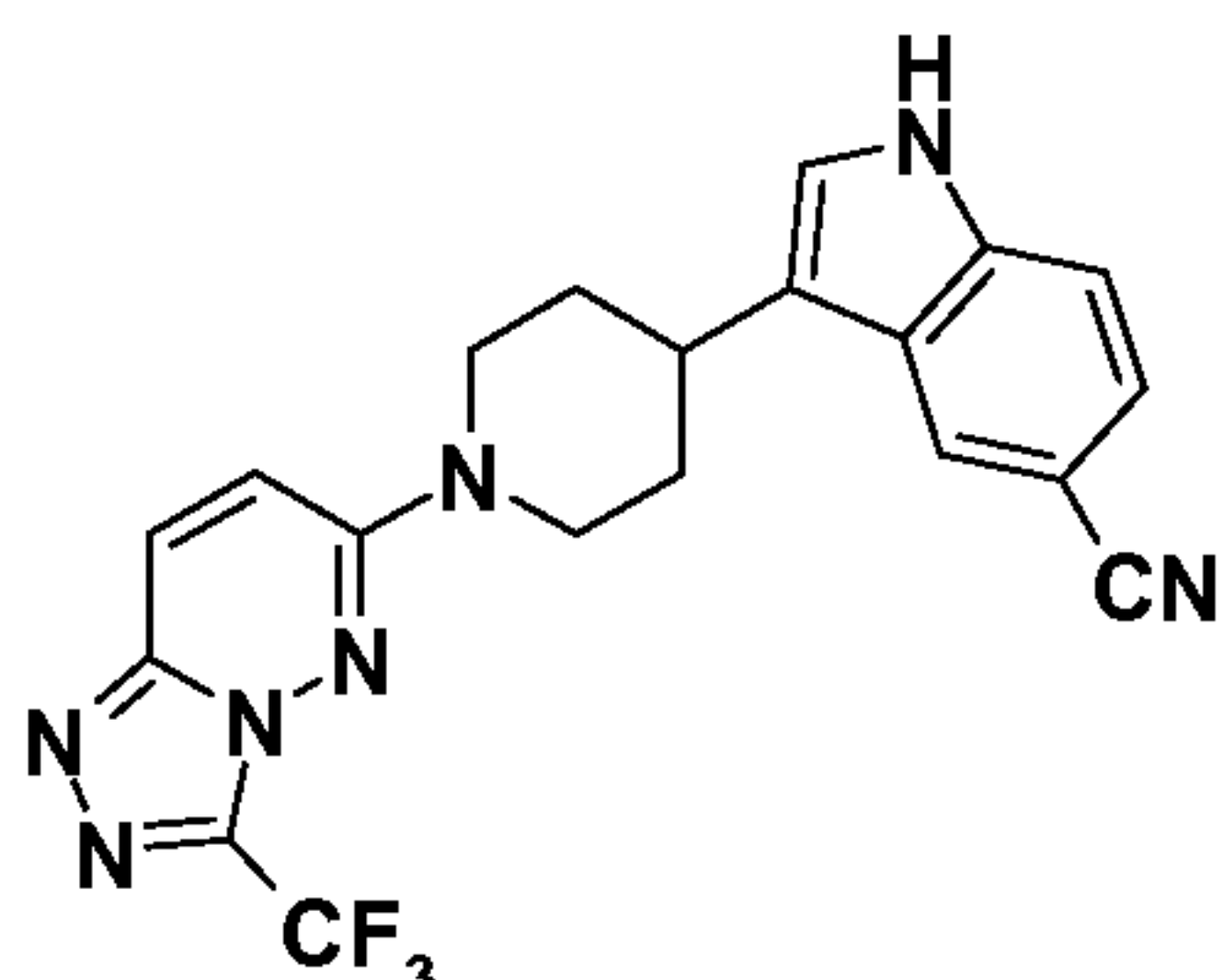
#### **Example 494**

#### **Preparation of 6-[4-(5-methoxy-1H-indol-3-yl)piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine**



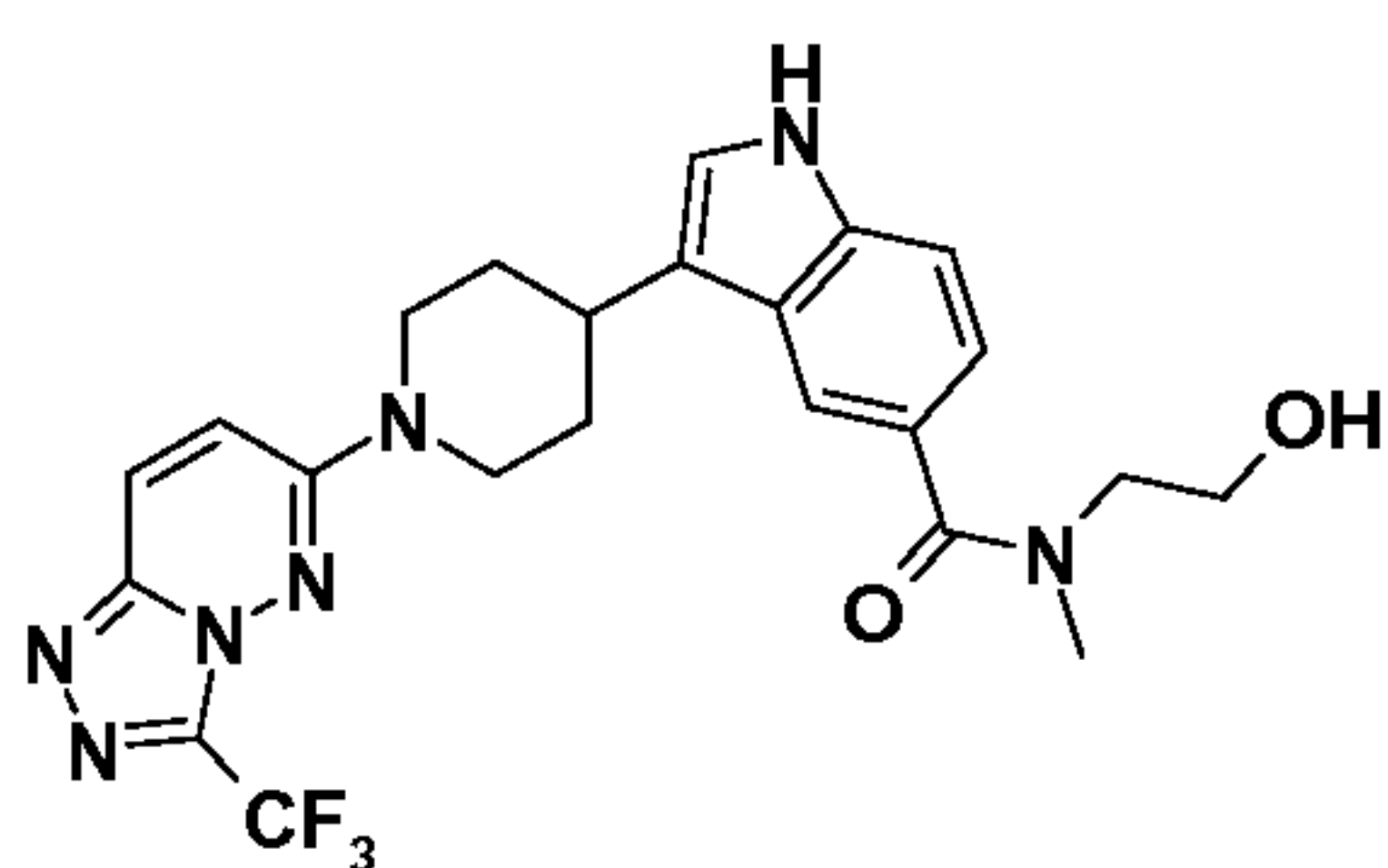
6-Chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (160 mg, 0.72 mmol), 5-methoxy-3-(piperidin-4-yl)-1H-indole (obtained as described in PCT Int. Appl. WO 2004006922, Intermediate 37) (166 mg, 0.72 mmol) and DIPEA (0.138 mL, 0.79 mmol) in DMF (2 mL) were stirred and heated at 80°C for 1 hour. The resulting mixture was cooled to room temperature and quenched in water (10 mL) to give a precipitate. The solid was collected by filtration, washed sequentially with water, acetonitrile and ether, and air dried to give 6-[4-(5-methoxy-1H-indol-3-yl)piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine (189 mg, 63%) as a colourless solid. <sup>1</sup>H NMR (399.9 MHz, DMSO-d<sub>6</sub>) δ 1.67 - 1.75 (2H, m), 2.10 - 2.13 (2H, m), 3.08 - 3.14 (1H, m), 3.18 - 3.25 (2H, m), 3.76 (3H, s), 4.39 - 4.42 (2H, m), 6.73 (1H, d), 7.07 (2H, s), 7.23 (1H, d), 7.67 (1H, d), 8.24 (1H, d), 10.63 (1H, s); m/z 417 [M+H]<sup>+</sup>.



**Example 495****Preparation of 3-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]-1H-indole-5-carbonitrile**

5 Obtained in 88% yield by an analogous procedure to Example 494, starting from 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine and 3-(piperidin-4-yl)-1H-indole-5-carbonitrile (obtained as described in PCT Int. Appl. WO 2001043740, Example 3).

1H NMR (399.9 MHz, DMSO-d<sub>6</sub>)  $\delta$  1.68 - 1.78 (2H, m), 2.11 - 2.13 (2H, m), 3.18 - 3.24 (3H, m), 4.40 - 4.43 (2H, m), 7.36 (1H, s), 7.42 (1H, d), 7.51 (1H, d), 7.68 (1H, d), 8.24 (2H, m), 11.43 (1H, s); m/z 410 [M-H]<sup>-</sup>.

**Example 496****Preparation of N-(2-hydroxyethyl)-N-methyl-3-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]-1H-indole-5-carboxamide**

15 HATU (139 mg, 0.37 mmol) was added portionwise at ambient temperature to a stirred mixture of 3-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]-1H-indole-5-carboxylic acid (150 mg, 0.35 mmol), 2-(methylamino)ethanol (0.034 mL, 0.42 mmol) and DIPEA (0.073 mL, 0.42 mmol) in DMF (2.0 mL). The resulting solution  
20 was stirred for 2 hours then purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5 $\mu$  silica, 19 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 1% ammonia) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford N-(2-hydroxyethyl)-N-methyl-



3-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]-1H-indole-5-carboxamide (155 mg, 91%) as a colourless solid .

1H NMR (399.9 MHz, DMSO-d<sub>6</sub>)  $\delta$  1.68 - 1.78 (2H, m), 2.09 - 2.13 (2H, m), 3.01 (3H, s), 3.13 - 3.24 (3H, m), 3.29 - 3.70 (4H, m), 4.40 - 4.43 (2H, m), 4.78 (1H, t), 7.14 (1H, dd),  
5 7.21 (1H, d), 7.36 (1H, d), 7.68 (1H, d), 7.71 (1H, s), 8.25 (1H, d), 11.03 (1H, s); m/z = 488 [M+H]<sup>+</sup>.

The 3-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]-1H-indole-5-carboxylic acid used as starting material was prepared as follows:-

**Preparation of 3-[1-(tert-butoxycarbonyl)-1,2,3,6-tetrahydropyridin-4-yl]-1H-indole-5-carboxylic acid**

Potassium hydroxide (5.17 g, 92.08 mmol) was added to 1H-indole-5-carboxylic acid (3.71 g, 23.02 mmol) and tert-butyl 4-oxopiperidine-1-carboxylate (9.17 g, 46.04 mmol) in methanol (80 mL) at ambient temperature and the resulting solution was stirred at 65°C for 18 hours. The mixture was then cooled to ambient temperature, quenched in  
15 water (100 mL) and extracted with ethyl acetate (2 x 100 mL). The extracts were discarded and the aqueous phase acidified to pH 2-3 with 2M hydrochloric acid to give a pale yellow solid. The solid was collected by filtration, washed sequentially with water and ether and air dried to give 3-[1-(tert-butoxycarbonyl)-1,2,3,6-tetrahydropyridin-4-yl]-1H-indole-5-carboxylic acid (5.62 g, 71.3%) as a colourless solid.

20 1H NMR (399.9 MHz, DMSO-d<sub>6</sub>)  $\delta$  1.45 (9H, s), 2.50 - 2.55 (2H, m), 3.59 (2H, t), 4.06 - 4.11 (2H, m), 6.16 (1H, m), 7.46 (1H, d), 7.55 (1H, d), 7.76 (1H, dd), 8.48 (1H, s), 11.51 (1H, s), 12.45 (1H, br s); m/z = 341 [M-H]<sup>-</sup>.

**Preparation of methyl 3-[1-(tert-butoxycarbonyl)-1,2,3,6-tetrahydropyridin-4-yl]-1H-indole-5-carboxylate**

25 Iodomethane (1.22 mL, 19.63 mmol) was added in one portion to 3-[1-(tert-butoxycarbonyl)-1,2,3,6-tetrahydropyridin-4-yl]-1H-indole-5-carboxylic acid (6.72 g, 19.63 mmol) and potassium carbonate (3.26 g, 23.55 mmol) in DMF (60 mL) at ambient temperature. The resulting mixture was stirred at ambient temperature for 3 hours then quenched in water (200 mL) and extracted with MTBE (2 x 100 mL). The extract was  
30 washed sequentially with water (3 x 100 mL) and saturated brine, dried over MgSO<sub>4</sub> and concentrated by evaporation then purified by flash silica chromatography, elution gradient 20 to 35% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford methyl



3-[1-(tert-butoxycarbonyl)-1,2,3,6-tetrahydropyridin-4-yl]-1H-indole-5-carboxylate (5.09 g, 73%) as a colourless solid.

<sup>1</sup>H NMR (399.9 MHz, CDCl<sub>3</sub>) δ 1.51 (9H, s), 2.55 - 2.58 (2H, m), 3.67 - 3.70 (2H, m), 3.95 (3H, s), 4.14 - 4.18 (2H, m), 6.23 (1H, m), 7.22 (1H, d), 7.38 (1H, d), 7.93 (1H, dd), 8.42 (1H, s), 8.63 (1H, s); m/z = 355 [M-H]<sup>-</sup>.

**Preparation of methyl 3-[1-(tert-butoxycarbonyl)piperidin-4-yl]-1H-indole-5-carboxylate**

Methyl 3-[1-(tert-butoxycarbonyl)-1,2,3,6-tetrahydropyridin-4-yl]-1H-indole-5-carboxylate (5.0 g, 14.03 mmol), ammonium formate (4.42 g, 70.14 mmol) and palladium (5% on activated carbon, 200 mg) in ethanol (80 mL) were stirred and refluxed for 1 hour. The resulting mixture was cooled to ambient temperature and filtered through diatomaceous earth. The filtrate was concentrated by evaporation then treated with dilute aqueous ammonium chloride (100 mL) and extracted with ethyl acetate. The extract was washed sequentially with water and saturated brine, dried over MgSO<sub>4</sub> and evaporated to a colourless solid. The solid was triturated with ether, then collected by filtration and air dried to give methyl 3-[1-(tert-butoxycarbonyl)piperidin-4-yl]-1H-indole-5-carboxylate (4.59 g, 91%) as a colourless solid.

<sup>1</sup>H NMR (399.9 MHz, CDCl<sub>3</sub>) δ 1.49 (9H, s), 1.60 - 1.70 (2H, m), 2.03 - 2.06 (2H, m), 2.88 - 2.95 (2H, m), 3.03 (1H, tt), 3.94 (3H, s), 4.17 - 4.32 (2H, m), 7.01 (1H, d), 7.37 (1H, d), 7.90 (1H, dd), 8.26 (1H, s), 8.39 (1H, s); m/z = 357 [M-H]<sup>-</sup>.

**Preparation of methyl 3-(piperidin-4-yl)-1H-indole-5-carboxylate**

TFA (10 mL) was added in one portion at ambient temperature to a stirred solution of methyl 3-[1-(tert-butoxycarbonyl)piperidin-4-yl]-1H-indole-5-carboxylate (4.58 g, 12.78 mmol) in DCM (30 mL). The resulting solution was stirred for 30 minutes then applied to an SCX column and eluted with methanol followed by 2M ammonia in methanol. Pure fractions were combined and concentrated by evaporation then triturated with ether to give a solid which was collected by filtration and air dried to give methyl 3-(piperidin-4-yl)-1H-indole-5-carboxylate (2.69 g, 81%) as a pale yellow solid.

<sup>1</sup>H NMR (399.9 MHz, DMSO-d<sub>6</sub>) δ 1.53 - 1.63 (2H, m), 1.86 - 1.89 (2H, m), 2.64 - 2.70 (2H, m), 2.86 - 2.92 (1H, m), 3.02 - 3.05 (2H, m), 3.85 (3H, s), 7.21 (1H, d), 7.42 (1H, d), 7.71 (1H, dd), 8.26 (1H, s), 11.20 (1H, s); m/z = 257 [M-H]<sup>-</sup>.



**Preparation of methyl 3-[1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]-1H-indole-5-carboxylate**

6-Chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (1.8 g, 8.09 mmol), methyl 3-(piperidin-4-yl)-1H-indole-5-carboxylate (2.09 g, 8.09 mmol) and DIPEA (1.55 mL, 8.90 mmol) in DMF (25 mL) were stirred and heated at 80°C for 1 hour. The resulting mixture was then cooled to ambient temperature and quenched in water (60 mL) to give a precipitate which was collected by filtration, washed sequentially with water, acetonitrile and ether and dried under vacuum to give methyl 3-[1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]-1H-indole-5-carboxylate (3.29 g, 92%) as a cream solid.

<sup>1</sup>H NMR (399.9 MHz, DMSO-d<sub>6</sub>) δ 1.70 - 1.80 (2H, m), 2.09 - 2.12 (2H, m), 3.21 - 3.28 (3H, m), 3.85 (3H, s), 4.40 - 4.43 (2H, m), 7.28 (1H, d), 7.44 (1H, d), 7.68 (1H, d), 7.73 (1H, dd), 8.25 (1H, d), 8.31 (1H, d), 11.26 (1H, s); m/z = 445 [M+H]<sup>+</sup>.

**Preparation of 3-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]-1H-indole-5-carboxylic acid**

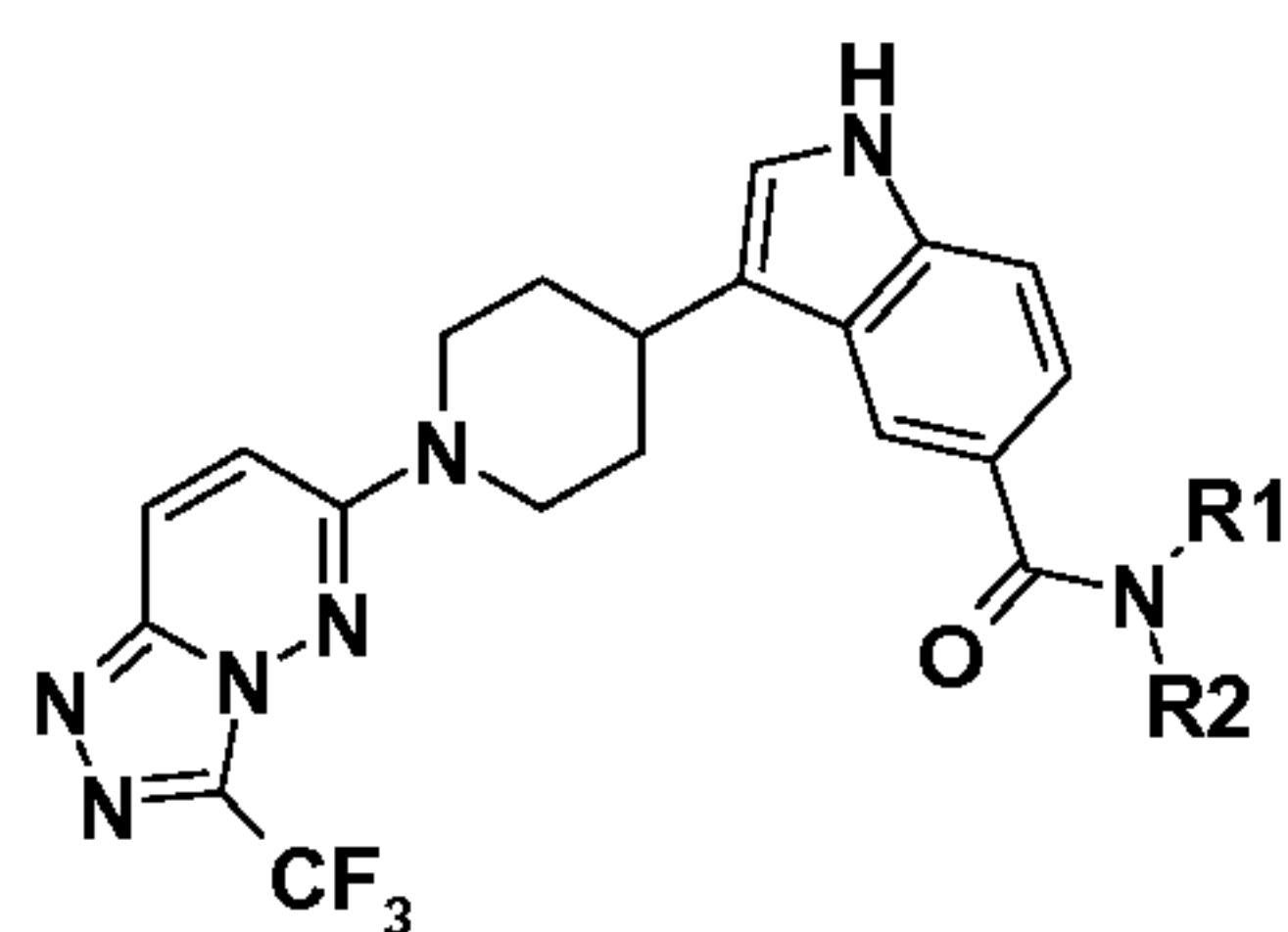
Methyl 3-[1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]-1H-indole-5-carboxylate (3.28 g, 7.38 mmol) and 2M NaOH (10 mL, 7.38 mmol) in methanol (80 mL) were heated under reflux for 40 hours. The resulting solution was concentrated by evaporation, then acidified to pH 2-3 with 2M hydrochloric acid to give a colourless precipitate. The precipitate was collected by filtration, washed sequentially with water, acetonitrile and ether and dried under vacuum to afford 3-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]-1H-indole-5-carboxylic acid (2.83 g, 89%) as a colourless solid.

<sup>1</sup>H NMR (399.9 MHz, DMSO-d<sub>6</sub>) δ 1.69 - 1.79 (2H, m), 2.09 - 2.13 (2H, m), 3.18 - 3.26 (3H, m), 4.40 - 4.43 (2H, m), 7.23 (1H, d), 7.37 (1H, d), 7.68 (1H, d), 7.72 (1H, dd), 8.25 (1H, d), 8.29 (1H, s), 11.19 (1H, s); m/z = 431 [M+H]<sup>+</sup>.

**Examples 497-505**

The following compounds were prepared in 75-98% yield by an analogous method to Example 496, starting from 3-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]-1H-indole-5-carboxylic acid and the appropriate amine:-

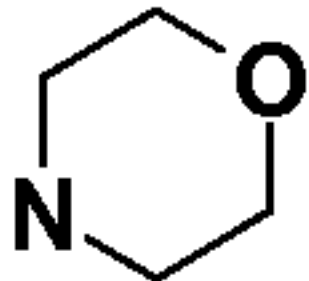
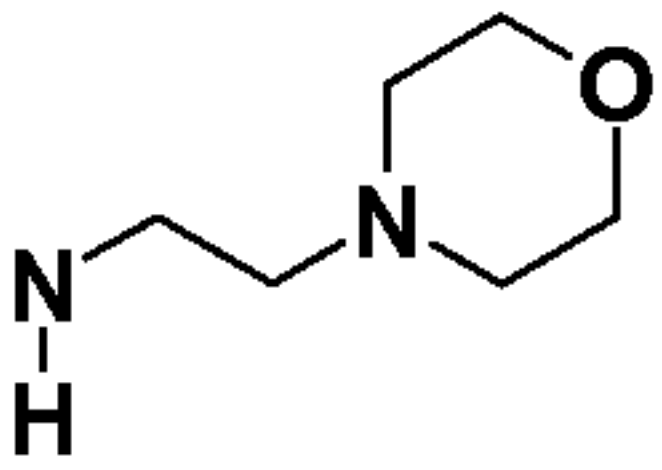
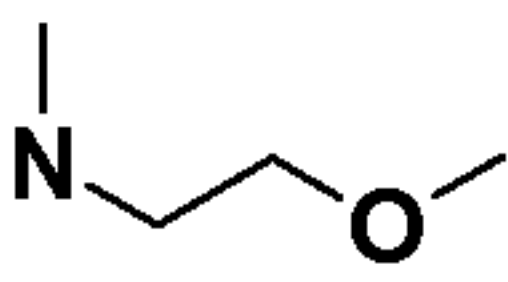
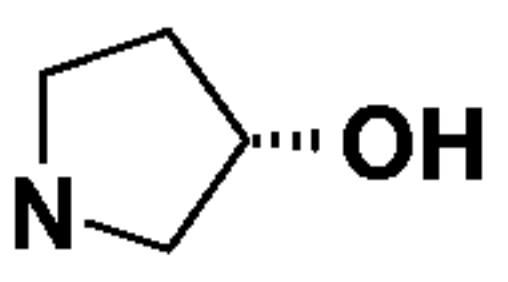




| Ex. | NR1R2            | <sup>1</sup> H NMR (399.9 MHz, DMSO-d <sub>6</sub> )                                                                                                                                                                                                           | m/z [M+H] <sup>+</sup> |
|-----|------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|
| 497 |                  | δ 1.68 - 1.78 (2H, m), 2.08 - 2.12 (2H, m), 2.18 (3H, s), 2.25 - 2.35 (4H, m), 3.15 - 3.24 (3H, m), 3.42 - 3.61 (4H, m), 4.40 - 4.43 (2H, m), 7.11 (1H, dd), 7.23 (1H, d), 7.38 (1H, d), 7.68 (1H, s), 7.69 (1H, d), 8.26 (1H, d), 11.07 (1H, s)               | 513                    |
| 498 |                  | δ 1.70 - 1.81 (2H, m), 2.14 - 2.17 (2H, m), 3.15 - 3.25 (3H, m), 3.29 (3H, s), 3.44 - 3.50 (4H, m), 4.43 - 4.46 (2H, m), 7.22 (1H, d), 7.36 (1H, d), 7.64 (1H, dd), 7.70 (1H, d), 8.20 (1H, s), 8.27 (1H, d), 8.41 (1H, t), 11.09 (1H, s)                      | 488                    |
| 499 | NMe <sub>2</sub> | δ 1.68 - 1.78 (2H, m), 2.09 - 2.12 (2H, m), 2.99 (6H, s), 3.13 - 3.24 (3H, m), 4.40 - 4.43 (2H, m), 7.14 (1H, dd), 7.21 (1H, d), 7.37 (1H, d), 7.69 (1H, d), 7.70 (1H, s), 8.25 (1H, d), 11.05 (1H, s).                                                        | 458                    |
| 500 |                  | δ 1.66 - 2.01 (4H, m), 2.09 - 2.12 (2H, m), 3.16 - 3.29 (3H, m), 3.46 - 3.70 (4H, m), 4.22 (m) & 4.34 (m, 1H), 4.40 - 4.43 (2H, m), 4.91 (d) & 5.02 (d, 1H), 7.22 (1H, d), 7.27 (1H, d), 7.37 (1H, d), 7.69 (1H, d), 7.82 (1H, s), 8.25 (1H, d), 11.06 (1H, s) | 500                    |
| 501 |                  | δ 1.68 - 1.93 (6H, m), 2.08 - 2.12 (2H, m), 3.15 - 3.24 (3H, m), 3.43 - 3.51 (4H, m), 4.40 - 4.43 (2H, m), 7.21 (1H, d), 7.27 (1H, dd), 7.36 (1H, d), 7.69 (1H, d), 7.82 (1H, s), 8.26 (1H, d), 11.05 (1H, s)                                                  | 484                    |

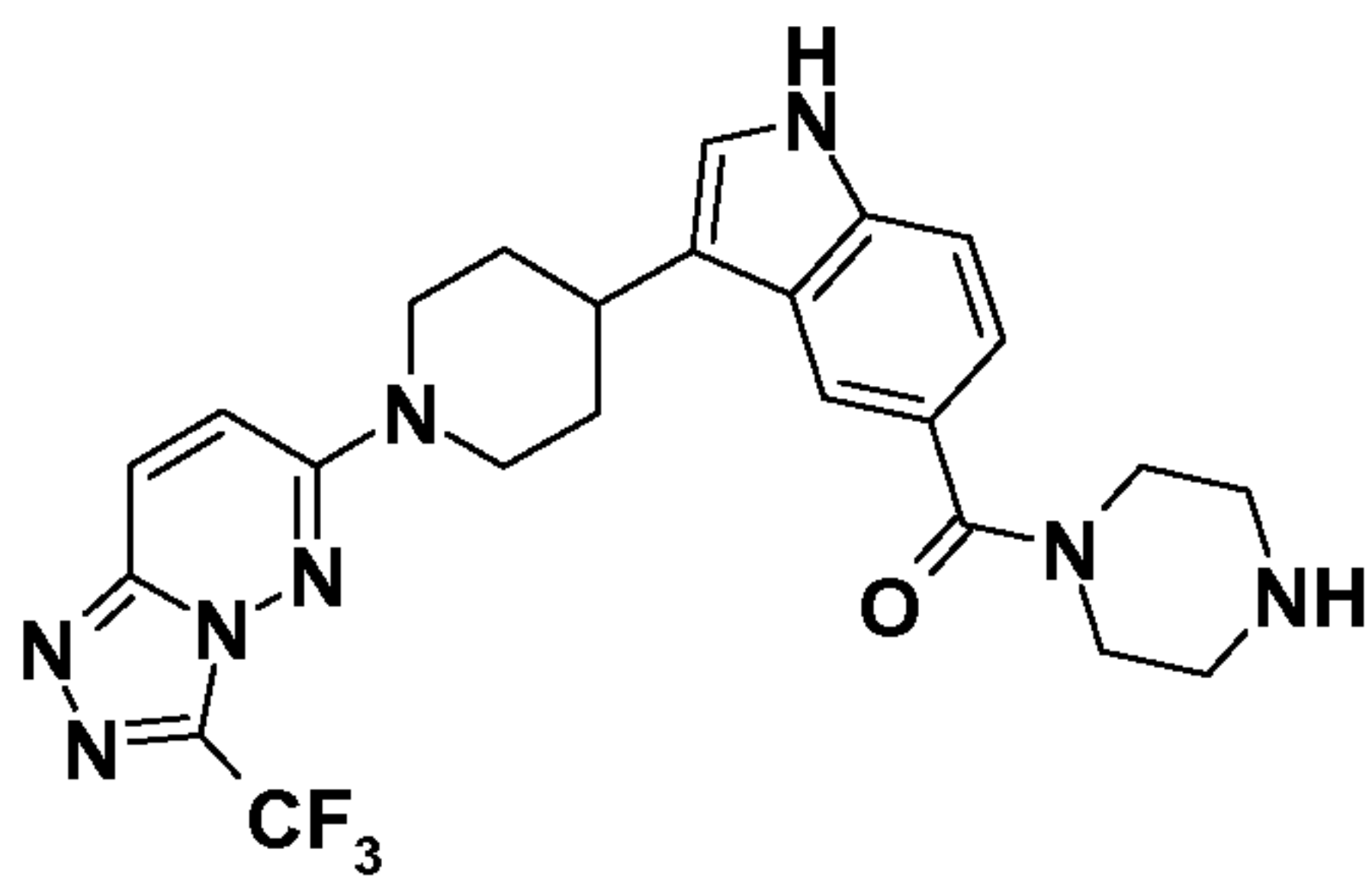


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|     |                                                                                     |                                                                                                                                                                                                                                                                              |     |
|-----|-------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
| 502 |    | $\delta$ 1.68 - 1.78 (2H, m), 2.09 - 2.12 (2H, m), 3.15 - 3.24 (3H, m), 3.47 - 3.65 (8H, m), 4.40 - 4.43 (2H, m), 7.14 (1H, dd), 7.23 (1H, d), 7.39 (1H, d), 7.69 (1H, d), 7.71 (1H, s), 8.26 (1H, d), 11.08 (1H, s)                                                         | 500 |
| 503 |    | $\delta$ 1.71 - 1.81 (2H, m), 2.14 - 2.16 (2H, m), 2.44 (4H, m), 2.47 - 2.50 (2H, m), 3.14 - 3.25 (3H, m), 3.42 (2H, q), 3.58 (4H, t), 4.43 - 4.46 (2H, m), 7.22 (1H, d), 7.37 (1H, d), 7.62 (1H, dd), 7.70 (1H, d), 8.16 (1H, s), 8.27 (1H, d), 8.28 (1H, t), 11.08 (1H, s) | 543 |
| 504 |  | $\delta$ 1.69 - 1.79 (2H, m), 2.09 - 2.12 (2H, m), 2.99 (3H, s), 3.14 - 3.29 (6H, m), 3.40 - 3.64 (4H, m), 4.40 - 4.44 (2H, m), 7.12 (1H, dd), 7.21 (1H, d), 7.37 (1H, d), 7.69 (1H, d), 7.70 (1H, s), 8.25 (1H, d), 11.04 (1H, s)                                           | 502 |
| 505 |  | $\delta$ 1.67 - 2.00 (4H, m), 2.09 - 2.12 (2H, m), 3.16 - 3.29 (3H, m), 3.45 - 3.70 (4H, m), 4.22 (m) & 4.34 (m, 1H), 4.40 - 4.43 (2H, m), 4.91 (d) & 5.02 (d, 1H), 7.22 (1H, d), 7.27 (1H, d), 7.37 (1H, d), 7.69 (1H, d), 7.82 (1H, s), 8.25 (1H, d), 11.06 (1H, s)        | 500 |

**Example 506**

**Preparation of 6-[4-[5-(piperazin-1-ylcarbonyl)-1H-indol-3-yl]piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine**





TFA (1 mL) was added in one portion at ambient temperature to a stirred solution of tert-butyl [4-[3-[1-(3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]-1H-indole-5-carbonyl]piperazine-1-carboxylate (190 mg, 0.32 mmol) in DCM (2 mL). The resulting solution was stirred for 1 hour then applied to an SCX column and eluted with MeOH followed by 2M ammonia in MeOH. Pure fractions were combined and concentrated by evaporation then triturated with ether to give a solid which was collected by filtration and air dried to give 6-[4-[5-(piperazin-1-ylcarbonyl)-1H-indol-3-yl]piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine (156 mg, 99%) as a colourless solid.

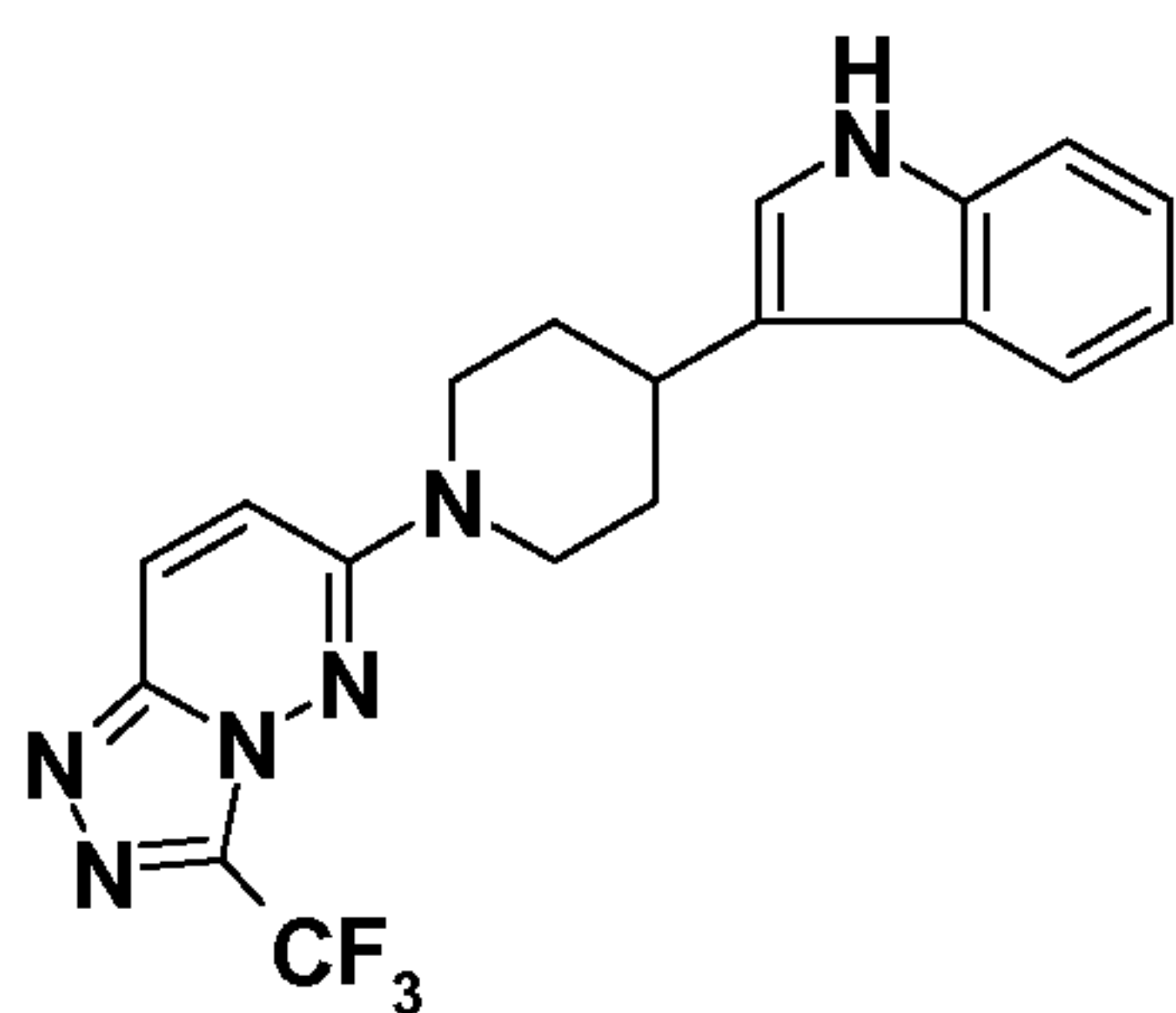
<sup>1</sup>H NMR (399.9 MHz, DMSO-d<sub>6</sub>) δ 1.68 - 1.78 (2H, m), 2.09 - 2.12 (2H, m), 2.83 - 2.93 (4H, m), 3.15 - 3.24 (3H, m), 3.50 - 3.64 (4H, m), 4.40 - 4.44 (2H, m), 7.14 (1H, dd), 7.23 (1H, d), 7.39 (1H, d), 7.69 (1H, d), 7.71 (1H, s), 8.26 (1H, d), 11.09 (1H, s); m/z = 499 [M+H]<sup>+</sup>.

The tert-butyl [4-[3-[1-(3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]-1H-indole-5-carbonyl]piperazine-1-carboxylate used as starting material was prepared in 91% yield by an analogous method to Example 496, starting from 3-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]-1H-indole-5-carboxylic acid and tert-butyl 1-piperazinecarboxylate.

m/z = 599 [M+H]<sup>+</sup>.

## **Example 507**

### **Preparation of 6-[4-(1H-indol-3-yl)piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine**



A stirred solution of 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (0.223 g, 1.0 mmol), 3-(piperidin-4-yl)-1H-indole (0.240 g, 1.20 mmol) and DIPEA (0.257 mL, 1.50 mmol) in DMF (3 mL) was heated at 70°C for 1 hour. The reaction mixture was run onto an SCX cartridge, which was washed with MeOH and eluted with 2M ammonia in

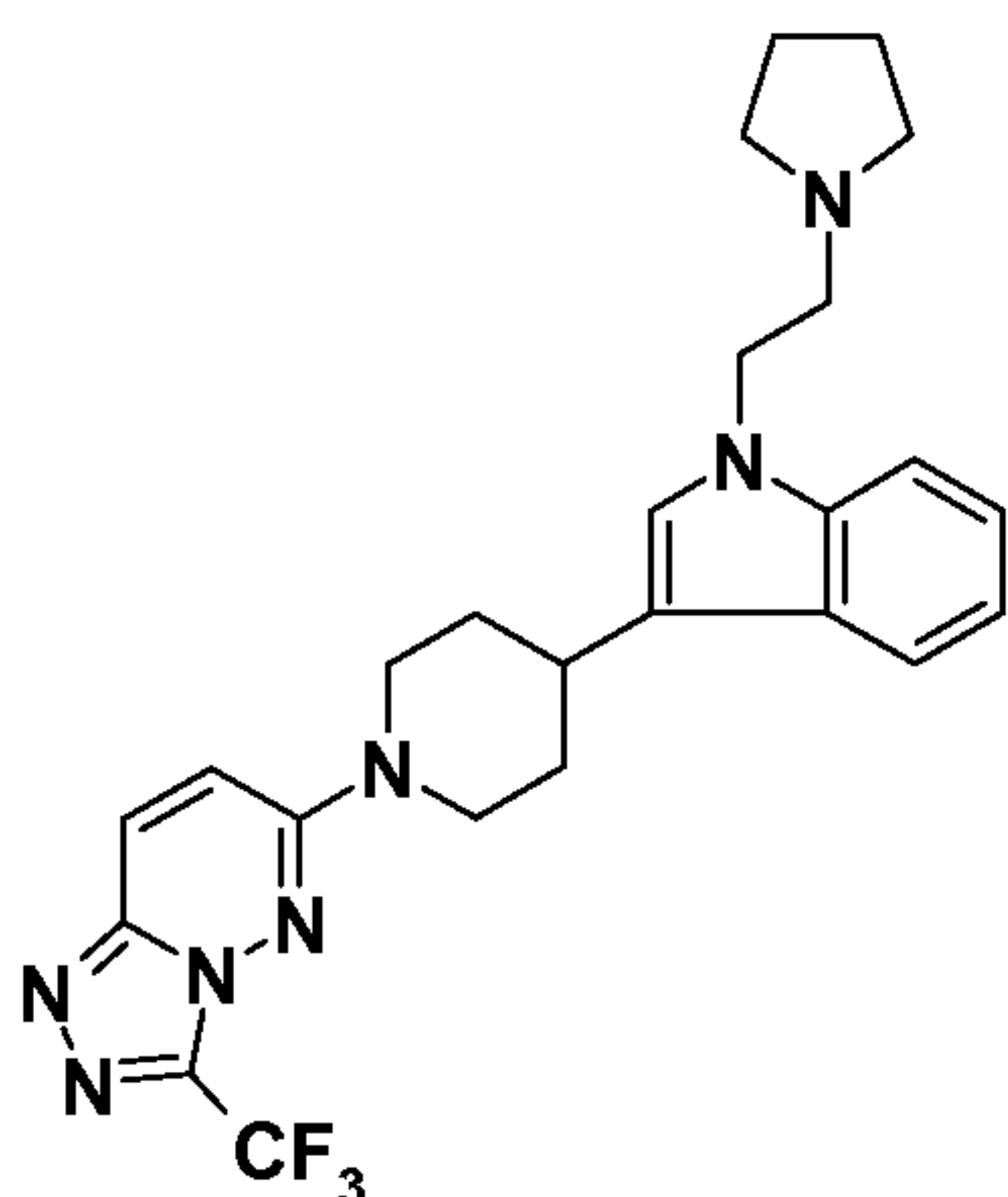


methanol. The crude product was purified by MPLC silica chromatography, eluting with ethyl acetate. Pure fractions were evaporated to a gum which crystallised on trituration with ether to afford 6-[4-(1H-indol-3-yl)piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine (0.119 g, 31%) as a colourless crystalline solid.

<sup>1</sup>H NMR (399.9 MHz, CDCl<sub>3</sub>) δ 1.81 - 1.92 (2H, m), 2.25 (2H, d), 3.15 - 3.27 (3H, m), 4.37 (2H, d), 6.99 - 6.99 (1H, m), 7.11 - 7.15 (2H, m), 7.19 - 7.24 (1H, m), 7.38 - 7.40 (1H, m), 7.64 (1H, d), 7.92 (1H, d), 8.02 (1H, s); m/z = 387 [M+H]<sup>+</sup>.

### **Example 508**

#### **Preparation of 6-[4-[1-(2-pyrrolidin-1-ylethyl)-1H-indol-3-yl]piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine**



Sodium hydride (60% dispersion in oil, 31 mg, 0.75 mmol) was added to 6-[4-(1H-indol-3-yl)piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine (obtained as described in Example 507) (150 mg, 0.39 mmol) suspended in DMF (2 mL) at 0°C under nitrogen. The resulting mixture was stirred at 0°C for 30 minutes, then 1-(2-chloroethyl)pyrrolidine hydrochloride (72.6 mg, 0.43 mmol) in DMF (1 mL) was added. The resulting mixture was stirred at ambient temperature for 18 hours. The reaction mixture was evaporated to afford crude product. The crude product was purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5μ silica, 19 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 1% ammonia) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to give 6-[4-[1-(2-pyrrolidin-1-ylethyl)-1H-indol-3-yl]piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine (52.0 mg, 27.7%) as a white solid.

<sup>1</sup>H NMR (399.9 MHz, DMSO-d<sub>6</sub>) δ 1.63 - 1.67 (4H, m), 1.71 - 1.76 (2H, m), 2.09 (1H, d), 2.11 (1H, s), 2.45 - 2.48 (4H, m), 2.76 (2H, t), 3.15 (1H, t), 3.19 - 3.25 (2H, m), 3.38 (1H,

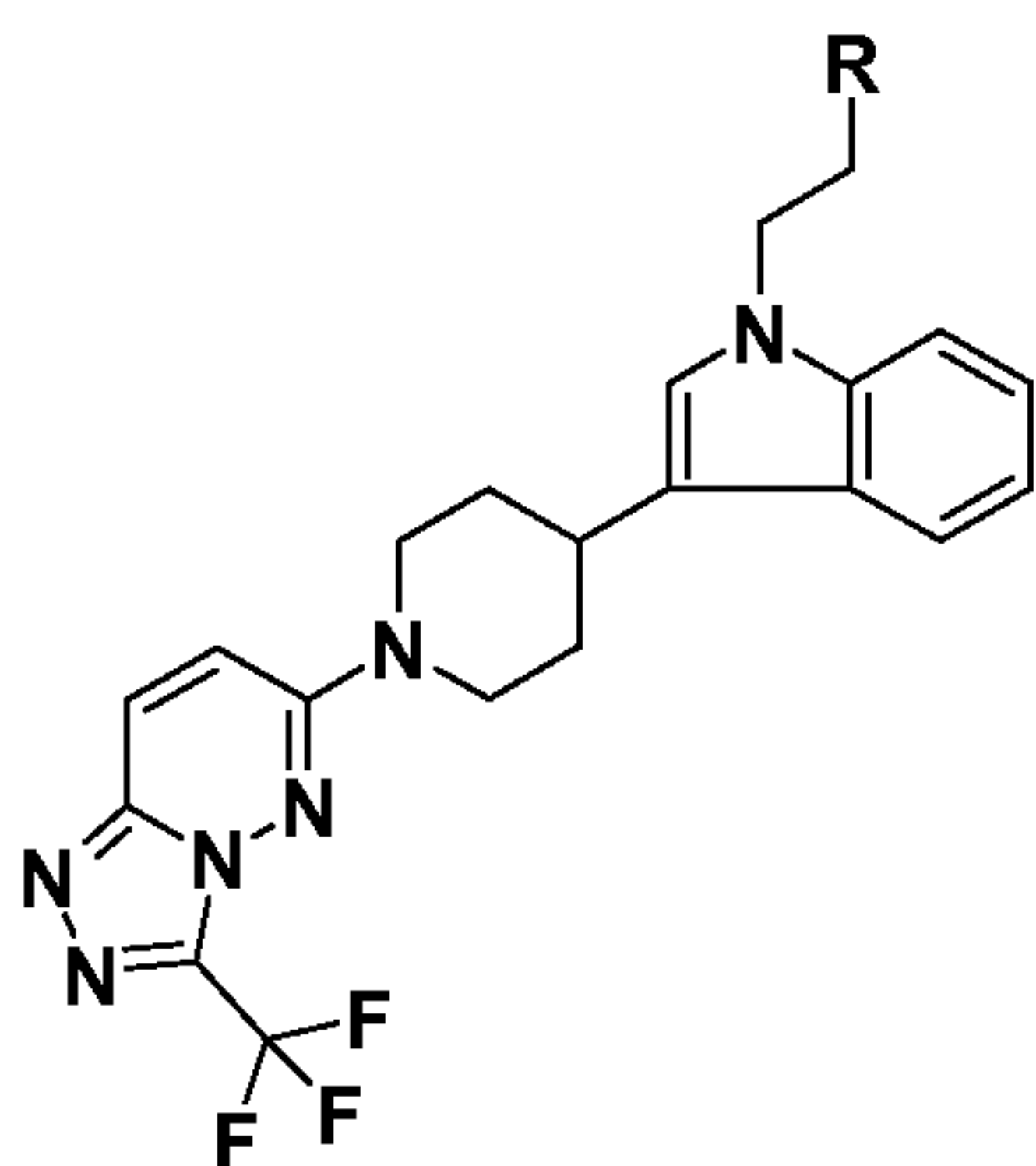


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s), 4.20 (2H, t), 4.40 (2H, d), 6.99 - 7.03 (1H, m), 7.10 - 7.14 (1H, m), 7.18 (1H, s), 7.42 (1H, d), 7.61 (1H, s), 7.67 (1H, d), 8.24 (1H, d); m/z 485 [M+H]<sup>+</sup>.

### **Examples 509-510**

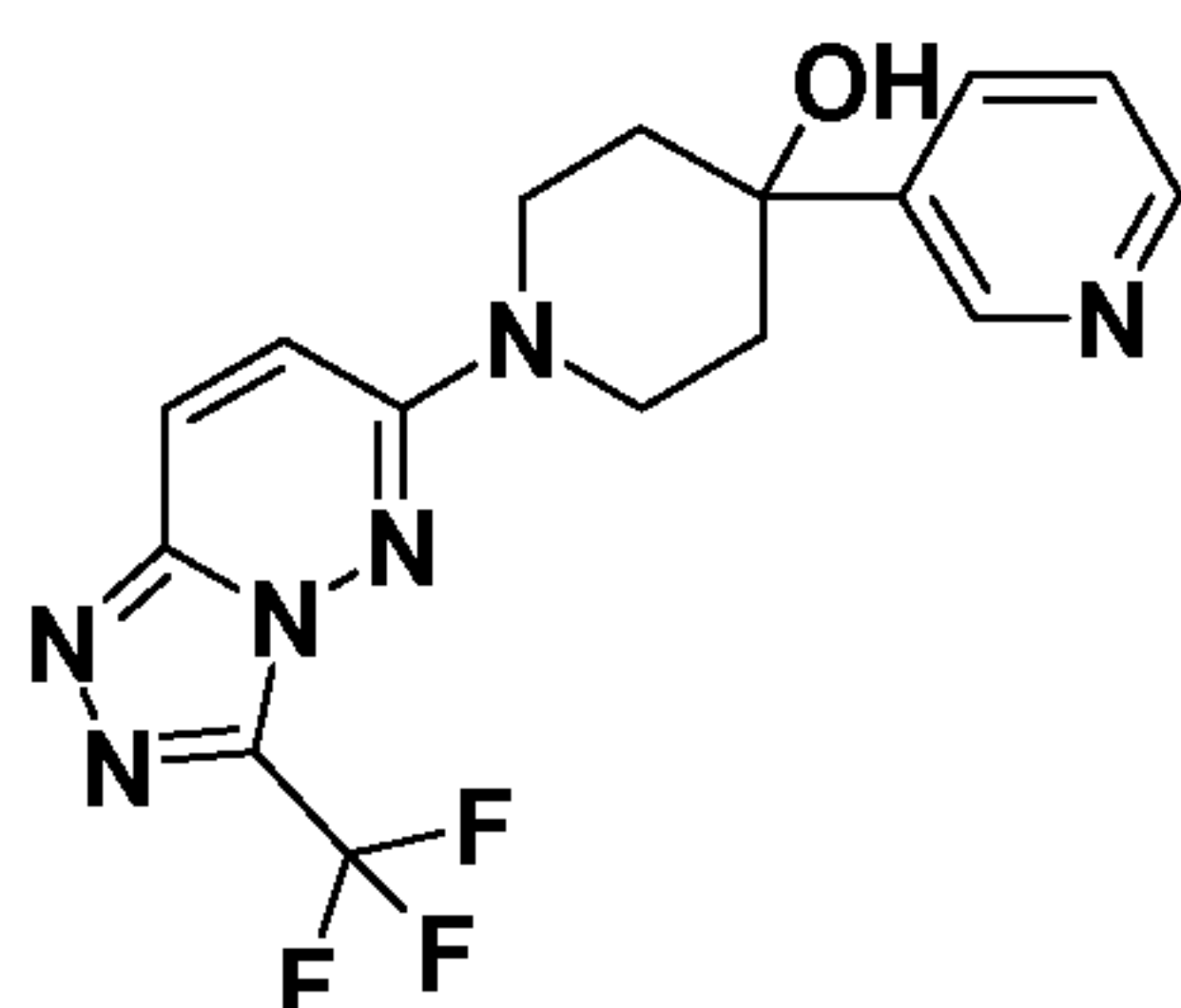
The following compounds were prepared in 26-32% yield by an analogous procedure to  
 5 Example 508, starting from 6-[4-(1H-indol-3-yl)piperidin-1-yl]-3-(trifluoromethyl)-  
 [1,2,4]triazolo[4,3-b]pyridazine and the appropriate alkyl chloride:-



| Ex. | R                 | <sup>1</sup> H NMR (399.9 MHz, DMSO-d <sub>6</sub> )                                                                                                                                                                                                                | m/z [M+H] <sup>+</sup> |
|-----|-------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|
| 509 | Me <sub>2</sub> N | δ 1.70 - 1.74 (1H, m), 2.11 (2H, d), 2.18 (6H, s), 2.58 (2H, t), 3.15 (1H, t), 3.21 (1H, d), 3.25 - 3.26 (1H, m), 3.35 (1H, d), 4.18 (2H, t), 4.41 (2H, d), 7.00 (1H, t), 7.10 - 7.13 (1H, m), 7.18 (1H, s), 7.42 (1H, d), 7.63 (1H, s), 7.67 (1H, d), 8.24 (1H, d) | 459                    |
| 510 | MeO               | δ 1.70 - 1.74 (2H, m), 2.10 (1H, d), 2.12 (1H, s), 3.15 - 3.19 (1H, m), 3.22 (4H, s), 3.64 (2H, t), 4.26 (2H, t), 4.39 - 4.43 (2H, m), 6.99 - 7.03 (1H, m), 7.10 - 7.14 (1H, m), 7.15 (1H, s), 7.44 (1H, d), 7.61 (1H, s), 7.67 (1H, d), 8.25 (1H, d)               | 446                    |

### **Example 511**

### **Preparation of 4-pyridin-3-yl-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol**





A stirred solution of 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (0.445 g, 2.0 mmol), 4-(pyridin-3-yl)piperidin-4-ol (obtained as described in Canadian Patent Application CA2076191, Example 87 (see also Example 87 in EP0533344B1)) (0.392 g, 2.20 mmol) and DIPEA (0.453 mL, 2.60 mmol) in DMF (4 mL) was heated at 70°C for 1 hour. The solution was evaporated and partitioned between DCM (20 mL) and 1M aqueous potassium carbonate (20 mL). The organic phase was washed with saturated aqueous sodium chloride, dried over MgSO<sub>4</sub> and evaporated to dryness, and the residue was triturated with ether. The precipitated solid was collected by filtration, washed with ether and dried under vacuum to afford 4-pyridin-3-yl-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol (0.270 g, 37%) as a white crystalline solid.

<sup>1</sup>H NMR (399.9 MHz, DMSO-d<sub>6</sub>) δ 1.76 - 1.79 (2H, m), 2.03 - 2.11 (2H, m), 3.43 - 3.49 (2H, m), 4.23 (2H, d), 5.43 (1H, s), 7.33 - 7.37 (1H, m), 7.67 (1H, d), 7.87 - 7.90 (1H, m), 8.25 (1H, d), 8.45 - 8.46 (1H, m), 8.74 (1H, d); m/z = 363 [M-H]-.

#### **Example 511.1**

##### **Large scale preparation of 4-pyridin-3-yl-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol**

A stirred solution of 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (24.29 g, 109.15 mmol), 4-(pyridin-3-yl)piperidin-4-ol (21.40 g, 120.07 mmol) and DIPEA (24.72 mL, 141.90 mmol) in DMF (95 mL) was heated at 80°C for 1 hour. The solution was cooled to ambient temperature and slowly diluted with water, with seeding, to give a crystalline precipitate. The precipitate was collected by filtration, washed with water, acetonitrile and ether and dried under vacuum to afford 4-pyridin-3-yl-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol (36.1 g, 91%) as a solid.

<sup>1</sup>H NMR (399.9 MHz, DMSO-d<sub>6</sub>) δ 1.76 (2H, d), 2.03 - 2.09 (2H, m), 3.41 - 3.47 (2H, m), 4.23 (2H, d), 5.47 (1H, s), 7.33 - 7.37 (1H, m), 7.68 (1H, d), 7.87 - 7.90 (1H, m), 8.26 (1H, d), 8.44 - 8.46 (1H, m), 8.74 (1H, d); m/z = 365 [M+H]<sup>+</sup>.

The 4-(pyridin-3-yl)piperidin-4-ol used as starting material was prepared as follows:-

##### **Preparation of benzyl 4-hydroxy-4-(pyridin-3-yl)piperidine-1-carboxylate**

A solution of 3-bromopyridine (9.09 mL, 94.31 mmol) in diethyl ether (50 mL) was added



dropwise to a stirred solution of 1.6M n-butyl lithium in hexane (58.9 mL, 94.31 mmol) in diethyl ether (500 mL) cooled to -78°C, over a period of 15 minutes under nitrogen. The resulting suspension was stirred at -78°C for 1 hour. A solution of benzyl 4-oxopiperidine-1-carboxylate (20 g, 85.74 mmol) in diethyl ether (50 mL) and THF (50 mL) was added dropwise over 15 minutes. The reaction mixture was stirred at -78°C for 1 hour, warmed to 0°C over 2.5 hours and quenched with saturated ammonium chloride solution (500 mL). The mixture was extracted with ethyl acetate (2 x 500 mL) and the combined extracts were washed with brine (200 mL) then dried over MgSO<sub>4</sub> and filtered through a short pad of silica. The silica pad was washed through with ethyl acetate (4 x 250 mL) and the filtrate was concentrated under vacuum. The residue was purified by flash silica chromatography eluting with ethyl acetate. Pure fractions were evaporated to dryness to afford benzyl 4-hydroxy-4-(pyridin-3-yl)piperidine-1-carboxylate (12.8 g, 48%) as an oil.

<sup>1</sup>H NMR (400.1 MHz, CDCl<sub>3</sub>) δ 1.71 - 1.82 (2H, m), 1.84 - 2.02 (2H, m), 3.25 - 3.43 (2H, m), 3.48 - 3.66 (1H, m), 4.03 - 4.19 (2H, m), 5.15 (2H, s), 7.27 - 7.39 (6H, m), 7.79 - 7.82 (1H, m), 8.37 - 8.40 (1H, m), 8.69 (1H, d); m/z = 313 [M+H]<sup>+</sup>.

#### **Preparation of 4-(pyridin-3-yl)piperidin-4-ol**

Benzyl 4-hydroxy-4-(pyridin-3-yl)piperidine-1-carboxylate (32.7 g, 104.69 mmol) was dissolved in ethanol (350 mL) and hydrogenated over 10% palladium on carbon (3.2 g) at 2 bar pressure at 30°C. After hydrogen uptake was complete, the mixture was filtered through a pad of diatomaceous earth to remove the catalyst and the pad was washed with ethanol. The filtrate was concentrated to dryness under vacuum to give an oil which crystallised on standing overnight. The solid was triturated with MTBE (100 mL), collected by filtration, washed with MTBE (2 x 50 mL) and dried in a vacuum oven at 40°C to afford 4-(pyridin-3-yl)piperidin-4-ol (14.9 g, 80%) as a solid.

