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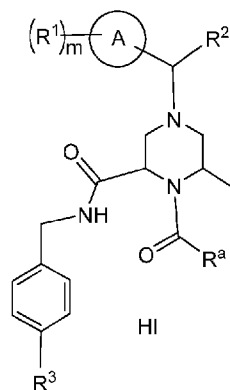
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(54) Title: OREXIN RECEPTOR AGONISTS



(I)

(57) **Abstract:** The present invention is directed to compounds of Formula I which are agonists of orexin receptors. The present invention is also directed to uses of the compounds described herein in the potential treatment or prevention of neurological and psychiatric disorders and diseases in which orexin receptors are involved. The present invention is also directed to compositions comprising these compounds. The present invention is also directed to uses of these compositions in the potential prevention or treatment of such diseases in which orexin receptors are involved.

OREXIN RECEPTOR AGONISTS

BACKGROUND OF THE INVENTION

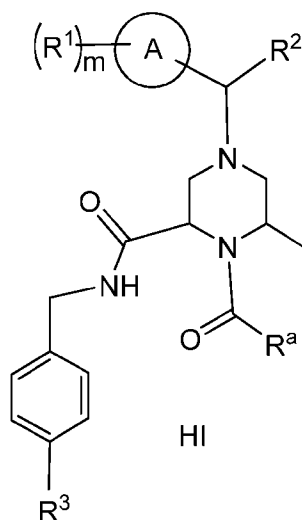
The orexins (hypocretins) comprise two neuropeptides produced in the hypothalamus: orexin A (OX-A) (a 33 amino acid peptide) and the orexin B (OX-B) (a 28 amino acid peptide) (Sakurai T. et al., Cell, 1998, 92, 573-585). Orexins regulate states of sleep and wakefulness opening potentially novel therapeutic approaches for narcolepsy, idiopathic hypersomnia, excessive daytime sleepiness, shift work disorder, obstructive sleep apnea and insomnia (Chemelli R.M. et al., Cell, 1999, 98, 437-451). Orexins are found to stimulate food consumption in rats suggesting a physiological role for these peptides as mediators in the central feedback mechanism that regulates feeding behavior (Sakurai T. et al., Cell, 1998, 92, 573-585). Orexins have also been indicated as playing a role in arousal, emotion, energy homeostasis, reward, learning and memory (Peyron, et al., Journal Neurosci., 1998,18(23):9996-100150, Harris, et al., Trends Neurosci., 2006, 29 (10), 571-577). Two orexin receptors have been cloned and characterized in mammals. They belong to the super family of G-protein coupled receptors (Sakurai T. et al., Cell, 1998, 92, 573-585): the orexin-1 receptor (OX or OX1R) is partially selective for OX-A and the orexin-2 receptor (OX2 or OX2R) is capable of binding OX-A as well as OX-B with similar affinity. The physiological actions in which orexins are presumed to participate are thought to be expressed via one or both of the OX1 receptor and the OX2 receptor as the two subtypes of orexin receptors.

SUMMARY OF THE INVENTION

The present invention is directed to agonists of orexin receptors. The present invention is also directed to uses of the compounds described herein in the potential treatment or prevention of neurological and psychiatric disorders and diseases in which orexin receptors are involved. The present invention is also directed to compositions comprising these compounds. The present invention is also directed to uses of these compositions in the potential prevention or treatment of such diseases in which orexin receptors are involved.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to compounds of the formula I:



wherein:

Ring A is selected from aryl and heteroaryl;

- 5 R is independently selected from H, -C₁₋₆alkyl, O-C₁₋₆alkyl, CF₃, CHF₂, CH₂F, and C₃₋₆ cycloalkyl;

R^a is selected from -C₁₋₆alkyl and -C₃₋₆ cycloalkyl;

- 10 R¹ is independently selected from:

- (1) -(CR₂)_n-heteroaryl, where the heteroaryl is unsubstituted or substituted with one to six substituents independently selected from R⁴,
- (2) -(CR₂)_n-heterocyclyl, where the heterocyclyl is unsubstituted or substituted with one to six substituents independently selected from R⁴,
- 15 (3) -(CR₂)_n- C₃₋₆ cycloalkyl, where the cycloalkyl is unsubstituted or substituted with one to six substituents independently selected from R⁴,
- (4) -C₁₋₆ alkyl, where the alkyl is unsubstituted or substituted with one to six substituents independently selected from R⁴,
- (5) -O(CR₂)_pR⁴,
- 20 (6) -OR,
- (7) halo,

- (8) $-\text{OCR}_2\text{C}(\text{O})\text{NR}_2$,
 (9) $-\text{OCR}_2\text{CF}_3$,
 (10) $-\text{O}(\text{CR}_2)_t\text{OCR}_3$,
 (11) $-(\text{CR}_2)_n\text{CN}$
 5 (12) $-(\text{CR}_2)_n\text{NR}_2$,
 (13) $-\text{O}(\text{CR}_2)_t\text{NR}_2$
 (14) $-\text{C}_2\text{-C}_6$ alkenyl, where the alkenyl is unsubstituted or substituted with one to six
 substituents independently selected from R^4 , and
 (15) $-\text{C}_2\text{-C}_6$ alkynyl, where the alkynyl is unsubstituted or substituted with one to six
 10 substituents independently selected from R^4 ;

R^2 is selected from:

- (1) H,
 (2) $-\text{C}_{1-6}$ alkyl, where the alkyl is unsubstituted or substituted with one to three
 15 substituents selected from R^5 ,
 (3) halo,
 (4) $-(\text{CR}_2)_s\text{OR}$,
 (5) $-(\text{CR}_2)_s\text{CN}$
 (6) $-(\text{CR}_2)_s\text{S}(\text{O})_z\text{R}$,
 20 (7) $-(\text{CR}_2)_s\text{C}(\text{O})\text{OR}$,
 (8) aryl, where the aryl is unsubstituted or substituted with one to three substituents
 selected from R^5 ; and
 (9) $-(\text{CR}_2)_s$ -heterocyclyl, where the heterocyclyl is unsubstituted or substituted with
 one to three substituents selected from R^5 ;

25

R^3 is independently selected from:

- (1) $-\text{C}_{1-6}$ alkyl, where the alkyl is unsubstituted or substituted with one to four
 substituents independently selected from R^7 ,
 (2) $-\text{C}_{3-6}$ cycloalkyl, where the cycloalkyl is unsubstituted or substituted with one to
 30 four substituents independently selected from R^7 ,

- (3) aryl, where the aryl is unsubstituted or substituted with one to four substituents independently selected from R⁷,
- (4) heteroaryl, where the heteroaryl is unsubstituted or substituted with one to four substituents independently selected from R⁷,
- 5 (5) -(CH₂)_x-C₂-C₆ alkenyl, where the alkenyl is unsubstituted or substituted with one to four substituents independently selected from R⁷,
- (6) -(CH₂)_x-C₂-C₆ alkynyl, where the alkynyl is unsubstituted or substituted with one to four substituents independently selected from R⁷, and
- (7) -OCF₂CH₃;

10

R⁴ is independently selected from:

- (1) H,
- (2) -C₁₋₆alkyl, which is unsubstituted or substituted with one to six substituents independently selected from R⁶,
- 15 (3) aryl, which is unsubstituted or substituted with one to six substituents independently selected from R⁶,
- (4) heteroaryl, which is unsubstituted or substituted with one to six substituents independently selected from R⁶,
- (5) heterocyclyl, which is unsubstituted or substituted with one to six substituents independently selected from R⁶,
- 20 (6) halo,
- (7) -OR,
- (8) -CN,
- (9) -S(O)_zR, and
- 25 (10) -C(O)OR;

R⁵ is independently selected from:

- (1) halo,
- (2) -OR,
- 30 (3) -CN,
- (4) -S(O)_zR,
- (5) -C(O)OR,

- (6) -CF₃,
- (7) heterocyclyl, and
- (8) -C₁₋₆alkyl;

5 R⁶ is independently selected from: H, halo, -OR, -NR₂, -CF₃, and -C₁₋₆ alkyl;

R⁷ is independently selected from: halo, -OR, C₃₋₆ cycloalkyl, -CF₃, -CHF₂, -CH₂F, and -C₁₋₆ alkyl;

- 10 m is independently selected from 0, 1, 2, 3 and 4;
n is independently selected from 0, 1 and 2;
p is independently selected from 0, 1 and 2;
s is independently selected from 0, 1, 2 and 3;
t is independently selected from 1, 2, 3 and 4;
- 15 x is independently selected from 0, 1, and 2; and
z is independently selected from 0, 1 and 2;

or a pharmaceutically acceptable salt thereof.

- 20 In another embodiment, the instant invention is directed to compounds of the formula 1, wherein:

Ring A is selected from pyrazinyl, naphthyl, pyrimidinyl, thiazolyl, oxazolyl, pyrazolyl, triazolyl, imidazolyl, quinoliny, pyradazinyl, phenyl and pyridinyl;

25

R^a is -C₁₋₆alkyl;

R¹ is independently selected from:

- (1) H,
- (2) -(CR₂)_n-heteroaryl, where the heteroaryl is unsubstituted or substituted with one to
30 six substituents independently selected from R⁴,
- (3) -(CR₂)_n-heterocyclyl, where the heterocyclyl is unsubstituted or substituted with
one to six substituents independently selected from R⁴,

- (4) -C₁₋₆ alkyl, where the alkyl is unsubstituted or substituted with one to six substituents independently selected from R⁴,
- (5) -O(CR₂)_pR⁴,
- (6) -OR,
- 5 (7) halo,
- (8) -OCR₂C(O)NR₂,
- (9) -OCR₂CF₃,
- (10) -O(CR₂)_tOCR₃,
- (11) -(CR₂)_nCN
- 10 (12) -(CR₂)_nNR₂, and
- (13) -O(CR₂)_tNR₂;

R² is selected from:

- (1) H,
- 15 (2) -C₁₋₆alkyl, where the alkyl is unsubstituted or substituted with one to three substituents selected from R⁵,
- (3) halo,
- (4) -(CR₂)_sOR, and
- (5) -(CR₂)_sC(O)OR;
- 20

R³ is independently selected from:

- (1) -C₁₋₆ alkyl, where the alkyl is unsubstituted or substituted with one to four substituents independently selected from R⁷,
- (2) aryl, where the aryl is unsubstituted or substituted with one to four substituents
- 25 independently selected from R⁷,
- (3) heteroaryl, where the heteroaryl is unsubstituted or substituted with one to four substituents independently selected from R⁷, and
- (4) -OCF₂CH₃;

30 R⁴ is independently selected from:

- (1) -C₁₋₆alkyl, which is unsubstituted or substituted with one to six substituents independently selected from R⁶,
(2) aryl, which is unsubstituted or substituted with one to six substituents independently selected from R⁶,
5 (3) heteroaryl, which is unsubstituted or substituted with one to six substituents independently selected from R⁶,
(4) heterocyclyl, which is unsubstituted or substituted with one to six substituents independently selected from R⁶
(5) halo, and
10 (6) -OR;

R⁵ is independently selected from:

- (1) halo,
(2) -OR,
15 (3) -CN,
(4) -S(O)₂R,
(5) -C(O)OR,
(6) -CF₃,
(7) heterocyclyl, and
20 (8) -C₁₋₆alkyl;

R⁶ is independently selected from: H, halo, -OR, -NR₂, -CF₃, and -C₁₋₆ alkyl;

R⁷ is independently selected from: halo, -OR, C₃₋₆ cycloalkyl, -CF₃, -CHF₂, -CH₂F, and -C₁₋₆
25 alkyl;

m is independently selected from 0, 1, 2 and 3;

n is independently selected from 0, 1 and 2;

p is independently selected from 0, 1 and 2;

30 s is independently selected from 0, 1, 2 and 3;

t is independently selected from 1, 2, 3 and 4;

x is independently selected from 0, 1, and 2; and

z is independently selected from 0, 1 and 2;

or a pharmaceutically acceptable salt thereof.

5

In a further embodiment, the instant invention is directed to compounds of the formula 1, wherein:

Ring A is selected from phenyl and pyridinyl;

10

R^a is -C₁₋₆alkyl;

R¹ is independently selected from:

- (1) -C₁₋₆ alkyl, where the alkyl is unsubstituted or substituted with one to six substituents independently selected from R⁴,
- 15 (2) -O(CR₂)_pR⁴,
- (3) -OR, and
- (4) Halo;

R² is selected from:

- 20 (1) H,
- (2) -C₁₋₆alkyl, where the alkyl is unsubstituted or substituted with one to three substituents selected from R⁵,
- (3) -(CR₂)_sOR, and
- (4) -(CR₂)_sC(O)OR;

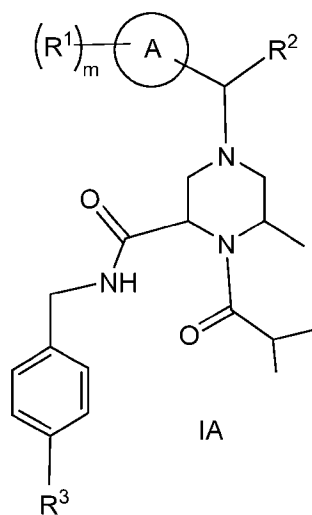
25

R³ is independently selected from:

- (1) Heteroaryl which is selected from pyrimidinyl, pyridinyl, or oxazolyl, where the heteroaryl is unsubstituted or substituted with one to four substituents independently selected from R⁷, and
- 30 (2) -OCF₂CH₃;

or a pharmaceutically acceptable salt thereof.

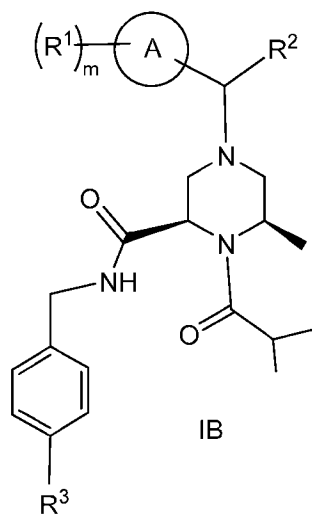
Another embodiment of the instant invention is directed to compounds of the formula IA:



and all substituents are as defined above for Formula I.

5

Another embodiment of the instant invention is directed to compounds of the formula IB:



wherein:

- 10 Ring A is selected from aryl and heteroaryl;

R is independently selected from H, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -CF₃, -CHF₂, -CH₂F, and -C₃₋₆ cycloalkyl;

R¹ is independently selected from:

- 5 (1) -(CR₂)_n-heteroaryl, where the heteroaryl is unsubstituted or substituted with one to six substituents independently selected from R⁴,
- (2) -(CR₂)_n-heterocyclyl, where the heterocyclyl is unsubstituted or substituted with one to six substituents independently selected from R⁴,
- (3) -(CR₂)_n-C₃₋₆ cycloalkyl, where the cycloalkyl is unsubstituted or substituted with
10 one to six substituents independently selected from R⁴,
- (4) -C₁₋₆ alkyl, where the alkyl is unsubstituted or substituted with one to six substituents independently selected from R⁴,
- (5) -O(CR₂)_pR⁴,
- (6) -OR,
- 15 (7) halo,
- (8) -OCR₂C(O)NR₂,
- (9) -OCR₂CF₃,
- (10) -O(CR₂)_tOCR₃,
- (11) -(CR₂)_nCN
- 20 (12) -(CR₂)_nNR₂,
- (13) -O(CR₂)_tNR₂
- (14) C₂₋₆ alkenyl, where the alkenyl is unsubstituted or substituted with one to six substituents independently selected from R⁴, and
- (15) C₂₋₆ alkynyl, where the alkynyl is unsubstituted or substituted with one to six
25 substituents independently selected from R⁴;

R² is selected from:

- (1) H,
- (2) -C₁₋₆alkyl, where the alkyl is unsubstituted or substituted with one to three
30 substituents selected from R⁵,
- (3) halo,

- (4) $-(\text{CR}_2)_s\text{OR}$,
(5) $-(\text{CR}_2)_s\text{CN}$
(6) $-(\text{CR}_2)_s\text{S}(\text{O})_z\text{R}$,
(7) $-(\text{CR}_2)_s\text{C}(\text{O})\text{OR}$,
5 (8) aryl, where the aryl is unsubstituted or substituted with one to three substituents selected from R^5 ; and
(9) $-(\text{CR}_2)_s$ -heterocyclyl, where the heterocyclyl is unsubstituted or substituted with one to three substituents selected from R^5 ;
- 10 R^3 is independently selected from:
- (1) $-\text{C}_{1-6}$ alkyl, where the alkyl is unsubstituted or substituted with one to four substituents independently selected from R^7 ,
(2) $-\text{C}_{3-6}$ cycloalkyl, where the cycloalkyl is unsubstituted or substituted with one to four substituents independently selected from R^7 ,
15 (3) aryl, where the aryl is unsubstituted or substituted with one to four substituents independently selected from R^7 ,
(4) heteroaryl, where the heteroaryl is unsubstituted or substituted with one to four substituents independently selected from R^7 ,
(5) $-(\text{CH}_2)_x-\text{C}_2-\text{C}_6$ alkenyl, where the alkenyl is unsubstituted or substituted with one
20 to four substituents independently selected from R^7 ,
(6) $-(\text{CH}_2)_x-\text{C}_2-\text{C}_6$ alkynyl, where the alkynyl is unsubstituted or substituted with one to four substituents independently selected from R^7 , and
(7) $-\text{OCF}_2\text{CH}_3$;
- 25 R^4 is independently selected from:
- (1) hydrogen,
(2) $-\text{C}_{1-6}$ alkyl, which is unsubstituted or substituted with one to six substituents independently selected from R^6 ,
(3) aryl, which is unsubstituted or substituted with one to six substituents
30 independently selected from R^6 ,

- (4) heteroaryl, which is unsubstituted or substituted with one to six substituents independently selected from R⁶,
- (5) heterocyclyl, which is unsubstituted or substituted with one to six substituents independently selected from R⁶,
- 5 (6) halo,
- (7) -OR,
- (8) -CN,
- (9) -S(O)_zR, and
- (10) -C(O)OR;

10

R⁵ is independently selected from:

- (1) halo,
- (2) -OR,
- (3) -CN,
- 15 (4) -S(O)_zR,
- (5) -C(O)OR,
- (6) -CF₃,
- (7) heterocyclyl, and
- (8) -C₁₋₆alkyl;

20

R⁶ is independently selected from: H, halo, -OR, -NR₂, -CF₃, and -C₁₋₆ alkyl;

R⁷ is independently selected from: halo, -OR, C₃₋₆ cycloalkyl, -CF₃, -CHF₂, -CH₂F, and -C₁₋₆ alkyl;

25

m is independently selected from 0, 1, 2, 3 and 4;

n is independently selected from 0, 1 and 2;

p is independently selected from 0, 1 and 2;

s is independently selected from 0, 1, 2 and 3;

30 t is independently selected from 1, 2, 3 and 4;

x is independently selected from 0, 1, and 2; and

z is independently selected from 0, 1 and 2;

or a pharmaceutically acceptable salt thereof.

It is understood that reference herein to “compounds of Formula I” also encompasses compounds of Formula IA and Formula IB, unless otherwise indicated.

5 Certain embodiments of the present invention include a compound which is selected from the group consisting of the subject compounds of the Examples herein or a pharmaceutically acceptable salt thereof.

Certain embodiments of the present invention include a compound which is selected from:

- 10 cis-4-benzyl-N-(4-(furan-2-yl)benzyl)-1-isobutyryl-6-methylpiperazine-2-carboxamide (1-1);
(2R,6R)-N-{{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)-4-{{[2-(morpholin-4-yl)phenyl]methyl}piperazine-2-carboxamide (1-2);
N-{{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)-4-[(2-phenoxyphenyl)methyl]piperazine-2-carboxamide (1-3);
15 4-[(2,6-difluorophenyl)methyl]-N-{{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (1-4);
N-{{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)-4-{{[2-[(pyridin-3-yl)oxy]phenyl]methyl}piperazine-2-carboxamide (1-5);
4-{{[2-(2-amino-2-oxoethoxy)phenyl]methyl}-N-{{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (1-6);
20 4-{{[2-fluoro-6-(morpholin-4-yl)phenyl]methyl}-N-{{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (1-7);
N-{{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)-4-{{[2-(morpholin-4-yl)phenyl]methyl}piperazine-2-carboxamide (1-8);
25 N-{{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)-4-{{[2-[(1H-pyrazol-1-yl)methyl]phenyl]methyl}piperazine-2-carboxamide (1-9);
4-[(3-fluoropyridin-2-yl)methyl]-N-{{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (1-10);
4-[(2-fluoro-6-methoxyphenyl)methyl]-N-{{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (1-11);
30 N-{{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)-4-{{[2-[(pyrazin-2-yl)oxy]phenyl]methyl}piperazine-2-carboxamide (1-12);

- 4-[(2-fluoro-5-methylphenyl)methyl]-N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (1-13);
N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)-4-({2-[(pyridin-2-yl)oxy]phenyl}methyl)piperazine-2-carboxamide (1-14);
- 5 4-[(2-fluorophenyl)methyl]-N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (1-15);
N-{[4-(furan-2-yl)phenyl]methyl}-4-{[2-(2-methoxyethoxy)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (1-16);
N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)-4-{[2-(2,2,2-trifluoroethoxy)phenyl]methyl}piperazine-2-carboxamide (1-17);
- 10 N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)-4-({2-[(oxolan-2-yl)methoxy]phenyl}methyl)piperazine-2-carboxamide (1-18);
4-[(2-chloro-6-fluorophenyl)methyl]-N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (1-19);
- 15 N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)-4-[(pyrimidin-2-yl)methyl]piperazine-2-carboxamide (1-20);
N-{[4-(furan-2-yl)phenyl]methyl}-4-{[2-(4-hydroxypiperidin-1-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (1-21);
N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)-4-[(4-methyl-1,3-thiazol-2-yl)methyl]piperazine-2-carboxamide (1-22);
- 20 N-{[4-(furan-2-yl)phenyl]methyl}-4-[(2-methoxyphenyl)methyl]-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (1-23);
4-{[2-(difluoromethoxy)phenyl]methyl}-N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (1-24);
- 25 4-[(2-ethoxyphenyl)methyl]-N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (1-25);
N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)-4-{[4-(propan-2-yl)-1,3-thiazol-2-yl]methyl}piperazine-2-carboxamide (1-26);
4-[(2-cyanophenyl)methyl]-N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (1-27);
- 30 4-[(3-cyanophenyl)methyl]-N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (1-28);

- N- {[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)-4- {[2-(pyridin-4-yl)phenyl]methyl} piperazine-2-carboxamide (1-29);
- N- {[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)-4- [(pyridin-2-yl)methyl] piperazine-2-carboxamide (1-30);
- 5 N- {[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)-4- [(pyridin-3-yl)methyl] piperazine-2-carboxamide (1-31);
- 4- [(2,3-difluorophenyl)methyl]-N- {[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl) piperazine-2-carboxamide (1-32);
- 4- [(2-fluoro-3-methoxyphenyl)methyl]-N- {[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl) piperazine-2-carboxamide (1-33);
- 10 4- [(2-fluoro-5-methoxyphenyl)methyl]-N- {[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl) piperazine-2-carboxamide (1-34);
- N- {[4-(furan-2-yl)phenyl]methyl}-6-methyl-4- [(3-methylphenyl)methyl]-1-(2-methylpropanoyl) piperazine-2-carboxamide (1-35);
- 15 N- {[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)-4- {[2-(1H-1,2,4-triazol-1-yl)phenyl]methyl} piperazine-2-carboxamide (1-36);
- N- {[4-(furan-2-yl)phenyl]methyl}-4- [(3-methoxyphenyl)methyl]-6-methyl-1-(2-methylpropanoyl) piperazine-2-carboxamide (1-37);
- 4- [(3-fluorophenyl)methyl]-N- {[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl) piperazine-2-carboxamide (1-38);
- 20 4- [(4-fluorophenyl)methyl]-N- {[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl) piperazine-2-carboxamide (1-39);
- N- {[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)-4- {[2-(trifluoromethoxy)phenyl]methyl} piperazine-2-carboxamide (1-40);
- 25 N- {[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)-4- {[2-(pyridin-3-yl)phenyl]methyl} piperazine-2-carboxamide (1-41);
- 4- [(2-fluoro-6-hydroxyphenyl)methyl]-N- {[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl) piperazine-2-carboxamide (1-42);
- 4- [(3-chloro-2-fluorophenyl)methyl]-N- {[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl) piperazine-2-carboxamide (1-43);
- 30 4- [(2-cyclopropylphenyl)methyl]-N- {[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl) piperazine-2-carboxamide (1-44);

- 4-{[2-(cyanomethyl)phenyl]methyl}-N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (1-45);
- N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)-4-{[2-(pyrimidin-5-yl)phenyl]methyl}piperazine-2-carboxamide (1-46);
- 5 N-{[4-(furan-2-yl)phenyl]methyl}-4-[(2-hydroxyphenyl)methyl]-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (1-47);
- N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)-4-[(5-methyl-1,3-thiazol-2-yl)methyl]piperazine-2-carboxamide (1-48);
- 4-{[3-(dimethylamino)phenyl]methyl}-N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (1-49);
- 10 4-[(3-fluoropyridin-4-yl)methyl]-N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (1-50);
- 4-{[2-fluoro-5-(trifluoromethyl)phenyl]methyl}-N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (1-51);
- 15 N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)-4-{[2-(1H-pyrazol-1-yl)phenyl]methyl}piperazine-2-carboxamide (1-52);
- 4-{[2-(difluoromethyl)phenyl]methyl}-N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (1-53);
- N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)-4-{[2-(piperidin-1-yl)phenyl]methyl}piperazine-2-carboxamide (1-54);
- 20 N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)-4-{[2-(pyrrolidin-1-yl)phenyl]methyl}piperazine-2-carboxamide (1-55);
- N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-4-[(3-methyl-1,2-oxazol-5-yl)methyl]-1-(2-methylpropanoyl)piperazine-2-carboxamide (1-56);
- 25 N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)-4-[(5-methyl-1H-pyrazol-3-yl)methyl]piperazine-2-carboxamide (1-57);
- N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-4-[(2-methylphenyl)methyl]-1-(2-methylpropanoyl)piperazine-2-carboxamide (1-58);
- N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)-4-({2-[(morpholin-4-yl)methyl]phenyl}methyl)piperazine-2-carboxamide (1-59);
- 30 4-({2-[2-(dimethylamino)ethoxy]phenyl}methyl)-N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (1-60);

- N- {[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)-4-[(2-methyl-1,3-thiazol-5-yl)methyl]piperazine-2-carboxamide (1-61);
- N- {[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)-4- {[2-(1H-1,2,3-triazol-1-yl)phenyl]methyl}piperazine-2-carboxamide (1-62);
- 5 N- {[4-(furan-2-yl)phenyl]methyl}-6-methyl-4- {[2-(4-methylpiperazin-1-yl)phenyl]methyl}-1-(2-methylpropanoyl)piperazine-2-carboxamide (1-63);
- 4-[(2-ethylphenyl)methyl]-N- {[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (1-64);
- 4- {[2-fluoro-3-(trifluoromethyl)phenyl]methyl}-N- {[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (1-65);
- 10 N- {[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)-4- {[2-(trifluoromethyl)phenyl]methyl}piperazine-2-carboxamide (1-66);
- N- {[4-(furan-2-yl)phenyl]methyl}-4-[(3-hydroxypyridin-2-yl)methyl]-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (1-67);
- 15 4-[(5-cyano-2-fluorophenyl)methyl]-N- {[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (1-68);
- N- {[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)-4-[(pyridin-4-yl)methyl]piperazine-2-carboxamide (1-69);
- 4- {[2-(dimethylamino)phenyl]methyl}-N- {[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (1-70);
- 20 4-[(1,3-dimethyl-1H-pyrazol-5-yl)methyl]-N- {[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (1-71);
- N- {[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)-4-[(1-methyl-1H-pyrazol-5-yl)methyl]piperazine-2-carboxamide (1-72);
- 25 N- {[4-(furan-2-yl)phenyl]methyl}-6-methyl-4-[(1-methyl-1H-imidazol-5-yl)methyl]-1-(2-methylpropanoyl)piperazine-2-carboxamide (1-73);
- 4-[(4-cyanophenyl)methyl]-N- {[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (1-74);
- 4- {[2-[(dimethylamino)methyl]phenyl]methyl}-N- {[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (1-75);
- 30 N- {[4-(furan-2-yl)phenyl]methyl}-6-methyl-4-[(4-methyl-1H-imidazol-2-yl)methyl]-1-(2-methylpropanoyl)piperazine-2-carboxamide (1-76);

- N- {[4-(furan-2-yl)phenyl]methyl}-6-methyl-4-[(2-methyl-1H-imidazol-4-yl)methyl]-1-(2-methylpropanoyl)piperazine-2-carboxamide (1-77);
- N- {[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)-4-[(4-methyl-4H-1,2,4-triazol-3-yl)methyl]piperazine-2-carboxamide (1-78);
- 5 4- {[4-(dimethylamino)phenyl]methyl}-N- {[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (1-79);
- N- {[4-(furan-2-yl)phenyl]methyl}-4-[(4-methoxyphenyl)methyl]-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (1-80);
- N- {[4-(furan-2-yl)phenyl]methyl}-6-methyl-4-[(4-methylphenyl)methyl]-1-(2-methylpropanoyl)piperazine-2-carboxamide (1-81);
- 10 cis-N-(4-(furan-2-yl)benzyl)-1-isobutyl-6-methyl-4-(quinolin-8-ylmethyl)piperazine-2-carboxamide (2-1);
- 4-[(2,6-difluoro-3-methylphenyl)methyl]-N- {[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (2-2);
- 15 N- {[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)-4-[(2,4,6-trifluorophenyl)methyl]piperazine-2-carboxamide (2-3);
- N- {[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)-4-[(2,3,5,6-tetrafluorophenyl)methyl]piperazine-2-carboxamide (2-4);
- N- {[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)-4-[(1,3-thiazol-2-yl)methyl]piperazine-2-carboxamide (2-5);
- 20 N- {[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)-4-(pent-2-yn-1-yl)piperazine-2-carboxamide (2-6);
- 4-(but-2-yn-1-yl)-N- {[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (2-7);
- 25 4-[(2-bromo-6-fluorophenyl)methyl]-N- {[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (2-8);
- 4-[(2-chlorophenyl)methyl]-N- {[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (2-9);
- N- {[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)-4-[(pyridazin-3-yl)methyl]piperazine-2-carboxamide (2-10);
- 30 N- {[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)-4-[(naphthalen-1-yl)methyl]piperazine-2-carboxamide (2-11);

- cis-4-(2-fluoro-6-phenoxybenzyl)-N-(4-(furan-2-yl)benzyl)-1-isobutyryl-6-methylpiperazine-2-carboxamide (3);
- cis-4-(2-(benzyloxy)-6-fluorobenzyl)-N-(4-(furan-2-yl)benzyl)-1-isobutyryl-6-methylpiperazine-2-carboxamide (4);
- 5 cis-4-(2-ethoxy-6-fluorobenzyl)-N-(4-(furan-2-yl)benzyl)-1-isobutyryl-6-methylpiperazine-2-carboxamide (5);
- cis-4-(2-fluoro-6-hydroxybenzyl)-N-(4-(furan-2-yl)benzyl)-1-isobutyryl-6-methylpiperazine-2-carboxamide (6);
- cis-N-(4-(furan-2-yl)benzyl)-1-isobutyryl-6-methyl-4-(2-(pyridin-4-yloxy)benzyl)piperazine-2-carboxamide (7);
- 10 cis-N-(4-(furan-2-yl)benzyl)-1-isobutyryl-6-methyl-4-(2-(pyridin-4-yloxy)benzyl)piperazine-2-carboxamide (8);
- cis-N-(4-(furan-2-yl)benzyl)-1-isobutyryl-6-methyl-4-(2-(oxazol-2-ylmethyl)benzyl)piperazine-2-carboxamide (9);
- 15 cis-4-(2-((4H-1,2,4-triazol-4-yl)methyl)benzyl)-N-(4-(furan-2-yl)benzyl)-1-isobutyryl-6-methylpiperazine-2-carboxamide (10);
- cis-N-(4-(furan-2-yl)benzyl)-1-isobutyryl-6-methyl-4-(2-(tetrahydro-2H-pyran-4-yl)benzyl)piperazine-2-carboxamide (11);
- (2R,6R)-4-(2,6-difluorobenzyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (12);
- 20 (2R,6R)-4-(2-fluoro-6-(2-methoxyphenoxy)benzyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (13-1)
- (2R,6R)-4-({2-[(2-ethyl-5-methylpyridin-3-yl)oxy]-6-fluorophenyl}methyl)-6-methyl-1-(2-methylpropanoyl)-N-{{4-(pyrimidin-2-yl)phenyl}methyl}piperazine-2-carboxamide (13-2);
- 25 (2R,6R)-4-({2-[2-(dimethylamino)phenoxy]-6-fluorophenyl}methyl)-6-methyl-1-(2-methylpropanoyl)-N-{{4-(pyrimidin-2-yl)phenyl}methyl}piperazine-2-carboxamide (13-3);
- (2R,6R)-4-{{2-(2-ethylphenoxy)-6-fluorophenyl}methyl}-6-methyl-1-(2-methylpropanoyl)-N-{{4-(pyrimidin-2-yl)phenyl}methyl}piperazine-2-carboxamide (13-4);
- (2R,6R)-4-({2-[(2-ethylpyridin-3-yl)oxy]-6-fluorophenyl}methyl)-6-methyl-1-(2-methylpropanoyl)-N-{{4-(pyrimidin-2-yl)phenyl}methyl}piperazine-2-carboxamide (13-5);
- 30 (2R,6R)-4-({2-fluoro-6-[2-(trifluoromethyl)phenoxy]phenyl}methyl)-6-methyl-1-(2-methylpropanoyl)-N-{{4-(pyrimidin-2-yl)phenyl}methyl}piperazine-2-carboxamide (13-6);

- (2R,6R)-4-({2-fluoro-6-[(imidazo[1,2-a]pyridin-8-yl)oxy]phenyl}methyl)-6-methyl-1-(2-methylpropanoyl)-N-{{4-(pyrimidin-2-yl)phenyl}methyl}piperazine-2-carboxamide (13-7);
- (2R,6R)-4-({2-[(2,6-dimethylpyridin-3-yl)oxy]-6-fluorophenyl}methyl)-6-methyl-1-(2-methylpropanoyl)-N-{{4-(pyrimidin-2-yl)phenyl}methyl}piperazine-2-carboxamide (13-8);
- 5 (2R,6R)-4-{{2-[(2,6-dimethylphenoxy)-6-fluorophenyl]methyl}-6-methyl-1-(2-methylpropanoyl)-N-{{4-(pyrimidin-2-yl)phenyl}methyl}piperazine-2-carboxamide (13-9);
- (2R,6R)-4-({2-fluoro-6-[(2-methylpyridin-3-yl)oxy]phenyl}methyl)-6-methyl-1-(2-methylpropanoyl)-N-{{4-(pyrimidin-2-yl)phenyl}methyl}piperazine-2-carboxamide (13-10);
- (2R,6R)-4-({2-fluoro-6-[(3-methoxy-2-methylpyridin-4-yl)oxy]phenyl}methyl)-6-methyl-1-(2-methylpropanoyl)-N-{{4-(pyrimidin-2-yl)phenyl}methyl}piperazine-2-carboxamide (13-11);
- 10 (2R,6R)-4-{{2-fluoro-6-(2-methylphenoxy)phenyl}methyl}-6-methyl-1-(2-methylpropanoyl)-N-{{4-(pyrimidin-2-yl)phenyl}methyl}piperazine-2-carboxamide (13-12);
- (2R,6R)-4-({2-fluoro-6-[2-(trifluoromethoxy)phenoxy]phenyl}methyl)-6-methyl-1-(2-methylpropanoyl)-N-{{4-(pyrimidin-2-yl)phenyl}methyl}piperazine-2-carboxamide (13-13);
- 15 (2R,6R)-4-{{2-[(2-chlorophenoxy)-6-fluorophenyl]methyl}-6-methyl-1-(2-methylpropanoyl)-N-{{4-(pyrimidin-2-yl)phenyl}methyl}piperazine-2-carboxamide (13-14);
- (2R,6R)-4-({2-[(6-ethylpyridin-3-yl)oxy]-6-fluorophenyl}methyl)-6-methyl-1-(2-methylpropanoyl)-N-{{4-(pyrimidin-2-yl)phenyl}methyl}piperazine-2-carboxamide (13-15);
- (2R,6R)-4-({2-[(2-chloro-6-methylpyridin-3-yl)oxy]-6-fluorophenyl}methyl)-6-methyl-1-(2-methylpropanoyl)-N-{{4-(pyrimidin-2-yl)phenyl}methyl}piperazine-2-carboxamide (13-16);
- 20 (2R,6R)-4-({2-fluoro-6-[(4-methylpyridin-3-yl)oxy]phenyl}methyl)-6-methyl-1-(2-methylpropanoyl)-N-{{4-(pyrimidin-2-yl)phenyl}methyl}piperazine-2-carboxamide (13-17);
- (2R,6R)-4-{{2-fluoro-6-(2-methoxy-6-methylphenoxy)phenyl}methyl}-6-methyl-1-(2-methylpropanoyl)-N-{{4-(pyrimidin-2-yl)phenyl}methyl}piperazine-2-carboxamide (13-18);
- 25 (2R,6R)-4-({2-[(6-chloropyridin-3-yl)oxy]-6-fluorophenyl}methyl)-6-methyl-1-(2-methylpropanoyl)-N-{{4-(pyrimidin-2-yl)phenyl}methyl}piperazine-2-carboxamide (13-19);
- (2R,6R)-4-[(2-fluoro-6-phenoxyphenyl)methyl]-6-methyl-1-(2-methylpropanoyl)-N-{{4-(pyrimidin-2-yl)phenyl}methyl}piperazine-2-carboxamide (13-20);
- (2R,6R)-4-({2-[(2,6-dichloropyridin-3-yl)oxy]-6-fluorophenyl}methyl)-6-methyl-1-(2-methylpropanoyl)-N-{{4-(pyrimidin-2-yl)phenyl}methyl}piperazine-2-carboxamide (13-21);
- 30 (2R,6R)-4-({2-fluoro-6-[(4-methoxypyridin-3-yl)oxy]phenyl}methyl)-6-methyl-1-(2-methylpropanoyl)-N-{{4-(pyrimidin-2-yl)phenyl}methyl}piperazine-2-carboxamide (13-22);