<sup>1</sup>H NMR (400.1 MHz, DMSO-d<sub>6</sub>) δ 1.53 - 1.61 (2H, m), 1.86 (2H, m), 2.74 - 2.83 (2H, m), 2.96 (2H, m), 7.34 (1H, m), 7.83 (1H, m), 8.43 (1H, m), 8.69 (1H, d).

#### **Example 511.2**

#### **Preparation of crystalline 4-pyridin-3-yl-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol Anhydrous Form A**

A stirred solution of 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (16.69 g, 75 mmol), 4-(pyridin-3-yl)piperidin-4-ol (14.70 g, 82.50 mmol) and N-ethyldiisopropylamine (16.98 mL, 97.50 mmol) in DMF (75 mL) was heated at 80 °C for



1hr. The solution was cooled to ambient temperature and slowly diluted with water, with seeding, giving a crystalline precipitate. The precipitate was collected by filtration, washed with water, acetonitrile and ether and dried under vacuum at 50°C to afford 4-(pyridin-3-yl)-1-(3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)piperidin-4-ol anhydrous  
5 Form A (25.2 g, 92 %) as a cream crystalline solid, which was used without further purification. Approximately 30mg of material was then slurried in approximately 1ml of ethyl acetate and stirred using a magnetic stirrer bar for 3 days at ambient temperature. The resultant material was air dried and analysed.

4-Pyridin-3-yl-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-  
10 4-ol Anhydrous Form A is characterised by providing an X-ray powder diffraction pattern substantially as shown in Figure 1. The intensity of the peaks at the corresponding 2θ values are shown in Table A below.

4-Pyridin-3-yl-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-  
4-ol Anhydrous Form A may thus also be characterised by providing at least one of the  
15 following 2θ values when measured using CuKα radiation: 9.18°, 15.51°, 16.01°, 18.94° and 24.59°.

Table A

| Angle<br>2-Theta ° (2θ) | Intensity % |
|-------------------------|-------------|
| 8.296                   | 42          |
| 9.176                   | 87.2        |
| 9.961                   | 16.7        |
| 10.411                  | 11.7        |
| 14.352                  | 49          |
| 15.022                  | 25.7        |
| 15.513                  | 68.9        |
| 16.007                  | 100         |
| 17.026                  | 33.5        |
| 18.458                  | 9.3         |
| 18.939                  | 69.6        |
| 19.181                  | 28          |

| Angle<br>2-Theta ° (2θ) | Intensity % |
|-------------------------|-------------|
| 20.609                  | 17.9        |
| 21.804                  | 51.4        |
| 22.653                  | 17.5        |
| 23.377                  | 38.5        |
| 24.151                  | 10.5        |
| 24.585                  | 71.2        |
| 25.43                   | 55.6        |
| 26.12                   | 18.3        |
| 26.349                  | 40.1        |
| 26.592                  | 14.4        |
| 27.431                  | 15.6        |
| 29.375                  | 25.7        |



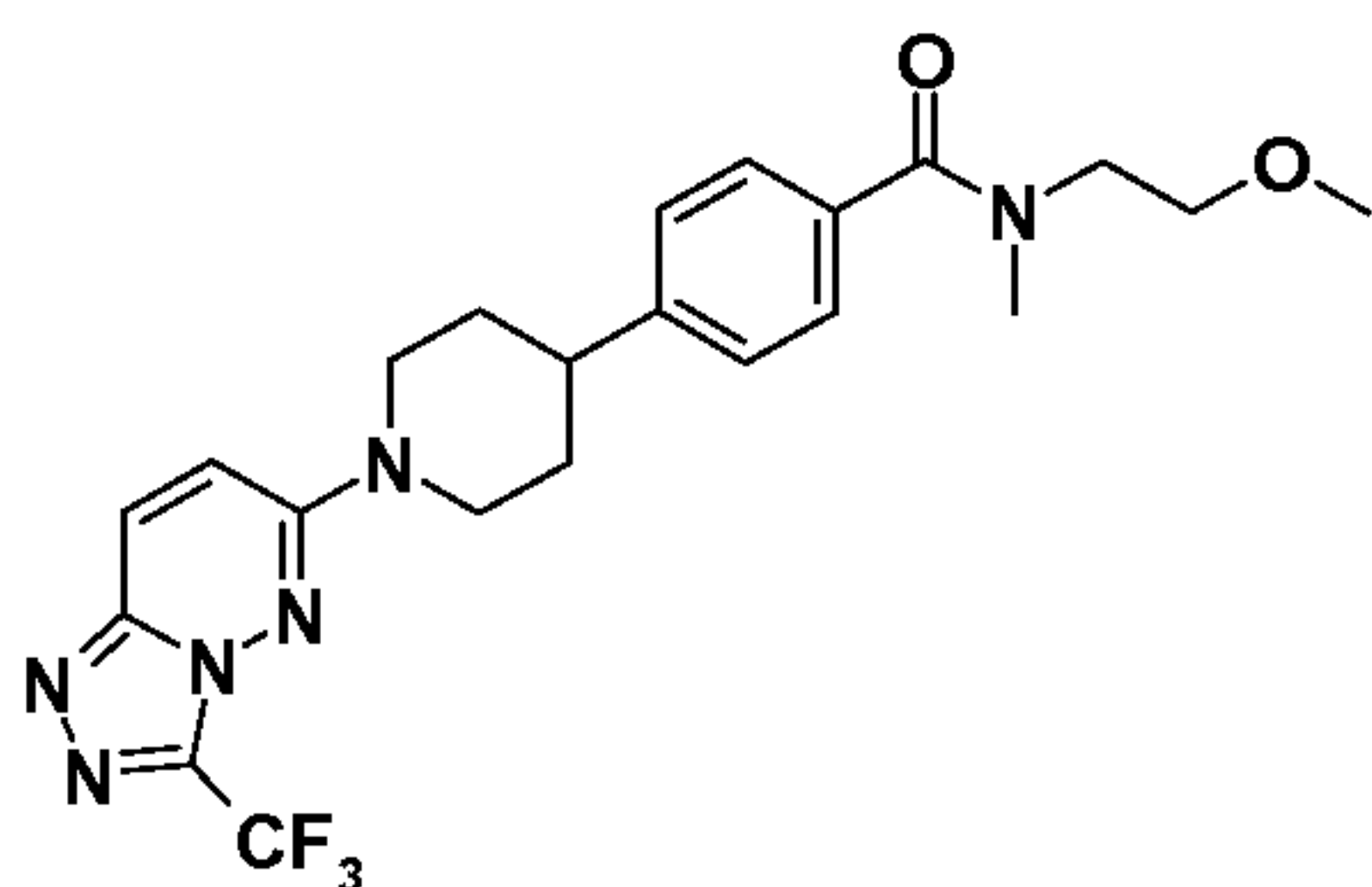
|        |      |
|--------|------|
| 19.823 | 27.6 |
| 20.353 | 36.2 |

|        |      |
|--------|------|
| 31.83  | 22.6 |
| 37.332 | 12.1 |

DSC analysis showed that 4-pyridin-3-yl-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol Anhydrous Form A has an onset of melting at about 230°C and a peak of melting at about 232°C.

### 5 **Example 512**

#### **Preparation of N-(2-methoxyethyl)-N-methyl-4-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]benzamide**



A mixture of 4-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]benzoic acid (79 mg, 0.20 mmol), N-(2-methoxyethyl)methylamine (21 mg, 0.24 mmol), DIPEA (0.105 mL, 0.61 mmol) and HATU (92 mg, 0.24 mmol) in DMA (3 mL) was stirred at ambient temperature for 16 hours. The reaction mixture was purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5 $\mu$  silica, 19 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 1% ammonia) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to give N-(2-methoxyethyl)-N-methyl-4-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]benzamide (77 mg, 82%) as a solid.

<sup>1</sup>H NMR (399.9 MHz, CDCl<sub>3</sub>)  $\delta$  1.81 (2H, m), 2.02 (2H, m), 2.86 (1H, m), 3.04 - 3.17 (5H, m), 3.29 - 3.48 (5H, m), 3.69 (2H, m), 4.39 (2H, m), 7.13 (1H, d), 7.24 (2H, d), 7.38 (2H, d), 7.94 (1H, d); m/z = 463 [M+H]<sup>+</sup>.

The 4-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]benzoic acid used as starting material was prepared as follows:-

#### **Preparation of methyl 4-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]benzoate**

6-Chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (2 g, 8.99 mmol), methyl 4-(piperidin-4-yl)benzoate (CAS 281235-04-9, 2.168 g, 9.89 mmol) and DIPEA



(3.91 mL, 22.47 mmol) were dissolved in DMA (10 mL) and sealed into a microwave tube. The mixture was heated to 110°C for 5 minutes in the microwave reactor and cooled to room temperature. The reaction mixture was added dropwise to stirred water (30 mL), stirred for 10 minutes then the precipitate was collected by filtration, washed with ether (2 x 2 mL) and dried to give methyl 4-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]benzoate (3.32 g, 91%) as a solid.

<sup>1</sup>H NMR (399.9 MHz, DMSO-d<sub>6</sub>) δ 1.73 (2H, m), 1.92 (2H, m), 2.98 (1H, m), 3.13 (2H, m), 3.84 (3H, s), 4.44 (2H, m), 7.44 (2H, d), 7.68 (1H, d), 7.91 (2H, d), 8.27 (1H, d); m/z = 406 [M+H]<sup>+</sup>.

#### **Preparation of 4-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]benzoic acid**

Lithium hydroxide monohydrate (0.154 g, 3.66 mmol) was added to methyl 4-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]benzoate (1.35 g, 3.33 mmol) in a mixture of methanol (30 mL) and water (15 mL). The resulting suspension was stirred at 50°C for 16 hours. The mixture was cooled to room temperature, the methanol evaporated and the aqueous residue treated with 1M citric acid until precipitation ceased. The precipitate was collected by filtration, washed with water and dried to give 4-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]benzoic acid (1.26 g, 97%) as a solid.

<sup>1</sup>H NMR (399.9 MHz, DMSO-d<sub>6</sub>) δ 1.69 - 1.79 (2H, m), 1.93 (2H, m), 2.94 - 3.02 (1H, m), 3.11 - 3.17 (2H, m), 4.44 (2H, m), 7.41 (2H, d), 7.67 (1H, d), 7.89 (2H, d), 8.25 (1H, d), 12.79 (1H, s); m/z = 392 [M+H]<sup>+</sup>.

#### **Example 512.1**

#### **Alternative method for the preparation of N-(2-methoxyethyl)-N-methyl-4-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]benzamide**

4-Methylmorpholine (17.56 mL, 159.70 mmol) was added dropwise to 4-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]benzoic acid (25 g, 63.88 mmol) and 2-chloro-4,6-dimethoxy-1,3,5-triazine (13.46 g, 76.66 mmol) suspended in DMF (250 mL) at 0°C. The resulting suspension was stirred for 10 minutes, then 2-methoxy-N-methylethanamine (5.69 g, 63.88 mmol) was added and the mixture warmed to ambient temperature and stirred for 16 hours. The reaction mixture was concentrated and diluted with DCM (1000 mL) and washed with water (500 mL). The aqueous phase was



re-extracted with DCM (500 mL), then the combined organics were washed with saturated NaHCO<sub>3</sub> (500 mL) and saturated brine (250 mL), and dried over MgSO<sub>4</sub>, filtered and evaporated to afford crude product. The crude product was titrated with ether, and the resulting solid was collected by filtration and dried under vacuum, then purified by flash silica chromatography, elution gradient 0 to 5% MeOH in DCM. Pure fractions were evaporated to dryness to afford N-(2-methoxyethyl)-N-methyl-4-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]benzamide (23.45 g, 79%) as a solid.

<sup>1</sup>H NMR (399.9 MHz, CDCl<sub>3</sub>) δ 1.81 (2H, m), 2.02 (2H, m), 2.86 (1H, m), 3.04 - 3.17 (5H, m), 3.30 - 3.49 (5H, m), 3.69 (2H, m), 4.39 (2H, m), 7.13 (1H, d), 7.24 (2H, d), 7.39 (2H, d), 7.93 (1H, d); m/z = 463 [M+H]<sup>+</sup>.

The 4-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]benzoic acid used as starting material was prepared as follows:-

#### **Preparation of sodium 4-(pyridin-4-yl)benzoate**

A solution of sodium carbonate (830 g, 7834.20 mmol) in water (6800 mL) was added dropwise over 30 minutes to a stirred suspension of 4-boronobenzoic acid (520 g, 3133.68 mmol), 4-bromopyridine hydrochloride (622 g, 3196.35 mmol) and palladium(II) acetate (1.407 g, 6.27 mmol) in ethanol (2600 mL) and water (3600 mL) at 20°C. The reaction was stirred for 10 minutes then 3,3',3''-phosphinidynetris(benzenesulfonic acid) trisodium salt (30% w/w solution in water) (36.8 g, 18.80 mmol) was added and the mixture was heated to 85°C for 4 hours. The reaction mixture was cooled to 55°C and stirred for 2 hours, then the resulting suspension was stirred at 20°C for 16 hours. The solid was collected by filtration, washed with acetone (3 x 1250 mL), and dried in a vacuum oven at 60°C to afford sodium 4-(pyridin-4-yl)benzoate (690 g, 99%) as a solid.

<sup>1</sup>H NMR (400.1 MHz, DMSO-d<sub>6</sub>) δ 7.72 (4H, m), 7.97 (2H, d), 8.62 (2H, d); m/z = 200 [M+H]<sup>+</sup>.

#### **Preparation of methyl 4-(pyridin-4-yl)benzoate**

Thionyl chloride (683 mL, 9358.59 mmol) was added dropwise over 20 minutes to a suspension of sodium 4-(pyridin-4-yl)benzoate (690 g, 3119.53 mmol) in methanol (15 L) at -10°C, keeping the temperature below 15°C. The mixture was stirred for 10 minutes then heated to 65°C for 15 hours. The reaction mixture was cooled to 20°C and the solvent was evaporated. The solid residue was partitioned between ethyl acetate (14 L) and



aqueous saturated sodium bicarbonate solution (14 L). The organic layer was separated and the aqueous layer extracted with ethyl acetate (7 L). The combined organics were washed with water (14 L), saturated brine (7 L) dried over magnesium sulfate, filtered and evaporated to dryness to afford methyl 4-(pyridin-4-yl)benzoate (570 g, 86%) as a solid.

5 <sup>1</sup>H NMR (400.1 MHz, DMSO-d<sub>6</sub>) δ 3.89 (3H, s), 7.78 (2H, d), 7.97 (2H, d), 8.09 (2H, d), 8.69 (2H, d); m/z = 214 [M+H]<sup>+</sup>.

#### **Preparation of methyl 4-(piperidin-4-yl)benzoate**

Methyl 4-(pyridin-4-yl)benzoate (285 g, 1336.57 mmol) and palladium (5% on carbon, 50% wet, JM Type 87L) (57 g, 13.39 mmol) in methanol (2850 mL) were stirred under an atmosphere of hydrogen at 5 bar and 70°C for 15 hours. The catalyst was removed by  
10 filtration and washed with methanol (2850 mL). The solvent was evaporated to dryness to afford methyl 4-(piperidin-4-yl)benzoate (291 g, 99%) as a solid.

<sup>1</sup>H NMR (400.1 MHz, DMSO-d<sub>6</sub>) δ 1.51 (2H, m), 1.68 (2H, m), 2.54 - 2.69 (3H, m), 3.02 (2H, m), 3.84 (3H, s), 7.37 (2H, d), 7.89 (2H, d); m/z = 220 [M+H]<sup>+</sup>.

#### **15 Preparation of methyl 4-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]benzoate**

DIPEA (88 mL, 505.27 mmol) was added to 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (45.0 g, 202.11 mmol) and methyl 4-(piperidin-4-yl)benzoate (48.75 g, 222.32 mmol) in DMA (250 mL). The resulting suspension was  
20 stirred at 100°C for 1 hour then cooled to room temperature. The reaction mixture was added dropwise to water (1500 mL) with stirring. Stirring was continued for 10 minutes then the precipitate was collected by filtration, washed with water (300 mL) and ether (250 mL x 2) and dried to afford methyl 4-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]benzoate (76 g, 93%) as a solid.

25 <sup>1</sup>H NMR (400.1 MHz, DMSO-d<sub>6</sub>) δ 1.63 - 1.83 (2H, m), 1.85 - 2.01 (2H, m), 2.94 - 3.03 (1H, m), 3.08 - 3.18 (2H, m), 3.84 (3H, s), 4.36 - 4.52 (2H, m), 7.44 (2H, d), 7.68 (1H, d), 7.91 (2H, d), 8.27 (1H, d); m/z = 406 [M+H]<sup>+</sup>.

#### **Preparation of 4-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]benzoic acid**

30 Lithium hydroxide monohydrate (9.06 g, 215.94 mmol) was added to methyl 4-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]benzoate (79.58 g, 196.31 mmol) in a mixture of MeOH (800 mL) and water (400 mL). The resulting



suspension was stirred at 65°C for 16 hours. The mixture was cooled to room temperature, the methanol evaporated and the aqueous residues diluted with water (600 mL), filtered then treated with 1M citric acid until precipitation ceased. The precipitate was collected by filtration, washed with water and dried to afford 4-[1-[3-

5 (trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]benzoic acid (77 g, 101%) as a solid.

<sup>1</sup>H NMR (400.1 MHz, DMSO-d<sub>6</sub>) δ 1.67 - 1.79 (2H, m), 1.88 - 1.96 (2H, m), 2.91 - 3.02 (1H, m), 3.07 - 3.18 (2H, m), 4.39 - 4.48 (2H, m), 7.41 (2H, d), 7.68 (1H, d), 7.88 (2H, d), 8.26 (1H, d); m/z = 392 [M+H]<sup>+</sup>.

#### 10 **Example 512.2**

##### **Preparation of crystalline N-(2-methoxyethyl)-N-methyl-4-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]benzamide Anhydrous Form A**

4-methylmorpholine (17.56 mL, 159.70 mmol) was added dropwise to 4-(1-(3-  
15 (trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)piperidin-4-yl)benzoic acid (25 g, 63.88 mmol) and 2-chloro-4,6-dimethoxy-1,3,5-triazine (13.46 g, 76.66 mmol) suspended in DMF (250 mL) cooled to 0°C. The resulting suspension was stirred for 10 minutes then 2-methoxy-N-methylethanamine (5.69 g, 63.88 mmol) was added and the mixture warmed to ambient temperature and stirred for 16 hours. The reaction mixture was concentrated  
20 and diluted with DCM (1 L) and washed with water (500 mL). The aqueous was reextracted with DCM (500 mL) then the combined organics were washed with saturated NaHCO<sub>3</sub> (500 mL) followed by saturated brine (25 mL) then dried over MgSO<sub>4</sub>, filtered and evaporated to afford crude product. This was then titrated in ether, filtered off the solid and dried under vacuum. LCMS shows there to be 2.5% impurity. The crude product  
25 was purified by flash silica chromatography, elution gradient 0 to 5% MeOH in DCM. Pure fractions were evaporated to dryness to afford N-(2-methoxyethyl)-N-methyl-4-(1-(3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)piperidin-4-yl)benzamide anhydrous Form A (23.45 g, 79%) as an off-white solid.

N-(2-methoxyethyl)-N-methyl-4-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-  
30 b]pyridazin-6-yl]piperidin-4-yl]benzamide Anhydrous Form A is characterised by providing an X-ray powder diffraction pattern substantially as shown in Figure 2. The intensity of the peaks at the corresponding 2θ values are shown in Table B below.



N-(2-methoxyethyl)-N-methyl-4-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]benzamide Anhydrous Form A may thus also be characterised by providing at least one of the following 2 $\theta$  values when measured using CuK $\alpha$  radiation: 12.34°, 15.78°, 20.42°, 23.75° and 24.73°.

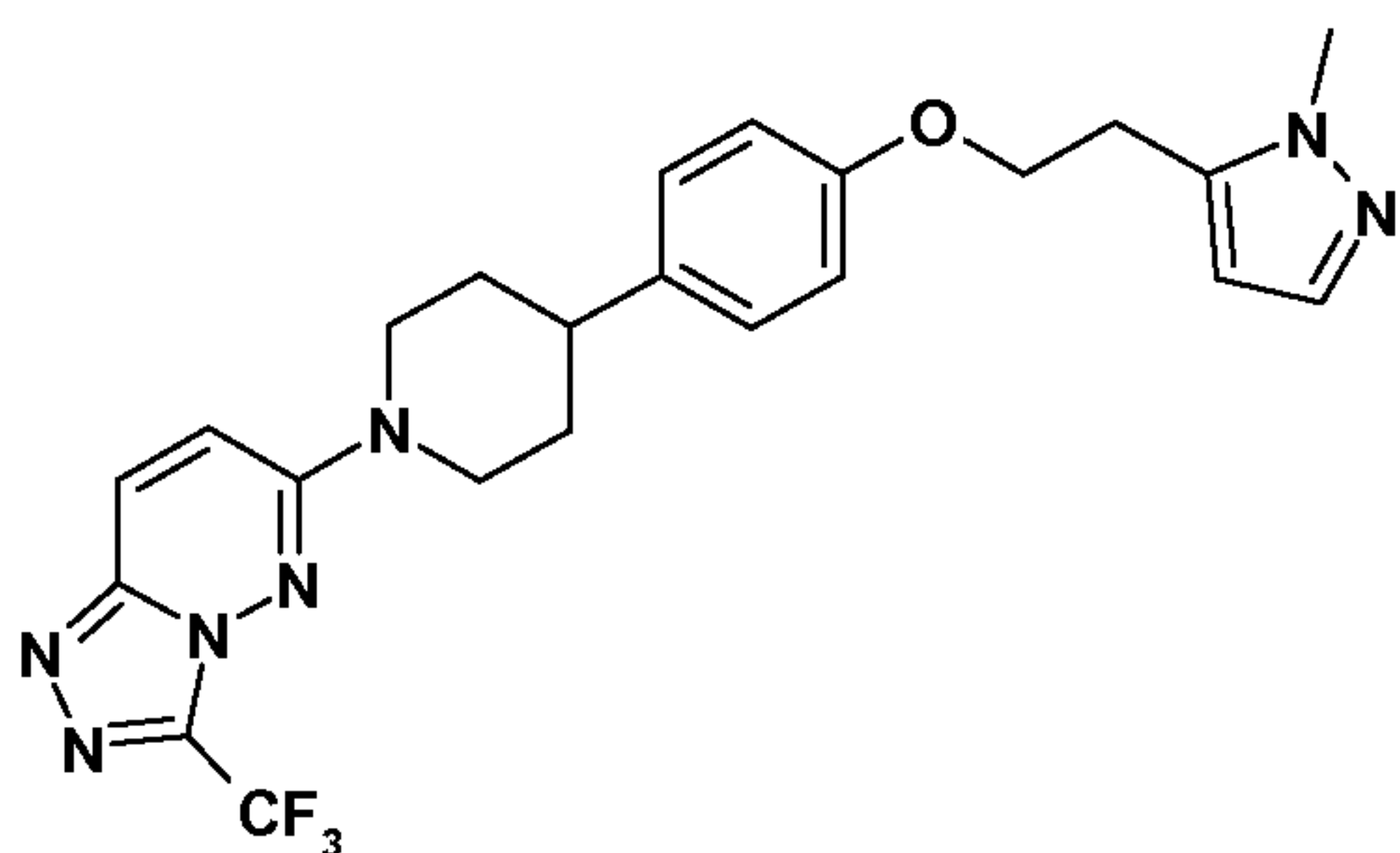
5 Table B

| Angle<br>2-Theta ° (2 $\theta$ ) | Intensity % |
|----------------------------------|-------------|
| 6.283                            | 8.3         |
| 7.922                            | 1.3         |
| 9.65                             | 1.5         |
| 12.341                           | 12.3        |
| 12.689                           | 7.1         |
| 14.92                            | 4.6         |
| 15.78                            | 100         |
| 16.893                           | 1.5         |
| 18.783                           | 4           |
| 19.283                           | 7.9         |
| 20.424                           | 17.7        |
| 20.986                           | 3.3         |
| 21.574                           | 2.7         |
| 22.494                           | 3.9         |
| 23.311                           | 2.6         |
| 23.746                           | 18.8        |

| Angle<br>2-Theta ° (2 $\theta$ ) | Intensity % |
|----------------------------------|-------------|
| 24.339                           | 3.7         |
| 24.728                           | 9.5         |
| 25.375                           | 3.4         |
| 26.93                            | 4.9         |
| 28.138                           | 2.7         |
| 29.08                            | 1.6         |
| 31.16                            | 1.3         |
| 31.855                           | 1.6         |
| 32.496                           | 1.2         |
| 33.141                           | 3.3         |
| 34.793                           | 1.3         |
| 36.343                           | 1.5         |
| 36.782                           | 1.4         |
| 38.01                            | 1.3         |
| 38.637                           | 1.6         |

DSC analysis showed that N-(2-methoxyethyl)-N-methyl-4-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]benzamide Anhydrous Form A has an onset of melting at about 167°C and a peak of melting at about 169°C.



**Example 513****Preparation of 6-[4-[4-[2-(1-methyl-1H-pyrazol-5-yl)ethoxy]phenyl]piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine**

DIAD (78  $\mu$ l, 0.386 mmol) was added dropwise to 4-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]phenol (117 mg, 0.322 mmol), triphenylphosphine (101 mg, 0.386 mmol) and 2-(1-methyl-1H-pyrazol-5-yl)ethanol (obtained as described in PCT Int. Appl. WO 2007017222, Intermediate 1) (49 mg, 0.386 mmol) in THF (2 mL). The resulting mixture was stirred at ambient temperature for 16 hours and then added to a SCX column. The crude product was eluted using 2M ammonia in methanol and the product-containing fractions were evaporated. The product was purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5 $\mu$  silica, 19 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 1% ammonia) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to give 6-[4-[4-[2-(1-methyl-1H-pyrazol-5-yl)ethoxy]phenyl]piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine (79 mg, 52%) as a solid.

<sup>1</sup>H NMR (399.9 MHz, DMSO-d<sub>6</sub>)  $\delta$  1.67 (2H, m), 1.88 (2H, m), 2.77 - 2.84 (3H, m), 3.10 (2H, m), 3.78 (3H, s), 4.05 (2H, t), 4.41 (2H, m), 6.88 (2H, d), 7.18 (2H, d), 7.33 (1H, s), 7.55 (1H, s), 7.66 (1H, d), 8.24 (1H, d); m/z = 472 [M+H]<sup>+</sup>.

The 4-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]phenol used as starting material was prepared as follows:-

DIPEA (5.84 mL, 33.54 mmol) was added to 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (2.99 g, 13.41 mmol) and 4-(piperidin-4-yl)phenol hydrochloride (CAS 263139-27-1, 3.01 g, 14.08 mmol) in DMF (30 mL). The resulting solution was stirred at 80°C for 1 hour. The mixture was cooled to room temperature, evaporated to dryness and re-dissolved in DCM (200 mL). The solution was washed with



water (200 mL) and saturated brine (200 mL), dried over MgSO<sub>4</sub> and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 50 to 70% ethyl acetate in isohexane. Pure fractions were evaporated to dryness to afford 4-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-

5 yl]phenol (4.47 g, 92%) as a solid.

<sup>1</sup>H NMR (399.9 MHz, DMSO-d<sub>6</sub>) δ 1.63 (2H, m), 1.86 (2H, m), 2.74 (1H, m), 3.08 (2H, m), 4.40 (2H, m), 6.69 (2H, d), 7.05 (2H, d), 7.66 (1H, d), 8.25 (1H, d), 9.19 (1H, s); m/z = 364 [M+H]<sup>+</sup>.

### **Example 513.1**

#### **10 Large scale preparation of 6-[4-[4-[2-(1-methyl-1H-pyrazol-5-yl)ethoxy]phenyl]piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine**

DIAD (19.73 mL, 100.18 mmol) was added dropwise to 4-[1-[3-

(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]phenol (28 g, 77.06 mmol), 2-(1-methyl-1H-pyrazol-5-yl)ethanol (14.53 g, 100.18 mmol) and

15 triphenylphosphine (26.3 g, 100.18 mmol) in THF (250 mL). The resulting solution was stirred at ambient temperature for 3 days. The reaction mixture was evaporated to dryness and re-dissolved in DCM (1 L), and the solution was washed sequentially with 2M NaOH (300 mL x 2) and saturated brine (250 mL). The organic layer was dried over MgSO<sub>4</sub>, filtered and evaporated to afford crude product. The crude product was purified by flash

20 silica chromatography, eluting with 75% EtOAc in isohexane followed by a gradient of 0 to 3% MeOH in DCM. Fractions containing the desired product were evaporated to dryness then re-dissolved in DCM (500 mL) and the solution washed with 2M NaOH (300 mL x 2) followed by brine (250 mL), then dried over MgSO<sub>4</sub>, filtered and evaporated.

The residue was further purified by flash silica chromatography, elution gradient 80 to

25 100% EtOAc in isohexane. Pure fractions were evaporated to dryness to afford 6-[4-[4-[2-(1-methyl-1H-pyrazol-5-yl)ethoxy]phenyl]piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine (18.21 g, 50.1%) as a solid.

<sup>1</sup>H NMR (399.9 MHz, DMSO-d<sub>6</sub>) δ 1.67 (2H, m), 1.88 (2H, m), 2.81 (1H, m), 3.07 - 3.14 (4H, m), 3.79 (3H, s), 4.18 (2H, t), 4.41 (2H, m), 6.14 (1H, d), 6.89 (2H, d), 7.19 (2H, d),

30 7.30 (1H, d), 7.66 (1H, d), 8.24 (1H, d); m/z = 472 [M+H]<sup>+</sup>.

The 2-(1-methyl-1H-pyrazol-5-yl)ethanol used as starting material was prepared as follows:-



n-Butyl lithium (1.6M in hexanes) (1226 mL, 1961.78 mmol) was added dropwise to 1-methyl-1H-pyrazole (153.4 g, 1868.37 mmol) in THF (3000 mL) cooled to  $-78^{\circ}\text{C}$  over a period of 1 hour under nitrogen. The resulting solution was stirred at  $-60^{\circ}\text{C}$  for 30 minutes, then warmed to  $-10^{\circ}\text{C}$  and stirred for a further 40 minutes. A solution of oxirane (210 mL, 4203.82 mmol) in THF (600 mL) was added slowly at  $-10^{\circ}\text{C}$  followed by further THF (1000 mL) and the resulting slurry was stirred at  $-10^{\circ}\text{C}$  for 30 minutes, then at  $0^{\circ}\text{C}$  for 30 minutes. The mixture was then allowed to gradually warm to room temp under nitrogen and stirred for 16 hours. The reaction mixture was quenched with saturated  $\text{NH}_4\text{Cl}$  solution (2000 ml), the layers separated and the aqueous phase extracted with n-butanol (3 x 1000 ml). The combined organics were washed with saturated brine (1500 ml), dried over  $\text{MgSO}_4$ , filtered and evaporated to give an oil, which was azeotroped with toluene (1000 ml) to leave an oil with some solid. The oil was dissolved in DCM and the insoluble solid was filtered off and washed with DCM. The filtrate was purified by chromatography using a silica Novasep prep HPLC column, eluting with a gradient of 5-10% methanol in DCM. Pure fractions were evaporated to dryness to afford 2-(1-methyl-1H-pyrazol-5-yl)ethanol (195 g, 83%) as an oil.

$^1\text{H}$  NMR (400.1 MHz,  $\text{DMSO}-d_6$ )  $\delta$  2.77 (2H, t), 3.63 (2H, m), 3.74 (3H, s), 4.74 (1H, t), 6.04 (1H, m), 7.26 (1H, d).

The 4-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]phenol used as starting material was prepared as follows:-

**Preparation of benzyl 4-(trifluoromethylsulfonyloxy)-5,6-dihydropyridine-1(2H)-carboxylate**

A solution of benzyl 4-oxopiperidine-1-carboxylate (88.57 g, 379.70 mmol) in THF (300 mL) was added dropwise to lithium bis(trimethylsilyl)amide (1M in THF) (418 mL, 417.67 mmol) at  $-78^{\circ}\text{C}$ , over a period of 1 hour under nitrogen. The resulting mixture was stirred at  $-78^{\circ}\text{C}$  for 90 minutes then a solution of 1,1,1-trifluoro-N-phenyl-N-(trifluoromethylsulfonyl)methanesulfonamide (142 g, 398.68 mmol) in THF (600 mL) was added dropwise over a period of 1 hour. The resulting mixture was stirred at  $-78^{\circ}\text{C}$  for 30 minutes, then allowed to warm to room temperature and stirred for 16 hours. The reaction mixture was quenched with 2M NaOH (450 mL). The layers were separated and the organic layer was washed with 2M NaOH (360 mL). The solvent was evaporated, then the residue was re-dissolved in diethyl ether (1500 mL) and the solution washed with water



(500 mL). The organic layer was dried over  $\text{MgSO}_4$ , filtered and evaporated to afford benzyl 4-(trifluoromethylsulfonyloxy)-5,6-dihydropyridine-1(2H)-carboxylate (124 g, 81%) as an oil.

$^1\text{H}$  NMR (399.9 MHz,  $\text{DMSO-d}_6$ )  $\delta$  2.43 (2H, m), 3.62 (2H, m), 4.06 (2H, m), 5.10 (2H, s), 6.02 (1H, m), 7.34 (5H, m).

#### **Preparation of benzyl 4-(4-hydroxyphenyl)-5,6-dihydropyridine-1(2H)-carboxylate**

Sodium carbonate (96 g, 909.79 mmol) was added to benzyl 4-

(trifluoromethylsulfonyloxy)-5,6-dihydropyridine-1(2H)-carboxylate (123.1 g, 303.26 mmol) and 4-hydroxyphenylboronic acid (46.0 g, 333.59 mmol) in a mixture of dioxane (1000 mL) and water (250 mL). The resulting mixture was bubbled with nitrogen for 10

minutes then 1,1'-bis(diphenylphosphino)ferrocenedichloropalladium(II) (5.49 g, 7.58 mmol) was added and the reaction mixture was heated at  $80^\circ\text{C}$  for 1 hour, then cooled to room temperature. The reaction mixture was diluted with DCM (2 L) and washed with water (2 L). The aqueous washing was re-extracted with DCM (1 L), then the combined

organics were washed with saturated brine (500 mL), dried over  $\text{MgSO}_4$ , filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 10 to 30% EtOAc in isohexane. Fractions containing the desired product were evaporated to dryness then triturated with isohexane, filtered and dried to afford benzyl 4-(4-hydroxyphenyl)-5,6-dihydropyridine-1(2H)-carboxylate (62.3 g, 66.4%) as a solid.

$^1\text{H}$  NMR (399.9 MHz,  $\text{DMSO-d}_6$ )  $\delta$  2.44 (2H, m), 3.61 (2H, m), 4.05 (2H, m), 5.12 (2H, s), 5.99 (1H, m), 6.73 (2H, d), 7.26 (2H, d), 7.32 - 7.40 (5H, m), 9.45 (1H, s);  $m/z = 310$   $[\text{M}+\text{H}]^+$ .

#### **Preparation of 4-(piperidin-4-yl)phenol**

Benzyl 4-(4-hydroxyphenyl)-5,6-dihydropyridine-1(2H)-carboxylate (37.7 g, 121.86 mmol) and 5% palladium on carbon (7.6 g, 3.57 mmol) in methanol (380 mL) were stirred under an atmosphere of hydrogen at 5 bar and  $25^\circ\text{C}$  for 2 hours. The catalyst was removed by filtration, washed with MeOH and the solvents evaporated. The crude material was triturated with diethyl ether, then the desired product collected by filtration and dried under vacuum to afford 4-(piperidin-4-yl)phenol (20.36 g, 94%) as a solid.

$^1\text{H}$  NMR (399.9 MHz,  $\text{DMSO-d}_6$ )  $\delta$  1.46 (2H, m), 1.65 (2H, m), 2.45 (1H, m), 2.58 (2H, m), 3.02 (2H, m), 6.68 (2H, d), 7.00 (2H, d), 9.15 (1H, s);  $m/z = 178$   $[\text{M}+\text{H}]^+$ .



**Preparation of 4-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]phenol**

DIPEA (48.2 mL, 276.86 mmol) was added to 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (24.65 g, 110.74 mmol) and 4-(piperidin-4-yl)phenol (20.61 g, 116.28 mmol) in DMF (200 mL). The resulting solution was stirred at 80°C for 1 hour. The reaction mixture was cooled to room temperature, then evaporated to dryness and re-dissolved in DCM (1 L) and washed with water (2 x 1 L). The organic layer was washed with saturated brine (500 mL), then dried over MgSO<sub>4</sub>, filtered and evaporated to afford crude product. The crude product was triturated with ether to afford 4-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]phenol (36.6 g, 91%) as a solid.

<sup>1</sup>H NMR (399.9 MHz, DMSO-d<sub>6</sub>) δ 1.64 (2H, m), 1.87 (2H, m), 2.75 (1H, m), 3.09 (2H, m), 4.40 (2H, m), 6.69 (2H, d), 7.05 (2H, d), 7.65 (1H, d), 8.24 (1H, d), 9.15 (1H, s); m/z = 364 [M+H]<sup>+</sup>.

**Example 513.2**

**Preparation of crystalline 6-[4-[4-[2-(1-methyl-1H-pyrazol-5-yl)ethoxy]phenyl]piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine Anhydrous Form A**

DIAD (3.70 mL, 18.77 mmol) was added to 4-(1-(3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl)piperidin-4-yl)phenol (6.2 g, 17.06 mmol), 2-(1-methyl-1H-pyrazol-5-yl)ethanol (2.368 g, 18.77 mmol) and triphenylphosphine (4.92 g, 18.77 mmol) in THF (150 mL) under nitrogen. The resulting solution was stirred at ambient temperature for 1 day. The crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 2M NH<sub>3</sub>/MeOH and pure fractions were evaporated to dryness to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 5% MeOH in DCM. Pure fractions were evaporated to dryness to afford crude product. Product was dissolved in DCM (100 mL) and washed with 2M NaOH (100 mL) twice. Organic layer was evaporated to afford 6-(4-(4-(2-(1-methyl-1H-pyrazol-5-yl)ethoxy)phenyl)piperidin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine anhydrous Form A (4.95 g, 61.5 %) as a white solid.

6-[4-[4-[2-(1-Methyl-1H-pyrazol-5-yl)ethoxy]phenyl]piperidin-1-yl]-3-



(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine Anhydrous Form A is characterised by providing an X-ray powder diffraction pattern substantially as shown in Figure 3. The intensity of the peaks at the corresponding  $2\theta$  values are shown in Table C below.

- 6-[4-[4-[2-(1-Methyl-1H-pyrazol-5-yl)ethoxy]phenyl]piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine Anhydrous Form A may thus also be characterised by providing at least one of the following  $2\theta$  values when measured using CuK $\alpha$  radiation: 4.90°, 13.47°, 15.93°, 16.64° and 22.83°.

Table C

| Angle<br>2-Theta ° (2 $\theta$ ) | Intensity % |
|----------------------------------|-------------|
| 4.898                            | 100         |
| 9.784                            | 8           |
| 11.503                           | 17.1        |
| 11.942                           | 2.7         |
| 12.966                           | 4           |
| 13.473                           | 24          |
| 14.719                           | 13.8        |
| 15.934                           | 26.6        |
| 16.642                           | 33.4        |
| 17.359                           | 6.5         |
| 18.322                           | 1.8         |
| 18.669                           | 6.5         |
| 19.195                           | 22.1        |
| 19.666                           | 4.9         |
| 20.257                           | 2.8         |
| 20.581                           | 11          |
| 20.866                           | 2.2         |
| 21.334                           | 3.4         |
| 21.641                           | 2.4         |
| 22.834                           | 24          |
| 23.7                             | 3.1         |

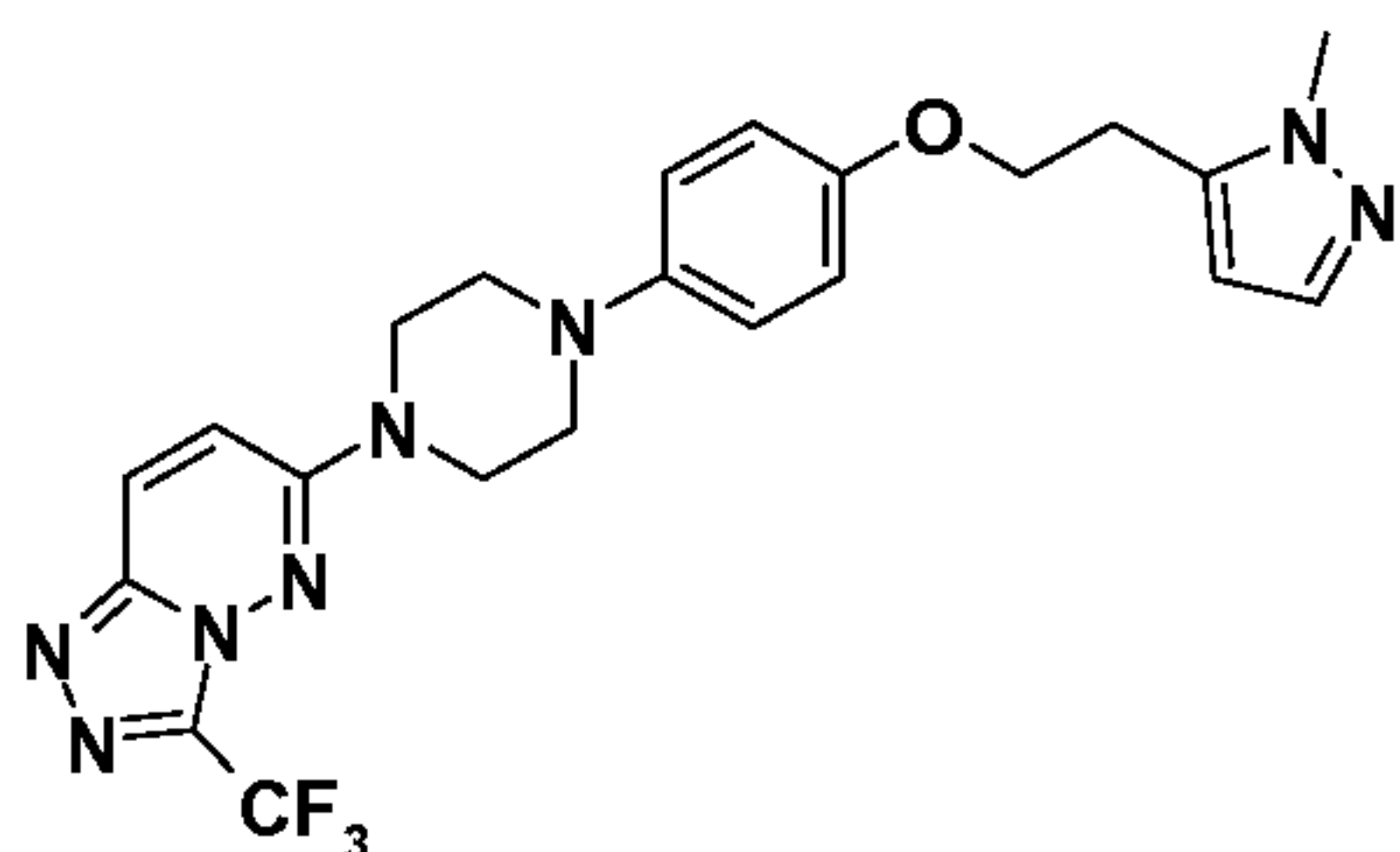
| Angle<br>2-Theta ° (2 $\theta$ ) | Intensity % |
|----------------------------------|-------------|
| 24                               | 13.5        |
| 24.396                           | 14.8        |
| 25.985                           | 6.4         |
| 26.752                           | 6.5         |
| 27.146                           | 6.5         |
| 28.104                           | 1.8         |
| 28.545                           | 2.7         |
| 29.016                           | 2           |
| 29.461                           | 8.7         |
| 29.737                           | 5.8         |
| 30.121                           | 4.7         |
| 30.654                           | 3           |
| 31.371                           | 1.3         |
| 31.853                           | 1.8         |
| 33.656                           | 3.4         |
| 34.28                            | 1.4         |
| 35.851                           | 2.2         |
| 36.424                           | 2.3         |
| 37.617                           | 1.8         |
| 38.531                           | 1.3         |



DSC analysis showed that 6-[4-[4-[2-(1-methyl-1H-pyrazol-5-yl)ethoxy]phenyl]piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine Anhydrous Form A has an onset of melting at about 159°C and a peak of melting at about 162°C.

5 **Example 514**

**Preparation of 6-[4-[4-[2-(1-methyl-1H-pyrazol-5-yl)ethoxy]phenyl]piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine**



DIAD (0.162 mL, 0.82 mmol) was added to 4-[4-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]phenol (250 mg, 0.69 mmol), 2-(1-methyl-1H-pyrazol-5-yl)ethanol (obtained as described in PCT Int. Appl. WO 2007017222, Intermediate 1) (130 mg, 1.03 mmol) and triphenylphosphine (270 mg, 1.03 mmol) in THF (5 mL). The resulting solution was stirred at ambient temperature for 18 hours then added to a SCX column. The crude product was eluted using 2M ammonia in methanol and the product-containing fractions were evaporated. The product was purified by flash silica chromatography, elution gradient 0 to 3% methanol in DCM. Pure fractions were evaporated to dryness to afford 6-[4-[4-[2-(1-methyl-1H-pyrazol-5-yl)ethoxy]phenyl]piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine (111 mg, 34%) as a solid.

1H NMR (399.9 MHz, DMSO-d<sub>6</sub>) δ 2.81 (2H, t), 3.17 (4H, m), 3.75 (4H, m), 3.78 (3H, s), 4.02 (2H, t), 6.87 (2H, d), 6.96 (2H, d), 7.33 (1H, s), 7.56 (1H, s), 7.69 (1H, d), 8.30 (1H, d); m/z = 473 [M+H]<sup>+</sup>.

The 4-[4-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]phenol used as starting material was prepared as follows:-

25 DIPEA (12.15 mL, 69.78 mmol) was added to 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (10.35 g, 46.52 mmol) and 1-(4-hydroxyphenyl)piperazine (CAS 56621-48-8, 9.12 g, 51.17 mmol) in DMF (80 mL). The resulting solution was stirred at 80°C for 1 hour. The reaction mixture was cooled to room temperature,



evaporated to dryness and the residue re-dissolved in DCM (250 mL). The solution was washed with water (200 mL), dried over MgSO<sub>4</sub> and evaporated to afford crude product, which was triturated with diethyl ether. The resulting solid was collected by filtration and dried under vacuum to give 4-[4-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]phenol (14.27 g, 84%) as a solid.

<sup>1</sup>H NMR (399.9 MHz, DMSO-d<sub>6</sub>) δ 3.12 (4H, m), 3.75 (4H, m), 6.69 (2H, d), 6.87 (2H, d), 7.67 (1H, d), 8.28 (1H, d), 8.87 (1H, s); m/z = 365 [M+H]<sup>+</sup>.

### **Example 514.1**

#### **Large scale preparation of 6-[4-[4-[2-(1-methyl-1H-pyrazol-5-**

#### **yl)ethoxy]phenyl]piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine**

DIAD (20.73 mL, 105.27 mmol) was added dropwise to 4-[4-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]phenol (32.0 g, 87.72 mmol), 2-(1-methyl-1H-pyrazol-5-yl)ethanol (prepared as described in Example 513, preparation of starting materials) (16.6 g, 131.58 mmol) and triphenylphosphine (34.5 g, 131.58 mmol) in THF (320 mL) at 0°C under nitrogen. The resulting solution was stirred at ambient temperature for 3 days. The reaction mixture was evaporated to dryness and re-dissolved in DCM (700 mL), and the solution was washed sequentially with 2M NaOH (200 mL x 2) and saturated brine (200 mL). The organic layer was dried over MgSO<sub>4</sub>, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, eluting with a gradient of 80 to 100% EtOAc in isohexane followed by EtOAc, then a gradient of 0 to 3% MeOH in DCM. Pure fractions were evaporated to dryness to afford 6-[4-[4-[2-(1-methyl-1H-pyrazol-5-yl)ethoxy]phenyl]piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine (28.7 g, 69.3%) as a solid.

<sup>1</sup>H NMR (399.9 MHz, DMSO-d<sub>6</sub>) δ 3.07 (2H, t), 3.18 (4H, m), 3.76 (4H, m), 3.79 (3H, s), 4.15 (2H, t), 6.14 (1H, d), 6.88 (2H, d), 6.97 (2H, d), 7.30 (1H, d), 7.67 (1H, d), 8.28 (1H, d); m/z = 473 [M+H]<sup>+</sup>.

The 4-[4-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]phenol used as starting material was prepared as follows:-

DIPEA (52.4 mL, 300.84 mmol) was added to 6-chloro-3-(trifluoromethyl)-

[1,2,4]triazolo[4,3-b]pyridazine (44.6 g, 200.56 mmol) and 1-(4-hydroxyphenyl)piperazine (39.32 g, 220.61 mmol) in DMF (450 mL). The resulting solution was stirred at 80°C for 2 hours. The reaction mixture was cooled to room temperature, then evaporated to dryness



and partitioned between DCM (2 L) and water (1 L) containing methanol (250 mL) to aid solubility. The insoluble material was collected by filtration, washed with methanol and dried to give the desired product. The organic filtrate was separated from the aqueous, then washed with saturated brine (500 mL), dried over  $\text{MgSO}_4$  and evaporated to a brown gum. This was triturated with ether, the resulting solid was collected by filtration, washed with DCM followed by methanol, combined with the previous precipitate and dried to afford 4-[4-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]phenol (63.8 g, 87%) as a solid.

$^1\text{H}$  NMR (399.9 MHz,  $\text{DMSO-d}_6$ )  $\delta$  3.12 (4H, m), 3.75 (4H, m), 6.69 (2H, d), 6.87 (2H, d), 7.67 (1H, d), 8.28 (1H, d), 8.87 (1H, s);  $m/z$  = 365  $[\text{M}+\text{H}]^+$ .

#### **Example 514.2**

#### **Preparation of crystalline 6-[4-[4-[2-(1-methyl-1H-pyrazol-5-yl)ethoxy]phenyl]piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine Anhydrous Form A**

DIAD (7.78 mL, 39.53 mmol) was added dropwise to 4-(4-(3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)piperazin-1-yl)phenol (12 g, 32.94 mmol), 2-(1-methyl-1H-pyrazol-5-yl)ethanol (6.23 g, 49.41 mmol) and triphenylphosphine (12.96 g, 49.41 mmol) in THF (250 mL). The resulting solution was stirred at ambient temperature for 18 hours then split and added to a series of SCX columns (6). The crude product was eluted from the columns using 2M  $\text{NH}_3/\text{MeOH}$  and the solvents evaporated. The crude product was diluted with DCM (200 mL) and washed with 2M NaOH (200 mL x 2). The organic layer was dried over  $\text{MgSO}_4$ , filtered and evaporated then purified by flash silica chromatography, elution gradient 0 to 3% MeOH in DCM. Pure fractions were evaporated to dryness giving a yellow solid, which was triturated with ether then dried to afford 6-(4-(4-(2-(1-methyl-1H-pyrazol-5-yl)ethoxy)phenyl)piperazin-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine anhydrous Form A (9.18g, 59.0 %) as a cream solid.

6-[4-[4-[2-(1-Methyl-1H-pyrazol-5-yl)ethoxy]phenyl]piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine Anhydrous Form A is characterised by providing an X-ray powder diffraction pattern substantially as shown in Figure 4. The intensity of the peaks at the corresponding  $2\theta$  values are shown in Table D below.

6-[4-[4-[2-(1-Methyl-1H-pyrazol-5-yl)ethoxy]phenyl]piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine Anhydrous Form A may thus also be



characterised by providing at least one of the following 2 $\theta$  values when measured using CuK $\alpha$  radiation: 6.90°, 15.38°, 21.55°, 24.48° and 27.56°.

Table D

| Angle<br>2-Theta ° (2 $\theta$ ) | Intensity % |
|----------------------------------|-------------|
| 6.903                            | 23.4        |
| 9.6                              | 8.6         |
| 10.776                           | 11.2        |
| 12.818                           | 13.3        |
| 13.162                           | 3.3         |
| 13.845                           | 10          |
| 14.436                           | 3.1         |
| 15.376                           | 19.2        |
| 16.436                           | 11          |
| 17.457                           | 4.1         |
| 18.247                           | 3.6         |
| 18.916                           | 14.9        |
| 19.266                           | 3.4         |
| 20.182                           | 3           |
| 21.03                            | 4.3         |
| 21.545                           | 100         |
| 22.36                            | 12.4        |
| 22.625                           | 3.3         |
| 23.552                           | 5.6         |
| 23.76                            | 4.7         |

| Angle<br>2-Theta ° (2 $\theta$ ) | Intensity % |
|----------------------------------|-------------|
| 24.479                           | 40.9        |
| 25.2                             | 2.2         |
| 25.755                           | 7.2         |
| 26.465                           | 2.7         |
| 27.561                           | 17.1        |
| 27.833                           | 11.8        |
| 28.206                           | 6.2         |
| 29.098                           | 2.1         |
| 29.928                           | 2.1         |
| 30.587                           | 1.6         |
| 31.201                           | 4.8         |
| 32.489                           | 1.8         |
| 33.326                           | 1.8         |
| 34.042                           | 2.3         |
| 34.618                           | 3           |
| 36.18                            | 1.7         |
| 36.538                           | 1.7         |
| 37.448                           | 1.3         |
| 38.17                            | 1.5         |
| 39.324                           | 2.4         |

5 DSC analysis showed that 6-[4-[4-[2-(1-methyl-1H-pyrazol-5-yl)ethoxy]phenyl]piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine Anhydrous Form A has an onset of melting at about 178°C and a peak of melting at about 179°C.



**Example 514.3****Preparation of 6-[4-[4-[2-(1-methyl-1H-pyrazol-5-yl)ethoxy]phenyl]piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine fumarate**

3ml of acetone was added to 50mg of 6-[4-[4-[2-(1-methyl-1H-pyrazol-5-yl)ethoxy]phenyl]piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine and heated to form a solution. 12.3mg of fumaric acid was dissolved in 3ml of acetone. The compound solution was added to the counter-ion solution and the resultant mixture shaken with heat. The solution was dried under air and once the volume had dramatically reduced, solid 6-[4-[4-[2-(1-methyl-1H-pyrazol-5-yl)ethoxy]phenyl]piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine fumarate precipitated out.

6-[4-[4-[2-(1-Methyl-1H-pyrazol-5-yl)ethoxy]phenyl]piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine fumarate is characterised by providing an X-ray powder diffraction pattern substantially as shown in Figure 5. The intensity of the peaks at the corresponding 2 $\theta$  values are shown in Table E below.

6-[4-[4-[2-(1-Methyl-1H-pyrazol-5-yl)ethoxy]phenyl]piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine fumarate may thus also be characterised by providing at least one of the following 2 $\theta$  values when measured using CuK $\alpha$  radiation: 11.72°, 16.46°, 17.58° and 21.89°.

**Table E**

| Angle<br>2-Theta ° (2 $\theta$ ) | Intensity % |
|----------------------------------|-------------|
| 4.514                            | 20.3        |
| 5.897                            | 14.2        |
| 11.724                           | 56.6        |
| 12.215                           | 12.3        |
| 13.225                           | 6.9         |
| 16.464                           | 73.5        |
| 17.582                           | 61.3        |
| 19.738                           | 17.4        |
| 20.261                           | 15          |

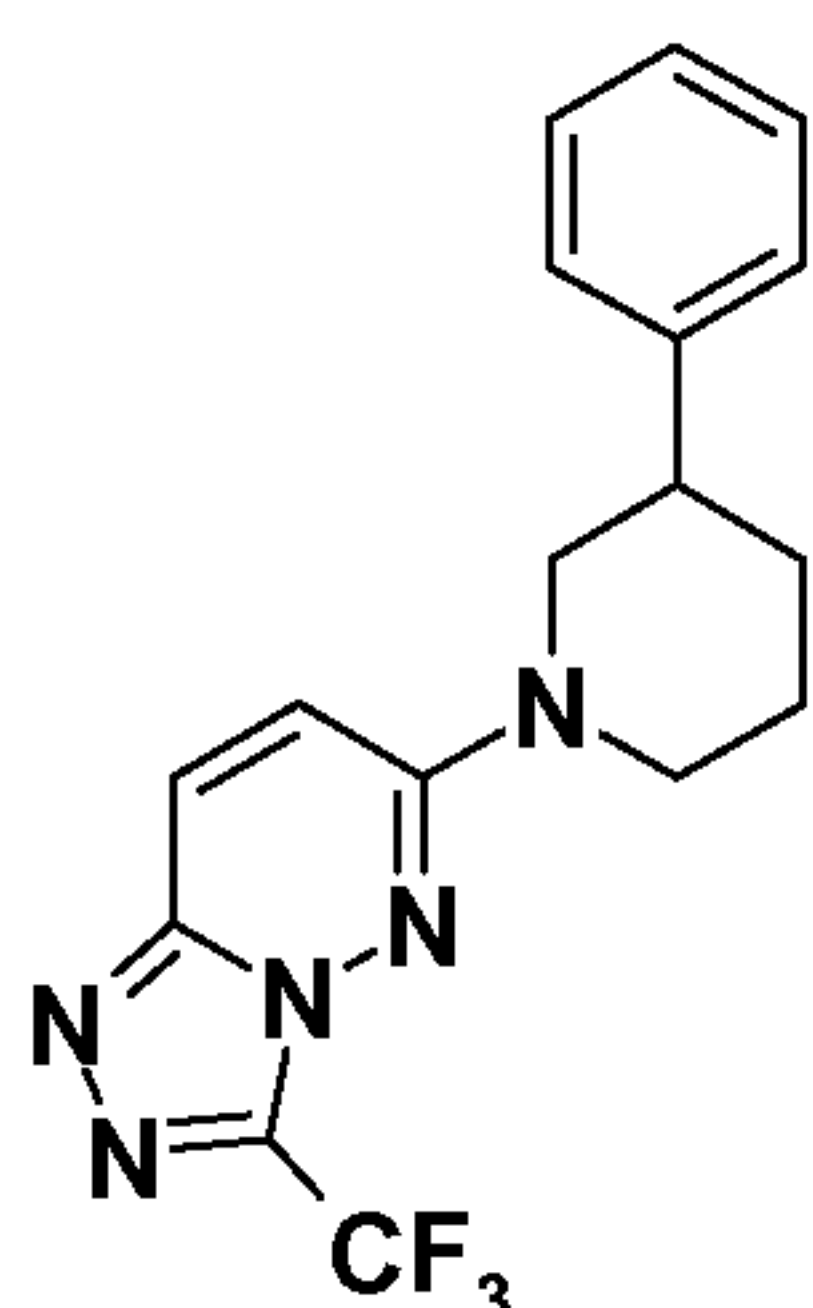
| Angle<br>2-Theta ° (2 $\theta$ ) | Intensity % |
|----------------------------------|-------------|
| 21.18                            | 21.1        |
| 21.894                           | 100         |
| 23.863                           | 13          |
| 24.174                           | 12.7        |
| 25.826                           | 8.6         |
| 26.752                           | 8.8         |
| 28.776                           | 7.8         |
| 30.541                           | 18.9        |
| 31.509                           | 8.1         |



DSC analysis showed that 6-[4-[4-[2-(1-methyl-1H-pyrazol-5-yl)ethoxy]phenyl]piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine fumarate has a melting endotherm with onset at about 153°C and a peak at about 155°C (this is followed by a recrystallisation event and subsequent melt).