- (2R,6R)-4-({2-[(2-chloropyrimidin-5-yl)oxy]-6-fluorophenyl}methyl)-6-methyl-1-(2-methylpropanoyl)-N-{{4-(pyrimidin-2-yl)phenyl}methyl}piperazine-2-carboxamide (13-23);
- (2R,6R)-4-({2-fluoro-6-[(6-methylpyridin-3-yl)oxy]phenyl}methyl)-6-methyl-1-(2-methylpropanoyl)-N-{{4-(pyrimidin-2-yl)phenyl}methyl}piperazine-2-carboxamide (13-24);
- 5 (2R,6R)-4-({2-fluoro-6-[(6-fluoropyridin-3-yl)oxy]phenyl}methyl)-6-methyl-1-(2-methylpropanoyl)-N-{{4-(pyrimidin-2-yl)phenyl}methyl}piperazine-2-carboxamide (13-25);
- (2R,6R)-4-({2-fluoro-6-[(2-fluoropyridin-3-yl)oxy]phenyl}methyl)-6-methyl-1-(2-methylpropanoyl)-N-{{4-(pyrimidin-2-yl)phenyl}methyl}piperazine-2-carboxamide (13-26);
- (2R,6R)-4-({2-fluoro-6-[(2-fluoro-6-methylpyridin-3-yl)oxy]phenyl}methyl)-6-methyl-1-(2-methylpropanoyl)-N-{{4-(pyrimidin-2-yl)phenyl}methyl}piperazine-2-carboxamide (13-27);
- 10 (2R,6R)-4-({2-fluoro-6-[(4-methylpyridin-2-yl)oxy]phenyl}methyl)-6-methyl-1-(2-methylpropanoyl)-N-{{4-(pyrimidin-2-yl)phenyl}methyl}piperazine-2-carboxamide (13-28);
- (2R,6R)-4-({2-fluoro-6-[(5-methoxypyridin-2-yl)oxy]phenyl}methyl)-6-methyl-1-(2-methylpropanoyl)-N-{{4-(pyrimidin-2-yl)phenyl}methyl}piperazine-2-carboxamide (13-29);
- 15 (2R,6R)-4-({2-fluoro-6-[(2-methoxypyridin-4-yl)oxy]phenyl}methyl)-6-methyl-1-(2-methylpropanoyl)-N-{{4-(pyrimidin-2-yl)phenyl}methyl}piperazine-2-carboxamide (13-30);
- (2R,6R)-4-({2-fluoro-6-[(pyridin-3-yl)oxy]phenyl}methyl)-6-methyl-1-(2-methylpropanoyl)-N-{{4-(pyrimidin-2-yl)phenyl}methyl}piperazine-2-carboxamide (13-31);
- (2R,6R)-4-({2-fluoro-6-[(6-methylpyridin-2-yl)oxy]phenyl}methyl)-6-methyl-1-(2-methylpropanoyl)-N-{{4-(pyrimidin-2-yl)phenyl}methyl}piperazine-2-carboxamide (13-32);
- 20 (2R,6R)-4-({2-fluoro-6-[(5-methylpyridin-2-yl)oxy]phenyl}methyl)-6-methyl-1-(2-methylpropanoyl)-N-{{4-(pyrimidin-2-yl)phenyl}methyl}piperazine-2-carboxamide (13-33);
- (2R,6R)-4-({2-fluoro-6-[(5-methylpyridin-3-yl)oxy]phenyl}methyl)-6-methyl-1-(2-methylpropanoyl)-N-{{4-(pyrimidin-2-yl)phenyl}methyl}piperazine-2-carboxamide (13-34);
- 25 (2R,6R)-4-({2-fluoro-6-[(2-methoxypyrimidin-5-yl)oxy]phenyl}methyl)-6-methyl-1-(2-methylpropanoyl)-N-{{4-(pyrimidin-2-yl)phenyl}methyl}piperazine-2-carboxamide (13-35);
- (2R,6R)-4-({2-fluoro-6-[(pyridin-2-yl)oxy]phenyl}methyl)-6-methyl-1-(2-methylpropanoyl)-N-{{4-(pyrimidin-2-yl)phenyl}methyl}piperazine-2-carboxamide (13-36);
- (2R,6R)-4-(2-fluoro-6-(2-methoxyphenoxy)benzyl)-1-isobutyl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (14);
- 30 (2R,6R)-1-isobutyl-6-methyl-4-(2-phenoxybenzyl)-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (15);

- (2R,6R)-4-(1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (16-1);
- (2R,6R)-4-[(1R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl]-6-methyl-1-(2-methylpropanoyl)-N-{{[4-(1,3-thiazol-2-yl)phenyl]methyl} piperazine-2-carboxamide (16-2);
- 5 (2R,6R)-N-{{[4-(1,1-difluoroethoxy)phenyl]methyl}-4-[(1R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl]-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (16-3);
- (2R,6R)-4-[(1R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl]-6-methyl-1-(2-methylpropanoyl)-N-{{[4-(1,3-oxazol-2-yl)phenyl]methyl} piperazine-2-carboxamide (16-4);
- (2R,6R)-4-[(1R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl]-6-methyl-1-(2-methylpropanoyl)-N-{{[4-(2H-1,2,3-triazol-2-yl)phenyl]methyl} piperazine-2-carboxamide (16-5);
- 10 (2R,6R)-4-[(1R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl]-6-methyl-1-(2-methylpropanoyl)-N-[[4-propylphenyl]methyl]piperazine-2-carboxamide (16-6);
- (2R,6R)-N-[[4-cyclopropylphenyl]methyl]-4-[(1R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl]-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (16-7);
- 15 (2R,6R)-N-[[4-tert-butylphenyl]methyl]-4-[(1R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl]-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (16-8);
- (2R,6R)-4-[(1R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl]-6-methyl-1-(2-methylpropanoyl)-N-{{[4-(propan-2-yl)phenyl]methyl} piperazine-2-carboxamide (16-9);
- (2R,6R)-N-[[4-ethylphenyl]methyl]-4-[(1R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl]-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (16-10);
- 20 (2R,6R)-4-[(1R)-1-(3-fluoro-6-methylpyridin-2-yl)-3-methoxypropyl]-6-methyl-1-(2-methylpropanoyl)-N-{{[4-(pyrimidin-2-yl)phenyl]methyl} piperazine-2-carboxamide (16-11);
- (2R,6R)-4-[(1R)-1-(3-fluoropyridin-2-yl)-3-methoxypropyl]-6-methyl-1-(2-methylpropanoyl)-N-{{[4-(pyrimidin-2-yl)phenyl]methyl} piperazine-2-carboxamide (16-12);
- 25 (2R,6R)-4-[(1R)-1-(3,5-difluoropyridin-2-yl)-3-methoxypropyl]-6-methyl-1-(2-methylpropanoyl)-N-{{[4-(pyrimidin-2-yl)phenyl]methyl} piperazine-2-carboxamide (16-13);
- (2R,6R)-N-(4-(5-chloro-6-methoxypyridin-2-yl)benzyl)-4-((R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl)-1-isobutyryl-6-methylpiperazine-2-carboxamide (17);
- (2R,6R)-N-(4-(5-cyclopropyl-6-methoxypyridin-2-yl)benzyl)-4-((R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl)-1-isobutyryl-6-methylpiperazine-2-carboxamide (18);
- 30 (2R,6R)-4-((R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl)-1-isobutyryl-N-(4-(6-methoxy-5-methylpyridin-2-yl)benzyl)-6-methylpiperazine-2-carboxamide (19);

- (2R,6R)-4-((R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl)-N-(4-(5-fluoro-6-methoxypyridin-2-yl)benzyl)-1-isobutyl-6-methylpiperazine-2-carboxamide (20-1);
(2R,6R)-N-{{4-(4,6-dimethoxypyridin-2-yl)phenyl}methyl}-4-[(1R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl]-6-methyl-1-(2-methylpropanoyl) piperazine-2-carboxamide (20-2);
5 (2R,6R)-4-[(1R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl]-N-{{4-(6-methoxy-4-methylpyridin-2-yl) phenyl}methyl}-6-methyl-1-(2-methylpropanoyl) piperazine-2-carboxamide (20-3);
(2R,6R)-4-[(1R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl]-N-{{4-(4-methoxypyrimidin-2-yl)phenyl}methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (20-4);
10 (2R,6R)-4-[(1R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl]-N-({4-[6-methoxy-4-(trifluoromethyl)pyridin-2-yl]phenyl}methyl)-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (20-5);
15 (2R,6R)-N-{{4-(6-ethoxypyridin-2-yl)phenyl}methyl}-4-[(1R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl]-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (20-6);
(2R,6R)-N-{{4-(3,6-dimethoxypyridin-2-yl)phenyl}methyl}-4-[(1R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl]-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (20-7);
20 (2R,6R)-N-({4-[6-(difluoromethyl)pyridin-2-yl]phenyl}methyl)-4-[(1R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl]-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (20-8);
(2R,6R)-N-[(2'-fluoro-3'-methoxy[1,1'-biphenyl]-4-yl)methyl]-4-[(1R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl]-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (20-9);
25 (2R,6R)-4-[(1R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl]-N-{{4-(5-fluoropyrimidin-2-yl)phenyl}methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (20-10);
(2R,6R)-4-[(1R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl]-6-methyl-1-(2-methylpropanoyl)-N-{{4-(thieno[2,3-b]pyridin-6-yl)phenyl}methyl} piperazine-2-carboxamide
30 (20-11);
(2R,6R)-N-({4-[6-(difluoromethoxy)pyridin-2-yl]phenyl}methyl)-4-[(1R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl]-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (20-12);

- (2R,6R)-4-[(1R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl]-N-{[4-(6-methoxypyrazin-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (20-13);
- (2R,6R)-4-[(1R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl]-6-methyl-1-(2-methylpropanoyl)-N-{[4-(1-methyl-1H-pyrrolo[2,3-b]pyridin-6-yl)phenyl]methyl}piperazine-2-carboxamide (20-14);
- (2R,6R)-4-[(1R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl]-6-methyl-1-(2-methylpropanoyl)-N-({4-[6-(trifluoromethoxy)pyridin-2-yl]phenyl}methyl)piperazine-2-carboxamide (20-15);
- (2R,6R)-4-[(1R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl]-6-methyl-N-{[4-(1-methyl-6-oxo-1,6-dihydropyridin-2-yl)phenyl]methyl}-1-(2-methylpropanoyl)piperazine-2-carboxamide (20-16);
- (2R,6R)-N-{[4-(3-fluoro-6-methoxypyridin-2-yl)phenyl]methyl}-4-[(1R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl]-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (20-17);
- (2R,6R)-4-((R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl)-1-isobutyl-6-methyl-N-(4-(pyridin-2-yl)benzyl)piperazine-2-carboxamide (21);
- (2R,6R)-N-(4-(4-cyclopropyl-6-methoxypyridin-2-yl)benzyl)-4-((R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl)-1-isobutyl-6-methylpiperazine-2-carboxamide (22);
- (2R,6R)-4-((R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl)-N-((2'-fluoro-5'-methoxy-[1,1'-biphenyl]-4-yl)methyl)-1-isobutyl-6-methylpiperazine-2-carboxamide (23);
- (2R,6R)-N-(4-(6-cyclopropoxy-pyridin-2-yl)benzyl)-4-((R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl)-1-isobutyl-6-methylpiperazine-2-carboxamide (24);
- (2R,6R)-4-((R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl)-1-isobutyl-N-(4-(6-methoxypyridin-2-yl)benzyl)-6-methylpiperazine-2-carboxamide (25);
- (2R,6R)-4-((R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl)-1-isobutyl-N-(4-(3-methoxypyridin-2-yl)benzyl)-6-methylpiperazine-2-carboxamide (26);
- 1-(cyclopropanecarbonyl)-4-(2,6-difluorobenzyl)-N-(4-(furan-2-yl)benzyl)-6-methylpiperazine-2-carboxamide (27);
- (2R,6R)-4-((R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl)-1-isobutyl-6-methyl-N-(4-(prop-1-yn-1-yl)benzyl)piperazine-2-carboxamide (28);
- (2R,6R)-N-(4-(cyclopropylethynyl)benzyl)-4-((R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl)-1-isobutyl-6-methylpiperazine-2-carboxamide (29);

- (2R,6R)-4-((R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl)-1-isobutyryl-6-methyl-N-(4-(3,3,3-trifluoroprop-1-yn-1-yl)benzyl)piperazine-2-carboxamide (30);
- (2R,6R)-N-(4-(but-2-yn-1-yl)benzyl)-4-((R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl)-1-isobutyryl-6-methylpiperazine-2-carboxamide (31);
- 5 (2R,6R)-4-((R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl)-1-isobutyryl-6-methyl-N-(4-(4-methyl-2H-1,2,3-triazol-2-yl)benzyl)piperazine-2-carboxamide (32);
- (2R,6R)-N-(4-(4,5-dimethyl-2H-1,2,3-triazol-2-yl)benzyl)-4-((R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl)-1-isobutyryl-6-methylpiperazine-2-carboxamide (33);
- (2R,6R)-4-((R)-1-(3,5-difluoro-4-methylpyridin-2-yl)-3-methoxypropyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (34);
- 10 (2R,6R)-4-((R)-1-(3-fluoro-4,6-dimethylpyridin-2-yl)-3-methoxypropyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (35-1);
- (2R,6R)-4-[(1R)-3-methoxy-1-(2,4,6-trifluorophenyl)propyl]-6-methyl-1-(2-methylpropanoyl)-N-{{4-(pyrimidin-2-yl)phenyl}methyl}piperazine-2-carboxamide (35-2);
- 15 (2R,6R)-4-{{(1R)-1-[3-fluoro-6-(trifluoromethyl)pyridin-2-yl]-3-methoxypropyl}-6-methyl-1-(2-methylpropanoyl)-N-{{4-(pyrimidin-2-yl)phenyl}methyl}piperazine-2-carboxamide (35-3);
- (2R,6R)-4-[(1R)-1-(5-fluoropyrimidin-2-yl)-3-methoxypropyl]-6-methyl-1-(2-methylpropanoyl)-N-{{4-(pyrimidin-2-yl)phenyl}methyl}piperazine-2-carboxamid (35-4);
- (2R,6R)-4-[(1R)-3-methoxy-1-(pyrimidin-2-yl)propyl]-6-methyl-1-(2-methylpropanoyl)-N-{{4-(pyrimidin-2-yl)phenyl}methyl}piperazine-2-carboxamide (35-5);
- 20 (2R,6R)-1-isobutyryl-4-((R)-3-methoxy-1-(2,4,6-trifluorophenyl)propyl)-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (36);
- (2R,6R)-4-((R)-1-(3,5-difluoropyridin-4-yl)-3-methoxypropyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (37);
- 25 (2R,6R)-4-((R)-1-(4-ethyl-3-fluoropyridin-2-yl)-3-methoxypropyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (38);
- (2R,6R)-4-((R)-1-(6-chloro-3-fluoropyridin-2-yl)-3-methoxypropyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (39);
- (2R,6R)-4-((R)-1-(3-fluoro-5-methylpyridin-2-yl)-3-methoxypropyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (40);
- 30 (2R,6R)-4-((R)-1-(3-fluoro-6-(prop-1-yn-1-yl)pyridin-2-yl)-3-methoxypropyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (41);

- (2R,6R)-4-((R)-1-(6-cyclopropyl-3-fluoropyridin-2-yl)-3-methoxypropyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (42);
- (2R,6R)-4-((R)-1-(6-ethyl-3-fluoropyridin-2-yl)-3-methoxypropyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (43);
- 5 (2R,6R)-4-((R)-1-(3-fluoro-4,5-dimethylpyridin-2-yl)-3-methoxypropyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (44);
- (2R,6R)-4-((R)-1-(4-cyclopropyl-3-fluoropyridin-2-yl)-3-methoxypropyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (45);
- (2R,6R)-4-((R)-1-(3-fluoro-4-(prop-1-yn-1-yl)pyridin-2-yl)-3-methoxypropyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (46);
- 10 (2R,6R)-4-((R)-1-(5-fluoro-2-(prop-1-yn-1-yl)pyridin-4-yl)-3-methoxypropyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (47);
- (2R,6R)-4-((R)-1-(3,5-difluoro-2-methylpyridin-4-yl)-3-methoxypropyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (48);
- 15 (2R,6R)-1-isobutyryl-4-((R)-3-methoxy-1-(pyrazin-2-yl)propyl)-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (49);
- (2R,6R)-4-((R)-1-(5-fluoro-2-methylpyrimidin-4-yl)-3-methoxypropyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (50);
- (2R,6R)-1-isobutyryl-4-(3-methoxy-1-phenylpropyl)-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (51);
- 20 (2R,6R)-4-(3-ethoxy-1-phenylpropyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (52);
- (2R,6R)-1-isobutyryl-4-((S)-(1-(methoxymethyl)cyclobutyl)(phenyl)methyl)-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (53);
- 25 (2R,6R)-1-isobutyryl-4-((1R)-3-methoxy-2-methyl-1-phenylpropyl)-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (54);
- (2R,6R)-4-((R)-1-(2,6-difluorophenyl)-3-methoxypropyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (55);
- (2R,6R)-4-((R)-1-(2,6-difluorophenyl)-3-(methylthio)propyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (56);
- 30 (2R,6R)-4-((1R)-1-(2,6-difluorophenyl)-3-(methylsulfinyl)propyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (57);

- (2R,6R)-4-((R)-1-(2,6-difluorophenyl)-3-(methylsulfonyl)propyl)-1-isobutyl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (58);
- (2R,6R)-4-((R)-(2,6-difluorophenyl)(tetrahydro-2H-pyran-4-yl)methyl)-1-isobutyl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (59);
- 5 (2R,6R)-4-((1S)-(2,6-difluorophenyl)(1,4-dioxan-2-yl)methyl)-1-isobutyl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (60);
- (2R,6R)-4-((R)-3-cyano-1-(2,6-difluorophenyl)propyl)-1-isobutyl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (61);
- methyl 3-(2,6-difluorophenyl)-3-((3R,5R)-4-isobutyl-3-methyl-5-((4-(pyrimidin-2-yl)benzyl)carbamoyl)piperazin-1-yl)propanoate (62);
- 10 (2R,6R)-4-(2-fluoro-6-((1,1,1-trifluoropropan-2-yl)oxy)benzyl)-1-isobutyl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (63);
- (2R,6R)-4-(2-(1-cyclopropyl-2,2,2-trifluoroethoxy)-6-fluorobenzyl)-1-isobutyl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (64);
- 15 (2R,6R)-4-(2-fluoro-6-((1,1,1-trifluoro-3,3-dimethylbutan-2-yl)oxy)benzyl)-1-isobutyl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (65);
- (2R,6R)-4-(2-fluoro-6-((1,1,1-trifluorobutan-2-yl)oxy)benzyl)-1-isobutyl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (66);
- (2R,6R)-4-(2-fluoro-6-((1,1,1-trifluoro-3-methylbutan-2-yl)oxy)benzyl)-1-isobutyl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (67);
- 20 (2R,6R)-1-isobutyl-6-methyl-4-(1-phenylpropyl)-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (68);
- (2R,6R)-4-((R)-3-hydroxy-1-phenylpropyl)-1-isobutyl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (69);
- 25 (2R,6R)-1-isobutyl-6-methyl-4-((1R)-1-phenyl-2-(tetrahydrofuran-2-yl)ethyl)-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (70);
- (2R,6R)-4-((R)-3-(difluoromethoxy)-1-phenylpropyl)-1-isobutyl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (71);
- (2R,6R)-1-isobutyl-6-methyl-4-((R)-1-phenyl-3-(trifluoromethoxy)propyl)-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (72);
- 30 (2R,6R)-1-isobutyl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)-4-((R)-4,4,4-trifluoro-1-phenylbutyl)piperazine-2-carboxamide (73);

- (2R,6R)-4-((1R)-1-(2,6-difluorophenyl)-2-(tetrahydrofuran-2-yl)ethyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (74);
- (2R,6R)-4-((R)-1-(2,6-difluorophenyl)-3-hydroxypropyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (75);
- 5 (2R,6R)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)-4-((1R)-4,4,4-trifluoro-3-hydroxy-3-methyl-1-phenylbutyl)piperazine-2-carboxamide (76);
- (2R,6R)-4-((1R)-1-(2,6-difluorophenyl)-3-hydroxybutyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (77);
- (2R,6R)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)-4-((1R)-4,4,4-trifluoro-3-hydroxy-1-phenylbutyl)piperazine-2-carboxamide (78);
- 10 (2R,6R)-4-((R)-1-(2,6-difluorophenyl)-3-hydroxy-3-methylbutyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (79);
- (2R,6R)-4-((S)-1-(2,6-difluorophenyl)-2-hydroxyethyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (80);
- 15 (2R,6R)-4-(2-((2-ethylpyridin-3-yl)oxy)-6-fluorobenzyl)-1-isobutyryl-6-methyl-N-(4-(oxazol-2-yl)benzyl)piperazine-2-carboxamide (81);
- 1-acetyl-4-(2-(2-ethylphenoxy)-6-fluorobenzyl)-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (82);
- (2R,6R)-4-(2-((2-ethylpyridin-3-yl)oxy)-6-fluorobenzyl)-1-isobutyryl-6-methyl-N-(4-(pyridin-2-yl)benzyl)piperazine-2-carboxamide (83);
- 20 (2R,6R)-N-(4-(1,1-difluoroethoxy)benzyl)-4-(2-((2-ethylpyridin-3-yl)oxy)-6-fluorobenzyl)-1-isobutyryl-6-methylpiperazine-2-carboxamide (84);
- (2R,6R)-N-(4-(2H-1,2,3-triazol-2-yl)benzyl)-4-(2-((2-ethylpyridin-3-yl)oxy)-6-fluorobenzyl)-1-isobutyryl-6-methylpiperazine-2-carboxamide (85); and
- 25 (2R,6R)-4-(2-((2-ethylpyridin-3-yl)oxy)-6-fluorobenzyl)-1-isobutyryl-N-(4-(6-methoxypyridin-2-yl)benzyl)-6-methylpiperazine-2-carboxamide (86);
- or a pharmaceutically acceptable salt thereof.

Further embodiments of the present invention include a compound which is selected from

- 30 2R,6R)-4-(2-fluoro-6-(2-methoxyphenoxy)benzyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (13-1);
- (2R,6R)-4-({2-[(2-ethyl-5-methylpyridin-3-yl)oxy]-6-fluorophenyl}methyl)-6-methyl-1-(2-methylpropanoyl)-N-{[4-(pyrimidin-2-yl)phenyl]methyl}piperazine-2-carboxamide (13-2);

- (2R,6R)-4-({2-[2-(dimethylamino)phenoxy]-6-fluorophenyl}methyl)-6-methyl-1-(2-methylpropanoyl)-N-{{4-(pyrimidin-2-yl)phenyl}methyl}piperazine-2-carboxamide (13-3);
- (2R,6R)-4-{{2-(2-ethylphenoxy)-6-fluorophenyl}methyl}-6-methyl-1-(2-methylpropanoyl)-N-{{4-(pyrimidin-2-yl)phenyl}methyl}piperazine-2-carboxamide (13-4);
- 5 (2R,6R)-N-{{4-(1,1-difluoroethoxy)phenyl}methyl}-4-[(1R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl]-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (16-3);
- (2R,6R)-4-[(1R)-1-(3-fluoro-6-methylpyridin-2-yl)-3-methoxypropyl]-6-methyl-1-(2-methylpropanoyl)-N-{{4-(pyrimidin-2-yl)phenyl}methyl}piperazine-2-carboxamide (16-11);
- (2R,6R)-4-((R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl)-1-isobutyl-N-(4-(6-methoxy-5-methylpyridin-2-yl)benzyl)-6-methylpiperazine-2-carboxamide (19);
- 10 (2R,6R)-N-{{4-(4,6-dimethoxypyridin-2-yl)phenyl}methyl}-4-[(1R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl]-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (20-2);
- (2R,6R)-4-((R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl)-1-isobutyl-N-(4-(6-methoxypyridin-2-yl)benzyl)-6-methylpiperazine-2-carboxamide (25);
- 15 (2R,6R)-4-(2-((2-ethylpyridin-3-yl)oxy)-6-fluorobenzyl)-1-isobutyl-6-methyl-N-(4-(oxazol-2-yl)benzyl)piperazine-2-carboxamide (81);

or a pharmaceutically acceptable salt thereof.

20

Further embodiments of the present invention include a compound which is selected from

- (2R,6R)-N-{{4-(1,1-difluoroethoxy)phenyl}methyl}-4-[(1R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl]-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (16-3);
- 25 (2R,6R)-4-[(1R)-1-(3-fluoro-6-methylpyridin-2-yl)-3-methoxypropyl]-6-methyl-1-(2-methylpropanoyl)-N-{{4-(pyrimidin-2-yl)phenyl}methyl}piperazine-2-carboxamide (16-11);
- (2R,6R)-4-((R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl)-1-isobutyl-N-(4-(6-methoxypyridin-2-yl)benzyl)-6-methylpiperazine-2-carboxamide (25);

- 30 or a pharmaceutically acceptable salt thereof.

An embodiment of the present invention includes compounds of Formula I wherein Ring A is selected from: pyrazinyl, naphthyl, pyrimidinyl, thiazolyl, oxazolyl, pyrazolyl,

triazolyl, imidazolyl, quinolinyl, pyradazinyl, phenyl and pyridinyl. A further embodiment of the present invention includes compounds wherein Ring A is selected from: pyrazinyl, naphthyl, pyrimidinyl, thiazolyl, oxazolyl, pyrazolyl, triazolyl, imidazolyl, quinolinyl, pyradazinyl, phenyl and pyridinyl. In an embodiment, Ring A is phenyl. In an embodiment, Ring A is pyridinyl.

5 An embodiment of the present invention includes compounds of Formula I wherein R^1 is selected from:

- (1) $-(CR_2)_n$ -heteroaryl, where the heteroaryl is unsubstituted or substituted with one to six substituents independently selected from R^4 ,
- (2) $-(CR_2)_n$ -heterocyclyl, where the heterocyclyl is unsubstituted or substituted with
10 one to six substituents independently selected from R^4 ,
- (3) $-C_{1-6}$ alkyl, where the alkyl is unsubstituted or substituted with one to six substituents independently selected from R^4 ,
- (4) $-O(CR_2)_pR^4$,
- (5) $-OR$,
- 15 (6) halo,
- (7) $-OCR_2C(O)NR_2$,
- (8) $-OCR_2CF_3$,
- (9) $-O(CR_2)_tOCR_3$,
- (10) $-(CR_2)_nCN$
- 20 (11) $-(CR_2)_nNR_2$, and
- (12) $-O(CR_2)_tNR_2$.

In a further embodiment, the present invention includes compounds of Formula I wherein R^1 is selected from: C_{1-6} alkyl, where the alkyl is unsubstituted or substituted with one to six substituents independently selected from R^4 , $-O(CR_2)_pR^4$, halo, $-OR$, $-OCR_2C(O)NR_2$, and
25 $-OCR_2CF_3$. In a further embodiment, R^1 is selected from halo, $-O(CR_2)_pR^4$ or C_{1-6} alkyl, where the alkyl is unsubstituted or substituted with one to six substituents independently selected from R^4 . In an embodiment, R^1 is C_{1-6} alkyl, where the alkyl is unsubstituted or substituted with one to six substituents independently selected from R^4 . In an embodiment, R^1 is halo. In an embodiment, R^1 is $-O(CR_2)_pR^4$. In an embodiment, R^1 is $-CF_3$.

30 An embodiment of the present invention includes compounds of Formula I wherein R^2 is selected from H, $-(CR_2)_sOR$, $-C_{1-6}$ alkyl, where the alkyl is unsubstituted or

substituted with one to three substituents selected from R^5 , and $-(CR_2)_sC(O)OR$. In an embodiment, the present invention includes compounds of Formula I wherein R^2 is selected from H, $-(CR_2)_sOR$, and $-C_{1-6}alkyl$, where the alkyl is unsubstituted or substituted with one to three substituents selected from R^5 . In a further embodiment, the present invention includes compounds of Formula I wherein R^2 is H, $-CF_3$, or $-(CR_2)_sOR$. In a further embodiment, the present invention includes compounds of Formula I wherein R^2 is H or $-(CR_2)_sOR$. In an embodiment, the present invention includes compounds of Formula I wherein R^2 is $-(CR_2)_sOR$. In an embodiment, the present invention includes compounds of Formula I wherein R^2 is H.

10 An embodiment of the present invention includes compounds of Formula I wherein R^3 is selected from

- (1) $-C_{1-6}alkyl$, where the alkyl is unsubstituted or substituted with one to four substituents independently selected from R^7 ,
- (2) aryl, where the aryl is unsubstituted or substituted with one to four substituents independently selected from R^7 ,
- 15 (3) heteroaryl, where the heteroaryl is unsubstituted or substituted with one to four substituents independently selected from R^7 ,
- (4) $-OCF_2CH_3$.

In a further embodiment, the present invention includes compounds of Formula I wherein R^3 is selected from unsubstituted or substituted pyrimidinyl, unsubstituted or substituted pyridinyl, unsubstituted or substituted oxazolyl, unsubstituted or substituted furanyl or $-OCF_2CH_3$, wherein pyrimidinyl, pyridinyl, furanyl or oxazolyl is optionally substituted with one to four substituents independently selected from R^7 .

20 An embodiment of the present invention includes compounds of Formula I wherein R^4 is selected from $-OR$, halo, $-C_{1-6}alkyl$, aryl, heteroaryl, and heterocyclyl, where said alkyl, aryl, heteroaryl or heterocyclyl is unsubstituted or substituted with one to six substituents independently selected from R^6 . In a further embodiment, the present invention includes compounds of Formula I wherein R^4 is selected from aryl, heteroaryl, and heterocyclyl, where said aryl, heteroaryl or heterocyclyl is unsubstituted or substituted with one to six substituents independently selected from R^6 . In an embodiment, R^4 is selected from phenyl or pyridinyl,

where said phenyl or pyridinyl is unsubstituted or substituted with one to six substituents independently selected from R⁶.

An embodiment of the present invention includes compounds of Formula I wherein m is selected from 0, 1, 2 or 3. An embodiment of the present invention includes
5 compounds of Formula I wherein m is 2. An embodiment of the present invention includes compounds of Formula I wherein m is 1.

An embodiment of the present invention includes compounds of Formula I wherein n is selected from 0 or 1. An embodiment of the present invention includes compounds of Formula I wherein n is 0. An embodiment of the present invention includes compounds of
10 Formula I wherein n is 1.

An embodiment of the present invention includes compounds of Formula I wherein p is selected from 0 or 1. In an embodiment, the present invention includes compounds of Formula I wherein p is 0. In an embodiment, the present invention includes compounds of Formula I wherein p is 1.

15 An embodiment of the present invention includes compounds of Formula I wherein s is selected from 0, 1, 2 or 3. An embodiment of the present invention includes compounds of Formula I wherein s is 2. An embodiment of the present invention includes compounds of Formula I wherein s is 1.

The present invention includes compounds that may contain one or more
20 asymmetric centers. Thus, compounds of the present invention include those that can occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. Additional asymmetric centers may be present depending upon the nature of the various substituents on the molecule. Each such asymmetric center will independently produce two optical isomers and it is intended that all of the possible optical isomers and diastereomers in
25 mixtures and as pure or partially purified compounds are included within the ambit of this invention. The present invention is meant to comprehend all such isomeric forms of these compounds. Likewise, the present invention includes tautomeric forms of the compounds disclosed herein. Formula I shows the structure of the class of compounds without specific stereochemistry. At least some of the chemical names of compounds of the invention as set forth
30 in this application may have been generated on an automated basis by use of commercially available chemical naming software programs, and have not been independently verified.

The independent syntheses of these diastereomers or their chromatographic separations may be achieved as known in the art by appropriate modification of the methodology disclosed herein. Their absolute stereochemistry may be determined by the x-ray crystallography of crystalline products or crystalline intermediates which are derivatized, if necessary, with a reagent containing an asymmetric center of known absolute configuration. Absolute stereochemistry may also be elucidated through other techniques known in the art, such as cryogenic electron microscopy. Relative stereochemistry may be determined using nuclear magnetic resonance with methods known in the art. Stereochemistry may be assigned by analogy to a set of isomers based on their relative biological activity following the same trend established by a similar stereochemically defined group of isomers. If desired, racemic mixtures of the compounds may be separated so that the individual enantiomers are isolated. The separation can be carried out by methods well known in the art, such as the coupling of a racemic mixture of compounds to an enantiomerically pure compound to form a diastereomeric mixture, followed by separation of the individual diastereomers by standard methods, such as fractional crystallization or chromatography. The coupling reaction is often the formation of salts using an enantiomerically pure acid or base. The diastereomeric derivatives may then be converted to the pure enantiomers by cleavage of the added chiral residue. The racemic mixture of the compounds can also be separated directly by chromatographic methods utilizing chiral stationary phases, which methods are well known in the art. Compounds of the present invention may also be separated by supercritical fluid chromatography (SFC). Furthermore, some separations required multiple rounds of purifications by the same method of purification and/or an alternative purification system to resolve mixtures into single isomers. Additionally, a mixture may be a mixture of 2 to 4 stereoisomers. Alternatively, any enantiomer of a compound may be obtained by stereoselective synthesis using optically pure starting materials or reagents of known configuration by methods well known in the art.

As appreciated by those of skill in the art, halogen or halo as used herein are intended to include fluoro, chloro, bromo and iodo. Similarly, C₁₋₆, as in C₁₋₆alkyl is defined to identify the group as having 1, 2, 3, 4, 5 or 6 carbons in a linear or branched arrangement, such that C₁₋₆alkyl specifically includes methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl, pentyl, and hexyl.

As used herein, "aryl" is intended to mean any stable monocyclic or bicyclic carbon ring of up to 7 members in each ring, wherein at least one ring is aromatic. Examples of

such aryl elements include phenyl, naphthyl, tetrahydronaphthyl, indanyl, biphenyl, phenanthryl, anthryl or acenaphthyl. In an embodiment of the instant invention, aryl is phenyl or naphthyl. In a further embodiment, aryl is phenyl.

The term heterocyclyl, heterocycle or heterocyclic, as used herein, represents
 5 a stable 5- to 7-membered monocyclic or stable 8- to 11-membered bicyclic heterocyclic ring which is either saturated or unsaturated, and which consists of carbon atoms and from one to four heteroatoms selected from the group consisting of N, O, and S, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation of a stable
 10 structure. The term heterocyclyl, heterocycle or heterocyclic can include heteroaryl moieties when two rings are fused together. Examples of heterocyclic elements include, but are not limited to, azabicyclo[2.2.1]heptanyl, azepanyl, azetidiny, benzodioxolyl, chromanyl, dihydrobenzofuryl, dihydrobenzothieryl, dihydrobenzothiopyranyl, dihydrobenzothiopyranyl sulfone, dihydro-pyrrolo[1,2-b]pyrazolyl, 1,3-dioxolanyl, 1,4-dioxanyl, imidazolidinyl, indolinyl,
 15 isochromanyl, isoindolinyl, morpholinyl, oxa-5-azabicyclo[2.2.1]heptanyl, oxetanyl, 2-oxopiperazinyl, 2-oxopiperdiny, 2-oxopyrrolidinyl, piperidyl, piperidinyl, piperazinyl, pyrazolidinyl, pyrrolidinyl, tetrahydrofuryl, tetrahydroisoquinolinyl, tetrahydrofuranlyl, tetrahydroquinolinyl, thiomorpholinyl and the like.

In an embodiment, heterocyclyl is selected from azabicyclo[2.2.1]heptanyl,
 20 azepanyl, azetidiny, dihydro-pyrrolo[1,2-b]pyrazolyl, morpholinyl, oxa-5-azabicyclo[2.2.1]heptanyl, piperidyl, piperazinyl, pyrazolidinyl, pyrrolidinyl, pyrrolyl, and tetrahydrofuryl. In another embodiment, heterocyclyl is selected from azabicyclo[2.2.1]heptanyl, azepanyl, azetidiny, dihydro-pyrrolo[1,2-b]pyrazolyl, oxa-5-azabicyclo[2.2.1]heptanyl, piperazinyl, and pyrrolidinyl.

"Heteroaryl" is intended to mean any stable monocyclic or bicyclic carbon ring of
 25 up to 7 members in each ring, wherein at least one ring is aromatic and wherein from one to four carbon atoms are replaced by heteroatoms selected from the group consisting of N, O, and S. Examples of such heterocyclic elements include, but are not limited to, azepinyl, furanyl, furyl, imidazolyl, indolinyl, indolyl, isochromanyl, isoindolinyl, isoxazolyl, isoquinolinyl, isothiazolyl,
 30 naphthyridinyl, oxazolyl, oxadiazolyl, pyridyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridinyl, pyrimidinyl, 5H-pyrrolo[2,3-b]pyrazinyl, pyrrolyl, quinazolinyl, quinolinyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, tetrazolyl, thiazolyl, thienofuryl, thiophenyl, thienothienyl, thienyl, triazinyl, triazolyl and the like. In an embodiment, heteroaryl is selected

from furyl, imidazolyl, indolyl, isoxazolyl, oxazolyl, oxadiazolyl, pyridyl, pyrazinyl, pyrazolyl, pyridazinyl, pyrimidinyl, 5H-pyrrolo[2,3-b]pyrazinyl, tetrazolyl, thiazolyl, thienyl, triazolyl and the like.

The present invention also includes all pharmaceutically acceptable isotopic variations of a compound of the Formula I in which one or more atoms is replaced by atoms having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Such compounds are identical to those disclosed herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes suitable for inclusion in the compounds of the invention include isotopes of hydrogen such as ^2H and ^3H , carbon such as ^{11}C , ^{13}C and ^{14}C , nitrogen such as ^{13}N and ^{15}N , oxygen such as ^{15}O , ^{17}O and ^{18}O , phosphorus such as ^{32}P , sulfur such as ^{35}S , fluorine such as ^{18}F , iodine such as ^{123}I and ^{125}I , and chlorine such as ^{36}Cl . Certain isotopically-labelled compounds of Formula I, for example those incorporating a radioactive isotope, are useful in drug and/or substrate tissue distribution studies. The radioactive isotopes tritium, i.e., ^3H , and carbon-14, i.e., ^{14}C , are particularly useful for this purpose in view of their ease of incorporation and ready means of detection. Substitution with heavier isotopes such as deuterium, i.e., ^2H , may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased *in vivo* half-life or reduced dosage requirements, and hence may be preferred in some circumstances. Substitution with positron emitting isotopes, such as ^{11}C , ^{18}F , ^{15}O and ^{13}N , can be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy. An embodiment of the present invention includes compounds that are substituted with a positron emitting isotope. An embodiment of the present invention includes compounds that are substituted with a ^{11}C isotope. An embodiment of the present invention includes compounds that are substituted with an ^{18}F isotope. In the compounds of the invention, the atoms may exhibit their natural isotopic abundances, or one or more of the atoms may be artificially enriched in a particular isotope having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number predominantly found in nature. The present invention is meant to include all suitable isotopic variations of the compounds of the invention. For example, different isotopic forms of hydrogen (H) include protium (^1H) and deuterium (^2H). Protium is the predominant hydrogen isotope found in nature. Enriching for deuterium may afford certain therapeutic advantages, such as increasing *in vivo* half-life or

reducing dosage requirements, or may provide a compound useful as a standard for characterization of biological samples. Isotopically-enriched compounds of the invention can be prepared without undue experimentation by conventional techniques well known to those skilled in the art or by processes analogous to those described in the schemes and examples herein using
5 appropriate isotopically-enriched reagents and/or intermediates.

When any variable (*e.g.*, R¹, R⁵ etc.) occurs more than one time in any substituent or in Formula I, its definition on each occurrence is independent of its definition at every other occurrence unless otherwise specified at the point of definition. One of ordinary skill in the art will recognize that choice of combinations of the various substituents defined in a structural
10 representation, *i.e.*, R¹, R², R⁵, etc., are to be chosen in conformity with well-known principles of chemical structure connectivity and stability, and combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

A "stable" compound is a compound which can be prepared and isolated and whose structure and properties remain or can be caused to remain essentially unchanged for a
15 period of time sufficient to allow use of the compound for the purposes described herein (*e.g.*, therapeutic administration to a subject). The compounds of the present invention are limited to stable compounds embraced by Formula I.

Those skilled in the art will recognize those instances in which the compounds of the invention may form salts. In such instances, another embodiment provides pharmaceutically
20 acceptable salts of the compounds of the invention. Thus, reference to a compound of the invention herein is understood to include reference to salts thereof, unless otherwise indicated. The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids including inorganic or organic bases and inorganic or organic acids. In addition, when a compound of the invention contains both a basic moiety, such as, but
25 not limited to a pyridine or imidazole, and an acidic moiety, such as, but not limited to a carboxylic acid, zwitterions ("inner salts") may be formed and are included within the present invention. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like. Particular embodiments include the ammonium, calcium, magnesium, potassium, and
30 sodium salts. Salts in the solid form may exist in more than one crystal structure, and may also be in the form of hydrates or solvates. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including

naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N'-dibenzylethylene-diamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, and the like.

When the compound of the present invention is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid, and the like. Particular embodiments include the citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric, fumaric, and tartaric acids. It will be understood that, as used herein, references to the compounds of Formula I are meant to also include the pharmaceutically acceptable salts. Salts of the compounds of the invention may be formed by methods known to those of ordinary skill in the art, for example, by reacting a compound of the invention with an amount of acid or base, such as an equivalent amount, in a medium such as one in which the salt precipitates or in an aqueous medium followed by lyophilization.

Exemplifying the invention is the use of the compounds disclosed in the Examples and herein. Specific compounds within the present invention include a compound which is selected from the compounds disclosed in the following Examples and pharmaceutically acceptable salts thereof and individual enantiomers or diastereomers thereof.

The present invention is also directed to the use of the compounds disclosed herein as agonists of orexin receptor activity. The subject compounds and pharmaceutically acceptable salts thereof are useful in a method of agonizing orexin receptor activity in a subject such as a mammal comprising the administration of an amount of the compound. In addition to primates, especially humans, a variety of other mammals may be administered with a compound of the present invention. The present invention is directed to a compound of the present invention or a pharmaceutically acceptable salt thereof that could be useful in therapy. The present invention may further be directed to a use of a compound of the present invention or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for agonizing

orexin receptor activity or treating the disorders and diseases noted herein in humans and animals.

A subject administered with a compound of the present invention, or a pharmaceutically acceptable salt thereof, is generally a mammal, such as a human being, male or female. The amount of compound administered to the subject is an amount sufficient to agonize the orexin receptor in the subject. In an embodiment, the amount of compound can be an "effective amount", wherein the subject compound is administered in an amount that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by the researcher, veterinarian, medical doctor or other clinician. An effective amount does not necessarily include considerations of toxicity and safety related to the administration of the compound. It is recognized that one skilled in the art may affect neurological and psychiatric disorders associated with orexin receptor activation by treating a subject presently afflicted with the disorders, or by prophylactically treating a subject likely to be afflicted with the disorders, with an effective amount of a compound of the present invention. As used herein, the terms "treatment" and "treating" refer to all processes wherein there may be a slowing, interrupting, arresting, controlling, or stopping of the progression of the neurological and psychiatric disorders described herein, but does not necessarily indicate a total elimination of all disorder symptoms, as well as the prophylactic therapy of the mentioned conditions, particularly in a subject that is predisposed to such disease or disorder. The terms "administration of" and or "administering a" compound should be understood to mean providing a compound of the invention or a prodrug of a compound of the invention to to the subject.

The term "composition" as used herein is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts. Such term is intended to encompass a product comprising the active ingredient(s), and the inert ingredient(s) that make up the carrier, as well as any product which results, directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients. Accordingly, the compositions of the present invention encompass any composition made by admixing a compound of the present invention and a pharmaceutically acceptable carrier. By "pharmaceutically acceptable" it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The utility of the compounds in accordance with the present invention as orexin receptor OX1R and/or OX2R agonists may be readily determined without undue experimentation by methodology well known in the art. Both the OX1R and/or OX2R G-coupled protein receptors (GPCRs) couple through the Gαq signaling pathway, which ultimately promotes calcium mobilization via inositol triphosphate (IP3) production. The half-life of IP-3 is relatively short, being rapidly metabolized to inositol monophosphate (IP-1), which can be readily detected using a commercially available assay kit (IP-One; Cisbio; cat# 621PAPEC) coupled with a cell line expressing the target receptor(s) of interest. The utility of the compounds in accordance with the present invention as orexin receptor OX1R and/or OX2R agonists may be determined utilizing this assay.

In a typical experiment, the OX1 and OX2 receptor agonist activity is determined in accordance with the following general experimental method. Chinese hamster ovary (CHO) cells expressing human OX1R and/or the human OX2R were grown in Iscove's modified DMEM containing glutaMAX™, 1% G418, 100 U/mL penicillin, 100 µg /mL streptomycin and 10 % heat-inactivated qualified fetal bovine serum (FBS). The OX2R cells were seeded at 10,000 cells/well/50 µL and the OX1R cells were seeded at 20,000 cells/well/50 µL into 384-well white tissue culture plates (Greiner; cat# 781080). All cell/media reagents were from GIBCO-Invitrogen Corp. The seeded cell plate(s) were incubated at 37°C with 5% CO₂ and 85% humidity for 20-24 hours. On the day of the assay, assay-ready compound plates were prepared using an acoustic liquid handler (ECHO; Labcyte), which dispensed sufficient volume of test compound stock (10 mM in DMSO) or 100% DMSO to prepare 10 point, ½-log dilutions in a final volume of 202.5 nL/well in all test wells of a 384-well diamond plate (Labcyte). Following completion of assay-ready plates, importantly, the next three steps were performed with minimal delay: 1) 20 µl of 1x stimulation buffer was added to the compound plate using a Multidrop Combi (small cassette, Thermo Fisher Scientific cat# 24073290); 2) culture medium was removed from the cell plate using the Bluewasher plate washer (gentle spin; BlueCatBio); 3) 14 µl of compound/stimulation buffer mixture was added to the cell plate using a Bravo liquid handler (Agilent) prior to incubating cell plates at 37°C with 5% CO₂ and 85% humidity for 1 or 2 hours (OX1R and OX2R, respectively). During this incubation, IP-one detection reagents were prepared (38:1:1 lysis buffer:D2:AB-cryptate reagents). Six µL of mixed detection reagents were added to the cell plate using a Multidrop Combi (small cassette, Thermo Fisher Scientific cat #24073290) and incubated 60 minutes at room temperature in the dark. Fluorescence signal was

detected using an Envision plate reader (Perkin Elmer) [LANCE/DELFI A Dual Enh (Em: APC 665; Ex: Cy5 620)].

For each compound, data were fit to a four parameter logistic fit (ActivityBase software) and the EC₅₀ was reported as the inflection point of the resulting curve. Percent effect for each test compound was determined as the percentage of sample raw value/mean max effect, where the mean max effect was derived from the mean raw value of 32 control wells per assay plate (using Orexin A (cat# 003-30) at 1 μ M for human OX1R and a reference compound at 1 μ M with 100% activity previously established by comparison to Orexin A for human OX2R). The intrinsic orexin receptor agonist activity of a compound which may be used in the present invention may be determined by these assays.

All of the final compounds of the following examples had activity in agonizing the human orexin-2 receptor in the aforementioned IPOne assay with an EC₅₀ of about 0.01 nM to 5000 nM. Additional data is provided in the following Examples. Such a result is indicative of the intrinsic activity of the compounds in use as agonists of orexin-1 receptor and/or the orexin-2 receptor. In general, one of ordinary skill in the art would appreciate that a substance is considered to effectively agonize the orexin receptor if it has an EC₅₀ in the IPOne assay of less than about 50 μ M, or more specifically less than about 1000 nM.

The orexin receptors have been implicated in a wide range of biological functions. This has suggested a potential role for these receptors in a variety of disease processes in humans or other species. The compounds of the present invention could therefore potentially have utility in treating, preventing, ameliorating, controlling or reducing the risk of a variety of disorders associated with orexin receptors, including one or more of the following conditions or diseases: narcolepsy, narcolepsy syndrome accompanied by narcolepsy-like symptoms, cataplexy in narcolepsy, excessive daytime sleepiness (EDS) in narcolepsy, hypersomnia, idiopathic hypersomnia, repeatability hypersomnia, intrinsic hypersomnia, hypersomnia accompanied by daytime hypersomnia, interrupted sleep, sleep apnea, wakefulness, nocturnal myoclonus, disturbances of consciousness, such as coma, REM sleep interruptions, jet-lag, excessive daytime sleepiness, shift workers' sleep disturbances, dyssomnias, sleep disorders, sleep disturbances, hypersomnia associated with depression, emotional/mood disorders, Alzheimer's disease or cognitive impairment, Parkinson's disease, Guillain-Barre syndrome, Kleine Levin syndrome, and sleep disorders which accompany aging; Alzheimer's sundowning; conditions associated with circadian rhythmicity as well as mental and physical disorders associated with travel across

time zones and with rotating shift-work schedules; fibromyalgia; cardiac failure; diseases related to bone loss; sepsis; syndromes which are manifested by non-restorative sleep and muscle pain or sleep apnea which is associated with respiratory disturbances during sleep; conditions which result from a diminished quality of sleep; and other diseases related to general orexin system dysfunction.

Thus, in certain embodiments the present invention may provide methods for: treating or controlling narcolepsy, narcolepsy syndrome accompanied by narcolepsy-like symptoms, cataplexy in narcolepsy, excessive daytime sleepiness (EDS) in narcolepsy, hypersomnia, idiopathic hypersomnia, repeatability hypersomnia, intrinsic hypersomnia, hypersomnia accompanied by daytime hypersomnia, interrupted sleep, sleep apnea, disturbances of consciousness, REM sleep interruptions, jet-lag, shift workers' sleep disturbances, dyssomnias, night terror, insomnias associated with depression, emotional/mood disorders, Alzheimer's disease or cognitive impairment; treating or controlling sleep disturbances associated with diseases such as neurological disorders including neuropathic pain and restless leg syndrome; treating or controlling addiction disorders; treating or controlling psychoactive substance use and abuse; enhancing cognition; increasing memory retention; treating or controlling obesity; treating or controlling diabetes and appetite, taste, eating, or drinking disorders; treating or controlling insulin resistance syndrome; treating or controlling hypothalamic diseases; treating or controlling depression; treating, controlling, ameliorating or reducing the risk of epilepsy, including absence epilepsy; treating or controlling pain, including neuropathic pain; treating or controlling Parkinson's disease; treating or controlling Guillain-Barre syndrome; treating or controlling Klein Levin syndrome; treating or controlling psychosis; treating or controlling dysthymic, mood, psychotic and anxiety disorders; treating side effects or complications due to anesthesia; reversal of anesthesia; reversal of anesthesia following surgery; treating or controlling depression, including major depression and major depression disorder; treating or controlling bipolar disorder; or treating, controlling, ameliorating or reducing the risk of schizophrenia, in a mammalian subject which comprises administering to the subject a compound of the present invention.

The compounds of the present invention may also potentially have utility in treating, preventing, ameliorating, controlling or reducing the risk of a variety of other disorders associated with orexin receptors, including one or more of the following conditions or diseases including enhancing sleep quality, improving sleep quality, increasing sleep efficiency, augmenting sleep maintenance; increasing the value which is calculated from the time that a

subject sleeps divided by the time that a subject is attempting to sleep; improving sleep initiation; decreasing sleep latency or onset (the time it takes to fall asleep); decreasing difficulties in falling asleep; increasing sleep continuity; decreasing the number of awakenings during sleep; decreasing intermittent wakings during sleep; decreasing nocturnal arousals; decreasing the time spent awake following the initial onset of sleep; increasing the total amount of sleep; reducing the fragmentation of sleep; altering the timing, frequency or duration of REM sleep bouts; altering the timing, frequency or duration of slow wave (i.e., stages 3 or 4) sleep bouts; increasing the amount and percentage of stage 2 sleep; promoting slow wave sleep; enhancing EEG-delta activity during sleep; decreasing nocturnal arousals, especially early morning awakenings; increasing daytime alertness; reducing daytime drowsiness; treating or reducing excessive daytime sleepiness; increasing satisfaction with the intensity of sleep; increasing sleep maintenance; idiopathic insomnia; sleep problems; insomnia; night terror, insomnias associated with depression, emotional/mood disorders, Alzheimer's disease or cognitive impairment, as well as sleep walking and enuresis, and sleep disorders which accompany aging; Alzheimer's sundowning; conditions associated with circadian rhythmicity as well as mental and physical disorders associated with travel across time zones and with rotating shift-work schedules, conditions due to drugs which cause reductions in REM sleep as a side effect; fibromyalgia; syndromes which are manifested by non-restorative sleep and muscle pain or sleep apnea which is associated with respiratory disturbances during sleep; conditions which result from a diminished quality of sleep; increasing learning; augmenting memory; increasing retention of memory; eating disorders associated with excessive food intake and complications associated therewith, compulsive eating disorders, obesity (due to any cause, whether genetic or environmental), obesity-related disorders overeating, anorexia, bulimia, cachexia, dysregulated appetite control, hypertension, diabetes, elevated plasma insulin concentrations and insulin resistance, dyslipidemias, hyperlipidemia, endometrial, breast, prostate and colon cancer, osteoarthritis, obstructive sleep apnea, cholelithiasis, gallstones, heart disease, lung disease, abnormal heart rhythms and arrhythmias, myocardial infarction, congestive heart failure, coronary heart disease, acute and congestive heart failure; hypotension; hypertension; urinary retention; osteoporosis; angina pectoris; myocardial infarction; ischemic or haemorrhagic stroke; subarachnoid haemorrhage; ulcers; allergies; benign prostatic hypertrophy; chronic renal failure; renal disease; impaired glucose tolerance; sudden death, polycystic ovary disease, craniopharyngioma, the Prader-Willi Syndrome, Frohlich's syndrome, GH-deficient subjects, normal variant short stature, Turner's syndrome, and other pathological conditions showing

reduced metabolic activity or a decrease in resting energy expenditure as a percentage of total fat-free mass, e.g., children with acute lymphoblastic leukemia, metabolic syndrome, also known as syndrome X, insulin resistance syndrome, reproductive hormone abnormalities, sexual and reproductive dysfunction, such as impaired fertility, infertility, hypogonadism in males and

5 hirsutism in females, fetal defects associated with maternal obesity, gastrointestinal motility disorders, intestinal motility dyskinesias, obesity-related gastro-esophageal reflux, hypothalamic diseases, hypophysis diseases, respiratory disorders, such as obesity-hypoventilation syndrome (Pickwickian syndrome), breathlessness, cardiovascular disorders, inflammation, such as

10 systemic inflammation of the vasculature, arteriosclerosis, hypercholesterolemia, hyperuricaemia, lower back pain, gallbladder disease, gout, kidney cancer, increased anesthetic risk, reducing the risk of secondary outcomes of obesity, such as reducing the risk of left ventricular hypertrophy; diseases or disorders where abnormal oscillatory activity occurs in the brain, including depression, migraine, neuropathic pain, Parkinson's disease, psychosis and schizophrenia, as well as diseases or disorders where there is abnormal coupling of activity,

15 particularly through the thalamus; enhancing cognitive function, including cognitive dysfunctions that comprise deficits in all types of attention, learning and memory functions occurring transiently or chronically in the normal, healthy, young, adult or aging population, and also occurring transiently or chronically in psychiatric, neurologic, cardiovascular and immune disorders; treating or controlling Guillain-Barre syndrome; treating or controlling Klein Levin

20 syndrome; treating or controlling psychosis; treating or controlling dysthymic, mood, psychotic and anxiety disorders; treating complications due to anesthesia; enhancing memory; increasing memory retention; increasing immune response; increasing immune function; hot flashes; night sweats; extending life span; schizophrenia; muscle-related disorders that are controlled by the excitation/relaxation rhythms imposed by the neural system such as cardiac rhythm and other

25 disorders of the cardiovascular system; conditions related to proliferation of cells such as vasodilation or vasoconstriction and blood pressure; cancer; cardiac arrhythmia; hypertension; congestive heart failure; conditions of the genital/urinary system; disorders of sexual function and fertility; adequacy of renal function; responsiveness to anesthetics; mood disorders, such as depression or more particularly depressive disorders, for example, single episodic or recurrent

30 major depressive disorders and dysthymic disorders, or bipolar disorders, for example, bipolar I disorder, bipolar II disorder and cyclothymic disorder, mood disorders due to a general medical condition, and substance-induced mood disorders; affective neurosis; depressive neurosis; anxiety neurosis; anxiety disorders including acute stress disorder, agoraphobia, generalized

anxiety disorder, obsessive-compulsive disorder, panic attack, panic disorder, post-traumatic stress disorder, separation anxiety disorder, social phobia, specific phobia, substance-induced anxiety disorder and anxiety due to a general medical condition; acute neurological and psychiatric disorders such as cerebral deficits subsequent to cardiac bypass surgery and grafting,

5 stroke, ischemic stroke, cerebral ischemia, spinal cord trauma, head trauma, perinatal hypoxia, cardiac arrest, hypoglycemic neuronal damage; Huntington's Chorea; Huntington's disease and Tourette syndrome; Cushing's syndrome/disease; basophile adenoma; prolactinoma; hyperprolactinemia; hypophysis tumor/adenoma; hypothalamic diseases; inflammatory bowel disease; gastric dyskinesia; gastric ulcers; Froehlich's syndrome; adrenohypophysis disease;

10 hypophysis disease; adrenohypophysis hypofunction; adrenohypophysis hyperfunction; hypothalamic hypogonadism; Kallman's syndrome (anosmia, hyposmia); functional or psychogenic amenorrhea; hypopituitarism; hypothalamic hypothyroidism; hypothalamic- adrenal dysfunction; idiopathic hyperprolactinemia; hypothalamic disorders of growth hormone deficiency; idiopathic growth deficiency; dwarfism; gigantism; acromegaly; amyotrophic lateral

15 sclerosis; multiple sclerosis; ocular damage; retinopathy; cognitive disorders; idiopathic and drug-induced Parkinson's disease; muscular spasms and disorders associated with muscular spasticity including tremors, epilepsy, convulsions, seizure disorders, absence seizures, complex partial and generalized seizures; Lennox-Gastaut syndrome; cognitive disorders including dementia (associated with Alzheimer's disease, ischemia, trauma, vascular problems or stroke,

20 HIV disease, Parkinson's disease, Huntington's disease, Pick's disease, Creutzfeldt-Jacob disease, perinatal hypoxia, other general medical conditions or substance abuse); delirium, amnesic disorders or age related cognitive decline; schizophrenia or psychosis including schizophrenia (paranoid, disorganized, catatonic or undifferentiated), schizophreniform disorder, schizoaffective disorder, delusional disorder, brief psychotic disorder, shared psychotic disorder,

25 psychotic disorder due to a general medical condition and substance-induced psychotic disorder; dissociative disorders including multiple personality syndromes and psychogenic amnesias; substance-related disorders, substance use, substance abuse, substance seeking, substance reinstatement, all types of psychological and physical addictions and addictive behaviors, reward-related behaviors (including substance-induced delirium, persisting dementia, persisting

30 amnesic disorder, psychotic disorder or anxiety disorder; tolerance, addictive feeding, addictive feeding behaviors, binge/purge feeding behaviors, dependence, withdrawal or relapse from substances including alcohol, amphetamines, cannabis, cocaine, hallucinogens, inhalants, morphine, nicotine, opioids, phencyclidine, sedatives, hypnotics or anxiolytics); appetite, taste,

eating or drinking disorders; movement disorders, including akinesias and akinetic-rigid syndromes (including Parkinson's disease, drug-induced parkinsonism, postencephalitic parkinsonism, progressive supranuclear palsy, multiple system atrophy, corticobasal degeneration, parkinsonism-ALS dementia complex and basal ganglia calcification), chronic fatigue syndrome, fatigue, including Parkinson's fatigue, multiple sclerosis fatigue, fatigue caused by a sleep disorder or a circadian rhythm disorder, medication-induced parkinsonism (such as neuroleptic-induced parkinsonism, neuroleptic malignant syndrome, neuroleptic-induced acute dystonia, neuroleptic-induced acute akathisia, neuroleptic-induced tardive dyskinesia and medication-induced postural tremor), Gilles de la Tourette's syndrome, epilepsy, and dyskinesias [including tremor (such as rest tremor, essential tremor, postural tremor and intention tremor), chorea (such as Sydenham's chorea, Huntington's disease, benign hereditary chorea, neuroacanthocytosis, symptomatic chorea, drug-induced chorea and hemiballism), myoclonus (including generalised myoclonus and focal myoclonus), tics (including simple tics, complex tics and symptomatic tics), restless leg syndrome and dystonia (including generalised dystonia such as idiopathic dystonia, drug-induced dystonia, symptomatic dystonia and paroxysmal dystonia, and focal dystonia such as blepharospasm, oromandibular dystonia, spasmodic dysphonia, spasmodic torticollis, axial dystonia, dystonic writer's cramp and hemiplegic dystonia); neurodegenerative disorders including nosological entities such as disinhibition-dementia-parkinsonism-amyotrophy complex; pallido-ponto-nigral degeneration; epilepsy; seizure disorders; attention deficit/hyperactivity disorder (ADHD); conduct disorder; migraine (including migraine headache); headache; hyperalgesia; pain; enhanced or exaggerated sensitivity to pain such as hyperalgesia, causalgia, and allodynia; acute pain; burn pain; atypical facial pain; neuropathic pain; back pain; complex regional pain syndrome I and II; arthritic pain; sports injury pain; pain related to infection e.g., HIV, post-chemotherapy pain; post-stroke pain; post-operative pain; neuralgia; emesis, nausea, vomiting; gastric dyskinesia; gastric ulcers; Kallman's syndrome (anosmia); asthma; cancer; conditions associated with visceral pain such as irritable bowel syndrome, and angina; eating disorders; urinary incontinence; substance tolerance, substance withdrawal (including, substances such as opiates, nicotine, tobacco products, alcohol, benzodiazepines, cocaine, sedatives, hypnotics, etc.); psychosis; schizophrenia; anxiety (including generalized anxiety disorder, panic disorder, and obsessive compulsive disorder); mood disorders (including depression, mania, bipolar disorders); trigeminal neuralgia; hearing loss; tinnitus; neuronal damage including ocular damage; retinopathy; macular degeneration of the eye; emesis; brain edema; pain, including acute and chronic pain states, severe pain,

intractable pain, inflammatory pain, neuropathic pain, post-traumatic pain, bone and joint pain (osteoarthritis), repetitive motion pain, dental pain, cancer pain, myofascial pain (muscular injury, fibromyalgia), perioperative pain (general surgery, gynecological), chronic pain, neuropathic pain, post-traumatic pain, trigeminal neuralgia, migraine and migraine headache and
5 other diseases related to general orexin system dysfunction.

The subject compounds could further be of potential use in a method for the prevention, treatment, control, amelioration, or reduction of risk of the diseases, disorders and conditions noted herein. The dosage of active ingredient in the compositions of this invention may be varied, however, it is necessary that the amount of the active ingredient be such that a
10 suitable dosage form is obtained. The active ingredient may be administered to subjects (animals and human) in need of such treatment in dosages that will provide optimal pharmaceutical efficacy. The selected dosage depends upon the desired therapeutic effect, on the route of administration, and on the duration of the treatment. The dose will vary from subject to subject depending upon the nature and severity of disease, the subject's weight, special diets then being
15 followed by a subject, concurrent medication, and other factors which those skilled in the art will recognize.

Generally, dosage levels of between 0.0001 to 100 mg/kg. of body weight daily are administered to the subject, e.g., humans, adolescent humans and elderly humans, to obtain effective agonism of orexin receptors. The dosage range will generally be about 0.5 mg to 10.0 g.
20 per subject per day which may be administered in single or multiple doses. In one embodiment, the dosage range will be about 0.5 mg to 500 mg per subject per day; in another embodiment about 0.5 mg to 200 mg per subject per day; and in yet another embodiment about 5 mg to 50 mg per subject per day. Pharmaceutical compositions of the present invention may be provided in a solid dosage formulation such as comprising about 0.5 mg to 500 mg active ingredient, or
25 comprising about 1 mg to 250 mg active ingredient. The pharmaceutical composition may be provided in a solid dosage formulation comprising about 1 mg, 5 mg, 10 mg, 25 mg, 30 mg, 50 mg, 80 mg, 100 mg, 200 mg or 250 mg active ingredient. For oral administration, the compositions may be provided in the form of tablets containing 1.0 to 1000 milligrams of the active ingredient, such as 1, 5, 10, 15, 20, 25, 50, 75, 100, 150, 200, 250, 300, 400, 500, 600, 750,
30 800, 900, and 1000 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the subject to be treated. The compounds may be administered on a regimen of 1 to 4 times per day, such as once or twice per day. The compounds may be administered once or multiple times during the day. The compounds may be administered upon awakening or

otherwise in the morning, or during waking hours. For example, the compounds may be administered about 1 hour after awakening, about 30 minutes after awakening or immediately after awakening.

The compounds of the present invention may be used in combination with one or more other drugs in the treatment, prevention, control, amelioration, or reduction of risk of diseases or conditions for which compounds of the present invention or the other drugs may have utility, where the combination of the drugs together are safer or more effective than either drug alone. Such other drug(s) may be administered, by a route and in an amount commonly used therefor, contemporaneously or sequentially with a compound of the present invention. When a compound of the present invention is used contemporaneously with one or more other drugs, a pharmaceutical composition in unit dosage form containing such other drugs and the compound of the present invention is contemplated. However, the combination therapy may also include therapies in which the compound of the present invention and one or more other drugs are administered on different overlapping schedules. It is also contemplated that when used in combination with one or more other active ingredients, the compounds of the present invention and the other active ingredients may be used in lower doses than when each is used singly. Accordingly, the pharmaceutical compositions of the present invention include those that contain one or more other active ingredients, in addition to a compound of the present invention. The above combinations include combinations of a compound of the present invention not only with one other active compound, but also with two or more other active compounds.

The weight ratio of the compound of the present invention to the second active ingredient may be varied and will depend upon the effective dose of each ingredient. Generally, an effective dose of each will be used. Thus, for example, when a compound of the present invention is combined with another agent, the weight ratio of the compound of the present invention to the other agent will generally range from about 1000:1 to about 1:1000, such as about 200:1 to about 1:200. Combinations of a compound of the present invention and other active ingredients will generally also be within the aforementioned range, but in each case, an effective dose of each active ingredient should be used. In such combinations the compound of the present invention and other active agents may be administered separately or in conjunction. In addition, the administration of one element may be prior to, concurrent to, or subsequent to the administration of other agent(s).

The compounds of the present invention may be administered in combination with compounds which are known in the art to be useful for treating or controlling narcolepsy,

including e.g., methylphenidate, amphetamine, pemoline, phenelzine, protriptyline, gamma-hydroxybutyric acid, sodium oxybate, or other oxybate salts, modafinil, armodafinil, caffeine, and salts thereof, and combinations thereof, and the like,

The compounds of the present invention may be administered in combination with
5 compounds which are known in the art to be useful for preventing and treating sleep disorders and sleep disturbances, including e.g., sedatives, hypnotics, anxiolytics, antipsychotics, antianxiety agents, antihistamines, benzodiazepines, barbiturates, cyclopyrrolones, GABA agonists, 5HT-2 antagonists including 5HT-2A antagonists and 5HT-2A/2C antagonists, histamine antagonists including histamine H3 antagonists, histamine H3 inverse agonists,
10 imidazopyridines, minor tranquilizers, melatonin agonists and antagonists, melatonergic agents, orexin antagonists, other orexin agonists, prokineticin agonists and antagonists, pyrazolopyrimidines, T-type calcium channel antagonists, triazolopyridines, and the like, such as: adinazolam, allobarbitol, alonimid, alprazolam, amitriptyline, amobarbital, amoxapine, armodafinil, APD-125, bentazepam, benzocetamine, brotizolam, bupropion, busprione,
15 butabarbital, butalbital, capromorelin, capuride, carbocloral, chloral betaine, chloral hydrate, chlordiazepoxide, clomipramine, clonazepam, cloperidone, clorazepate, clorethate, clozapine, conazepam, cyprazepam, desipramine, dexclamol, diazepam, dichloralphenazone, divalproex, diphenhydramine, doxepin, EMD-281014, eplivanserin, estazolam, eszopiclone, ethchlorinol, etomidate, fenobam, flunitrazepam, flurazepam, fluvoxamine, fluoxetine, fosazepam, gaboxadol,
20 glutethimide, halazepam, hydroxyzine, ibutamoren, imipramine, indiplon, lithium, lorazepam, lormetazepam, LY-156735, maprotiline, MDL-100907, mecloqualone, melatonin, mephobarbital, meprobamate, methaqualone, methypylol, midaflur, midazolam, modafinil, nefazodone, NGD-2-73, nisobamate, nitrazepam, nortriptyline, ornortriptyline, oxazepam, paraldehyde, paroxetine, pentobarbital, perlapine, perphenazine, phenelzine, phenobarbital,
25 prazepam, promethazine, propofol, protriptyline, quazepam, ramelteon, reclazepam, roletamide, secobarbital, sertraline, suproclone, TAK-375, temazepam, thioridazine, tiagabine, tracazolate, tranlycypromaine, trazodone, triazolam, trepipam, tricetamide, triclofos, trifluoperazine, trimetozine, trimipramine, uldazepam, venlafaxine, zaleplon, zolazepam, zopiclone, zolpidem, and salts thereof, and combinations thereof, and the like, or the compound of the present
30 invention may be administered in conjunction with the use of physical methods such as with light therapy or electrical stimulation.

In another embodiment, the subject compound may be employed in combination with other compounds which are known in the art, either administered separately or in the same

pharmaceutical compositions, including, but are not limited to: insulin sensitizers including (i) PPAR γ antagonists such as glitazones (e.g. ciglitazone; darglitazone; englitazone; isaglitazone (MCC-555); pioglitazone; rosiglitazone; troglitazone; tularik; BRL49653; CLX-0921; 5-BTZD), GW-0207, LG-100641, and LY-300512, and the like); (iii) biguanides such as metformin and phenformin; (b) insulin or insulin mimetics, such as biota, LP-100, novarapid, insulin detemir, insulin lispro, insulin glargine, insulin zinc suspension (lente and ultralente); Lys-Pro insulin, GLP-1 (73-7) (insulintropin); and GLP-1 (7-36)-NH₂); (c) sulfonylureas, such as acetohexamide; chlorpropamide; diabinese; glibenclamide; glipizide; glyburide; glimepiride; gliclazide; glipentide; gliquidone; glisolamide; tolazamide; and tolbutamide; (d) α -glucosidase inhibitors, such as acarbose, adiposine; camiglibose; emiglitate; miglitol; voglibose; pradimicin-Q; salbostatin; CKD-711; MDL-25,637; MDL-73,945; and MOR 14, and the like; (e) cholesterol lowering agents such as (i) HMG-CoA reductase inhibitors (atorvastatin, itavastatin, fluvastatin, lovastatin, pravastatin, rivastatin, rosuvastatin, simvastatin, and other statins), (ii) bile acid absorbers/sequestrants, such as cholestyramine, colestipol, dialkylaminoalkyl derivatives of a cross-linked dextran; Colestid $\text{\textregistered}$; LoCholest $\text{\textregistered}$, and the like, (ii) nicotiny alcohol, nicotinic acid or a salt thereof, (iii) proliferator-activator receptor α agonists such as fenofibric acid derivatives (gemfibrozil, clofibrate, fenofibrate and benzaifibrate), (iv) inhibitors of cholesterol absorption such as stanol esters, beta-sitosterol, sterol glycosides such as tiqueside; and azetidinones such as ezetimibe, and the like, and (acyl CoA:cholesterol acyltransferase (ACAT)) inhibitors such as avasimibe, and melinamide, (v) anti-oxidants, such as probucol, (vi) vitamin E, and (vii) thyromimetics; (f) PPAR α agonists such as beclofibrate, benzaifibrate, ciprofibrate, clofibrate, etofibrate, fenofibrate, and gemfibrozil; and other fibric acid derivatives, such as Atromid $\text{\textregistered}$, Lopid $\text{\textregistered}$ and Tricor $\text{\textregistered}$, and the like, and PPAR α agonists as described in WO 97/36579; (g) PPAR δ agonists, such as those disclosed in WO 97/28149; (h) PPAR α/δ agonists, such as muraglitazar, and the compounds disclosed in US 6,414,002; (i) anti-obesity agents, such as (1) growth hormone secretagogues, growth hormone secretagogue receptor agonists/antagonists, such as NN703, hexarelin, MK-0677, SM-130686, CP-424,391, L-692,429, and L-163,255, and such as those disclosed in U.S. Patent Nos. 5,536,716, and 6,358,951, U.S. Patent Application Nos. 2002/049196 and 2002/022637, and PCT Application Nos. WO 01/56592 and WO 02/32888; (2) protein tyrosine phosphatase-1B (PTP-1B) inhibitors; (3) cannabinoid receptor ligands, such as cannabinoid CB₁ receptor antagonists or inverse agonists, such as rimonabant, taranabant, AMT-251, and SR-14778 and SR 141716A (Sanofi Synthelabo), SLV-319 (Solvay),

BAY 65-2520 (Bayer) and those disclosed in U.S. Patent Nos. 5,532,237, 4,973,587, 5,013,837, 5,081,122, 5,112,820, 5,292,736, 5,624,941, 6,028,084, PCT Application Nos. WO 96/33159, WO 98/33765, WO 98/43636, WO 98/43635, WO 01/09120, WO 98/31227, WO 98/41519, WO 98/37061, WO 00/10967, WO 00/10968, WO97/29079, WO99/02499, WO 01/58869, WO 01/64632, WO 01/64633, WO 01/64634, WO 02/076949, WO 03/007887, WO 04/048317, and WO 05/000809; (4) anti-obesity serotonergic agents, such as fenfluramine, dexfenfluramine, phentermine, and sibutramine; (5) β 3-adrenoreceptor agonists, such as AD9677/TAK677 (Dainippon/Takeda), CL-316,243, SB 418790, BRL-37344, L-796568, BMS-196085, BRL-35135A, CGP12177A, BTA-243, Trecadrine, Zeneca D7114, SR 59119A; (6) pancreatic lipase inhibitors, such as orlistat (Xenical®), Triton WR1339, RHC80267, lipstatin, tetrahydrolipstatin, teasaponin, diethylumbelliferyl phosphate, and those disclosed in PCT Application No. WO 01/77094; (7) neuropeptide Y1 antagonists, such as BIBP3226, J-115814, BIBO 3304, LY-357897, CP-671906, GI-264879A, and those disclosed in U.S. Patent No. 6,001,836, and PCT Patent Publication Nos. WO 96/14307, WO 01/23387, WO 99/51600, WO 01/85690, WO 01/85098, WO 01/85173, and WO 01/89528; (8) neuropeptide Y5 antagonists, such as GW-569180A, GW-594884A, GW-587081X, GW-548118X, FR226928, FR 240662, FR252384, 1229U91, GI-264879A, CGP71683A, LY-377897, PD-160170, SR-120562A, SR-120819A and JCF-104, and those disclosed in U.S. Patent Nos. 6,057,335; 6,043,246; 6,140,354; 6,166,038; 6,180,653; 6,191,160; 6,313,298; 6,335,345; 6,337,332; 6,326,375; 6,329,395; 6,340,683; 6,388,077; 6,462,053; 6,649,624; and 6,723,847, European Patent Nos. EP-01010691, and EP-01044970; and PCT International Patent Publication Nos. WO 97/19682, WO 97/20820, WO 97/20821, WO 97/20822, WO 97/20823, WO 98/24768; WO 98/25907; WO 98/25908; WO 98/27063, WO 98/47505; WO 98/40356; WO 99/15516; WO 99/27965; WO 00/64880, WO 00/68197, WO 00/69849, WO 01/09120, WO 01/14376; WO 01/85714, WO 01/85730, WO 01/07409, WO 01/02379, WO 01/02379, WO 01/23388, WO 01/23389, WO 01/44201, WO 01/62737, WO 01/62738, WO 01/09120, WO 02/22592, WO 0248152, and WO 02/49648; WO 02/094825; WO 03/014083; WO 03/10191; WO 03/092889; WO 04/002986; and WO 04/031175; (9) melanin-concentrating hormone (MCH) receptor antagonists, such as those disclosed in WO 01/21577 and WO 01/21169; (10) melanin-concentrating hormone 1 receptor (MCH1R) antagonists, such as T-226296 (Takeda), and those disclosed in PCT Patent Application Nos. WO 01/82925, WO 01/87834, WO 02/051809, WO 02/06245, WO 02/076929, WO 02/076947, WO 02/04433, WO 02/51809, WO 02/083134, WO 02/094799, WO 03/004027; (11) melanin-concentrating hormone 2 receptor (MCH2R) agonist/antagonists; (12) orexin

receptor antagonists, such as SB-334867-A, and those disclosed in patent publications herein; (13) serotonin reuptake inhibitors such as fluoxetine, paroxetine, and sertraline; (14) melanocortin agonists, such as Melanotan II; (15) Mc4r (melanocortin 4 receptor) agonists, such as CHIR86036 (Chiron), ME-10142, and ME-10145 (Melacure), CHIR86036 (Chiron); PT-141, and PT-14 (Palatin); (16) 5HT-2 agonists; (17) 5HT2C (serotonin receptor 2C) agonists, such as BVT933, DPCA37215, WAY161503, R-1065, and those disclosed in U.S. Patent No. 3,914,250, and PCT Application Nos. WO 02/36596, WO 02/48124, WO 02/10169, WO 01/66548, WO 02/44152, WO 02/51844, WO 02/40456, and WO 02/40457; (18) galanin antagonists; (19) CCK agonists; (20) CCK-A (cholecystokinin-A) agonists, such as AR-R 15849, GI 181771, JMV-180, A-71378, A-71623 and SR14613, and those disclosed in U.S. Patent No. 5,739,106; (21) GLP-1 agonists; (22) corticotropin-releasing hormone agonists; (23) histamine receptor-3 (H3) modulators; (24) histamine receptor-3 (H3) antagonists/inverse agonists, such as hioperamide, 3-(1H-imidazol-4-yl)propyl N-(4-pentenyl)carbamate, clobenpropit, iodophenpropit, imoproxifan, GT2394 (Gliatech), and O-[3-(1H-imidazol-4-yl)propanol]-carbamates; (25) β -hydroxy steroid dehydrogenase-1 inhibitors (β -HSD-1); (26) PDE (phosphodiesterase) inhibitors, such as theophylline, pentoxifylline, zaprinast, sildenafil, amrinone, milrinone, cilostamide, rolipram, and cilomilast; (27) phosphodiesterase-3B (PDE3B) inhibitors; (28) NE (norepinephrine) transport inhibitors, such as GW 320659, despiramine, talsupram, and nomifensine; (29) ghrelin receptor antagonists, such as those disclosed in PCT Application Nos. WO 01/87335, and WO 02/08250; (30) leptin, including recombinant human leptin (PEG-OB, Hoffman La Roche) and recombinant methionyl human leptin (Amgen); (31) leptin derivatives; (32) BRS3 (bombesin receptor subtype 3) agonists such as [D-Phe6,beta-Ala11,Phe13,Nle14]Bn(6-14) and [D-Phe6,Phe13]Bn(6-13)propylamide, and those compounds disclosed in Pept. Sci. 2002 Aug; 8(8): 461-75); (33) CNTF (Ciliary neurotrophic factors), such as GI-181771 (Glaxo-SmithKline), SR146131 (Sanofi Synthelabo), butabindide, PD170,292, and PD 149164 (Pfizer); (34) CNTF derivatives, such as axokine (Regeneron); (35) monoamine reuptake inhibitors, such as sibutramine; (36) UCP-1 (uncoupling protein-1), 2, or 3 activators, such as phytanic acid, 4-[(E)-2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)-1-propenyl]benzoic acid (TTNPB), retinoic acid; (37) thyroid hormone β agonists, such as KB-2611 (KaroBioBMS); (38) FAS (fatty acid synthase) inhibitors, such as Cerulenin and C75; (39) DGAT1 (diacylglycerol acyltransferase 1) inhibitors; (40) DGAT2 (diacylglycerol acyltransferase 2) inhibitors; (41) ACC2 (acetyl-CoA carboxylase-2) inhibitors; (42) glucocorticoid antagonists; (43) acyl-estrogens, such as oleoyl-estrone, disclosed in del Mar-Grasa, M. et al., Obesity Research, 9:202-9 (2001); (44) dipeptidyl peptidase IV (DP-

IV) inhibitors, such as isoleucine thiazolidide, valine pyrrolidide, NVP-DPP728, LAF237, P93/01, TSL 225, TMC-2A/2B/2C, FE 999011, P9310/K364, VIP 0177, SDZ 274-444, sitagliptin; and the compounds disclosed in US 6,699,871, WO 03/004498; WO 03/004496; EP 1 258 476; WO 02/083128; WO 02/062764; WO 03/000250; WO 03/002530; WO 03/002531; WO 03/002553; WO 03/002593; WO 03/000180; and WO 03/000181; (46) dicarboxylate transporter inhibitors; (47) glucose transporter inhibitors; (48) phosphate transporter inhibitors; (49) Metformin (Glucophage®); (50) Topiramate (Topimax®); (50) peptide YY, PYY 3-36, peptide YY analogs, derivatives, and fragments such as BIM-43073D, BIM-43004C (Olitvak, D.A. et al., Dig. Dis. Sci. 44(3):643-48 (1999)); (51) Neuropeptide Y2 (NPY2) receptor agonists such NPY3-36, N acetyl [Leu(28,31)] NPY 24-36, TASP-V, and cyclo-(28/32)-Ac-[Lys28-Glu32]-(25-36)-pNPY; (52) Neuropeptide Y4 (NPY4) agonists such as pancreatic peptide (PP), and other Y4 agonists such as 1229U91; (54) cyclooxygenase-2 inhibitors such as etoricoxib, celecoxib, valdecoxib, parecoxib, lumiracoxib, BMS347070, tiracoxib or JTE522, ABT963, CS502 and GW406381; (55) Neuropeptide Y1 (NPY1) antagonists such as BIBP3226, J-115814, BIBO 3304, LY-357897, CP-671906, GI-264879A; (56) Opioid antagonists such as nalmefene (Revex ®), 3-methoxynaltrexone, naloxone, naltrexone; (57) 11 β HSD-1 (11-beta hydroxy steroid dehydrogenase type 1) inhibitors such as BVT 3498, BVT 2733, and those disclosed in WO 01/90091, WO 01/90090, WO 01/90092, US 6,730,690 and US 2004-0133011; (58) aminorex; (59) amphetamine; (60) amphetamine; (61) benzphetamine; (62) chlorphentermine; (63) clobenzorex; (64) cloforex; (65) clominorex; (66) clortermine; (67) cyclexedrine; (68) dextroamphetamine; (69) diphemethoxidine, (70) N-ethylamphetamine; (71) fenbutrazate; (72) fenisorex; (73) fenproporex; (74) fludorex; (75) fluminorex; (76) furfurylmethylamphetamine; (77) levamfetamine; (78) levophacetoperane; (79) mefenorex; (80) metamfepramone; (81) methamphetamine; (82) norpseudoephedrine; (83) pentorex; (84) phendimetrazine; (85) phenmetrazine; (86) picilorex; (87) phytopharm 57; and (88) zonisamide., (89) neuromedin U and analogs or derivatives thereof, (90) oxyntomodulin and analogs or derivatives thereof, and (91) Neurokinin-1 receptor antagonists (NK-1 antagonists) such as the compounds disclosed in: U.S. Patent Nos. 5,162,339, 5,232,929, 5,242,930, 5,373,003, 5,387,595, 5,459,270, 5,494,926, 5,496,833, and 5,637,699.