5 **Example 515**

**Preparation of 6-(3-phenylpiperidin-1-yl)-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine**

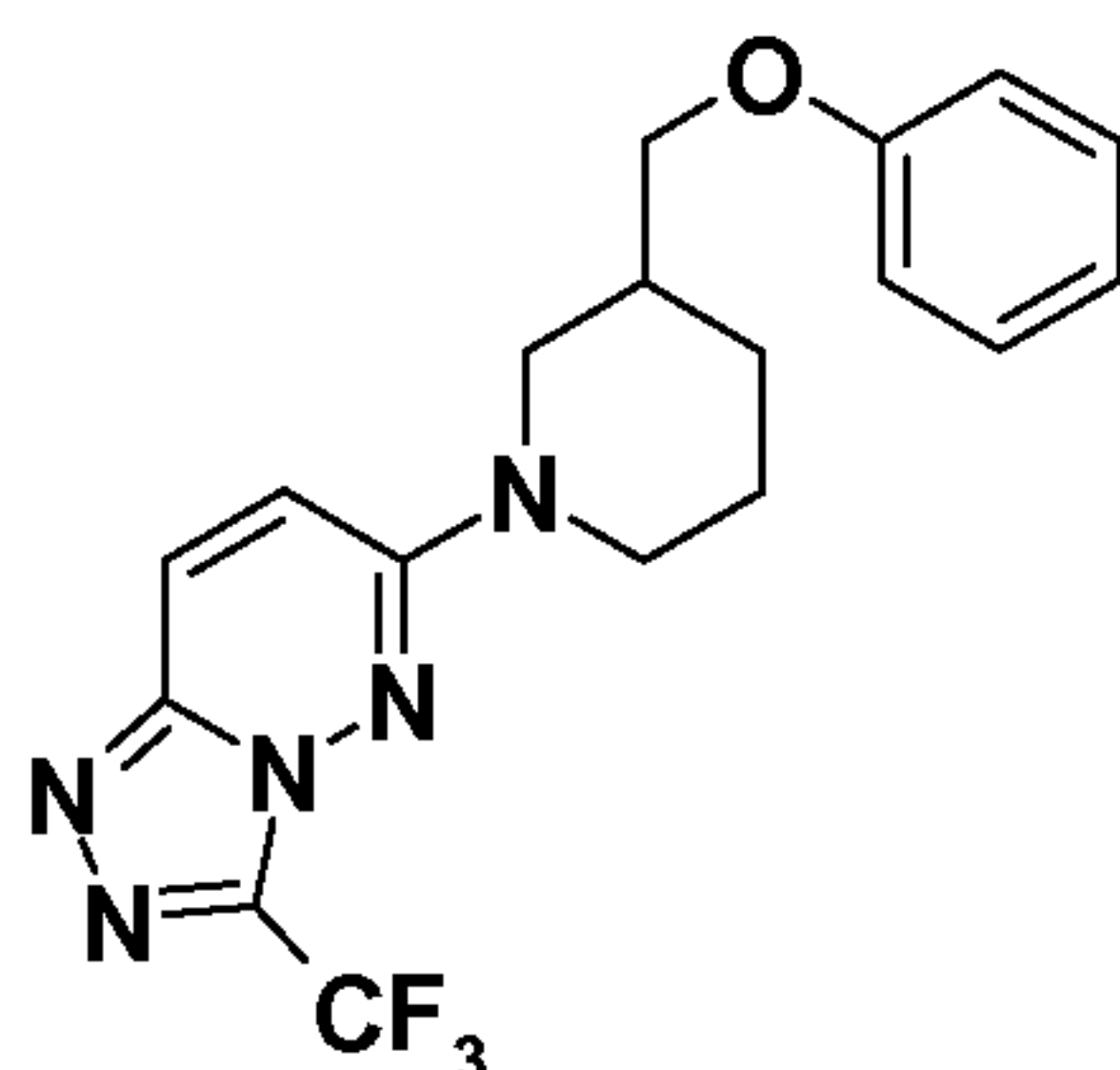


A solution of 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (49 mg, 0.22 mmol) in EtOH (1.0 mL) was added to a mixture of 3-phenylpiperidine (53 mg, 0.33 mmol) and DIPEA (57  $\mu$ L, 0.33 mmol) in EtOH (1.0 mL). The reaction mixture was heated to 70°C overnight and the crude product was purified by preparative LCMS (Waters XBridge Prep C18 OBD column, 5 $\mu$  silica, 19 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 5% ammonia) and MeCN as eluents.

15 Fractions containing the desired compound were evaporated to dryness to give 6-(3-phenylpiperidin-1-yl)-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine (46 mg, 61%).

<sup>1</sup>H NMR (700.03 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  1.62 - 1.68 (1H, m), 1.82 - 1.88 (2H, m), 1.96 - 1.98 (1H, m), 2.83 - 2.87 (1H, m), 3.10 - 3.15 (1H, m), 4.30 - 4.36 (3H, m), 7.25 - 7.28 (1H, m), 7.33 - 7.38 (4H, m), 7.68 (1H, d), 8.23 (1H, d); *m/z* = 348 [M+H]<sup>+</sup>.



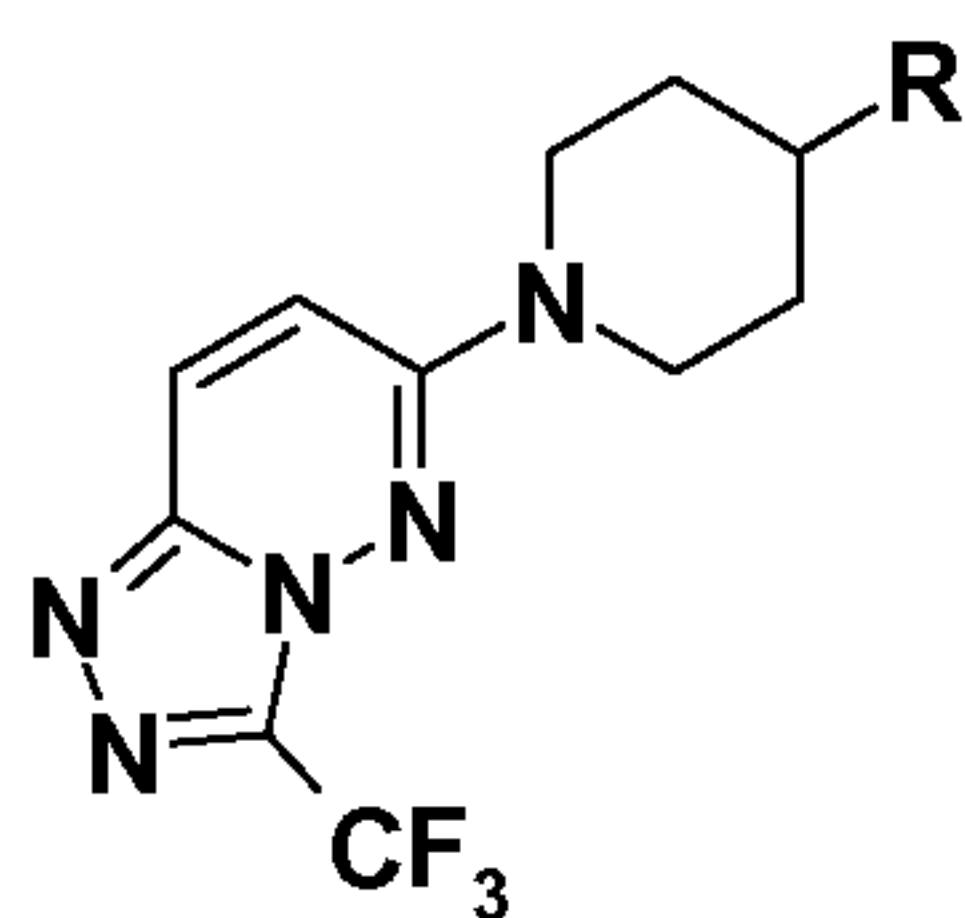
**Example 516****Preparation of 6-[3-(phoxymethyl)piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine**

5 Obtained in 60% yield by an analogous method to Example 515, starting from 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine and 3-(phoxymethyl)piperidine.

<sup>1</sup>H NMR (700.03 MHz, DMSO-d<sub>6</sub>) δ 1.45 - 1.50 (1H, m), 1.56 - 1.61 (1H, m), 1.79 - 1.82 (1H, m), 1.90 - 1.92 (1H, m), 2.08 - 2.11 (1H, m), 3.07 (1H, dd), 3.16 - 3.20 (1H, m), 3.91 (1H, dd), 3.96 (1H, dd), 4.10 - 4.13 (1H, m), 4.31 (1H, dd), 6.93 - 6.97 (3H, m), 7.28 - 7.31 (2H, m), 7.60 (1H, d), 8.21 (1H, d); m/z = 378 [M+H]<sup>+</sup>.

**Examples 517-518**

The following compounds were prepared in 45-46% yield by an analogous method to Example 515, starting from 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine and the appropriate 4-substituted piperidine:-



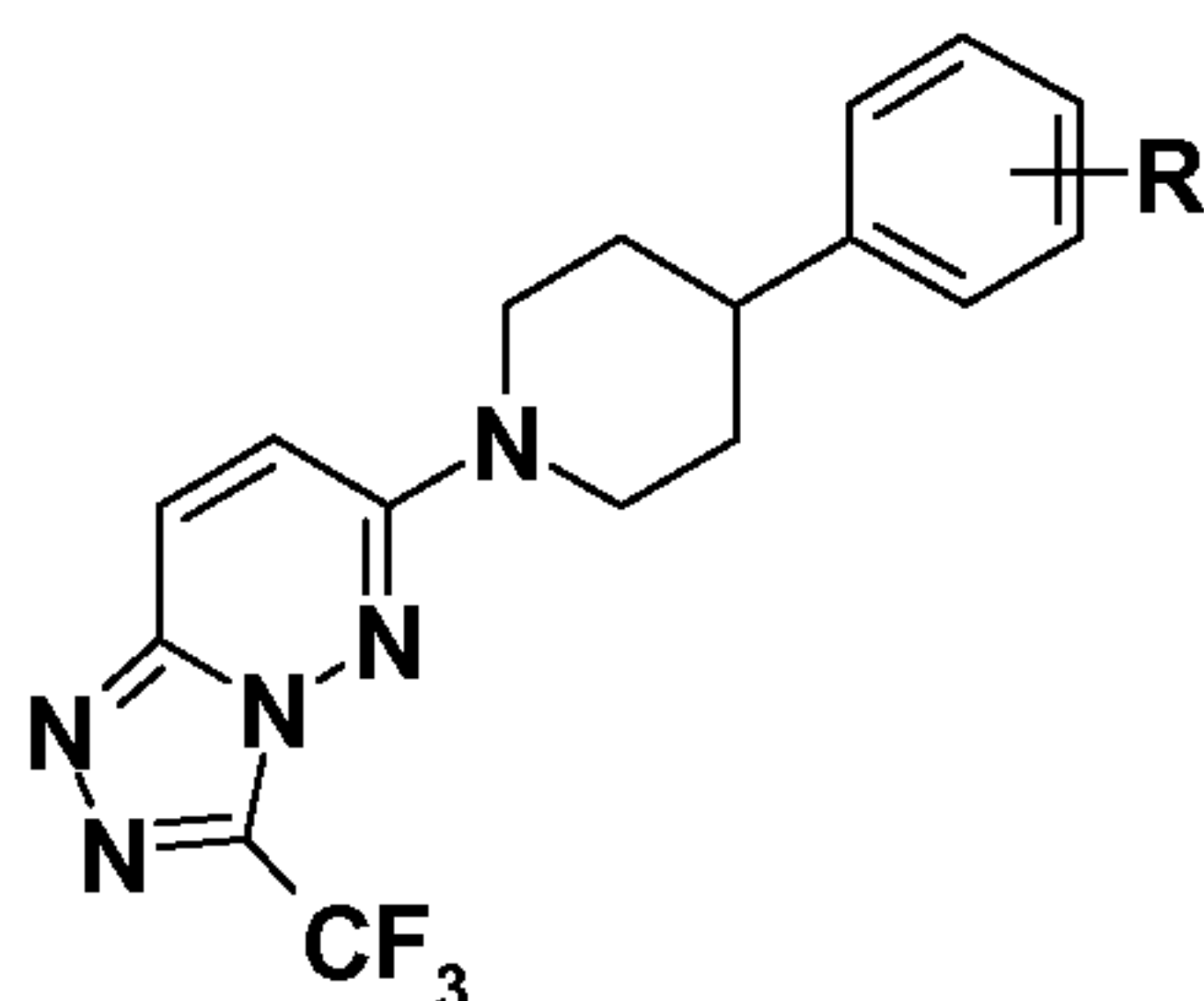
| Ex. | R            | <sup>1</sup> H NMR (700.03 MHz, DMSO-d <sub>6</sub> )                                                                                                                       | m/z<br>[M+H] <sup>+</sup> |
|-----|--------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|
| 517 | ethoxymethyl | δ 1.11 (3H, t), 1.21 - 1.27 (2H, m), 1.79 (2H, d), 1.85 - 1.88 (1H, m), 3.00 - 3.04 (2H, m), 3.42 (2H, q), 4.27 (2H, d), 7.60 (1H, d), 8.21 (1H, d), (2H obscured by water) | 330                       |
| 518 | propoxy      | δ 0.89 (3H, t), 1.50 - 1.56 (4H, m), 1.91 - 1.95 (2H, m), 3.36 - 3.40 (1H, m), 3.41 (2H, t), 3.55 - 3.59 (1H, m), 3.89 - 3.92 (2H, m), 7.62 (1H, d), 8.22                   | 330                       |



|  |  |                                 |  |
|--|--|---------------------------------|--|
|  |  | (1H, d), (1H obscured by water) |  |
|--|--|---------------------------------|--|

**Examples 519-526**

The following compounds were prepared in 23-63% yield by an analogous method to Example 515, starting from 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine and the appropriate 4-aryl piperidine:-



5

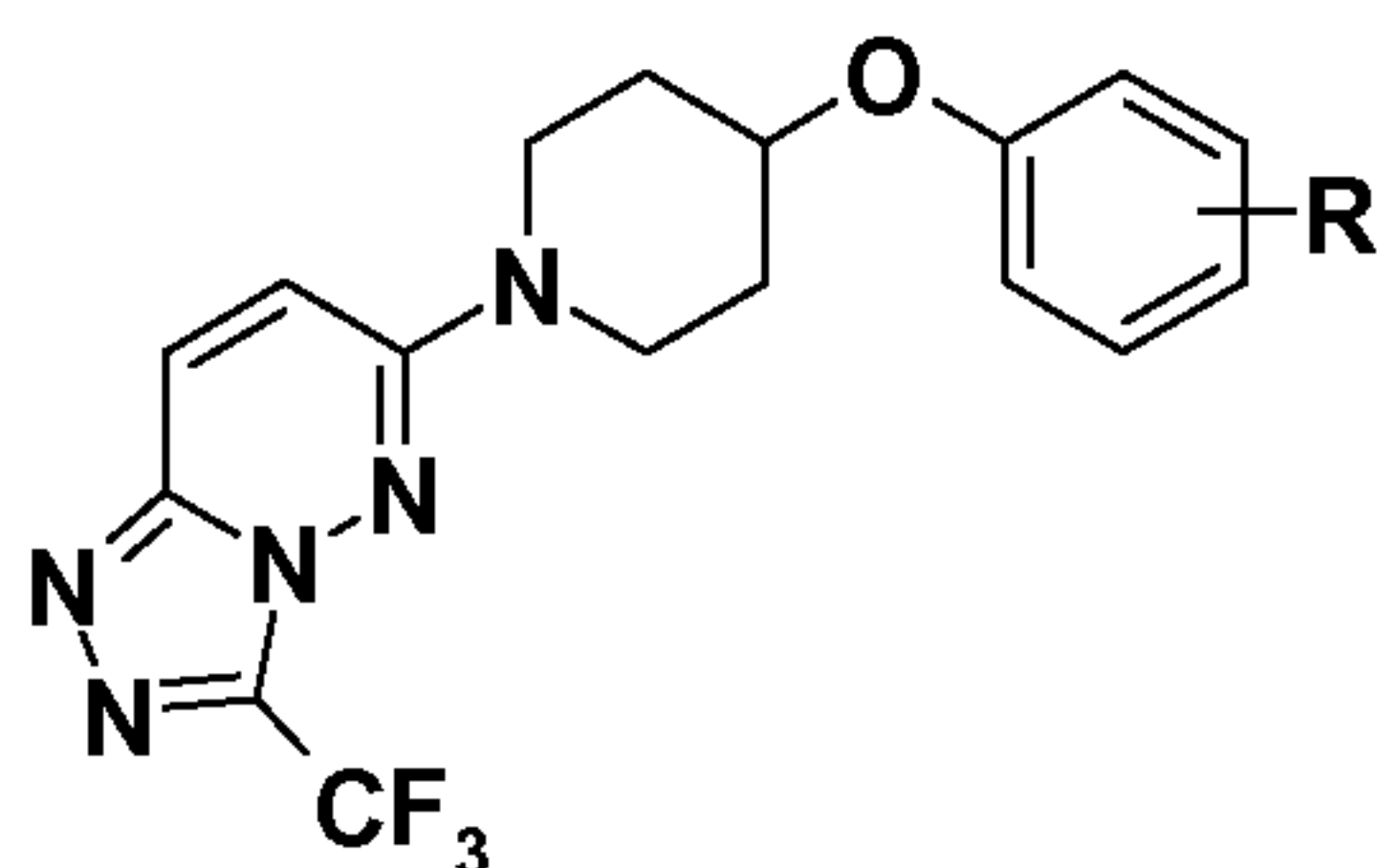
| Ex. | R                    | <sup>1</sup> H NMR (700.03 MHz, DMSO-d <sub>6</sub> )                                                                                                                                            | m/z [M+H] <sup>+</sup> |
|-----|----------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|
| 519 | H                    | δ 1.69 - 1.75 (2H, m), 1.92 (2H, d), 2.85 - 2.90 (1H, m), 3.10 - 3.14 (2H, m), 4.42 - 4.44 (2H, m), 7.20 - 7.22 (1H, m), 7.27 - 7.28 (2H, m), 7.30 - 7.32 (2H, m), 7.66 (1H, d), 8.24 (1H, d)    | 348                    |
| 520 | 2-OMe                | δ 1.67 - 1.73 (2H, m), 1.85 (2H, d), 3.10 - 3.14 (2H, m), 3.81 (3H, s), 4.42 (2H, d), 6.89 - 6.91 (1H, m), 6.99 (1H, d), 7.17 - 7.21 (2H, m), 7.65 (1H, d), 8.24 (1H, d), (2H obscured by water) | 378                    |
| 521 | 4-SO <sub>2</sub> Me | δ 1.73 - 1.79 (2H, m), 1.94 (2H, d), 3.01 - 3.06 (1H, m), 4.45 (2H, d), 7.57 (2H, d), 7.67 (1H, d), 7.86 - 7.87 (2H, m), 8.26 (1H, d), (5H obscured by water)                                    | 426                    |
| 522 | 4-CONHMe             | δ 1.70 - 1.76 (2H, m), 1.92 (2H, d), 2.78 (3H, d), 2.92 - 2.96 (1H, m), 3.11 - 3.15 (2H, m), 4.43 (2H, d), 7.36 (2H, d), 7.66 (1H, d), 7.76 - 7.78 (2H, m), 8.25 (1H, d), 8.32 (1H, q)           | 405                    |
| 523 | 4-OMe                | δ 1.64 - 1.70 (2H, m), 1.87 - 1.89 (2H, m), 2.79 - 2.84 (1H, m), 3.08 - 3.12 (2H, m), 3.73 (3H, s), 4.41 (2H, d), 6.86 - 6.88 (2H, m), 7.18 - 7.20 (2H, m), 7.66 (1H, d), 8.24 (1H, d)           | 378                    |
| 524 | 4-CF <sub>3</sub>    | δ 1.72 - 1.78 (2H, m), 1.94 (2H, d), 2.99 - 3.03 (1H, m), 3.10 - 3.14 (2H, m), 4.42 - 4.44 (2H, m), 7.20 - 7.22 (1H, m), 7.27 - 7.28 (2H, m), 7.30 - 7.32 (2H, m), 7.66 (1H, d), 8.24 (1H, d)    | 416                    |



|     |       |                                                                                                                                                                                                                    |     |
|-----|-------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
|     |       | m), 3.12 - 3.16 (2H, m), 4.44 (2H, d), 7.53 (2H, d), 7.66 - 7.68 (3H, m), 8.25 (1H, s)                                                                                                                             |     |
| 525 | 3-F   | $\delta$ 1.69 - 1.75 (2H, m), 1.92 (2H, d), 2.90 - 2.94 (1H, m), 3.09 - 3.14 (2H, m), 4.42 (2H, d), 7.01 - 7.04 (1H, m), 7.13 (2H, t), 7.34 - 7.37 (1H, m), 7.66 (1H, d), 8.25 (1H, d)                             | 366 |
| 526 | 3-OMe | $\delta$ 1.69 - 1.75 (2H, m), 1.90 - 1.92 (2H, m), 2.83 - 2.87 (1H, m), 3.09 - 3.13 (2H, m), 3.74 (3H, s), 4.42 (2H, d), 6.77 - 6.79 (1H, m), 6.83 (1H, d), 6.84 (1H, t), 7.22 (1H, t), 7.66 (1H, d), 8.24 (1H, d) | 378 |

**Examples 527-532**

The following compounds were prepared in 56-65% yield by an analogous method to Example 515, starting from 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine and the appropriate 4-aryloxy piperidine:-



5

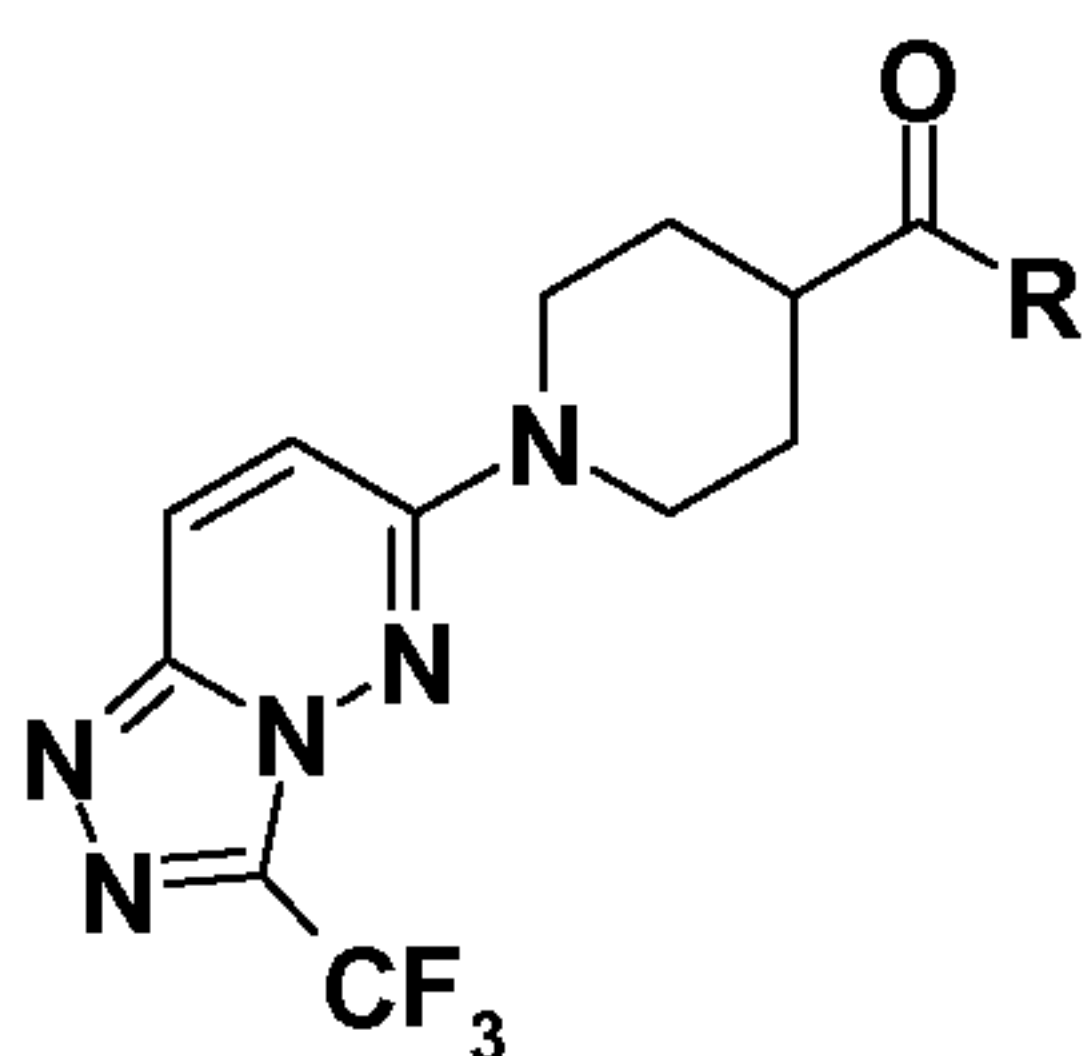
| Ex. | R     | <sup>1</sup> H NMR (700.03 MHz, DMSO-d <sub>6</sub> )                                                                                                                                                                     | m/z [M+H] <sup>+</sup> |
|-----|-------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|
| 527 | 3-OMe | $\delta$ 1.70 - 1.75 (2H, m), 2.05 - 2.08 (2H, m), 3.52 - 3.55 (2H, m), 3.74 (3H, s), 3.94 - 3.97 (2H, m), 4.67 - 4.70 (1H, m), 6.53 (1H, dd), 6.56 (1H, t), 6.60 (1H, dd), 7.20 (1H, t), 7.64 (1H, d), 8.25 (1H, d)      | 394                    |
| 528 | 4-OMe | $\delta$ 1.68 - 1.73 (2H, m), 2.01 - 2.05 (2H, m), 3.50 - 3.54 (2H, m), 3.72 (3H, s), 3.92 - 3.96 (2H, m), 4.52 - 4.56 (1H, m), 6.86 - 6.88 (2H, m), 6.94 - 6.97 (2H, m), 7.64 (1H, d), 8.25 (1H, d)                      | 394                    |
| 529 | 2-F   | $\delta$ 1.74 - 1.79 (2H, m), 2.07 - 2.10 (2H, m), 3.52 - 3.56 (2H, m), 3.94 - 3.98 (2H, m), 4.68 - 4.71 (1H, m), 6.98 - 7.01 (1H, m), 7.15 (1H, t), 7.22 - 7.25 (1H, m), 7.28 - 7.31 (1H, m), 7.64 (1H, d), 8.26 (1H, d) | 382                    |



|     |       |                                                                                                                                                                                                                                  |     |
|-----|-------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
| 530 | 2-Cl  | $\delta$ 1.78 - 1.83 (2H, m), 2.05 - 2.09 (2H, m), 3.62 - 3.66 (2H, m), 3.87 - 3.91 (2H, m), 4.79 - 4.82 (1H, m), 6.98 - 7.01 (1H, m), 7.29 - 7.30 (1H, m), 7.31 - 7.33 (1H, m), 7.44 - 7.46 (1H, m), 7.64 (1H, d), 8.26 (1H, d) | 398 |
| 531 | 2-OMe | $\delta$ 1.71 - 1.76 (2H, m), 2.01 - 2.04 (2H, m), 3.51 - 3.55 (2H, m), 3.77 (3H, s), 3.94 - 3.98 (2H, m), 4.55 - 4.58 (1H, m), 6.88 - 6.91 (1H, m), 6.95 - 6.97 (1H, m), 7.01 (1H, m), 7.08 (1H, m), 7.64 (1H, d), 8.25 (1H, d) | 394 |
| 532 | 3-F   | $\delta$ 1.71 - 1.75 (2H, m), 2.06 - 2.10 (2H, m), 3.51 - 3.54 (2H, m), 3.95 - 3.99 (2H, m), 4.71 - 4.74 (1H, m), 6.76 - 6.79 (1H, m), 6.86 (1H, dd), 6.90 - 6.93 (1H, m), 7.31 - 7.34 (1H, m), 7.64 (1H, d), 8.25 (1H, d)       | 382 |

**Examples 533-534**

The following compounds were prepared in 43-62% yield by an analogous method to Example 515, starting from 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine and the appropriate 4-substituted piperidine:-



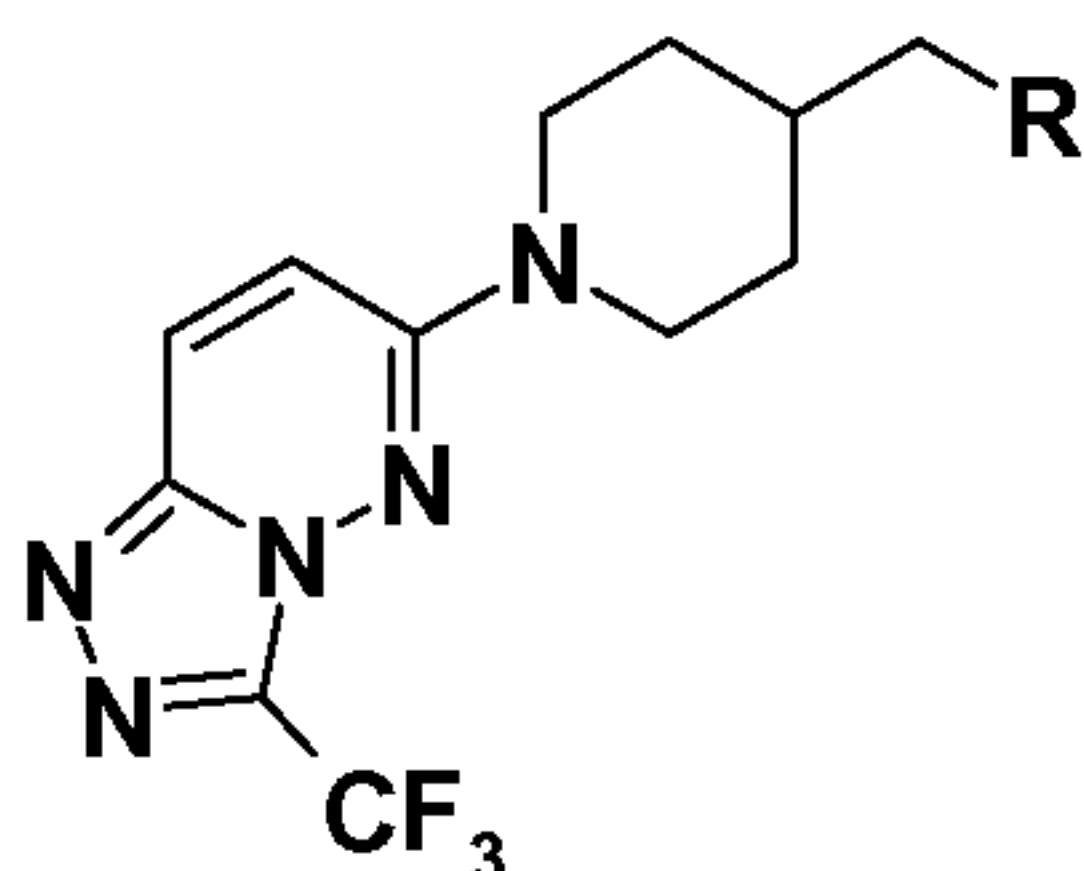
5

| Ex. | R              | <sup>1</sup> H NMR (700.03 MHz, DMSO-d <sub>6</sub> )                                                                                                                                                          | m/z [M+H] <sup>+</sup> |
|-----|----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|
| 533 | phenyl         | $\delta$ 1.62 - 1.68 (2H, m), 1.93 - 1.96 (2H, m), 3.79 - 3.84 (1H, m), 4.30 - 4.31 (2H, m), 7.56 - 7.58 (2H, m), 7.63 (1H, d), 7.66 - 7.69 (1H, m), 8.03 - 8.04 (2H, m), 8.24 (1H, d), (2H obscured by water) | 376                    |
| 534 | 4-fluorophenyl | $\delta$ 1.61 - 1.67 (2H, m), 1.92 - 1.95 (2H, m), 3.78 - 3.82 (1H, m), 4.30 (2H, d), 7.37 - 7.40 (2H, m), 7.63 (1H, d), 8.11 - 8.14 (2H, m), 8.24 (1H, d), (2H obscured by water)                             | 394                    |



**Examples 535-539**

The following compounds were prepared in 53-63% yield by an analogous method to Example 515, starting from 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine and the appropriate 4-substituted piperidine:-



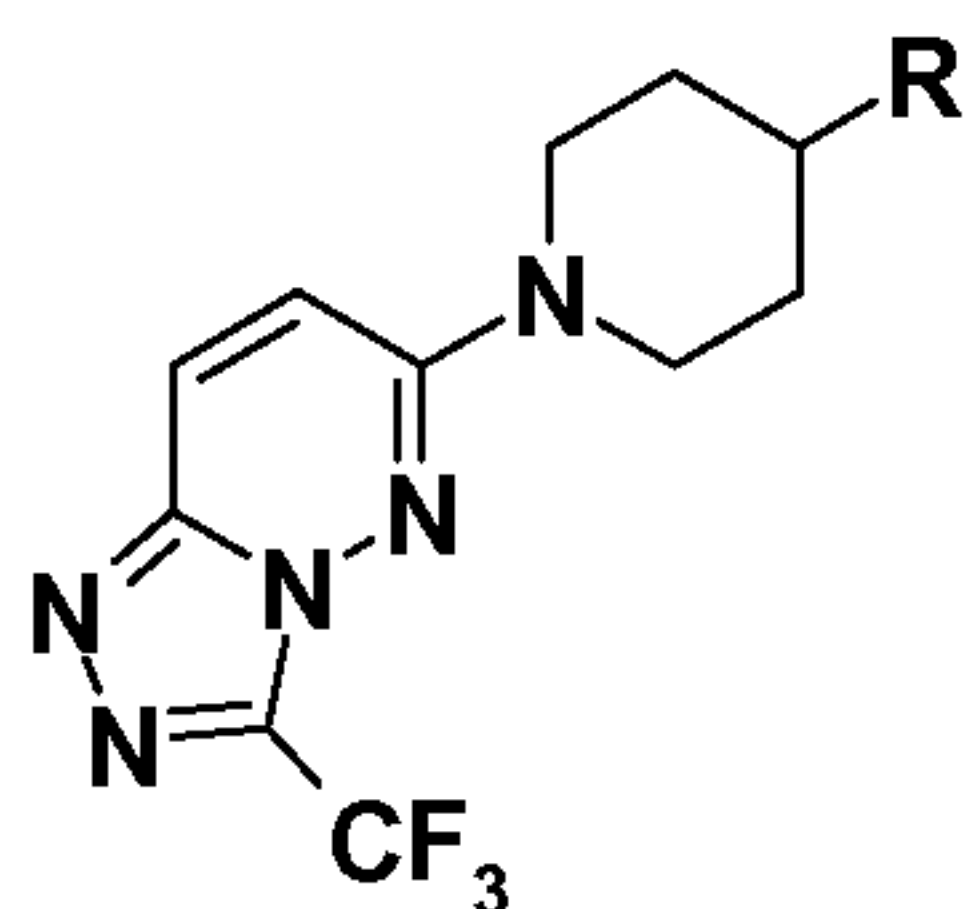
5

| Ex. | R              | <sup>1</sup> H NMR (700.03 MHz, DMSO-d <sub>6</sub> )                                                                                                                                                                     | m/z [M+H] <sup>+</sup> |
|-----|----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|
| 535 | phenyl         | δ 1.21 - 1.27 (2H, m), 1.68 - 1.71 (2H, m), 1.83 - 1.89 (1H, m), 2.55 (2H, d), 2.95 - 2.99 (2H, m), 4.25 (2H, d), 7.19 - 7.21 (3H, m), 7.29 - 7.31 (2H, m), 7.58 (1H, d), 8.21 (1H, d)                                    | 362                    |
| 536 | 4-fluorophenyl | δ 1.20 - 1.26 (2H, m), 1.67 - 1.69 (2H, m), 1.81 - 1.86 (1H, m), 2.55 (2H, d), 2.95 - 2.99 (2H, m), 4.25 (2H, d), 7.09 - 7.13 (2H, m), 7.21 - 7.24 (2H, m), 7.58 (1H, d), 8.21 (1H, d)                                    | 380                    |
| 537 | pyridin-2-yl   | δ 1.26 - 1.32 (2H, m), 1.68 - 1.70 (2H, m), 2.08 - 2.13 (1H, m), 2.70 (2H, d), 2.98 - 3.02 (2H, m), 4.24 (2H, d), 7.20 - 7.22 (1H, m), 7.25 (1H, d), 7.59 (1H, d), 7.69 - 7.72 (1H, m), 8.21 (1H, d), 8.50 - 8.51 (1H, m) | 363                    |
| 538 | pyridin-4-yl   | δ 1.23 - 1.29 (2H, m), 1.67 - 1.69 (2H, m), 1.90 - 1.95 (1H, m), 2.58 (2H, d), 2.97 - 3.01 (2H, m), 4.25 (2H, d), 7.23 - 7.24 (2H, m), 7.59 (1H, d), 8.21 (1H, d), 8.47 - 8.48 (2H, m)                                    | 363                    |
| 539 | pyridin-3-yl   | δ 1.23 - 1.29 (2H, m), 1.68 - 1.70 (2H, m), 1.86 - 1.91 (1H, m), 2.58 (2H, d), 2.96 - 3.00 (2H, m), 4.26 (2H, d), 7.33 (1H, dd), 7.59 (1H, d), 7.62 - 7.64 (1H, m), 8.21 (1H, d), 8.42 - 8.43 (2H, m)                     | 363                    |



**Examples 540-543**

The following compounds were prepared in 40-63% yield by an analogous method to Example 515, starting from 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine and the appropriate 4-substituted piperidine:-



5

| Ex. | R                             | <sup>1</sup> H NMR (700.03 MHz, DMSO-d <sub>6</sub> )                                                                                                                                                          | m/z [M+H] <sup>+</sup> |
|-----|-------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|
| 540 | pyridin-4-yl                  | δ 1.69 - 1.75 (2H, m), 1.94 (2H, d), 2.90 - 2.94 (1H, m), 3.11 - 3.15 (2H, m), 4.43 (2H, d), 7.31 - 7.32 (2H, m), 7.67 (1H, d), 8.25 (1H, d), 8.48 - 8.49 (2H, m)                                              | 349                    |
| 541 | benzotriazol-1-yl             | δ 2.27 - 2.32 (4H, m), 4.48 (2H, s), 5.27 - 5.32 (1H, m), 7.42 - 7.44 (1H, m), 7.57 - 7.59 (1H, m), 7.72 (1H, d), 7.98 (1H, d), 8.06 (1H, d), 8.30 (1H, d), (2H obscured by water)                             | 389                    |
| 542 | indol-1-yl                    | δ 2.03 - 2.10 (4H, m), 4.49 (2H, d), 4.75 - 4.80 (1H, m), 6.45 (1H, d), 7.02 - 7.05 (1H, m), 7.14 - 7.17 (1H, m), 7.49 (1H, d), 7.55 (1H, d), 7.61 (1H, d), 7.70 (1H, d), 8.28 (1H, d), (2H obscured by water) | 387                    |
| 543 | (3,5-dimethoxy)pyrimidin-2-yl | δ 1.81 - 1.87 (2H, m), 2.09 - 2.11 (2H, m), 3.00 - 3.04 (1H, m), 3.88 (6H, s), 4.31 - 4.33 (2H, m), 6.08                                                                                                       | 410                    |

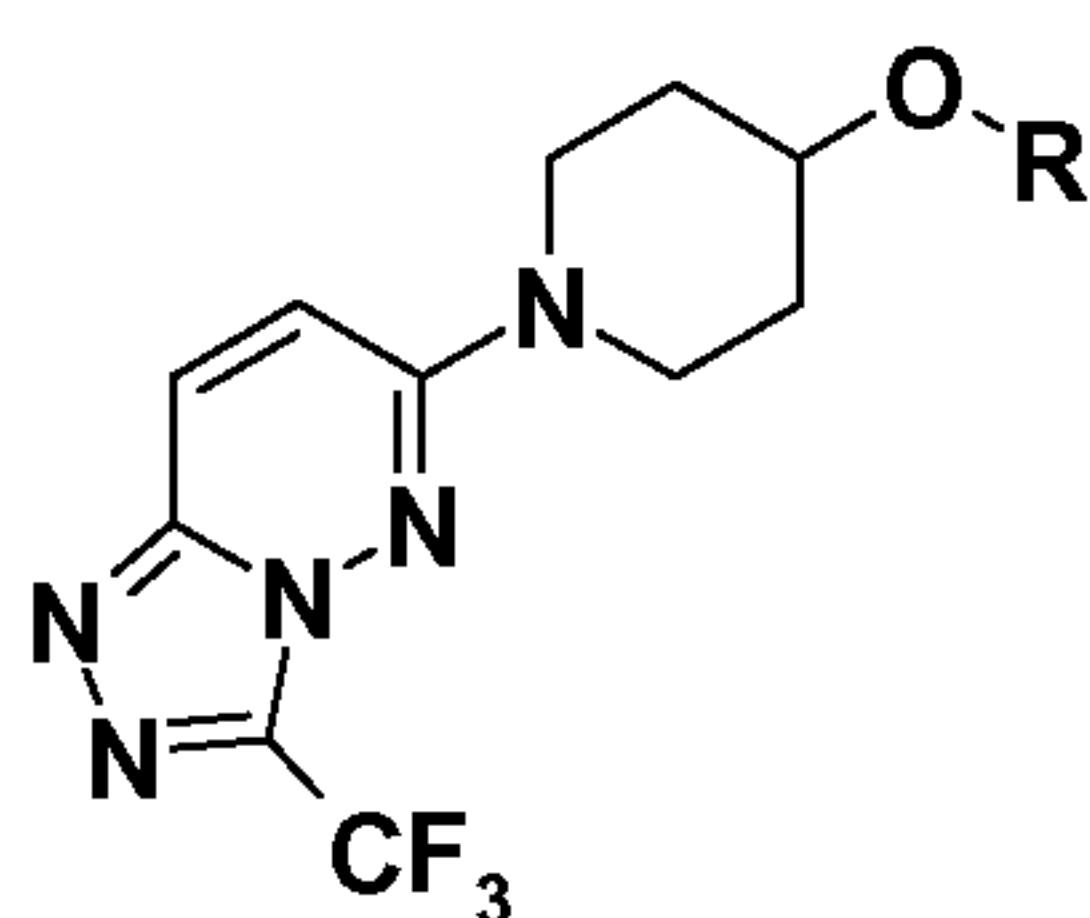


313

|  |  |                                                             |  |
|--|--|-------------------------------------------------------------|--|
|  |  | (1H, s), 7.65 (1H, d), 8.24 (1H, d), (2H obscured by water) |  |
|--|--|-------------------------------------------------------------|--|

**Examples 544-546**

The following compounds were prepared in 33-57% yield by an analogous method to Example 515, starting from 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine and the appropriate 4-substituted piperidine:-



5

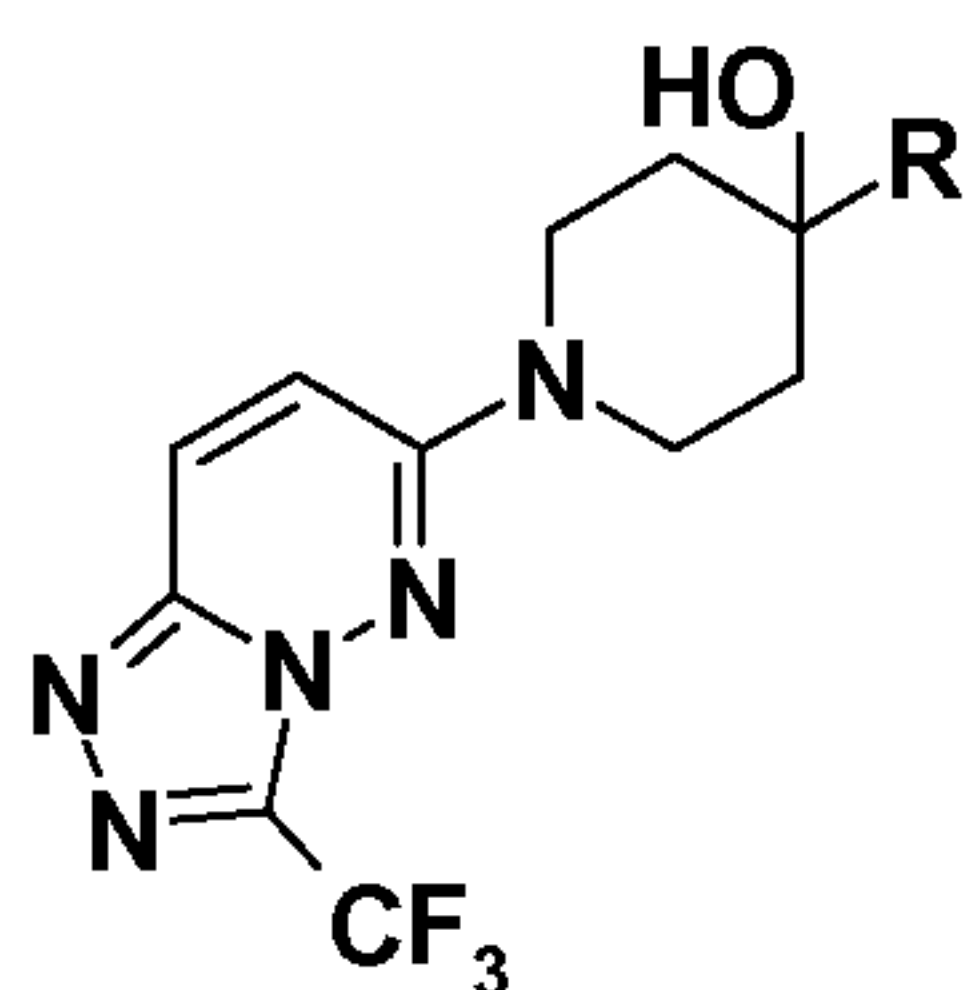
| Ex. | R            | <sup>1</sup> H NMR (700.03 MHz, DMSO-d <sub>6</sub> )                                                                                                                                                              | m/z [M+H] <sup>+</sup> |
|-----|--------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|
| 544 | pyrazinyl    | δ 1.79 - 1.84 (2H, m), 2.12 - 2.16 (2H, m), 3.54 - 3.57 (2H, m), 3.98 - 4.02 (2H, m), 5.30 - 5.34 (1H, m), 7.66 (1H, d), 8.22 - 8.23 (2H, m), 8.26 (1H, d), 8.31 (1H, d)                                           | 366                    |
| 545 | pyridin-4-yl | δ 1.73 - 1.78 (2H, m), 2.10 - 2.14 (2H, m), 3.51 - 3.55 (2H, m), 3.97 - 4.00 (2H, m), 4.84 - 4.87 (1H, m), 7.03 - 7.04 (2H, m), 7.65 (1H, d), 8.26 (1H, d), 8.39 - 8.40 (2H, m)                                    | 365                    |
| 546 | pyridin-2-yl | δ 1.74 - 1.79 (2H, m), 2.10 - 2.14 (2H, m), 3.51 - 3.54 (2H, m), 3.99 - 4.02 (2H, m), 5.30 - 5.33 (1H, m), 6.81 (1H, d), 6.97 - 6.99 (1H, m), 7.65 (1H, d), 7.70 - 7.73 (1H, m), 8.17 - 8.19 (1H, m), 8.25 (1H, d) | 365                    |

**Examples 547-550**

The following compounds were prepared in 25-65% yield by an analogous method to Example 515, starting from 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine and the appropriate 4-substituted piperidin-4-ol:-

10

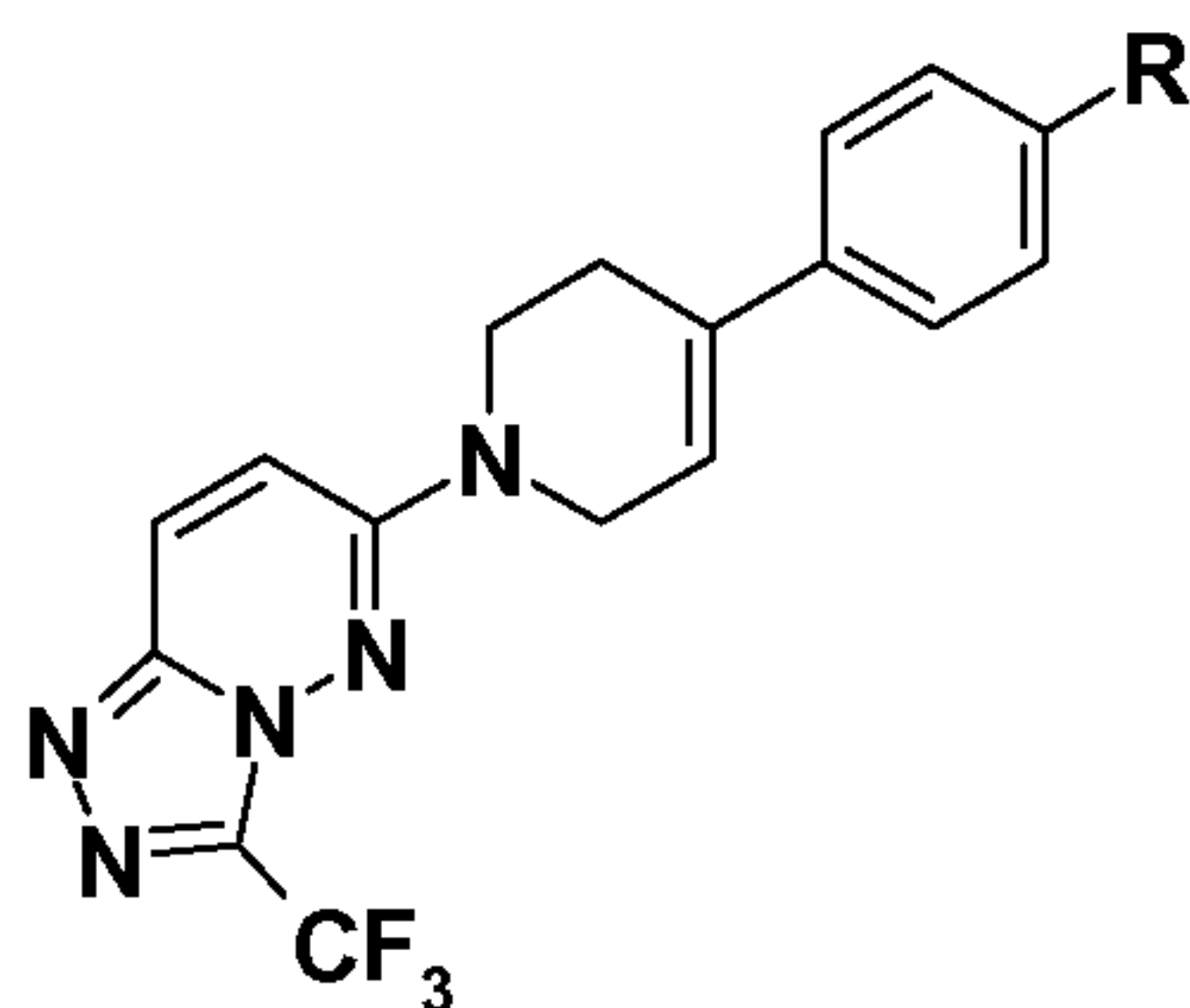




| Ex. | R              | <sup>1</sup> H NMR (700.03 MHz, DMSO-d <sub>6</sub> )                                                                                                                                     | m/z [M+H] <sup>+</sup> |
|-----|----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|
| 547 | phenyl         | δ 1.74 (2H, d), 2.01 - 2.05 (2H, m), 3.43 - 3.47 (2H, m), 4.20 - 4.22 (2H, m), 5.20 (1H, s), 7.22 - 7.24 (1H, m), 7.32 - 7.34 (2H, m), 7.50 - 7.52 (2H, m), 7.66 (1H, d), 8.24 (1H, d)    | 364                    |
| 548 | benzyl         | δ 1.50 (2H, d), 1.56 - 1.60 (2H, m), 2.73 (2H, s), 4.01 (2H, d), 4.51 (1H, s), 7.19 - 7.21 (1H, m), 7.23 - 7.24 (2H, m), 7.27 (2H, t), 7.58 (1H, d), 8.19 (1H, d), (2H obscured by water) | 378                    |
| 549 | 2-fluorophenyl | δ 1.76 (2H, d), 2.23 - 2.27 (2H, m), 3.45 (2H, t), 4.19 - 4.21 (2H, m), 5.47 (1H, s), 7.09 - 7.12 (1H, m), 7.21 - 7.23 (1H, m), 7.30 - 7.33 (1H, m), 7.66 - 7.70 (2H, m), 8.25 (1H, d)    | 382                    |
| 550 | pyridin-4-yl   | δ 1.71 (2H, d), 2.01 - 2.06 (2H, m), 3.42 - 3.46 (2H, m), 4.22 - 4.24 (2H, m), 7.49 - 7.50 (2H, m), 7.67 (1H, d), 8.25 (1H, d), 8.51 - 8.52 (2H, m)                                       | 365                    |

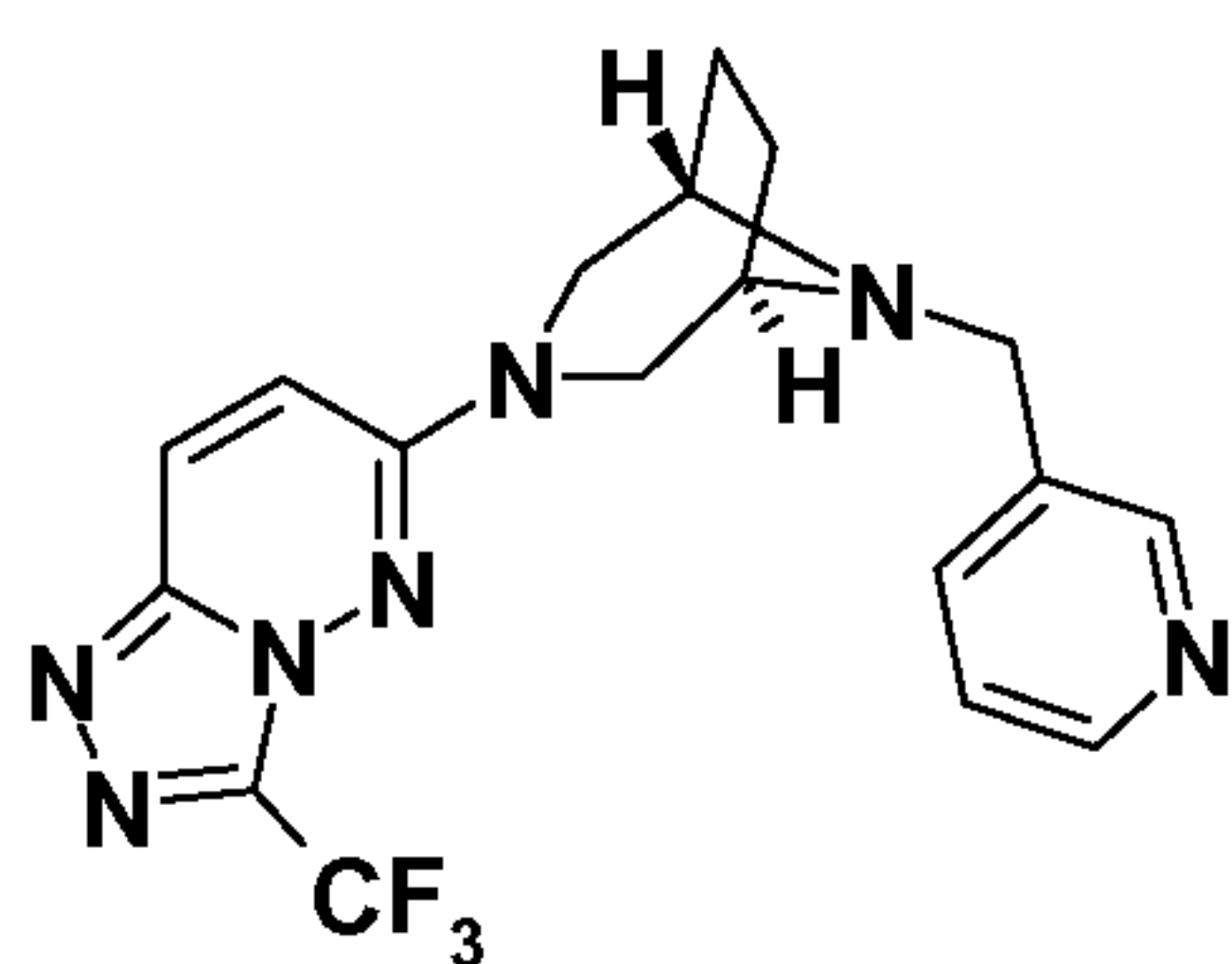
### **Examples 551-552**

The following compounds were prepared in 50-56% yield by an analogous method to Example 515, starting from 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine and the appropriate 4-aryl tetrahydropyridine:-





| Ex. | R | <sup>1</sup> H NMR (700.03 MHz, DMSO-d <sub>6</sub> )                                                                                                      | m/z [M+H] <sup>+</sup> |
|-----|---|------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|
| 551 | H | δ 2.67 - 2.69 (2H, m), 3.90 (2H, t), 4.27 (2H, q), 6.31 - 6.32 (1H, m), 7.29 (1H, t), 7.37 - 7.39 (2H, m), 7.49 - 7.51 (2H, m), 7.68 (1H, d), 8.29 (1H, d) | 346                    |
| 552 | F | δ 2.66 - 2.67 (2H, m), 3.89 (2H, t), 4.26 (2H, q), 6.29 - 6.30 (1H, m), 7.19 - 7.22 (2H, m), 7.52 - 7.55 (2H, m), 7.68 (1H, d), 8.29 (1H, d)               | 364                    |

**Example 553****Preparation of 6-[(1R,5S)-8-(pyridin-3-ylmethyl)-3,8-diazabicyclo[3.2.1]oct-3-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine**

A mixture of pyridine-3-carboxaldehyde and 6-[(1R,5S)-3,8-diazabicyclo[3.2.1]oct-3-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by General Synthetic Method 5 to give 6-[(1R,5S)-8-(pyridin-3-ylmethyl)-3,8-diazabicyclo[3.2.1]oct-3-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine in 68% yield.

<sup>1</sup>H NMR (399.9 MHz, DMSO-d<sub>6</sub>) δ 1.64 - 1.68 (2H, m), 2.03 - 2.06 (2H, m), 3.19 (2H, d), 3.31 - 3.34 (2H, m, partially obscured by solvent peak), 3.64 (2H, s), 3.82 - 3.85 (2H, m), 7.36 - 7.40 (1H, m), 7.51 (1H, d), 7.81 - 7.84 (1H, m), 8.24 (1H, d), 8.48 - 8.49 (1H, m), 8.59 (1H, d); m/z = 390 [M+H]<sup>+</sup>.

The 6-[(1R,5S)-3,8-diazabicyclo[3.2.1]oct-3-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine used as starting material was prepared as follows:-

**Preparation of (1R,5S)-tert-butyl 3-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate**

A stirred solution of 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (312 mg, 1.40 mmol), (1R,5S)-tert-butyl 3,8-diazabicyclo[3.2.1]octane-8-carboxylate (312 mg, 1.47 mmol) and DIPEA (0.36 ml, 2.10 mmol) in ethanol (7.00 ml) was heated at 70°C



for 18 hours. On cooling a white precipitate formed which was collected by filtration, washed with ethanol (10 mL) and dried under vacuum to afford (1R,5S)-tert-butyl 3-(3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (384 mg, 69%) as a white crystalline solid.

5 <sup>1</sup>H NMR (399.9 MHz, DMSO-d<sub>6</sub>) δ 1.44 (9H, s), 1.71 - 1.72 (2H, m), 1.88 - 1.90 (2H, m), 3.13 (2H, d), 3.97 (2H, d), 4.29 (2H, s), 7.54 (1H, d), 8.28 (1H, d); m/z = 399 [M+H]<sup>+</sup>.

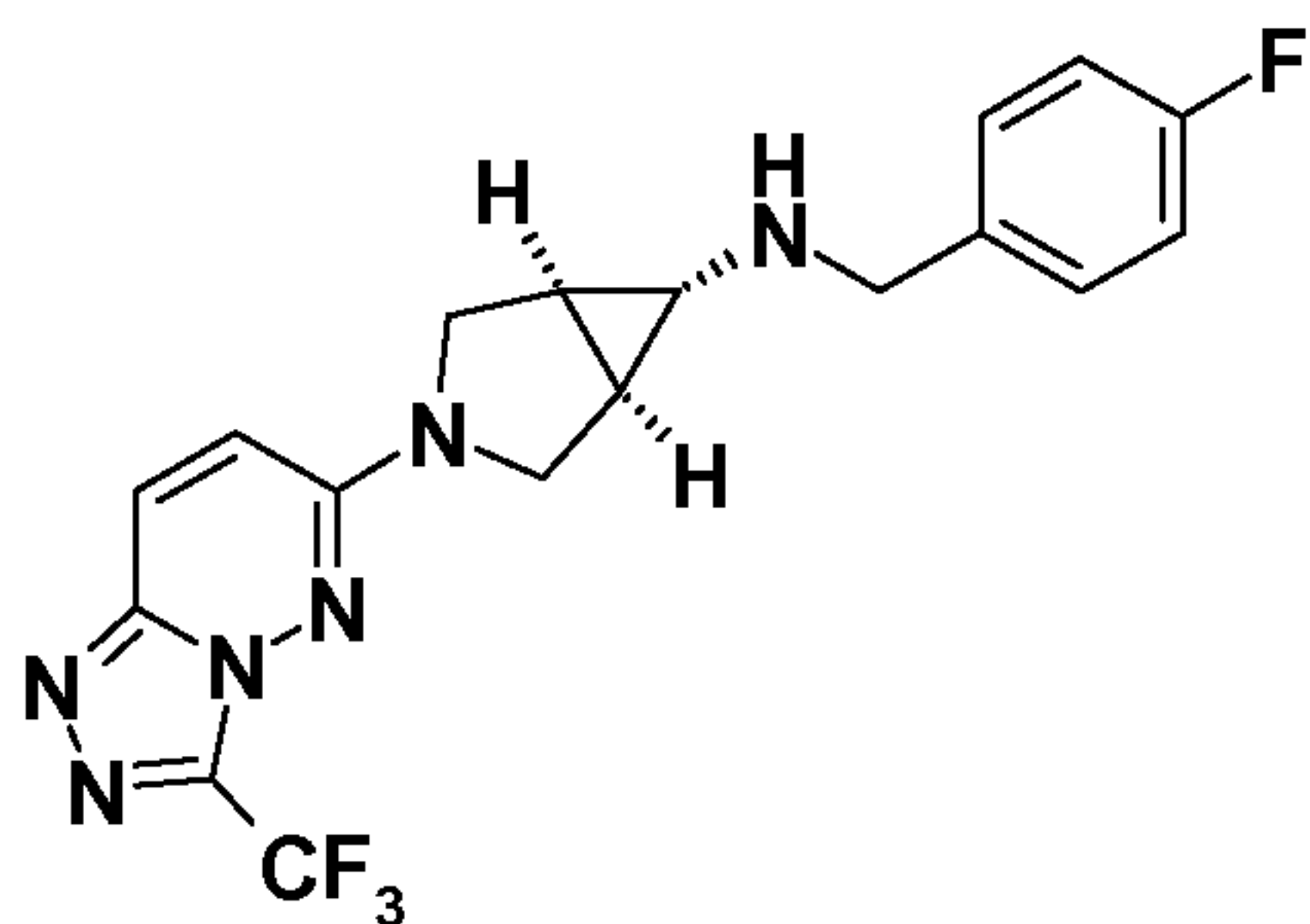
**Preparation of 6-((1R,5S)-3,8-diazabicyclo[3.2.1]octan-3-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**

TFA (2.42 ml, 31.4 mmol) was added to a stirred solution of (1R,5S)-tert-butyl 3-(3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (443 mg, 1.11 mmol) in DCM (4.50 ml) at 25°C. The resulting solution was stirred at ambient temperature for 18 hours. The reaction mixture was diluted with methanol and the crude product was purified by ion exchange chromatography, using an SCX column. The desired product was eluted using 7M ammonia in methanol and  
15 evaporated to dryness to afford 6-[(1R,5S)-3,8-diazabicyclo[3.2.1]oct-3-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine (336 mg, 100%) as a white solid.

<sup>1</sup>H NMR (399.9 MHz, DMSO-d<sub>6</sub>) δ 1.61 - 1.71 (4H, m), 3.05 - 3.08 (2H, m), 3.55 (2H, s), 3.81 - 3.84 (2H, m), 7.50 (1H, d), 8.22 (1H, d), NH not observed; m/z = 299 [M+H]<sup>+</sup>.

**Example 554**

20 **Preparation of (1α,5α,6α) N-(4-fluorobenzyl)-3-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]-3-azabicyclo[3.1.0]hexan-6-amine**



(1α,5α,6α) 3-[3-(Trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]-3-azabicyclo[3.1.0]hexan-6-amine (150 mg, 0.53 mmol), magnesium sulphate monohydrate  
25 (361 mg, 2.64 mmol) and 4-fluorobenzaldehyde (98 mg, 0.79 mmol) were added to DCM (10 mL) and the mixture was stirred overnight at 25°C. The crude mixture was purified by flash silica chromatography, elution gradient 0 to 10% MeOH in DCM. The appropriate



fractions were evaporated to dryness, and the intermediate imine and acetic acid (0.2 mL, 3.49 mmol) were added to MeOH (15 mL). Sodium cyanoborohydride (0.040 mL, 0.70 mmol) was added and the mixture was stirred for 20 minutes. The crude product was purified by ion exchange chromatography using an SCX column, eluting with 3.5M ammonia in methanol. The appropriate fractions were evaporated to dryness to afford a clear gum, which was purified by flash silica chromatography, elution gradient 0 to 10% MeOH in DCM. Product-containing fractions were evaporated to dryness and the residue was crystallised from a mixture of ether and isohexane to give (1 $\alpha$ ,5 $\alpha$ ,6 $\alpha$ ) N-(4-fluorobenzyl)-3-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]-3-azabicyclo[3.1.0]hexan-6-amine (125 mg, 60%).

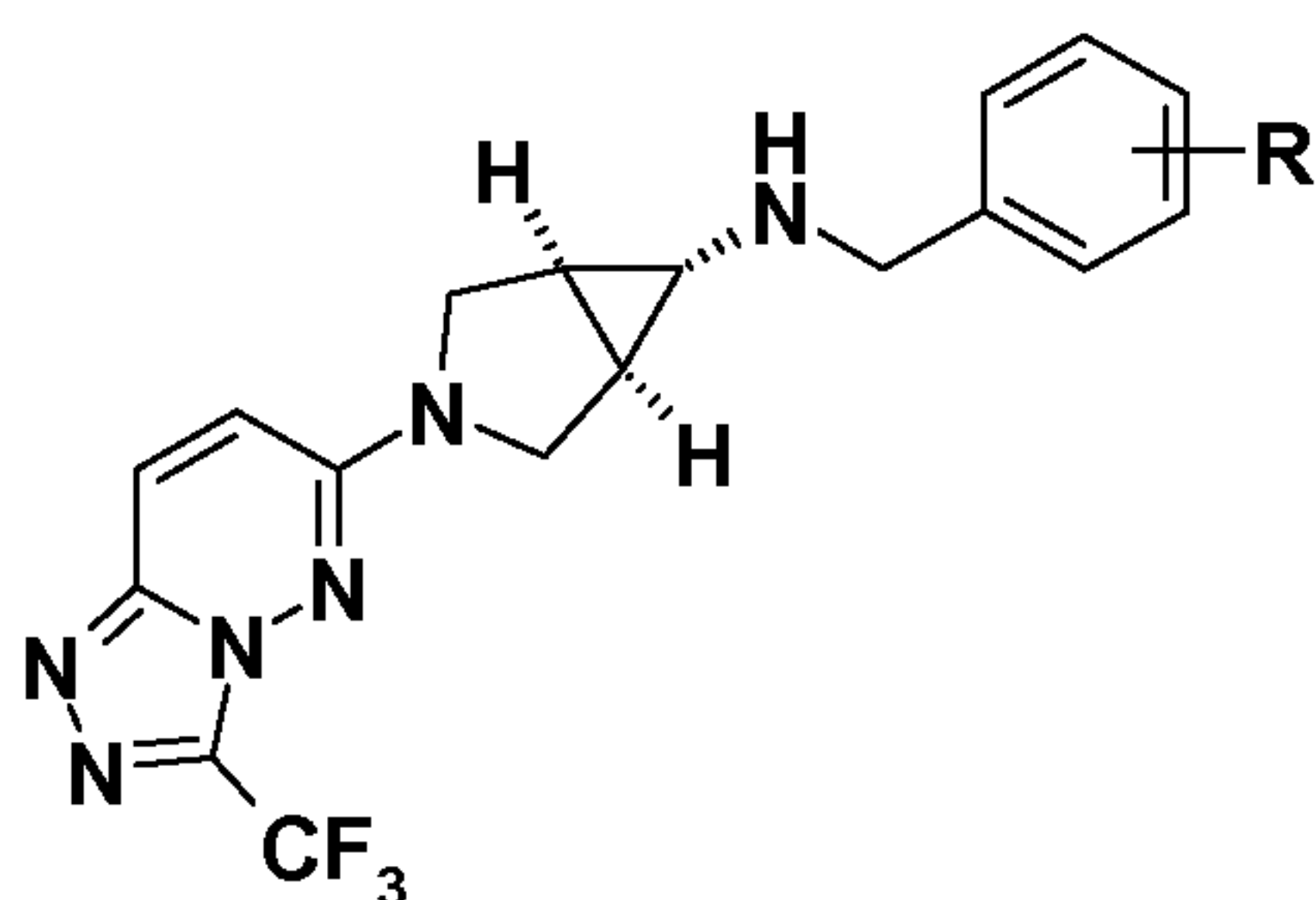
<sup>1</sup>H NMR (400.1 MHz, CDCl<sub>3</sub>)  $\delta$  1.81 (2H, s), 1.84 (1H, s), 2.02 (1H, t), 3.59 (2H, d), 3.68 (2H, d), 3.81 (2H, s), 6.76 (1H, d), 7.01 (2H, t), 7.27 (2H, t), 7.87 (1H, d); m/z = 393 [M+H]<sup>+</sup>.

The (1 $\alpha$ ,5 $\alpha$ ,6 $\alpha$ ) 3-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]-3-azabicyclo[3.1.0]hexan-6-amine used as starting material was prepared in 2 steps in 78% overall yield by an analogous method to Example 223, preparation of starting materials, starting from 6-chloro-3-(trifluoromethyl)-[1,2,4]-triazolo[4,3-b]pyridazine and (1 $\alpha$ ,5 $\alpha$ ,6 $\alpha$ ) tert-butyl 3-azabicyclo[3.1.0]hex-6-ylcarbamate (obtained as described in Synlett. 1996, 1097).

<sup>1</sup>H NMR (400.1 MHz, CDCl<sub>3</sub>)  $\delta$  1.60 (2H, s), 1.77 (2H, s), 2.21 (1H, s), 3.61 (2H, d), 3.72 (2H, d), 6.78 (1H, d), 7.87 (1H, d); m/z = 285 [M+H]<sup>+</sup>.

### **Examples 555-557**

The following compounds were prepared in 50-85% yield by an analogous method to Example 554, starting from (1 $\alpha$ ,5 $\alpha$ ,6 $\alpha$ ) 3-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]-3-azabicyclo[3.1.0]hexan-6-amine and the appropriate aldehyde:-

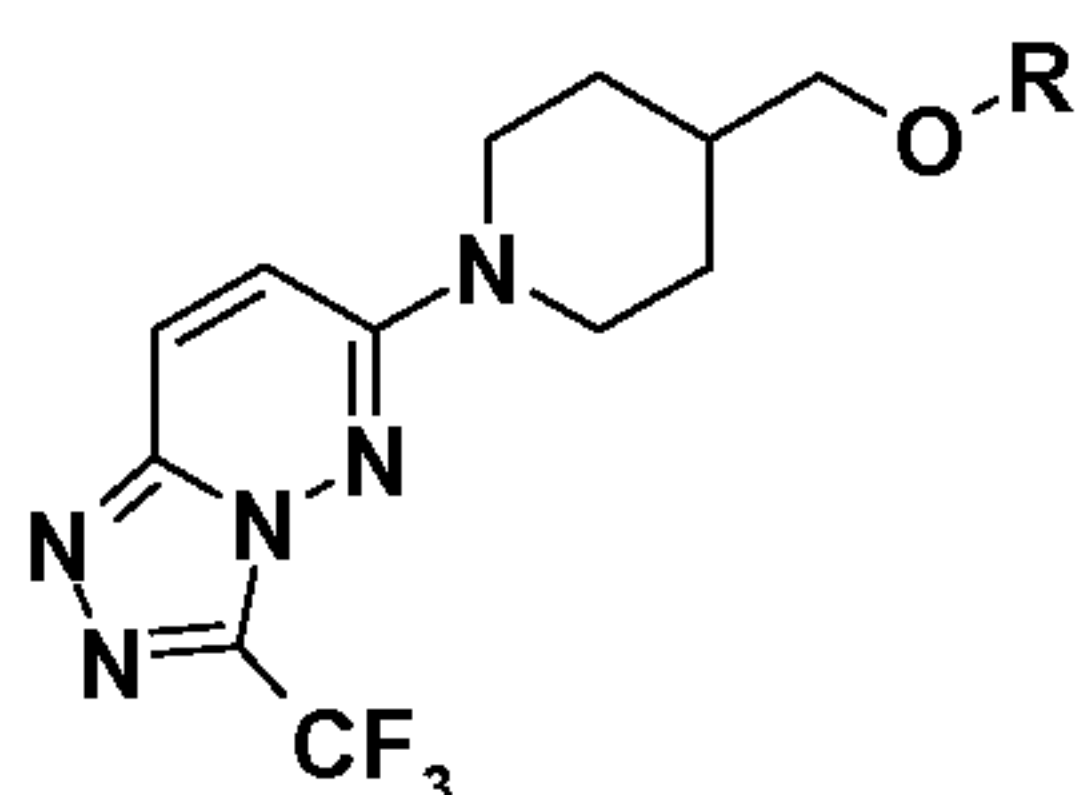




| Ex. | R    | <sup>1</sup> H NMR (400.1 MHz, CDCl <sub>3</sub> )                                                                                                                              | m/z [M+H] <sup>+</sup> |
|-----|------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|
| 555 | 3-Cl | δ 1.82 (2H, s), 1.89 (1H, s), 2.02 (1H, t), 3.60 (2H, d), 3.68 (2H, d), 3.82 (2H, s), 6.76 (1H, d), 7.17 (1H, d), 7.28 - 7.24 (2H, m), 7.31 (1H, s), 7.87 (1H, d)               | 409                    |
| 556 | 3-F  | δ 1.83 (2H, s), 1.89 (1H, s), 2.04 (1H, t), 3.59 (2H, d), 3.68 (2H, d), 3.84 (2H, s), 6.76 (1H, d), 6.95 (1H, t), 7.02 (1H, d), 7.07 (1H, d), 7.31 - 7.26 (1H, m), 7.87 (1H, d) | 393                    |
| 557 | 4-CN | δ 1.82 (2H, s), 1.89 (1H, s), 2.05 (1H, t), 3.60 (2H, d), 3.68 (2H, d), 3.91 (2H, s), 6.76 (1H, d), 7.43 (2H, d), 7.62 (2H, d), 7.87 (1H, d)                                    | 399                    |

**Examples 558-559**

The following compounds were prepared in 5-36% yield by an analogous method to Example 448, starting from [1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]methanol (obtained as described in Example 294, preparation of starting materials) and the appropriate chloro heterocycle:-

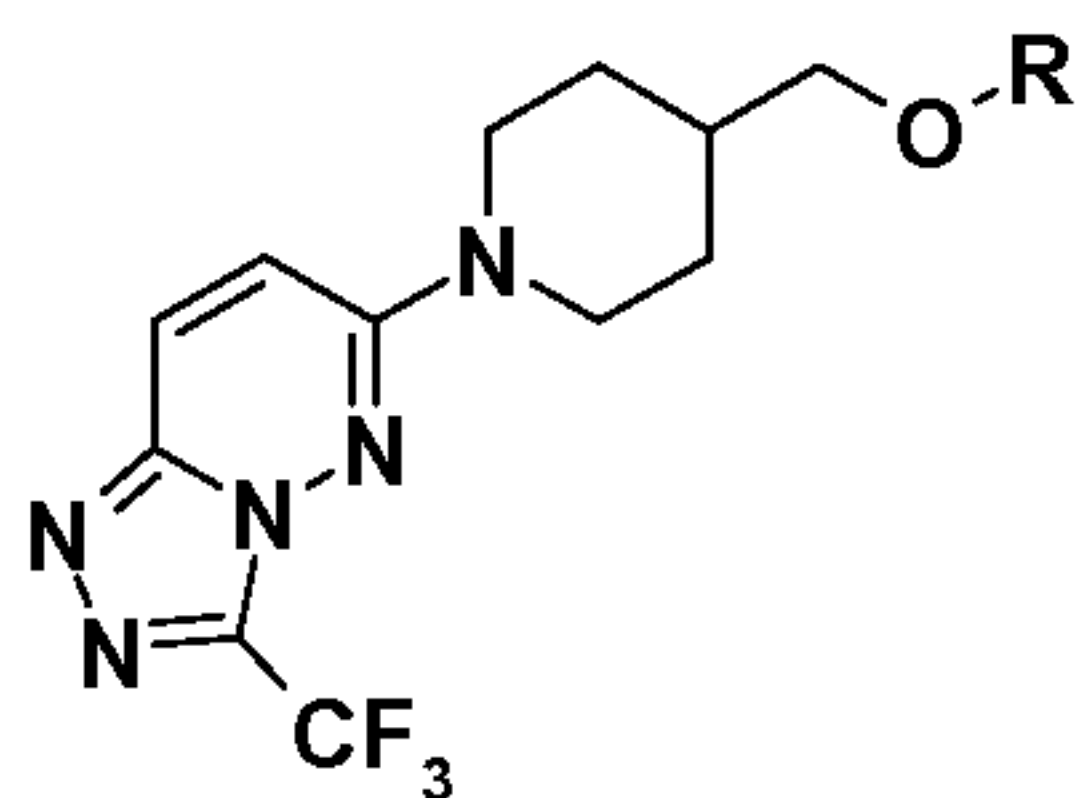


| Ex. | R                   | <sup>1</sup> H NMR (399.9 MHz, DMSO-d <sub>6</sub> )                                                                                                                                           | m/z [M+H] <sup>+</sup> |
|-----|---------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|
| 558 | pyrimidin-2-yl      | δ 1.39 (2H, ddd), 1.91 - 1.87 (2H, m), 2.21 - 2.08 (1H, m), 3.07 (2H, t), 4.21 (2H, d), 4.34 - 4.31 (2H, m), 7.14 (1H, t), 7.63 (1H, d), 8.23 (1H, d), 8.60 (2H, d)                            | 380                    |
| 559 | 3-bromopyridin-2-yl | δ 1.46 - 1.36 (2H, m), 1.91 - 1.87 (2H, m), 2.18 - 2.05 (1H, m), 3.11 - 3.04 (2H, m), 4.24 (2H, d), 4.34 - 4.31 (2H, m), 6.95 (1H, dd), 7.63 (1H, d), 8.03 (1H, d), 8.15 (1H, d), 8.23 (1H, d) | 458                    |



**Examples 560-561**

The following compounds were prepared in 30-37% yield by an analogous method to Example 294, starting from 6-[4-(methanesulfonyloxymethyl)piperidin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine and the appropriate pyridinol:-

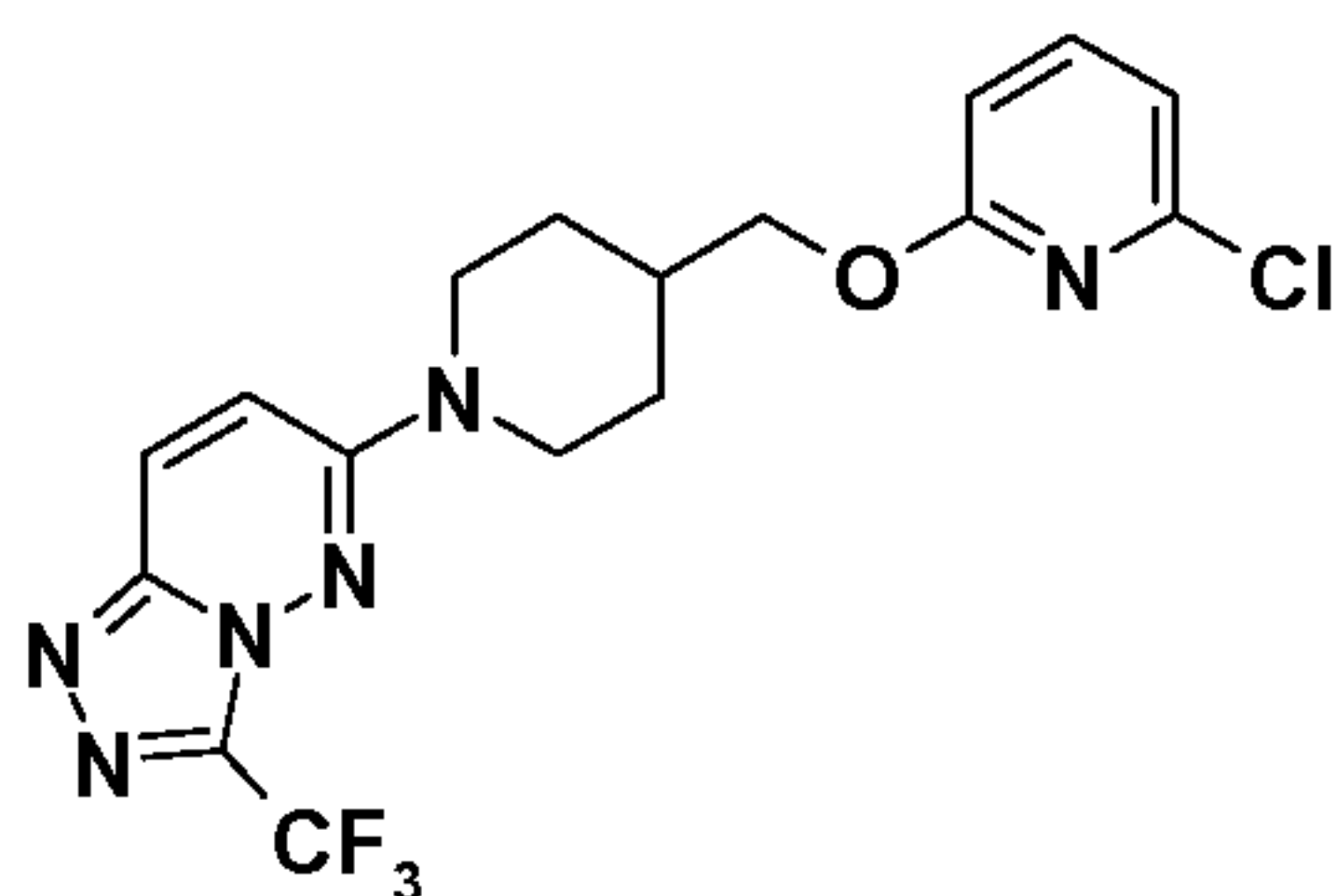


5

| Ex. | R            | <sup>1</sup> H NMR (400.1 MHz, DMSO-d <sub>6</sub> )                                                                                                                                                     | m/z [M+H] <sup>+</sup> |
|-----|--------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|
| 560 | pyridin-3-yl | 1.38 (2H, ddd), 1.93 - 1.90 (2H, m), 2.16 - 2.10 (1H, m), 3.11 - 3.04 (2H, m), 3.96 (2H, d), 4.33 - 4.30 (2H, m), 7.32 (1H, dd), 7.39 (1H, ddd), 7.63 (1H, d), 8.16 (1H, dd), 8.23 (1H, d), 8.30 (1H, d) | 379                    |
| 561 | pyridin-4-yl | δ 1.38 (2H, ddd), 1.91 - 1.88 (2H, m), 2.21 - 2.11 (1H, m), 3.11 - 3.04 (2H, m), 3.97 (2H, d), 4.33 - 4.30 (2H, m), 6.97 - 6.96 (2H, m), 7.62 (1H, d), 8.23 (1H, d), 8.38 - 8.37 (2H, m)                 | 379                    |

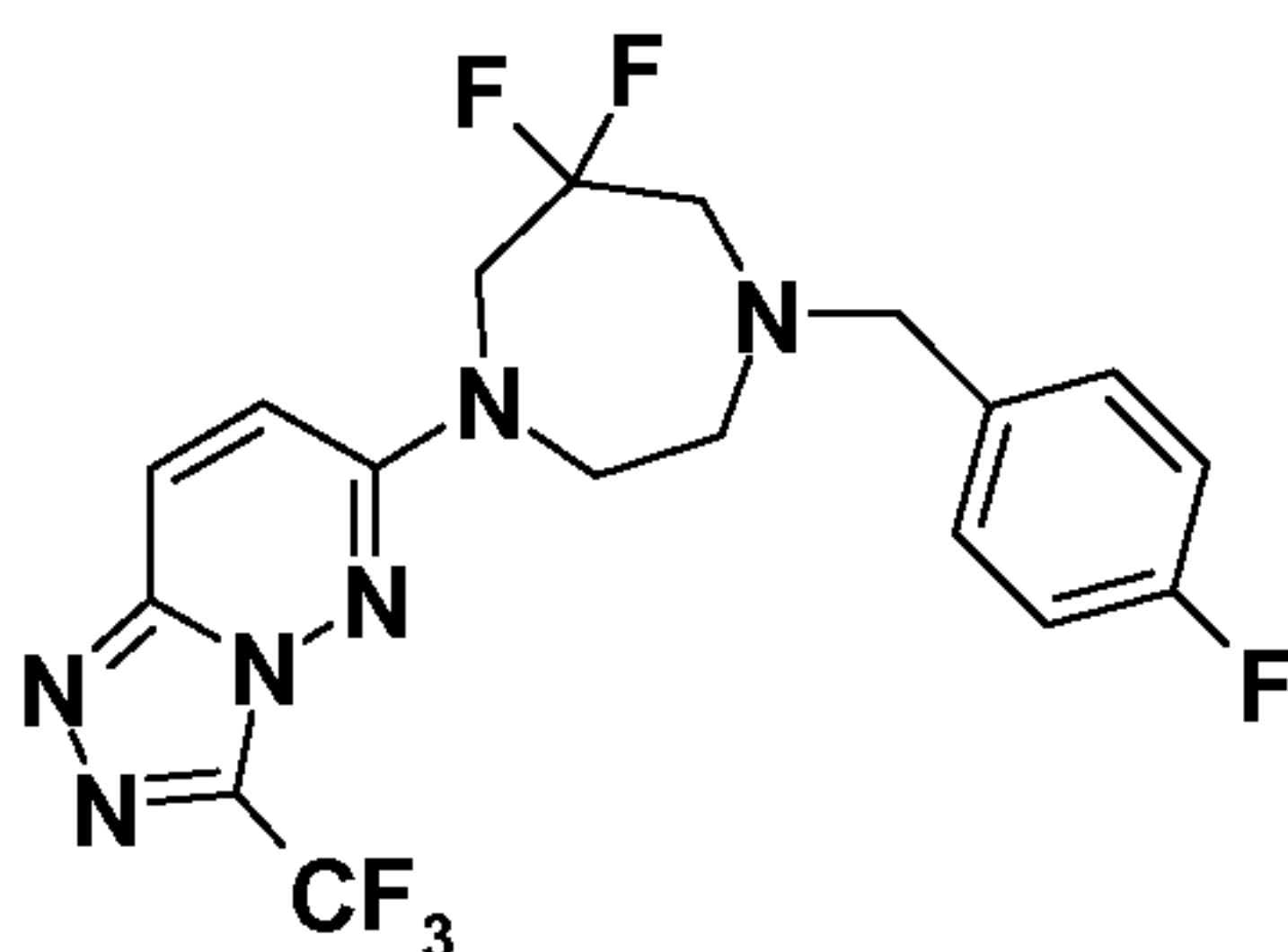
**Example 562**

**Preparation of 6-[4-[[6-chloropyridin-2-yl]oxy]methyl]piperidin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine**



- 10 Obtained in 75% yield by an analogous method to Example 447, starting from [1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]methanol (obtained as described in Example 294, preparation of starting materials) and 6-chloropyridin-2-ol.
- <sup>1</sup>H NMR (400.1 MHz, DMSO-d<sub>6</sub>) δ 1.37 (2H, ddd), 1.89 - 1.87 (2H, m), 2.14 - 2.08 (1H, m), 3.06 (2H, t), 4.14 (2H, d), 4.33 - 4.30 (2H, m), 6.84 (1H, d), 7.08 (1H, d), 7.62 (1H, d), 7.76 (1H, t), 8.22 (1H, d); m/z = 413 [M+H]<sup>+</sup>.
- 15



**Example 563****Preparation of 6-[6,6-difluoro-4-(4-fluorobenzyl)-1,4-diazepan-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine**

- 5 Sodium cyanotrihydroborate (58.5 mg, 0.93 mmol) was added to a stirred mixture of 6-(6,6-difluoro-1,4-diazepan-1-yl)-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine (200 mg, 0.62 mmol), 4-fluorobenzaldehyde (93 mg, 0.75 mmol) and acetic acid (71.1  $\mu$ l, 1.24 mmol) in methanol (10 mL) at room temperature. The resulting mixture was stirred at 21°C for 20 hours. The reaction mixture was concentrated to dryness, diluted with
- 10 methanol and a few drops of 7M ammonia in methanol were added. The mixture was concentrated to dryness, the residue was diluted with DCM and the salts were filtered off. The filtrate was concentrated and purified by flash chromatography on silica gel eluting with 0 to 20% acetonitrile in DCM. Product-containing fractions were concentrated to give to give 6-[6,6-difluoro-4-(4-fluorobenzyl)-1,4-diazepan-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine (154 mg, 55%).

<sup>1</sup>H NMR (500 MHz, DMSO-d<sub>6</sub>)  $\delta$  2.82-2.88 (m, 2H), 3.02-3.11 (m, 2H), 3.73 (s, 2H), 3.79-3.84 (m, 2H), 4.28-4.36 (m, 2H), 6.95 (dd, 2H), 7.23 (dd, 2H), 7.61 (d, 1H), 8.32 (d, 1H); m/z = 431[M+H]<sup>+</sup>.

- The 6-(6,6-difluoro-1,4-diazepan-1-yl)-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine used as starting material was prepared as follows:-

**Preparation of tert-butyl 6,6-difluoro-1,4-diazepane-1-carboxylate**

- Di-tert-butyl dicarbonate (5.29 ml, 23.0 mmol) in DCM (50 mL) was added dropwise to a ice-cooled mixture of 6,6-difluoro-1,4-diazepane (3.6 g, 26.4 mmol, obtained as described in Synthesis, 2003, 223) and DIPEA (2.30 mL, 13.2 mmol) in DCM (100 mL)
- 25 . The resulting mixture was stirred at room temperature for 15 hours. The mixture was concentrated to dryness and diluted with water and ethyl acetate. Insoluble material was removed by filtration and the organic phase was separated, washed with brine, dried over magnesium sulfate and concentrated. The residue was purified by flash chromatography



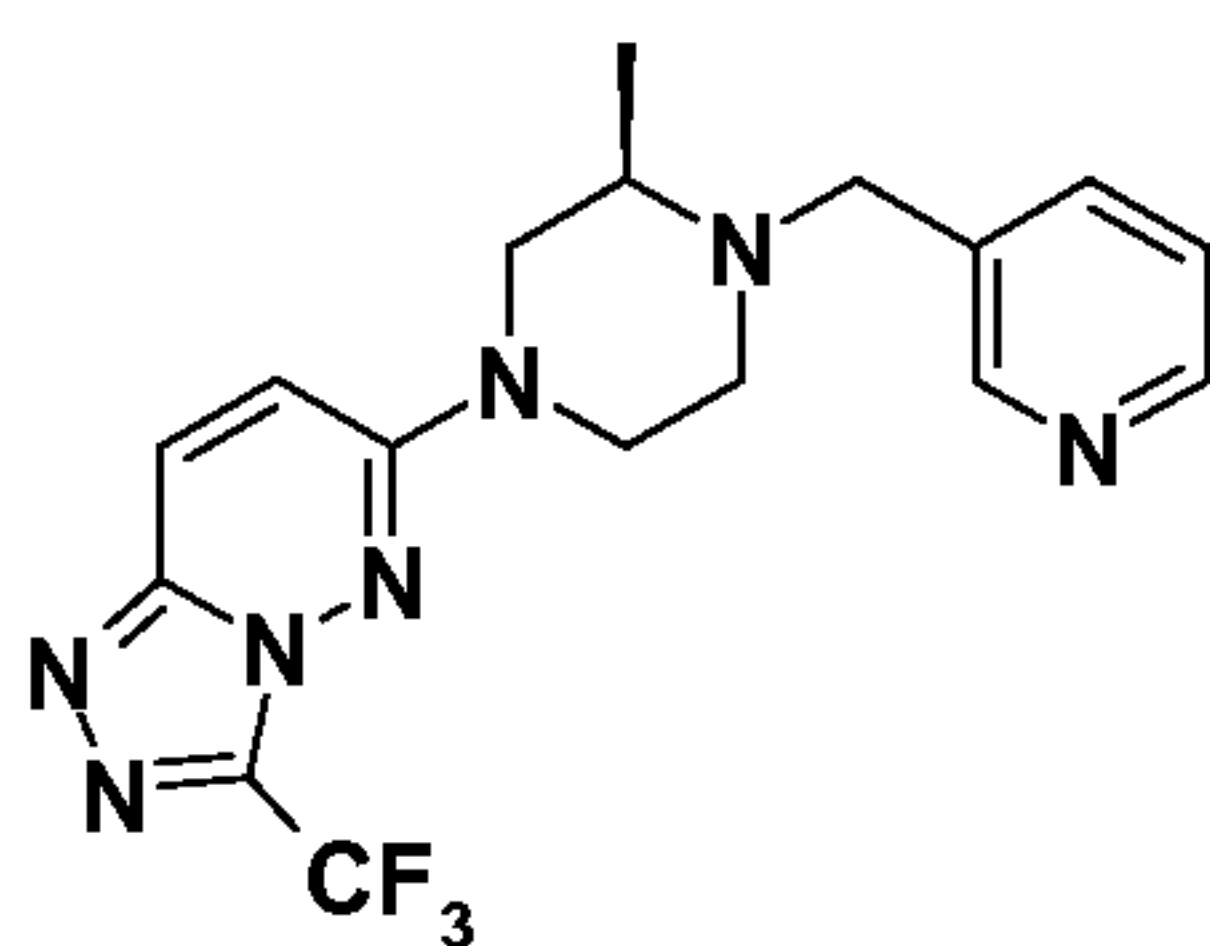
on silica gel eluting with 0 to 4% methanol in DCM. Product-containing fractions were concentrated to afford tert-butyl 6,6-difluoro-1,4-diazepane-1-carboxylate (3.45 g, 55.2%) as a white solid. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 1.47 (s, 9H), 2.90-3.00 (m, 2H), 3.05-3.15 (m, 2H), 3.41-3.54 (m, 2H), 3.78-3.94 (m, 2H).

5 **Preparation of 6-(6,6-difluoro-1,4-diazepan-1-yl)-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine**

A mixture of 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (1 g, 4.49 mmol), tert-butyl 6,6-difluoro-1,4-diazepane-1-carboxylate (1.06 g, 4.49 mmol) and DIPEA (1.56 ml, 8.99 mmol) in DMA (15 mL) was stirred at 135°C for 6 hours. The  
 10 reaction mixture was concentrated to dryness and DCM (30 mL) was added. The solution was cooled in an ice bath and TFA (15 mL) was added. The resulting mixture was stirred at room temperature for 4 hours. The reaction mixture was concentrated to dryness, diluted with water, basified with 6M aqueous sodium hydroxide and extracted with DCM. The  
 15 organic phase was washed with water and brine, dried over magnesium sulfate and concentrated. The residue was purified by flash chromatography on silica gel eluting with 0 to 4% methanol in DCM to give 6-(6,6-difluoro-1,4-diazepan-1-yl)-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (0.820 g, 56.6%) as a beige solid.  
<sup>1</sup>H NMR (500 MHz, DMSO-d<sub>6</sub>) δ 2.80 (bs, 1H), 2.94-3.07 (m, 4H), 3.74-3.81 (m, 2H), 4.24-4.31 (m, 2H), 7.58 (d, 1H), 8.30 (d, 1H); m/z = 323 [M+H]<sup>+</sup>.

20 **Example 564**

**Preparation of 6-[(3R)-3-methyl-4-(pyridin-3-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine**



A mixture of pyridine-3-carboxaldehyde and 6-[(3R)-3-methylpiperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by General  
 25 Synthetic Method 5, to give 6-[(3R)-3-methyl-4-(pyridin-3-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine in 58% yield.



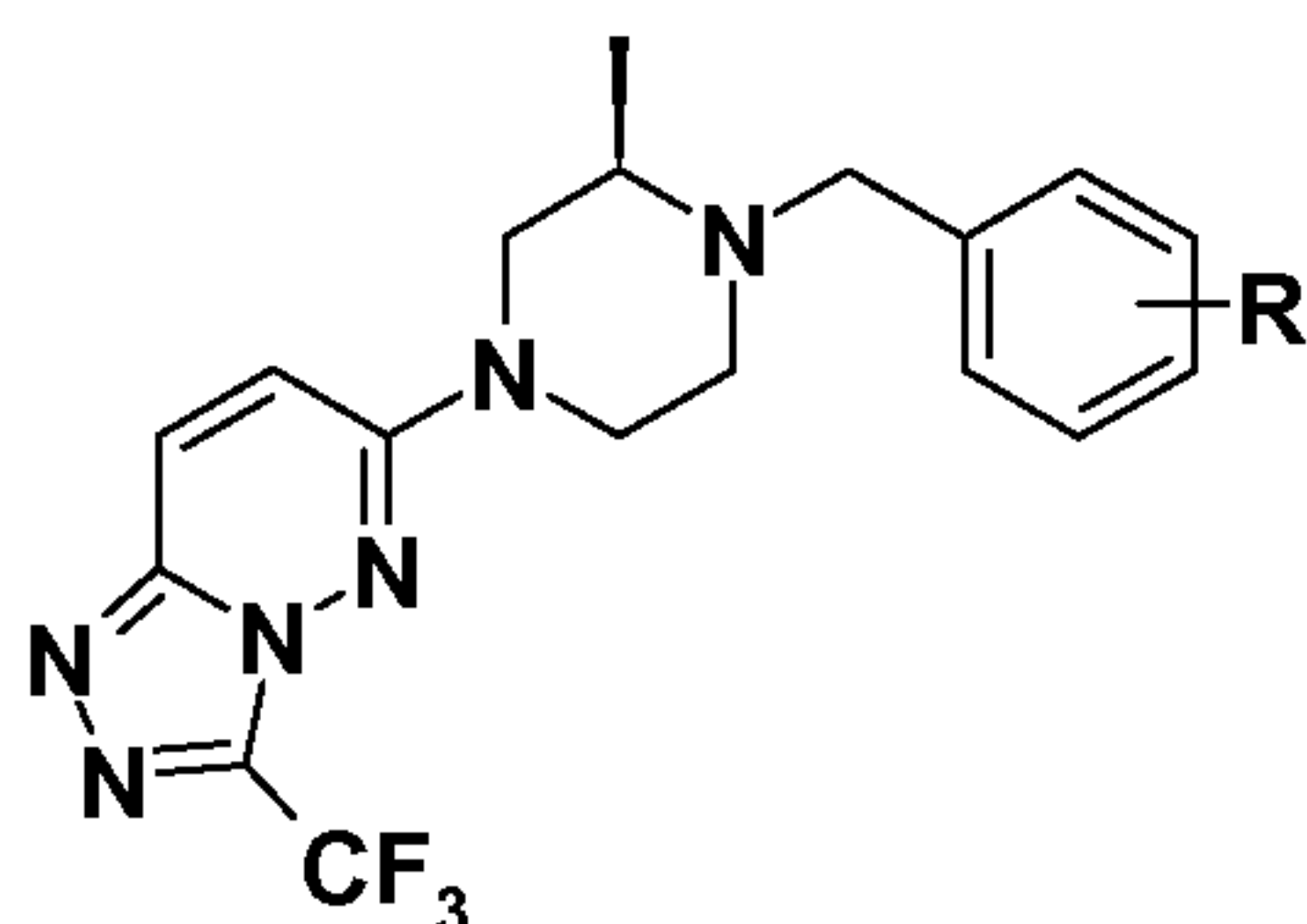
<sup>1</sup>H NMR (399.9 MHz, DMSO-d<sub>6</sub>) δ 1.16 (3H, d), 2.24 - 2.30 (1H, m), 2.53 - 2.63 (1H, m), 2.72 - 2.76 (1H, m), 3.09 - 3.14 (1H, m), 3.28 - 3.32 (1H + H<sub>2</sub>O, m), 3.35 (1H, d), 3.84 - 3.89 (1H, m), 3.92 - 4.00 (2H, m), 7.36 - 7.39 (1H, m), 7.61 (1H, d), 7.74 - 7.77 (1H, m), 8.25 (1H, d), 8.47 - 8.49 (1H, m), 8.54 (1H, d); m/z = 378 [M+H]<sup>+</sup>.

5 The 6-[(3R)-3-methylpiperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine used as starting material was prepared in 2 steps in 75% overall yield by an analogous method to Example 223, preparation of starting materials, starting from 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine and (3R)-tert-butyl 2-methylpiperazine-1-carboxylate.

10 <sup>1</sup>H NMR (399.9 MHz, DMSO-d<sub>6</sub>) δ 1.04 (3H, d), 2.37 (1H, s), 2.54 - 2.60 (1H, m), 2.68 - 2.75 (2H, m), 2.87 - 3.00 (2H, m), 4.07 - 4.11 (2H, m), 7.61 (1H, d), 8.23 (1H, d).

### **Examples 565-569**

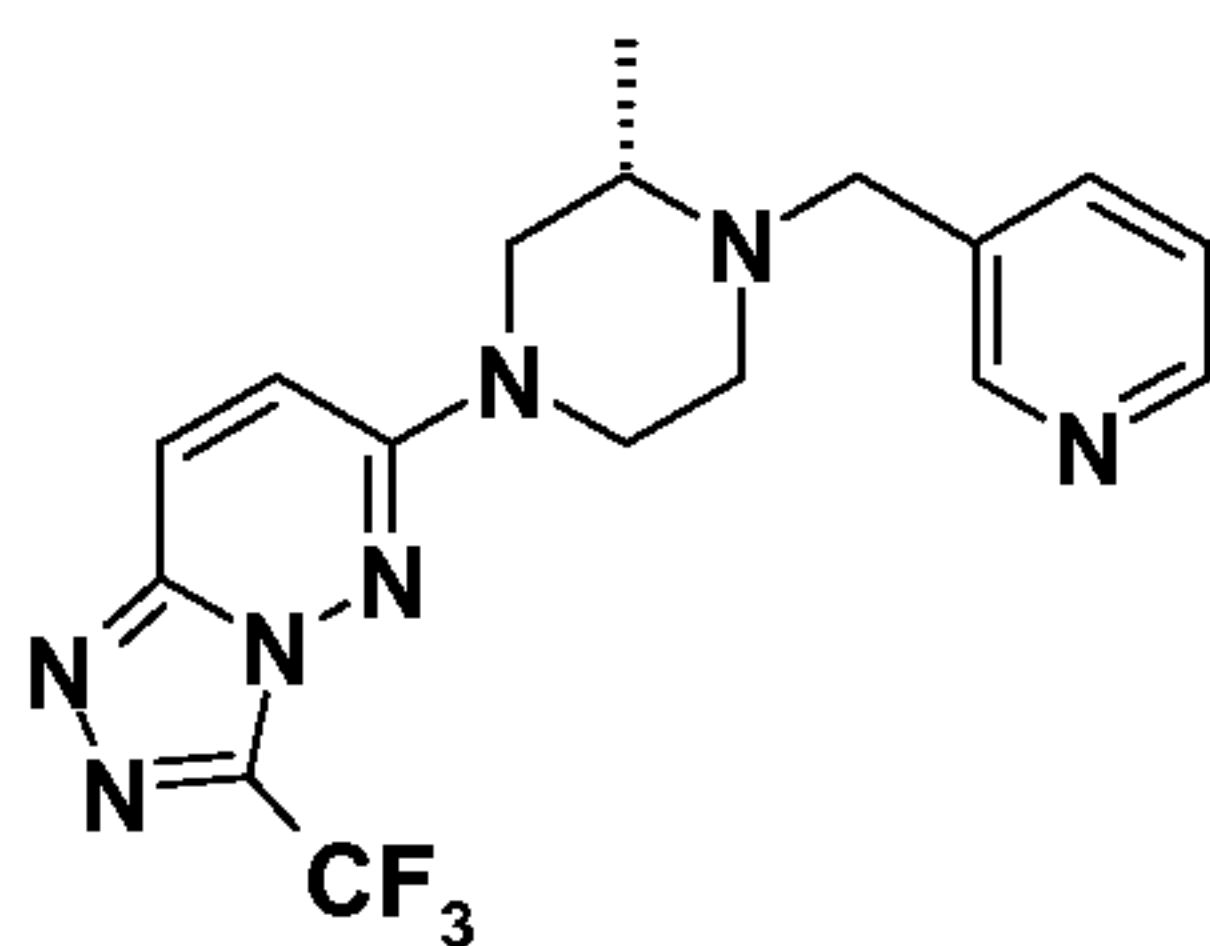
The following compounds were prepared in 29-45% yield by General Synthetic Method 5, starting from 6-[(3R)-3-methylpiperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (obtained as described in Example 564, preparation of starting materials) and  
15 the appropriate aldehyde:-



| Ex. | R        | <sup>1</sup> H NMR (399.9 MHz, DMSO-d <sub>6</sub> )                                                                                                                                                                                                                                   | m/z [M+H] <sup>+</sup> |
|-----|----------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|
| 565 | 4-CN     | δ 1.13 (3H, d), 2.26 - 2.32 (1H, m), 2.61 - 2.65 (1H, m), 2.70 - 2.75 (1H, m), 3.10 - 3.15 (1H, m), 3.28 - 3.32 (1H + H <sub>2</sub> O, m), 3.41 (1H, d), 3.85 - 3.89 (1H, m), 3.93 - 3.97 (1H, m), 4.03 (1H, d), 7.58 (2H, d), 7.60 - 7.63 (1H, m), 7.80 - 7.83 (2H, m), 8.26 (1H, d) | 402                    |
| 566 | 3,4-di-F | δ 1.13 (3H, d), 2.24 - 2.29 (1H, m), 2.59 - 2.63 (1H, m), 2.71 - 2.76 (1H, m), 3.10 - 3.15 (1H, m), 3.28 - 3.32 (2H + H <sub>2</sub> O, m), 3.84 - 3.89 (2H, m), 3.93 (1H, d), 7.18 - 7.21 (1H, m), 7.36 - 7.42 (2H, m), 7.61 (1H, d), 8.25 (1H, d)                                    | 413                    |



|     |           |                                                                                                                                                                                                                                                                                 |     |
|-----|-----------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
| 567 | 3,5-di-F  | $\delta$ 1.12 (3H, d), 2.27 - 2.32 (1H, m), 2.59 - 2.62 (1H, m), 2.74 - 2.78 (1H, m), 3.11 - 3.16 (1H, m), 3.33 - 3.38 (2H, m), 3.86 - 3.97 (3H, m), 7.08 - 7.13 (3H, m), 7.62 (1H, d), 8.26 (1H, d)                                                                            | 413 |
| 568 | 4-F       | $\delta$ 1.14 (3H, d), 2.20 - 2.26 (1H, m), 2.56 - 2.61 (1H, m), 2.70 - 2.75 (1H, m), 3.08 - 3.14 (1H, m), 3.26 - 3.33 (2H, m), 3.84 - 3.96 (3H, m), 7.14 - 7.18 (2H, m), 7.36 - 7.40 (2H, m), 7.61 (1H, d), 8.25 (1H, d)                                                       | 395 |
| 569 | 3-CN, 4-F | $\delta$ 1.13 (3H, d), 2.24 - 2.30 (1H, m), 2.60 - 2.65 (1H, m), 2.71 - 2.76 (1H, m), 3.10 - 3.16 (1H, m), 3.28 - 3.32 (1H + H <sub>2</sub> O, m), 3.36 (1H, d), 3.85 - 3.98 (3H, m), 7.49 - 7.53 (1H, m), 7.61 (1H, d), 7.75 - 7.79 (1H, m), 7.86 - 7.88 (1H, m), 8.26 (1H, d) | 420 |

**Example 570****Preparation of 6-[(3S)-3-methyl-4-(pyridin-3-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine**

5 A mixture of pyridine-3-carboxaldehyde and 6-[(3S)-3-methylpiperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by General Synthetic Method 5 to give 6-[(3S)-3-methyl-4-(pyridin-3-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine in 62% yield.

1H NMR (399.9 MHz, DMSO-d<sub>6</sub>)  $\delta$  1.16 (3H, d), 2.24 - 2.30 (1H, m), 2.53 - 2.63 (1H, m),  
 10 2.72 - 2.76 (1H, m), 3.09 - 3.14 (1H, m), 3.28 - 3.32 (1H + H<sub>2</sub>O, m), 3.35 (1H, d), 3.84 - 3.89 (1H, m), 3.92 - 4.00 (2H, m), 7.36 - 7.39 (1H, m), 7.61 (1H, d), 7.74 - 7.77 (1H, m), 8.25 (1H, d), 8.47 - 8.49 (1H, m), 8.54 (1H, d); m/z = 378 [M+H]<sup>+</sup>.

The 6-[(3S)-3-methylpiperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine used as starting material was prepared in 2 steps in 71.5% overall yield by an  
 15 analogous method to Example 223, preparation of starting materials, starting from 6-

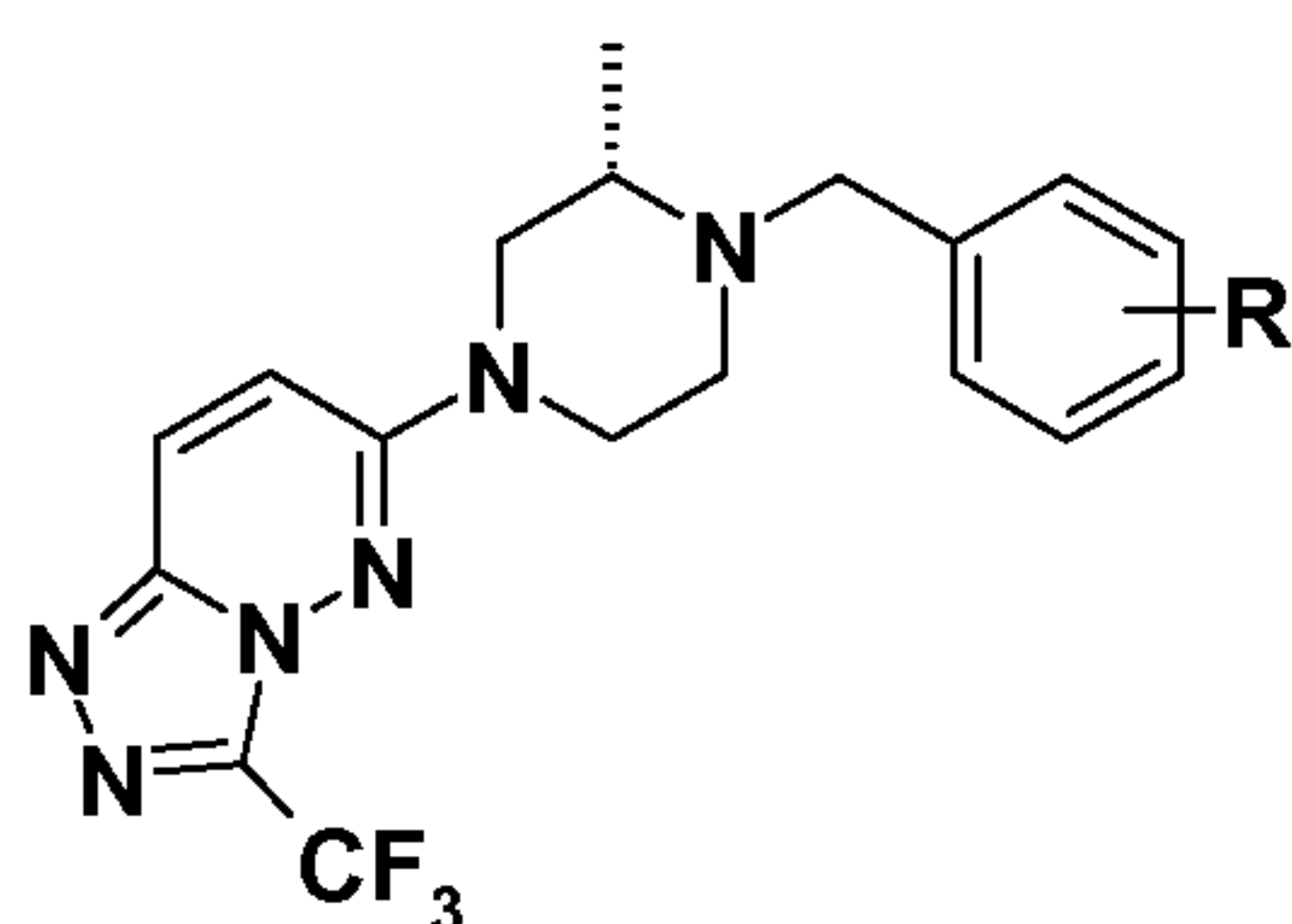


chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine and (3S)-tert-butyl 2-methylpiperazine-1-carboxylate.

<sup>1</sup>H NMR (399.9 MHz, DMSO-d<sub>6</sub>) δ 1.04 (3H, d), 2.37 (1H, s), 2.54 - 2.60 (1H, m), 2.68 - 2.75 (2H, m), 2.87 - 3.00 (2H, m), 4.07 - 4.11 (2H, m), 7.61 (1H, d), 8.23 (1H, d).

### 5 Examples 571-575

The following compounds were prepared in 36-55% yield by General Synthetic Method 5, starting from 6-[(3S)-3-methylpiperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (obtained as described in Example 570, preparation of starting materials) and the appropriate aldehyde:-

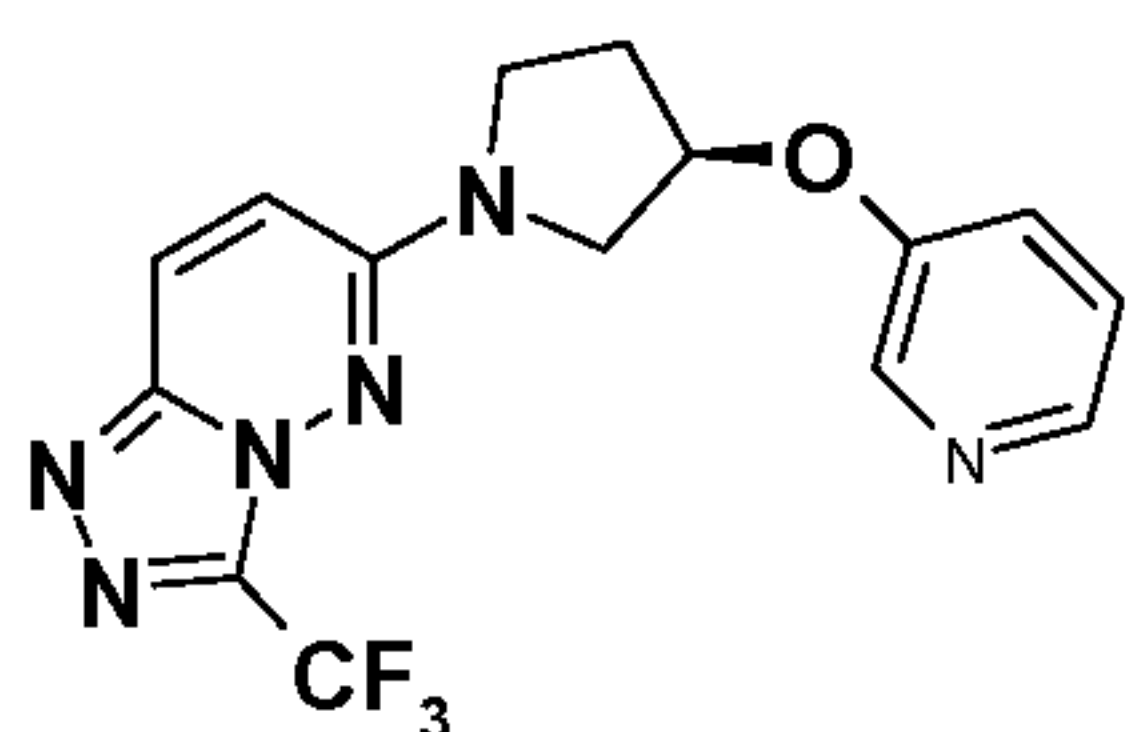


10

| Ex. | R        | <sup>1</sup> H NMR (399.9 MHz, DMSO-d <sub>6</sub> )                                                                                                                                                                                                                                   | m/z [M+H] <sup>+</sup> |
|-----|----------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|
| 571 | 4-CN     | δ 1.13 (3H, d), 2.26 - 2.32 (1H, m), 2.61 - 2.65 (1H, m), 2.70 - 2.75 (1H, m), 3.10 - 3.15 (1H, m), 3.28 - 3.32 (1H + H <sub>2</sub> O, m), 3.41 (1H, d), 3.85 - 3.89 (1H, m), 3.93 - 3.97 (1H, m), 4.03 (1H, d), 7.58 (2H, d), 7.60 - 7.63 (1H, m), 7.80 - 7.83 (2H, m), 8.26 (1H, d) | 402                    |
| 572 | 3,4-di-F | δ 1.13 (3H, d), 2.24 - 2.29 (1H, m), 2.59 - 2.63 (1H, m), 2.71 - 2.76 (1H, m), 3.10 - 3.15 (1H, m), 3.28 - 3.32 (2H + H <sub>2</sub> O, m), 3.84 - 3.89 (2H, m), 3.93 (1H, d), 7.18 - 7.21 (1H, m), 7.36 - 7.42 (2H, m), 7.61 (1H, d), 8.25 (1H, d)                                    | 413                    |
| 573 | 3,5-di-F | δ 1.12 (3H, d), 2.27 - 2.32 (1H, m), 2.59 - 2.62 (1H, m), 2.74 - 2.78 (1H, m), 3.11 - 3.16 (1H, m), 3.33 - 3.38 (2H, m), 3.86 - 3.97 (3H, m), 7.08 - 7.13 (3H, m), 7.62 (1H, d), 8.26 (1H, d)                                                                                          | 413                    |
| 574 | 4-F      | δ 1.14 (3H, d), 2.20 - 2.26 (1H, m), 2.56 - 2.61 (1H, m), 2.70 - 2.75 (1H, m), 3.08 - 3.14 (1H, m), 3.26 - 3.33 (2H, m), 3.84 - 3.96 (3H, m), 7.14 - 7.18 (2H, m), 7.61 (1H, d), 8.23 (1H, d)                                                                                          | 395                    |



|     |           |                                                                                                                                                                                                                                                                                 |     |
|-----|-----------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
|     |           | m), 7.36 - 7.40 (2H, m), 7.61 (1H, d), 8.25 (1H, d)                                                                                                                                                                                                                             |     |
| 575 | 3-CN, 4-F | $\delta$ 1.13 (3H, d), 2.24 - 2.30 (1H, m), 2.60 - 2.65 (1H, m), 2.71 - 2.76 (1H, m), 3.10 - 3.16 (1H, m), 3.28 - 3.32 (1H + H <sub>2</sub> O, m), 3.36 (1H, d), 3.85 - 3.98 (3H, m), 7.49 - 7.53 (1H, m), 7.61 (1H, d), 7.75 - 7.79 (1H, m), 7.86 - 7.88 (1H, m), 8.26 (1H, d) | 420 |

**Example 576****Preparation of 6-[(3R)-3-(pyridin-3-yloxy)pyrrolidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine**

- 5 Obtained in 68% yield by an analogous procedure to Example 216, starting from 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine and (3R)-3-(pyridin-3-yloxy)pyrrolidine.

1H NMR (399.9 MHz, DMSO-d<sub>6</sub>)  $\delta$  2.27 - 2.38 (2H, m), 3.63 - 3.88 (4H, m), 5.30 - 5.34 (1H, m), 7.32 (1H, d), 7.35 - 7.39 (1H, m), 7.47 - 7.50 (1H, m), 8.21 - 8.23 (1H, m), 8.25  
 10 (1H, d), 8.34 (1H, d); m/z = 351 [M+H]<sup>+</sup>.