In another embodiment, the subject compound may be employed in combination with an anti-depressant or anti-anxiety agent, including norepinephrine reuptake inhibitors (including tertiary amine tricyclics and secondary amine tricyclics), selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs), reversible inhibitors of monoamine

oxidase (RIMAs), serotonin and noradrenaline reuptake inhibitors (SNRIs), corticotropin releasing factor (CRF) antagonists, α -adrenoreceptor antagonists, neurokinin-1 receptor antagonists, atypical anti-depressants, benzodiazepines, 5-HT_{1A} agonists or antagonists, especially 5-HT_{1A} partial agonists, and corticotropin releasing factor (CRF) antagonists. Specific agents include: amitriptyline, clomipramine, doxepin, imipramine and trimipramine; amoxapine, desipramine, maprotiline, nortriptyline and protriptyline; citalopram, duloxetine, fluoxetine, fluvoxamine, paroxetine and sertraline; isocarboxazid, phenelzine, tranylcypromine and selegiline; moclobemide; venlafaxine; aprepitant; bupropion, lithium, nefazodone, trazodone and viloxazine; alprazolam, chlordiazepoxide, clonazepam, chlorazepate, diazepam, halazepam, lorazepam, oxazepam and prazepam; buspirone, flesinoxan, gepirone and ipsapirone, and pharmaceutically acceptable salts thereof.

In another embodiment, the subject compound may be employed in combination with anti-Alzheimer's agents; beta-secretase inhibitors, such as verubecestat; gamma-secretase inhibitors; growth hormone secretagogues; recombinant growth hormone; HMG-CoA reductase inhibitors; NSAID's including ibuprofen; vitamin E; anti-amyloid antibodies; CB-1 receptor antagonists or CB-1 receptor inverse agonists; antibiotics such as doxycycline and rifampin; N-methyl-D-aspartate (NMDA) receptor antagonists, such as memantine; cholinesterase inhibitors such as galantamine, rivastigmine, donepezil, and tacrine; growth hormone secretagogues such as ibutamoren, ibutamoren mesylate, and capromorelin; histamine H₃ antagonists; AMPA agonists; PDE IV inhibitors; GABA_A inverse agonists; or neuronal nicotinic agonists.

In another embodiment, the subject compound may be employed in combination with sedatives, hypnotics, anxiolytics, antipsychotics, antianxiety agents, cyclopyrrolones, imidazopyridines, pyrazolopyrimidines, minor tranquilizers, melatonin agonists and antagonists, melatonergic agents, benzodiazepines, barbiturates, 5HT-2 antagonists, and the like, such as: adinazolam, allobarbitol, alonimid, alprazolam, amitriptyline, amobarbital, amoxapine, bentazepam, benzoctamine, brotizolam, bupropion, busprione, butabarbital, butalbital, capuride, carbocloral, chloral betaine, chloral hydrate, chlordiazepoxide, clomipramine, clonazepam, cloperidone, clorazepate, clorethate, clozapine, cyprazepam, desipramine, dexclamol, diazepam, dichloralphenazone, divalproex, diphenhydramine, doxepin, estazolam, ethchlorvynol, etomidate, fenobam, flunitrazepam, flurazepam, fluvoxamine, fluoxetine, fosazepam, glutethimide, halazepam, hydroxyzine, imipramine, lithium, lorazepam, lormetazepam, maprotiline, mecloqualone, melatonin, mephobarbital, meprobamate, methaqualone, midaflur, midazolam,

nefazodone, nisobamate, nitrazepam, nortriptyline, oxazepam, paraldehyde, paroxetine, pentobarbital, perlapine, perphenazine, phenelzine, phenobarbital, prazepam, promethazine, propofol, protriptyline, quazepam, reclazepam, roletamide, secobarbital, sertraline, suproclone, temazepam, thioridazine, tracazolate, tranlycypromaine, trazodone, triazolam, trepipam, 5 tricotamide, triclofos, trifluoperazine, trimetozine, trimipramine, uldazepam, venlafaxine, zaleplon, zolazepam, zolpidem, and salts thereof, and combinations thereof, and the like, or the subject compound may be administered in conjunction with the use of physical methods such as with light therapy or electrical stimulation.

10 In another embodiment, the subject compound may be employed in combination with acetophenazine, alentemol, benzhexol, bromocriptine, biperiden, chlorpromazine, chlorprothixene, clozapine, diazepam, fenoldopam, fluphenazine, haloperidol, levodopa, levodopa with benserazide, levodopa with carbidopa, lisuride, loxapine, mesoridazine, molindolone, naxagolide, olanzapine, pergolide, perphenazine, pimozone, pramipexole, risperidone, sulpiride, tetrabenazine, trihexyphenidyl, thioridazine, thiothixene or trifluoperazine.

15 In another embodiment, the subject compound may be employed in combination with a compound from the phenothiazine, thioxanthene, heterocyclic dibenzazepine, butyrophenone, diphenylbutylpiperidine and indolone classes of neuroleptic agent. Suitable examples of phenothiazines include chlorpromazine, mesoridazine, thioridazine, acetophenazine, fluphenazine, perphenazine and trifluoperazine. Suitable examples of thioxanthenes include 20 chlorprothixene and thiothixene. An example of a dibenzazepine is clozapine. An example of a butyrophenone is haloperidol. An example of a diphenylbutylpiperidine is pimozone. An example of an indolone is molindolone. Other neuroleptic agents include loxapine, sulpiride and risperidone.

25 In another embodiment, the subject compound may be employed in combination with a nicotine agonist or a nicotine receptor partial agonist such as varenicline, opioid antagonists (e.g., naltrexone (including naltrexone depot), antabuse, and nalmefene), dopaminergic agents (e.g., apomorphine), ADD/ADHD agents (e.g., methylphenidate hydrochloride (e.g., Ritalin® and Concerta®), atomoxetine (e.g., Strattera®), a monoamine oxidase inhibitor (MAOI), amphetamines (e.g., Adderall®)) and anti-obesity agents, such as apo- 30 B/MTP inhibitors, 11Beta-hydroxy steroid dehydrogenase-1 (11Beta-HSD type 1) inhibitors, peptide YY3-36 or analogs thereof, MCR-4 agonists, CCK-A agonists, monoamine reuptake inhibitors, sympathomimetic agents, β 3 adrenergic receptor agonists, dopamine receptor agonists, melanocyte-stimulating hormone receptor analogs, 5-HT2c receptor agonists, melanin

concentrating hormone receptor antagonists, leptin, leptin analogs, leptin receptor agonists, galanin receptor antagonists, lipase inhibitors, bombesin receptor agonists, neuropeptide-Y receptor antagonists (e.g., NPY Y5 receptor antagonists), thyromimetic agents, dehydroepiandrosterone or analogs thereof, glucocorticoid receptor antagonists, orexin receptor antagonists, such as suvorexant, other orexin agonists, glucagon-like peptide-1 receptor agonists, ciliary neurotrophic factors, human agouti-related protein antagonists, ghrelin receptor antagonists, histamine 3 receptor antagonists or inverse agonists, and neuromedin U receptor agonists, and pharmaceutically acceptable salts thereof.

In another embodiment, the subject compound may be employed in combination with an agent such as aminorex, amphetamine, amphetamine, benzphetamine, chlorphentermine, clobenzorex, cloforex, clominorex, clortermine, cyclohexedrine, dexfenfluramine, dextroamphetamine, diethylpropion, diphenmethoxidine, N-ethylamphetamine, fenbutrazate, fenfluramine, fenisorex, fenproporex, fludorex, fluminorex, furfurylmethylamphetamine, levamphetamine, levophacetoperane, mazindol, mefenorex, metamfepramone, methamphetamine, norpseudoephedrine, pentorex, phendimetrazine, phenmetrazine, phentermine, phenylpropanolamine, picilorex and sibutramine; selective serotonin reuptake inhibitor (SSRI); halogenated amphetamine derivatives, including chlorphentermine, cloforex, clortermine, dexfenfluramine, fenfluramine, picilorex and sibutramine; and pharmaceutically acceptable salts thereof.

In another embodiment, the subject compound may be employed in combination with an opiate agonist, a lipoxygenase inhibitor, such as an inhibitor of 5-lipoxygenase, a cyclooxygenase inhibitor, such as a cyclooxygenase-2 inhibitor, an interleukin inhibitor, such as an interleukin-1 inhibitor, an NMDA antagonist, an inhibitor of nitric oxide or an inhibitor of the synthesis of nitric oxide, a non-steroidal antiinflammatory agent, or a cytokine-suppressing antiinflammatory agent, for example with a compound such as acetaminophen, aspirin, codiene, fentanyl, ibuprofen, indomethacin, ketorolac, morphine, naproxen, phenacetin, piroxicam, a steroidal analgesic, sufentanyl, sunlindac, tenidap, and the like. Similarly, the subject compound may be administered with a pain reliever; a potentiator such as caffeine, an H2-antagonist, simethicone, aluminum or magnesium hydroxide; a decongestant such as phenylephrine, phenylpropanolamine, pseudoephedrine, oxymetazoline, ephinephrine, naphazoline, xylometazoline, propylhexedrine, or levo-desoxy-ephedrine; an antiitussive such as codeine, hydrocodone, caramiphen, carbetapentane, or dexamethorphan; a diuretic; and a sedating or non-sedating antihistamine.

The compounds of the present invention may be administered by oral, parenteral (e.g., intramuscular, intraperitoneal, intravenous, ICV, intracisternal injection or infusion, subcutaneous injection, or implant), by inhalation spray, nasal, vaginal, rectal, sublingual, or topical routes of administration and may be formulated, alone or together, in suitable dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles appropriate for each route of administration. In addition to the treatment of warm-blooded animals such as mice, rats, horses, cattle, sheep, dogs, cats, monkeys, etc., the compounds of the invention may be effective for use in humans.

The pharmaceutical compositions for the administration of the compounds of this invention may conveniently be presented in dosage unit form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the active ingredient into association with the carrier which constitutes one or more accessory ingredients. In general, the pharmaceutical compositions are prepared by uniformly and intimately bringing the active ingredient into association with a liquid carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired formulation. In the pharmaceutical composition the active object compound is included in an amount sufficient to produce the desired effect upon the process or condition of diseases. As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

Pharmaceutical compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. Compositions for oral use may also be presented as hard gelatin capsules

wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil. Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Oily suspensions may be formulated by suspending the active ingredient in a suitable oil. Oil-in-water emulsions may also be employed. Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Pharmaceutical compositions of the present compounds may be in the form of a sterile injectable aqueous or oleagenous suspension. The compounds of the present invention may also be administered in the form of suppositories for rectal administration. For topical use, creams, ointments, jellies, solutions or suspensions, etc., containing the compounds of the present invention may be employed. The compounds of the present invention may also be formulated for administered by inhalation. The compounds of the present invention may also be administered by a transdermal patch by methods known in the art.

Several methods for preparing the compounds of this invention are illustrated in the following Schemes and Examples. Starting materials are made according to procedures known in the art or as illustrated herein. The following abbreviations are used herein: Me: methyl; Et: ethyl; t-Bu: *tert*-butyl; Ar: aryl; Ph: phenyl; Bn: benzyl; Ac: acetyl; ACN: acetonitrile; DAST: Diethylaminosulfur trifluoride; DCM (CH₂Cl₂): dichloromethane; DIPEA: N,N-diisopropylethylamine; DMA: N,N-dimethylacetamide; DMAP: 4-dimethylaminopyridine; DMF: N,N-dimethylformamide; DMSO: dimethylsulfoxide; DPPF: 1,1'-Bis(diphenylphosphino)ferrocene; DTBM-SEPHOS: 5,5'-Bis[di(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphino]-4,4'-bi-1,3-benzodioxole, [(4R)-(4,4'-bi-1,3-benzodioxole)-5,5'-diyl]bis[bis(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphine]; EA: Ethyl acetate; EDC: N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide; Et₃N: triethylamine; EtOAc: ethyl acetate; EtOH: ethanol; Et₃N: Triethylamine; h: hour(s); HABT: 1-Hydroxy-7-azabenzotriazole; HATU: (1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate; HCl: hydrogen chloride; HOBt: hydroxybenzotriazole hydrate; HPLC: high performance liquid chromatography; [IR(DTBBPY)(PPY)₂]PF₆: [4,4'-Bis(1,1-dimethylethyl)-2,2'-bipyridine-N1,N1']bis[2-(2-pyridinyl-N)phenyl-C]iridium(III) hexafluorophosphate; LCMS: Liquid chromatography-mass spectrometry; LDA: Lithium diisopropylamide; LRMS: Low resolution Mass Spectrometer; MeOH: methanol; MgSO₄:

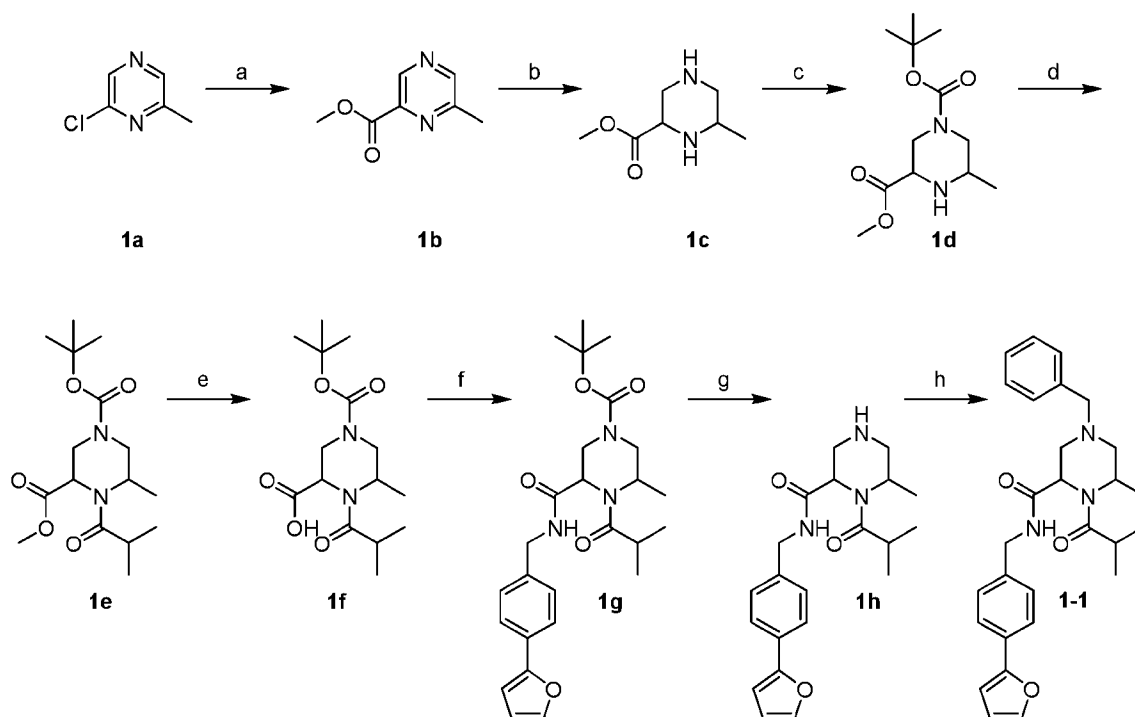
magnesium sulfate; Ms: methanesulfonyl; MsCl: methanesulfonyl chloride; MTBE: Methyl tertiary-butyl ether; NaHMDS: Sodium bis(trimethylsilyl)amide; [Ni(dtbbpy)(H₂O)₄]Cl₂: Nickel(2+), tetraaqua[4,4'-bis(1,1-dimethylethyl)-2,2'-bipyridine-κN1,κN1']-, chloride (1:2); Pd(OAc)₂: Palladium(II) acetate; PE: Petroleum ether; PSI: Pressurized sample infusion; R-DTBM-SEGPPOS: (R)-(-)-5,5'-Bis[di(3,5-di-tert-butyl-4-methoxyphenyl)phosphino]-4,4'-bi-1,3-benzodioxole, [(4R)-(4,4'-bi-1,3-benzodioxole)-5,5'-diyl]bis[bis(3,5-di-tert-butyl-4-methoxyphenyl)phosphine]; S-DTBM-SEGPPOS: (S)-(+)-5,5'-Bis[di(3,5-di-tert-butyl-4-methoxyphenyl)phosphino]-4,4'-bi-1,3-benzodioxole; SOCl₂: thionyl chloride; SFC: supercritical fluid chromatography; TBAF: Tetra-n-butylammonium fluoride; TBDMS-Cl: Tert-butyl dimethylsilyl chloride; TEA: triethylamine; THF: tetrahydrofuran; TFA: trifluoroacetic acid; TLC: Thin-layer chromatography; TMS-CF₃: Trifluoromethyltrimethylsilane.

The compounds of the present invention can be prepared in a variety of fashions. In some cases the final product may be further modified, for example, by manipulation of substituents. These manipulations may include, but are not limited to, reduction, oxidation, alkylation, acylation, and hydrolysis reactions which are commonly known to those skilled in the art. In some cases the order of carrying out the foregoing reaction schemes may be varied to facilitate the reaction or to avoid unwanted reaction products. The following examples are provided so that the invention might be more fully understood. These examples are illustrative only and should not be construed as limiting the invention in any way.

20

EXAMPLES

EXAMPLE 1



Preparation of cis-4-benzyl-N-(4-(furan-2-yl)benzyl)-1-isobutyryl-6-methylpiperazine-2-carboxamide (1-1)

- Step 1: Preparation of methyl 6-methylpyrazine-2-carboxylate (**1b**) To 2-chloro-6-methylpyrazine (**1a**, 50.0 g, 388.9 mmol) in MeOH (750 mL) was added triethylamine (81.2 mL, 583 mmol), DPPF (6.50 g, 11.7 mmol), and Pd(OAc)₂ (2.60 g, 11.7 mmol). The reaction vessel was charged with carbon monoxide and heated to 80°C for 16 hrs at 50PSI CO. The reactions were combined and the mixture was filtered through celite and concentrated. The crude material was taken up in ethyl acetate and filtered again. Flash column purification using a 0-25% Ethyl acetate/Petroleum ether gradient gave methyl 6-methylpyrazine-2-carboxylate (**1b**).
- Step 2: Preparation of cis-methyl 6-methylpiperazine-2-carboxylate (**1c**) To methyl 6-methylpyrazine-2-carboxylate (**1b**, 50.0 g, 328 mmol) and PtO₂ (5.0 g, 22 mmol) in MeOH (500 mL) was added 4M HCl in methanol (205 mL). The reaction vessel was charged with hydrogen and heated to 50°C for 16 hrs at 50PSI hydrogen. The reactions were combined and the mixture was filtered through celite and concentrated. The crude material was used directly in the next step - cis-methyl 6-methylpiperazine-2-carboxylate (**1c**).
- Step 3: Preparation of cis-1-(tert-butyl) 3-methyl 5-methylpiperazine-1,3-dicarboxylate (**1d**) To a solution of cis-methyl 6-methylpiperazine-2-carboxylate (**1c**, 160 g, 692 mmol) in MeOH/H₂O (0.8/0.8 L) was added tert-butoxycarbonyl tert-butyl carbonate (151.1 g, 692 mmol) and

triethylamine (96.4 mL, 692 mmol) and the resulting mixture was stirred 16hrs at room temperature. The reactions were combined and concentrated. The crude material was purified by flash column purification using a 0-50% Ethyl acetate/Petroleum ether gradient to give cis-1-(tert-butyl) 3-methyl 5-methylpiperazine-1,3-dicarboxylate (**1d**).

- 5 Step 4: Preparation of cis-1-(tert-butyl) 3-methyl 4-isobutyryl-5-methylpiperazine-1,3-dicarboxylate (**1e**) To a stirred solution of cis-1-(tert-butyl) 3-methyl 5-methylpiperazine-1,3-dicarboxylate (**1d**, 3.0 g, 11.61 mmol) in DCM (33.2 mL) was added triethylamine (3.24 mL, 23.2 mmol) and isobutyryl chloride (1.34 mL, 12.78 mmol). The resulting solution was stirred at room temperature for 30min, washed with 1N HCl solution, dried over sodium sulfate and
10 concentrated to give crude cis-1-(tert-butyl) 3-methyl 4-isobutyryl-5-methylpiperazine-1,3-dicarboxylate (**1e**). LRMS (ES) (M+H)⁺: observed = 329.3, calculated = 328.4.

- Step 5: Preparation of cis-4-(tert-butoxycarbonyl)-1-isobutyryl-6-methylpiperazine-2-carboxylic acid (**1f**) A stirred solution of cis-1-(tert-butyl) 3-methyl 4-isobutyryl-5-methylpiperazine-1,3-dicarboxylate (**1e**, 3.81 g, 11.61 mmol) in THF (39 mL) was chilled in an ice bath to 0°C. To this
15 was added potassium trimethylsilanolate (3.64 g, 25.5 mmol) and the resulting solution was stirred at 0°C for two hours. The reaction was quenched using 1N HCl solution and extracted several times with ethyl acetate. The organic layers were combined and dried over sodium sulfate and concentrated to give cis-4-(tert-butoxycarbonyl)-1-isobutyryl-6-methylpiperazine-2-carboxylic acid (**1f**).

- 20 Step 6: Preparation of cis-tert-butyl 3-((4-(furan-2-yl)benzyl)carbamoyl)-4-isobutyryl-5-methylpiperazine-1-carboxylate (**1g**) To a stirred solution of cis-4-(tert-butoxycarbonyl)-1-isobutyryl-6-methylpiperazine-2-carboxylic acid (**1f**, 1.0 g, 3.18 mmol) and (4-(furan-2-yl)phenyl)methanamine (0.72 g, 4.14 mmol) in DCM (9.0 mL) was added HBT (0.48 g, 3.50 mmol) and EDC (0.73 g, 3.82 mmol). The resulting mixture was stirred 1 hour, then washed with
25 1N HCl solution and concentrated. Flash column purification using a 0-50% ethyl acetate/hexane gradient gave cis-tert-butyl 3-((4-(furan-2-yl)benzyl)carbamoyl)-4-isobutyryl-5-methylpiperazine-1-carboxylate (**1g**).

- Step 7: Preparation of cis-N-(4-(furan-2-yl)benzyl)-1-isobutyryl-6-methylpiperazine-2-carboxamide (**1h**) To a stirred solution of cis-tert-butyl 3-((4-(furan-2-yl)benzyl)carbamoyl)-4-isobutyryl-5-methylpiperazine-1-carboxylate (**1g**, 1.49 g, 3.18 mmol) in Ethyl acetate (15.0 mL)
30 was chilled in an ice bath to 0°C and saturated with HCl gas. The resulting mixture was stirred for 2 hours and concentrated to give cis-N-(4-(furan-2-yl)benzyl)-1-isobutyryl-6-

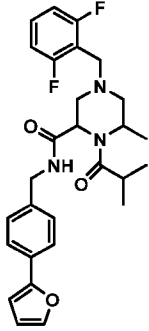
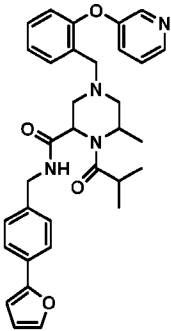
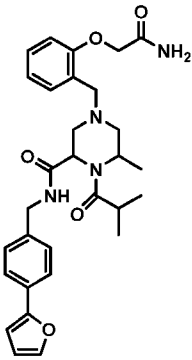
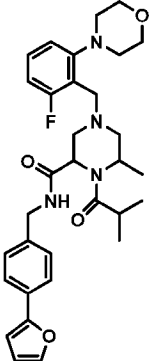
methylpiperazine-2-carboxamide (**1h**) as an HCl salt. LRMS (ES) (M+H)⁺: observed = 370.3, calculated = 369.4.

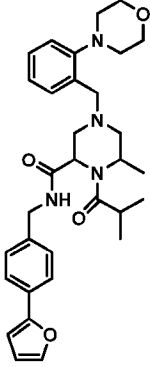
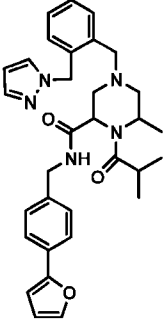
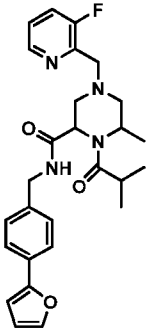
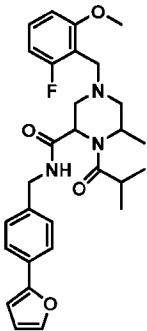
- Step 8: Preparation of cis-4-benzyl-N-(4-(furan-2-yl)benzyl)-1-isobutyryl-6-methylpiperazine-2-carboxamide (**1-1**) To a stirred solution of cis-N-(4-(furan-2-yl)benzyl)-1-isobutyryl-6-methylpiperazine-2-carboxamide (**1h**, 0.035 g, 0.086 mmol) in DCM (0.5 mL) was added benzaldehyde (0.011 g, 0.10 mmol) and sodium triacetoxyborohydride (0.037 g, 0.17 mmol). The resulting mixture was stirred at room temperature for 30 minutes and concentrated. The crude material was purified by reverse phase purification to give cis-4-benzyl-N-(4-(furan-2-yl)benzyl)-1-isobutyryl-6-methylpiperazine-2-carboxamide (**1-1**). LRMS (ES) (M+H)⁺: observed = 460.4, calculated = 459.6.

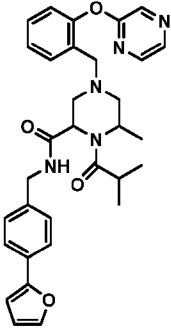
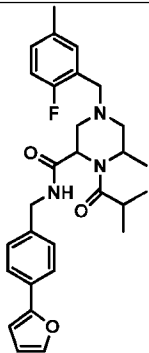
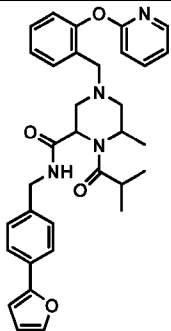
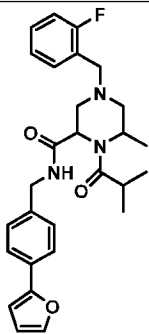
The following compounds were prepared in an analogous manner to example **1-1**.

Table 1

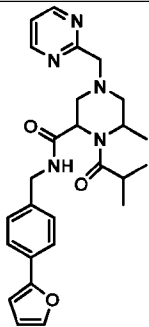
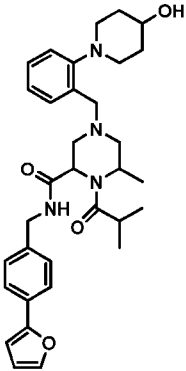
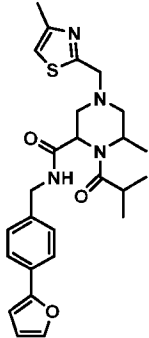
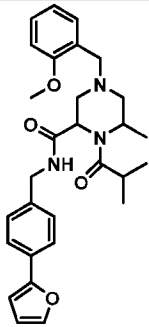
Example	Structure	Name	Calculated Mass	Observed Mass (M+H)
1-2		(2R,6R)-N-([4-(furan-2-yl)phenyl]methyl)-6-methyl-1-(2-methylpropanoyl)-4-{[2-(morpholin-4-yl)phenyl]methyl}piperazine-2-carboxamide	544.7	545.5
1-3		N-([4-(furan-2-yl)phenyl]methyl)-6-methyl-1-(2-methylpropanoyl)-4-[(2-phenoxyphenyl)methyl]piperazine-2-carboxamide	551.692	552.5

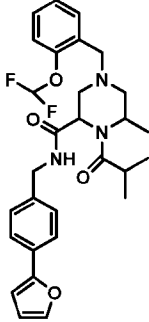
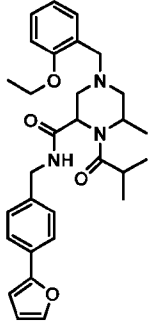
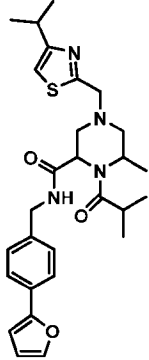
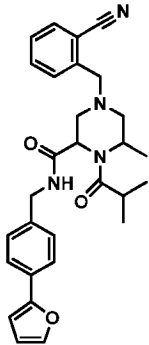
1-4		4-[(2,6-difluorophenyl)methyl]-N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide	495.574	496.1
1-5		N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)-4-({2-[(pyridin-3-yl)oxy]phenyl}methyl)piperazine-2-carboxamide	552.679	553.5
1-6		4-{[2-(2-amino-2-oxoethoxy)phenyl]methyl}-N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide	532.645	533.5
1-7		4-{[2-fluoro-6-(morpholin-4-yl)phenyl]methyl}-N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide	562.69	563.5

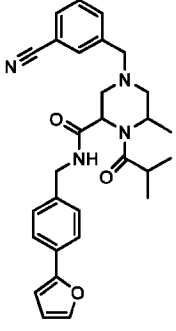
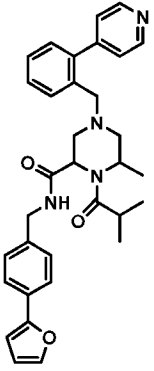
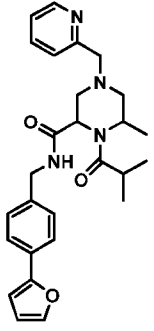
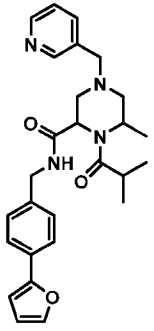
1-8		N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)-4-{[2-(morpholin-4-yl)phenyl]methyl}piperazine-2-carboxamide	544.7	545.1
1-9		N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)-4-({2-[(1H-pyrazol-1-yl)methyl]phenyl}methyl)piperazine-2-carboxamide	539.683	540.1
1-10		4-[(3-fluoropyridin-2-yl)methyl]-N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide	478.572	479
1-11		4-[(2-fluoro-6-methoxyphenyl)methyl]-N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide	507.61	508.1

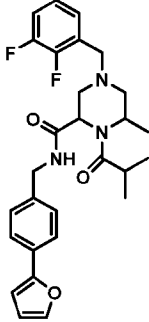
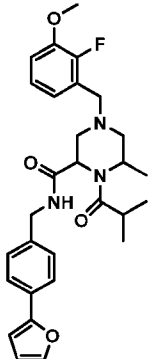
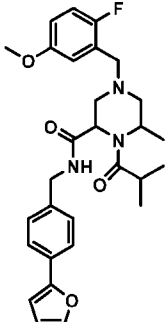
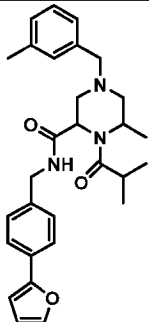
1-12		N-{{4-(furan-2-yl)phenyl}methyl}-6-methyl-1-(2-methylpropanoyl)-4-((2-[(pyrazin-2-yl)oxy]phenyl)methyl)piperazine-2-carboxamide	553.667	554.5
1-13		4-[(2-fluoro-5-methylphenyl)methyl]-N-{{4-(furan-2-yl)phenyl}methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide	491.611	492.1
1-14		N-{{4-(furan-2-yl)phenyl}methyl}-6-methyl-1-(2-methylpropanoyl)-4-((2-[(pyridin-2-yl)oxy]phenyl)methyl)piperazine-2-carboxamide	552.679	553.5
1-15		4-[(2-fluorophenyl)methyl]-N-{{4-(furan-2-yl)phenyl}methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide	477.584	478.1

1-16		N-{[4-(furan-2-yl)phenyl]methyl}-4-{[2-(2-methoxyethoxy)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide	533.674	534.5
1-17		N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)-4-{[2-(2,2,2-trifluoroethoxy)phenyl]methyl}piperazine-2-carboxamide	557.618	557.6
1-18		N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)-4-({2-[(oxolan-2-yl)methoxy]phenyl}methyl)piperazine-2-carboxamide	559.712	560.6
1-19		4-[(2-chloro-6-fluorophenyl)methyl]-N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide	512.029	512

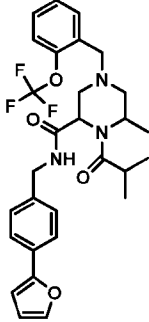
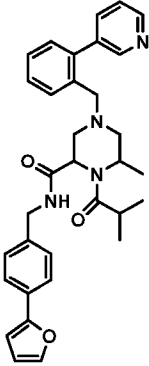
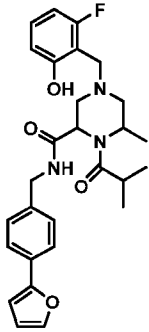
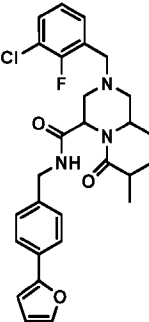
1-20		N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)-4-[(pyrimidin-2-yl)methyl]piperazine-2-carboxamide	461.569	462
1-21		N-{[4-(furan-2-yl)phenyl]methyl}-4-{[2-(4-hydroxypiperidin-1-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide	558.727	559.5
1-22		N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)-4-[(4-methyl-1,3-thiazol-2-yl)methyl]piperazine-2-carboxamide	480.634	481
1-23		N-{[4-(furan-2-yl)phenyl]methyl}-4-[(2-methoxyphenyl)methyl]-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide	489.62	490.1

1-24		4-([2-(difluoromethoxy)phenyl]methyl)-N-([4-(furan-2-yl)phenyl]methyl)-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide	525.601	526.1
1-25		4-([2-(ethoxyphenyl)methyl]-N-([4-(furan-2-yl)phenyl]methyl)-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide	503.647	504.1
1-26		N-([4-(furan-2-yl)phenyl]methyl)-6-methyl-1-(2-methylpropanoyl)-4-([4-(propan-2-yl)-1,3-thiazol-2-yl]methyl)piperazine-2-carboxamide	508.688	509.1
1-27		4-([2-(cyanophenyl)methyl]-N-([4-(furan-2-yl)phenyl]methyl)-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide	484.603	485.1

1-28		4-[(3-cyanophenyl)methyl]-N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide	484.603	485.1
1-29		N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)-4-{[2-(pyridin-4-yl)phenyl]methyl}piperazine-2-carboxamide	536.68	537.5
1-30		N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)-4-[(pyridin-2-yl)methyl]piperazine-2-carboxamide	460.581	461
1-31		N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)-4-[(pyridin-3-yl)methyl]piperazine-2-carboxamide	460.581	461

1-32		4-[(2,3-difluorophenyl)methyl]-N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide	495.574	496.1
1-33		4-[(2-fluoro-3-methoxyphenyl)methyl]-N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide	507.61	508.1
1-34		4-[(2-fluoro-5-methoxyphenyl)methyl]-N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide	507.61	508.1
1-35		N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-4-[(3-methylphenyl)methyl]-1-(2-methylpropanoyl)piperazine-2-carboxamide	473.621	474.1

1-36		N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)-4-{[2-(1H-1,2,4-triazol-1-yl)phenyl]methyl}piperazine-2-carboxamide	526.644	527.5
1-37		N-{[4-(furan-2-yl)phenyl]methyl}-4-[(3-methoxyphenyl)methyl]-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide	489.62	490.1
1-38		4-[(3-fluorophenyl)methyl]-N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide	477.584	478.1
1-39		4-[(4-fluorophenyl)methyl]-N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide	477.584	478.1

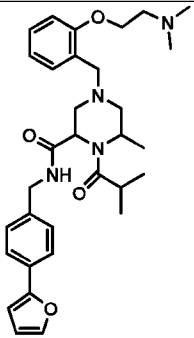
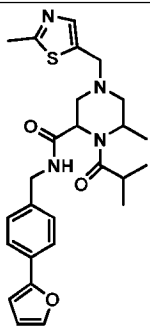
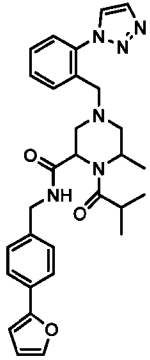
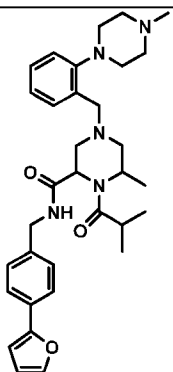
1-40		N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)-4-{[2-(trifluoromethoxy)phenyl]methyl}piperazine-2-carboxamide	543.591	544
1-41		N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)-4-{[2-(pyridin-3-yl)phenyl]methyl}piperazine-2-carboxamide	536.68	537.5
1-42		4-[(2-fluoro-6-hydroxyphenyl)methyl]-N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide	493.583	494.1
1-43		4-[(3-chloro-2-fluorophenyl)methyl]-N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide	512.029	512

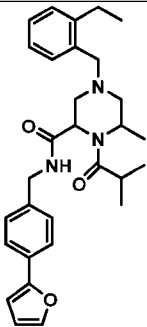
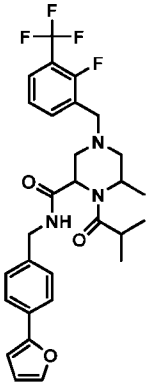
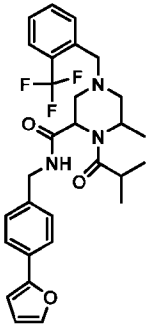
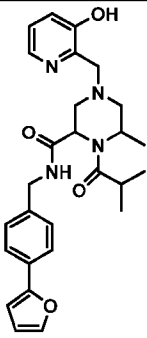
1-44		4-[(2-cyclopropylphenyl)methyl]-N-[[4-(furan-2-yl)phenyl]methyl]-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide	499.659	500.1
1-45		4-[[2-(cyanomethyl)phenyl]methyl]-N-[[4-(furan-2-yl)phenyl]methyl]-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide	498.63	499.5
1-46		N-[[4-(furan-2-yl)phenyl]methyl]-6-methyl-1-(2-methylpropanoyl)-4-[[2-(pyrimidin-5-yl)phenyl]methyl]piperazine-2-carboxamide	537.667	538.5
1-47		N-[[4-(furan-2-yl)phenyl]methyl]-4-[(2-hydroxyphenyl)methyl]-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide	475.593	476.1