The (3R)-3-(pyridin-3-yloxy)pyrrolidine used as starting material was prepared as follows:-

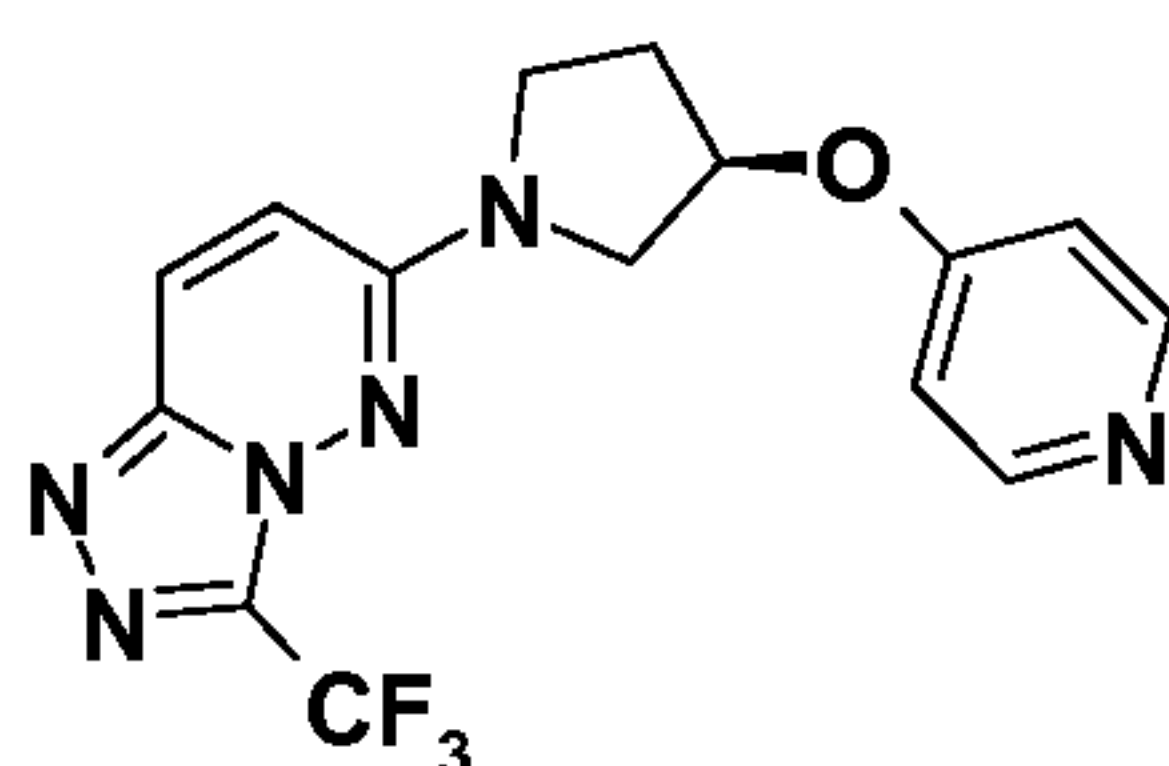
DIAD (0.631 mL, 3.20 mmol) in DCM (5 ml) was added dropwise to a mixture of (S)-tert-butyl 3-hydroxypyrrolidine-1-carboxylate (500 mg, 2.67 mmol), pyridin-3-ol (305  
 15 mg, 3.20 mmol) and triphenylphosphine (840 mg, 3.20 mmol) in DCM (20 ml), cooled in an ice bath. The mixture was allowed to warm to room temperature, stirred for 1 hour and then concentrated. The residue was dissolved in dioxan (15 mL) and 4M HCl in dioxan (15 mL) was added. The mixture was stirred for 1 hour and concentrated. The crude  
 product was purified by ion exchange chromatography, using an SCX column. The desired  
 20 product was eluted from the column using 7M ammonia in methanol and pure fractions were evaporated to dryness to afford (3R)-3-(pyridin-3-yloxy)pyrrolidine (405 mg, 92%) as a colourless oil.



<sup>1</sup>H NMR (399.9 MHz, DMSO-*d*<sub>6</sub>) δ 1.72 - 1.79 (1H, m), 1.99 - 2.08 (1H, m), 2.75 - 2.81 (1H, m), 2.84 - 2.95 (2H, m), 3.05 - 3.09 (1H, m), 4.90 - 4.95 (1H, m), 7.30 - 7.37 (2H, m), 8.15 - 8.16 (1H, m), 8.25 (1H, d); *m/z* = 165 [M+H]<sup>+</sup>.

### **Example 577**

#### **Preparation of 6-[(3R)-3-(pyridin-4-yloxy)pyrrolidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine**



Obtained in 60% yield by an analogous procedure to Example 216, starting from 3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine and (3R)-3-(pyridin-4-yloxy)pyrrolidine.

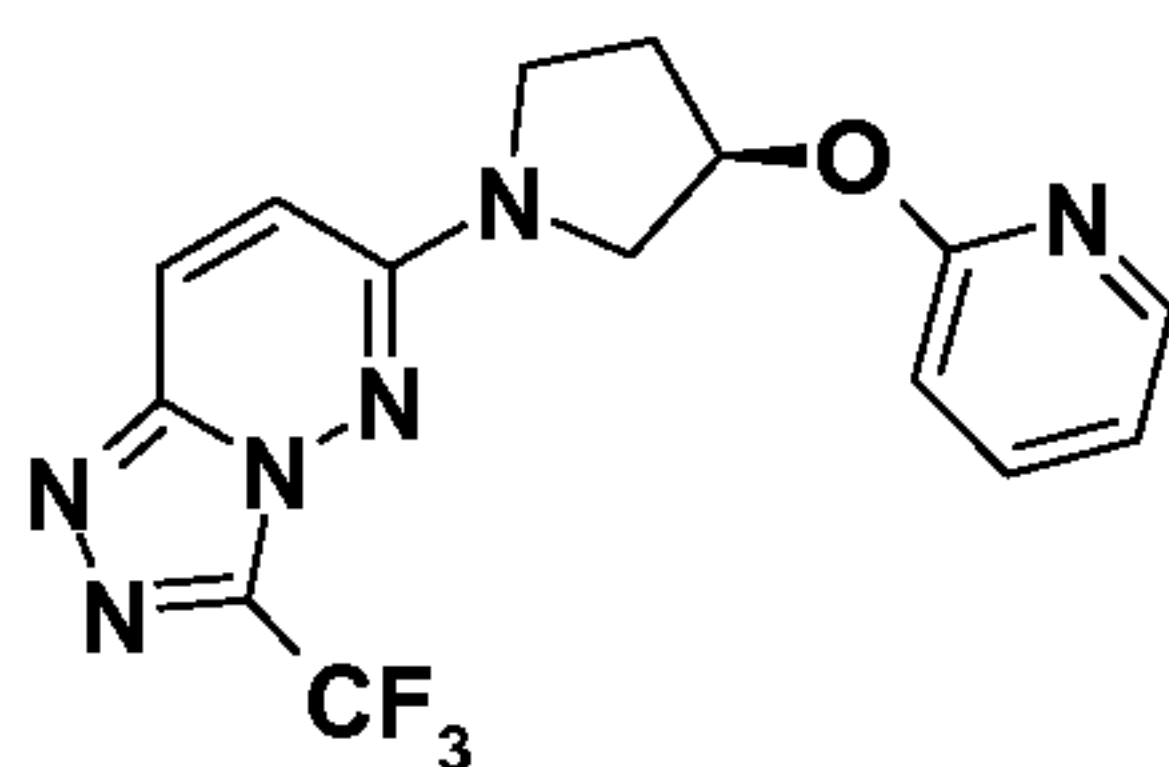
<sup>1</sup>H NMR (399.9 MHz, DMSO-*d*<sub>6</sub>) δ 2.25 - 2.30 (1H, m), 2.34 - 2.41 (1H, m), 3.61 - 3.90 (4H, m), 5.34 - 5.38 (1H, t), 7.03 - 7.04 (2H, m), 7.32 (1H, d), 8.25 (1H, d), 8.41 - 8.43 (2H, m); *m/z* = 351 [M+H]<sup>+</sup>.

The (3R)-3-(pyridin-4-yloxy)pyrrolidine used as starting material was prepared in 61% yield by an analogous method to Example 576, preparation of starting materials, starting from (3S)-tert-butyl 3-hydroxypyrrolidine-1-carboxylate and pyridin-4-ol.

<sup>1</sup>H NMR (399.9 MHz, DMSO-*d*<sub>6</sub>) δ 1.71 - 1.79 (1H, m), 2.01 - 2.10 (1H, m), 2.75 - 2.81 (1H, m), 2.86 - 2.93 (2H, m), 3.05 - 3.14 (1H, m), 4.93 - 4.97 (1H, m), 6.91 - 6.93 (2H, m), 8.36 - 8.38 (2H, m); *m/z* = 165 [M+H]<sup>+</sup>.

### **Example 578**

#### **Preparation of 6-[(3R)-3-(pyridin-2-yloxy)pyrrolidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine**



Obtained in 63% yield by an analogous procedure to Example 216, starting from 3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine and (3R)-3-(pyridin-2-yloxy)pyrrolidine.



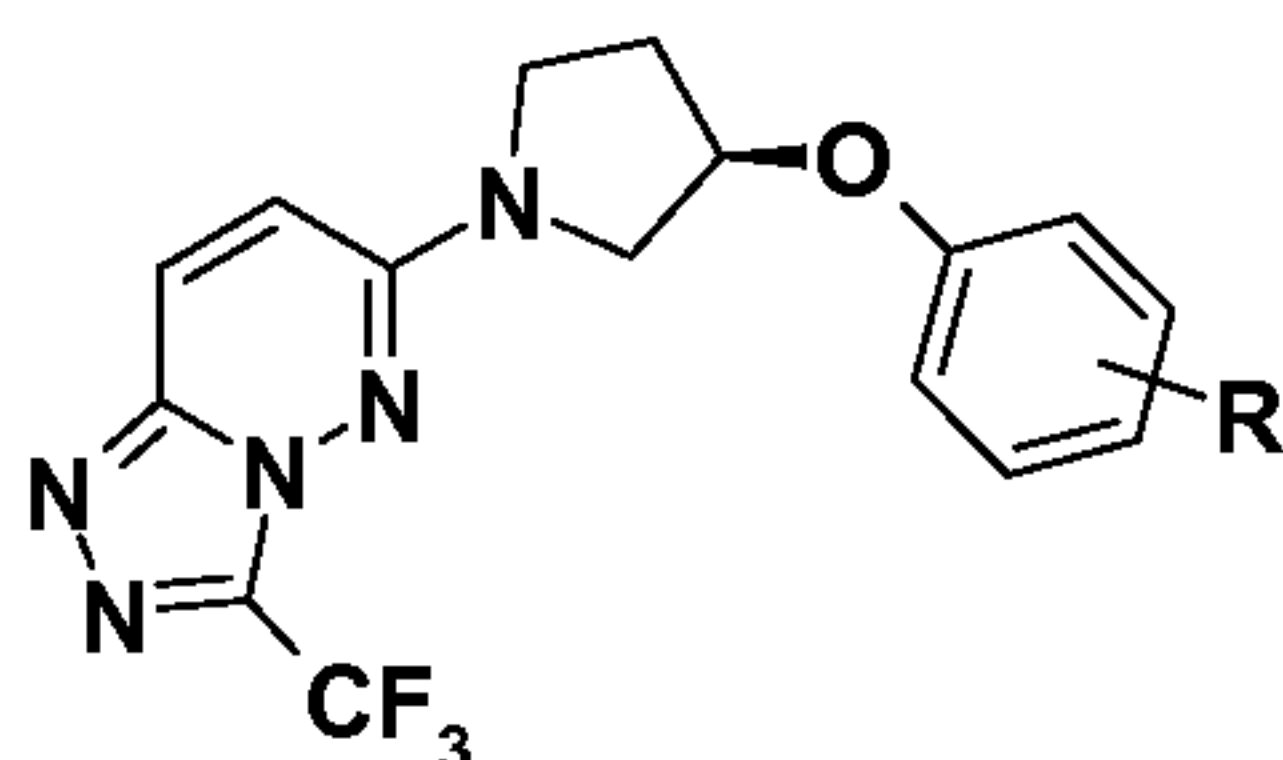
<sup>1</sup>H NMR (399.9 MHz, DMSO-d<sub>6</sub>) δ 2.25 - 2.30 (1H, m), 2.33 - 2.42 (1H, m), 3.65 - 3.76 (3H, m), 3.89 (1H, d), 5.69 - 5.72 (1H, m), 6.82 - 6.84 (1H, m), 7.00 - 7.04 (1H, m), 7.29 - 7.32 (1H, m), 7.71 - 7.75 (1H, m), 8.21 - 8.24 (2H, m); m/z = 351 [M+H]<sup>+</sup>.

The (3R)-3-(pyridin-2-yloxy)pyrrolidine used as starting material was prepared in 65% yield by an analogous method to Example 576, preparation of starting materials, starting from tert-butyl (3S)-3-hydroxypyrrolidine-1-carboxylate and pyridin-2-ol.

<sup>1</sup>H NMR (399.9 MHz, DMSO-d<sub>6</sub>) δ 1.72 - 1.80 (1H, m), 1.97 - 2.06 (1H, m), 2.75 - 2.84 (2H, m), 2.87 - 2.94 (1H, m), 3.05 - 3.10 (1H, m), 5.34 - 5.38 (1H, m), 6.75 - 6.77 (1H, m), 6.93 - 6.96 (1H, m), 7.66 - 7.70 (1H, m), 8.15 - 8.17 (1H, m); m/z = 165 [M+H]<sup>+</sup>.

### **Examples 579-586**

The following compounds were prepared in 29-45% yield by an analogous method to Example 447, starting from (3S)-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]pyrrolidin-3-ol and the appropriate phenol:-



| Ex. | R                 | <sup>1</sup> H NMR (399.9 MHz, DMSO-d <sub>6</sub> )                                                                                                       | m/z [M+H] <sup>+</sup> |
|-----|-------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|
| 579 | 4-CF <sub>3</sub> | δ 2.26 - 2.42 (2H, m), 3.63 - 3.90 (4H, m), 5.33 - 5.37 (1H, m), 7.20 (2H, d), 7.32 (1H, d), 7.69 (2H, d), 8.25 (1H, d)                                    | 418                    |
| 580 | 4-CN              | δ 2.25 - 2.29 (1H, m), 2.33 - 2.41 (1H, m), 3.62 - 3.90 (4H, m), 5.35 - 5.38 (1H, s), 7.17 - 7.21 (2H, m), 7.31 (1H, d), 7.79 - 7.82 (2H, m), 8.25 (1H, d) | 375                    |
| 581 | 4-F               | δ 2.22 - 2.34 (2H, m), 3.61 - 3.84 (4H, m), 5.17 - 5.20 (1H, m), 7.00 - 7.05 (2H, m), 7.12 - 7.18 (2H, m), 7.31 (1H, d), 8.24 (1H, d)                      | 368                    |
| 582 | 4-OMe             | δ 2.20 - 2.34 (2H, m), 3.54 - 3.89 (7H, m), 5.10 - 5.13 (1H, m), 6.87 - 6.90 (2H, m), 6.93 - 6.95 (2H, m), 7.31 (1H, d), 8.24 (1H, d)                      | 380                    |
| 583 | 3-CF <sub>3</sub> | δ 2.28 - 2.37 (2H, m), 3.63 - 3.86 (4H, m), 5.35 - 5.39 (1H, m), 7.31 - 7.34 (4H, m), 7.55 - 7.59 (1H, m), 8.25                                            | 418                    |



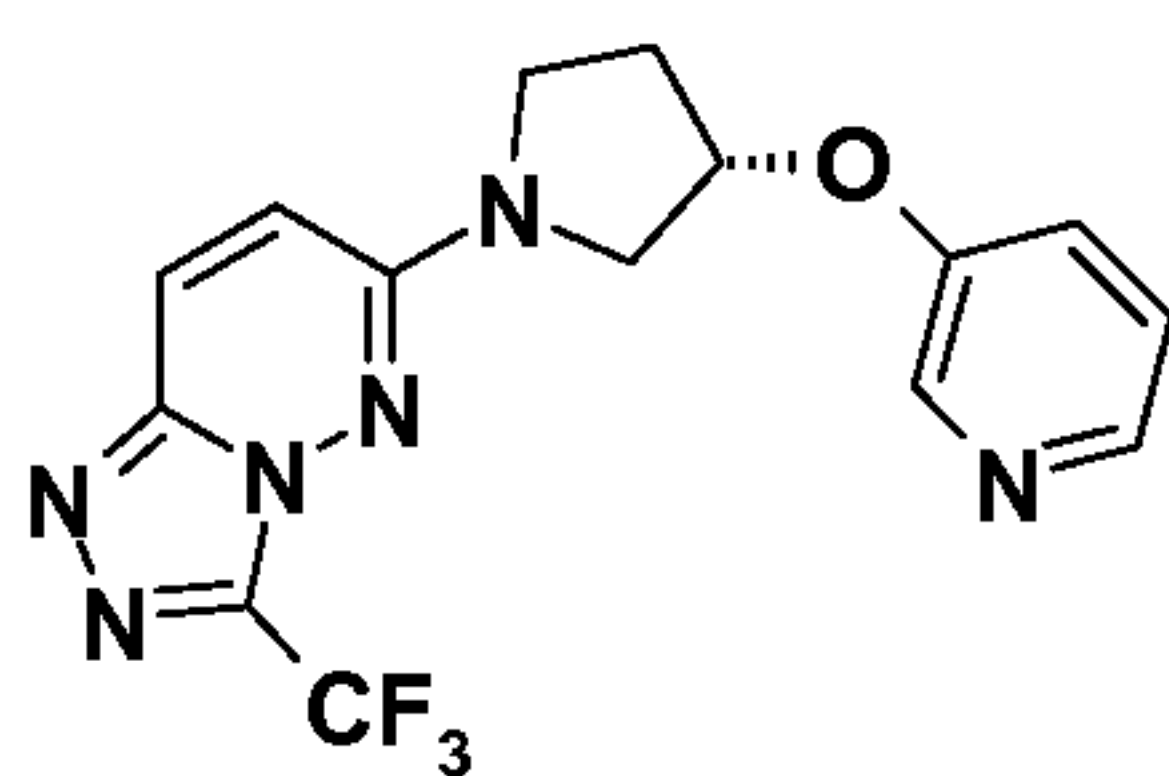
|     |       |                                                                                                                                                                                 |     |
|-----|-------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
|     |       | (1H, d)                                                                                                                                                                         |     |
| 584 | 3-CN  | $\delta$ 2.23 – 2.29 (1H, m), 2.31 - 2.38 (1H, m), 3.62 - 3.89 (4H, m), 5.31 – 5.35 (1H, m), 7.32 (1H, d), 7.34 - 7.37 (1H, m), 7.45 (1H, d), 7.51 - 7.55 (2H, m), 8.25 (1H, d) | 375 |
| 585 | 3-F   | $\delta$ 2.23 - 2.36 (2H, m), 3.61 - 3.87 (4H, m), 5.24 – 5.28 (1H, m), 6.78 - 6.86 (2H, m), 6.89 - 6.93 (1H, m), 7.30 - 7.38 (2H, m), 8.25 (1H, d)                             | 368 |
| 586 | 3-OMe | $\delta$ 2.23 - 2.37 (2H, m), 3.56 - 3.92 (7H, m), 5.20 - 5.24 (1H, m), 6.54 - 6.60 (3H, m), 7.22 (1H, t), 7.32 (1H, d), 8.24 (1H, d)                                           | 380 |

The (3S)-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]pyrrolidin-3-ol used as starting material was prepared in 77% yield by an analogous method to Example 216, preparation of starting materials, starting from 6-chloro-3-(trifluoromethyl)-[1,2,4]-triazolo[4,3-b]pyridazine and (S)-pyrrolidin-3-ol.

<sup>1</sup>H NMR (399.9 MHz, DMSO-d<sub>6</sub>)  $\delta$  1.93 - 1.98 (1H, m), 2.03 - 2.08 (1H, m), 3.42 (1H, d), 3.55 - 3.62 (3H, m), 4.43 - 4.45 (1H, m), 5.07 (1H, d), 7.26 (1H, d), 8.21 (1H, d); m/z = 274 [M+H]<sup>+</sup>.

### **Example 587**

#### **Preparation of 6-[(3S)-3-(pyridin-3-yloxy)pyrrolidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine**



Obtained in 74% yield by an analogous procedure to Example 447, starting from (3R)-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]pyrrolidin-3-ol and pyridin-3-ol.

<sup>1</sup>H NMR (399.9 MHz, DMSO-d<sub>6</sub>)  $\delta$  2.27 - 2.38 (2H, m), 3.63 - 3.88 (4H, m), 5.31 - 5.34 (1H, m), 7.32 (1H, d), 7.35 - 7.39 (1H, m), 7.47 - 7.50 (1H, m), 8.21 - 8.23 (1H, m), 8.25 (1H, d), 8.34 (1H, d); m/z = 351 [M+H]<sup>+</sup>.

The (3R)-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]pyrrolidin-3-ol used as starting material was prepared in 81% yield by an analogous method to Example

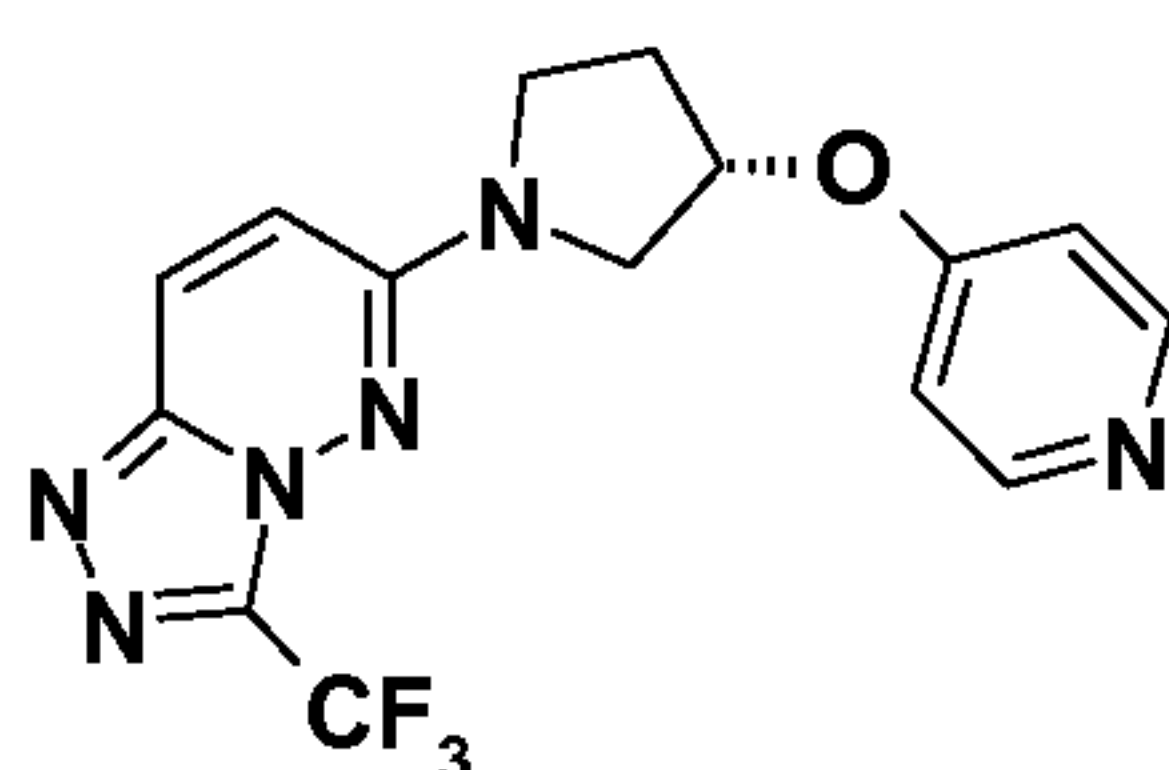


216, preparation of starting materials, starting from 6-chloro-3-(trifluoromethyl)-[1,2,4]-triazolo[4,3-b]pyridazine and (R)-pyrrolidin-3-ol.

<sup>1</sup>H NMR (399.9 MHz, DMSO-*d*<sub>6</sub>) δ 1.93 - 1.98 (1H, m), 2.03 - 2.08 (1H, m), 3.42 (1H, d), 3.55 - 3.62 (3H, m), 4.43 - 4.45 (1H, m), 5.07 (1H, d), 7.26 (1H, d), 8.21 (1H, d); *m/z* = 274 [M+H]<sup>+</sup>.

### **Example 588**

#### **Preparation of 6-[(3S)-3-(pyridin-4-yloxy)pyrrolidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine**

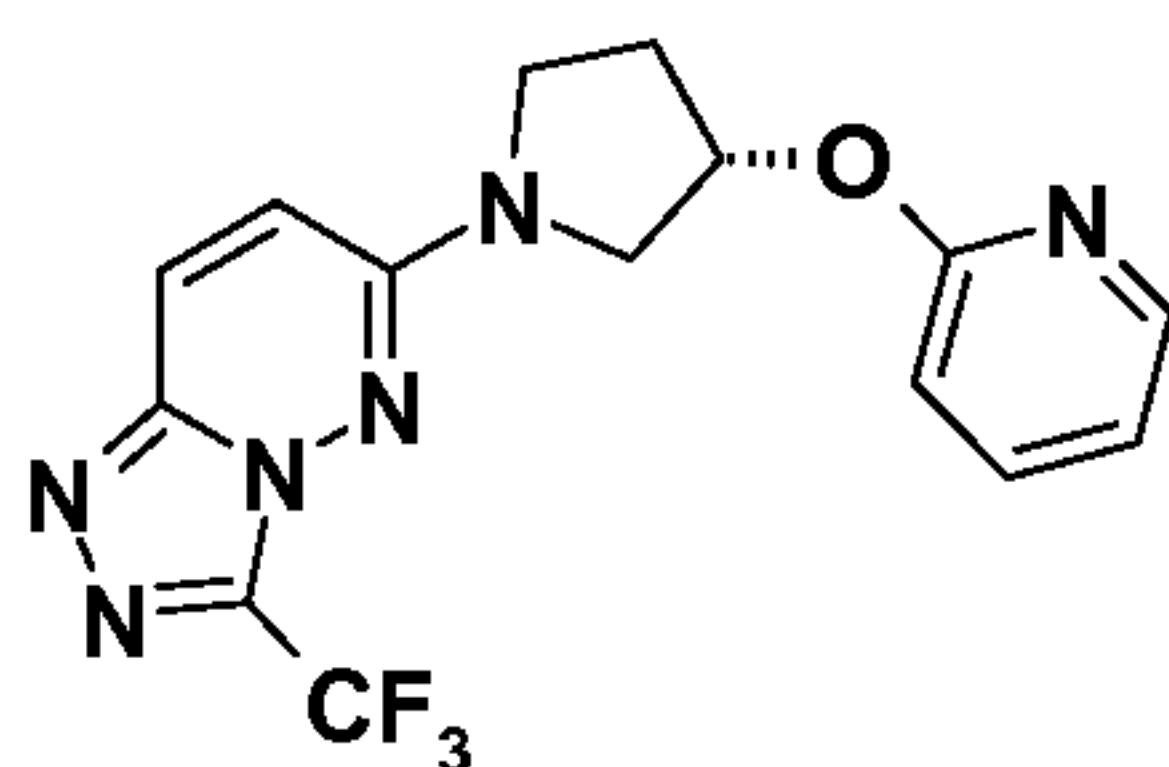


Obtained in 75% yield by an analogous procedure to Example 216, starting from 3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine and (3S)-3-(pyridin-4-yloxy)pyrrolidine. <sup>1</sup>H NMR (399.9 MHz, DMSO-*d*<sub>6</sub>) δ 2.25 - 2.30 (1H, m), 2.34 - 2.43 (1H, m), 3.61 - 3.90 (4H, m), 5.34 - 5.37 (1H, m), 7.03 - 7.04 (2H, m), 7.32 (1H, d), 8.25 (1H, d), 8.41 - 8.43 (2H, m); *m/z* = 351 [M+H]<sup>+</sup>.

The (3S)-3-(pyridin-4-yloxy)pyrrolidine used as starting material was prepared in 61% yield by an analogous method to Example 576, preparation of starting materials, starting from tert-butyl (3R)-3-hydroxypyrrolidine-1-carboxylate and pyridin-4-ol. <sup>1</sup>H NMR (399.9 MHz, DMSO-*d*<sub>6</sub>) δ 1.71 - 1.79 (1H, m), 2.01 - 2.10 (1H, m), 2.75 - 2.81 (1H, m), 2.86 - 2.93 (2H, m), 3.05 - 3.14 (1H, m), 4.93 - 4.97 (1H, m), 6.91 - 6.93 (2H, m), 8.36 - 8.38 (2H, m); *m/z* = 165 [M+H]<sup>+</sup>.

### **Example 589**

#### **Preparation of 6-[(3S)-3-(pyridin-2-yloxy)pyrrolidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine**



Obtained in 62% yield by an analogous procedure to Example 216, starting from 3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine and (3S)-3-(pyridin-2-yloxy)pyrrolidine.



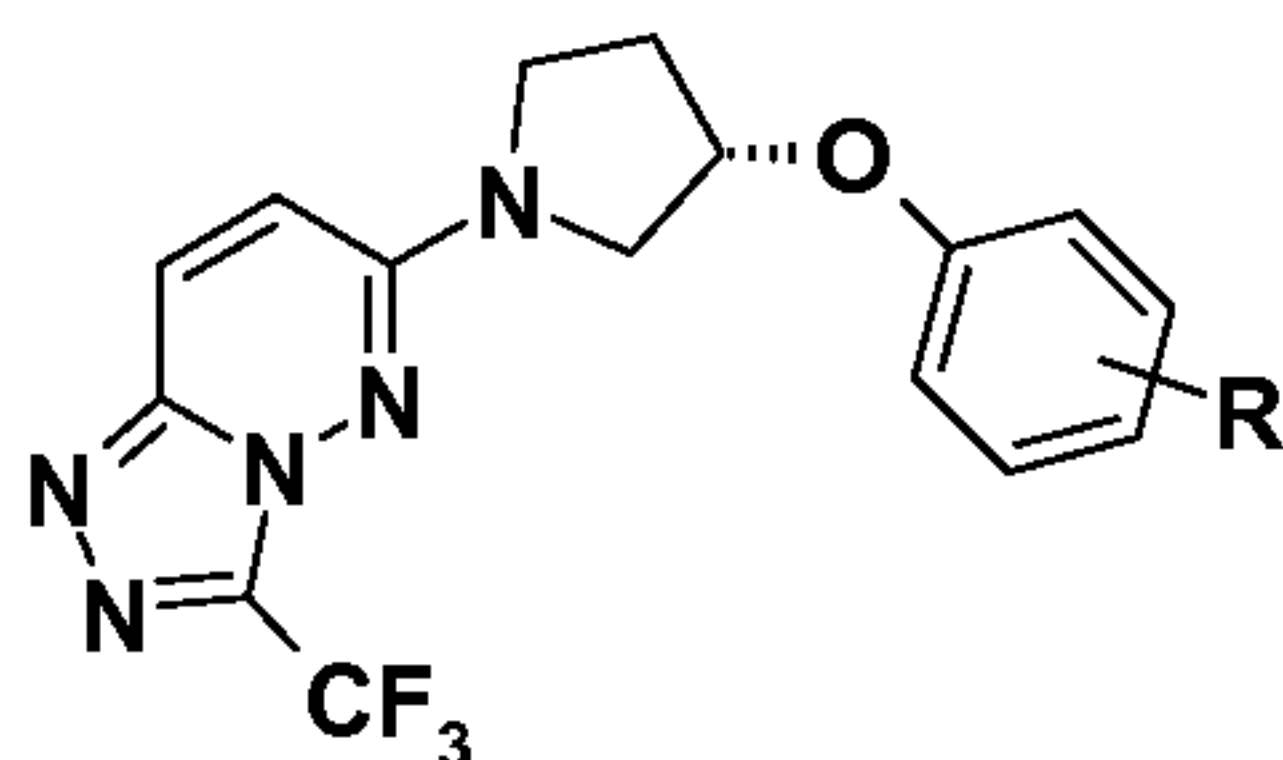
<sup>1</sup>H NMR (399.9 MHz, DMSO-d<sub>6</sub>) δ 2.25 - 2.30 (1H, m), 2.33 - 2.42 (1H, m), 3.65 - 3.76 (3H, m), 3.89 (1H, d), 5.70 - 5.72 (1H, m), 6.82 - 6.84 (1H, m), 7.01 - 7.04 (1H, m), 7.31 (1H, d), 7.71 - 7.75 (1H, m), 8.21 - 8.25 (2H, m); m/z = 351 [M+H]<sup>+</sup>.

The (3S)-3-(pyridin-2-yloxy)pyrrolidine used as starting material was prepared in 62% yield by an analogous method to Example 576, preparation of starting materials, starting from tert-butyl (3R)-3-hydroxypyrrolidine-1-carboxylate and pyridin-2-ol.

<sup>1</sup>H NMR (399.9 MHz, DMSO-d<sub>6</sub>) δ 1.72 - 1.80 (1H, m), 1.97 - 2.06 (1H, m), 2.75 - 2.84 (2H, m), 2.87 - 2.94 (1H, m), 3.05 - 3.10 (1H, m), 5.34 - 5.38 (1H, m), 6.75 - 6.77 (1H, m), 6.93 - 6.96 (1H, m), 7.66 - 7.70 (1H, m), 8.15 - 8.17 (1H, m); m/z = 165 [M+H]<sup>+</sup>.

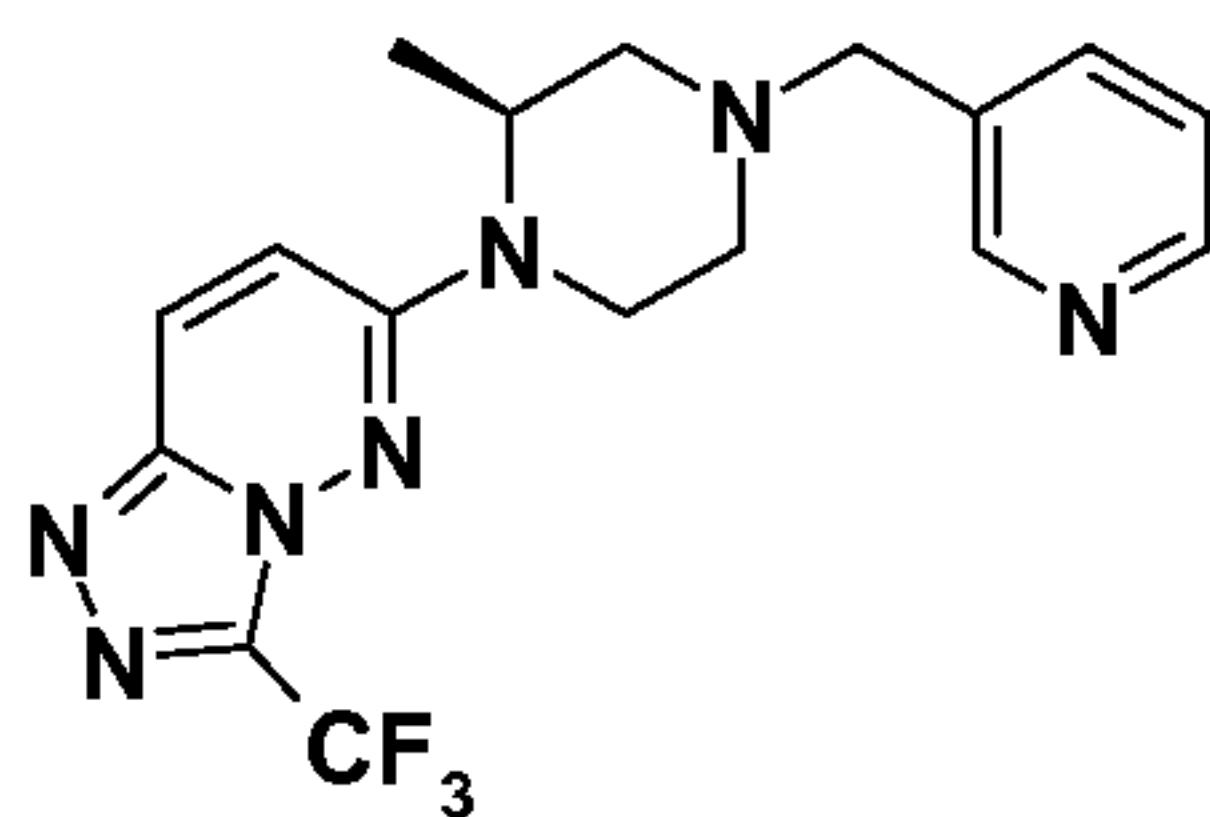
### **Examples 590-592**

The following compounds were prepared in 22-51% yield by an analogous method to Example 447, starting from (3R)-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]pyrrolidin-3-ol (obtained as described in Example 587, preparation of starting materials) and the appropriate phenol:-



| Ex. | R                 | <sup>1</sup> H NMR (399.9 MHz, DMSO-d <sub>6</sub> )                                                                                                                            | m/z [M+H] <sup>+</sup> |
|-----|-------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|
| 590 | 3-CN              | δ 2.24 - 2.29 (1H, m), 2.31 - 2.39 (1H, m), 3.62 - 3.89 (4H, m), 5.33 (1H, s), 7.32 (1H, d), 7.34 - 7.37 (1H, m), 7.43 - 7.46 (1H, m), 7.51 - 7.55 (2H, m), 8.24 - 8.26 (1H, m) | 375                    |
| 591 | 4-CN              | δ 2.27 - 2.30 (1H, m), 2.33 - 2.39 (1H, m), 3.62 - 3.90 (4H, m), 5.37 (1H, s), 7.17 - 7.21 (2H, m), 7.31 (1H, d), 7.79 - 7.83 (2H, m), 8.25 (1H, d)                             | 375                    |
| 592 | 4-CF <sub>3</sub> | δ 2.26 - 2.31 (1H, m), 2.33 - 2.40 (1H, m), 3.63 - 3.90 (4H, m), 5.35 (1H, s), 7.20 (2H, d), 7.32 (1H, d), 7.69 (2H, d), 8.25 (1H, d)                                           | 418                    |



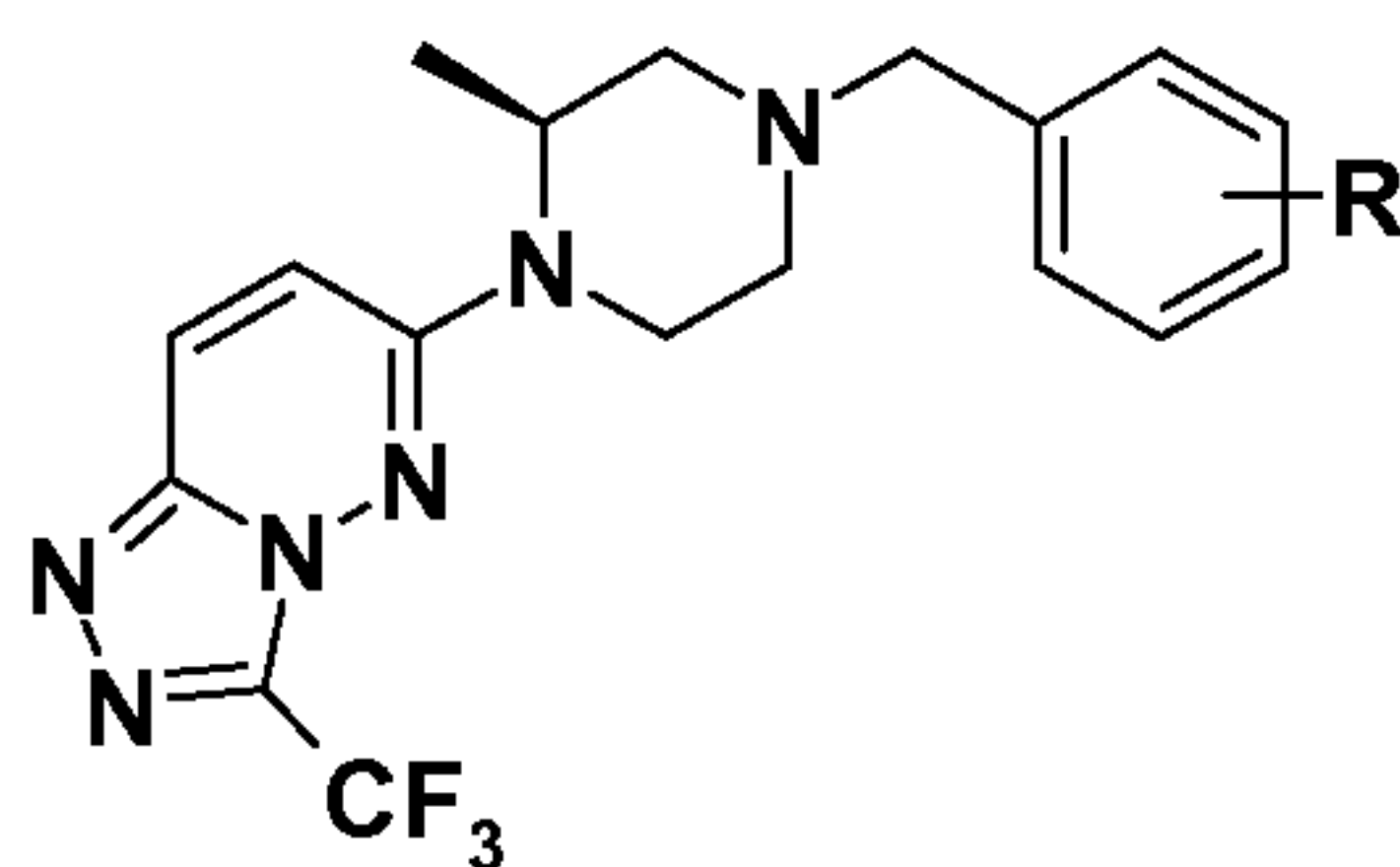
**Example 593****Preparation of 6-[(2S)-2-methyl-4-(pyridin-3-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine**

A mixture of pyridine-3-carboxaldehyde and 6-[(2S)-2-methylpiperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (obtained as described in Example 358, preparation of starting materials) was allowed to react by General Synthetic Method 5, to give 6-[(2S)-2-methyl-4-(pyridin-3-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine in 76% yield.

<sup>1</sup>H NMR (500.1MHz, DMSO-d<sub>6</sub>, 373K) δ 1.31 (3H, d), 2.42 (1H, m), 2.56 (1H, m), 2.88 (1H, m), 3.04 (1H, m), 3.33 (1H, m), 3.77 (2H, m), 4.05 (1H, m), 4.51 (1H, m), 7.47 (2H, m), 7.91 (1H, m), 8.15 (1H, d), 8.56 (1H, m), 8.63 (1H, m); m/z = 378 [M+H]<sup>+</sup>.

**Examples 594-598**

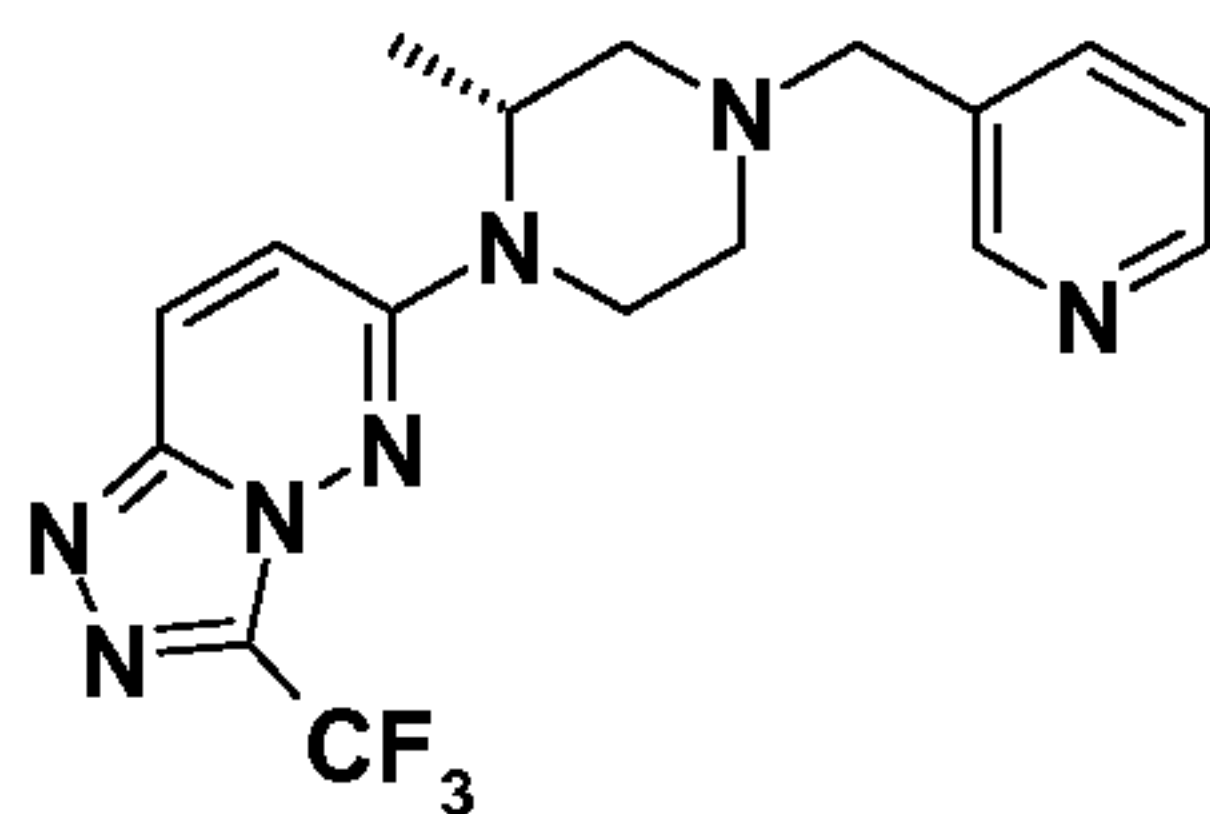
The following compounds were prepared in 43-89% yield by General Synthetic Method 5, starting from 6-[(2S)-2-methylpiperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine and the appropriate aldehyde:-



| Ex. | R        | <sup>1</sup> H NMR (400.1 MHz, CDCl <sub>3</sub> )                                                                                                                                     | m/z [M+H] <sup>+</sup> |
|-----|----------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|
| 594 | 4-CN     | δ 1.47 (3H, d), 2.70 (1H, m), 2.86 (1H, m), 3.20 (1H, m), 3.50 (1H, m), 3.63 (1H, m), 4.01 (1H, d), 4.15 (2H, m), 4.55 (1H, m), 7.05 (1H, d), 7.60 (2H, d), 7.73 (2H, d), 8.05 (1H, d) | 402                    |
| 595 | 3,4-di-F | δ 1.35 (3H, d), 2.22 (1H, m), 2.36 (1H, m), 2.76 (1H, m), 2.95 (1H, m), 3.33 (1H, m), 3.44 (1H, d), 3.55                                                                               | 413                    |



|     |           |                                                                                                                                                                                                             |     |
|-----|-----------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
|     |           | (1H, d), 3.98 (1H, m), 4.33 (1H, m), 7.04 - 7.16 (3H, m), 7.23 (1H, m), 7.93 (1H, d)                                                                                                                        |     |
| 596 | 3,5-di-F  | $\delta$ 1.48 (3H, d), 2.73 (1H, m), 2.90 (1H, m), 3.28 (1H, m), 3.57 (1H, m), 3.67 (1H, m), 4.00 (1H, d), 4.15 (2H, m), 4.58 (1H, m), 6.89 (1H, m), 7.01 (2H, m), 7.05 (1H, d), 8.06 (1H, d)               | 413 |
| 597 | 4-F       | $\delta$ 1.51 (3H, d), 2.83 (1H, m), 3.02 (1H, m), 3.41 (1H, m), 3.77 (2H, m), 4.18 (2H, m), 4.35 (1H, d), 4.64 (1H, m), 7.03 (1H, d), 7.15 (2H, m), 7.45 (2H, m), 8.05 (1H, d)                             | 395 |
| 598 | 3-CN, 4-F | $\delta$ 1.36 (3H, d), 2.25 (1H, m), 2.41 (1H, m), 2.74 (1H, m), 2.92 (1H, m), 3.33 (1H, m), 3.49 (1H, d), 3.58 (1H, d), 3.99 (1H, m), 4.34 (1H, m), 7.06 (1H, d), 7.21 (1H, m), 7.63 (2H, m), 7.94 (1H, d) | 420 |

**Example 599****Preparation of 6-[(2R)-2-methyl-4-(pyridin-3-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine**

- 5 A mixture of pyridine-3-carboxaldehyde and 6-[(2R)-2-methylpiperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine was allowed to react by General Synthetic Method 5 to give 6-[(2R)-2-methyl-4-(pyridin-3-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine in quantitative yield.

1H NMR (500.1MHz, DMSO-d<sub>6</sub>, 373K)  $\delta$  1.30 (3H, d), 2.37 (1H, m), 2.55 (1H, m), 2.85  
 10 (1H, m), 3.02 (1H, m), 3.32 (1H, m), 3.73 (2H, m), 4.04 (1H, m), 4.50 (1H, m), 7.45 (2H, m), 7.87 (1H, m), 8.15 (1H, d), 8.54 (1H, m), 8.61 (1H, m);  $m/z$  = 378 [M+H]<sup>+</sup>.

The 6-[(2R)-2-methylpiperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine used as starting material was prepared in 2 steps in 74% overall yield by an analogous method to Example 223, preparation of starting materials, starting from 6-



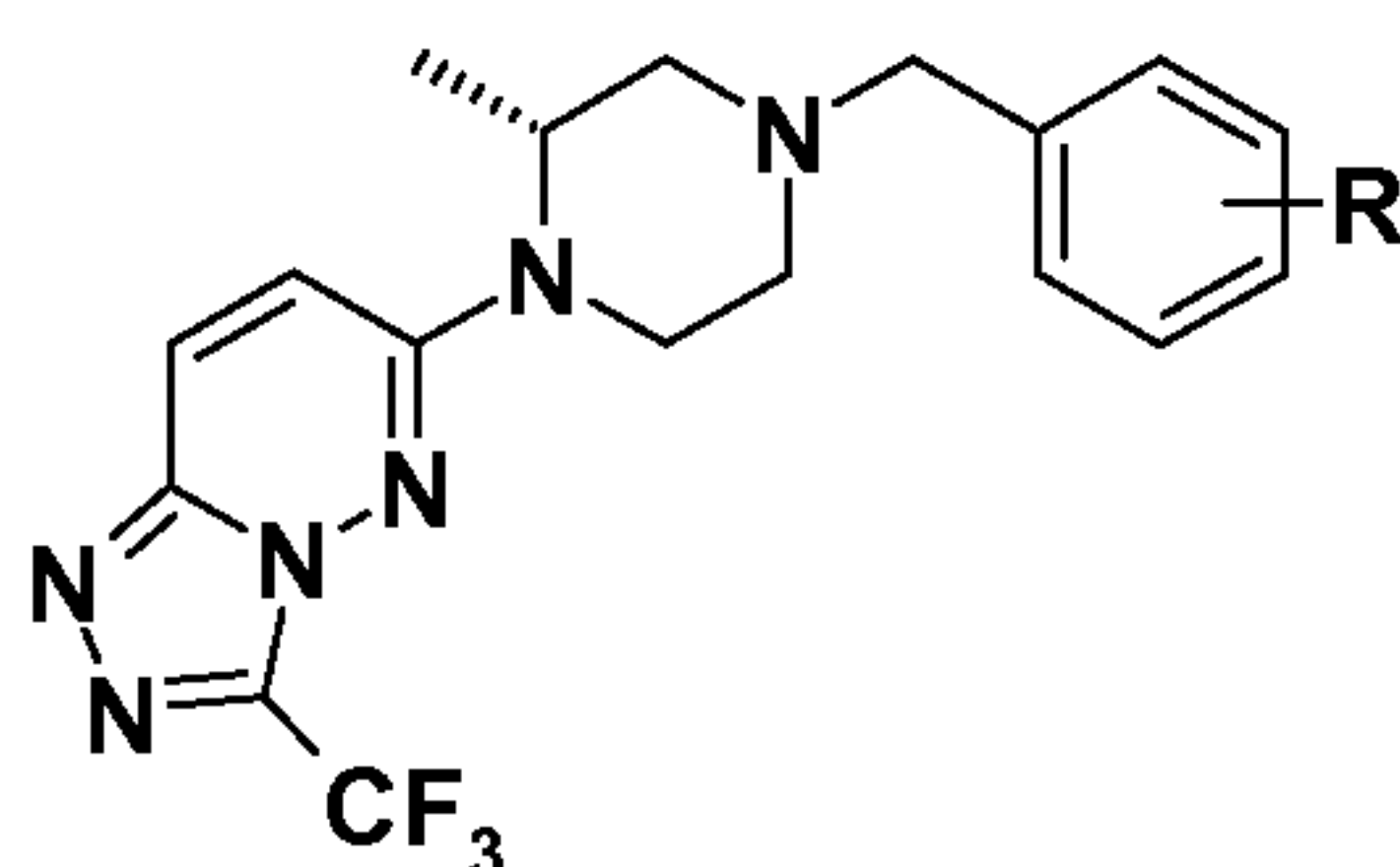
chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine and (3R)-tert-butyl 3-methylpiperazine-1-carboxylate.

<sup>1</sup>H NMR (399.1 MHz, DMSO-d<sub>6</sub>) δ 1.23 (3H, d), 2.43 (1H, m), 2.65 (1H, m), 2.85 (2H, m), 3.04 (2H, m), 3.91 (1H, m), 4.35 (1H, m), 7.56 (1H, d), 8.23 (1H, d); m/z = 287

5 [M+H]<sup>+</sup>.

#### **Examples 600-604**

The following compounds were prepared in 56-93% yield by by General Synthetic Method 5, starting from 6-[(2R)-2-methylpiperazin-1-yl]-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine and the appropriate aldehyde:-

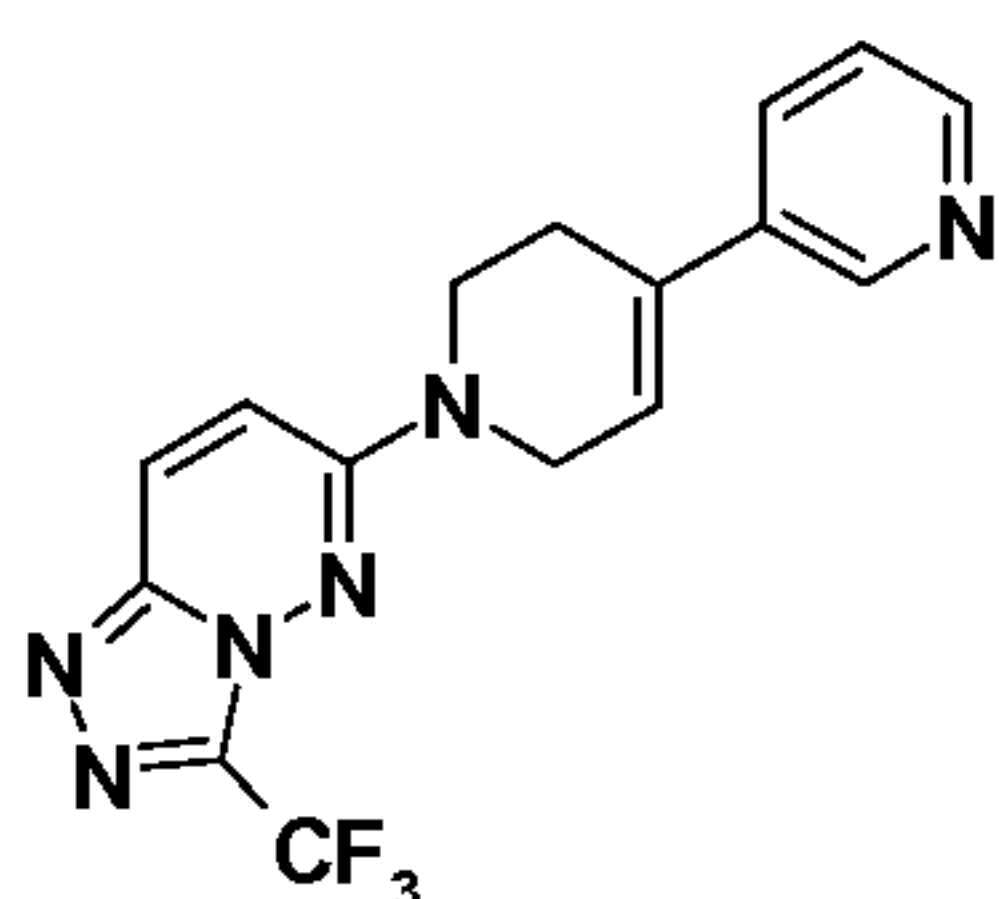


10

| Ex. | R        | <sup>1</sup> H NMR (400.1 MHz, CDCl <sub>3</sub> )                                                                                                                                     | m/z [M+H] <sup>+</sup> |
|-----|----------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|
| 600 | 4-CN     | δ 1.46 (3H, d), 2.68 (1H, m), 2.84 (1H, m), 3.18 (1H, m), 3.48 (1H, m), 3.62 (1H, m), 3.99 (1H, d), 4.14 (2H, m), 4.54 (1H, m), 7.05 (1H, d), 7.59 (2H, d), 7.72 (2H, d), 8.04 (1H, d) | 402                    |
| 601 | 3,4-di-F | δ 1.47 (3H, d), 2.70 (1H, m), 2.87 (1H, m), 3.25 (1H, m), 3.56 (1H, m), 3.66 (1H, m), 3.97 (1H, d), 4.14 (2H, m), 4.57 (1H, m), 7.02 - 7.33 (4H, m), 8.04 (1H, d)                      | 413                    |
| 602 | 3,5-di-F | δ 1.47 (3H, d), 2.68 (1H, m), 2.85 (1H, m), 3.23 (1H, m), 3.52 (1H, m), 3.64 (1H, m), 3.95 (1H, d), 4.12 (2H, m), 4.56 (1H, m), 6.88 (1H, m), 7.00 (2H, m), 7.05 (1H, d), 8.05 (1H, d) | 413                    |
| 603 | 4-F      | δ 1.50 (3H, d), 2.82 (1H, m), 3.00 (1H, m), 3.39 (1H, m), 3.75 (2H, m), 4.17 (2H, m), 4.33 (1H, d), 4.63 (1H, m), 7.02 (1H, d), 7.15 (2H, m), 7.45 (2H, m), 8.05 (1H, d)               | 395                    |
| 604 | 3-CN, 4- | δ 1.35 (3H, d), 2.25 (1H, m), 2.41 (1H, m), 2.74 (1H, m)                                                                                                                               | 420                    |



|  |   |                                                                                                                                                |  |
|--|---|------------------------------------------------------------------------------------------------------------------------------------------------|--|
|  | F | m), 2.93 (1H, m), 3.33 (1H, m), 3.49 (1H, d), 3.58 (1H, d), 3.99 (1H, m), 4.35 (1H, m), 7.06 (1H, d), 7.21 (1H, m), 7.63 (2H, m), 7.94 (1H, d) |  |
|--|---|------------------------------------------------------------------------------------------------------------------------------------------------|--|

**Example 605****Preparation of 1'-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]-1',2',3',6'-tetrahydro-3,4'-bipyridine**

- 5 Sodium carbonate (114 mg, 1.08 mmol) was added to 1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]-1,2,3,6-tetrahydropyridin-4-yl trifluoromethanesulfonate (150 mg, 0.36 mmol) and 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (81 mg, 0.40 mmol) in a mixture of DME (2 mL) and water (0.5 mL). The mixture was bubbled with nitrogen for 10 minutes then
- 10 tetrakis(triphenylphosphine)palladium(0) (20.77 mg, 0.02 mmol) was added and the mixture was stirred at 80°C for 3 hours. The reaction mixture was cooled to room temperature and diluted with EtOAc (3 mL) and water (2 mL). The organic layer was separated and dried, and the solvent was evaporated to give crude product. Purification by flash silica chromatography, elution gradient 0 to 3% MeOH in DCM, gave 1'-[3-
- 15 (trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]-1',2',3',6'-tetrahydro-3,4'-bipyridine (100 mg, 80%).

<sup>1</sup>H NMR (399.1 MHz, DMSO-d<sub>6</sub>) δ 2.70 (2H, m), 3.91 (2H, m), 4.29 (2H, m), 6.44 (1H, m), 7.41 (1H, m), 7.69 (1H, d), 7.89 (1H, m), 8.30 (1H, d), 8.50 (1H, m), 8.74 (1H, m); m/z = 347 [M+H]<sup>+</sup>.