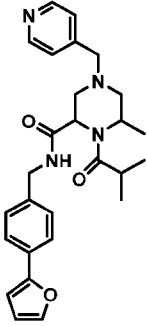
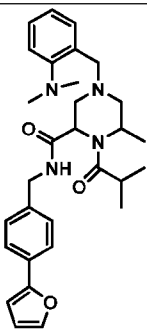
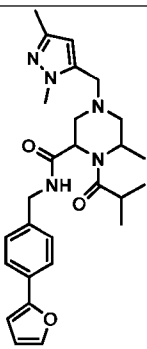
1-48		N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)-4-[(5-methyl-1,3-thiazol-2-yl)methyl]piperazine-2-carboxamide	480.634	481
1-49		4-{[3-(dimethylamino)phenyl]methyl}-N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide	502.662	503.1
1-50		4-[(3-fluoropyridin-4-yl)methyl]-N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide	478.572	479
1-51		4-{[2-fluoro-5-(trifluoromethyl)phenyl]methyl}-N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide	545.582	546

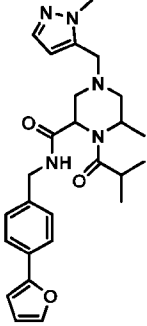
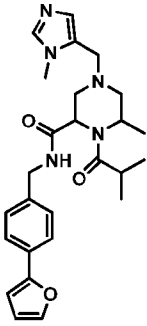
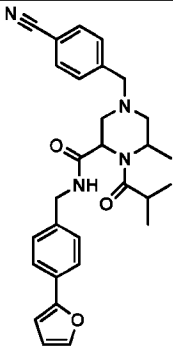
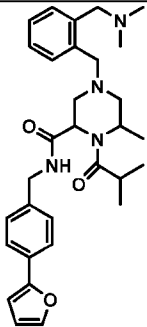
1-52		N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)-4-{[2-(1H-pyrazol-1-yl)phenyl]methyl}piperazine-2-carboxamide	525.656	526.5
1-53		4-{[2-(difluoromethyl)phenyl]methyl}-N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide	509.601	510
1-54		N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)-4-{[2-(piperidin-1-yl)phenyl]methyl}piperazine-2-carboxamide	542.728	543.6
1-55		N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)-4-{[2-(pyrrolidin-1-yl)phenyl]methyl}piperazine-2-carboxamide	528.701	529.5

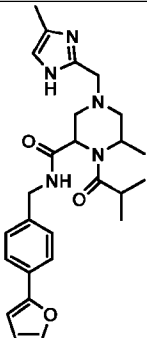
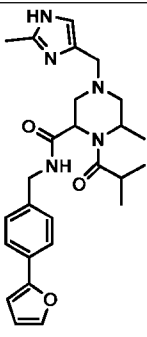
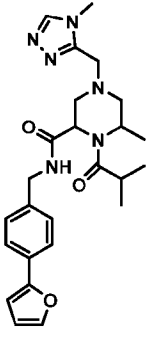
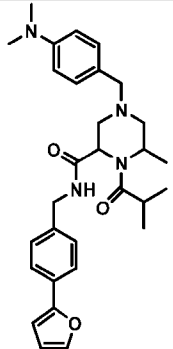
1-56		N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-4-[(3-methyl-1,2-oxazol-5-yl)methyl]-1-(2-methylpropanoyl)piperazine-2-carboxamide	464.569	465
1-57		N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)-4-[(5-methyl-1H-pyrazol-3-yl)methyl]piperazine-2-carboxamide	463.585	464.1
1-58		N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-4-[(2-methylphenyl)methyl]-1-(2-methylpropanoyl)piperazine-2-carboxamide	473.621	474.1
1-59		N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)-4-({2-[(morpholin-4-yl)methyl]phenyl}methyl)piperazine-2-carboxamide	558.727	559.6

1-60		4-({2-[2-(dimethylamino)ethoxy]phenyl}methyl)-N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide	546.716	547.6
1-61		N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)-4-[(2-methyl-1,3-thiazol-5-yl)methyl]piperazine-2-carboxamide	480.634	481
1-62		N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)-4-{[2-(1H-1,2,3-triazol-1-yl)phenyl]methyl}piperazine-2-carboxamide	526.644	527.5
1-63		N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-4-{[2-(4-methylpiperazin-1-yl)phenyl]methyl}-1-(2-methylpropanoyl)piperazine-2-carboxamide	557.742	558.6

1-64		4-[(2-ethylphenyl)methyl]-N-{{[4-(furan-2-yl)phenyl]methyl}}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide	487.648	488.1
1-65		4-{{[2-fluoro-3-(trifluoromethyl)phenyl]methyl}}-N-{{[4-(furan-2-yl)phenyl]methyl}}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide	545.582	546
1-66		N-{{[4-(furan-2-yl)phenyl]methyl}}-6-methyl-1-(2-methylpropanoyl)-4-{{[2-(trifluoromethyl)phenyl]methyl}}piperazine-2-carboxamide	527.592	528
1-67		N-{{[4-(furan-2-yl)phenyl]methyl}}-4-[[3-hydroxypyridin-2-yl)methyl]-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide	476.58	477.1

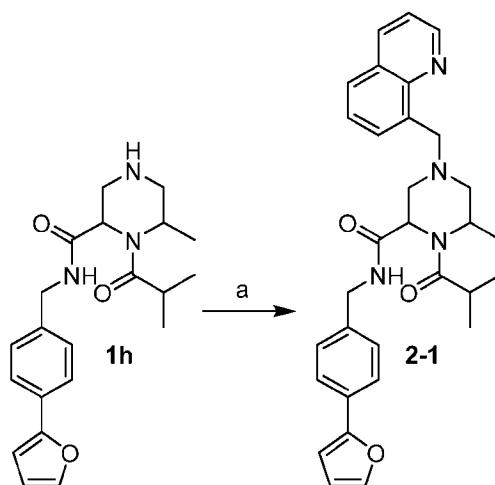
1-68		4-[(5-cyano-2-fluorophenyl)methyl]-N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide	502.594	503.1
1-69		N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)-4-[(pyridin-4-yl)methyl]piperazine-2-carboxamide	460.581	461
1-70		4-{[2-(dimethylamino)phenyl]methyl}-N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide	502.662	503.1
1-71		4-[(1,3-dimethyl-1H-pyrazol-5-yl)methyl]-N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide	477.612	478.1

1-72		N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)-4-[(1-methyl-1H-pyrazol-5-yl)methyl]piperazine-2-carboxamide	463.585	464
1-73		N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-4-[(1-methyl-1H-imidazol-5-yl)methyl]-1-(2-methylpropanoyl)piperazine-2-carboxamide	463.585	464
1-74		4-[(4-cyanophenyl)methyl]-N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide	484.603	485.1
1-75		4-({2-[(dimethylamino)methyl]phenyl}methyl)-N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide	516.689	517.1

1-76		N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-4-[(4-methyl-1H-imidazol-2-yl)methyl]-1-(2-methylpropanoyl)piperazine-2-carboxamide	463.585	464.1
1-77		N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-4-[(2-methyl-1H-imidazol-4-yl)methyl]-1-(2-methylpropanoyl)piperazine-2-carboxamide	463.585	464
1-78		N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)-4-[(4-methyl-4H-1,2,4-triazol-3-yl)methyl]piperazine-2-carboxamide	464.572	465
1-79		4-{[4-(dimethylamino)phenyl]methyl}-N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide	502.662	503.1

1-80		N-{[4-(furan-2-yl)phenyl]methyl}-4-[(4-methoxyphenyl)methyl]-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide	489.62	490.1
1-81		N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-4-[(4-methylphenyl)methyl]-1-(2-methylpropanoyl)piperazine-2-carboxamide	473.621	474.4

EXAMPLE 2

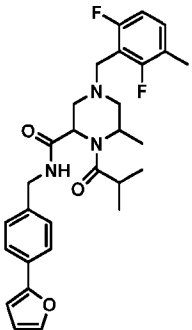
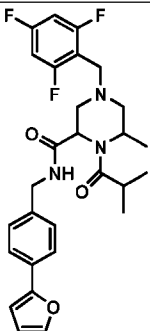
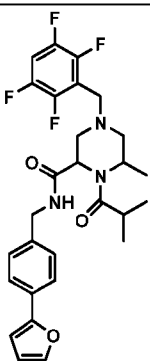


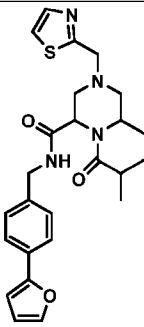
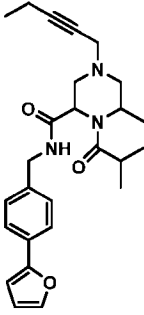
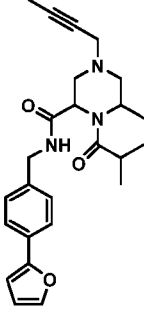
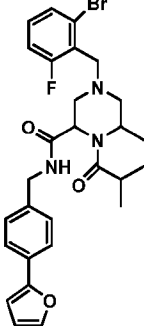
Preparation of cis-N-(4-(furan-2-yl)benzyl)-1-isobutyryl-6-methyl-4-(quinolin-8-ylmethyl)piperazine-2-carboxamide (**2-1**)

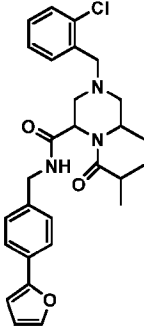
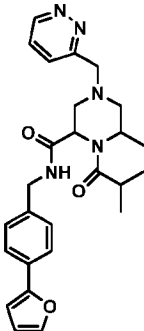
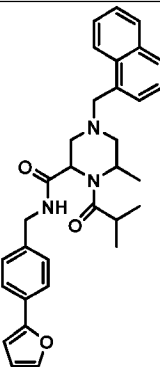
Step 1: To a stirred solution of cis-N-(4-(furan-2-yl)benzyl)-1-isobutyryl-6-methylpiperazine-2-carboxamide (**1h**, 0.02 g, 0.049 mmol) in DMF (0.5 mL) was added 8-(bromomethyl)quinoline (0.014 g, 0.10 mmol), Potassium iodide (0.008 g, 0.049 mmol), and triethylamine (0.021 mL, 0.15 mmol). The resulting mixture was stirred at room temperature overnight. The crude material

was purified by reverse phase purification to give cis-N-(4-(furan-2-yl)benzyl)-1-isobutyryl-6-methyl-4-(quinolin-8-ylmethyl)piperazine-2-carboxamide (**2-1**, 0.0045 g, 18%). LRMS (ES) (M+H)⁺: observed = 511.1, calculated = 510.6.

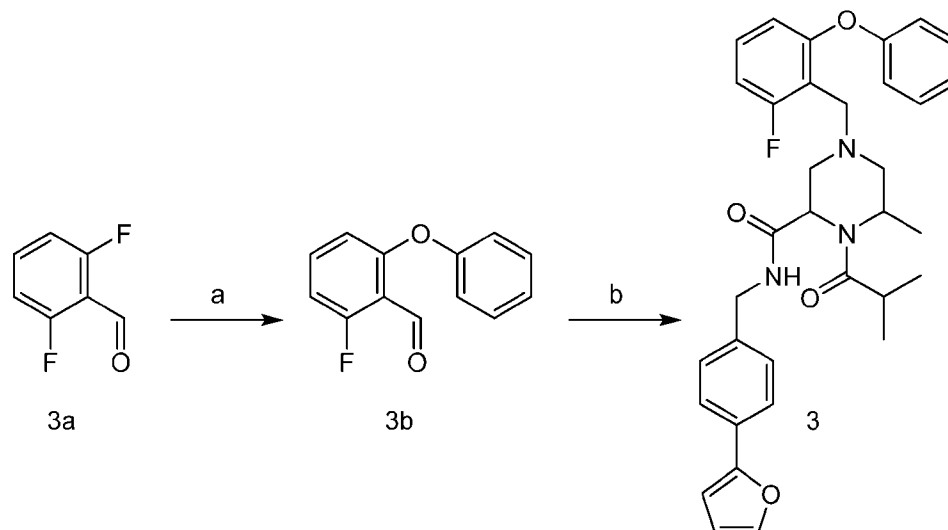
The following compounds were prepared in an analogous manner to example **2-1**.

Ex No	Structure	Name	Calc'd Mass	Observed Mass (M+H)
2-2		4-[(2,6-difluoro-3-methylphenyl)methyl]-N-[[4-(furan-2-yl)phenyl]methyl]-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide	509.601	510.4
2-3		N-[[4-(furan-2-yl)phenyl]methyl]-6-methyl-1-(2-methylpropanoyl)-4-[(2,4,6-trifluorophenyl)methyl]piperazine-2-carboxamide	513.565	514.1
2-4		N-[[4-(furan-2-yl)phenyl]methyl]-6-methyl-1-(2-methylpropanoyl)-4-[(2,3,5,6-tetrafluorophenyl)methyl]piperazine-2-carboxamide	531.555	532.1

2-5		N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)-4-[(1,3-thiazol-2-yl)methyl]piperazine-2-carboxamide	466.607	467.1
2-6		N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)-4-(pent-2-yn-1-yl)piperazine-2-carboxamide	435.571	436.1
2-7		4-(but-2-yn-1-yl)-N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide	421.544	422
2-8		4-[(2-bromo-6-fluorophenyl)methyl]-N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide	556.48	557.3

2-9		4-[(2-chlorophenyl)methyl]-N-{{[4-(furan-2-yl)phenyl]methyl}}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide	494.039	494.1
2-10		N-{{[4-(furan-2-yl)phenyl]methyl}}-6-methyl-1-(2-methylpropanoyl)-4-[(pyridazin-3-yl)methyl]piperazine-2-carboxamide	461.569	462.1
2-11		N-{{[4-(furan-2-yl)phenyl]methyl}}-6-methyl-1-(2-methylpropanoyl)-4-[(naphthalen-1-yl)methyl]piperazine-2-carboxamide	509.654	510.1

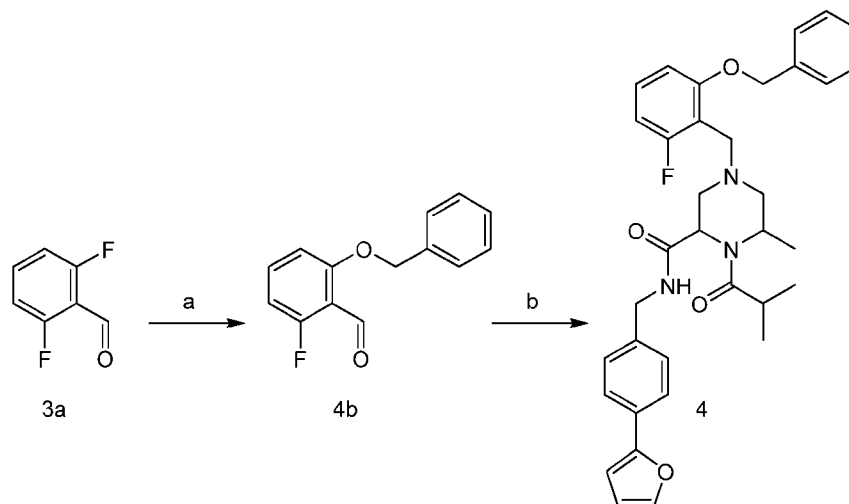
EXAMPLE 3



Preparation of cis-4-(2-fluoro-6-phenoxybenzyl)-N-(4-(furan-2-yl)benzyl)-1-isobutyryl-6-methylpiperazine-2-carboxamide (**3**)

- Step 1: Preparation of 2-fluoro-6-phenoxybenzaldehyde (**3b**) To a stirred solution of 2,6-difluorobenzaldehyde (**3a**, 0.200 g, 1.407 mmol) and phenol (0.146 g, 1.548 mmol) in DMF (5 mL), K₂CO₃ (0.39 g, 2.81 mmol) was added and the mixture was stirred at 15 °C for 12 h. The reaction mixture was brought to room temperature and partitioned between H₂O and CH₂Cl₂. The organic layer was dried over sodium sulfate, concentrated and purified by prep-TLC (PE: EtOAc = 10:1) to provide 2-fluoro-6-phenoxybenzaldehyde (**3b**, 0.100 g, 31%).
- Step 2: Preparation of cis-4-(2-fluoro-6-phenoxybenzyl)-N-(4-(furan-2-yl)benzyl)-1-isobutyryl-6-methylpiperazine-2-carboxamide (**3**) To the mixture of cis-N-(4-(furan-2-yl)benzyl)-1-isobutyryl-6-methylpiperazine-2-carboxamide (**1h**, 0.020 g, 0.054 mmol) in MeOH (10 mL) was added AcOH (3.10 μL, 0.054 mmol), the mixture was stirred for 5 min. Then 2-fluoro-6-phenoxybenzaldehyde (**3b**, 0.012 g, 0.054 mmol) was added. The mixture was stirred at 20 °C for 20 min, then NaBH₃CN (0.0102 g, 0.162 mmol) was added to the mixture. After stirring for 30 min the mixture was concentrated and the crude product was purified by prep-HPLC (water (10mM NH₄HCO₃)-ACN) to give cis-4-(2-fluoro-6-phenoxybenzyl)-N-(4-(furan-2-yl)benzyl)-1-isobutyryl-6-methylpiperazine-2-carboxamide (**3**, 0.00976 g, 31%). LRMS (ES) (M+H)⁺: observed = 570.3, calculated = 569.7.

EXAMPLE 4

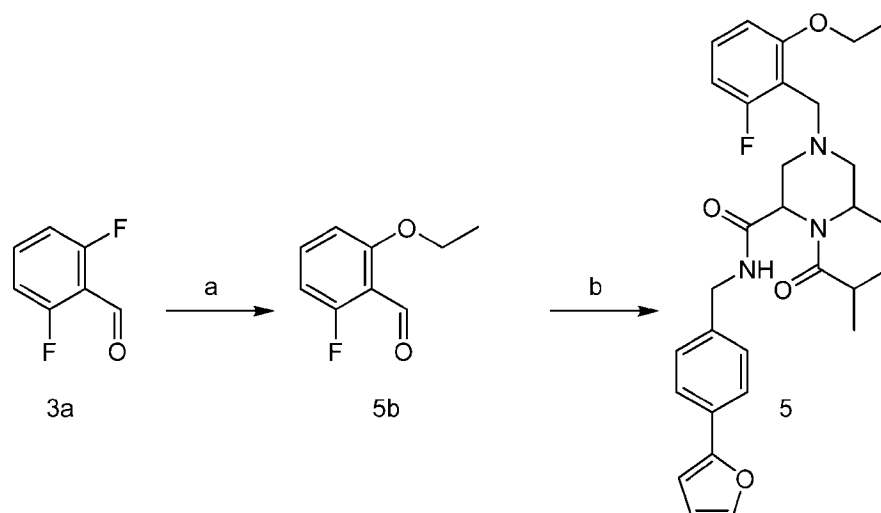


Preparation of cis-4-(2-(benzyloxy)-6-fluorobenzyl)-N-(4-(furan-2-yl)benzyl)-1-isobutyryl-6-methylpiperazine-2-carboxamide (**4**)

- 5 Step 1: Preparation of 2-(benzyloxy)-6-fluorobenzaldehyde (**4b**) To a stirred solution of 2,6-difluorobenzaldehyde (**3a**, 0.200 g, 1.407 mmol) and phenylmethanol (0.167 g, 1.548 mmol) in DMA (5 mL) was added Cs₂CO₃ (0.917 g, 2.81 mmol) and the mixture was stirred at 80 °C for 2 hours. The reaction mixture was brought to room temperature and partitioned between H₂O (10 mL) and CH₂Cl₂ (10 mL). The organic layer was dried over sodium sulfate, concentrated and
- 10 purified by silica gel chromatography to provide 2-(benzyloxy)-6-fluorobenzaldehyde (**4b**). Step 2: In an analogous manner to example **3**, cis-N-(4-(furan-2-yl)benzyl)-1-isobutyryl-6-methylpiperazine-2-carboxamide (**1h**) and 2-(benzyloxy)-6-fluorobenzaldehyde (**4b**) were used to prepare cis-4-(2-(benzyloxy)-6-fluorobenzyl)-N-(4-(furan-2-yl)benzyl)-1-isobutyryl-6-methylpiperazine-2-carboxamide (**4**) LRMS (ES) (M+H)⁺: observed = 584.3, calculated = 583.7.

15

EXAMPLE 5



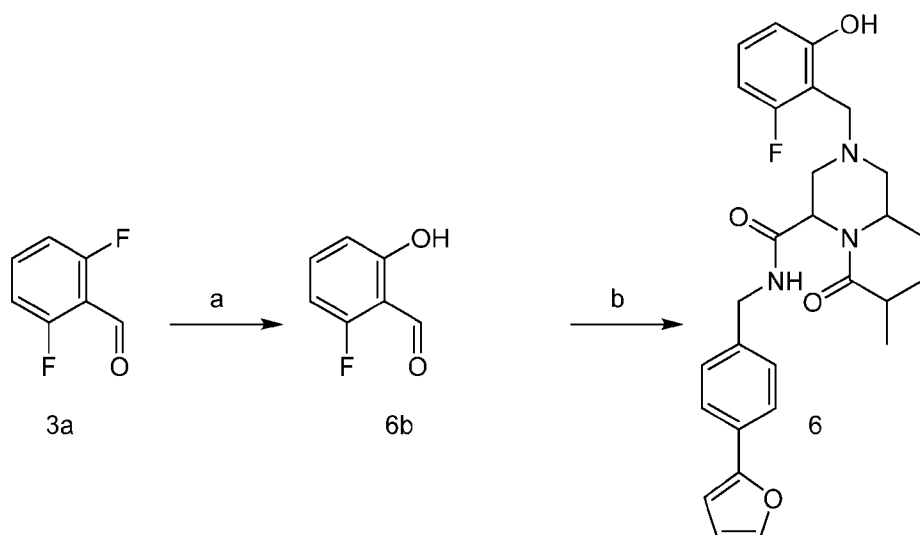
Preparation of cis-4-(2-ethoxy-6-fluorobenzyl)-N-(4-(furan-2-yl)benzyl)-1-isobutyryl-6-methylpiperazine-2-carboxamide (**5**)

Step 1: Preparation of 2-ethoxy-6-fluorobenzaldehyde (**5b**) To a mixture of 2,6-

- 5 difluorobenzaldehyde (**3a**, 0.200 g, 1.407 mmol) and NaOH (0.113 g, 2.81 mmol) was added EtOH (10 mL), and the solution was stirred at 15 °C for 12 hours. The mixture was partitioned between H₂O and CH₂Cl₂, dried over sodium sulfate, concentrated and purified by prep-TLC (PE: EtOAc = 10:1) to provide 2-ethoxy-6-fluorobenzaldehyde (**5b**)

- Step 2: In an analogous manner to example **3**, cis-N-(4-(furan-2-yl)benzyl)-1-isobutyryl-6-methylpiperazine-2-carboxamide (**1h**) and 2-ethoxy-6-fluorobenzaldehyde (**5b**) were used to
 10 prepare cis-4-(2-ethoxy-6-fluorobenzyl)-N-(4-(furan-2-yl)benzyl)-1-isobutyryl-6-methylpiperazine-2-carboxamide (**5**) LRMS (ES) (M+H)⁺: observed = 522.3, calculated = 521.6.

EXAMPLE 6



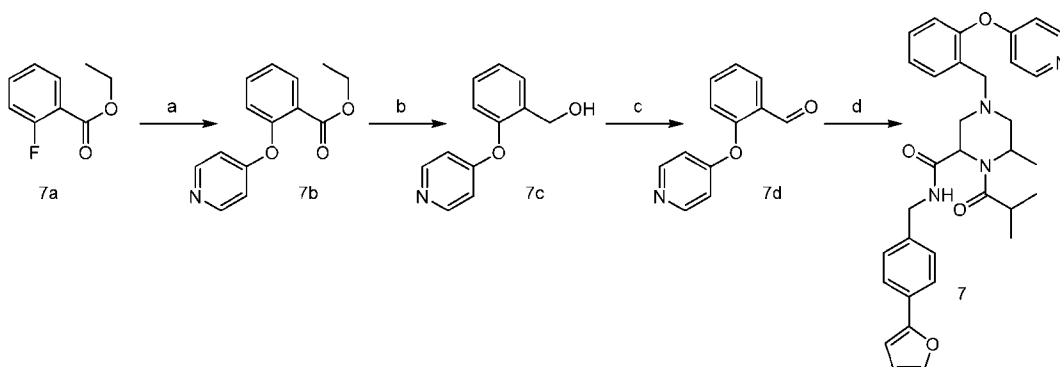
Preparation of cis-4-(2-fluoro-6-hydroxybenzyl)-N-(4-(furan-2-yl)benzyl)-1-isobutyryl-6-methylpiperazine-2-carboxamide (**6**)

- 5 Step 1: In an analogous manner to example **5b**, difluorobenzaldehyde and sodium hydroxide were used to prepare 2-fluoro-6-hydroxybenzaldehyde (**6b**).

Step 2: In an analogous manner to example **3**, cis-N-(4-(furan-2-yl)benzyl)-1-isobutyryl-6-methylpiperazine-2-carboxamide (**1h**) and 2-fluoro-6-hydroxybenzaldehyde (**6b**) were used to prepare cis-4-(2-fluoro-6-hydroxybenzyl)-N-(4-(furan-2-yl)benzyl)-1-isobutyryl-6-

- 10 methylpiperazine-2-carboxamide (**6**) LRMS (ES) (M+H)⁺: observed = 494.2, calculated = 493.6.

EXAMPLE 7



Preparation of cis-N-(4-(furan-2-yl)benzyl)-1-isobutyryl-6-methyl-4-(2-(pyridin-4-

- 15 yloxy)benzyl)piperazine-2-carboxamide (**7**)

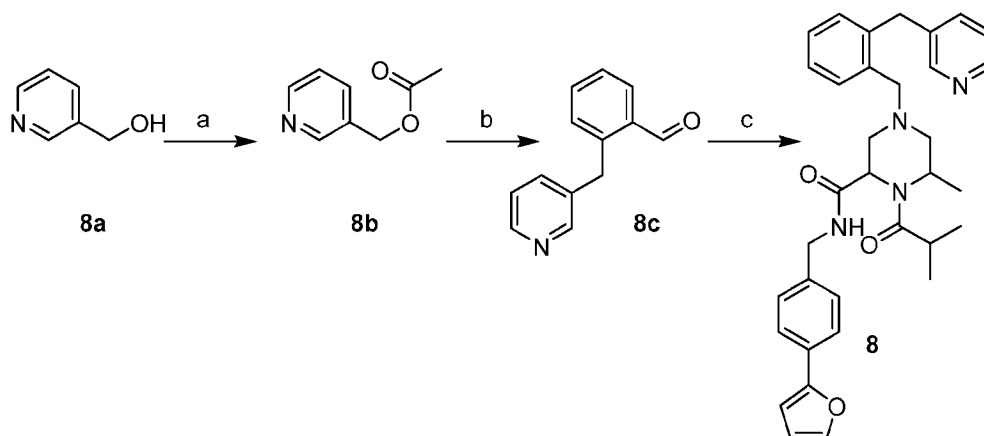
Step 1: Preparation of ethyl 2-(pyridin-4-yloxy)benzoate (**7b**) To a solution of pyridin-4-ol (0.50 g, 5.26 mmol) in DMF (10 mL) were added K₂CO₃ (1.45 g, 10.52 mmol) and ethyl 2-fluorobenzoate (0.884 g, 5.26 mmol). The mixture was stirred at 125 °C for 12 hours under N₂. The reaction mixture was brought to room temperature and partitioned between H₂O (10 mL) and CH₂Cl₂ (2 times 10 mL), the organic layer was dried by sodium sulfate, concentrated and purified by prep-TLC (DCM:MeOH=10:1) to provide ethyl 2-(pyridin-4-yloxy)benzoate (**7b**).

Step 2: Preparation of (2-(pyridin-4-yloxy)phenyl)methanol (**7c**) The mixture of NaBH₄ (0.233 g, 6.17 mmol), calcium chloride (0.684 g, 6.17 mmol) in THF (5 mL) was stirred at 15 °C for 1 hour under N₂, then ethyl 2-(pyridin-4-yloxy)benzoate (**7b**, 0.10 g, 0.411 mmol) was added to the mixture and then was stirred at 15 °C for 16 hours under N₂. The mixture was poured into water (10 mL), extracted with DCM, the organic layer were dried over sodium sulfate and then filtered. The filtrate was concentrated in vacuo. The crude product was purified by prep-TLC (DCM:MeOH=10:1) to give (2-(pyridin-4-yloxy)phenyl)methanol (**7c**).

Step 3: Preparation of 2-(pyridin-4-yloxy)benzaldehyde (**7d**) DMSO (0.042 mL, 0.596 mmol) in DCM (5 mL) was added to oxalyl chloride (0.026 mL, 0.298 mmol) in DCM (5 mL) at -78 °C. Then the mixture was stirred at -78 °C for 30 min. (2-(pyridin-4-yloxy)phenyl)methanol (**7c**, 0.030 g, 0.149 mmol) was added to the mixture at -78 °C and stirred at -78 °C for 30 minutes. Triethylamine (0.166 mL, 1.193 mmol) was added to the mixture and the mixture was stirred at -78 °C for 30 minutes and then 0 °C for 30 minutes. The reaction mixture was poured into water (10 mL) and extracted with DCM. The organic layer was dried over anhydrous sodium sulfate and evaporated under reduced pressure to give 2-(pyridin-4-yloxy)benzaldehyde (**7d**).

Step 4: In an analogous manner to example **3**, cis-N-(4-(furan-2-yl)benzyl)-1-isobutyryl-6-methylpiperazine-2-carboxamide (**1h**) and 2-(pyridin-4-yloxy)benzaldehyde (**7d**) were used to prepare cis-N-(4-(furan-2-yl)benzyl)-1-isobutyryl-6-methyl-4-(2-(pyridin-4-yloxy)benzyl)piperazine-2-carboxamide (**7**).

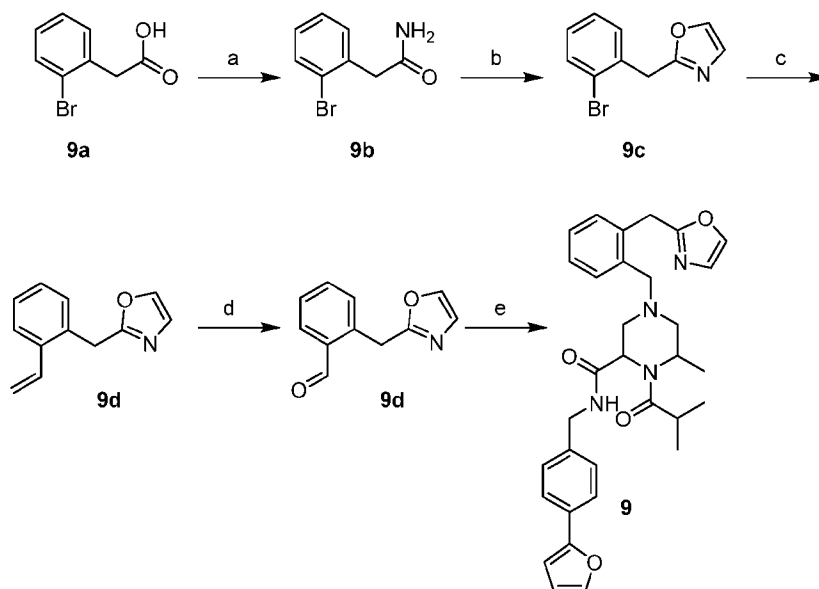
EXAMPLE 8



Preparation of cis-N-(4-(furan-2-yl)benzyl)-1-isobutyryl-6-methyl-4-(2-(pyridin-4-yloxy)benzyl)piperazine-2-carboxamide (**8**)

- 5 Step 1: To a preparation of pyridin-3-ylmethyl acetate (**8b**) pyridin-3-ylmethanol (0.50 g, 4.58 mmol) in DCM (20 mL) was added pyridine (7.41 mL, 92 mmol) and Ac₂O (0.865 mL, 9.16 mmol) at 20 °C for 16 hours. The mixture was concentrated to dryness, and the residue was dissolved in 20 mL of water and extracted DCM. The organic layer was dried by sodium sulfate, filtrated and concentrated to give pyridin-3-ylmethyl acetate (**8b**).
- 10 Step 2: Preparation of 2-(pyridin-3-ylmethyl)benzaldehyde (**8c**) (2-formylphenyl)boronic acid (0.20 g, 1.334 mmol), pyridin-3-ylmethyl acetate (**8b**, 0.202 g, 1.334 mmol), Pd(OAc)₂ (0.006 g, 0.027 mmol) and Ru-phos (0.025 mg, 0.053 mmol) in 2-Propanol (5 mL) and water (0.5 mL) were stirred for 5 min at N₂ atmosphere. K₂CO₃ (0.461 g, 3.33 mmol) was added under N₂ atmosphere and stirred for 5 minutes. The suspension was heated to 80 °C for 24 hours. Then the mixture was filtrated and the filtration was concentrated in vacuo, the crude product was purified by prep-TLC (PE: EtOAc = 2:1) to give 2-(pyridin-3-ylmethyl)benzaldehyde (**8c**).
- Step 3: In an analogous manner to example **3**, cis-N-(4-(furan-2-yl)benzyl)-1-isobutyryl-6-methylpiperazine-2-carboxamide (**1h**) and 2-(pyridin-3-ylmethyl)benzaldehyde (**8c**) were used to prepare cis-N-(4-(furan-2-yl)benzyl)-1-isobutyryl-6-methyl-4-(2-(pyridin-4-yloxy)benzyl)piperazine-2-carboxamide (**8**). LRMS (ES) (M+H)⁺: observed = 551.1, calculated = 550.7.
- 20

EXAMPLE 9



Preparation of cis-N-(4-(furan-2-yl)benzyl)-1-isobutyryl-6-methyl-4-(2-(oxazol-2-ylmethyl)benzyl)piperazine-2-carboxamide (**9**)

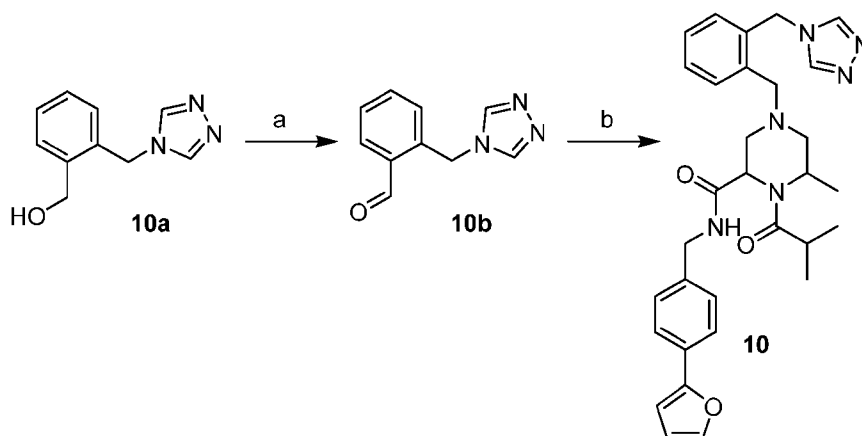
- 5 Step 1: Preparation of 2-(2-bromophenyl)acetamide (**9b**) To a solution of 2-(2-bromophenyl)acetic acid (10.0 g, 46.5 mmol) and DMF (0.576 mL, 7.44 mmol) in toluene (100 mL), sulfurous dichloride (5.81 g, 48.8 mmol) was added. The mixture was heated at 80 °C for 1 hour, then cooled down to 0 °C, 25% Ammonia (in water) (141 mL, 1628 mmol) was added. The reaction mixture was continued to stir for 30 min, then the precipitate was collected. The precipitate washed with water (50 mL) and pentane (80 mL). The precipitate was dried in a vacuum oven at 50°C to give 2-(2-bromophenyl)acetamide (**9b**).
- 10 Step 2: Preparation of 2-(2-bromobenzyl)oxazole (**9c**) A mixture of 2-(2-bromophenyl)acetamide (**9b**, 9.6 g, 44.8 mmol) and 1,3-dioxol-2-one (4.63 g, 53.8 mmol) in polyphosphoric acid (40 mL) was stirred at 170 °C for 3 h. The reaction mixture was added to water (100 mL) and extracted with EtOAc (50 mL x 3). The organic layers were washed with brine (20 mL), dried over Na₂SO₄. After filtration and concentration, the residue was purified by flash silica gel chromatography (ISCO®; 80 g SepaFlash® Silica Flash Column, eluent of [0~8]% ethyl acetate/Petroleum ether gradient @ 40 mL/min) to give 2-(2-bromobenzyl)oxazole (**9**). LRMS (ES) (M+H)⁺: observed = 237.9, calculated = 238.0.
- 20 Step 3: Preparation of 2-(2-vinylbenzyl)oxazole (**9d**)

To a solution of 2-(2-bromobenzyl)oxazole (**9c**, 1.0 g, 4.20 mmol), potassium trifluoro(vinyl)borate (1.125 g, 8.40 mmol) and K₂CO₃ (1.741 g, 12.60 mmol) in Dioxane (15 mL) and H₂O (5 mL) were added PdCl₂(dppf) (0.307 g, 0.420 mmol) under N₂ protection. The mixture was stirred at 100 °C for 3 hours. The reaction mixture was poured into water (30 mL), and extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine (20 mL), dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, eluent of [5~10]% ethyl acetate/ Petroleum ether gradient @ 40 mL/min) to give 2-(2-vinylbenzyl)oxazole (**9d**). LRMS (ES) (M+H)⁺: observed = 186.1, calculated = 185.2.

Step 4: Preparation of 2-(oxazol-2-ylmethyl)benzaldehyde (**9e**) To a solution of 2-(2-vinylbenzyl)oxazole (**9d**, 0.20 g, 1.08 mmol) in Dioxane (4 mL) was added NaIO₄ (0.924 g, 4.32 mmol) in Water (4 mL) and OsO₄ (0.0028 g, 10.80 μmol) in turn. The reaction mixture was stirred at 16 °C for 15 minutes. To the mixture was added water (10 mL), which was extracted with EtOAc (10 mL x 3). The combined organic layers were washed with aq. sat. Na₂S₂O₃ (5 mL), dried over Na₂SO₄, filtered and concentrated to give crude product 2-(oxazol-2-ylmethyl)benzaldehyde (**9e**).

Step 5: In an analogous manner to example 3, cis-N-(4-(furan-2-yl)benzyl)-1-isobutyryl-6-methylpiperazine-2-carboxamide (**1h**) and 2-(oxazol-2-ylmethyl)benzaldehyde (**9e**) were used to prepare cis-N-(4-(furan-2-yl)benzyl)-1-isobutyryl-6-methyl-4-(2-(oxazol-2-ylmethyl)benzyl)piperazine-2-carboxamide (**9**). LRMS (ES) (M+H)⁺: observed = 541.3, calculated = 540.6.

EXAMPLE 10

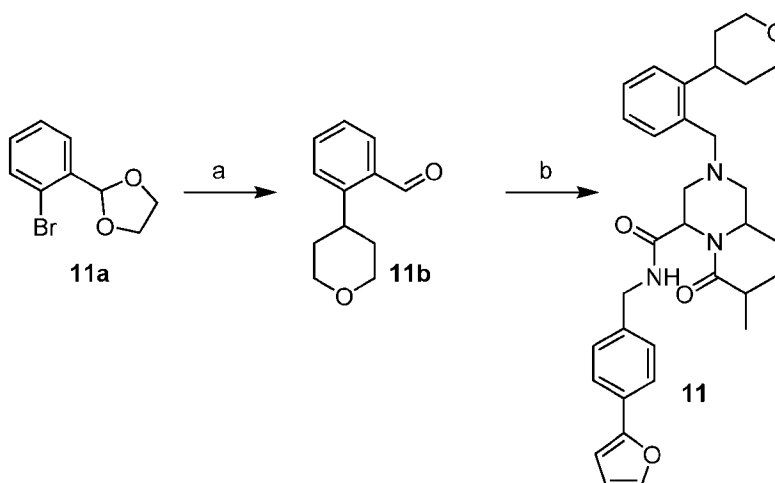


Preparation of cis-4-(2-((4H-1,2,4-triazol-4-yl)methyl)benzyl)-N-(4-(furan-2-yl)benzyl)-1-isobutyryl-6-methylpiperazine-2-carboxamide (**10**)

Step 1: Preparation of 2-((4H-1,2,4-triazol-4-yl)methyl)benzaldehyde (**10b**) To a solution of (2-((4H-1,2,4-triazol-4-yl)methyl)phenyl)methanol HCl (**10a**, 0.30 g, 1.33 mmol) and Hunig's base (1.74 mL, 9.97 mmol) in DCM (6 mL) and DMSO (1 mL) was added a solution of sulfur trioxide pyridine complex (2.12 g, 13.29 mmol) in DMSO (5 mL) slowly at room temperature. The reaction mixture was stirred for 2 hours at room temperature, diluted with DCM and washed with sat. sodium bicarbonate solution. The organic layer was concentrated and purified by reverse phase purification to give 2-((4H-1,2,4-triazol-4-yl)methyl)benzaldehyde (**10b**). LRMS (ES) (M+H)⁺: observed = 188.1, calculated = 187.2.