- 20 The 1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]-1,2,3,6-tetrahydropyridin-4-yl trifluoromethanesulfonate used as starting material was prepared as follows:-

- A solution of 1-(3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)piperidin-4-one (obtained as described in Example 310, preparation of starting materials) (11.08 g, 38.85 mmol) in THF (200 mL) was added dropwise to 1M lithium bis(trimethylsilyl)amide
- 25

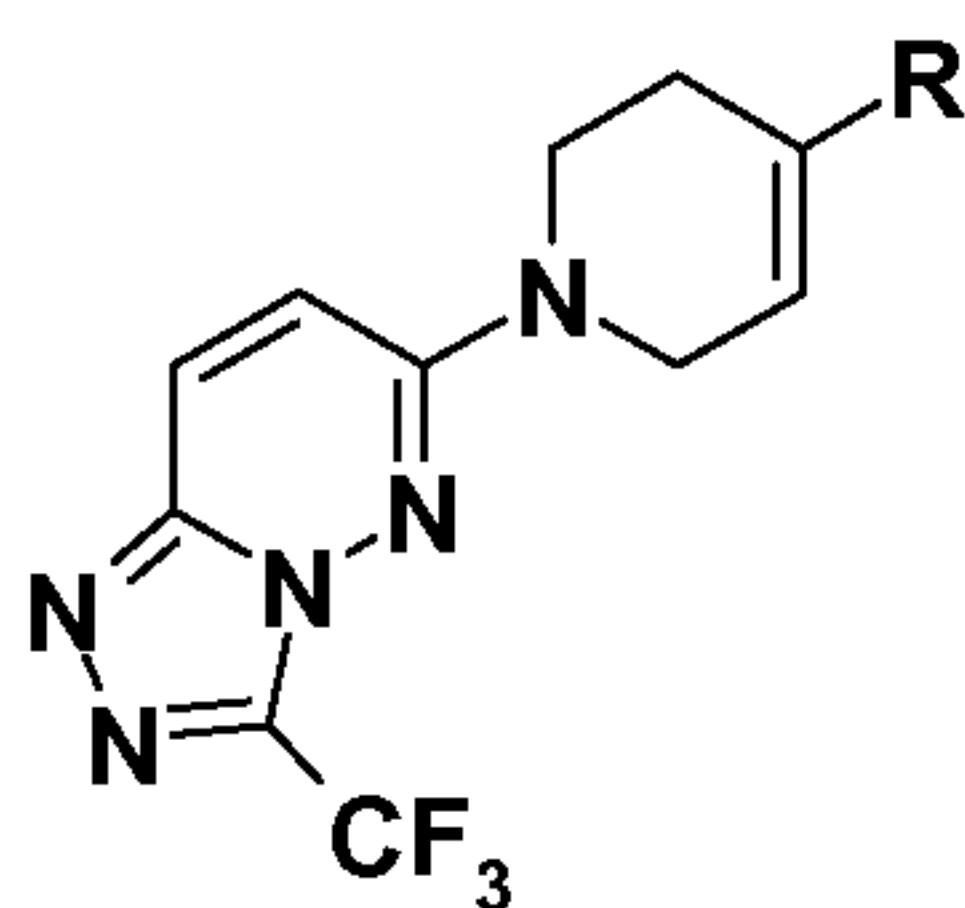


in THF (42.7 mL, 42.73 mmol) at -78 °C, over a period of 30 minutes under nitrogen. The resulting suspension was stirred at -78°C for 20 minutes, then a solution of N-phenyltrifluoromethanesulfonimide (15.27 g, 42.73 mmol) in THF (150 ml) was added dropwise over a period of 10 minutes. The mixture was stirred at -78°C for 30 minutes then allowed to warm to room temperature overnight. The reaction mixture was quenched with saturated aqueous ammonium chloride (5 mL), then concentrated and diluted with DCM (500 mL), washed with water (300 mL) then brine (300 mL) and evaporated to afford crude product. DCM (100 mL) was added to the crude product, the precipitate was collected by filtration and the filtrate was purified by flash silica chromatography, elution gradient 50 to 80% EtOAc in isohexane. Pure fractions were evaporated to dryness and combined with the previously collected precipitate to afford 1-(3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)-1,2,3,6-tetrahydropyridin-4-yl trifluoromethanesulfonate (12.91 g, 80%).

<sup>1</sup>H NMR (399.9 MHz, DMSO-d<sub>6</sub>) δ 2.63 (2H, m), 3.90 (2H, m), 4.25 (2H, m), 6.19 (1H, m), 7.67 (1H, d), 8.33 (1H, d); m/z = 418 [M+H]<sup>+</sup>.

### **Examples 606-609**

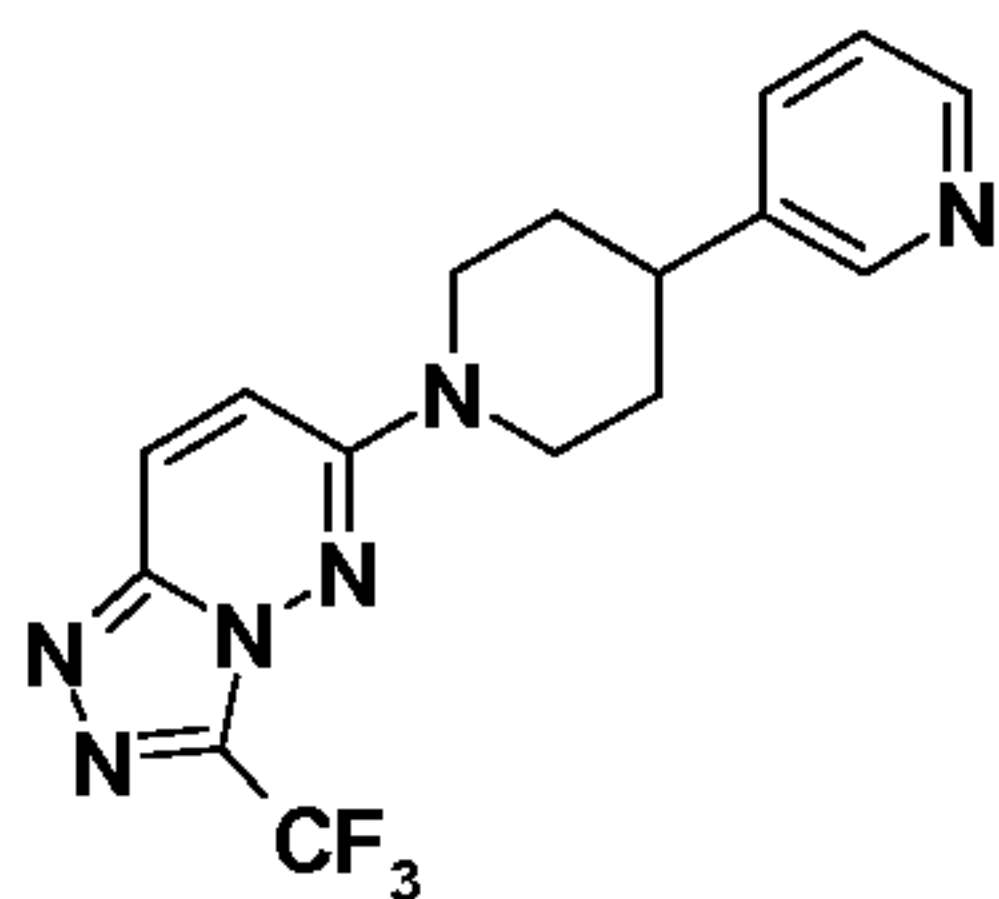
The following compounds were prepared in 54-77% yield by an analogous method to Example 605, starting from 1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]-1,2,3,6-tetrahydropyridin-4-yl trifluoromethanesulfonate and the appropriate heteroaryl boronic acid or boronic acid pinacol ester:-



| Ex. | R                    | <sup>1</sup> H NMR (399.9 MHz, DMSO-d <sub>6</sub> )                                                                           | m/z [M+H] <sup>+</sup> |
|-----|----------------------|--------------------------------------------------------------------------------------------------------------------------------|------------------------|
| 606 | 3-fluoropyridin-4-yl | δ 2.68 (2H, m), 3.90 (2H, m), 4.31 (2H, m), 6.47 (1H, m), 7.49 (1H, m), 7.68 (1H, d), 8.31 (1H, d), 8.44 (1H, m), 8.57 (1H, d) | 365                    |
| 607 | 5-fluoropyridin-3-yl | δ 2.71 (2H, m), 3.91 (2H, m),                                                                                                  | 365                    |



|     |                                |                                                                                                                                                     |     |
|-----|--------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------|-----|
|     |                                | 4.30 (2H, m), 6.55 - 6.57 (1H, m), 7.70 (1H, d), 7.84 - 7.88 (1H, m), 8.30 (1H, d), 8.50 (1H, m), 8.63 (1H, m)                                      |     |
| 608 | 5-(ethoxycarbonyl)pyridin-3-yl | $\delta$ 1.36 (3H, t), 2.75 (2H, m), 3.92 (2H, m), 4.31 (2H, m), 4.38 (2H, q), 6.56 (1H, m), 7.69 (1H, d), 8.29 - 8.32 (2H, m), 8.98 - 9.00 (2H, m) | 419 |
| 609 | 5-fluoro-6-methoxypyridin-3-yl | $\delta$ 2.66 (2H, m), 3.89 (2H, m), 3.97 (3H, s), 4.26 - 4.27 (2H, m), 6.38 (1H, m), 7.69 (1H, d), 7.87 - 7.91 (1H, m), 8.11 (1H, d), 8.29 (1H, d) | 395 |

**Example 610****Preparation of 6-(4-pyridin-3-ylpiperidin-1-yl)-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine**

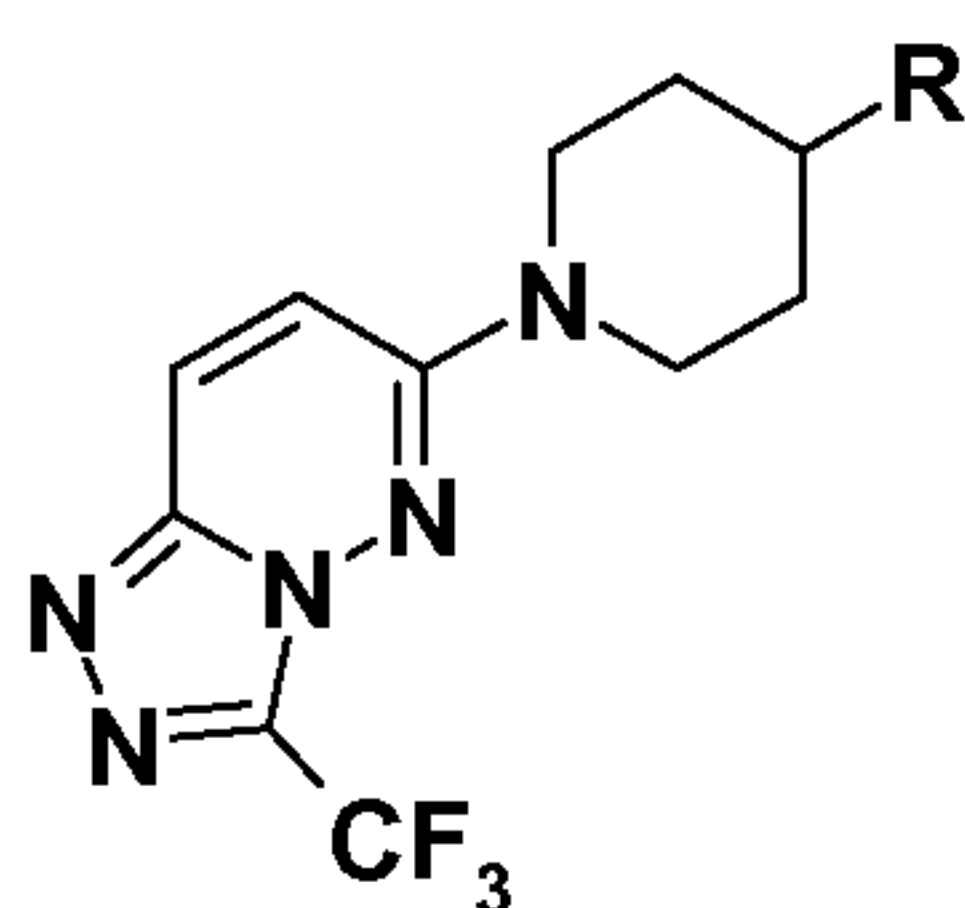
- 5 A mixture of 1'-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]-1',2',3',6'-tetrahydro-3,4'-bipyridine (obtained as described in Example 605) (82 mg, 0.24 mmol) and 10% palladium on carbon (25.2 mg, 0.02 mmol) in MeOH (10 mL) was stirred under an atmosphere of hydrogen at atmospheric pressure for 3 days. The catalyst was removed by filtration and the solvent evaporated to give crude product, which was purified by flash
- 10 silica chromatography, elution gradient 0 to 3% MeOH in DCM. Fractions containing the desired product were evaporated to dryness to give 6-(4-pyridin-3-ylpiperidin-1-yl)-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine (24 mg, 29%).



<sup>1</sup>H NMR (399.1 MHz, DMSO-d<sub>6</sub>)  $\delta$  1.75 (2H, m), 1.93 (2H, m), 2.94 (1H, m), 3.14 (2H, m), 4.44 (2H, m), 7.33 (1H, m), 7.69 (2H, m), 8.26 (1H, d), 8.43 (1H, m), 8.53 (1H, d);  
m/z = 349 [M+H]<sup>+</sup>.

### **Examples 611-614**

- 5 The following compounds were prepared in 13-57% yield by an analogous method to Example 610, starting from the appropriate tetrahydro bipyridine (obtained as described in Examples 606-609):-



| Ex. | R                              | <sup>1</sup> H NMR (399.9 MHz, DMSO-d <sub>6</sub> )                                                                                                                            | m/z [M+H] <sup>+</sup> |
|-----|--------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|
| 611 | 3-fluoropyridin-4-yl           | $\delta$ 1.79 (2H, m), 1.91 (2H, m), 3.21 (3H, m), 4.44 (2H, m), 7.44 (1H, m), 7.67 (1H, d), 8.26 (1H, d), 8.38 (1H, d), 8.51 (1H, d)                                           | 367                    |
| 612 | 5-fluoropyridin-3-yl           | $\delta$ 1.75 - 1.79 (2H, m), 1.94 (2H, m), 2.98 - 3.17 (3H, m), 4.43 - 4.46 (2H, m), 7.66 - 7.72 (2H, m), 8.26 (1H, d), 8.43 (2H, m)                                           | 367                    |
| 613 | 5-(ethoxycarbonyl)pyridin-3-yl | $\delta$ 1.34 (3H, t), 1.78 - 1.82 (2H, m), 1.96 (2H, m), 3.08 - 3.17 (3H, m), 4.36 (2H, q), 4.46 (2H, m), 7.67 (1H, d), 8.16 (1H, m), 8.26 (1H, d), 8.79 (1H, m), 8.96 (1H, m) | 462 [1]                |
| 614 | 5-fluoro-6-methoxypyridin-3-yl | $\delta$ 1.70 - 1.74 (2H, m), 1.90 (2H, m), 2.92 (1H, m), 3.08 - 3.14 (2H, m), 3.92 (3H, s), 4.43 (2H, m), 7.65 - 7.69 (2H, m), 7.91                                            | 397                    |

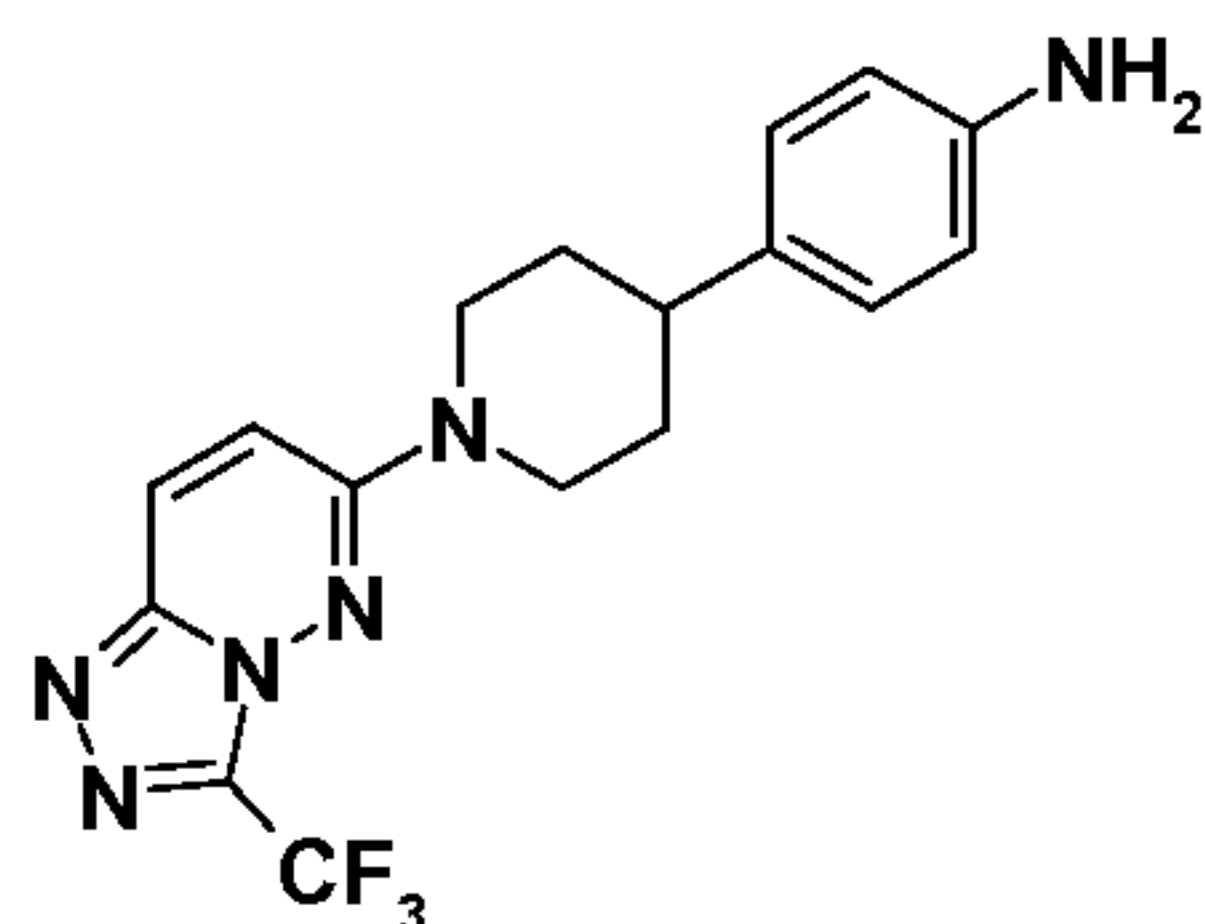


|  |                       |  |
|--|-----------------------|--|
|  | (1H, m), 8.25 (1H, d) |  |
|--|-----------------------|--|

[1] Detected as adduct with acetonitrile used as solvent in mass spectral determination

### **Example 615**

#### **Preparation of 4-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]aniline**



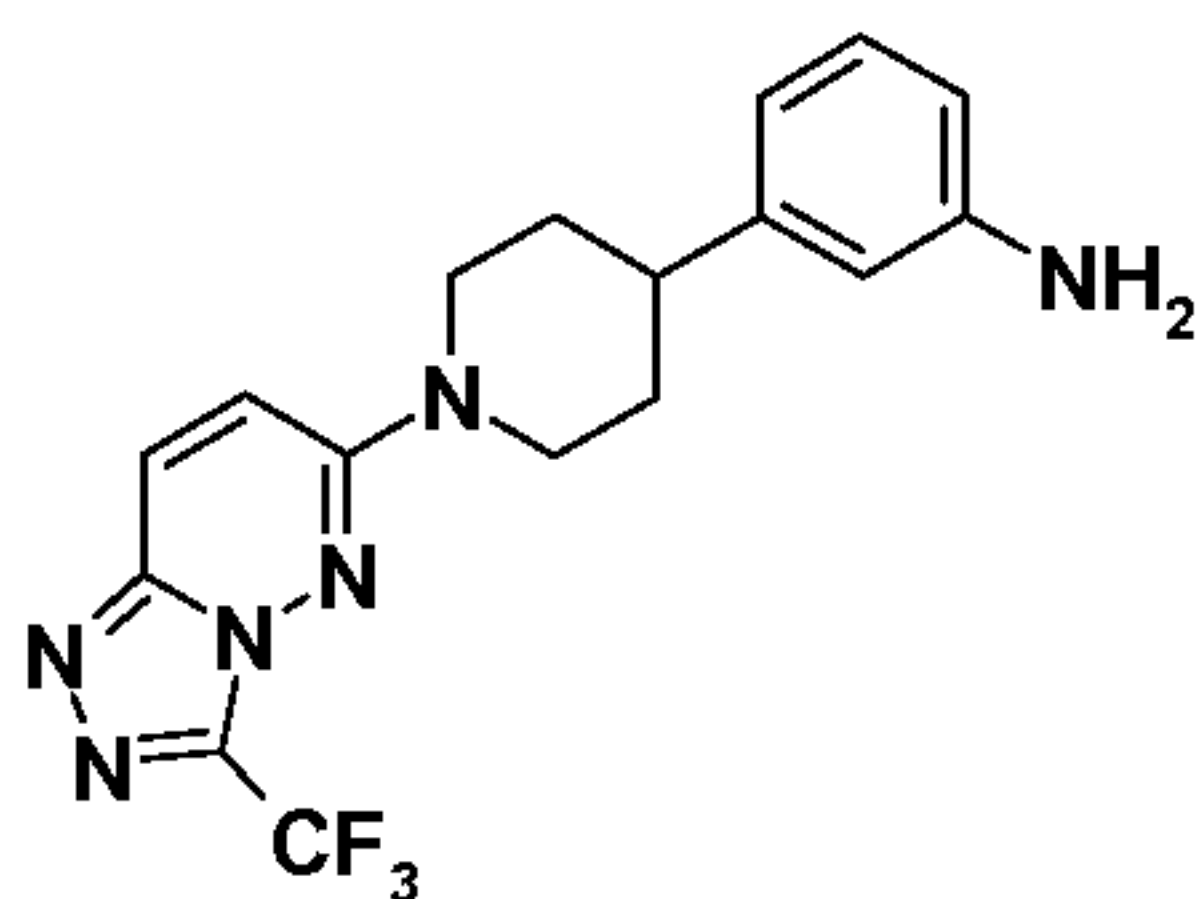
DIPEA (1.631 mL, 9.36 mmol) was added to 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (1.389 g, 6.24 mmol) and 4-(piperidin-4-yl)aniline (1.21 g, 6.86 mmol) in DMF (30 mL). The resulting solution was stirred at 80°C for 2 hours. The reaction mixture was evaporated to dryness, redissolved in DCM and purified by flash chromatography on silica gel, elution gradient 0 to 3% MeOH in DCM. Pure fractions were evaporated to dryness to give 4-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]aniline (1.910 g, 84%) as a solid.

1H NMR (399.9 MHz, CDCl<sub>3</sub>) δ 1.72 - 1.79 (2H, m), 1.96 - 2.00 (2H, m), 2.70 - 2.73 (1H, m), 3.06 - 3.14 (2H, m), 3.60 (2H, s), 4.33 - 4.38 (2H, m), 6.65 (2H, d), 7.01 (2H, d), 7.12 (1H, d), 7.91 (1H, d); m/z = 363 [M+H]<sup>+</sup>.

The 4-(piperidin-4-yl)aniline used as starting material was prepared as follows;

TFA (5 mL) was added to tert-butyl 4-(4-aminophenyl)piperidine-1-carboxylate (1.9 g, 6.87 mmol, CAS 170011-57-1) in DCM (5 mL). The resulting solution was stirred at ambient temperature for 2 hours then added to an SCX column. The desired product was eluted from the column using 2M ammonia in methanol and the solvent evaporated to dryness to give 4-(piperidin-4-yl)aniline (1.210 g, 100%) as a solid. m/z = 177 [M+H]<sup>+</sup>.



**Example 616****Preparation of 3-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]aniline**

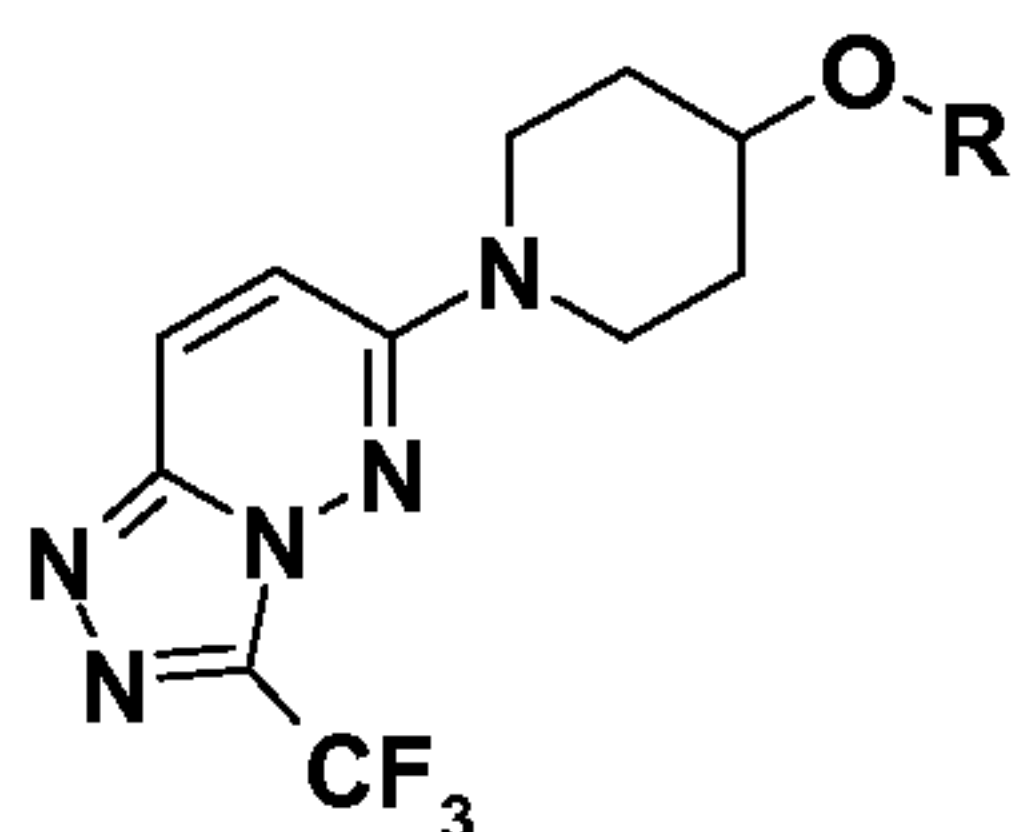
- 5 Obtained in 78% yield by an analogous procedure to Example 615, starting from 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine and 3-(piperidin-4-yl)aniline.

<sup>1</sup>H NMR (399.9 MHz, CDCl<sub>3</sub>) δ 1.76 - 1.80 (2H, m), 2.00 (2H, m), 2.74 (1H, m), 3.07 - 3.14 (2H, m), 3.64 (2H, s), 4.34 - 4.39 (2H, m), 6.54 - 6.63 (3H, m), 7.11 (2H, m), 7.92 (1H, d); m/z = 363 [M+H]<sup>+</sup>.

- 10 The 3-(piperidin-4-yl)aniline used as starting material was prepared in 97% yield by an analogous procedure to Example 616, preparation of starting materials, starting from tert-butyl 4-(3-aminophenyl)piperidine-1-carboxylate (CAS 387827-19-2).  
m/z = 177 [M+H]<sup>+</sup>.

**Examples 617-622**

- 15 The following compounds were prepared in 9-67% yield by an analogous method to Example 447, starting from 1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol (obtained as described in Example 412, preparation of starting materials) and the appropriate hydroxy heterocycle:-



| Ex. | R                    | <sup>1</sup> H NMR (399.9 MHz, DMSO-d <sub>6</sub> )                                                                           | m/z [M+H] <sup>+</sup> |
|-----|----------------------|--------------------------------------------------------------------------------------------------------------------------------|------------------------|
| 617 | 5-chloropyridin-3-yl | δ 1.75 (2H, m), 2.10 (2H, m), 3.52 (2H, m), 3.99 (2H, m), 4.85 (1H, m), 7.65 (1H, d), 7.74 (1H, m), 8.25 (2H, m), 8.33 (1H, d) | 399                    |
| 618 | 5-chloropyridin-2-yl | δ 1.73 - 1.81 (2H, m), 2.08 - 2.14                                                                                             | 399                    |

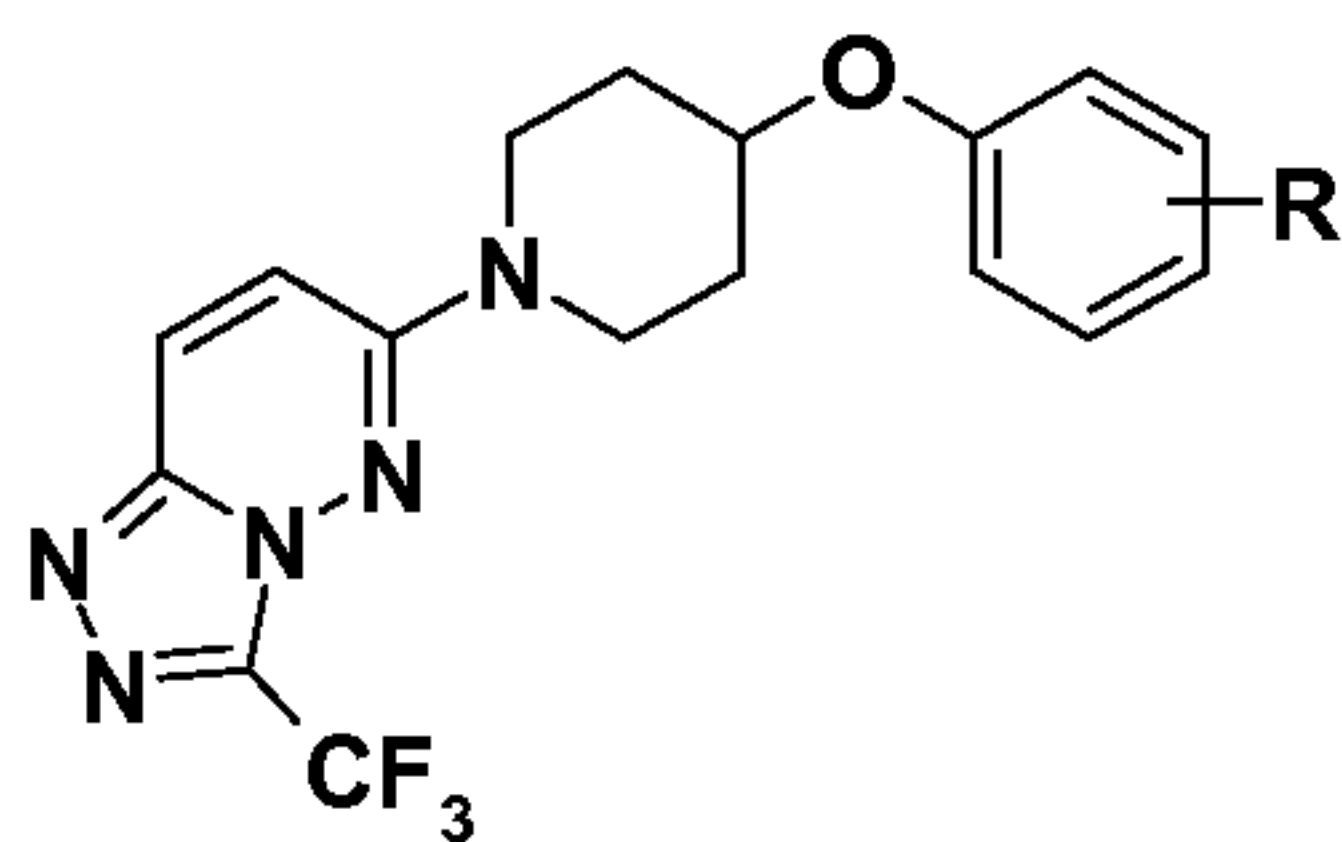


|     |                               |                                                                                                                                                                                               |     |
|-----|-------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
|     |                               | (2H, m), 3.49 - 3.56 (2H, m), 3.96 - 4.02 (2H, m), 5.25 - 5.28 (1H, m), 6.88 (1H, d), 7.65 (1H, d), 7.80 - 7.83 (1H, m), 8.22 - 8.27 (2H, m)                                                  |     |
| 619 | pyrimidin-4-yl                | $\delta$ 1.78 - 1.83 (2H, m), 2.12 - 2.17 (2H, m), 3.51 - 3.58 (2H, m), 3.97 - 4.03 (2H, m), 5.41 (1H, m), 6.95 - 6.97 (1H, m), 7.66 (1H, d), 8.27 (1H, d), 8.53 - 8.55 (1H, m), 8.80 (1H, m) | 366 |
| 620 | 5-bromopyrimidin-2-yl         | $\delta$ 1.80 - 1.86 (2H, m), 2.12 - 2.16 (2H, m), 3.51 - 3.58 (2H, m), 3.96 - 4.02 (2H, m), 5.22 - 5.25 (1H, m), 7.66 (1H, d), 8.26 (1H, d), 8.78 (2H, s)                                    | 444 |
| 621 | 4-trifluoromethylpyridin-2-yl | $\delta$ 1.76 - 1.85 (2H, m), 2.11 - 2.16 (2H, m), 3.53 - 3.60 (2H, m), 3.97 - 4.03 (2H, m), 5.37 - 5.41 (1H, m), 7.20 (1H, d), 7.33 - 7.34 (1H, m), 7.66 (1H, d), 8.27 (1H, d), 8.46 (1H, d) | 433 |
| 622 | 4-methylpyrimidin-2-yl        | $\delta$ 1.78 - 1.82 (2H, m), 2.10 - 2.15 (2H, m), 2.41 (3H, s), 3.53 - 3.59 (2H, m), 3.95 - 4.01 (2H, m), 5.26 (1H, m), 7.02 (1H, d), 7.66 (1H, d), 8.26 (1H, d), 8.45 (1H, d)               | 380 |

**Examples 623-627**

The following compounds were prepared in 12-29% yield by an analogous method to Example 447, starting from 1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol (obtained as described in Example 412, preparation of starting materials) and the appropriate phenol:-

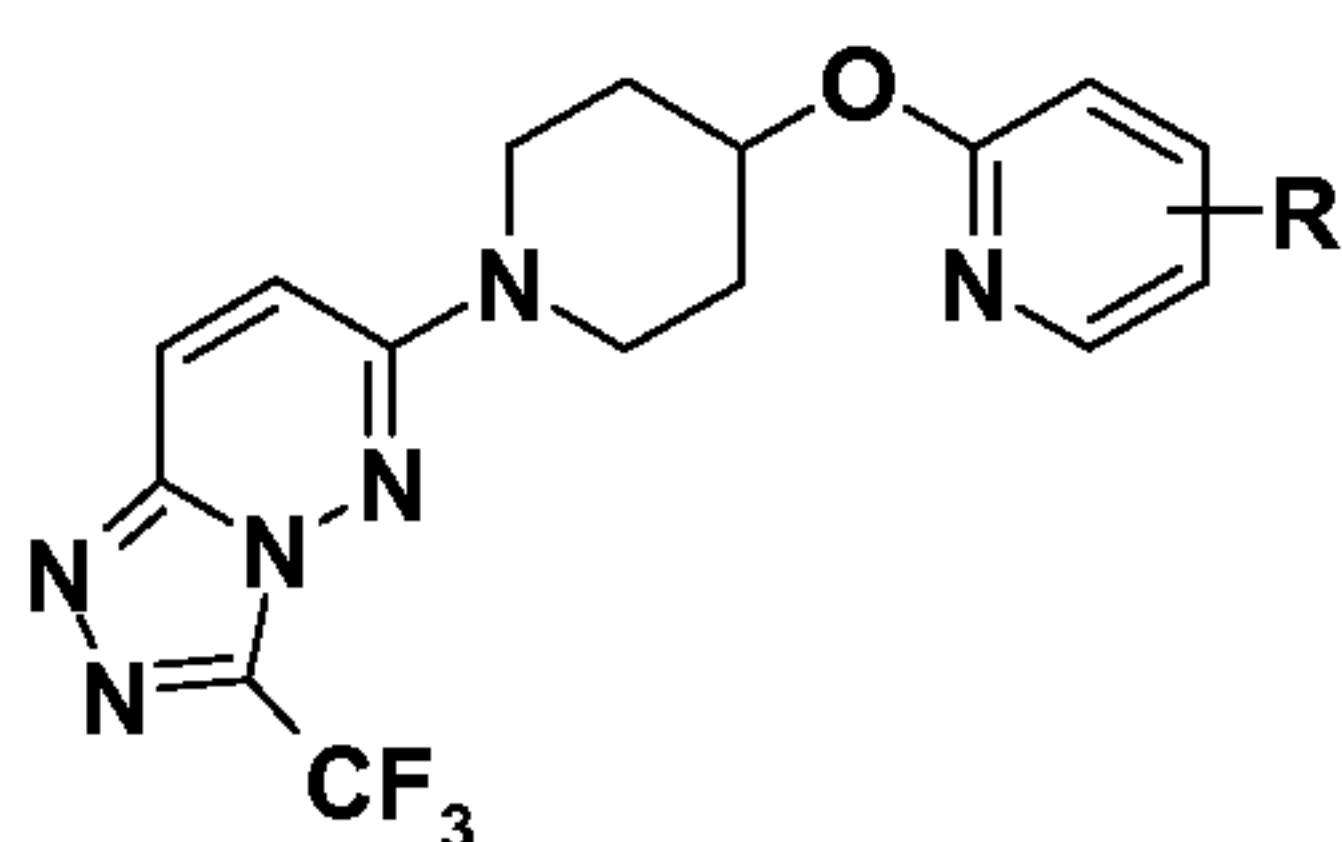




| Ex. | R                 | <sup>1</sup> H NMR (399.9 MHz, DMSO-d <sub>6</sub> )                                                                                                                                          | m/z [M+H] <sup>+</sup> |
|-----|-------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|
| 623 | 3-CN              | δ 1.72 - 1.75 (2H, m), 2.08 - 2.13 (2H, m), 3.48 - 3.55 (2H, m), 3.96 - 4.01 (2H, m), 4.80 (1H, m), 7.35 - 7.38 (1H, m), 7.40 - 7.43 (1H, m), 7.49 - 7.56 (2H, m), 7.65 (1H, d), 8.26 (1H, d) | 389                    |
| 624 | 4-CF <sub>3</sub> | δ 1.75 - 1.78 (2H, m), 2.09 - 2.11 (2H, m), 3.52 - 3.58 (2H, m), 3.96 - 4.00 (2H, m), 4.84 (1H, m), 7.21 (2H, d), 7.64 - 7.68 (3H, m), 8.27 (1H, d)                                           | 432                    |
| 625 | 4-F               | δ 1.69 - 1.76 (2H, m), 2.03 - 2.09 (2H, m), 3.49 - 3.55 (2H, m), 3.93 - 3.99 (2H, m), 4.62 - 4.65 (1H, m), 7.02 - 7.06 (2H, m), 7.11 - 7.15 (2H, m), 7.64 (1H, d), 8.25 (1H, d)               | 382                    |
| 626 | 3-CF <sub>3</sub> | δ 1.73 - 1.78 (2H, m), 2.07 - 2.12 (2H, m), 3.52 - 3.59 (2H, m), 3.95 - 4.00 (2H, m), 4.84 (1H, m), 7.30 - 7.35 (3H, m), 7.53 - 7.57 (1H, m), 7.65 (1H, d), 8.26 (1H, d)                      | 432                    |
| 627 | 4-CN              | δ 1.74 - 1.77 (2H, m), 2.09 (2H, m), 3.51 - 3.56 (2H, m), 3.96 - 4.00 (2H, m), 4.86 (1H, m), 7.20 (2H, d), 7.65 (1H, d), 7.79 (2H, d), 8.26 (1H, d)                                           | 389                    |

#### **Examples 628-629**

The following compounds were prepared in 23-48% yield by an analogous method to Example 448, starting from 1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol (obtained as described in Example 412, preparation of starting materials) and the appropriate chloropyridine:-

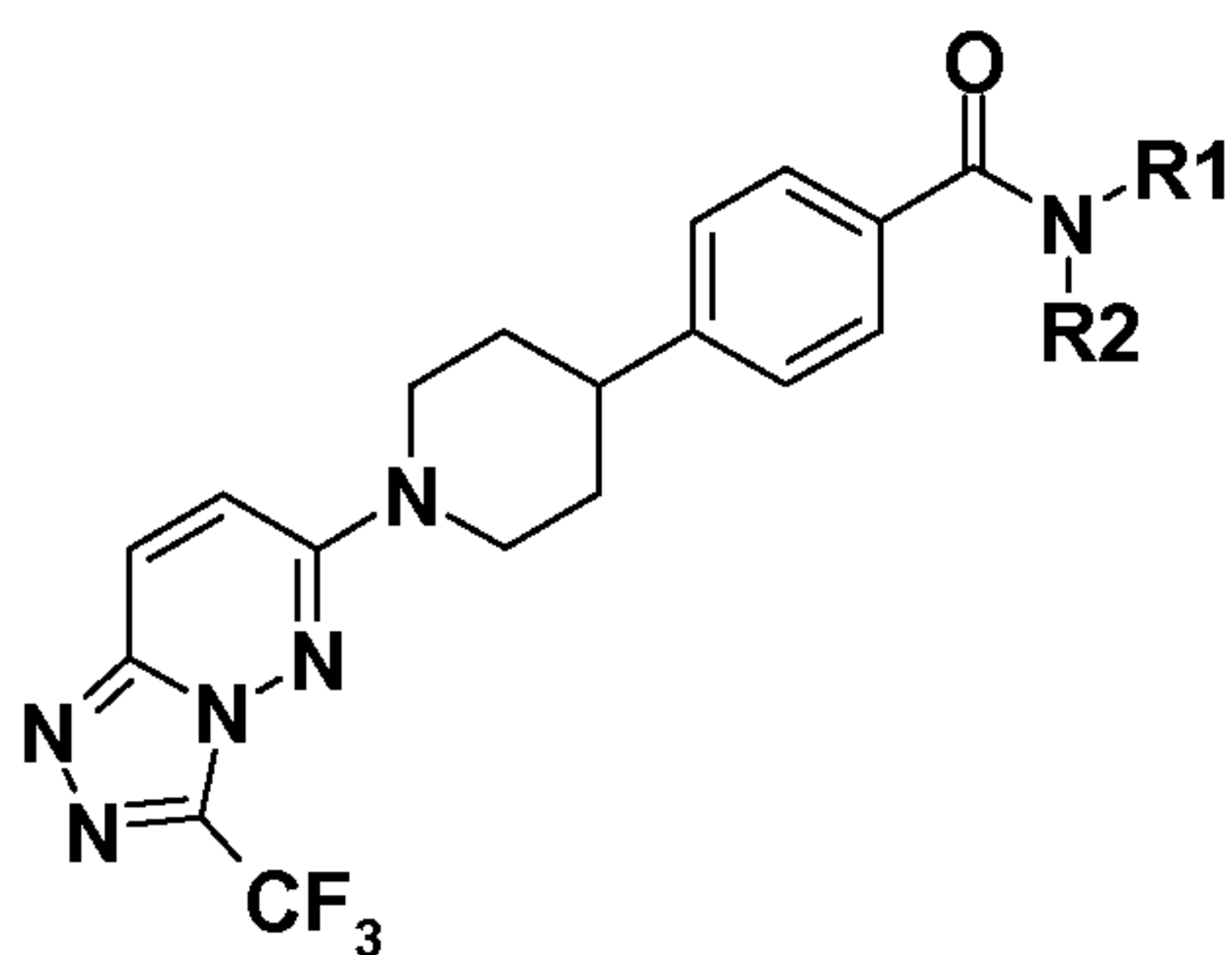




| Ex. | R    | <sup>1</sup> H NMR (399.9 MHz, DMSO-d <sub>6</sub> )                                                                                                                                   | m/z [M+H] <sup>+</sup> |
|-----|------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|
| 628 | 5-CN | δ 1.78 - 1.84 (2H, m), 2.13 - 2.16 (2H, m), 3.51 - 3.57 (2H, m), 3.97 - 4.03 (2H, m), 5.39 - 5.42 (1H, m), 7.01 (1H, d), 7.66 (1H, d), 8.16 - 8.18 (1H, m), 8.27 (1H, d), 8.71 (1H, d) | 390                    |
| 629 | 4-CN | δ 1.78 - 1.81 (2H, m), 2.11 (2H, m), 3.51 - 3.57 (2H, m), 3.98 - 4.02 (2H, m), 5.35 (1H, m), 7.38 (1H, m), 7.41 - 7.43 (1H, m), 7.66 (1H, d), 8.27 (1H, d), 8.42 - 8.43 (1H, m)        | 390                    |

**Examples 630-635**

The following compounds were prepared in 10-90% yield by an analogous method to Example 512, starting from 4-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]benzoic acid and the appropriate amine:-

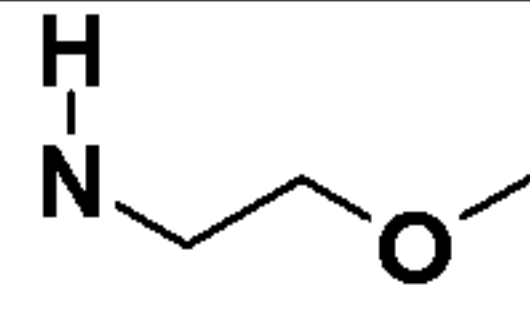
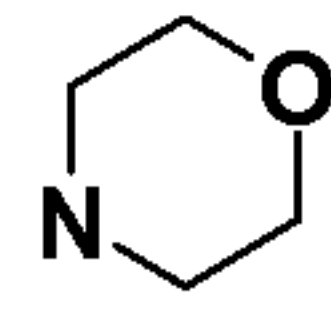


5

| Ex. | NR <sub>1</sub> R <sub>2</sub> | <sup>1</sup> H NMR (399.9 MHz, CDCl <sub>3</sub> )                                                                                                                                                                               | m/z [M+H] <sup>+</sup> |
|-----|--------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|
| 630 |                                | δ 1.76 - 1.86 (2H, m), 2.03 (2H, m), 2.84 - 2.90 (1H, m), 3.08 - 3.17 (5H, m), 3.72 - 3.90 (4H, m), 4.37 - 4.41 (2H, m), 7.13 (1H, d), 7.26 (2H, d), 7.42 (2H, d), 7.94 (1H, d)                                                  | 449                    |
| 631 |                                | δ 1.77 - 1.84 (6H, m), 2.02 - 2.05 (2H, m), 2.54 - 2.57 (4H, m), 2.70 (2H, m), 2.89 (1H, m), 3.10 - 3.18 (2H, m), 3.52 - 3.57 (2H, m), 4.38 - 4.41 (2H, m), 6.79 (1H, t), 7.13 (1H, d), 7.29 (2H, d), 7.75 (2H, d), 7.94 (1H, d) | 488                    |
| 632 |                                | δ 1.81 (2H, m), 2.02 (2H, m), 2.33 (3H, s), 2.43 (4H, m), 2.87 (1H, m), 3.13 (2H, m), 3.48 - 3.78 (4H, m),                                                                                                                       | 474                    |

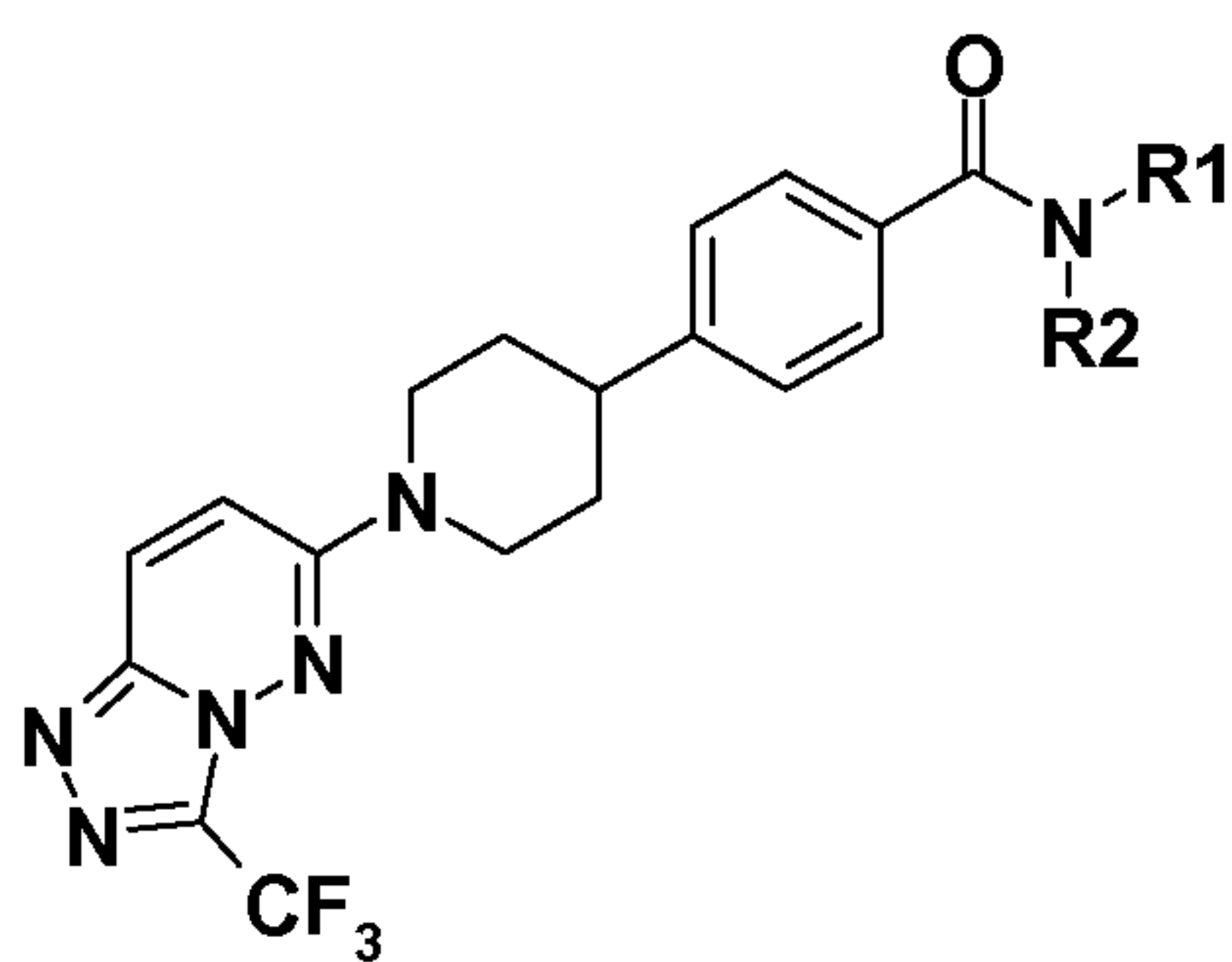


343

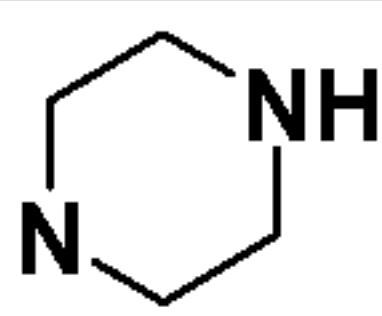
|     |                                                                                     |                                                                                                                                                                                                                                         |     |
|-----|-------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
|     |                                                                                     | 4.39 (2H, m), 7.13 (1H, d), 7.26 (2H, d), 7.37 (2H, d), 7.94 (1H, d)                                                                                                                                                                    |     |
| 633 |    | $\delta$ 1.76 - 1.87 (2H, m), 2.01 - 2.05 (2H, m), 2.87 - 2.93 (1H, m), 3.10 - 3.18 (2H, m), 3.38 (3H, s), 3.56 (2H, m), 3.63 - 3.67 (2H, m), 4.38 - 4.41 (2H, m), 6.48 (1H, t), 7.14 (1H, d), 7.29 (2H, d), 7.75 (2H, d), 7.95 (1H, d) | 449 |
| 634 | NMe <sub>2</sub>                                                                    | $\delta$ 1.79 - 1.86 (2H, m), 2.00 - 2.04 (2H, m), 2.85 (1H, s), 2.98 - 3.17 (8H, m), 4.37 - 4.41 (2H, m), 7.13 (1H, d), 7.24 (2H, d), 7.38 (2H, d), 7.94 (1H, d)                                                                       | 419 |
| 635 |  | $\delta$ 1.79 - 1.83 (2H, m), 2.00 - 2.04 (2H, m), 2.87 (1H, m), 3.10 - 3.17 (2H, m), 3.69 (8H, m), 4.37 - 4.41 (2H, m), 7.13 (1H, d), 7.27 (2H, d), 7.38 (2H, d), 7.95 (1H, d)                                                         | 461 |

**Examples 636-642**

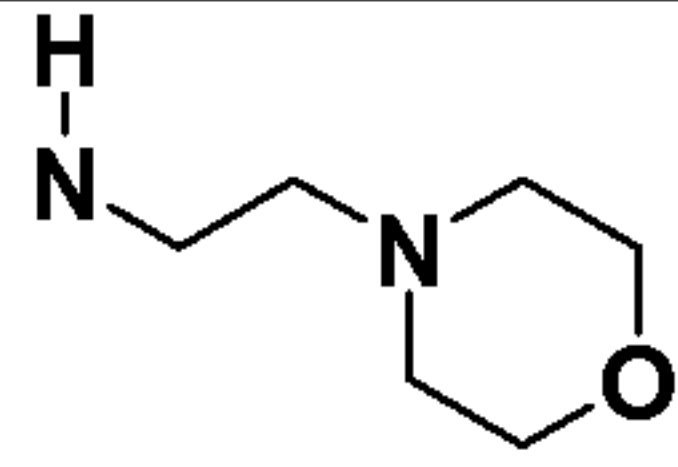
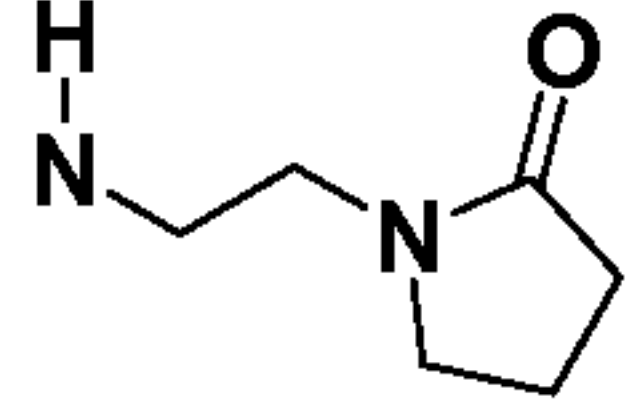
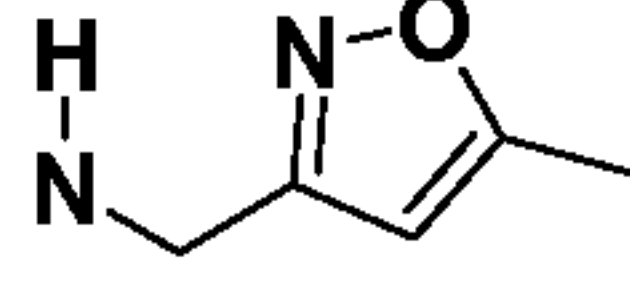
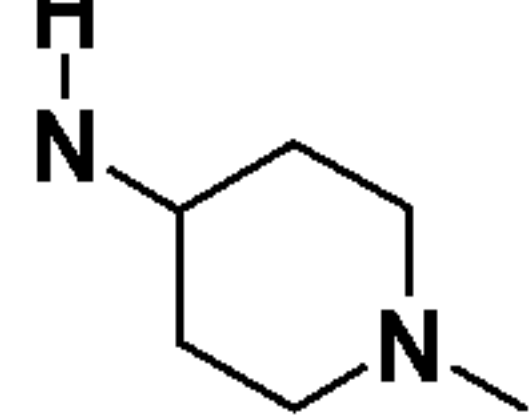
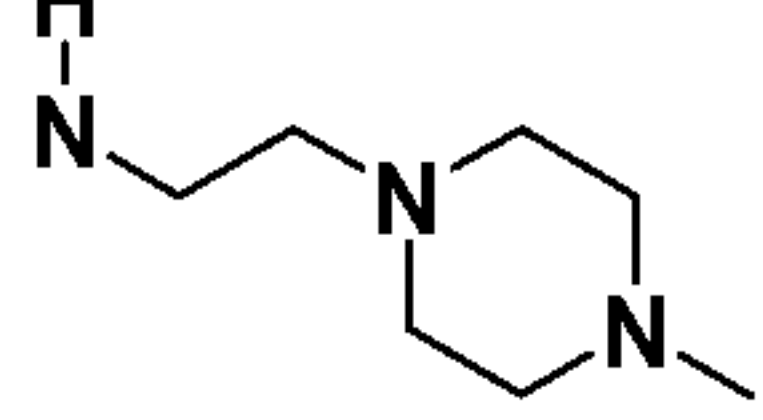
The following compounds were prepared in 5-85% yield by an analogous method to Example 512, starting from 4-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]benzoic acid and the appropriate amine:-



5

| Ex. | NR <sub>1</sub> R <sub>2</sub>                                                      | <sup>1</sup> H NMR (399.9 MHz, DMSO-d <sub>6</sub> )                                                                                                                                                 | m/z [M+H] <sup>+</sup> |
|-----|-------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|
| 636 |  | $\delta$ 1.68 - 1.78 (2H, m), 1.92 - 1.97 (2H, m), 2.65 (4H, m), 2.89 - 2.97 (1H, m), 3.09 - 3.16 (2H, m), 3.44 - 3.52 (4H, m), 4.47 (2H, m), 7.38 (2H, d), 7.67 (1H, d), 7.81 (2H, d), 8.26 (1H, d) | 460                    |
| 637 | NHEt                                                                                | $\delta$ 1.14 (3H, t), 1.68 - 1.79 (2H, m), 1.92 (2H, m), 2.91 - 2.97 (1H, m), 3.10 - 3.16 (2H, m), 4.44                                                                                             | 419                    |