Step 2: In an analogous manner to example **1-1**, cis-N-(4-(furan-2-yl)benzyl)-1-isobutyryl-6-methylpiperazine-2-carboxamide (**1h**) and 2-((4H-1,2,4-triazol-4-yl)methyl)benzaldehyde (**10b**) were used to prepare cis-4-(2-((4H-1,2,4-triazol-4-yl)methyl)benzyl)-N-(4-(furan-2-yl)benzyl)-1-isobutyryl-6-methylpiperazine-2-carboxamide (**10**). LRMS (ES) (M+H)⁺: observed = 541.5, calculated = 540.6.

EXAMPLE 11



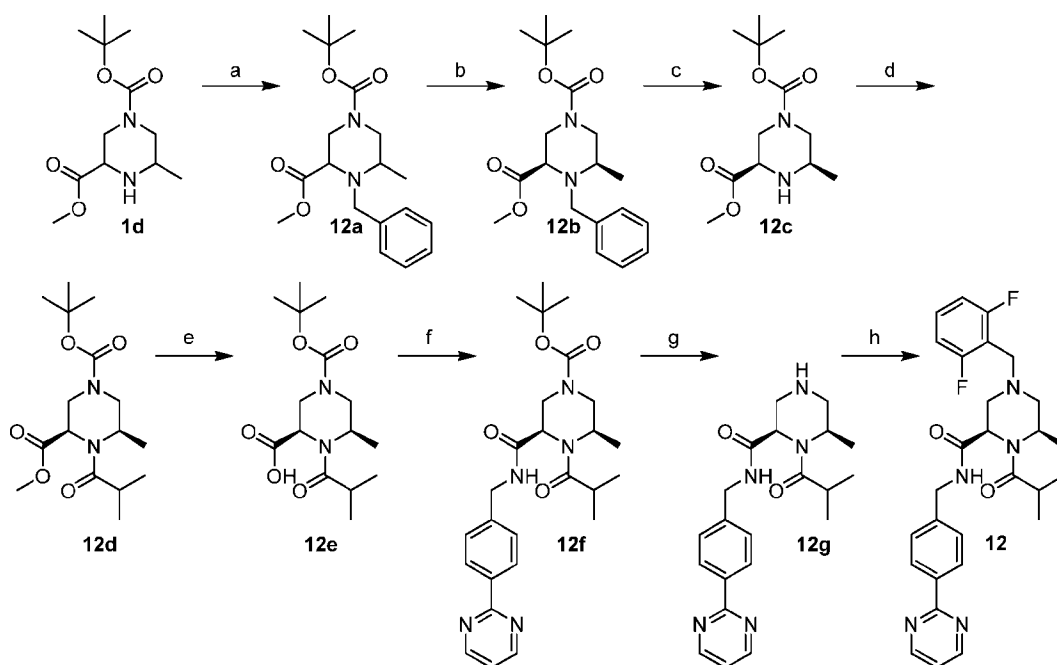
Preparation of cis-N-(4-(furan-2-yl)benzyl)-1-isobutyryl-6-methyl-4-(2-(tetrahydro-2H-pyran-4-yl)benzyl)piperazine-2-carboxamide (**11**)

Step 1: Preparation of 2-(tetrahydro-2H-pyran-4-yl)benzaldehyde (**11b**) In a clear vial were added 2-(2-bromophenyl)-1,3-dioxolane (**11a**, 0.162 g, 0.982 mmol), [Ni(dtbbpy)(H₂O)₄]Cl₂ (0.0128 g, 0.033 mmol), 2,4,5,6-tetra(9H-carbazol-9-yl)isophthalonitrile (0.010 g, 0.013 mmol),

tris(trimethylsilyl)silane (0.20 mL, 0.66 mmol), 2,6-lutidine (0.15 mL, 1.31 mmol) and Dimethoxyethane (6.5 mL) under nitrogen. The resulting mixture was stirred overnight under Kessell lamps with fan cooling. The mixture was then concentrated and taken up in acetonitrile (2 mL) and 1M HCl solution (2 mL). This mixture was allowed to stir at room temperature overnight, extracted with ethyl acetate and the organic phase concentrated. Reverse phase purification provided 2-(tetrahydro-2H-pyran-4-yl)benzaldehyde (**11b**).

Step 2: In an analogous manner to example 1-1, cis-N-(4-(furan-2-yl)benzyl)-1-isobutyl-6-methylpiperazine-2-carboxamide (**1h**) and 2-(tetrahydro-2H-pyran-4-yl)benzaldehyde (**11b**) were used to prepare cis-N-(4-(furan-2-yl)benzyl)-1-isobutyl-6-methyl-4-(2-(tetrahydro-2H-pyran-4-yl)benzyl)piperazine-2-carboxamide (**11**). LRMS (ES) (M+H)⁺: observed = 544.6, calculated = 543.7.

EXAMPLE 12



- 15 Preparation of (2R,6R)-4-(2,6-difluorobenzyl)-1-isobutyl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**12**)

Step 1: Preparation of 1-(tert-butyl) 3-methyl 4-benzyl-5-methylpiperazine-1,3-dicarboxylate (**12a**) To a stirred solution of cis-1-(tert-butyl) 3-methyl 5-methylpiperazine-1,3-dicarboxylate (**1d**, 60.0 g, 232.0 mmol) in DMF (420 mL) was added potassium carbonate (80.3 g, 581.0

mmol) and benzyl bromide (55.2 mL, 464.0 mmol) and resulting mixture was stirred at room temperature for 16 hours. This reaction was run 4 times and combined. The mixture was poured into water and extracted several times with MTBE. The combined organic layer was washed with brine, dried over sodium sulfate and concentrated. The residue was purified by silica gel chromatography (Petroleum ether/Ethyl acetate = 100/1, 5/1). TLC (Petroleum ether / Ethyl acetate = 5:1 to give 1-(tert-butyl) 3-methyl 4-benzyl-5-methylpiperazine-1,3-dicarboxylate (**12a**).

Step 2: Preparation of 1-(tert-butyl) 3-methyl (3R,5R)-4-benzyl-5-methylpiperazine-1,3-dicarboxylate (**12b**) Compound 1-(tert-butyl) 3-methyl 4-benzyl-5-methylpiperazine-1,3-dicarboxylate (**12a**) was separated by SFC using a Thar 200 preparative SFC (SFC-7) with a ChiralPak IC, 300×50 mm I.D., 10 µm. column using a 15% IPA/CO₂ gradient with a flow rate of 180 mL/min. The sample was dissolved in 3.5 L of MeOH with 4 mL per injection to give 1-(tert-butyl) 3-methyl (3R,5R)-4-benzyl-5-methylpiperazine-1,3-dicarboxylate (**12b**)

Step 3: Preparation of 1-(tert-butyl) 3-methyl (3R,5R)-5-methylpiperazine-1,3-dicarboxylate (**12c**) To a stirred solution of 1-(tert-butyl) 3-methyl (3R,5R)-4-benzyl-5-methylpiperazine-1,3-dicarboxylate (**12b**, 20.0 g, 57.4 mmol) in MeOH (140 mL) was added Pd/C 10% (4.0 g, 57.4 mmol). The reaction was stirred under hydrogen for 5 hours, filtered through celite and concentrated to give 1-(tert-butyl) 3-methyl (3R,5R)-5-methylpiperazine-1,3-dicarboxylate (**12c**).

Step 4: In an analogous manner to example **1e**, 1-(tert-butyl) 3-methyl (3R,5R)-5-methylpiperazine-1,3-dicarboxylate (**12c**) and isobutyryl chloride were used to prepare 1-(tert-butyl) 3-methyl (3R,5R)-4-isobutyryl-5-methylpiperazine-1,3-dicarboxylate (**12d**). LRMS (ES) (M+H)⁺: observed = 329.3, calculated = 328.4.

Step 5: In an analogous manner to example **1f**, 1-(tert-butyl) 3-methyl (3R,5R)-4-isobutyryl-5-methylpiperazine-1,3-dicarboxylate (**12d**) and potassium trimethylsilanolate were used to prepare (2R,6R)-4-(tert-butoxycarbonyl)-1-isobutyryl-6-methylpiperazine-2-carboxylic acid (**12e**). LRMS (ES) (M+H)⁺: observed = 315.3, calculated = 314.4.

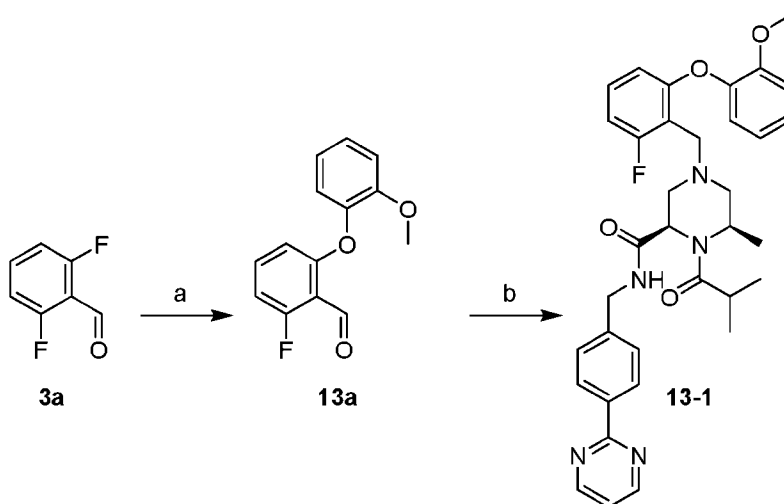
Step 6: Preparation of tert-butyl (3R,5R)-4-isobutyryl-3-methyl-5-((4-(pyrimidin-2-yl)benzyl)carbamoyl)piperazine-1-carboxylate To a stirred solution of (2R,6R)-4-(tert-butoxycarbonyl)-1-isobutyryl-6-methylpiperazine-2-carboxylic acid (**12e**, 0.15 g, 0.47 mmol) and (4-(pyrimidin-2-yl)phenyl)methanamine, HCl (0.125 g, 0.56 mmol) in DMF (1.34 mL) was added HATU (0.197 g, 0.52 mmol) and triethylamine (0.196 mL, 1.41 mmol). The resulting mixture was stirred at room temperature for 1 hour. The solution was poured into sat. sodium bicarbonate solution and extracted several times with ethyl acetate. The combined organic layers

were concentrated and flash column purification using a 0-100% ethyl acetate/ hexane gradient gave tert-butyl (3R,5R)-4-isobutyryl-3-methyl-5-((4-(pyrimidin-2-yl)benzyl)carbamoyl)piperazine-1-carboxylate (**12f**).

Step 7: Preparation of (2R,6R)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**12g**) To a stirred solution of tert-butyl (3R,5R)-4-isobutyryl-3-methyl-5-((4-(pyrimidin-2-yl)benzyl)carbamoyl)piperazine-1-carboxylate (**12f**, 0.47 mmol) in EtOAc (3 mL) chilled to 0°C in an ice bath was added HCl gas until saturated. The resulting solution was stirred at 0°C for 30 minutes and concentrated to give (2R,6R)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**12g**)

Step 8: In an analogous manner to example 2-1, (2R,6R)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**12g**) and 2-(bromomethyl)-1,3-difluorobenzene were used to prepare (2R,6R)-4-(2,6-difluorobenzyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**12**). LRMS (ES) (M+H)⁺: observed = 508.3, calculated = 507.6.

EXAMPLE 13



Preparation of (2R,6R)-4-(2-fluoro-6-(2-methoxyphenoxy)benzyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**13-1**)

Step 1: Preparation of 2-fluoro-6-(2-methoxyphenoxy)benzaldehyde (**13a**) To a stirred solution of 2,6-difluorobenzaldehyde (**3a**, 0.200 g, 1.407 mmol) and 2-methoxyphenol (0.175 g, 1.407 mmol) in DMA (4.7 mL) was added K₂CO₃ (0.58 g, 4.22 mmol) and the mixture was stirred at 120 °C for 20 minutes. The reaction mixture was brought to room temperature and partitioned between 1N HCl and Ethyl acetate. The organic layer was concentrated and flash column

purification using a 0-10% ethyl acetate/ hexane gradient gave 2-fluoro-6-(2-methoxyphenoxy)benzaldehyde (**13a**). LRMS (ES) (M+H)⁺: observed = 247.1, calculated = 246.2.

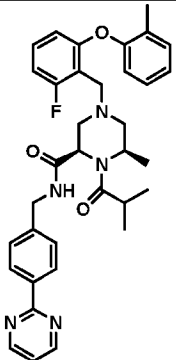
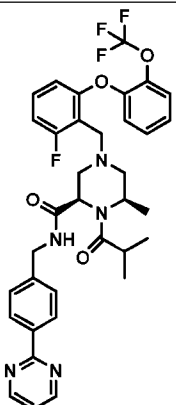
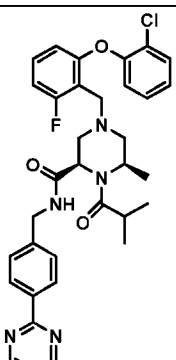
Step 2: In an analogous manner to example **1-1**, (2R,6R)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**12g**) and 2-fluoro-6-(2-methoxyphenoxy)benzaldehyde (**13a**) were used to prepare (2R,6R)-4-(2-fluoro-6-(2-methoxyphenoxy)benzyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**13-1**). LRMS (ES) (M+H)⁺: observed = 612.4, calculated = 611.7.

10 The following compounds were prepared in an analogous manner to example **13-1**.

Example	Structure	Name	Calculated Mass	Observed Mass (M+H)
13-2		(2R,6R)-4-({2-[(2-ethyl-5-methylpyridin-3-yl)oxy]-6-fluorophenyl}methyl)-6-methyl-1-(2-methylpropanoyl)-N-{[4-(pyrimidin-2-yl)phenyl]methyl}piperazine-2-carboxamide	624.765	625.6
13-3		(2R,6R)-4-({2-[2-(dimethylamino)phenoxy]-6-fluorophenyl}methyl)-6-methyl-1-(2-methylpropanoyl)-N-{[4-(pyrimidin-2-yl)phenyl]methyl}piperazine-2-carboxamide	624.765	625.5

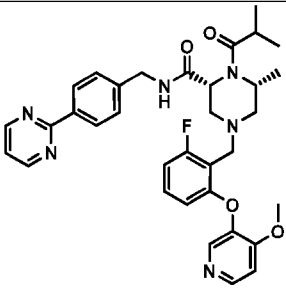
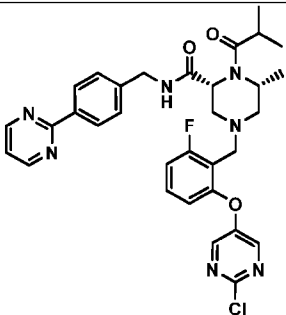
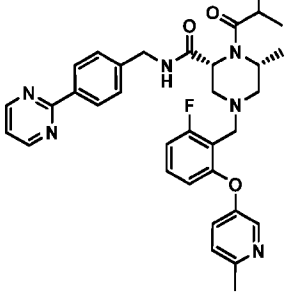
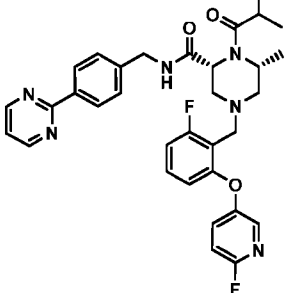
13-4		(2R,6R)-4-([2-(2-ethylphenoxy)-6-fluorophenyl]methyl)-6-methyl-1-(2-methylpropanoyl)-N-{[4-(pyrimidin-2-yl)phenyl]methyl}piperazine-2-carboxamide	609.75	610.5
13-5		(2R,6R)-4-([2-((2-ethylpyridin-3-yl)oxy)-6-fluorophenyl]methyl)-6-methyl-1-(2-methylpropanoyl)-N-{[4-(pyrimidin-2-yl)phenyl]methyl}piperazine-2-carboxamide	610.738	611.5
13-6		(2R,6R)-4-([2-fluoro-6-[2-(trifluoromethyl)phenoxy]phenyl]methyl)-6-methyl-1-(2-methylpropanoyl)-N-{[4-(pyrimidin-2-yl)phenyl]methyl}piperazine-2-carboxamide	649.694	650.4
13-7		(2R,6R)-4-([2-fluoro-6-[(imidazo[1,2-a]pyridin-8-yl)oxy]phenyl]methyl)-6-methyl-1-(2-methylpropanoyl)-N-{[4-(pyrimidin-2-yl)phenyl]methyl}piperazine-2-carboxamide	621.721	622.4

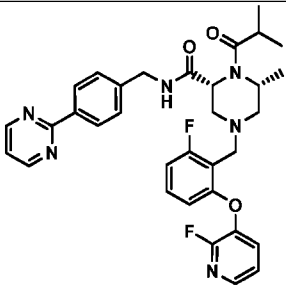
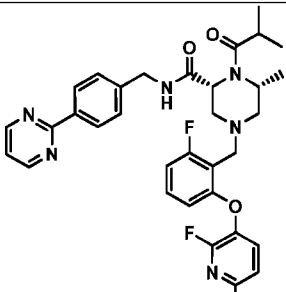
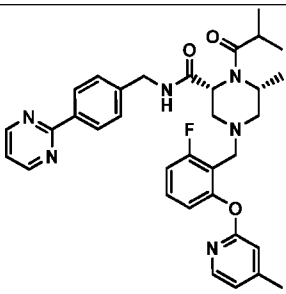
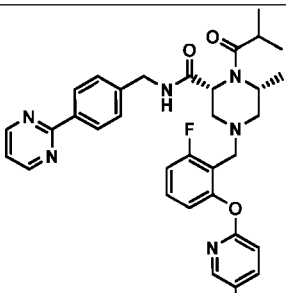
13-8		(2R,6R)-4-({2-[(2,6-dimethylpyridin-3-yl)oxy]-6-fluorophenyl}methyl)-6-methyl-1-(2-methylpropanoyl)-N-{[4-(pyrimidin-2-yl)phenyl]methyl}piperazine-2-carboxamide	610.738	611.5
13-9		(2R,6R)-4-({2-(2,6-dimethylphenoxy)-6-fluorophenyl}methyl)-6-methyl-1-(2-methylpropanoyl)-N-{[4-(pyrimidin-2-yl)phenyl]methyl}piperazine-2-carboxamide	609.75	610.5
13-10		(2R,6R)-4-({2-fluoro-6-[(2-methylpyridin-3-yl)oxy]phenyl}methyl)-6-methyl-1-(2-methylpropanoyl)-N-{[4-(pyrimidin-2-yl)phenyl]methyl}piperazine-2-carboxamide	596.711	597.4
13-11		(2R,6R)-4-({2-fluoro-6-[(3-methoxy-2-methylpyridin-4-yl)oxy]phenyl}methyl)-6-methyl-1-(2-methylpropanoyl)-N-{[4-(pyrimidin-2-yl)phenyl]methyl}piperazine-2-carboxamide	626.737	649.6

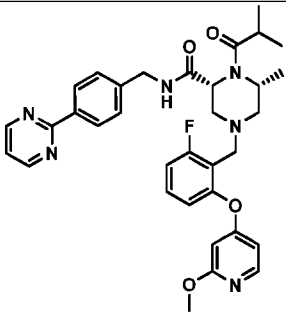
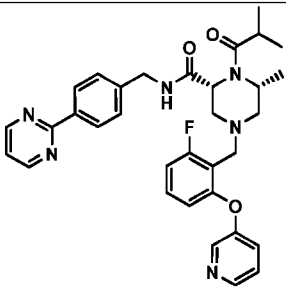
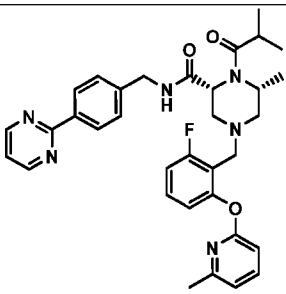
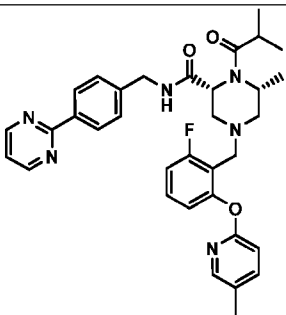
		yl)phenyl]methyl} piperazine-2-carboxamide		
13-12		(2R,6R)-4-([2-fluoro-6-(2-methylphenoxy)phenyl]methyl)-6-methyl-1-(2-methylpropanoyl)-N-{[4-(pyrimidin-2-yl)phenyl]methyl} piperazine-2-carboxamide	595.723	596.4
13-13		(2R,6R)-4-([2-fluoro-6-(2-(trifluoromethoxy)phenoxy)phenyl]methyl)-6-methyl-1-(2-methylpropanoyl)-N-{[4-(pyrimidin-2-yl)phenyl]methyl} piperazine-2-carboxamide	665.694	666.4
13-14		(2R,6R)-4-([2-(2-chlorophenoxy)-6-fluorophenyl]methyl)-6-methyl-1-(2-methylpropanoyl)-N-{[4-(pyrimidin-2-yl)phenyl]methyl} piperazine-2-carboxamide	616.141	617.4

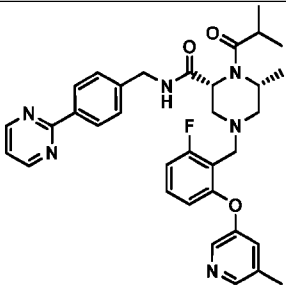
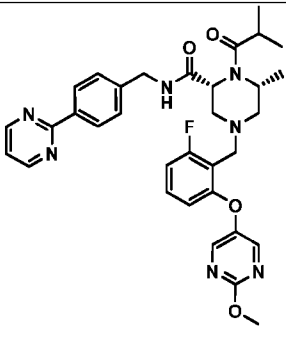
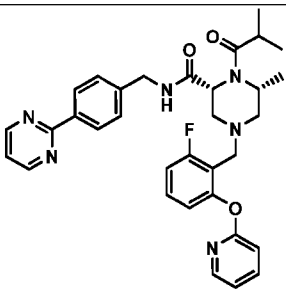
13-15		(2R,6R)-4-({2-[(6-ethylpyridin-3-yl)oxy]-6-fluorophenyl}methyl)-6-methyl-1-(2-methylpropanoyl)-N-{[4-(pyrimidin-2-yl)phenyl]methyl}piperazine-2-carboxamide	610.738	611.5
13-16		(2R,6R)-4-({2-[(2-chloro-6-methylpyridin-3-yl)oxy]-6-fluorophenyl}methyl)-6-methyl-1-(2-methylpropanoyl)-N-{[4-(pyrimidin-2-yl)phenyl]methyl}piperazine-2-carboxamide	631.156	631
13-17		(2R,6R)-4-({2-fluoro-6-[(4-methylpyridin-3-yl)oxy]phenyl}methyl)-6-methyl-1-(2-methylpropanoyl)-N-{[4-(pyrimidin-2-yl)phenyl]methyl}piperazine-2-carboxamide	596.711	597.5

13-18		(2R,6R)-4-([2-fluoro-6-(2-methoxy-6-methylphenoxy)phenyl]methyl)-6-methyl-1-(2-methylpropanoyl)-N-([4-(pyrimidin-2-yl)phenyl]methyl)piperazine-2-carboxamide	625.75	626.4
13-19		(2R,6R)-4-([2-((6-chloropyridin-3-yl)oxy)-6-fluorophenyl]methyl)-6-methyl-1-(2-methylpropanoyl)-N-([4-(pyrimidin-2-yl)phenyl]methyl)piperazine-2-carboxamide	617.129	617.4
13-20		(2R,6R)-4-([2-(2-fluoro-6-phenoxyphenyl)methyl]-6-methyl-1-(2-methylpropanoyl)-N-([4-(pyrimidin-2-yl)phenyl]methyl)piperazine-2-carboxamide	581.696	582.4
13-21		(2R,6R)-4-([2-((2,6-dichloropyridin-3-yl)oxy)-6-fluorophenyl]methyl)-6-methyl-1-(2-methylpropanoyl)-N-([4-(pyrimidin-2-yl)phenyl]methyl)piperazine-2-carboxamide	651.574	651

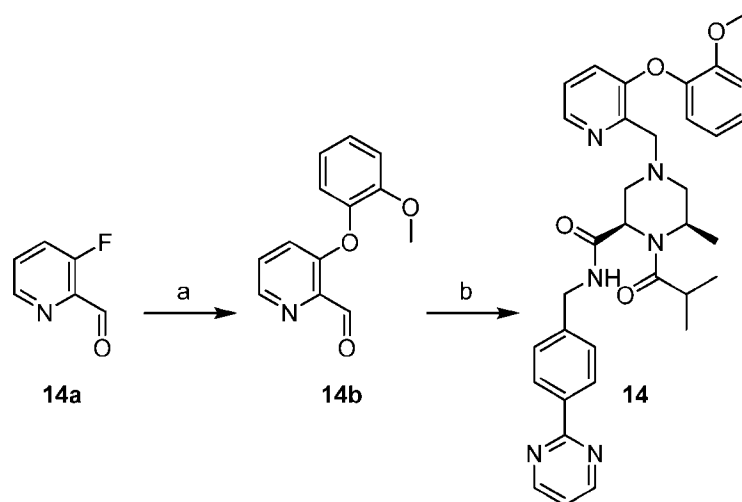
13-22		(2R,6R)-4-({2-fluoro-6-[(4-methoxypyridin-3-yl)oxy]phenyl}methyl)-6-methyl-1-(2-methylpropanoyl)-N-{{4-(pyrimidin-2-yl)phenyl}methyl}piperazine-2-carboxamide	612.71	613.5
13-23		(2R,6R)-4-({2-[(2-chloropyrimidin-5-yl)oxy]-6-fluorophenyl}methyl)-6-methyl-1-(2-methylpropanoyl)-N-{{4-(pyrimidin-2-yl)phenyl}methyl}piperazine-2-carboxamide	618.116	618
13-24		(2R,6R)-4-({2-fluoro-6-[(6-methylpyridin-3-yl)oxy]phenyl}methyl)-6-methyl-1-(2-methylpropanoyl)-N-{{4-(pyrimidin-2-yl)phenyl}methyl}piperazine-2-carboxamide	596.711	597.5
13-25		(2R,6R)-4-({2-fluoro-6-[(6-fluoropyridin-3-yl)oxy]phenyl}methyl)-6-methyl-1-(2-methylpropanoyl)-N-{{4-(pyrimidin-2-yl)phenyl}methyl}piperazine-2-carboxamide	600.674	601.5

13-26		(2R,6R)-4-({2-fluoro-6-[(2-fluoropyridin-3-yl)oxy]phenyl}methyl)-6-methyl-1-(2-methylpropanoyl)-N-{[4-(pyrimidin-2-yl)phenyl]methyl}piperazine-2-carboxamide	600.674	601.5
13-27		(2R,6R)-4-({2-fluoro-6-methylpyridin-3-yl}oxy]phenyl}methyl)-6-methyl-1-(2-methylpropanoyl)-N-{[4-(pyrimidin-2-yl)phenyl]methyl}piperazine-2-carboxamide	614.701	615.5
13-28		(2R,6R)-4-({2-fluoro-6-[(4-methylpyridin-2-yl)oxy]phenyl}methyl)-6-methyl-1-(2-methylpropanoyl)-N-{[4-(pyrimidin-2-yl)phenyl]methyl}piperazine-2-carboxamide	596.711	597.5
13-29		(2R,6R)-4-({2-fluoro-6-[(5-methoxypyridin-2-yl)oxy]phenyl}methyl)-6-methyl-1-(2-methylpropanoyl)-N-{[4-(pyrimidin-2-yl)phenyl]methyl}piperazine-2-carboxamide	612.71	613.5

13-30		(2R,6R)-4-({2-fluoro-6-[(2-methoxypyridin-4-yl)oxy]phenyl}methyl)-6-methyl-1-(2-methylpropanoyl)-N-{[4-(pyrimidin-2-yl)phenyl]methyl}piperazine-2-carboxamide	612.71	613.5
13-31		(2R,6R)-4-({2-fluoro-6-[(pyridin-3-yl)oxy]phenyl}methyl)-6-methyl-1-(2-methylpropanoyl)-N-{[4-(pyrimidin-2-yl)phenyl]methyl}piperazine-2-carboxamide	582.684	583.5
13-32		(2R,6R)-4-({2-fluoro-6-[(6-methylpyridin-2-yl)oxy]phenyl}methyl)-6-methyl-1-(2-methylpropanoyl)-N-{[4-(pyrimidin-2-yl)phenyl]methyl}piperazine-2-carboxamide	596.711	619.4
13-33		(2R,6R)-4-({2-fluoro-6-[(5-methylpyridin-2-yl)oxy]phenyl}methyl)-6-methyl-1-(2-methylpropanoyl)-N-{[4-(pyrimidin-2-yl)phenyl]methyl}piperazine-2-carboxamide	596.711	597.5

13-34		(2R,6R)-4-({2-fluoro-6-[(5-methylpyridin-3-yl)oxy]phenyl}methyl)-6-methyl-1-(2-methylpropanoyl)-N-{[4-(pyrimidin-2-yl)phenyl]methyl}piperazine-2-carboxamide	596.711	597.5
13-35		(2R,6R)-4-({2-fluoro-6-[(2-methoxypyrimidin-5-yl)oxy]phenyl}methyl)-6-methyl-1-(2-methylpropanoyl)-N-{[4-(pyrimidin-2-yl)phenyl]methyl}piperazine-2-carboxamide	613.698	614
13-36		(2R,6R)-4-({2-fluoro-6-[(pyridin-2-yl)oxy]phenyl}methyl)-6-methyl-1-(2-methylpropanoyl)-N-{[4-(pyrimidin-2-yl)phenyl]methyl}piperazine-2-carboxamide	582.684	583.5

EXAMPLE 14

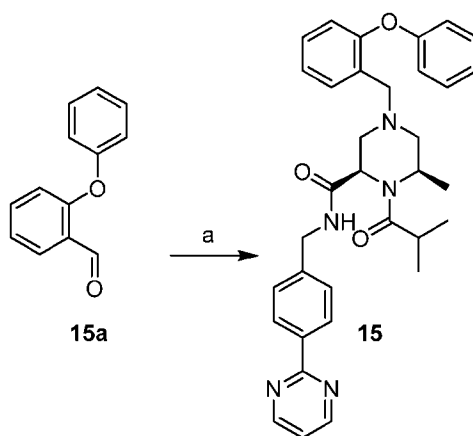


Preparation of (2R,6R)-4-(2-fluoro-6-(2-methoxyphenoxy)benzyl)-1-isobutryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**14**)

Step 1: In an analogous manner to example **13a**, 3-fluoropicolinaldehyde (**14a**) and 2-methoxyphenol were used to prepare 3-(2-methoxyphenoxy)picolinaldehyde (**14b**). LRMS (ES) (M+H)⁺: observed = 230.1, calculated = 229.2.

Step 2: In an analogous manner to example **1-1**, (2R,6R)-1-isobutryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**12g**) and 3-(2-methoxyphenoxy)picolinaldehyde (**14b**) were used to prepare (2R,6R)-1-isobutryl-4-((3-(2-methoxyphenoxy)pyridin-2-yl)methyl)-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**14**). LRMS (ES) (M+H)⁺: observed = 595.5, calculated = 594.7.

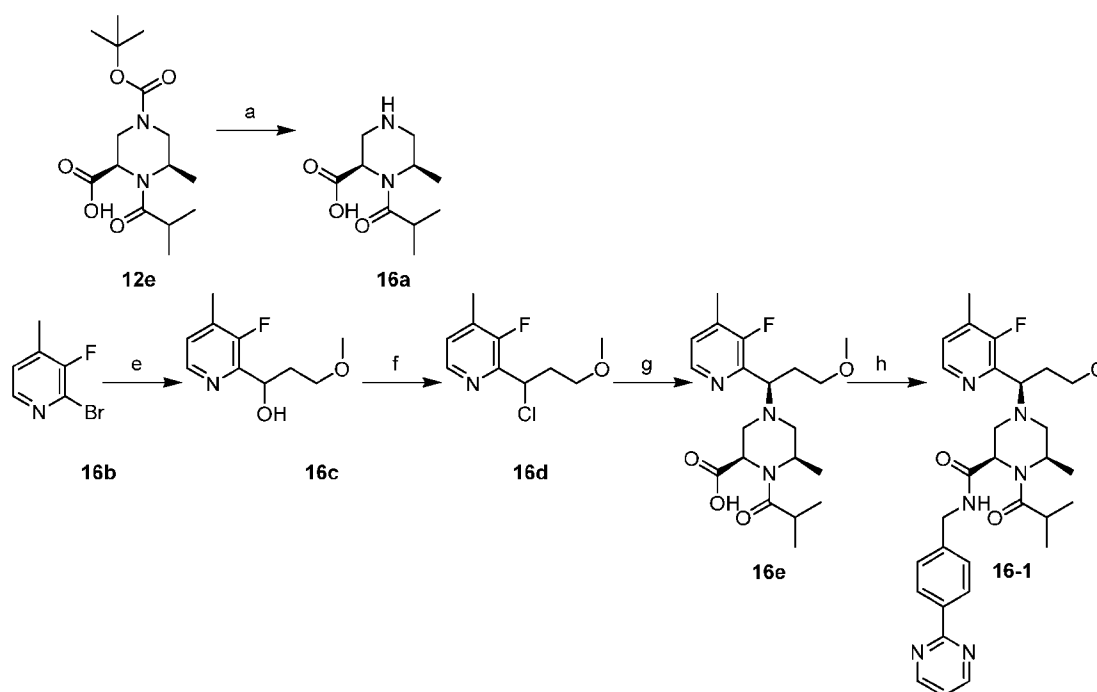
EXAMPLE 15



Preparation of (2R,6R)-1-isobutyryl-6-methyl-4-(2-phenoxybenzyl)-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**15**)

Step 1: In an analogous manner to example **1-1**, (2R,6R)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**12g**) and 2-phenoxybenzaldehyde (**15a**) were used to prepare (2R,6R)-1-isobutyryl-6-methyl-4-(2-phenoxybenzyl)-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**15**). LRMS (ES) (M+H)⁺: observed = 564.4, calculated = 563.7.

EXAMPLE 16



10 Preparation of (2R,6R)-4-(1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**16-1**)

Step 1: In an analogous manner to example **12g**, (2R,6R)-4-(tert-butoxycarbonyl)-1-isobutyryl-6-methylpiperazine-2-carboxylic acid (**12e**) and HCl were used to prepare (2R,6R)-1-isobutyryl-6-methylpiperazine-2-carboxylic acid (**16a**). LRMS (ES) (M+H)⁺: observed = 215.4, calculated = 214.2.

Step 2: Preparation of 1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropan-1-ol (**16c**) To a stirred solution of 2-bromo-3-fluoro-4-methylpyridine (**16b**, 1.00 g, 5.26 mmol) in THF (13.2 mL) chilled in an ice bath to 0°C under nitrogen was added a 1.3M isopropyl magnesium chloride lithium chloride solution (4.05 mL, 5.26 mmol) dropwise over 5 minutes. The resulting solution

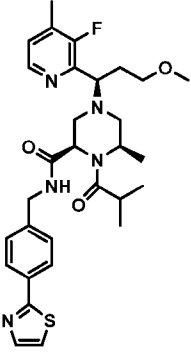
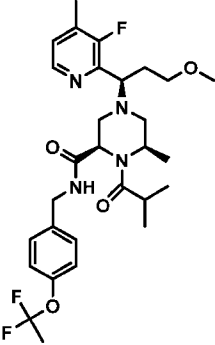
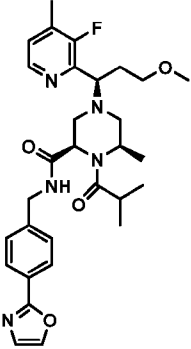
was allowed to warm to room temperature and stirred 3.5 hours. The reaction was recharged to 0°C and a solution of 3-methoxypropanal (0.47 g, 5.26 mmol) dissolved in THF (1 mL) was added dropwise. The resulting mixture was allowed to stir at room temperature overnight, quenched with sat. ammonium chloride solution and extracted several times with ethyl acetate. The organic layers were combined, concentrated, and flash column purification using a 0-50% ethyl acetate/hexane gradient gave 1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropan-1-ol (**16c**). LRMS (ES) (M+H)⁺: observed = 200.1, calculated = 199.2.

Step 3: Preparation of 2-(1-chloro-3-methoxypropyl)-3-fluoro-4-methylpyridine (**16d**) To a vial containing 1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropan-1-ol (**16c**, 0.444 g, 0.223 mmol) was added thionyl chloride (1.0 mL, 13.70 mmol) dropwise. The resulting solution was heated to 80°C for 1 hour. The mixture was allowed to cool to room temperature and concentrated. The concentrate was taken up in ethyl ether and concentrated to dryness several times. The crude material 2-(1-chloro-3-methoxypropyl)-3-fluoro-4-methylpyridine (**16d**).

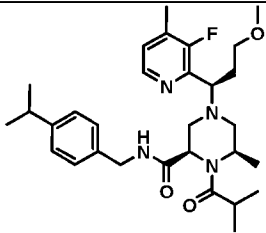
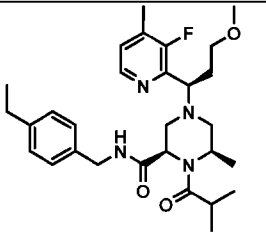
Step 4: Preparation of (2R,6R)-4-((R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl)-1-isobutyryl-6-methylpiperazine-2-carboxylic acid (**16e**) To a vial containing 2-(1-chloro-3-methoxypropyl)-3-fluoro-4-methylpyridine (**16d**, 0.223 mmol), potassium iodide (0.36 g, 2.20 mmol), potassium carbonate (0.91 g, 6.58 mmol), and (2R,6R)-1-isobutyryl-6-methylpiperazine-2-carboxylic acid (**16a**, 0.55 g, 2.20 mmol) was added acetonitrile (3.65 mL). The resulting mixture was stirred at 80°C overnight. The mixture was filtered through celite and concentrated. The crude material was purified by reverse phase purification to give (2R,6R)-4-((R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl)-1-isobutyryl-6-methylpiperazine-2-carboxylic acid (**16e**). LRMS (ES) (M+H)⁺: observed = 396.3, calculated = 395.5.

Step 5: Preparation of (2R,6R)-4-(1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**16-1**) To a stirred solution of (2R,6R)-4-((R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl)-1-isobutyryl-6-methylpiperazine-2-carboxylic acid (**16e**, 0.010 g, 0.02 mmol) and (4-(pyrimidin-2-yl)phenyl)methanamine (0.006 g, 0.02 mmol) in DMF (0.07 mL) was added HATU (0.008 g, 0.022 mmol) followed by triethylamine (0.008 mL, 0.06 mmol). The resulting solution was stirred 1 hour and purified by reverse phase purification to give (2R,6R)-4-(1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**16-1**). LRMS (ES) (M+H)⁺: observed = 585.5, calculated = 562.7.

The following compounds were prepared in an analogous manner to example 16-1.

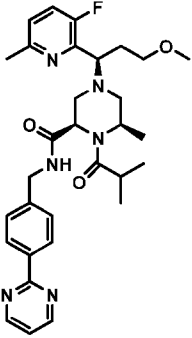
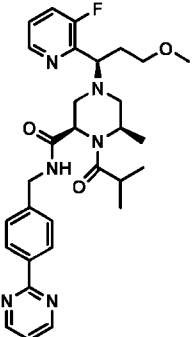
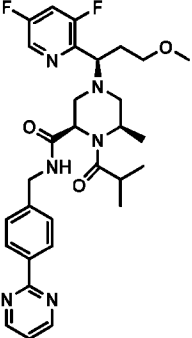
Example	Structure	Name	Calculated Mass	Observed Mass (M+H)
16-2		(2R,6R)-4-[(1R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl]-6-methyl-1-(2-methylpropanoyl)-N-{{[4-(1,3-thiazol-2-yl)phenyl]methyl}piperazine-2-carboxamide	567.731	568.4
16-3		(2R,6R)-N-{{[4-(1,1-difluoroethoxy)phenyl]methyl}-4-[(1R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl]-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide	564.654	565.4
16-4		(2R,6R)-4-[(1R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl]-6-methyl-1-(2-methylpropanoyl)-N-{{[4-(1,3-oxazol-2-yl)phenyl]methyl}piperazine-2-carboxamide	551.667	574.4

16-5		(2R,6R)-4-[(1R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl]-6-methyl-1-(2-methylpropanoyl)-N-{[4-(2H-1,2,3-triazol-2-yl)phenyl]methyl}piperazine-2-carboxamide	551.67	552.4
16-6		(2R,6R)-4-[(1R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl]-6-methyl-1-(2-methylpropanoyl)-N-[(4-propylphenyl)methyl]piperazine-2-carboxamide	526.701	527.5
16-7		(2R,6R)-N-[(4-cyclopropylphenyl)methyl]-4-[(1R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl]-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide	524.685	525.5
16-8		(2R,6R)-N-[(4-tert-butylphenyl)methyl]-4-[(1R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl]-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide	540.728	541.6

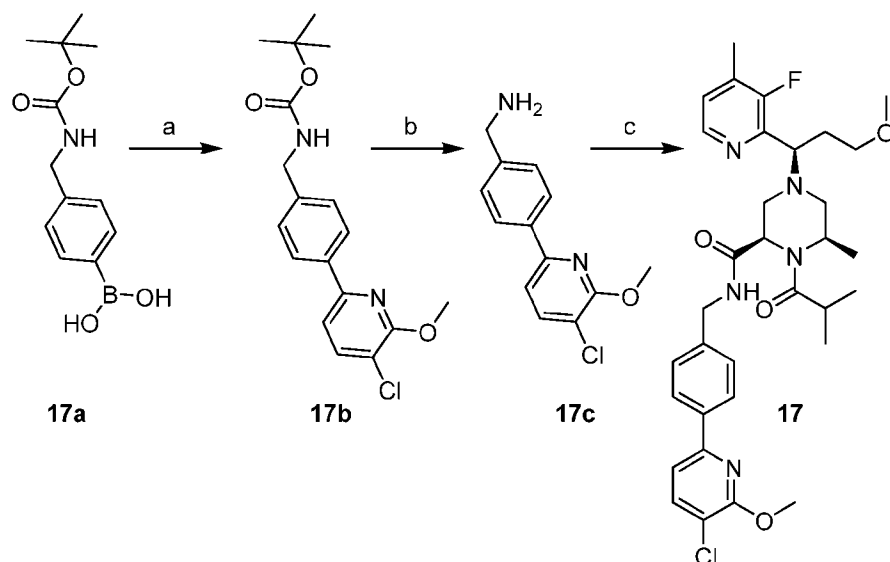
		methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide		
16-9		(2R,6R)-4-[(1R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl]-6-methyl-1-(2-methylpropanoyl)-N-{{[4-(propan-2-yl)phenyl]methyl}piperazine-2-carboxamide	526.701	527.6
16-10		(2R,6R)-N-[(4-ethylphenyl)methyl]-4-[(1R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl]-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide	512.674	513.5

The following compounds were prepared in an analogous manner to example **16-1** using the appropriately substituted bromopyridine.

Example	Structure	Name	Calculated Mass	Observed Mass (M+H)

16-11		(2R,6R)-4-[(1R)-1-(3-fluoro-6-methylpyridin-2-yl)-3-methoxypropyl]-6-methyl-1-(2-methylpropanoyl)-N-{[4-(pyrimidin-2-yl)phenyl]methyl}piperazine-2-carboxamide	562.693	563.6
16-12		(2R,6R)-4-[(1R)-1-(3-fluoropyridin-2-yl)-3-methoxypropyl]-6-methyl-1-(2-methylpropanoyl)-N-{[4-(pyrimidin-2-yl)phenyl]methyl}piperazine-2-carboxamide	548.666	549.4
16-13		(2R,6R)-4-[(1R)-1-(3,5-difluoropyridin-2-yl)-3-methoxypropyl]-6-methyl-1-(2-methylpropanoyl)-N-{[4-(pyrimidin-2-yl)phenyl]methyl}piperazine-2-carboxamide	566.657	567

EXAMPLE 17



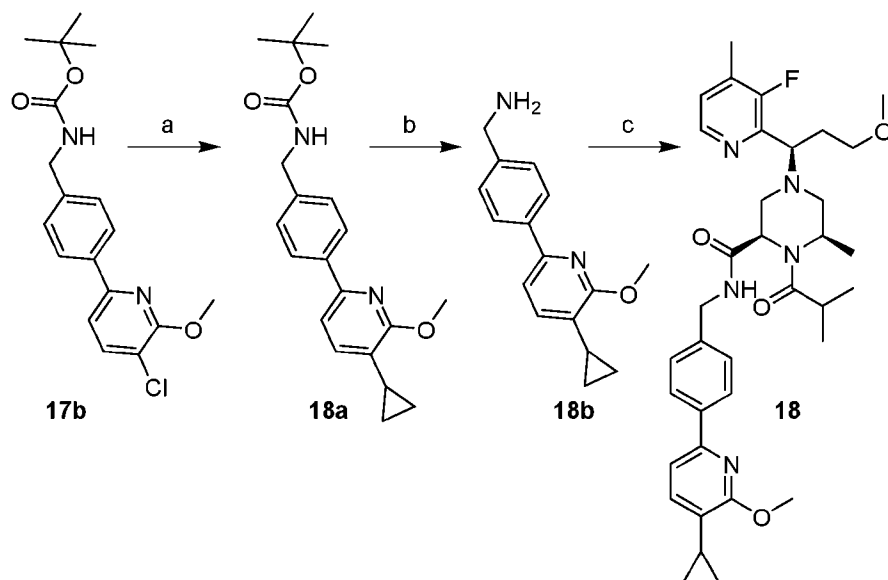
Preparation of (2R,6R)-N-(4-(5-chloro-6-methoxypyridin-2-yl)benzyl)-4-((R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl)-1-isobutyl-6-methylpiperazine-2-carboxamide (**17**)

Step 1: Preparation of tert-butyl (4-(5-chloro-6-methoxypyridin-2-yl)benzyl)carbamate (**17b**) To a vial containing 4-(((tert-butoxycarbonyl)amino)methyl)phenylboronic acid (**17a**, 0.20 g, 0.80 mmol), 6-bromo-3-chloro-2-methoxypyridine (0.266 g, 1.195 mmol), Potassium phosphate (0.254 g, 1.195 mmol), and Tetrakis(triphenylphosphine)palladium(0) (0.092 g, 0.08 mmol) under nitrogen was added Dioxane (2 mL) and water (2 mL) and the resulting mixture was heated overnight at 80°C. The mixture was allowed to cool to room temperature and concentrated. The crude material was partitioned between water and ethyl acetate. The organic phase was concentrated and flash column purification using a 0-30% ethyl acetate/ hexane gradient gave tert-butyl (4-(5-chloro-6-methoxypyridin-2-yl)benzyl)carbamate (**17b**). LRMS (ES) (M+H)⁺: observed = 349.2, calculated = 348.8.

Step 2: In an analogous manner to example **12g**, tert-butyl (4-(5-chloro-6-methoxypyridin-2-yl)benzyl)carbamate (**17b**) and HCl were used to prepare 4-(5-chloro-6-methoxypyridin-2-yl)phenylmethanamine (**17c**, 98%). LRMS (ES) (M+H)⁺: observed = 249.1, calculated = 248.7.

Step 3: In an analogous manner to example **16-1**, (2R,6R)-4-((R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl)-1-isobutyl-6-methylpiperazine-2-carboxylic acid (**16e**) and 4-(5-chloro-6-methoxypyridin-2-yl)phenylmethanamine (**17c**) were used to prepare (2R,6R)-N-(4-(5-chloro-6-methoxypyridin-2-yl)benzyl)-4-((R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl)-1-isobutyl-6-methylpiperazine-2-carboxamide (**17**). LRMS (ES) (M+H)⁺: observed = 627.4, calculated = 626.2.

EXAMPLE 18



Preparation of (2R,6R)-N-(4-(5-cyclopropyl-6-methoxypyridin-2-yl)benzyl)-4-((R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl)-1-isobutyryl-6-methylpiperazine-2-carboxamide (**18**)

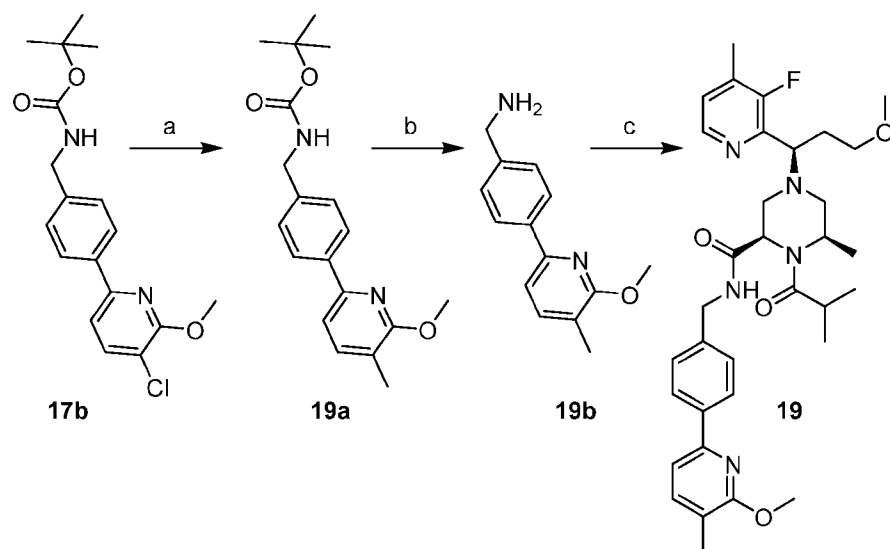
- 5 Step 1: Preparation of tert-butyl (4-(5-cyclopropyl-6-methoxypyridin-2-yl)benzyl)carbamate (**18a**) To a vial containing tert-butyl (4-(5-chloro-6-methoxypyridin-2-yl)benzyl)carbamate (**17b**, 0.06 g, 0.172 mmol), cyclopropyl boronic acid (0.022 g, 0.258 mmol), Potassium carbonate (0.036 g, 0.258 mmol), and Chloro(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) (0.014 g, 0.017 mmol) under nitrogen was added Dioxane (0.43 mL) and water (0.43 mL) and the resulting mixture was heated overnight at 90°C. The mixture was allowed to cool to room temperature and concentrated. The crude material was partitioned between water and ethyl acetate. The organic phase was concentrated and flash column purification using a 0-20% ethyl acetate/ hexane gradient gave tert-butyl (4-(5-cyclopropyl-6-methoxypyridin-2-yl)benzyl)carbamate (**18a**). LRMS (ES) (M+H)⁺: observed = 355.3, calculated = 354.5.

Step 2: In an analogous manner to example **12g**, tert-butyl (4-(5-cyclopropyl-6-methoxypyridin-2-yl)benzyl)carbamate (**18a**) and HCl were used to prepare (4-(5-cyclopropyl-6-methoxypyridin-2-yl)phenyl)methanamine (**18b**). LRMS (ES) (M+H)⁺: observed = 255.1, calculated = 254.3.

- Step 3: In an analogous manner to example **16-1**, (2R,6R)-4-((R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl)-1-isobutyryl-6-methylpiperazine-2-carboxylic acid (**16e**) and (4-(5-cyclopropyl-6-methoxypyridin-2-yl)phenyl)methanamine (**18b**) were used to prepare (2R,6R)-N-

(4-(5-cyclopropyl-6-methoxypyridin-2-yl)benzyl)-4-((R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl)-1-isobutyryl-6-methylpiperazine-2-carboxamide (**18**). LRMS (ES) (M+H)⁺: observed = 632.4, calculated = 631.8.

EXAMPLE 19



5

Preparation of (2R,6R)-4-((R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl)-1-isobutyryl-N-(4-(6-methoxy-5-methylpyridin-2-yl)benzyl)-6-methylpiperazine-2-carboxamide (**19**)

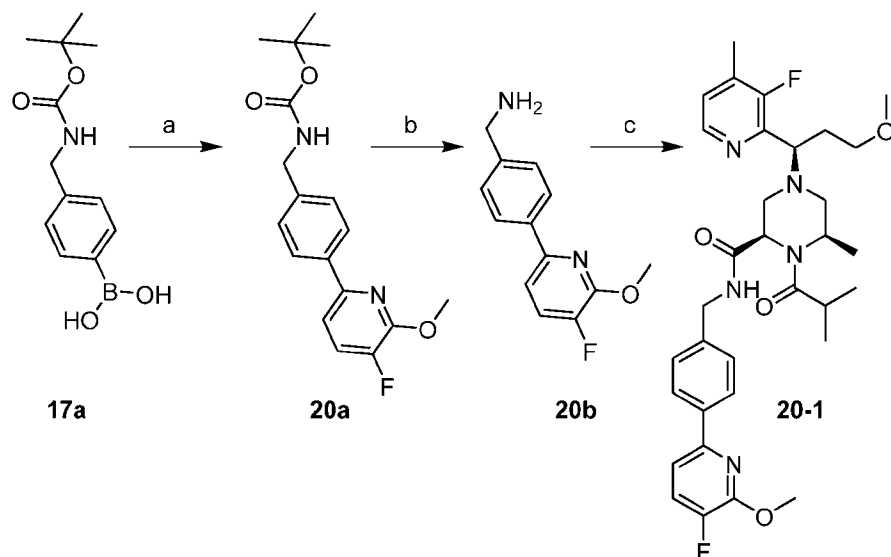
Step 1: In an analogous manner to example **18a**, tert-butyl (4-(5-chloro-6-methoxypyridin-2-yl)benzyl)carbamate (**17b**) and Trimethylboroxine were used to prepare tert-butyl (4-(6-methoxy-5-methylpyridin-2-yl)benzyl)carbamate (**19a**). LRMS (ES) (M+H)⁺: observed = 329.2, calculated = 328.4.

Step 2: In an analogous manner to example **12g**, tert-butyl (4-(6-methoxy-5-methylpyridin-2-yl)benzyl)carbamate (**19a**) and HCl were used to prepare (4-(6-methoxy-5-methylpyridin-2-yl)phenyl)methanamine (**19b**). LRMS (ES) (M+H)⁺: observed = 229.1, calculated = 228.3.

Step 3: In an analogous manner to example **16-1**, (2R,6R)-4-((R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl)-1-isobutyryl-6-methylpiperazine-2-carboxylic acid (**16e**) and (4-(6-methoxy-5-methylpyridin-2-yl)phenyl)methanamine (**19b**) were used to prepare (2R,6R)-4-((R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl)-1-isobutyryl-N-(4-(6-methoxy-5-methylpyridin-2-yl)benzyl)-6-methylpiperazine-2-carboxamide (**19**). LRMS (ES) (M+H)⁺: observed = 606.5, calculated = 605.8.

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EXAMPLE 20



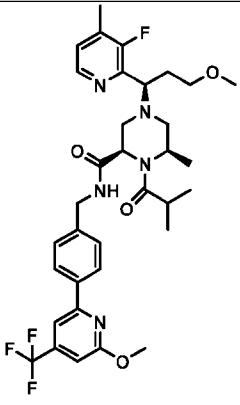
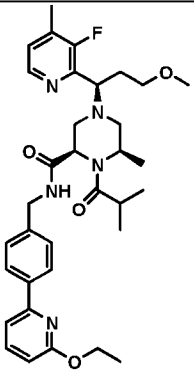
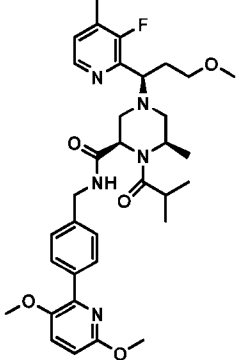
Preparation of (2R,6R)-4-((R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl)-N-(4-(5-fluoro-6-methoxypyridin-2-yl)benzyl)-1-isobutyryl-6-methylpiperazine-2-carboxamide (**20-1**)

- 5 Step 1: Preparation of tert-butyl (4-(5-fluoro-6-methoxypyridin-2-yl)benzyl)carbamate (**20a**) To a vial containing 4-(((tert-butoxycarbonyl)amino)methyl)phenyl)boronic acid (**17a**, 0.15 g, 0.60 mmol), 6-bromo-3-fluoro-2-methoxypyridine (0.185 g, 0.90 mmol), Potassium phosphate (0.19 g, 0.90 mmol), and [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (0.049 g, 0.06 mmol) under nitrogen was added Dioxane (1.5 mL) and water
- 10 (1.5 mL) and the resulting mixture was heated 3 hours at 90°C. The mixture was allowed to cool and partitioned between water and ethyl acetate. The organic phase was concentrated and flash column purification using a 0-20% ethyl acetate/ hexane gradient gave tert-butyl (4-(5-fluoro-6-methoxypyridin-2-yl)benzyl)carbamate (**20a**). LRMS (ES) (M+H)⁺: observed = 333.2, calculated = 332.4.
- 15 Step 2: In an analogous manner to example **12g**, tert-butyl (4-(5-fluoro-6-methoxypyridin-2-yl)benzyl)carbamate (**20a**) and HCl were used to prepare 4-(5-fluoro-6-methoxypyridin-2-yl)phenyl)methanamine (**20b**). LRMS (ES) (M+H)⁺: observed = 233.1, calculated = 232.3.
- Step 3: In an analogous manner to example **16-1**, (2R,6R)-4-((R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl)-1-isobutyryl-6-methylpiperazine-2-carboxylic acid (**16e**) and 4-(5-fluoro-6-methoxypyridin-2-yl)phenyl)methanamine (**20b**) were used to prepare (2R,6R)-4-((R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl)-N-(4-(5-fluoro-6-methoxypyridin-2-yl)benzyl)-
- 20

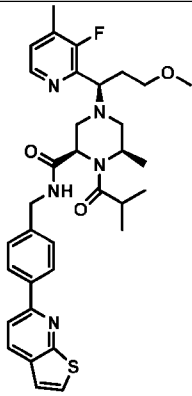
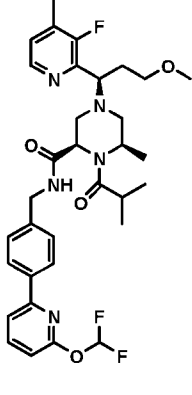
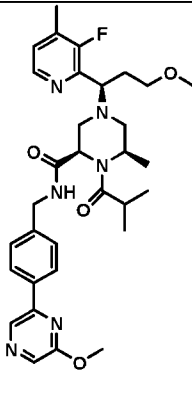
1-isobutyryl-6-methylpiperazine-2-carboxamide (**20-1**). LRMS (ES) (M+H)⁺: observed = 610.4, calculated = 609.7.

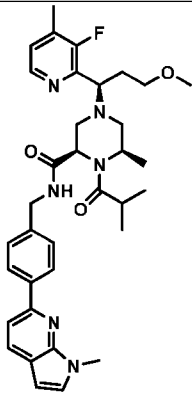
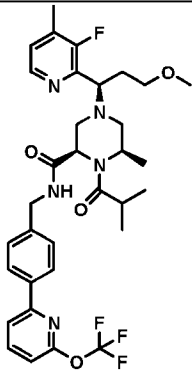
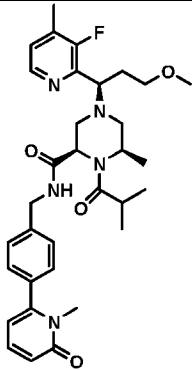
The following compounds were prepared in an analogous manner to example **20-1** using the appropriate aryl halide.

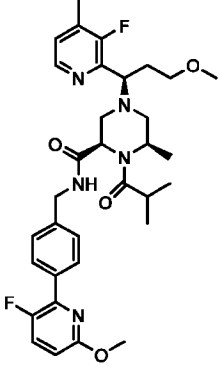
Example	Structure	Name	Calculated Mass	Observed Mass (M+H)
20-2		(2R,6R)-N-([4-(4,6-dimethoxypyridin-2-yl)phenyl]methyl)-4-[(1R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl]-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide	621.759	622.1
20-3		(2R,6R)-4-[(1R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl]-N-([4-(6-methoxy-4-methylpyridin-2-yl)phenyl]methyl)-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide	605.759	606.5
20-4		(2R,6R)-4-[(1R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl]-N-([4-(4-methoxypyrimidin-2-yl)phenyl]methyl)-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide	592.72	593.3

20-5		(2R,6R)-4-[(1R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl]-N-({4-[6-methoxy-4-(trifluoromethyl)pyridin-2-yl]phenyl}methyl)-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide	659.731	660.4
20-6		(2R,6R)-N-({4-(6-ethoxypyridin-2-yl)phenyl}methyl)-4-[(1R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl]-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide	605.759	606.4
20-7		(2R,6R)-N-({4-(3,6-dimethoxypyridin-2-yl)phenyl}methyl)-4-[(1R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl]-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide	621.759	622.4

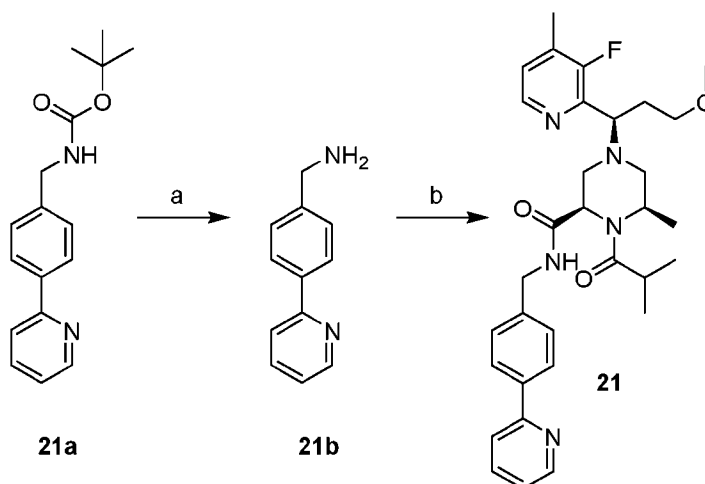
20-8		(2R,6R)-N-({4-[6-(difluoromethyl)pyridin-2-yl]phenyl}methyl)-4-[(1R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl]-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide	611.714	612.4
20-9		(2R,6R)-N-[(2'-fluoro-3'-methoxy[1,1'-biphenyl]-4-yl)methyl]-4-[(1R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl]-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide	608.735	609.4
20-10		(2R,6R)-4-[(1R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl]-N-{[4-(5-fluoropyrimidin-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide	580.684	581.3

20-11		(2R,6R)-4-[(1R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl]-6-methyl-1-(2-methylpropanoyl)-N-{{4-(thieno[2,3-b]pyridin-6-yl)phenyl}methyl}piperazine-2-carboxamide	617.792	618.4
20-12		(2R,6R)-N-({4-[6-(difluoromethoxy)pyridin-2-yl]phenyl}methyl)-4-[(1R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl]-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide	627.713	628.5
20-13		(2R,6R)-4-[(1R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl]-N-{{4-(6-methoxypyrazin-2-yl)phenyl}methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide	592.72	593.4

20-14		(2R,6R)-4-[(1R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl]-6-methyl-1-(2-methylpropanoyl)-N-([4-(1-methyl-1H-pyrrolo[2,3-b]pyridin-6-yl)phenyl]methyl)piperazine-2-carboxamide	614.77	615.4
20-15		(2R,6R)-4-[(1R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl]-6-methyl-1-(2-methylpropanoyl)-N-([4-[6-(trifluoromethoxy)pyridin-2-yl]phenyl]methyl)piperazine-2-carboxamide	645.703	646.2
20-16		(2R,6R)-4-[(1R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl]-6-methyl-N-([4-(1-methyl-6-oxo-1,6-dihydropyridin-2-yl)phenyl]methyl)-1-(2-methylpropanoyl)piperazine-2-carboxamide	591.732	592.4

20-17		(2R,6R)-N-([4-(3-fluoro-6-methoxypyridin-2-yl)phenyl]methyl)-4-[(1R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl]-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide	609.723	610.4
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EXAMPLE 21

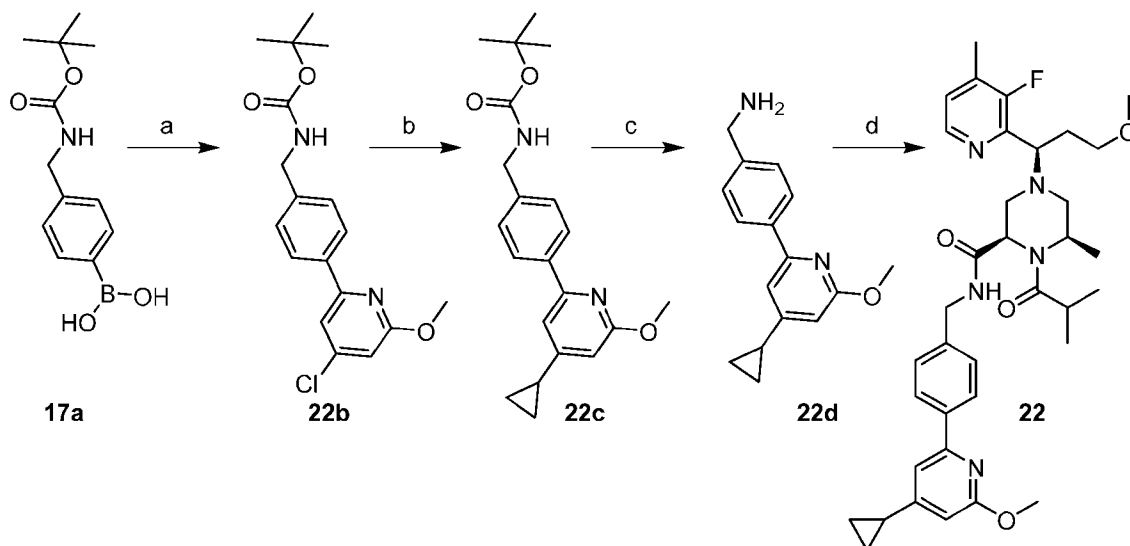


Preparation of (2R,6R)-4-((R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl)-1-isobutyryl-6-methyl-N-(4-(pyridin-2-yl)benzyl)piperazine-2-carboxamide (**21**)

Step 1: In an analogous manner to example **12g**, tert-butyl (4-(pyridin-2-yl)benzyl)carbamate (**21a**) and HCl were used to prepare 4-(pyridin-2-yl)phenylmethanamine (**21b**, used directly).

Step 2: In an analogous manner to example **16-1**, (2R,6R)-4-((R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl)-1-isobutyryl-6-methylpiperazine-2-carboxylic acid (**16e**) and 4-(pyridin-2-yl)phenylmethanamine (**21b**) were used to prepare (2R,6R)-4-((R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl)-1-isobutyryl-6-methyl-N-(4-(pyridin-2-yl)benzyl)piperazine-2-carboxamide (**21**). LRMS (ES) (M+H)⁺: observed = 562.4, calculated = 561.7.

EXAMPLE 22



Preparation of (2R,6R)-N-(4-(4-cyclopropyl-6-methoxypyridin-2-yl)benzyl)-4-((R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl)-1-isobutyryl-6-methylpiperazine-2-carboxamide (**22**)

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Step 1: Preparation of tert-butyl (4-(4-chloro-6-methoxypyridin-2-yl)benzyl)carbamate (**22b**) To a vial containing (4-(((tert-butoxycarbonyl)amino)methyl)phenyl)boronic acid (**17a**, 0.20 g, 0.80 mmol), 6-bromo-4-chloro-2-methoxypyridine (0.23 g, 1.04 mmol), Potassium phosphate (0.25 g, 1.20 mmol), and Tetrakis(triphenylphosphine)palladium(0) (0.092 g, 0.08 mmol) under nitrogen was added Dioxane (2 mL) and water (2 mL) and the resulting mixture was heated 2 hours at 90°C. The mixture was allowed to cool to room temperature and concentrated. The crude material was partitioned between water and ethyl acetate. The organic phase was concentrated and flash column purification using a 0-20% ethyl acetate/ hexane gradient gave tert-butyl (4-(4-chloro-6-methoxypyridin-2-yl)benzyl)carbamate (**22b**). LRMS (ES) (M+H)⁺: observed = 349.2, calculated = 348.8.

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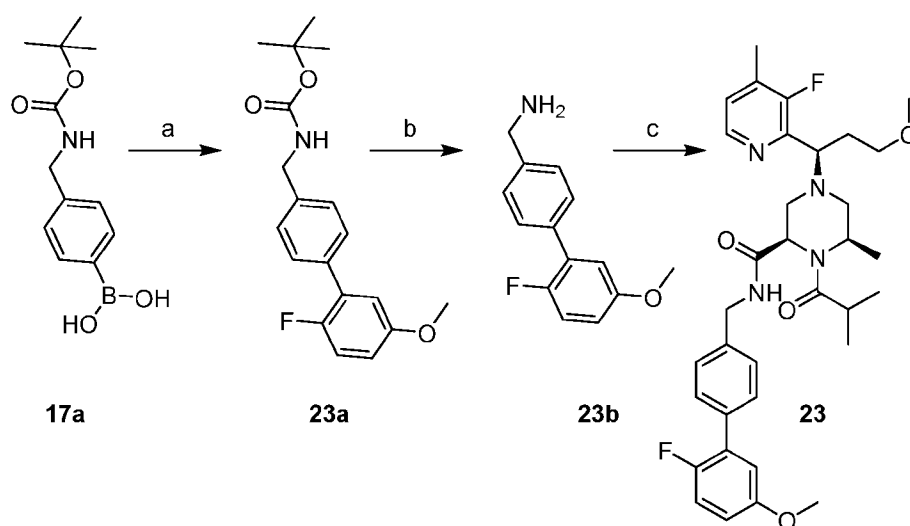
Step 2: In an analogous manner to example **18a**, tert-butyl (4-(4-chloro-6-methoxypyridin-2-yl)benzyl)carbamate (**22b**) and cyclopropyl boronic acid were used to prepare tert-butyl (4-(4-cyclopropyl-6-methoxypyridin-2-yl)benzyl)carbamate (**22c**). LRMS (ES) (M+H)⁺: observed = 355.2, calculated = 354.5.

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Step 3: In an analogous manner to example **12g**, tert-butyl (4-(4-cyclopropyl-6-methoxypyridin-2-yl)benzyl)carbamate (**22c**) and HCl were used to prepare (4-(4-cyclopropyl-6-methoxypyridin-2-yl)phenyl)methanamine (**22d**). LRMS (ES) (M+H)⁺: observed = 255.1, calculated = 254.3.

Step 4: In an analogous manner to example **16-1**, (2R,6R)-4-((R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl)-1-isobutyryl-6-methylpiperazine-2-carboxylic acid (**16e**) and (4-(4-cyclopropyl-6-methoxypyridin-2-yl)phenyl)methanamine (**22d**) were used to prepare (2R,6R)-N-(4-(4-cyclopropyl-6-methoxypyridin-2-yl)benzyl)-4-((R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl)-1-isobutyryl-6-methylpiperazine-2-carboxamide (**22**). LRMS (ES) (M+H)⁺: observed = 632.5, calculated = 631.8.

EXAMPLE 23



Preparation of (2R,6R)-4-((R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl)-N-((2'-fluoro-5'-methoxy-[1,1'-biphenyl]-4-yl)methyl)-1-isobutyryl-6-methylpiperazine-2-carboxamide (**23**)

Step 1: Preparation of tert-butyl ((2'-fluoro-5'-methoxy-[1,1'-biphenyl]-4-yl)methyl)carbamate (**23a**) To a vial containing (4-(((tert-butoxycarbonyl)amino)methyl)phenyl)boronic acid (**17a**, 0.20 g, 0.80 mmol), 2-chloro-1-fluoro-4-methoxybenzene (0.19 g, 1.20 mmol), Potassium phosphate (0.25 g, 1.20 mmol), Pd(OAc)₂ (0.018 g, 0.08 mmol) and 2-Dicyclohexylphosphino-2',6'-dimethoxybiphenyl (0.065 g, 0.16 mmol) under nitrogen was added Dioxane (2 mL) and water (2 mL) and the resulting mixture was heated overnight at 90°C. The mixture was allowed to cool to room temperature and partitioned between water and ethyl acetate. Both phases were filtered through celite and the organic phase was concentrated and flash column purification

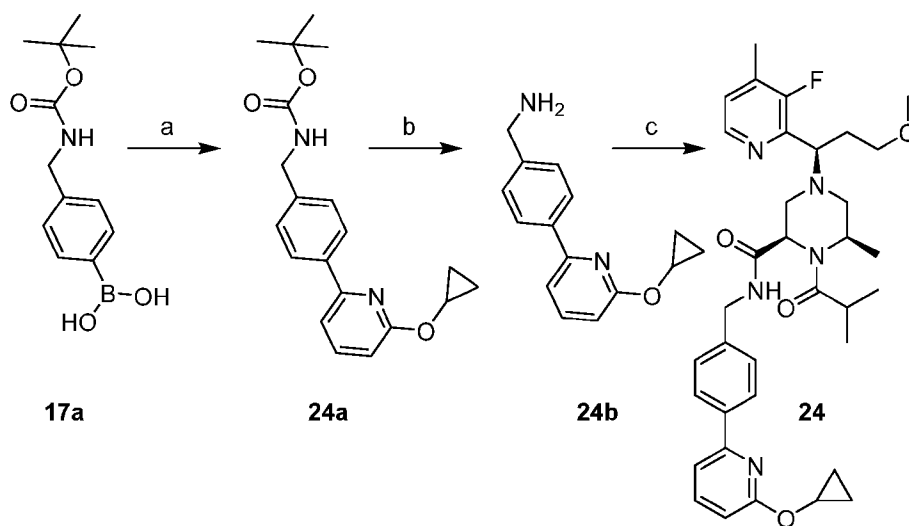
using a 0-100% ethyl acetate/ hexane gradient gave tert-butyl ((2'-fluoro-5'-methoxy-[1,1'-biphenyl]-4-yl)methyl)carbamate (**23a**).

Step 2: In an analogous manner to example **12g**, tert-butyl ((2'-fluoro-5'-methoxy-[1,1'-biphenyl]-4-yl)methyl)carbamate (**23a**) and HCl were used to prepare (2'-fluoro-5'-methoxy-[1,1'-

5 biphenyl]-4-yl)methanamine (**23b**). LRMS (ES) (M+H)⁺: observed = 232.1, calculated = 231.3.

Step 3: In an analogous manner to example **16-1**, (2R,6R)-4-((R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl)-1-isobutyryl-6-methylpiperazine-2-carboxylic acid (**16e**) and (2'-fluoro-5'-methoxy-[1,1'-biphenyl]-4-yl)methanamine (**23b**) were used to prepare (2R,6R)-4-((R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl)-N-((2'-fluoro-5'-methoxy-[1,1'-biphenyl]-4-yl)methyl)-1-isobutyryl-6-methylpiperazine-2-carboxamide (**23**). LRMS (ES) (M+H)⁺: observed = 609.4, calculated = 608.7.

EXAMPLE 24



Preparation of (2R,6R)-N-(4-(6-cyclopropoxypyridin-2-yl)benzyl)-4-((R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl)-1-isobutyryl-6-methylpiperazine-2-carboxamide (**24**)

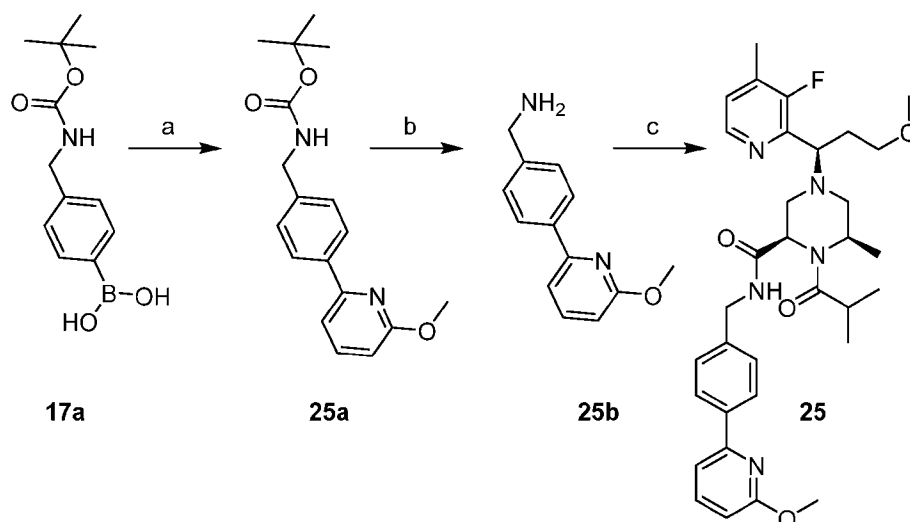
Step 1: Preparation of tert-butyl (4-(6-cyclopropoxypyridin-2-yl)benzyl)carbamate (**24a**) To a vial containing 4-(((tert-butoxycarbonyl)amino)methyl)phenylboronic acid (**17a**, 0.15 g, 0.60 mmol), 2-bromo-6-cyclopropoxypyridine (0.166 g, 0.78 mmol), Potassium phosphate (0.19 g, 0.90 mmol), and Chloro(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) (0.047 g, 0.06 mmol) under nitrogen was added Dioxane (1.5 mL) and water (1.5 mL) and the resulting mixture was heated overnight at 90°C. The mixture

was allowed to cool and partitioned between water and ethyl acetate. The organic phase was concentrated and flash column purification using a 0-20% ethyl acetate/ hexane gradient gave tert-butyl (4-(6-cyclopropoxy-pyridin-2-yl)benzyl)carbamate (**24a**). LRMS (ES) (M+H)⁺: observed = 341.1, calculated = 340.4.

5 Step 2: In an analogous manner to example **12g**, tert-butyl (4-(6-cyclopropoxy-pyridin-2-yl)benzyl)carbamate (**24a**) and HCl were used to prepare (4-(6-cyclopropoxy-pyridin-2-yl)phenyl)methanamine (**24b**). LRMS (ES) (M+H)⁺: observed = 241.1, calculated = 240.3.

Step 3: In an analogous manner to example **16-1**, (2R,6R)-4-((R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl)-1-isobutyryl-6-methylpiperazine-2-carboxylic acid (**16e**) and (4-(6-cyclopropoxy-pyridin-2-yl)phenyl)methanamine (**24b**) were used to prepare (2R,6R)-N-(4-(6-cyclopropoxy-pyridin-2-yl)benzyl)-4-((R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl)-1-isobutyryl-6-methylpiperazine-2-carboxamide (**24**). LRMS (ES) (M+H)⁺: observed = 618.4, calculated = 617.8.