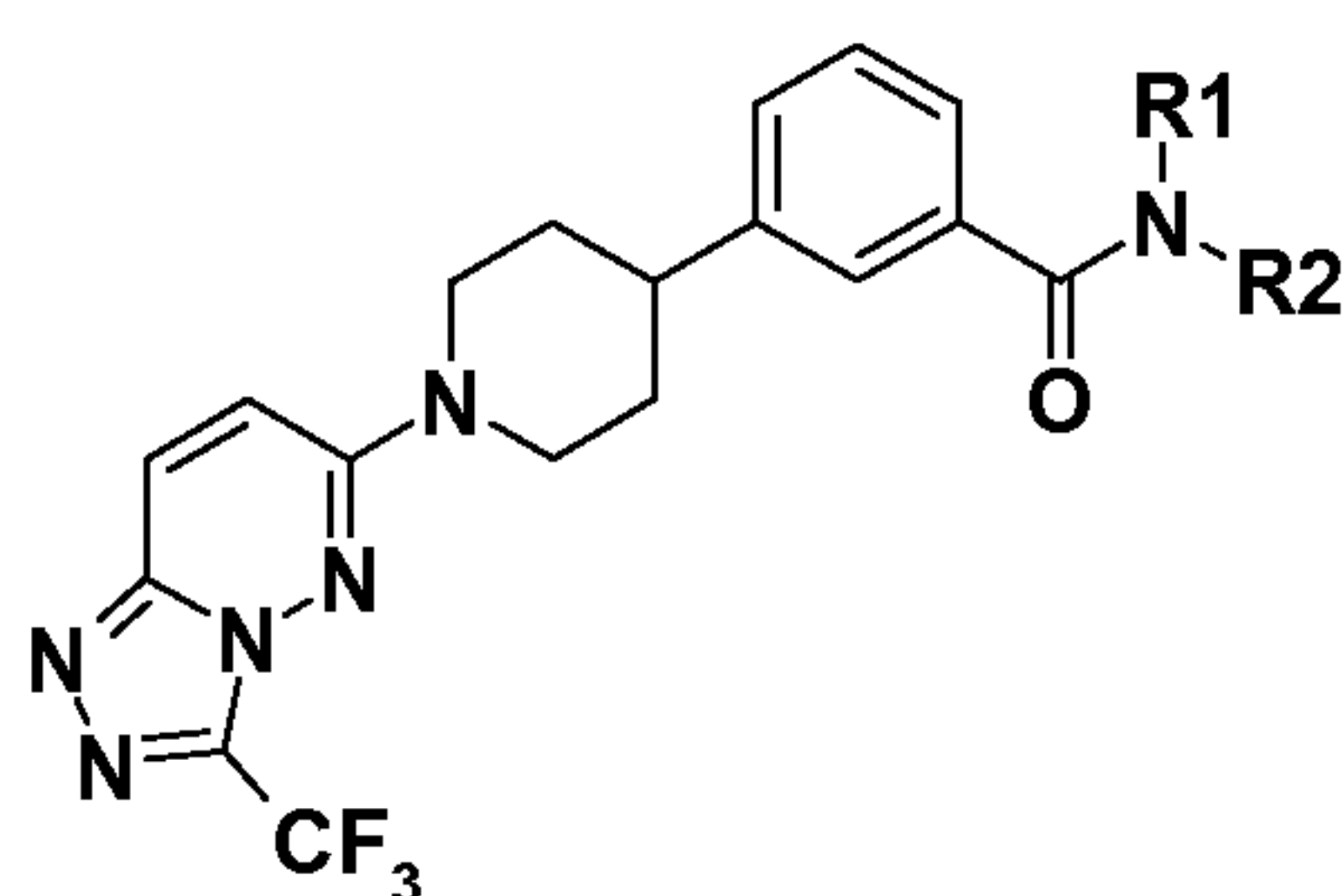
|     |                                                                                     |                                                                                                                                                                                                                                                |     |
|-----|-------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
|     |                                                                                     | (2H, d), 7.36 (2H, d), 7.67 (1H, d), 7.78 (2H, d), 8.25 (1H, d), 8.36 (1H, t), (2H obscured by water)                                                                                                                                          |     |
| 638 |    | $\delta$ 1.74 (2H, m), 1.92 (2H, m), 2.94 (1H, m), 3.14 (2H, m), 3.40 (2H, m), 3.60 (4H, m), 4.44 (2H, m), 7.37 (2H, d), 7.67 (1H, d), 7.78 (2H, d), 8.26 (1H, d), 8.33 (1H, t), (2H obscured by water, 4H obscured by DMSO)                   | 504 |
| 639 |   | $\delta$ 1.72 - 1.79 (2H, m), 1.87 - 1.94 (4H, m), 2.16 - 2.20 (2H, m), 2.91 - 2.97 (1H, m), 3.10 - 3.16 (2H, m), 3.33 - 3.43 (6H, m), 4.44 (2H, d), 7.37 (2H, d), 7.67 (1H, d), 7.75 (2H, d), 8.25 (1H, d), 8.43 (1H, t)                      | 502 |
| 640 |  | $\delta$ 1.72 - 1.78 (2H, m), 1.92 (2H, m), 2.37 (3H, s), 2.96 (1H, m), 3.11 - 3.17 (2H, m), 4.42 - 4.46 (4H, m), 6.14 (1H, s), 7.39 (2H, d), 7.67 (1H, d), 7.83 (2H, d), 8.26 (1H, d), 8.97 (1H, t)                                           | 486 |
| 641 |  | $\delta$ 1.54 - 1.78 (6H, m), 1.92 (2H, m), 2.00 - 2.10 (2H, m), 2.21 (3H, s), 2.81 (2H, m), 2.91 - 2.98 (1H, m), 3.10 - 3.16 (2H, m), 3.72 - 3.76 (1H, m), 4.44 (2H, m), 7.36 (2H, d), 7.67 (1H, d), 7.79 (2H, d), 8.14 (1H, d), 8.25 (1H, d) | 488 |
| 642 |  | $\delta$ 1.74 (2H, m), 1.92 (2H, m), 2.17 (3H, s), 2.32 - 2.48 (10H, m), 2.94 (1H, m), 3.13 (2H, m), 3.36 (2H, m), 4.44 (2H, m), 7.36 (2H, d), 7.67 (1H, d), 7.77 (2H, d), 8.27 (2H, m)                                                        | 517 |

**Examples 643-652**

The following compounds were prepared in 16-73% yield by an analogous method to Example 512, starting from 3-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]benzoic acid and the appropriate amine:-

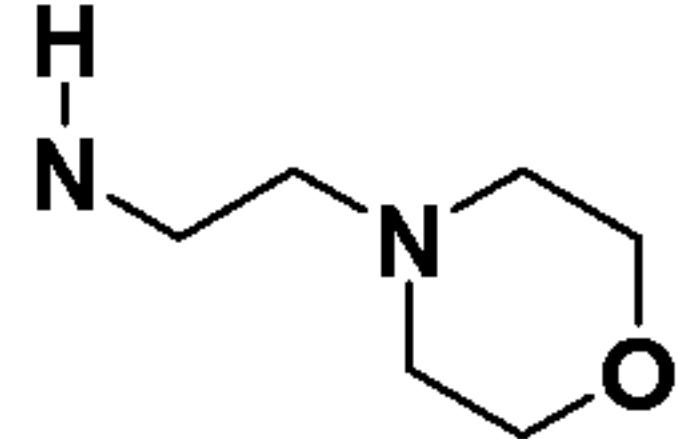
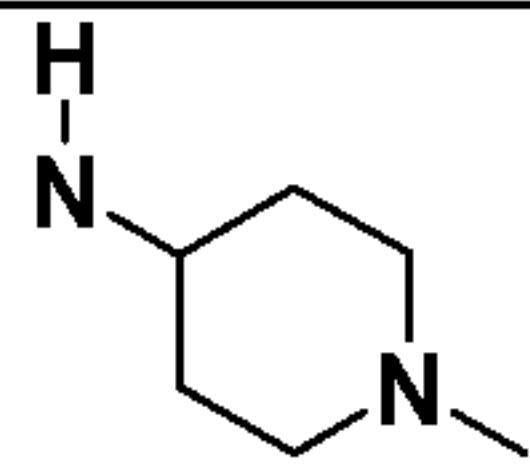
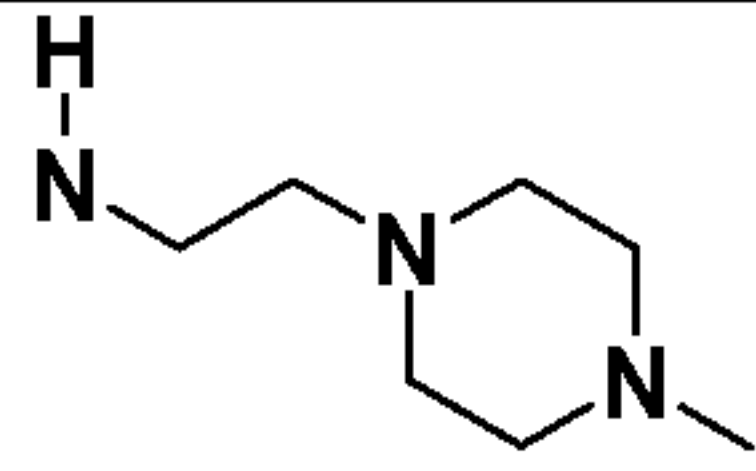


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| Ex. | NR <sub>1</sub> R <sub>2</sub> | <sup>1</sup> H NMR (399.9 MHz, DMSO-d <sub>6</sub> )                                                                                                                                                                                                         | m/z [M+H] <sup>+</sup> |
|-----|--------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|
| 643 |                                | δ 1.69 - 1.77 (2H, m), 1.93 (2H, m), 2.89 - 2.97 (4H, m), 3.10 - 3.16 (2H, m), 3.49 - 3.61 (4H, m), 4.43 (2H, m), 4.75 (1H, t), 7.23 - 7.24 (1H, m), 7.30 - 7.35 (3H, m), 7.67 (1H, d), 8.25 (1H, d)                                                         | 449                    |
| 644 |                                | δ 1.64 - 1.71 (4H, m), 1.73 - 1.80 (2H, m), 1.94 (2H, m), 2.46 - 2.49 (4H, m), 2.56 (2H, m), 2.91 - 2.97 (1H, m), 3.11 - 3.17 (2H, m), 3.35 - 3.39 (2H, m), 4.45 (2H, m), 7.37 - 7.44 (2H, m), 7.67 - 7.69 (2H, m), 7.74 (1H, s), 8.26 (1H, d), 8.38 (1H, t) | 488                    |
| 645 |                                | δ 1.73 (2H, m), 1.93 (2H, m), 2.19 (3H, s), 2.30 (4H, m), 2.94 (1H, m), 3.13 (2H, m), 3.33 - 3.66 (4H, m), 4.43 (2H, m), 7.21 (1H, m), 7.27 (1H, s), 7.38 (2H, m), 7.67 (1H, d), 8.25 (1H, d)                                                                | 474                    |
| 646 |                                | δ 1.68 - 1.78 (2H, m), 1.92 - 1.97 (2H, m), 2.69 (4H, m), 2.89 - 2.97 (1H, m), 3.09 - 3.16 (2H, m), 3.44 - 3.52 (4H, m), 4.43 (2H, m), 7.19 - 7.22 (1H, m), 7.26 (1H, s), 7.31 - 7.40 (2H, m), 7.67 (1H, d), 8.25 (1H, d)                                    | 460                    |
| 647 | NMe <sub>2</sub>               | δ 1.68 - 1.79 (2H, m), 1.93 (2H, m), 2.88 - 2.97 (7H, m), 3.09 - 3.16 (2H, m), 4.42 - 4.45 (2H, m), 7.22 - 7.25 (1H, m), 7.29 (1H, s), 7.34 - 7.39 (2H, m), 7.67 (1H, d), 8.25 (1H, d)                                                                       | 419                    |
| 648 |                                | δ 1.69 - 1.78 (2H, m), 1.93 (2H, m), 2.90 - 2.96 (1H, m), 3.10 - 3.16 (2H, m), 3.60 (8H, m), 4.43                                                                                                                                                            | 461                    |



|     |                                                                                     |                                                                                                                                                                                                                           |     |
|-----|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
|     |                                                                                     | (2H, m), 7.23 - 7.26 (1H, m), 7.31 (1H, s), 7.36 - 7.41 (2H, m), 7.67 (1H, d), 8.25 (1H, d)                                                                                                                               |     |
| 649 | NHMe                                                                                | $\delta$ 1.75 (2H, m), 1.94 (2H, m), 2.78 (3H, d), 2.94 (1H, m), 3.14 (2H, m), 4.45 (2H, m), 7.40 (2H, m), 7.68 (2H, m), 7.74 (1H, s), 8.26 (1H, d), 8.38 (1H, m)                                                         | 405 |
| 650 |    | $\delta$ 1.75 (2H, m), 1.94 (2H, m), 2.44 (6H, m), 2.95 (1H, m), 3.14 (2H, m), 3.38 (2H, m), 3.57 (4H, m), 4.46 (2H, m), 7.41 (2H, m), 7.68 (2H, m), 7.73 (1H, s), 8.26 (1H, d), 8.36 (1H, t)                             | 504 |
| 651 |  | $\delta$ 1.58 (2H, m), 1.76 (4H, m), 1.94 (4H, m), 2.16 (3H, s), 2.77 (2H, m), 2.94 (1H, m), 3.13 (2H, m), 3.73 (1H, m), 4.46 (2H, m), 7.40 (2H, m), 7.68 (2H, m), 7.74 (1H, s), 8.18 (1H, d), 8.26 (1H, d)               | 488 |
| 652 |  | $\delta$ 1.75 (2H, m), 1.94 (2H, m), 2.14 (3H, s), 2.30 (4H, m), 2.43 (4H, m), 2.56 (2H, m), 2.95 (1H, m), 3.14 (2H, m), 3.36 (2H, m), 4.45 (2H, m), 7.41 (2H, m), 7.68 (2H, m), 7.73 (1H, s), 8.26 (1H, d), 8.33 (1H, t) | 517 |

The 3-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]benzoic acid used as starting material was prepared as follows:-

#### Preparation of ethyl 3-(pyridin-4-yl)benzoate

5 Obtained in 92% yield by an analogous procedure to Example 605, starting from 4-bromopyridine hydrochloride and 3-(ethoxycarbonyl)phenylboronic acid.

$^1\text{H}$  NMR (399.9 MHz, DMSO- $d_6$ )  $\delta$  1.37 (3H, t), 4.38 (2H, q), 7.71 (1H, m), 7.76 (2H, d), 8.08 (2H, m), 8.30 (1H, s), 8.69 (2H, d);  $m/z$  = 228  $[\text{M}+\text{H}]^+$ .

#### Preparation of ethyl 3-(piperidin-4-yl)benzoate

10 Ethyl 3-(pyridin-4-yl)benzoate (1.46 g, 6.42 mmol), 5% palladium on carbon (50% wet) (0.301 g, 0.07 mmol) and citric acid monohydrate (0.601 g, 2.86 mmol) in a mixture of isopropanol (50 mL) and water (5 mL) were stirred under an atmosphere of hydrogen at 20 atmosphere and 70°C for 15 hours. The reaction was cooled to room temperature, the



catalyst removed by filtration and the solvent evaporated to give the crude product, which was purified by ion exchange chromatography, using an SCX column. The desired product was eluted from the column using 2M ammonia in methanol to give ethyl 3-(piperidin-4-yl)benzoate (1.190 g, 79%) as a liquid.

5  $m/z = 275 [M+H]^+$  (acetonitrile adduct).

**Preparation of ethyl 3-[1-(3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)piperidin-4-yl]benzoate**

Ethyl 3-(piperidin-4-yl)benzoate (1.195 g, 5.12 mmol) was added to 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (1 g, 4.49 mmol) and DIPEA (1.174 mL, 6.74 mmol) in DMA (10 mL). The resulting solution was stirred at 125°C for 2 hours. The reaction mixture was evaporated to dryness, redissolved in DCM and purified by flash silica chromatography, eluting with 50% EtOAc in isohexane. Pure fractions were evaporated to dryness to give a beige solid, which was triturated with ether to give ethyl 3-[1-(3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)piperidin-4-yl]benzoate (0.805 g, 42.7%) as a solid.

$^1H$  NMR (399.9 MHz, DMSO- $d_6$ )  $\delta$  1.33 (3H, t), 1.74 (2H, m), 1.94 (2H, m), 2.99 (1H, m), 3.14 (2H, m), 4.32 (2H, q), 4.44 (2H, m), 7.47 (1H, m), 7.59 (1H, m), 7.67 (1H, d), 7.83 (2H, m), 8.25 (1H, d);  $m/z = 420 [M+H]^+$ .

**Preparation of 3-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]benzoic acid**

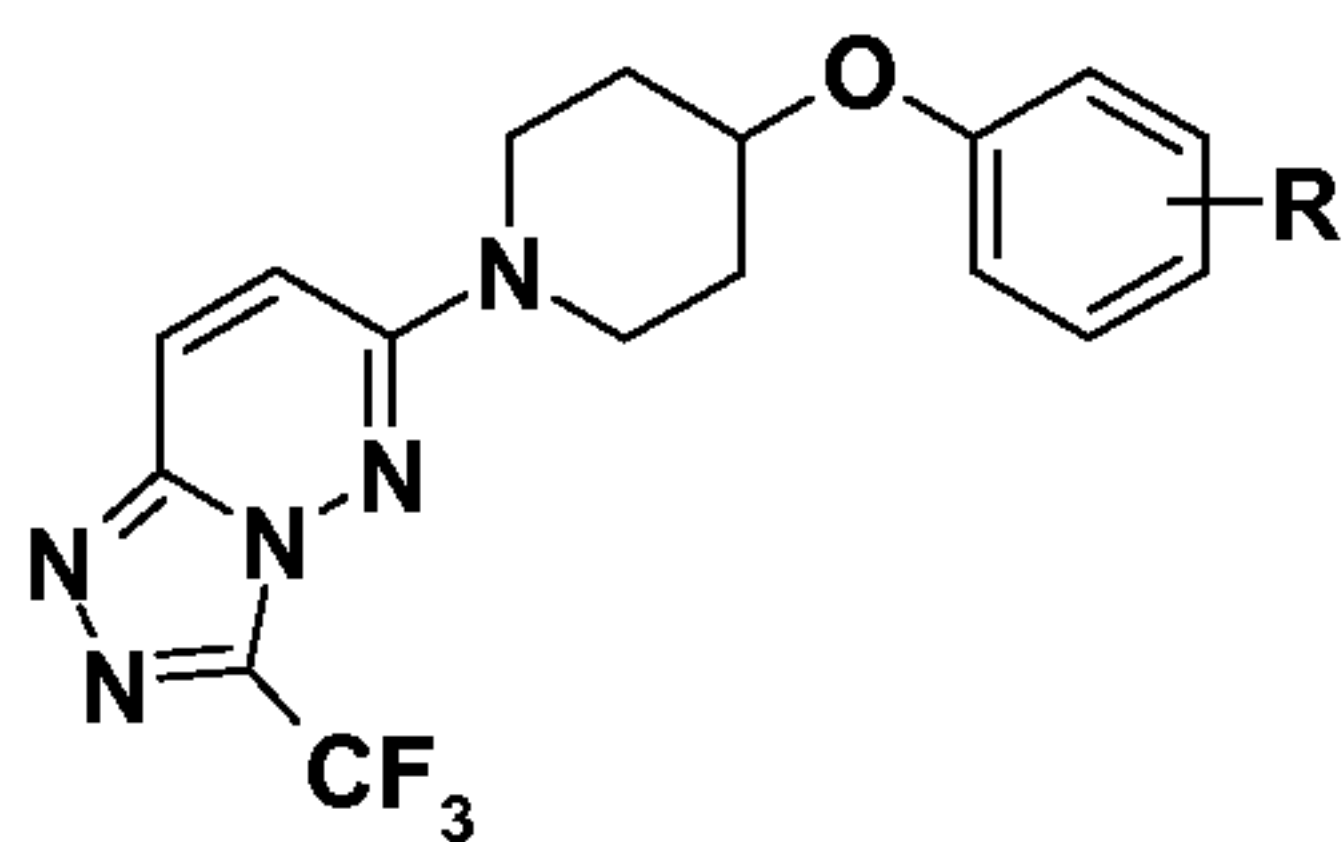
Obtained in 100% yield by an analogous procedure to Example 512, preparation of starting materials, starting from ethyl 3-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]benzoate.

$^1H$  NMR (399.9 MHz, DMSO- $d_6$ )  $\delta$  1.69 - 1.79 (2H, m), 1.94 (2H, m), 2.95 - 3.01 (1H, m), 3.14 (2H, m), 4.44 (2H, m), 7.45 (1H, m), 7.54 - 7.56 (1H, m), 7.67 (1H, d), 7.79 - 7.82 (1H, m), 7.84 (1H, m), 8.25 (1H, d), 12.78 (1H, s);  $m/z = 392 [M+H]^+$ .

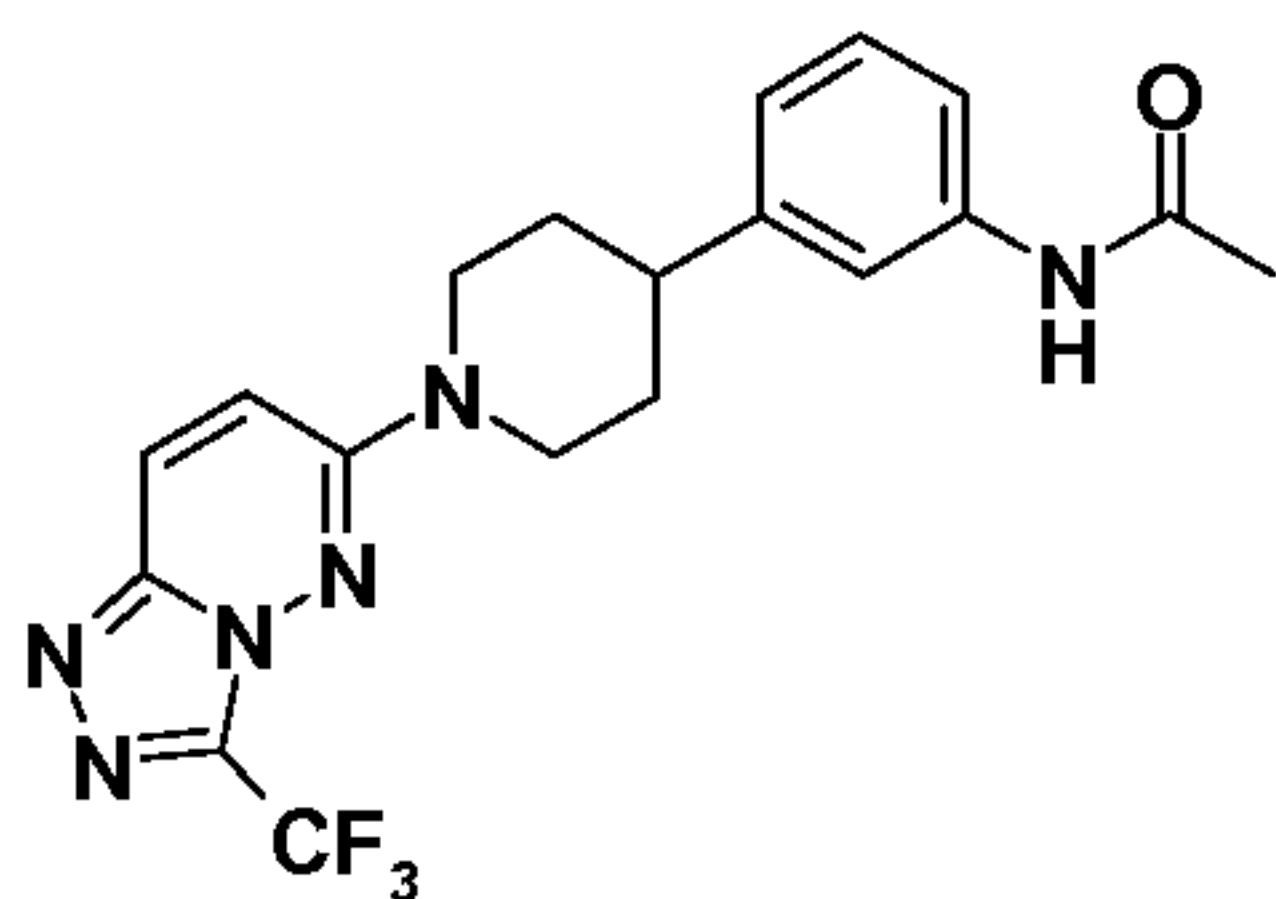
**Examples 653-654**

The following compounds were prepared in 25-37% yield by an analogous method to Example 447, starting from 1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol (obtained as described in Example 412, preparation of starting materials) and the appropriate phenol:-





| Ex. | R                 | <sup>1</sup> H NMR (399.9 MHz, DMSO-d <sub>6</sub> )                                                                                         | m/z [M+H] <sup>+</sup> |
|-----|-------------------|----------------------------------------------------------------------------------------------------------------------------------------------|------------------------|
| 653 | 2-CF <sub>3</sub> | δ 1.81 (2H, m), 2.08 (2H, m), 3.69 (2H, m), 3.80 (2H, m), 4.94 (1H, m), 7.11 (1H, m), 7.40 (1H, m), 7.64 (3H, m), 8.26 (1H, d)               | 432                    |
| 654 | 2-CN              | δ 1.82 (2H, m), 2.11 (2H, m), 3.65 (2H, m), 3.90 (2H, m), 4.94 (1H, m), 7.12 (1H, m), 7.41 (1H, m), 7.68 (2H, m), 7.75 (1H, m), 8.27 (1H, d) | 389                    |

**Example 655****Preparation of N-[3-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]phenyl]acetamide**

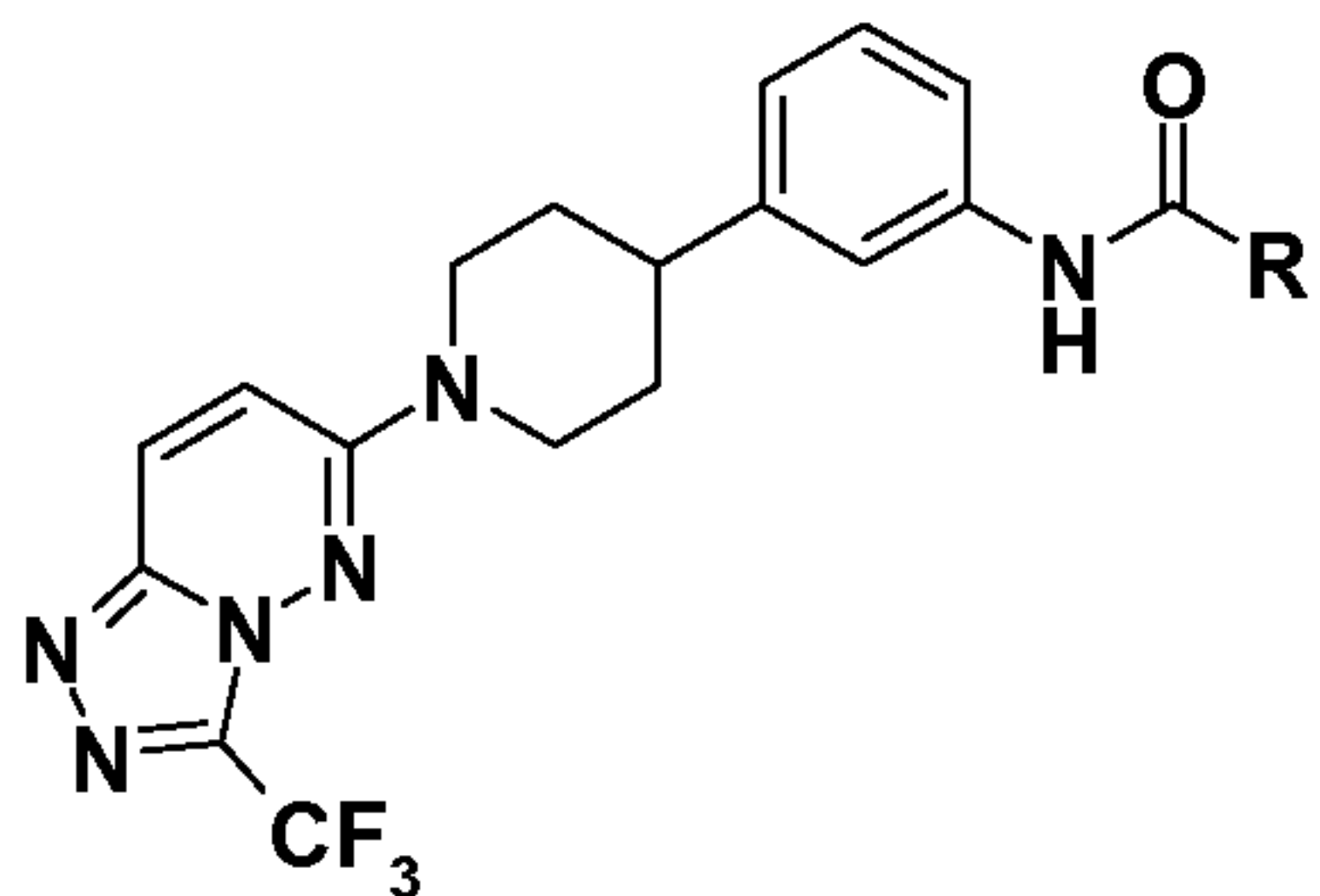
DIPEA (123  $\mu$ l, 0.70 mmol) was added to 3-[1-(3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)piperidin-4-yl]aniline (obtained as described in Example 616) (85 mg, 0.23 mmol), acetic acid (16  $\mu$ l, 0.28 mmol) and HATU (107 mg, 0.28 mmol) in DMA (2 mL). The resulting solution was stirred at ambient temperature for 2 hours then purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5 $\mu$  silica, 19 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 1% ammonia) and acetonitrile as eluents. Fractions containing the desired compound were evaporated to dryness to give N-[3-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]phenyl]acetamide (89 mg, 94%) as a solid.

<sup>1</sup>H NMR (399.9 MHz, DMSO-d<sub>6</sub>) δ 1.66 (2H, m), 1.91 (2H, m), 2.02 (3H, s), 2.84 (1H, m), 3.13 (2H, m), 4.42 (2H, m), 6.95 (1H, m), 7.22 (1H, m), 7.41 (1H, m), 7.49 (1H, s), 7.67 (1H, d), 8.25 (1H, d), 9.84 (1H, s); m/z = 405 [M+H]<sup>+</sup>.



**Examples 656-658**

The following compounds were prepared in 71-86% yield by an analogous method to Example 655, starting from 3-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]aniline and the appropriate carboxylic acid:-



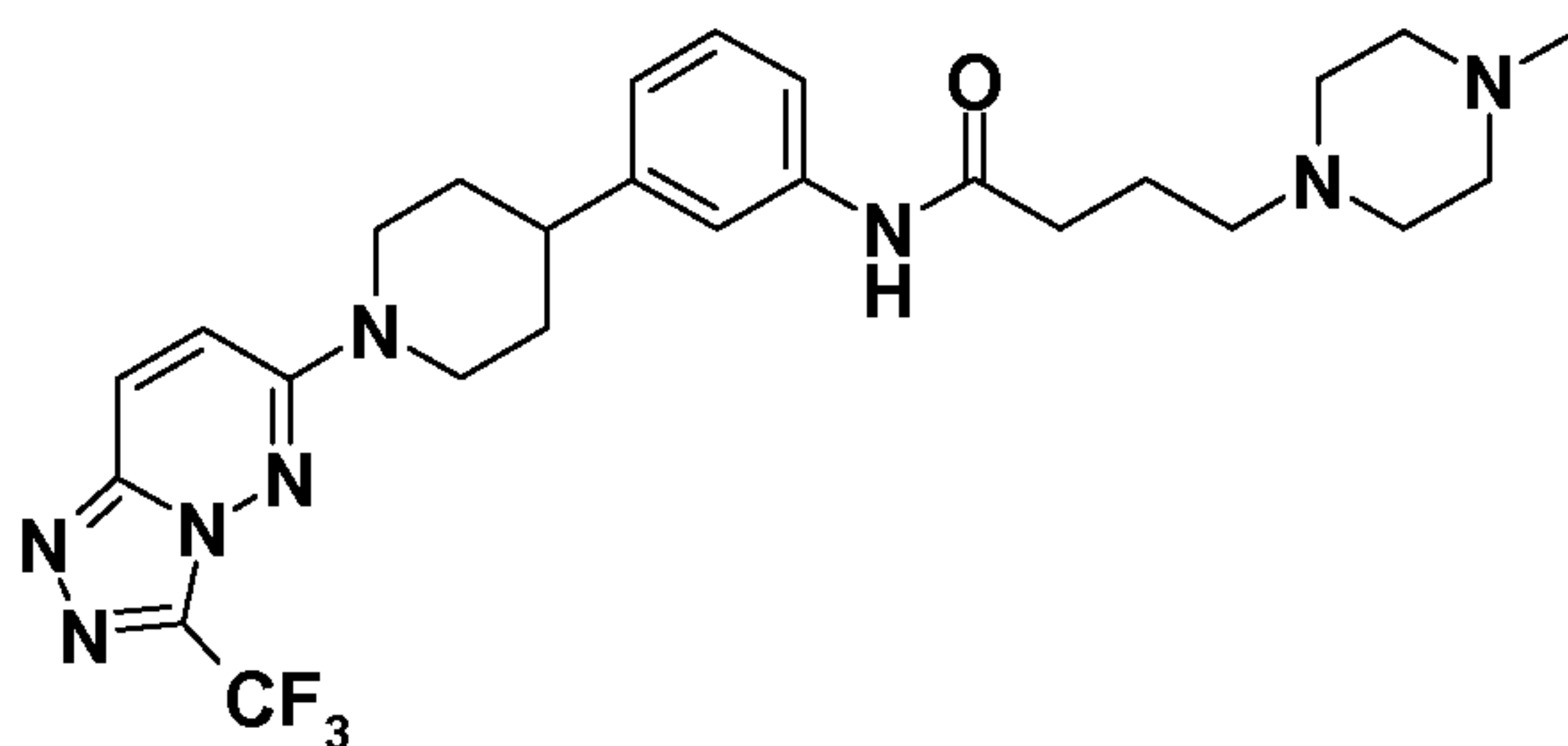
5

| Ex. | NHCOR | <sup>1</sup> H NMR (399.9 MHz, DMSO-d <sub>6</sub> )                                                                                                                                                               | m/z [M+H] <sup>+</sup> |
|-----|-------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|
| 656 |       | δ 1.68 (6H, m), 1.88 (4H, m), 2.17 (3H, s), 2.25 (1H, m), 2.83 (3H, m), 3.13 (2H, m), 4.42 (2H, m), 6.94 (1H, m), 7.21 (1H, m), 7.42 (1H, m), 7.56 (1H, s), 7.67 (1H, d), 8.25 (1H, d), 9.77 (1H, s)               | 488                    |
| 657 |       | δ 1.67 (2H, m), 1.92 (2H, m), 2.85 (1H, m), 3.14 (2H, m), 3.38 (3H, s), 3.98 (2H, s), 4.43 (2H, m), 6.99 (1H, m), 7.24 (1H, m), 7.53 (1H, m), 7.59 (1H, s), 7.67 (1H, d), 8.25 (1H, d), 9.64 (1H, s)               | 435                    |
| 658 |       | δ 1.66 (6H, m), 1.91 (2H, m), 2.58 (1H, m), 2.84 (1H, m), 3.13 (2H, m), 3.35 (2H, m), 3.91 (2H, m), 4.42 (2H, m), 6.95 (1H, m), 7.22 (1H, m), 7.43 (1H, m), 7.56 (1H, s), 7.67 (1H, d), 8.25 (1H, d), 9.80 (1H, s) | 475                    |

**Example 659**

**Preparation of 4-(4-methylpiperazin-1-yl)-N-[3-[1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]phenyl]butanamide**





1-Methylpiperazine (152  $\mu$ l, 1.37 mmol) was added to 4-chloro-N-[3-[1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]phenyl]butanamide (160 mg, 0.343 mmol) and sodium iodide (10 mg, 0.069 mmol) in a mixture of THF (2 mL) and DMA (0.5 mL). The resulting solution was heated at 60°C for 16 hours, then cooled and evaporated to give the crude product, which was purified by flash chromatography on silica, eluting with a gradient of 0 – 10% 2M ammonia in methanol in DCM. The solvents were evaporated, then the resulting gum triturated with ether and the precipitate filtered and dried to give 4-(4-methylpiperazin-1-yl)-N-[3-[1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]phenyl]butanamide (87 mg, 48%) as a solid.

<sup>1</sup>H NMR (399.9 MHz, DMSO-d<sub>6</sub>)  $\delta$  1.60 - 1.76 (4H, m), 1.91 (2H, m), 2.12 (3H, s), 2.25 - 2.35 (12H, m), 2.84 (1H, m), 3.13 (2H, m), 4.42 (2H, m), 6.94 (1H, m), 7.21 (1H, m), 7.42 (1H, m), 7.52 (1H, m), 7.67 (1H, d), 8.25 (1H, d), 9.77 (1H, s); m/z = 531 [M+H]<sup>+</sup>.

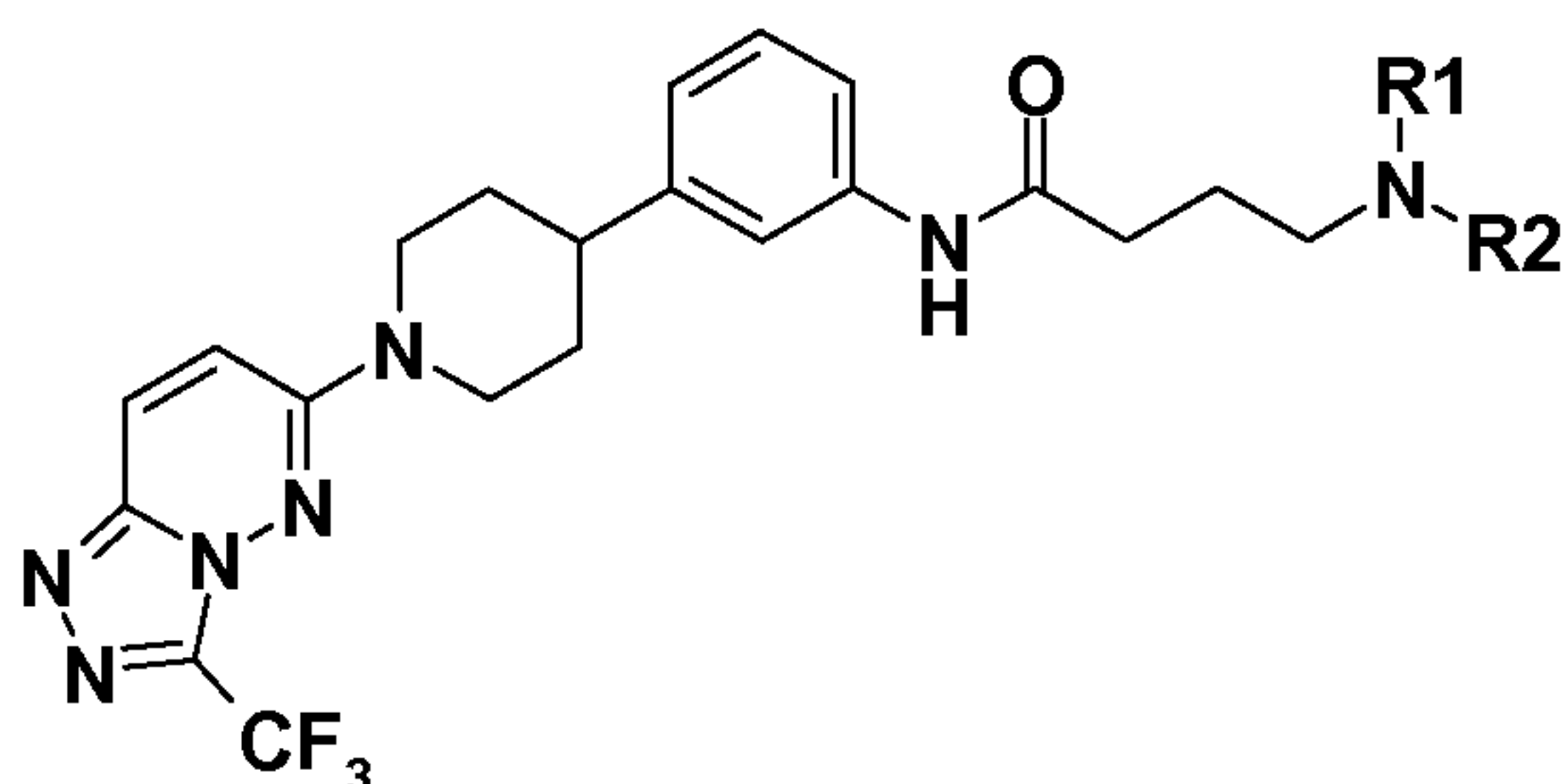
The 4-chloro-N-[3-[1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]phenyl]butanamide used as starting material was prepared as follows:- A solution of 4-chlorobutyryl chloride (175 mg, 1.24 mmol) in DCM (2 mL) was added dropwise to a stirred suspension of 3-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]aniline (obtained as described in Example 616) (375 mg, 1.03 mmol) and pyridine (164 mg, 2.07 mmol) in DCM (3 mL) under nitrogen. The resulting solution was stirred at ambient temperature for 16 hours. The reaction mixture was diluted with DCM (5 mL), washed with saturated sodium bicarbonate (10 mL), dried and the solvents evaporated to a yellow gum, which was triturated with ether to give 4-chloro-N-[3-[1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]phenyl]butanamide (480 mg, 99%) as a solid.

m/z = 467 [M+H]<sup>+</sup>.

### **Examples 660-661**



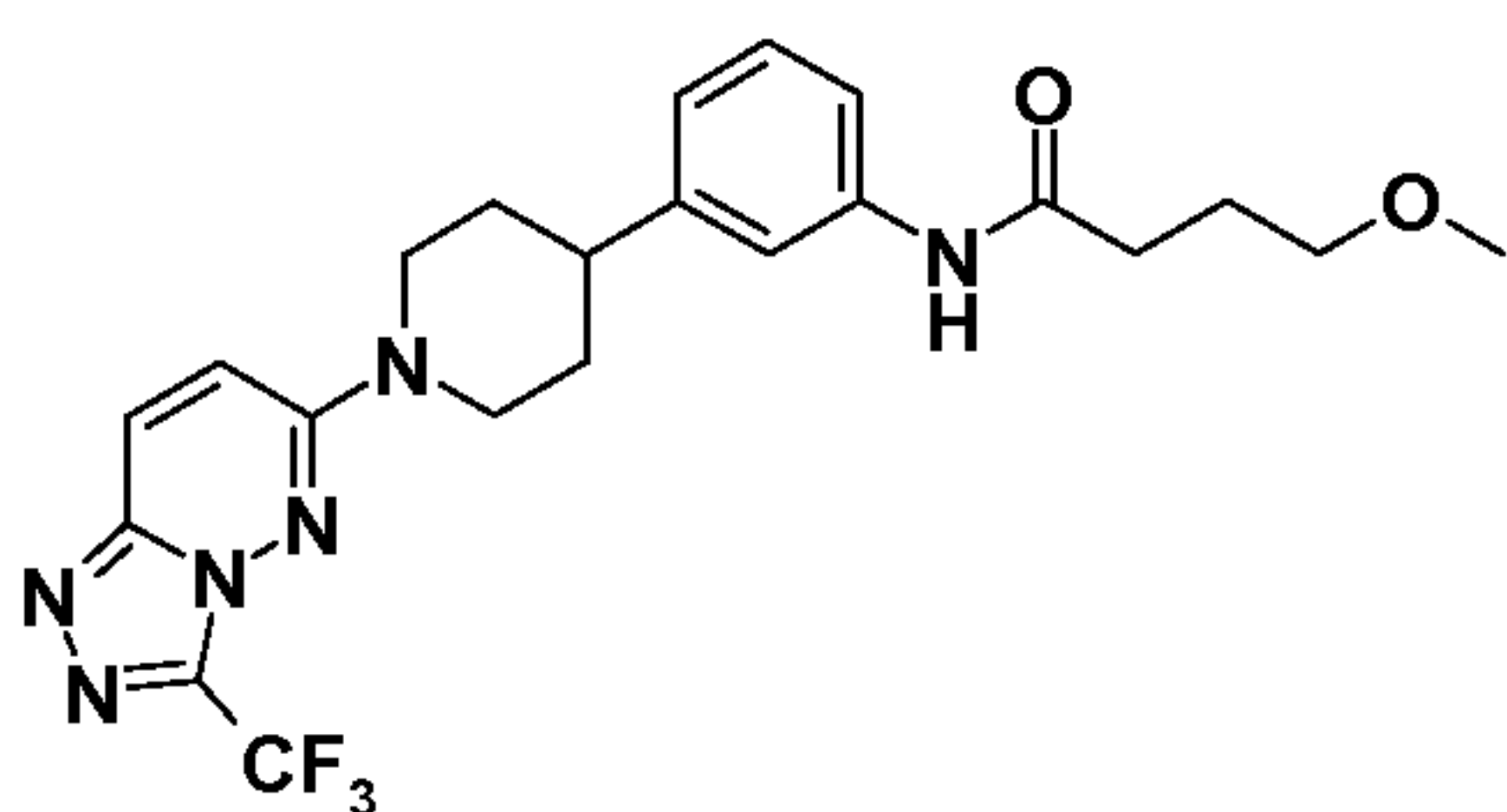
The following compounds were prepared in 5-34% yield by an analogous method to Example 659, starting from 4-chloro-N-[3-[1-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]phenyl]butanamide and the appropriate amine:-



| Ex. | NR1R2 | <sup>1</sup> H NMR (399.9 MHz, DMSO-d <sub>6</sub> )                                                                                                                                                               | m/z [M+H] <sup>+</sup> |
|-----|-------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|
| 660 |       | δ 1.66 (2H, m), 1.85 - 1.95 (8H, m), 2.40 (2H, t), 2.85 (1H, m), 2.98 - 3.19 (8H, m), 4.43 (2H, m), 6.97 (1H, m), 7.24 (1H, m), 7.43 (1H, m), 7.51 (1H, m), 7.67 (1H, d), 8.26 (1H, d), 9.90 (1H, s)               | 502                    |
| 661 |       | δ 1.61 - 1.77 (4H, m), 1.86 (2H, m), 2.27 - 2.40 (8H, m), 2.84 (1H, m), 3.13 (2H, m), 3.59 (4H, m), 4.45 (2H, m), 6.92 (1H, m), 7.22 (1H, m), 7.46 (1H, m), 7.54 (1H, m), 7.69 (1H, d), 8.26 (1H, d), 9.78 (1H, s) | 518                    |

5 **Example 662**

**Preparation of 4-methoxy-N-[3-[1-(3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)piperidin-4-yl]phenyl]butanamide**



Obtained in 68% yield by an analogous procedure to Example 655, starting from 3-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]aniline and 4-methoxybutanoic acid.

<sup>1</sup>H NMR (399.9 MHz, DMSO-d<sub>6</sub>) δ 1.66 (2H, m), 1.80 (2H, m), 1.91 (2H, m), 2.34 (2H, t), 2.84 (1H, m), 3.13 (2H, m), 3.24 (3H, s), 3.35 (2H, t), 4.42 (2H, m), 6.94 (1H, d), 7.22 (1H, m), 7.42 (1H, d), 7.53 (1H, s), 7.67 (1H, d), 8.25 (1H, d), 9.81 (1H, s); m/z = 463

[M+H]<sup>+</sup>.



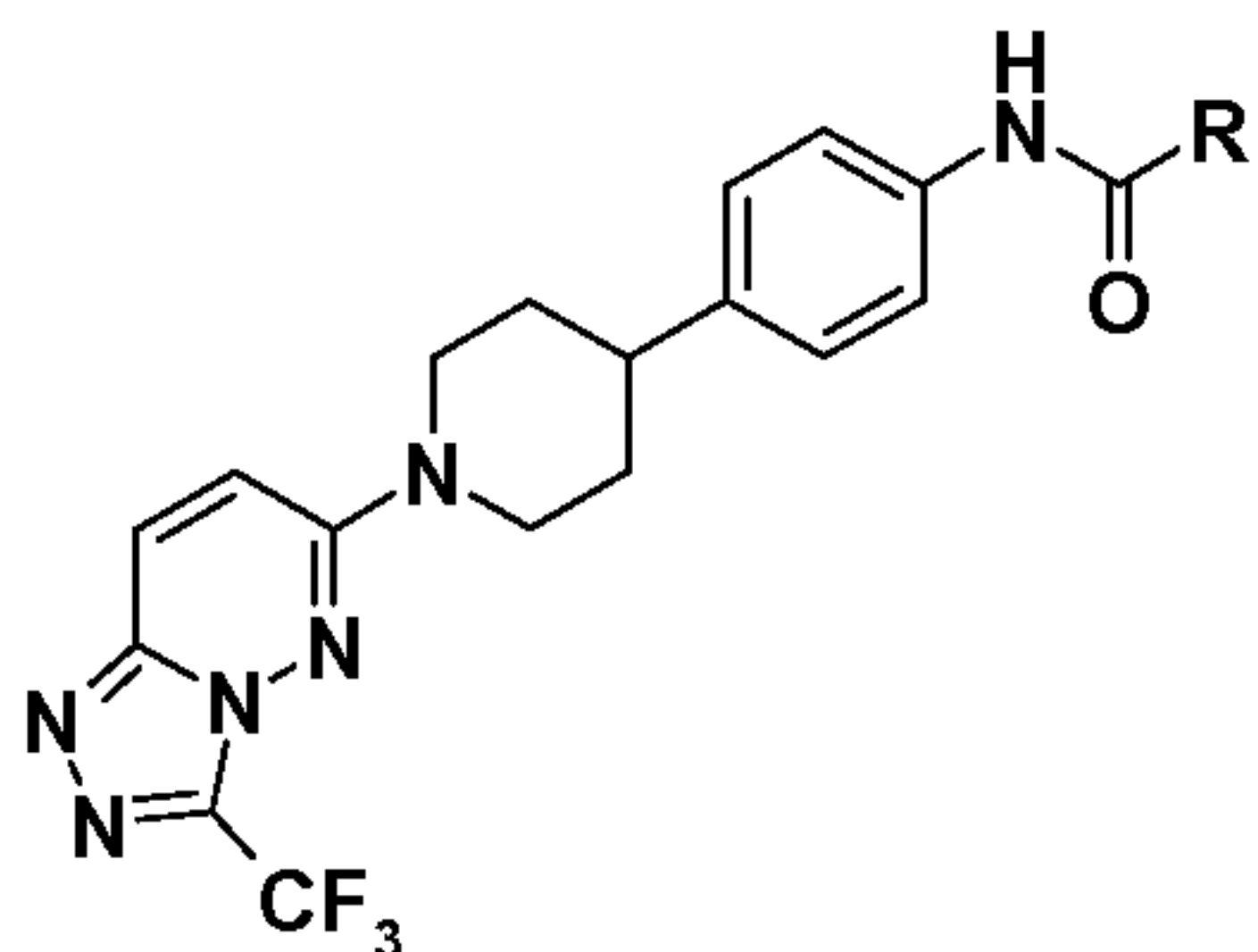
The 4-methoxybutanoic acid used as starting material was prepared as follows:-

Lithium hydroxide monohydrate (0.381 g, 9.08 mmol) was added to methyl 4-methoxybutanoate (1g, 7.57 mmol) in a mixture of MeOH (20 mL) and water (10 mL). The resulting suspension was stirred at 50°C for 16 hours. The reaction was cooled to  
 5 room temperature, the MeOH evaporated and the aqueous residues diluted with water (50 mL) and washed with EtOAc (2 x 50 mL). The aqueous layer was then acidified to pH 4 with 1M citric acid and extracted with EtOAc (2 x 50 mL). The combined extracts were dried over MgSO<sub>4</sub> and the solvent evaporated to afford 4-methoxybutanoic acid (0.709 g, 79%) as a liquid.

10 <sup>1</sup>H NMR (399.9 MHz, CDCl<sub>3</sub>) δ 1.91 (2H, m), 2.46 (2H, t), 3.34 (3H, s), 3.44 (2H, t), 10.92 (1H, br s).

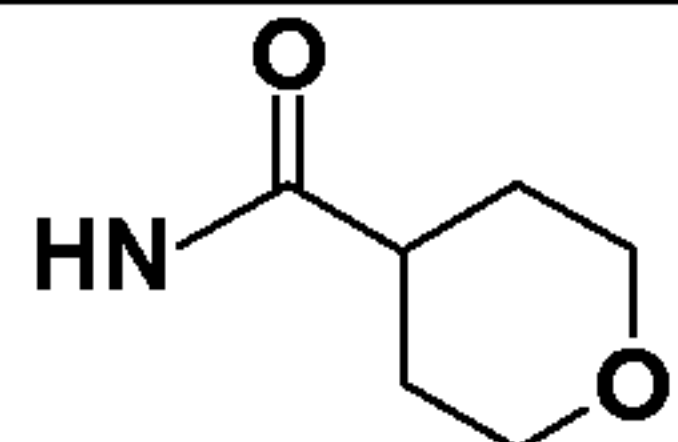
### **Examples 663-665**

The following compounds were prepared in 22-68% yield by an analogous method to Example 655, starting from 4-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]aniline (obtained as described in Example 615) and the appropriate  
 15 carboxylic acid:-



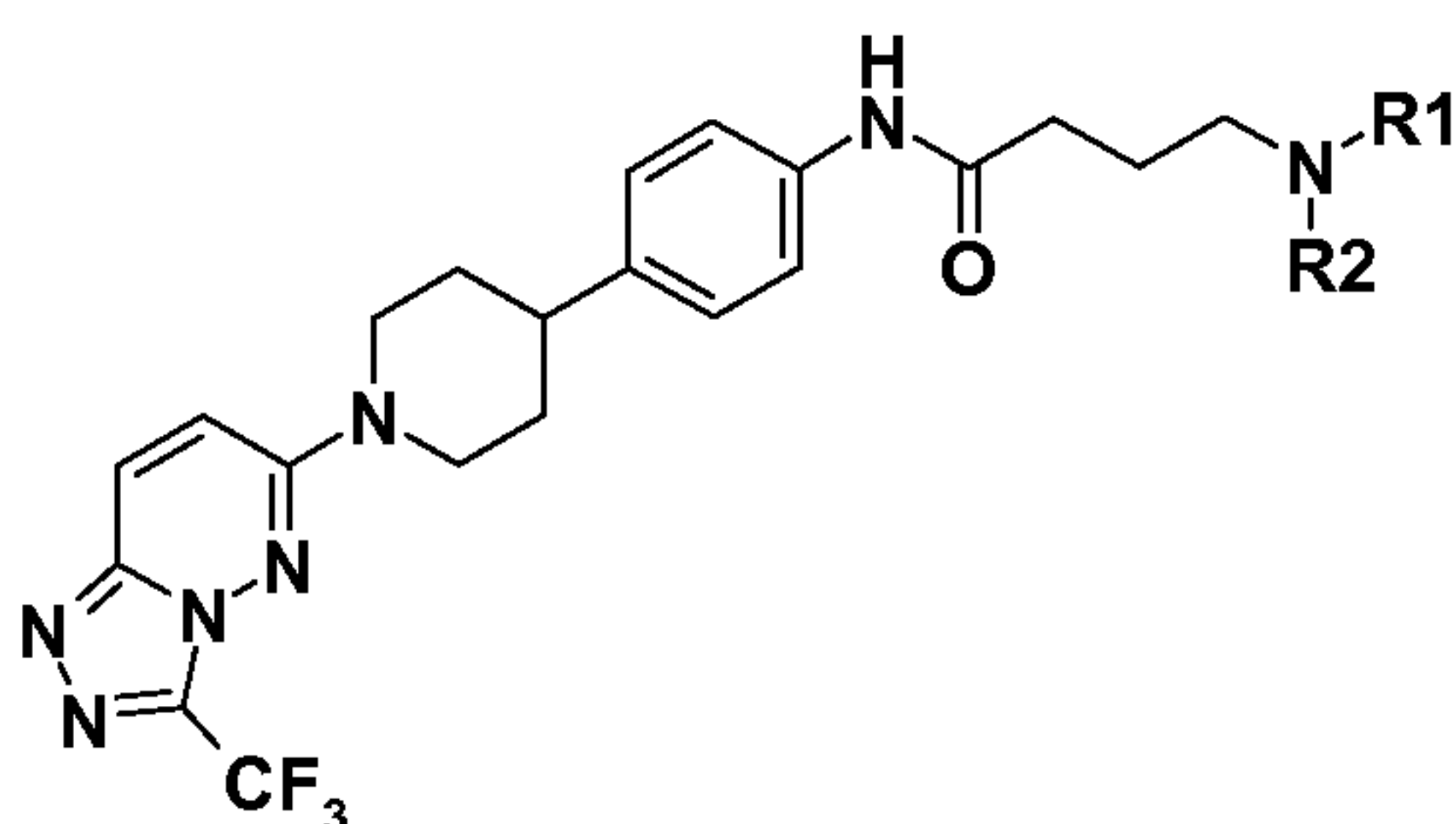
| Ex. | NHCOR | <sup>1</sup> H NMR (399.9 MHz, DMSO-d <sub>6</sub> )                                                                                                                            | m/z [M+H] <sup>+</sup> |
|-----|-------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|
| 663 |       | δ 1.60 - 1.75 (6H, m), 1.88 (4H, m), 2.18 (3H, s), 2.26 (1H, m), 2.83 (3H, m), 3.10 (2H, m), 4.41 (2H, m), 7.18 (2H, d), 7.52 (2H, d), 7.66 (1H, d), 8.24 (1H, d), 9.75 (1H, s) | 488                    |
| 664 |       | δ 1.68 (2H, m), 1.89 (2H, m), 2.83 (1H, m), 3.11 (2H, m), 3.38 (3H, s), 3.98 (2H, s), 4.42 (2H, m), 7.21 (2H, d), 7.58 (2H, d), 7.66 (1H, d), 8.24 (1H, d), 9.66 (1H, s)        | 435                    |



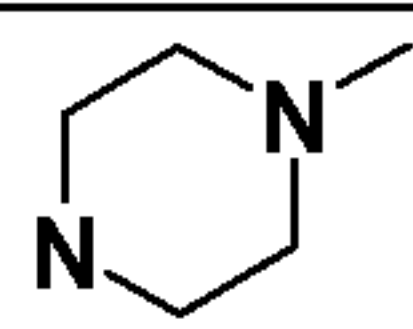
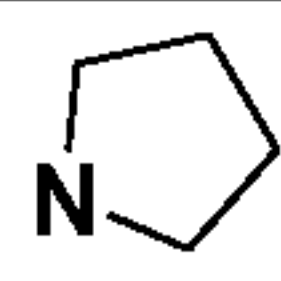
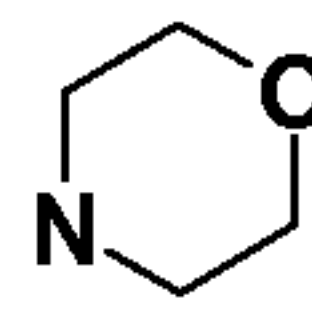
|     |                                                                                   |                                                                                                                                                                                                        |     |
|-----|-----------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
| 665 |  | $\delta$ 1.67 (6H, m), 1.89 (2H, m), 2.82 (1H, m), 3.11 (2H, m), 3.36 (2H, m), 3.91 (2H, m), 4.41 (2H, m), 7.19 (2H, d), 7.53 (2H, d), 7.66 (1H, d), 8.25 (1H, d), 9.79 (1H, s), (1H obscured by DMSO) | 475 |
|-----|-----------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|

**Examples 666-668**

The following compounds were prepared in 27-68% yield by an analogous method to Example 659, starting from 4-chloro-N-[4-[1-(3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)piperidin-4-yl]phenyl]butanamide and the appropriate amine:-



5

| Ex. | NR <sub>1</sub> R <sub>2</sub>                                                      | <sup>1</sup> H NMR (399.9 MHz, DMSO-d <sub>6</sub> )                                                                                                                                           | m/z [M+H] <sup>+</sup> |
|-----|-------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|
| 666 |  | $\delta$ 1.62 - 1.76 (4H, m), 1.88 (2H, m), 2.13 (3H, s), 2.26 - 2.37 (12H, m), 2.81 (1H, m), 3.11 (2H, m), 4.41 (2H, m), 7.18 (2H, d), 7.51 (2H, d), 7.66 (1H, d), 8.24 (1H, d), 9.76 (1H, s) | 531                    |
| 667 |  | $\delta$ 1.62 - 1.79 (8H, m), 1.89 (2H, m), 2.33 (2H, m), 2.41 - 2.50 (6H, m), 2.82 (1H, m), 3.11 (2H, m), 4.42 (2H, m), 7.18 (2H, d), 7.51 (2H, d), 7.66 (1H, d), 8.24 (1H, d), 9.80 (1H, s)  | 502                    |
| 668 |  | $\delta$ 1.62 - 1.78 (4H, m), 1.89 (2H, m), 2.27 - 2.40 (8H, m), 2.82 (1H, m), 3.11 (2H, m), 3.56 (4H, m), 4.41 (2H, m), 7.19 (2H, d), 7.51 (2H, d), 7.66 (1H, d), 8.24 (1H, d), 9.78 (1H, s)  | 518                    |

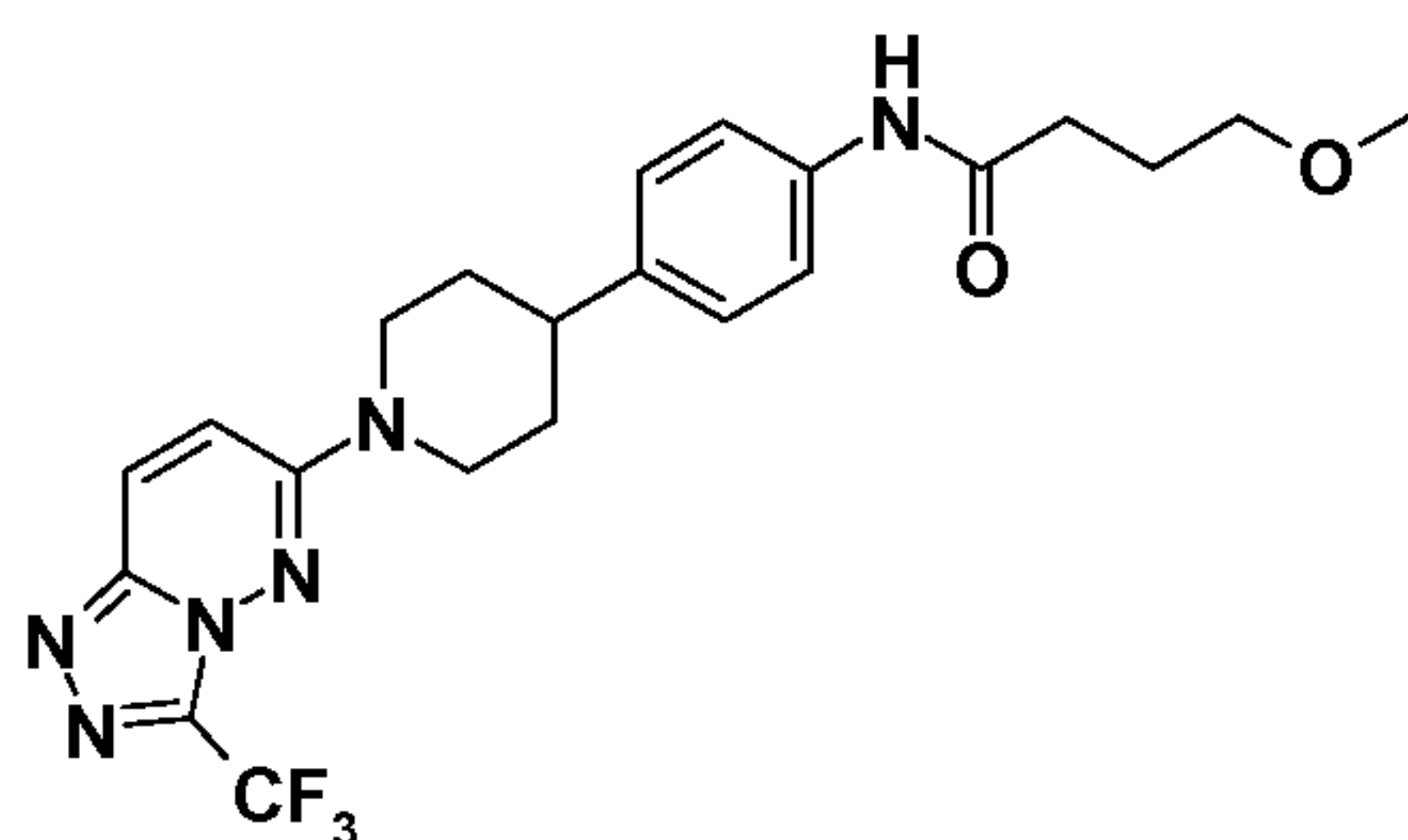
The 4-chloro-N-[4-[1-(3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)piperidin-4-yl]phenyl]butanamide used as starting material was obtained in 80% yield by an analogous procedure to Example 659, preparation of starting materials, starting from 4-[1-[3-



(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]aniline (obtained as described in Example 615).

$m/z = 467 [M+H]^+$ .

### **Example 669**

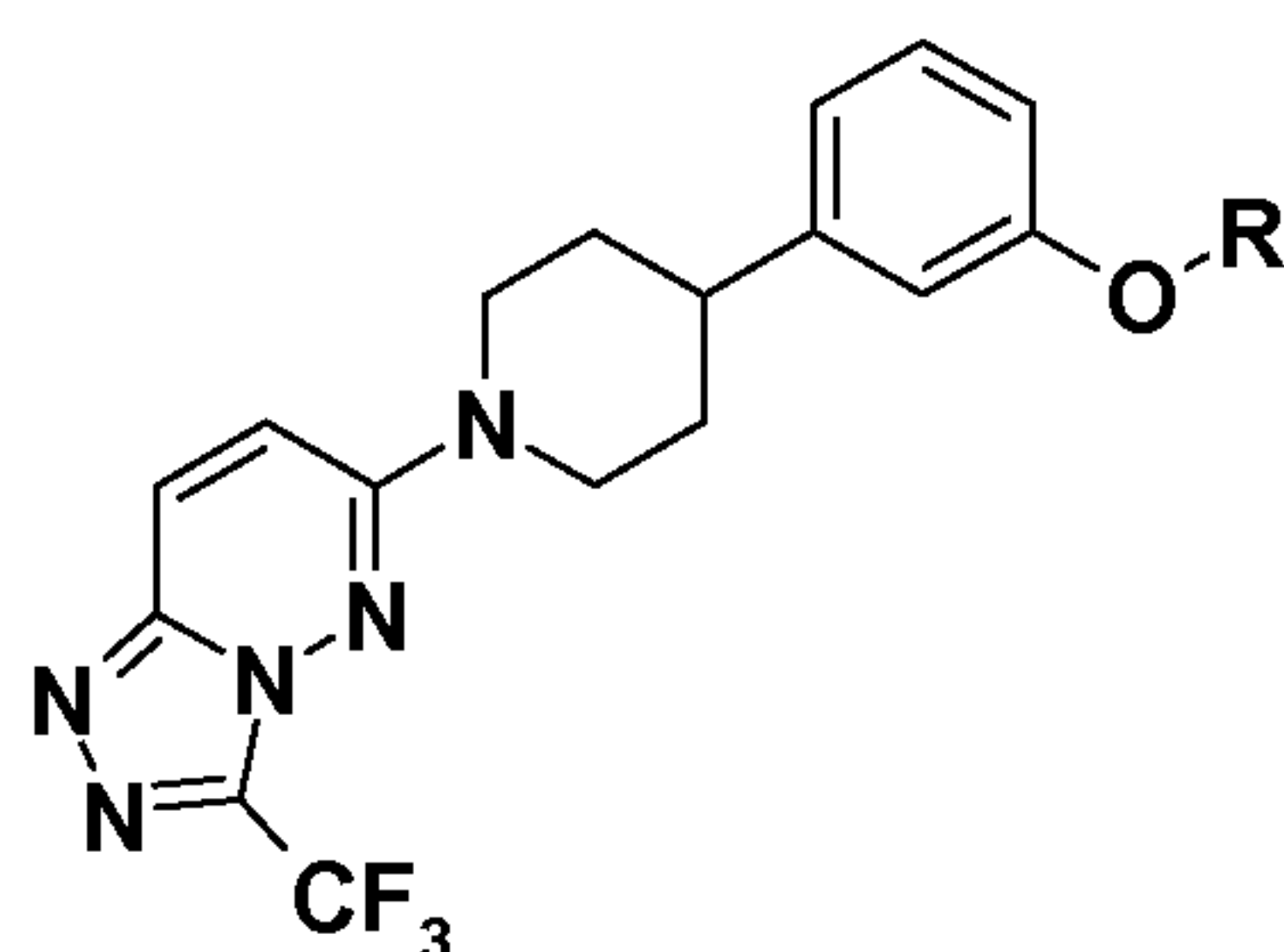


Obtained in 38% yield by an analogous procedure to Example 655, starting from 4-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]aniline (obtained as described in Example 615) and 4-methoxybutanoic acid (obtained as described in Example 662, preparation of starting materials).

$^1\text{H}$  NMR (399.9 MHz, DMSO- $d_6$ )  $\delta$  1.68 (2H, m), 1.80 (2H, m), 1.89 (2H, m), 2.34 (2H, t), 2.82 (1H, m), 3.11 (2H, m), 3.24 (3H, s), 3.35 (2H, t), 4.41 (2H, m), 7.18 (2H, d), 7.51 (2H, d), 7.66 (1H, d), 8.24 (1H, d), 9.80 (1H, s);  $m/z = 463 [M+H]^+$ .

### **Examples 670-684**

The following compounds were prepared in 17-64% yield by an analogous method to Example 513, starting from 3-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]phenol and the appropriate alcohol:-



| Ex. | OR | $^1\text{H}$ NMR (399.9 MHz, DMSO- $d_6$ )                                                                                                                                                    | $m/z [M+H]^+$ |
|-----|----|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------|
| 670 |    | $\delta$ 1.71 (2H, m), 1.85 (4H, m), 2.14 (6H, s), 2.35 (2H, t), 2.84 (1H, m), 3.10 (2H, m), 3.98 (2H, t), 4.42 (2H, m), 6.76 (1H, m), 6.83 (2H, m), 7.20 (1H, m), 7.66 (1H, d), 8.24 (1H, d) | 449           |



## DEMANDE OU BREVET VOLUMINEUX

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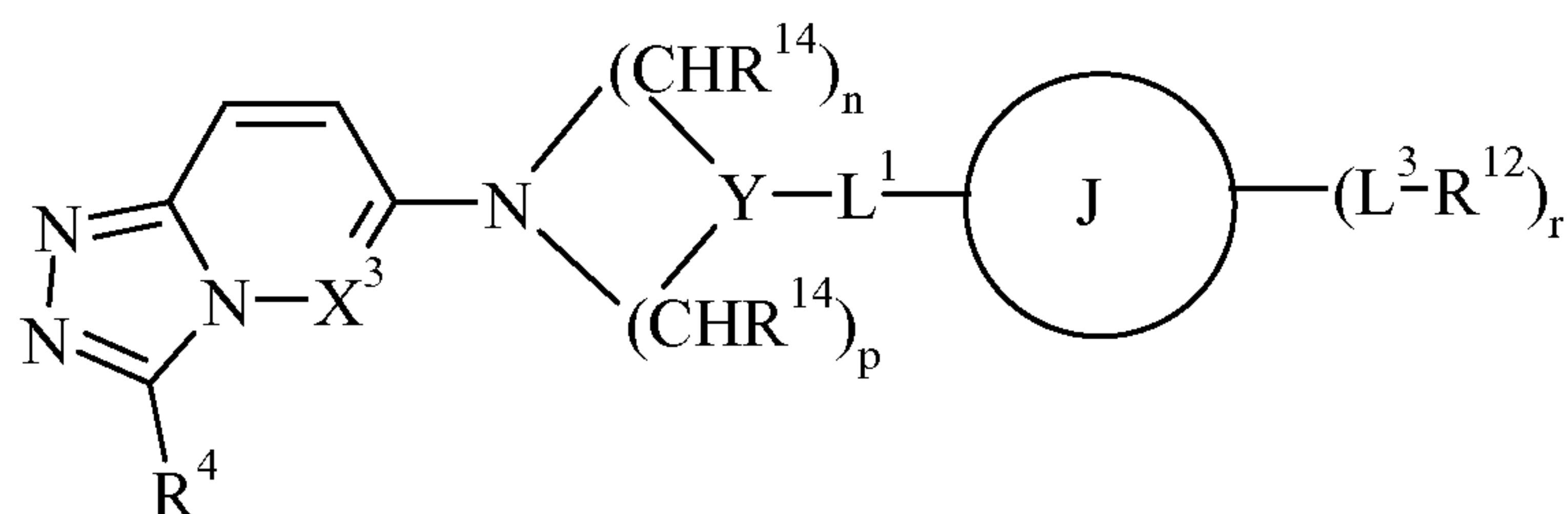
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**Claims**

1. A compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, for use as a medicament:



(Ic)

wherein

$X^3$  represents CH or N;

$R^4$  represents haloC<sub>1-4</sub>alkyl;

10  $Y$  represents CH, COH or N;

$R^{14}$ , identically or differently on each occurrence, represents hydrogen or methyl;

$n$  and  $p$  independently represent 1 or 2;

$L^1$  represents a direct bond,  $-(CR^9R^{10})_t-$ ,  $-(CR^9R^{10})_v-O-(CR^9R^{10})_v-$ ,  $-N(R^{11})-(CH_2)_q-$  or  $-S-$ ,  $-S(O)-$  or  $-S(O)_2-$ ;

15  $R^9$  and  $R^{10}$ , identically or differently on each occurrence, represent hydrogen or methyl;

$q$ , identically or differently on each occurrence, represents 0, 1, 2 or 3;

$t$  represents 1, 2 or 3;

$v$ , identically or differently on each occurrence, represents 0, 1 or 2;

$J$  represents:

20 aryl;

a totally saturated monocyclic 3 to 6 membered carbocyclic ring;

a monocyclic 4, 5, 6 or 7 membered heterocyclic ring which comprises 1, 2, 3 or 4 heteroatoms independently selected from O, N or S;

a monocyclic 5 or 6 membered heteroaryl ring which comprises 1, 2, 3 or 4

25 heteroatoms independently selected from O, N or S; or

a bicyclic 9 or 10 membered heteroaryl ring system which comprises 1, 2, 3, 4 or 5 heteroatoms independently selected from O, N or S;



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$L^3$  represents a direct bond,  $-(CR^9R^{10})_t-$ ,  $-C(O)N(R^{11})-(CH_2)_q-$ ,  $-C(O)N(R^{11})-(CH_2)_q-S(O)_2-$ ,  $-NR^{11}C(O)-(CH_2)_q-$ ,  $-C(O)-(CH_2)_q-$ ,  $-O-(CH_2)_q-$ ,  $-O-(CH_2)_q-NR^{11}-(CH_2)_q-$ ,  $-O-(CH_2)_q-C(O)NR^{11}-(CH_2)_q-$ ,  $-S-$ ,  $-S(O)-$  or  $-S(O)_2-$ ;

$R^{11}$  represents hydrogen or methyl;

5  $R^{12}$  represents:

halo,  $C_{1-6}$ alkyl,  $C_{2-6}$ alkenyl,  $C_{2-6}$ alkynyl, carboxy,  $C_{1-6}$ alkoxy, cyano, oxo, fluoro $C_{1-6}$ alkyl, hydroxy, amino,  $N-C_{1-4}$ alkylamino or  $N,N$ -di- $C_{1-4}$ alkylamino; aryl, wherein the aryl ring is optionally substituted with 1, 2 or 3 substituents selected from  $R^{13}$ ;

10 a monocyclic 5 or 6 membered heteroaryl ring which comprises 1, 2, 3 or 4 heteroatoms independently selected from O, N or S and wherein the heteroaryl ring is optionally substituted with 1, 2 or 3 substituents selected from  $R^{13}$ ; or

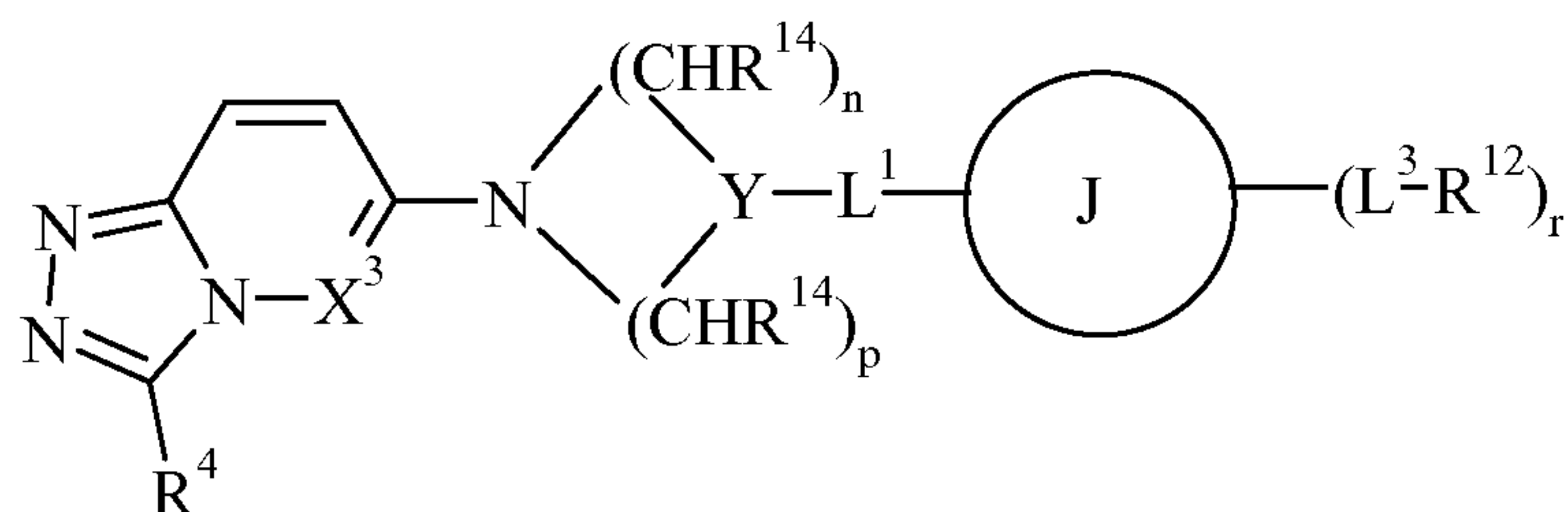
a monocyclic 4, 5, 6 or 7 membered heterocyclic ring which comprises 1, 2, 3 or 4 heteroatoms independently selected from O, N or S and wherein the heterocyclic ring is optionally substituted with 1, 2 or 3 substituents selected from  $R^{13}$ ;

$R^{13}$  represents amino, halo,  $C_{1-6}$ alkyl,  $C_{2-6}$ alkenyl,  $C_{2-6}$ alkynyl,  $C_{1-6}$ alkoxy,  $C_{2-6}$ alkanoyl,  $C_{1-6}$ alkoxy $C_{1-6}$ alkyl, carboxy, cyano, oxo, fluoro $C_{1-6}$ alkyl, hydroxy, hydroxy $C_{1-6}$ alkyl,  $C_{1-6}$ alkylsulphanyl,  $C_{1-6}$ alkylsulphinyl,  $C_{1-6}$ alkylsulphonyl,  $N-C_{1-4}$ alkylamino,  $N,N$ -di- $C_{1-4}$ alkylamino or  $-C(O)NR^{14}R^{15}$  wherein  $R^{14}$  and  $R^{15}$

20 independently represent hydrogen or methyl; and

$r$  represents 0, 1, 2 or 3.

2. A compound of Formula (Ic), or a pharmaceutically acceptable salt thereof, for use in the treatment of prostate cancer:



(Ic)

wherein

$X^3$  represents CH or N;



$R^4$  represents haloC<sub>1-4</sub>alkyl;

Y represents CH, COH or N;

$R^{14}$ , identically or differently on each occurrence, represents hydrogen or methyl;

n and p independently represent 1 or 2;

5  $L^1$  represents a direct bond,  $-(CR^9R^{10})_t-$ ,  $-(CR^9R^{10})_v-O-(CR^9R^{10})_v-$ ,  $-N(R^{11})-(CH_2)_q-$  or  $-S-$ ,  $-S(O)-$  or  $-S(O)_2-$ ;

$R^9$  and  $R^{10}$ , identically or differently on each occurrence, represent hydrogen or methyl;

q, identically or differently on each occurrence, represents 0, 1, 2 or 3;

t represents 1, 2 or 3;

10  $v$ , identically or differently on each occurrence, represents 0, 1 or 2;

J represents:

aryl;

a totally saturated monocyclic 3 to 6 membered carbocyclic ring;

a monocyclic 4, 5, 6 or 7 membered heterocyclic ring which comprises 1, 2, 3 or 4

15 heteroatoms independently selected from O, N or S;

a monocyclic 5 or 6 membered heteroaryl ring which comprises 1, 2, 3 or 4

heteroatoms independently selected from O, N or S; or

a bicyclic 9 or 10 membered heteroaryl ring system which comprises 1, 2, 3, 4 or 5

heteroatoms independently selected from O, N or S;

20  $L^3$  represents a direct bond,  $-(CR^9R^{10})_t-$ ,  $-C(O)N(R^{11})-(CH_2)_q-$ ,  $-C(O)N(R^{11})-(CH_2)_q-S(O)_2-$ ,  $-NR^{11}C(O)-(CH_2)_q-$ ,  $-C(O)-(CH_2)_q-$ ,  $-O-(CH_2)_q-$ ,  $-O-(CH_2)_q-NR^{11}-(CH_2)_q-$ ,  $-O-(CH_2)_q-C(O)NR^{11}-(CH_2)_q-$ ,  $-S-$ ,  $-S(O)-$  or  $-S(O)_2-$ ;

$R^{11}$  represents hydrogen or methyl;

$R^{12}$  represents:

25 halo, C<sub>1-6</sub>alkyl, C<sub>2-6</sub>alkenyl, C<sub>2-6</sub>alkynyl, carboxy, C<sub>1-6</sub>alkoxy, cyano, oxo, fluoroC<sub>1-6</sub>alkyl, hydroxy, amino, N-C<sub>1-4</sub>alkylamino or N,N-di-C<sub>1-4</sub>alkylamino;

aryl, wherein the aryl ring is optionally substituted with 1, 2 or 3 substituents selected from  $R^{13}$ ;

a monocyclic 5 or 6 membered heteroaryl ring which comprises 1, 2, 3 or 4

30 heteroatoms independently selected from O, N or S and wherein the heteroaryl ring is optionally substituted with 1, 2 or 3 substituents selected from  $R^{13}$ ; or



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a monocyclic 4, 5, 6 or 7 membered heterocyclic ring which comprises 1, 2, 3 or 4 heteroatoms independently selected from O, N or S and wherein the heterocyclic ring is optionally substituted with 1, 2 or 3 substituents selected from  $R^{13}$ ;

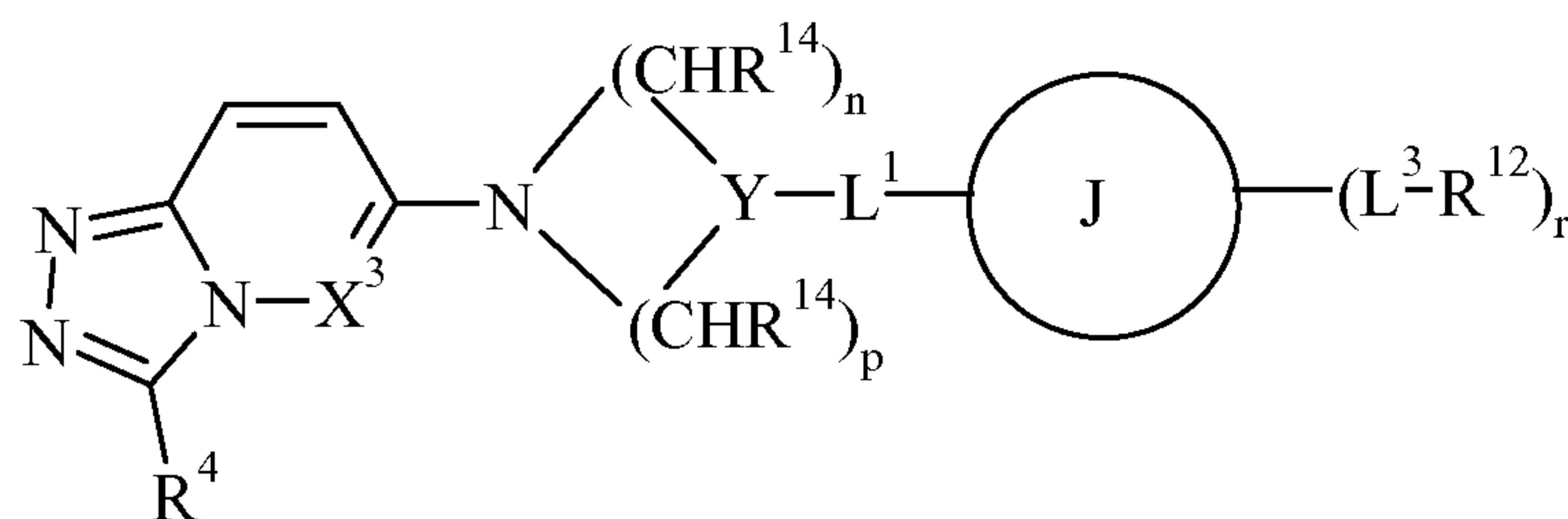
$R^{13}$  represents amino, halo,  $C_{1-6}$ alkyl,  $C_{2-6}$ alkenyl,  $C_{2-6}$ alkynyl,  $C_{1-6}$ alkoxy,

5  $C_{2-6}$ alkanoyl,  $C_{1-6}$ alkoxy $C_{1-6}$ alkyl, carboxy, cyano, oxo, fluoro $C_{1-6}$ alkyl, hydroxy, hydroxy $C_{1-6}$ alkyl,  $C_{1-6}$ alkylsulphanyl,  $C_{1-6}$ alkylsulphinyl,  $C_{1-6}$ alkylsulphonyl, N- $C_{1-4}$ alkylamino, N,N-di- $C_{1-4}$ alkylamino or  $-C(O)NR^{14}R^{15}$  wherein  $R^{14}$  and  $R^{15}$  independently represent hydrogen or methyl; and

r represents 0, 1, 2 or 3.

10

3. A compound of Formula (Ic), or a pharmaceutically acceptable salt thereof:



(Ic)

wherein

15  $X^3$  represents CH or N;

$R^4$  represents halo $C_{1-4}$ alkyl;

$Y$  represents CH, COH or N;

$R^{14}$ , identically or differently on each occurrence, represents hydrogen or methyl;

$n$  and  $p$  independently represent 1 or 2;

20  $L^1$  represents a direct bond,  $-(CR^9R^{10})_t-$ ,  $-(CR^9R^{10})_v-O-(CR^9R^{10})_v-$ ,  $-N(R^{11})-(CH_2)_q-$  or  $-S-$ ,  $-S(O)-$  or  $-S(O)_2-$ ;

$R^9$  and  $R^{10}$ , identically or differently on each occurrence, represent hydrogen or methyl;

$q$ , identically or differently on each occurrence, represents 0, 1, 2 or 3;

$t$  represents 1, 2 or 3;

25  $v$ , identically or differently on each occurrence, represents 0, 1 or 2;

$J$  represents:

aryl;

a totally saturated monocyclic 3 to 6 membered carbocyclic ring;



furanyl, imidazolyl, isothiazolyl, morpholinyl, oxadiazolyl, oxazolyl, isoxazolyl, oxetanyl, tetrahydro-2*H*-pyranyl, pyrazolyl, pyridazinyl, pyridinyl, pyrrolyl or thiadiazolyl; or

a bicyclic 9 membered heteroaryl ring system which comprises 1 or 2 nitrogen atoms, 1 or 2 oxygen atoms, 1 sulphur atom, or 1 nitrogen atom and 1 sulphur atom;

$L^3$  represents a direct bond,  $-(CR^9R^{10})_t-$ ,  $-C(O)N(R^{11})-(CH_2)_q-$ ,  $-C(O)N(R^{11})-(CH_2)_q-S(O)_2-$ ,  $-NR^{11}C(O)-(CH_2)_q-$ ,  $-C(O)-(CH_2)_q-$ ,  $-O-(CH_2)_q-$ ,  $-O-(CH_2)_q-NR^{11}-(CH_2)_q-$ ,  $-O-(CH_2)_q-C(O)NR^{11}-(CH_2)_q-$ ,  $-S-$ ,  $-S(O)-$  or  $-S(O)_2-$ ;

$R^{11}$  represents hydrogen or methyl;

$R^{12}$  represents:

halo,  $C_{1-6}$ alkyl,  $C_{2-6}$ alkenyl,  $C_{2-6}$ alkynyl, carboxy,  $C_{1-6}$ alkoxy, cyano, oxo, fluoro $C_{1-6}$ alkyl, hydroxy, amino,  $N-C_{1-4}$ alkylamino or  $N,N$ -di- $C_{1-4}$ alkylamino;

aryl, wherein the aryl ring is optionally substituted with 1, 2 or 3 substituents

selected from  $R^{13}$ ;

a monocyclic 5 or 6 membered heteroaryl ring which comprises 1, 2, 3 or 4

heteroatoms independently selected from O, N or S and wherein the heteroaryl ring is optionally substituted with 1, 2 or 3 substituents selected from  $R^{13}$ ; or

a monocyclic 4, 5, 6 or 7 membered heterocyclic ring which comprises 1, 2, 3 or 4

heteroatoms independently selected from O, N or S and wherein the heterocyclic ring is optionally substituted with 1, 2 or 3 substituents selected from  $R^{13}$ ;

$R^{13}$  represents amino, halo,  $C_{1-6}$ alkyl,  $C_{2-6}$ alkenyl,  $C_{2-6}$ alkynyl,  $C_{1-6}$ alkoxy,

$C_{2-6}$ alkanoyl,  $C_{1-6}$ alkoxy $C_{1-6}$ alkyl, carboxy, cyano, oxo, fluoro $C_{1-6}$ alkyl, hydroxy,

hydroxy $C_{1-6}$ alkyl,  $C_{1-6}$ alkylsulphanyl,  $C_{1-6}$ alkylsulphinyl,  $C_{1-6}$ alkylsulphonyl,

$N-C_{1-4}$ alkylamino,  $N,N$ -di- $C_{1-4}$ alkylamino or  $-C(O)NR^{14}R^{15}$  wherein  $R^{14}$  and  $R^{15}$

independently represent hydrogen or methyl;

$r$  represents 1, 2 or 3 when  $J$  represents aryl;

$r$  represents 0 when  $J$  represents a totally saturated monocyclic 3 to 6 membered carbocyclic ring; and

$r$  represents 0, 1, 2 or 3 when  $J$  represents furanyl, imidazolyl, isothiazolyl, morpholinyl, oxadiazolyl, oxazolyl, isoxazolyl, oxetanyl, tetrahydro-2*H*-pyranyl, pyrazolyl, pyridazinyl, pyridinyl, pyrrolyl, thiadiazolyl, or a bicyclic 9 membered heteroaryl ring system which



comprises 1 or 2 nitrogen atoms, 1 or 2 oxygen atoms, 1 sulphur atom, or 1 nitrogen atom and 1 sulphur atom;

with the proviso that the compound of Formula (Ic) is other than:

4-{4-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazin-6-yl]piperazin-1-yl}phenol;

5 6-[4-(pyridin-3-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazine;

6-[4-(2-fluorobenzyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazine;

6-[4-(imidazo[1,2-*a*]pyridin-2-ylmethyl)piperazin-1-yl]-3-

(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazine;

10 6-[4-(3,4-dimethoxybenzyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazine;

6-[4-(1*H*-indol-3-yl)piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazine;

6-{4-[2-(3,5-dimethoxyphenyl)ethyl]piperidin-1-yl}-3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazine;

15 6-[4-(4-methoxybenzyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazine;

6-[4-(3-chlorobenzyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazine;

6-[4-(4-chlorobenzyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazine;

6-[4-(2-methylbenzyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazine;

6-[4-(pyridin-4-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-

20 *b*]pyridazine;

6-[4-(2,6-dimethylphenyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-

*b*]pyridazine;

6-[4-(4-methoxyphenyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-

*b*]pyridazine;

25 6-[4-(3-chlorophenyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazine;

6-[4-(4-fluorophenyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazine;

or

6-{4-[(2,6-difluorophenyl)sulfonyl]piperazin-1-yl}-3-(trifluoromethyl)[1,2,4]triazolo[4,3-*b*]pyridazine.

30

4. A compound according to Claim 3, or a pharmaceutically acceptable salt thereof, wherein X<sup>3</sup> represents N.



5. A compound according to either of Claims 3 or 4, or a pharmaceutically acceptable salt thereof, wherein  $R^4$  represents difluoromethyl, trifluoromethyl or chloro(difluoro)methyl.

5

6. A compound according to either of Claims 3 or 4, or a pharmaceutically acceptable salt thereof, wherein  $R^4$  represents trifluoromethyl.

7. A compound according to any one of Claims 3 to 6, or a pharmaceutically acceptable salt thereof, wherein  $R^{14}$  represents hydrogen.

10

8. A compound according to any one of Claims 3 to 7, or a pharmaceutically acceptable salt thereof, wherein n and p both represent 2.

9. A compound according to any one of Claims 3 to 8, or a pharmaceutically acceptable salt thereof, wherein Y represents CH or COH.

15

10. A compound according to any one of Claims 3 to 9, or a pharmaceutically acceptable salt thereof, wherein Y represents N.

20

11. A compound according to any one of Claims 3 to 10, or a pharmaceutically acceptable salt thereof, wherein  $L^1$  represents a direct bond.

12. A compound according to any one of Claims 3 to 11, or a pharmaceutically acceptable salt thereof, wherein J represents phenyl, pyridinyl, indolyl, indazolyl or pyrrolopyridinyl.

25

13. A compound according to any one of Claims 3 to 12, or a pharmaceutically acceptable salt thereof, wherein  $L^3$  represents  $-C(O)N(R^{11})-(CH_2)_q-$ ,  $-NR^{11}C(O)-(CH_2)_q-$ ,  $-C(O)-(CH_2)_q-$  or  $-O-(CH_2)_q-$ .

30



14. A compound according to Claim 13, or a pharmaceutically acceptable salt thereof, wherein R<sup>11</sup> represents methyl.

15. A compound according to any one of Claims 3 to 14, or a pharmaceutically acceptable salt thereof, wherein R<sup>12</sup> represents fluoro, chloro, methyl, methoxy, difluoromethyl, trifluoromethyl, cyano, hydroxy, methylsulphonyl, dimethylamino, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl or pyrazolyl.

16. A compound according to any one of Claims 3 to 15, or a pharmaceutically acceptable salt thereof, wherein R<sup>13</sup> represents methyl, oxo or hydroxy.

17. A compound according to any one of Claims 3 to 16, or a pharmaceutically acceptable salt thereof, wherein r represents 1.

18. A compound according to any one of Claims 3 to 16, or a pharmaceutically acceptable salt thereof, wherein J does not represent aryl and r represents 0.

19. A compound according to Claim 3 selected from:

4-[[4-[3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperazin-1-yl]methyl]benzonitrile;  
 3-(trifluoromethyl)-6-[4-[[3-(trifluoromethyl)phenyl]methyl]piperazin-1-yl]-[1,2,4]triazolo[4,3-b]pyridazine;  
 4-pyridin-3-yl-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol;  
 3-(difluoromethyl)-6-{4-[(1R)-1-(4-fluorophenyl)ethyl]piperazin-1-yl}[1,2,4]triazolo[4,3-b]pyridazine;  
 4-(4-fluorophenyl)-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol;  
 N-(2-methoxyethyl)-N-methyl-4-{1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl}benzamide;  
 N-(2-hydroxyethyl)-N-methyl-4-{1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl}benzamide;



6-(4-{4-[(4-methylpiperazin-1-yl)carbonyl]phenyl}piperidin-1-yl)-3-

(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine;

N-[2-(2-oxopyrrolidin-1-yl)ethyl]-4-{1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl}benzamide;

5 6-[4-(1H-indazol-3-ylmethyl)piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine;

N-(2-methoxyethyl)-N-methyl-3-({1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl}oxy)benzamide;

2-morpholin-4-yl-N-(4-{1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl}phenyl)acetamide;

6-(4-{4-[2-(1-methyl-1H-pyrazol-5-yl)ethoxy]phenyl}piperidin-1-yl)-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine;

6-{4-[2-(difluoromethyl)-5-fluorobenzyl]piperazin-1-yl}-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine;

15 6-{4-[(6-methylpyridin-3-yl)methyl]piperazin-1-yl}-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine;

6-[4-(1H-pyrrolo[2,3-b]pyridin-3-yl)piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine;

6-[4-(5-methoxy-1H-indol-3-yl)piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine;

1-[(4-{1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl}phenyl)carbonyl]piperidin-4-ol;

N-methyl-N-[2-(methylsulfonyl)ethyl]-4-{1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl}benzamide;

25 6-[3-(4-methoxyphenoxy)azetidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine;

6-(4-{4-[2-(1-methyl-1H-pyrazol-5-yl)ethoxy]phenyl}piperazin-1-yl)-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine; and

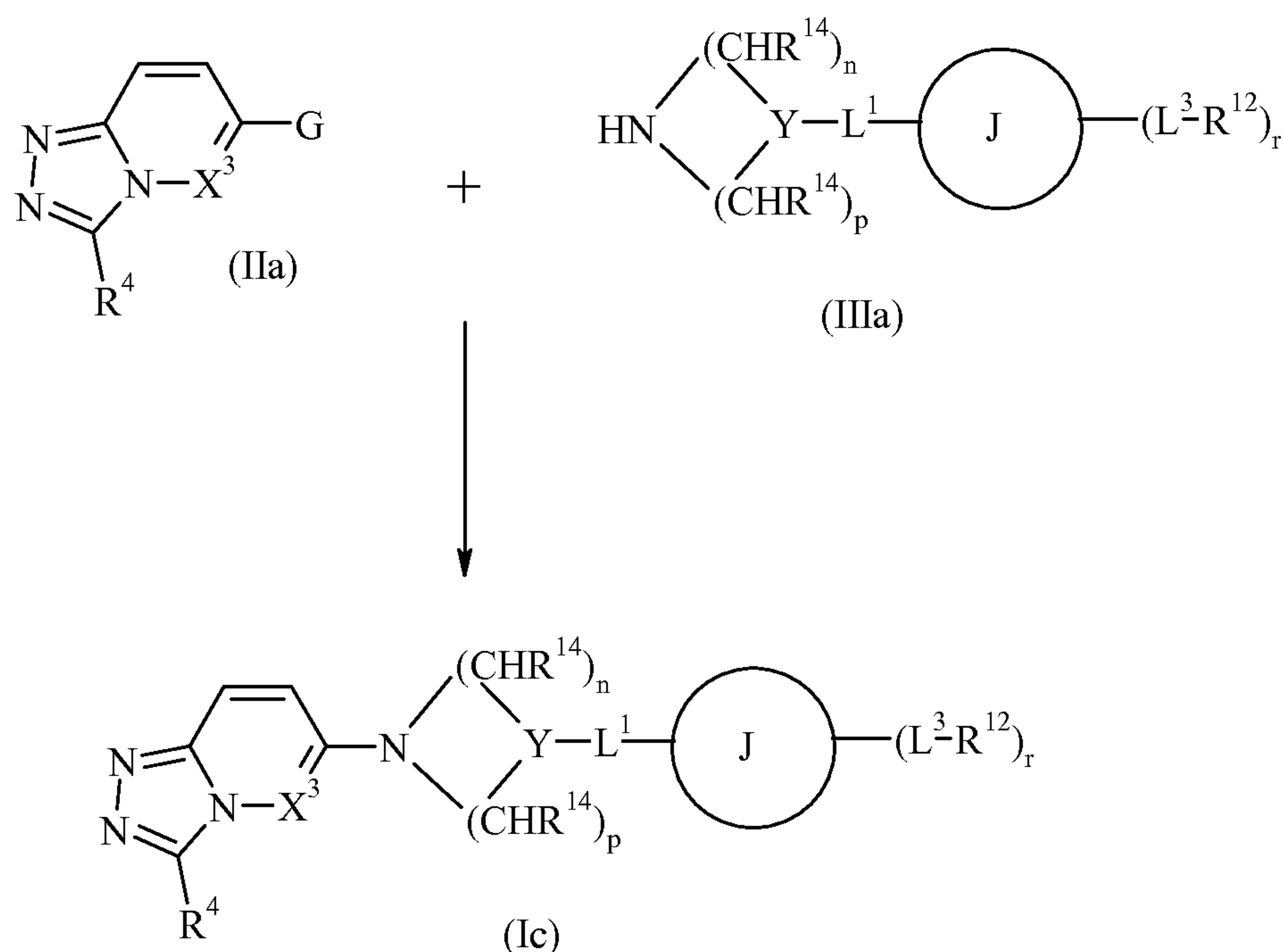
4-[4-[2-(1-methyl-1H-pyrazol-5-yl)ethoxy]phenyl]-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol;

and pharmaceutically acceptable salts thereof.



20. A pharmaceutical composition which comprises a compound according to any one of Claims 3 to 19, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable diluent or carrier.

21. A process for the preparation of compounds of Formula (Ic) which comprises reacting a compound of Formula (IIa), wherein G represents halogen and  $R^4$  and  $X^3$  are as defined hereinbefore in relation to Formula (Ic), with an amine of Formula (IIIa), wherein J, Y,  $L^1$ ,  $L^3$ ,  $R^{12}$ ,  $R^{14}$ , n, p and r are as defined hereinbefore in relation to Formula (Ic):



10 and thereafter, if necessary:

- (i) converting a functional group of one compound of the invention into another functional group;
- (ii) introducing a new functional group into one compound of the invention;
- (iii) removing any protecting groups;
- 15 (iv) for compounds of the invention in the form of a single enantiomer separating a racemic compound of the invention into separate enantiomers;
- (v) preparing a pharmaceutically acceptable salt thereof; and/or
- (vi) preparing a crystalline form thereof.



**Figure1:** X-Ray Powder Diffraction Pattern for 4-pyridin-3-yl-1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-ol Anhydrous Form A when measured using CuK $\alpha$  radiation

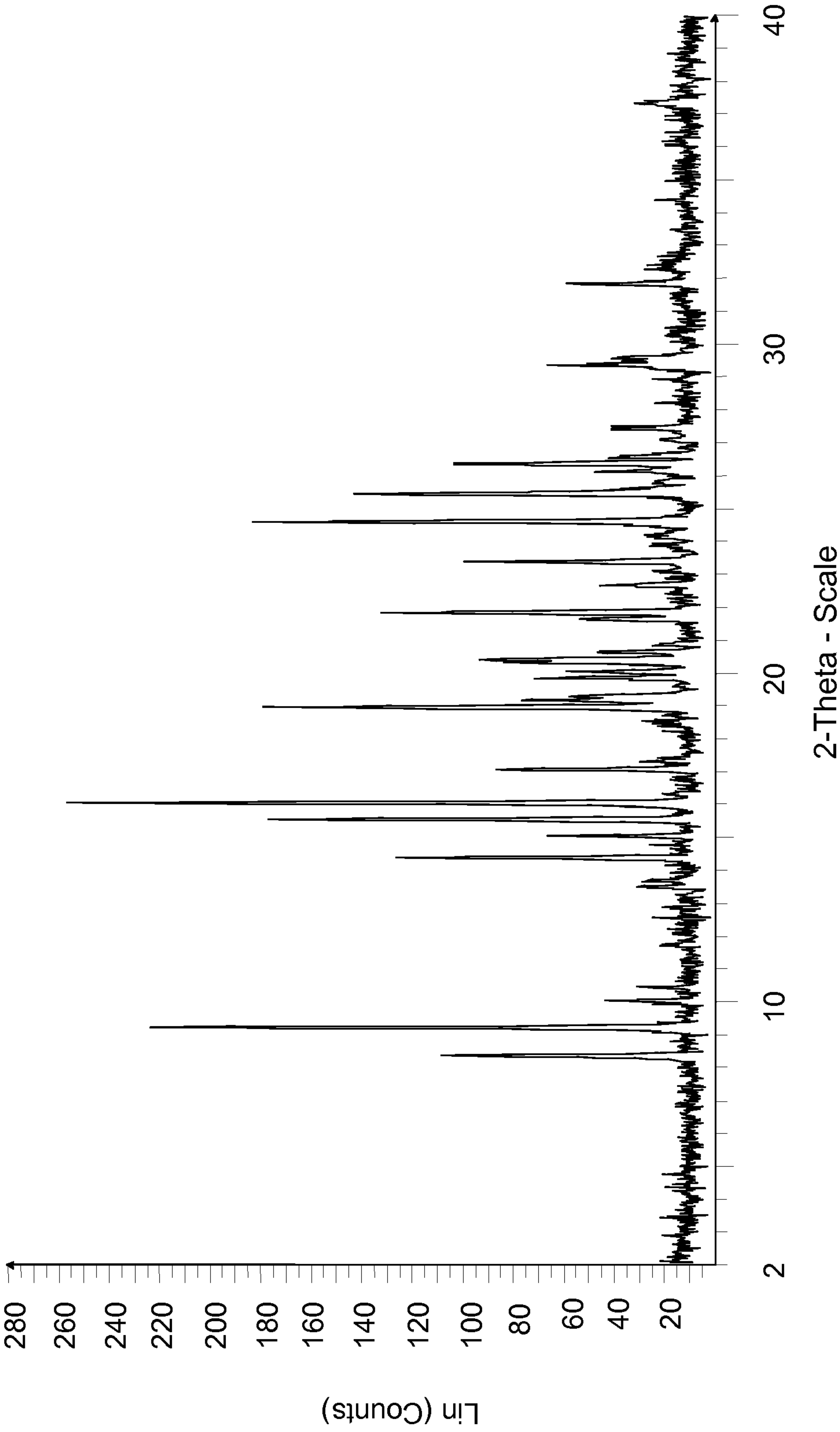


Figure 1



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**Figure 2:** X-Ray Powder Diffraction Pattern for N-(2-methoxyethyl)-N-methyl-4-[1-[3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazin-6-yl]piperidin-4-yl]benzamide Anhydrous Form A when measured using CuK $\alpha$  radiation

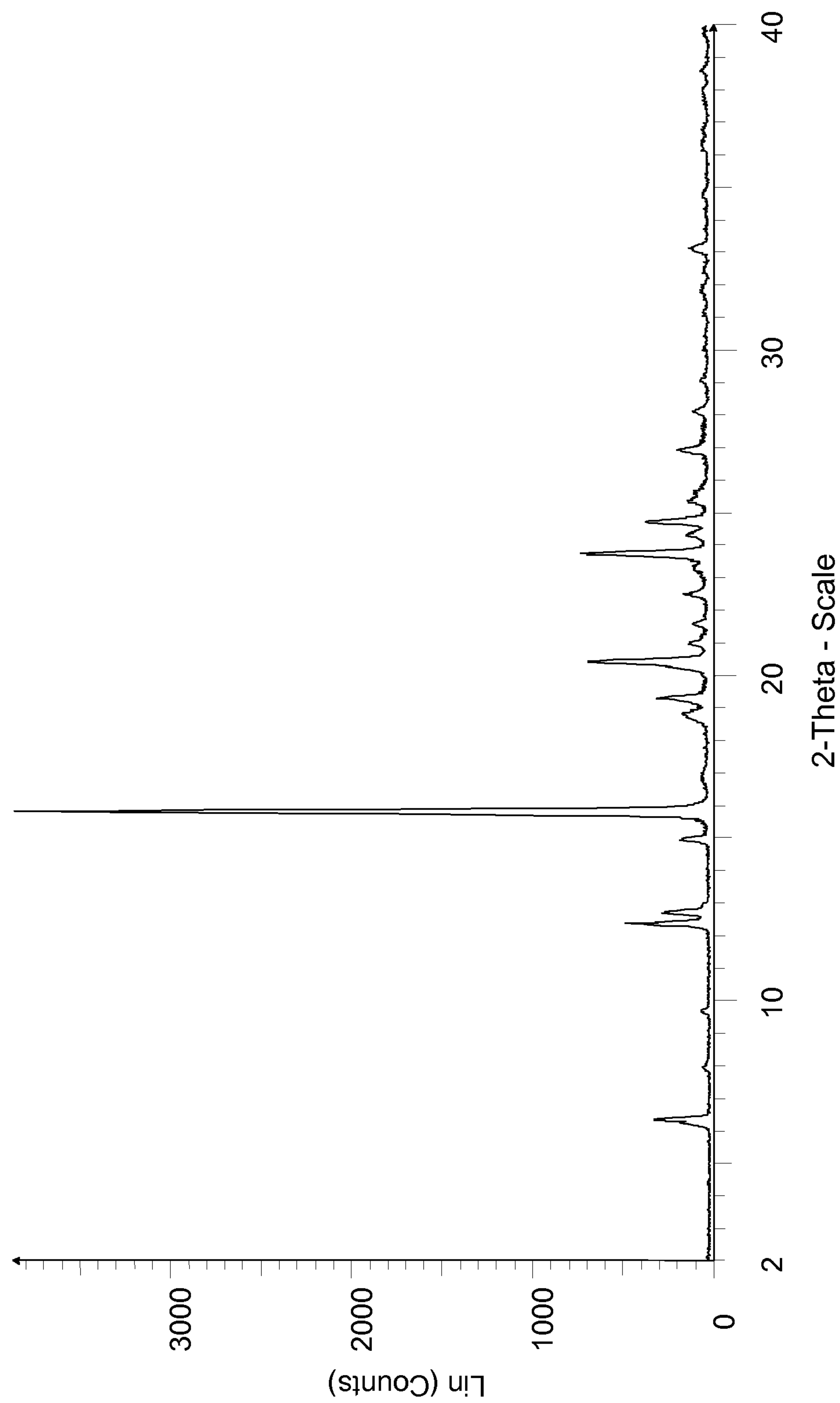


Figure 2



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**Figure 3:** X-Ray Powder Diffraction Pattern for 6-[4-[4-[2-(1-Methyl-1H-pyrazol-5-yl)ethoxy]phenyl]piperidin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine Anhydrous Form A when measured using CuK $\alpha$  radiation

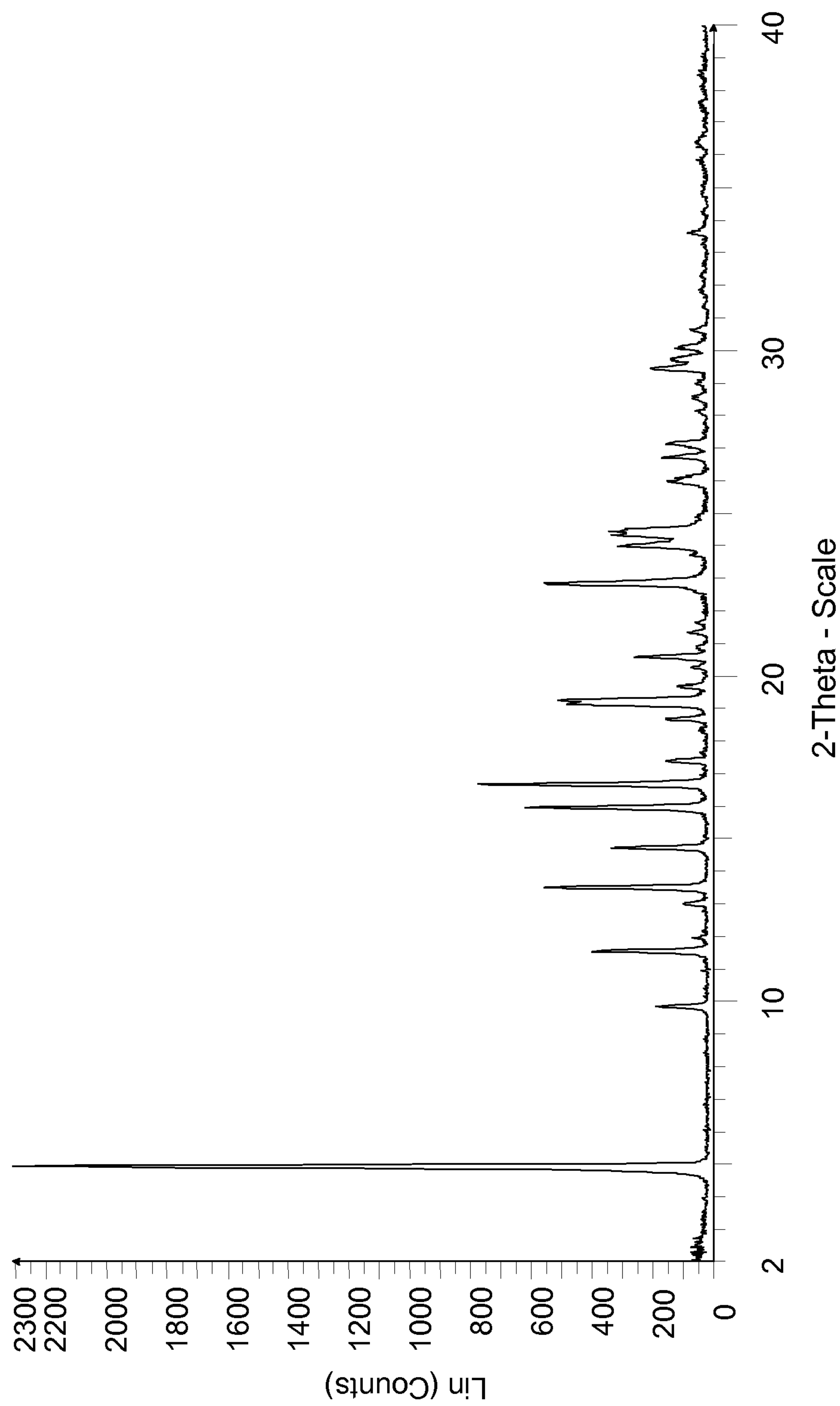


Figure 3



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**Figure 4:** X-Ray Powder Diffraction Pattern for 6-[4-[4-[2-(1-methyl-1H-pyrazol-5-yl)ethoxy]phenyl]piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine Anhydrous Form A when measured using CuK $\alpha$  radiation

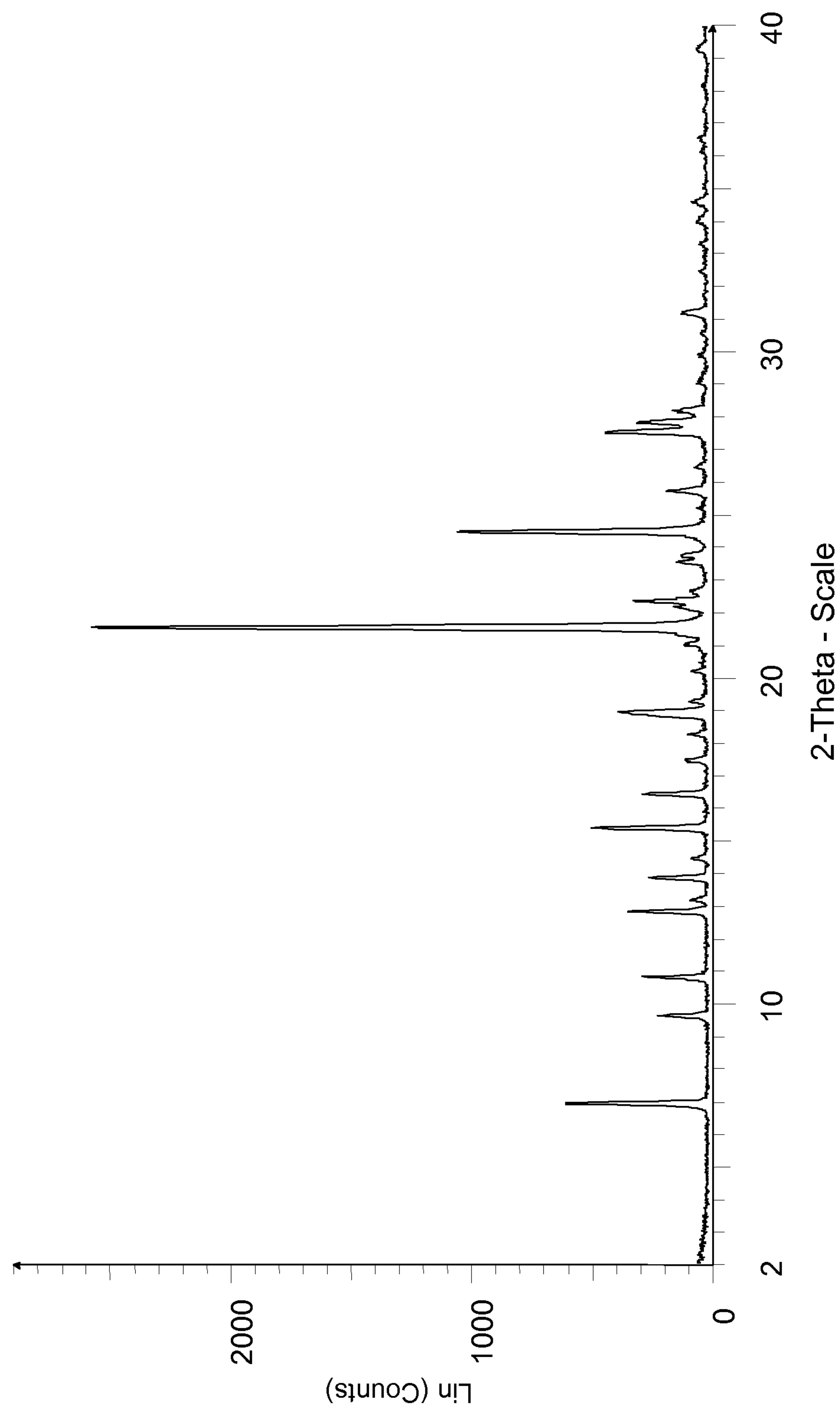


Figure 4



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**Figure 5:** X-Ray Powder Diffraction Pattern for 6-[4-[4-[2-(1-methyl-1H-pyrazol-5-yl)ethoxy]phenyl]piperazin-1-yl]-3-(trifluoromethyl)[1,2,4]triazolo[4,3-b]pyridazine fumarate when measured using CuK $\alpha$  radiation

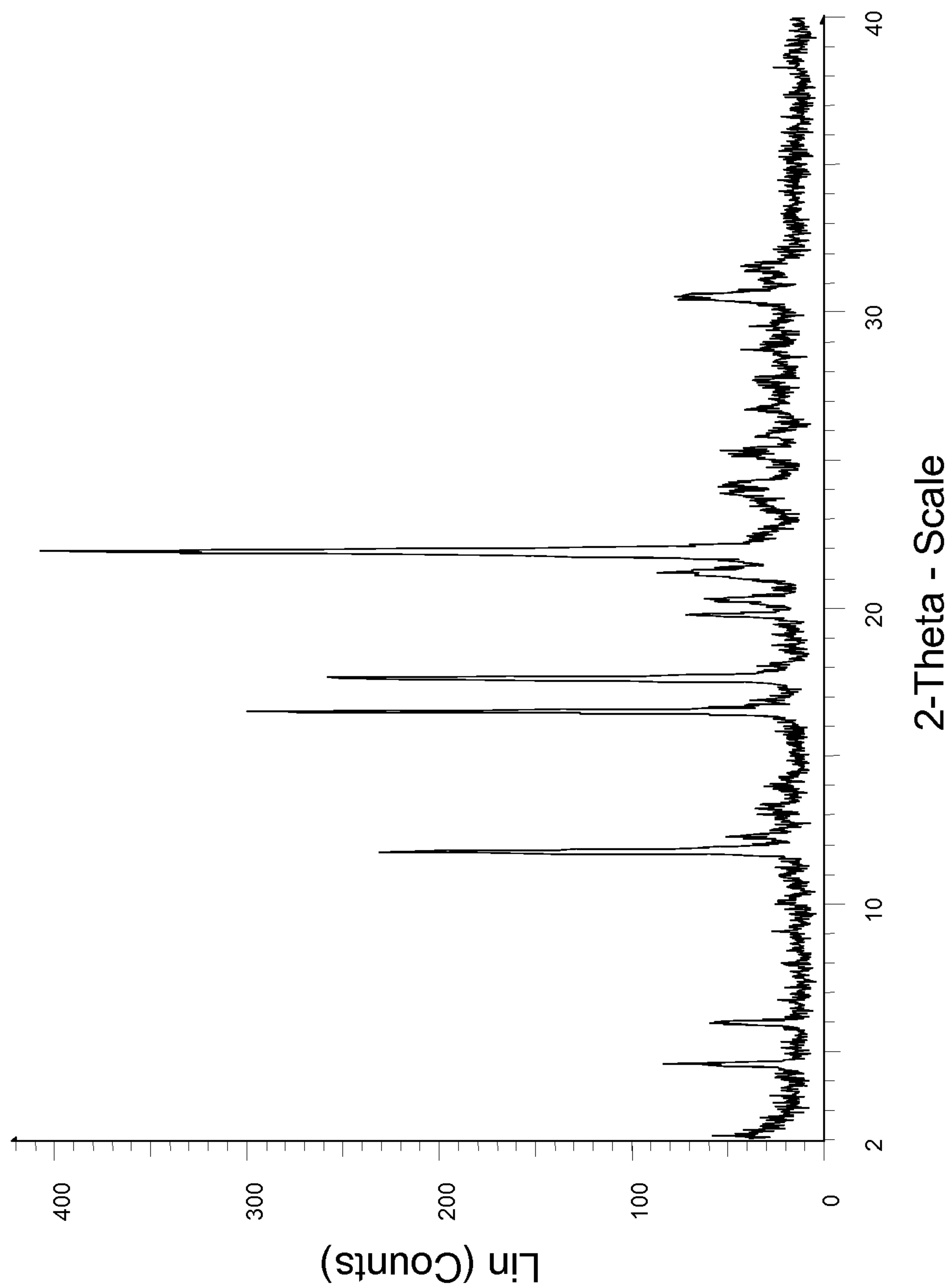


Figure 5