EXAMPLE 25



Preparation of (2R,6R)-4-((R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl)-1-isobutyryl-N-(4-(6-methoxypyridin-2-yl)benzyl)-6-methylpiperazine-2-carboxamide (**25**)

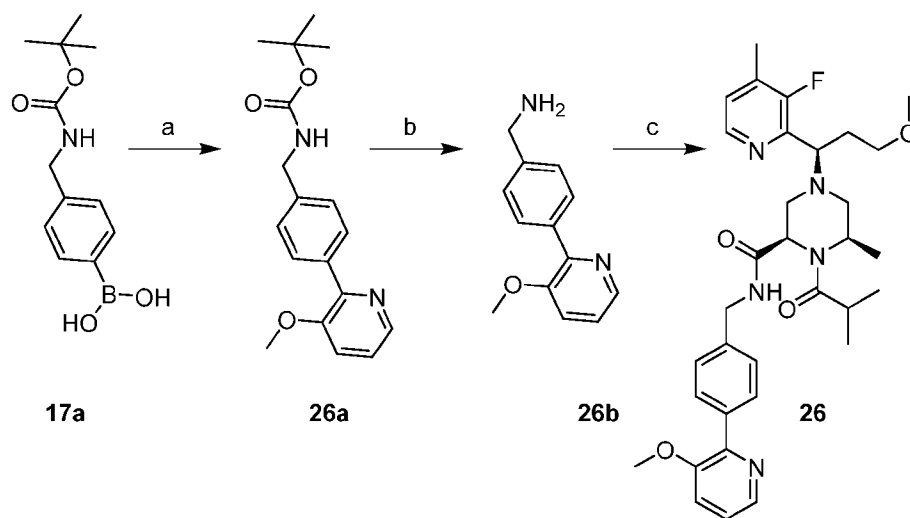
15 Step 1: In an analogous manner to example **24a**, 4-(((tert-butoxycarbonyl)amino)methyl)phenyl)boronic acid (**17a**) and 2-bromo-6-methoxypyridine were used to prepare tert-butyl (4-(6-methoxypyridin-2-yl)benzyl)carbamate (**25a**, 26%). LRMS (ES) (M+H)⁺: observed = 315.1, calculated = 314.4.

Step 2: In an analogous manner to example **12g**, tert-butyl (4-(6-methoxypyridin-2-yl)benzyl)carbamate (**25a**) and HCl were used to prepare (4-(6-methoxypyridin-2-yl)phenyl)methanamine (**25b**). LRMS (ES) (M+H)⁺: observed = 215.0, calculated = 214.2.

Step 3: In an analogous manner to example **16-1**, (2R,6R)-4-((R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl)-1-isobutyryl-6-methylpiperazine-2-carboxylic acid (**16e**) and (4-(6-methoxypyridin-2-yl)phenyl)methanamine (**25b**) were used to prepare (2R,6R)-4-((R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl)-1-isobutyryl-N-(4-(6-methoxypyridin-2-yl)benzyl)-6-methylpiperazine-2-carboxamide (**25**). LRMS (ES) (M+H)⁺: observed = 592.4, calculated = 591.7.

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EXAMPLE 26



Preparation of (2R,6R)-4-((R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl)-1-isobutyryl-N-(4-(3-methoxypyridin-2-yl)benzyl)-6-methylpiperazine-2-carboxamide (**26**)

Step 1: In an analogous manner to example **24a**, 4-(((tert-

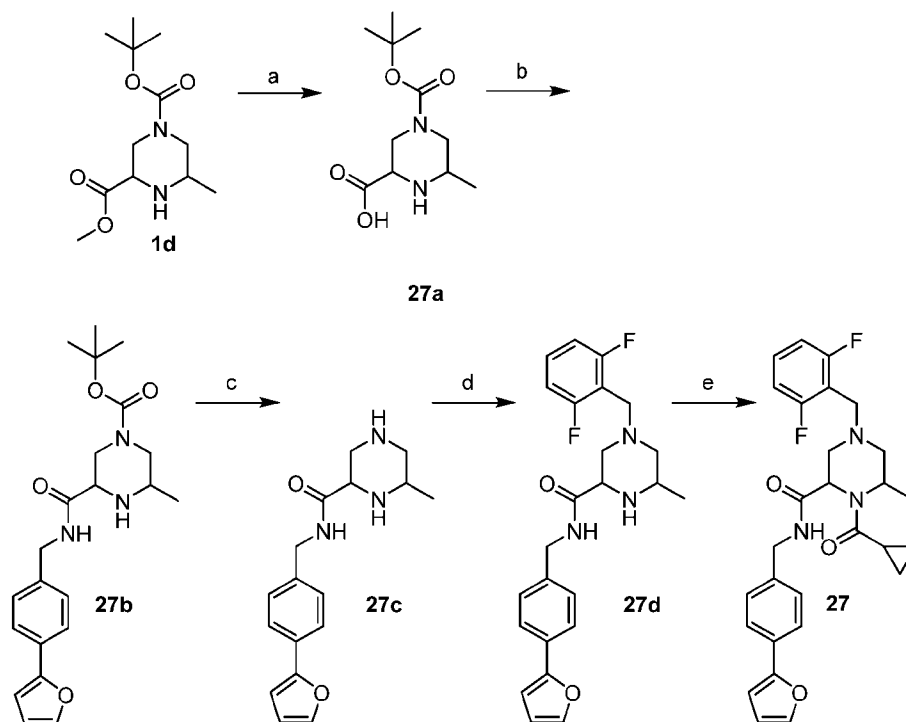
15 butoxycarbonyl)amino)methyl)phenyl)boronic acid (**17a**) and 2-bromo-3-methoxypyridine were used to prepare tert-butyl (4-(3-methoxypyridin-2-yl)benzyl)carbamate (**26a**).

Step 2: In an analogous manner to example **12g**, tert-butyl (4-(3-methoxypyridin-2-yl)benzyl)carbamate (**26a**) and HCl were used to prepare (4-(3-methoxypyridin-2-yl)phenyl)methanamine (**26b**). LRMS (ES) (M+H)⁺: observed = 215.1, calculated = 214.2.

20 Step 3: In an analogous manner to example **16-1**, (2R,6R)-4-((R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl)-1-isobutyryl-6-methylpiperazine-2-carboxylic acid (**16e**) and (4-(3-methoxypyridin-2-yl)phenyl)methanamine (**26b**) were used to prepare (2R,6R)-4-((R)-1-(3-

fluoro-4-methylpyridin-2-yl)-3-methoxypropyl)-1-isobutyl-N-(4-(3-methoxypyridin-2-yl)benzyl)-6-methylpiperazine-2-carboxamide (**26**). LRMS (ES) (M+H)⁺: observed = 592.5, calculated = 591.7.

EXAMPLE 27



Preparation of 1-(cyclopropanecarbonyl)-4-(2,6-difluorobenzyl)-N-(4-(furan-2-yl)benzyl)-6-methylpiperazine-2-carboxamide (**27**)

Step 1: In an analogous manner to example 1f, cis-1-(tert-butyl) 3-methyl 5-methylpiperazine-1,3-dicarboxylate (**1d**) and potassium trimethylsilanolate were used to prepare 4-(tert-butoxycarbonyl)-6-methylpiperazine-2-carboxylic acid (**27a**, Quant.). LRMS (ES) (M+H)⁺: observed = 245.1, calculated = 244.3.

Step 2: Preparation of tert-butyl 3-((4-(furan-2-yl)benzyl)carbamoyl)-5-methylpiperazine-1-carboxylate (**27b**) To a stirred solution of 4-(tert-butoxycarbonyl)-6-methylpiperazine-2-carboxylic acid (**27a**, 0.47 g, 1.93 mmol) and (4-(furan-2-yl)phenyl)methanamine (0.40 g, 2.32 mmol) in DCM (8.7 mL) and DMSO (0.96 mL) was added HATU (0.88 g, 2.32 mmol) and N-methyl morpholine (0.85 mL, 7.74 mmol). The resulting mixture was stirred overnight, then concentrated. Flash column purification using a 0-100% (3:1 ethyl acetate/ethanol) /hexane

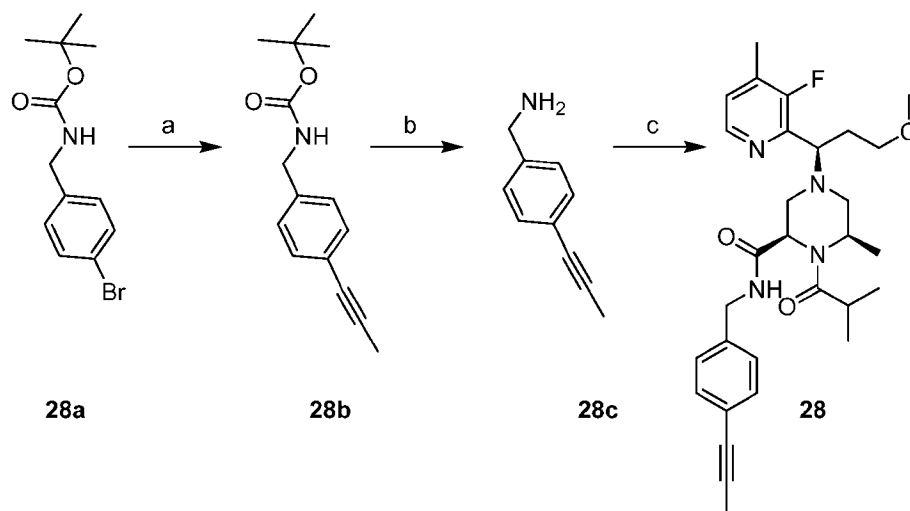
gradient gave tert-butyl 3-((4-(furan-2-yl)benzyl)carbamoyl)-5-methylpiperazine-1-carboxylate (27b, 66%). LRMS (ES) (M+H)⁺: observed = 400.3, calculated = 399.5.

Step 3: In an analogous manner to example 1h, tert-butyl 3-((4-(furan-2-yl)benzyl)carbamoyl)-5-methylpiperazine-1-carboxylate (27b) and HCl in DCM were used to prepare N-(4-(furan-2-yl)benzyl)-6-methylpiperazine-2-carboxamide (27c, Quant.). LRMS (ES) (M+H)⁺: observed = 300.2, calculated = 299.3.

Step 3: In an analogous manner to example 2-1 N-(4-(furan-2-yl)benzyl)-6-methylpiperazine-2-carboxamide (27c) and 2-(bromomethyl)-1,3-difluorobenzene were used to prepare 4-(2,6-difluorobenzyl)-N-(4-(furan-2-yl)benzyl)-6-methylpiperazine-2-carboxamide (27d, 63%). LRMS (ES) (M+H)⁺: observed = 426.2, calculated = 425.4.

Step 4: In an analogous manner to example 1e, 4-(2,6-difluorobenzyl)-N-(4-(furan-2-yl)benzyl)-6-methylpiperazine-2-carboxamide (27d) and cyclopropanecarbonyl chloride in DCM were used to prepare 1-(cyclopropanecarbonyl)-4-(2,6-difluorobenzyl)-N-(4-(furan-2-yl)benzyl)-6-methylpiperazine-2-carboxamide (27). LRMS (ES) (M+H)⁺: observed = 494.5, calculated = 493.5.

EXAMPLE 28



Preparation of (2R,6R)-4-((R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl)-1-isobutyryl-6-methyl-N-(4-(prop-1-yn-1-yl)benzyl)piperazine-2-carboxamide (**28**)

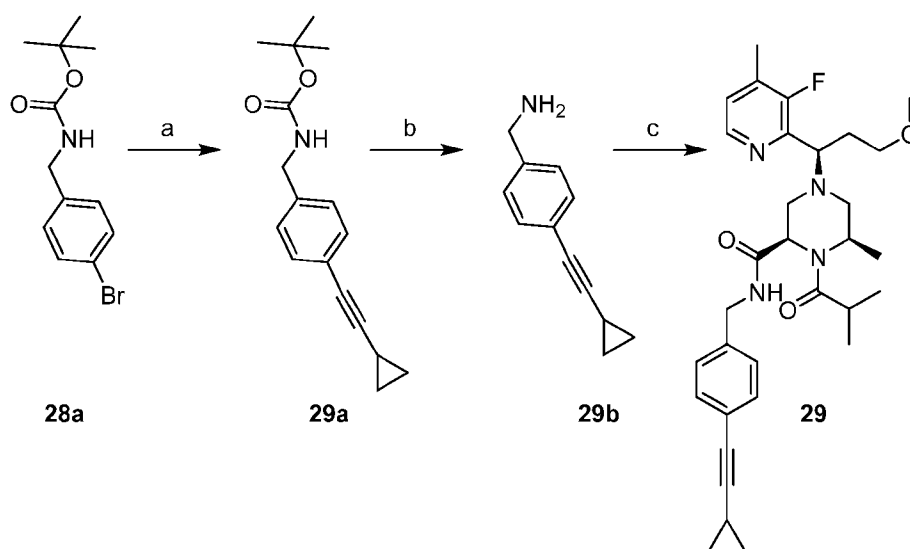
Step 1: Preparation of tert-butyl (4-(prop-1-yn-1-yl)benzyl)carbamate (**28b**) To a vial containing tert-butyl (4-bromobenzyl)carbamate (**28a**, 0.30 g, 1.05 mmol) and

Tetrakis(triphenylphosphine)palladium(0) (0.12 g, 0.10 mmol) under nitrogen was added Dioxane (3.5 mL) and tributyl(prop-1-yn-1-yl)stannane (0.48 ml, 1.57 mmol) and the resulting solution was microwave irradiated at 120°C for 1 hour. The mixture was allowed to cool and partitioned between ethyl acetate and a sat. ammonium chloride solution. The organic phase was concentrated and flash column purification using a 0-20% ethyl acetate/ hexane gradient gave tert-butyl (4-(prop-1-yn-1-yl)benzyl)carbamate (**28b**).

Step 2: In an analogous manner to example **12g**, tert-butyl (4-(prop-1-yn-1-yl)benzyl)carbamate (**28b**) and HCl were used to prepare (4-(prop-1-yn-1-yl)phenyl)methanamine (**28c**).

Step 3: In an analogous manner to example **16-1**, (2R,6R)-4-((R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl)-1-isobutyryl-6-methylpiperazine-2-carboxylic acid (**16e**) and (4-(prop-1-yn-1-yl)phenyl)methanamine (**28c**) were used to prepare (2R,6R)-4-((R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl)-1-isobutyryl-6-methyl-N-(4-(prop-1-yn-1-yl)benzyl)piperazine-2-carboxamide (**28**). LRMS (ES) (M+H)⁺: observed = 523.0, calculated = 522.6.

EXAMPLE 29



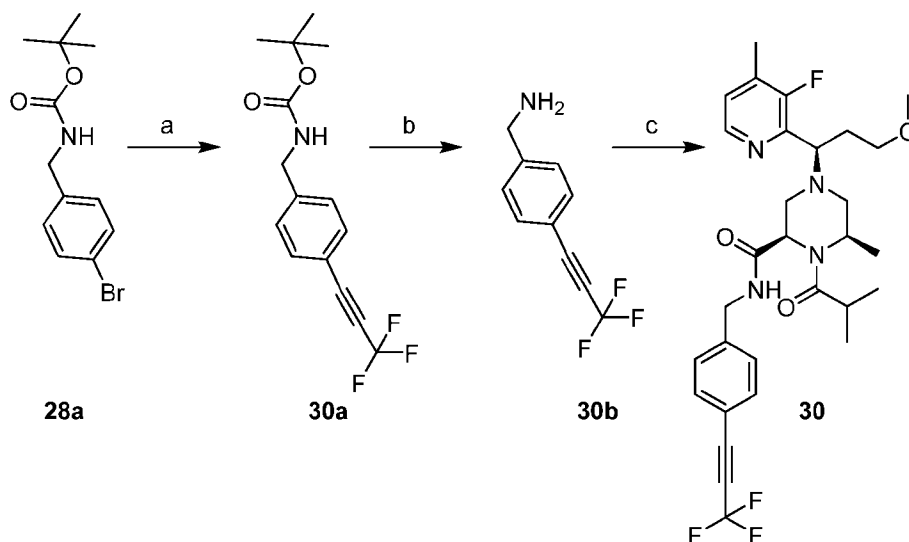
Preparation of (2R,6R)-N-(4-(cyclopropylethynyl)benzyl)-4-((R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl)-1-isobutyryl-6-methylpiperazine-2-carboxamide (**29**)

Step 1: In an analogous manner to example **28b**, tert-butyl (4-bromobenzyl)carbamate (**28a**) and tributyl(cyclopropylethynyl)stannane were used to prepare tert-butyl (4-(cyclopropylethynyl)benzyl)carbamate (**29a**).

Step 2: In an analogous manner to example **12g** tert-butyl (4-(cyclopropylethynyl)benzyl)carbamate (**29a**) and HCl were used to prepare (4-(cyclopropylethynyl)phenyl)methanamine (**29b**). LRMS (ES) (M+H)⁺: observed = 172.1, calculated = 171.2.

- 5 Step 3: In an analogous manner to example **16-1**, (2R,6R)-4-((R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl)-1-isobutyryl-6-methylpiperazine-2-carboxylic acid (**16e**) and (4-(cyclopropylethynyl)phenyl)methanamine (**29b**) were used to prepare (2R,6R)-N-(4-(cyclopropylethynyl)benzyl)-4-((R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl)-1-isobutyryl-6-methylpiperazine-2-carboxamide (**29**). LRMS (ES) (M+H)⁺: observed = 549.5,
- 10 calculated = 548.7.

EXAMPLE 30



Preparation of (2R,6R)-4-((R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl)-1-isobutyryl-6-methyl-N-(4-(3,3,3-trifluoroprop-1-yn-1-yl)benzyl)piperazine-2-carboxamide (**30**)

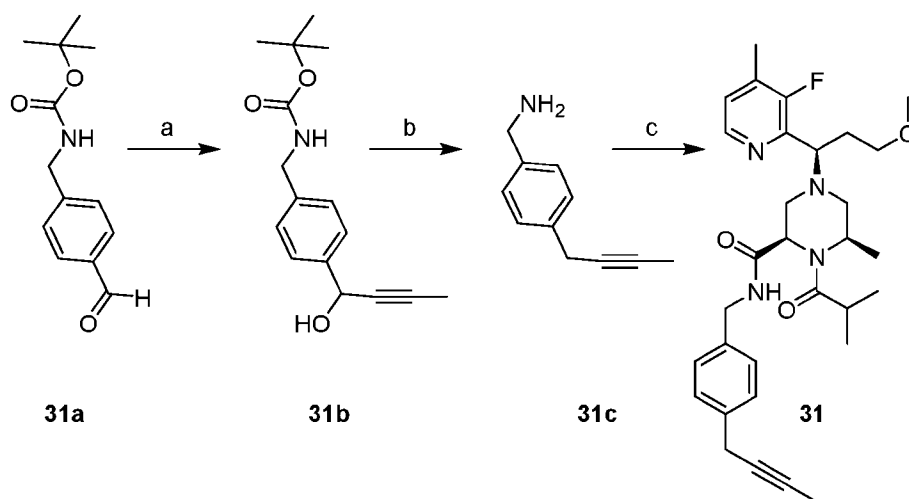
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Step 1: In an analogous manner to example **28b**, tert-butyl (4-bromobenzyl)carbamate (**28a**) and tributyl(3,3,3-trifluoroprop-1-yn-1-yl)stannane were used to prepare tert-butyl (4-(3,3,3-trifluoroprop-1-yn-1-yl)benzyl)carbamate (**30a**).

- 20 Step 2: In an analogous manner to example **12g** tert-butyl (4-(3,3,3-trifluoroprop-1-yn-1-yl)benzyl)carbamate (**30a**) and HCl were used to prepare (4-(3,3,3-trifluoroprop-1-yn-1-yl)phenyl)methanamine (**30b**). LRMS (ES) (M+H)⁺: observed = 200.1, calculated = 199.2.

Step 3: In an analogous manner to example **16-1**, (2R,6R)-4-((R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl)-1-isobutyryl-6-methylpiperazine-2-carboxylic acid (**16e**) and (4-(3,3,3-trifluoroprop-1-yn-1-yl)phenyl)methanamine (**30b**) were used to prepare (2R,6R)-4-((R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl)-1-isobutyryl-6-methyl-N-(4-(3,3,3-trifluoroprop-1-yn-1-yl)benzyl)piperazine-2-carboxamide (**30**). LRMS (ES) (M+H)⁺: observed = 577.4, calculated = 576.6.

EXAMPLE 31



Preparation of (2R,6R)-N-(4-(but-2-yn-1-yl)benzyl)-4-((R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl)-1-isobutyryl-6-methylpiperazine-2-carboxamide (**31**)

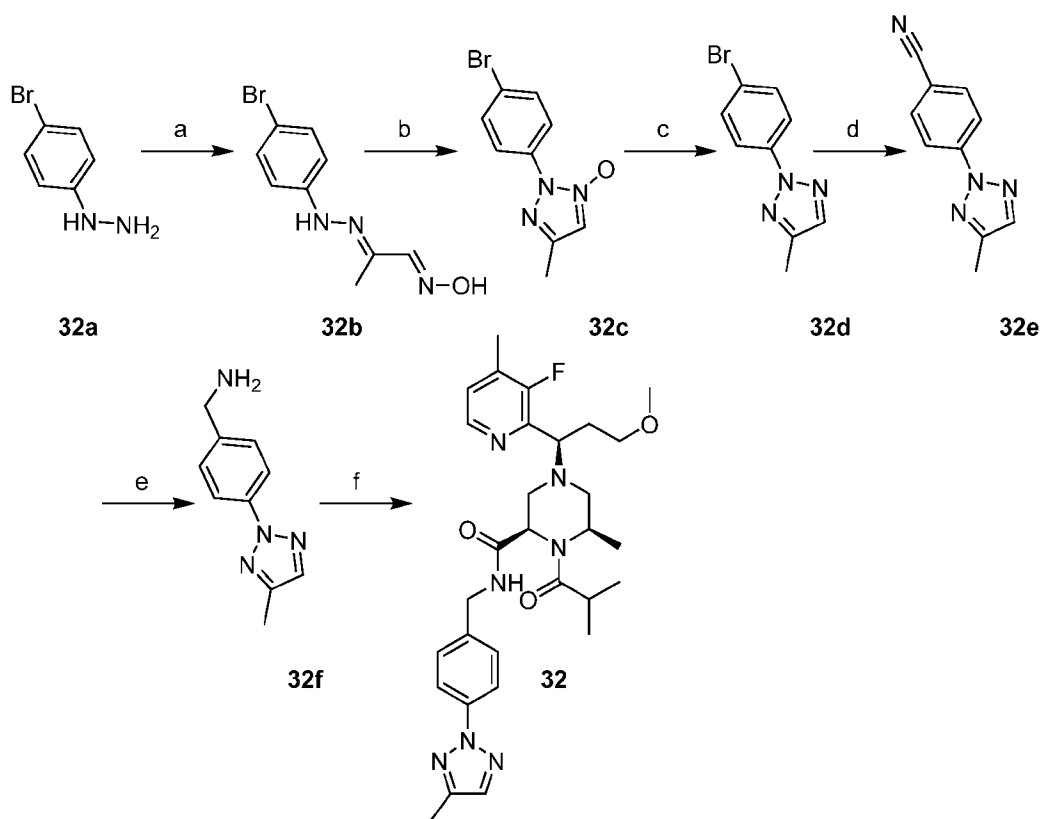
Step 1: Preparation of tert-butyl (4-(1-hydroxybut-2-yn-1-yl)benzyl)carbamate (**31b**) To a stirred solution of tert-butyl (4-formylbenzyl)carbamate (**31a**, 0.20 g, 0.85 mmol) in THF (10 mL) was added 1-propynylmagnesium bromide 0.5M (3.57 mL, 1.79 mmol) dropwise. The resulting solution was stirred 30 minutes and quenched with sat. ammonium chloride solution. The mixture was extracted several times with ethyl acetate and the combined organic layers were concentrated. Flash column purification using a 0-30% ethyl acetate/ hexane gradient gave tert-butyl (4-(1-hydroxybut-2-yn-1-yl)benzyl)carbamate (**31b**). LRMS (ES) (M+H)⁺: observed = 276.1, calculated = 275.3.

Step 2: Preparation of (4-(but-2-yn-1-yl)phenyl)methanamine (**31c**) To a stirred solution of tert-butyl (4-(1-hydroxybut-2-yn-1-yl)benzyl)carbamate (**31b**, 0.106 g, 0.385 mmol) in DCM (4.4 mL) was added triethylsilane (0.12 mL, 0.77 mmol). Trifluoroacetic acid (0.27 mL, 3.46 mmol) was then added dropwise. The resulting mixture was stirred at room temperature for 3 hours, poured into sat. sodium bicarbonate solution and extracted several times with dichloromethane.

The combined organic phases were concentrated to give (4-(but-2-yn-1-yl)phenyl)methanamine (**31c**) LRMS (ES) (M+H)⁺: observed = 160.1, calculated = 159.2.

Step 3: In an analogous manner to example **16-1**, (2R,6R)-4-((R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl)-1-isobutyryl-6-methylpiperazine-2-carboxylic acid (**16e**) and (4-(but-2-yn-1-yl)phenyl)methanamine (**31c**) were used to prepare (2R,6R)-N-(4-(but-2-yn-1-yl)benzyl)-4-((R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl)-1-isobutyryl-6-methylpiperazine-2-carboxamide (**31**). LRMS (ES) (M+H)⁺: observed = 537.5, calculated = 536.7.

EXAMPLE 32



10 Preparation of (2R,6R)-4-((R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl)-1-isobutyryl-6-methyl-N-(4-(4-methyl-2H-1,2,3-triazol-2-yl)benzyl)piperazine-2-carboxamide (**32**)

Step 1: Preparation of 2-(2-(4-bromophenyl)hydrazono)propanal oxime (**32b**) To a solution of (4-bromophenyl)hydrazine (**32a**, 16.0 g, 71.6 mmol) in anhydrous EtOH (200 mL) was added (E)-2-oxopropanal oxime (6.23 g, 71.6 mmol). The resulting mixture was stirred at 12 °C under N₂ protection for 15 hours. The reaction was poured into water (500 mL), extracted with EtOAc

(200 mL×3). The organic layer was dried over Na₂SO₄, filtered and concentrated. The crude product was purified by flash silica gel chromatography (ISCO®; 120 g SepaFlash® Silica Flash Column, eluent of 13% EtOAc gradient) to give 2-(2-(4-bromophenyl)hydrazono)propanal oxime (**32b**). LRMS (ES) (M+H)⁺: observed = 257.9, calculated = 256.1.

5 Step 2: Preparation of 2-(4-bromophenyl)-4-methyl-2H-1,2,3-triazole 1-oxide (**32c**) To a solution of 2-(2-(4-bromophenyl)hydrazono)propanal oxime (**32b**, 4.80 g, 18.74 mmol) in Pyridine (200 mL) was added a solution of CuSO₄ (5.98 g, 37.5 mmol) in Water (50 mL). The resulting mixture was stirred at 120 °C under N₂ protection for 1.5 hours. The mixture reaction was poured into ice-water (500 mL) and extracted with EtOAc (100 mL×3). The combined organic layers were dried
10 over Na₂SO₄, filtered and concentrated to give 2-(4-bromophenyl)-4-methyl-2H-1,2,3-triazole 1-oxide (**32c**). LRMS (ES) (M+H)⁺: observed = 254.3, calculated = 254.1.

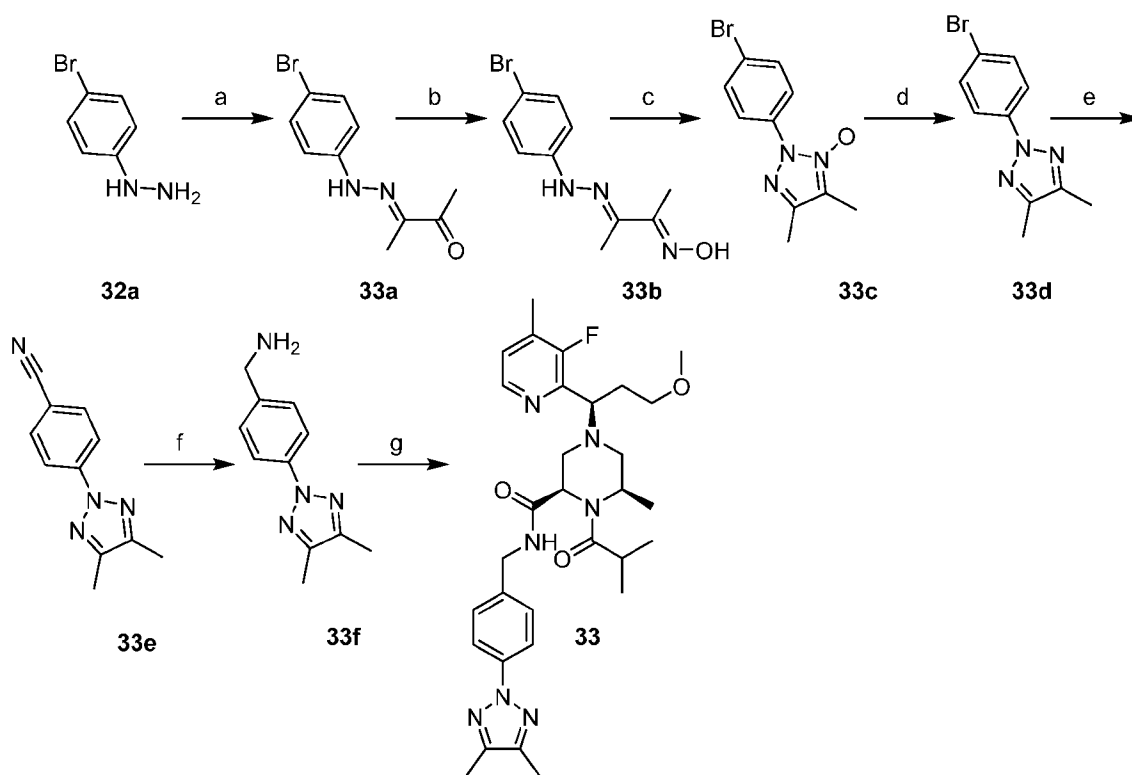
Step 3: Preparation of 2-(4-bromophenyl)-4-methyl-2H-1,2,3-triazole (**32d**) A solution of 2-(4-bromophenyl)-4-methyl-2H-1,2,3-triazole 1-oxide (**32c**, 3.10 g, 12.20 mmol) in triethyl phosphite (12 mL, 12.20 mmol) was stirred at 160 °C under N₂ protection for 5 hours. The
15 reaction mixture was poured into ice-water (100 mL) and extracted with EtOAc (30 mL×3). The combined organic layers were dried over Na₂SO₄, filtered and concentrated. The crude product was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, eluent of 7% EtOAc gradient) to give 2-(4-bromophenyl)-4-methyl-2H-1,2,3-triazole (**32d**).

Step 4: Preparation of 4-(4-methyl-2H-1,2,3-triazol-2-yl)benzonitrile (**32e**) To a solution of 2-(4-bromophenyl)-4-methyl-2H-1,2,3-triazole (**32d**, 1.40 g, 5.88 mmol) and zinc cyanide (1.38 g, 11.76 mmol) in DMF (20 mL) were added tetrakis(triphenylphosphine)palladium(0) (0.68 g, 0.59 mmol). The resulting mixture was stirred at 140 °C under MW for 30 minutes. The reaction mixture was poured into water (100 mL) and extracted with EtOAc (30 mL×3). The combined organic layers were washed with brine (100 mL), dried over Na₂SO₄, filtered and the filtrate was
20 concentrated. The crude product was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, eluent of 11% EtOAc gradient) to give 4-(4-methyl-2H-1,2,3-triazol-2-yl)benzonitrile (**32e**).

Step 5: Preparation of (4-(4-methyl-2H-1,2,3-triazol-2-yl)phenyl)methanamine (**32f**) To a solution of 4-(4-methyl-2H-1,2,3-triazol-2-yl)benzonitrile (**32e**, 0.85 g, 4.61 mmol) in MeOH (20 mL) was added ammonium hydroxide (1 mL, 4.61 mmol) and nickel (0.135 g, 2.31 mmol) at
30 12 °C. The mixture was stirred at 30 °C under H₂ (excess) (30 psi) for 6 hours. The reaction mixture was filtration and concentration to give (4-(4-methyl-2H-1,2,3-triazol-2-yl)phenyl)methanamine (**32f**). LRMS (ES) (M+H)⁺: observed = 189.5, calculated = 188.2.

Step 6: In an analogous manner to example **16-1**, (2R,6R)-4-((R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl)-1-isobutyl-6-methylpiperazine-2-carboxylic acid (**16e**) and (4-(4-methyl-2H-1,2,3-triazol-2-yl)phenyl)methanamine (**32f**) were used to prepare (2R,6R)-4-((R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl)-1-isobutyl-6-methyl-N-(4-(4-methyl-2H-1,2,3-triazol-2-yl)benzyl)piperazine-2-carboxamide (**32**). LRMS (ES) (M+H)⁺: observed = 566.4, calculated = 565.7.

EXAMPLE 33



10 Preparation of (2R,6R)-N-(4-(4,5-dimethyl-2H-1,2,3-triazol-2-yl)benzyl)-4-((R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl)-1-isobutyl-6-methylpiperazine-2-carboxamide (**33**)

Step 1: Preparation of 3-(2-(4-bromophenyl)hydrazono)butan-2-one (**33a**) A solution of (4-bromophenyl)hydrazine (**32a**, 10.86 g, 58.1 mmol) and biacetyl (50.0 g, 581 mmol) in EtOH
15 (500 mL), the mixture was stirred at 15 °C for 4 hours. The mixture was concentrated to give the crude product. After the crude product was stirred in 30 mL of Petroleum ether: EtOAc (1:1) for

10 minutes, the mixture was filtered to give 3-(2-(4-bromophenyl)hydrazono)butan-2-one (**33a**). LRMS (ES) (M+H)⁺: observed = 255.0, calculated = 255.1.

Step 2: Preparation of 3-(2-(4-bromophenyl)hydrazono)butan-2-one oxime (**33b**) To a solution of 3-(2-(4-bromophenyl)hydrazono)butan-2-one (**33a**, 8.0 g, 31.4 mmol) in EtOH (80 mL) was
5 added Hydroxylamine hydrochloride (2.18 g, 31.4 mmol), the mixture was stirred at 60 °C for 2 hours. The mixture was concentrated under reduced pressure to afford 3-(2-(4-bromophenyl)hydrazono)butan-2-one oxime (**33b**). LRMS (ES) (M+H)⁺: observed = 271.9, calculated = 270.1.

Step 3: In an analogous manner to example **32c**, 3-(2-(4-bromophenyl)hydrazono)butan-2-one
10 oxime (**33b**) was used to prepare 2-(4-bromophenyl)-4,5-dimethyl-2H-1,2,3-triazole 1-oxide (**33c**). LRMS (ES) (M+H)⁺: observed = 269.5, calculated = 268.1.

Step 4: In an analogous manner to example **32d**, 2-(4-bromophenyl)-4,5-dimethyl-2H-1,2,3-triazole 1-oxide (**33c**) and triethyl phosphite were used to prepare 2-(4-bromophenyl)-4,5-dimethyl-2H-1,2,3-triazole (**33d**). LRMS (ES) (M+H)⁺: observed = 253.5, calculated = 252.1.

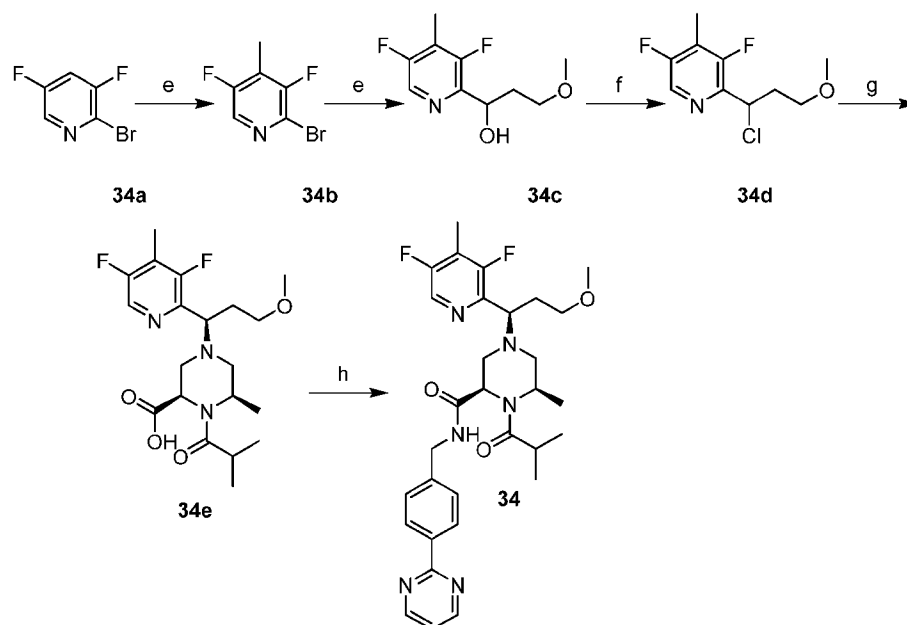
15 Step 5: In an analogous manner to example **32e**, 2-(4-bromophenyl)-4,5-dimethyl-2H-1,2,3-triazole (**33d**) and zinc cyanide were used to prepare 4-(4,5-dimethyl-2H-1,2,3-triazol-2-yl)benzonitrile (**33e**, 38%).

Step 6: In an analogous manner to example **32f**, 4-(4,5-dimethyl-2H-1,2,3-triazol-2-yl)benzonitrile (**33e**) was used to prepare (4-(4,5-dimethyl-2H-1,2,3-triazol-2-

20 yl)phenyl)methanamine (**33f**). LRMS (ES) (M+H)⁺: observed = 186.0(M+1-17), calculated = 202.3.

Step 7: In an analogous manner to example **16-1**, (2R,6R)-4-((R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl)-1-isobutyl-6-methylpiperazine-2-carboxylic acid (**16e**) and (4-(4,5-dimethyl-2H-1,2,3-triazol-2-yl)phenyl)methanamine (**33f**) were used to prepare (2R,6R)-N-(4-(4,5-dimethyl-2H-1,2,3-triazol-2-yl)benzyl)-4-((R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl)-1-isobutyl-6-methylpiperazine-2-carboxamide (**33**). LRMS (ES) (M+H)⁺:
25 observed = 580.4, calculated = 579.7.

EXAMPLE 34

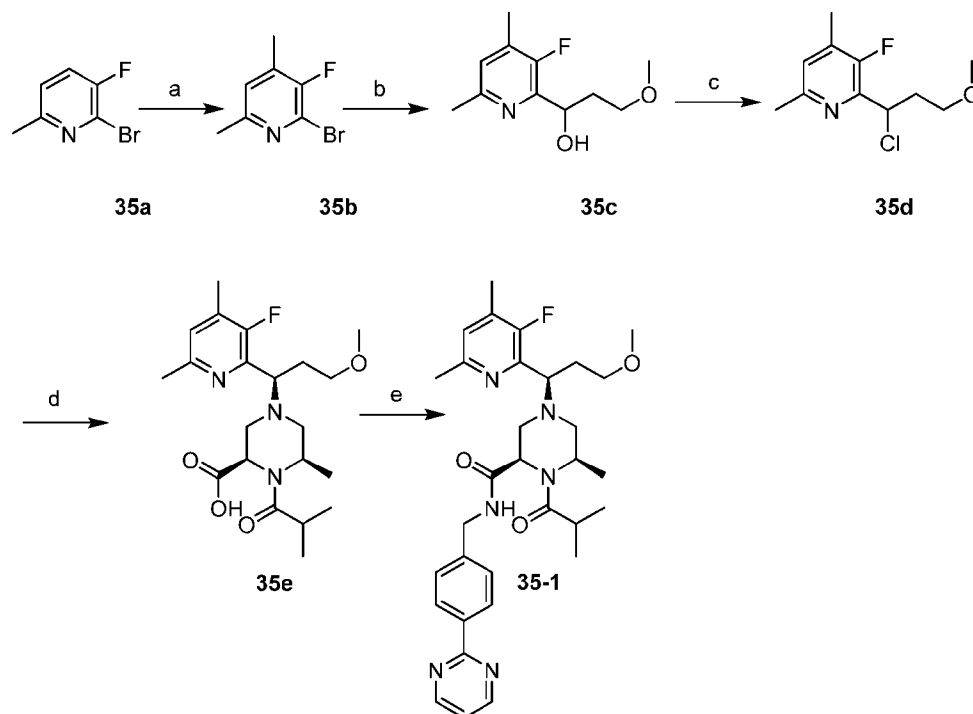


Preparation of (2R,6R)-4-((R)-1-(3,5-difluoro-4-methylpyridin-2-yl)-3-methoxypropyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**34**)

Step 1: Preparation of 2-bromo-3,5-difluoro-4-methylpyridine (**34b**) To a stirred solution of 2-bromo-3,5-difluoropyridine (**34a**, 0.50 g, 2.58 mmol) in THF (10 mL) chilled to -78°C was added LDA (2M, 1.4 mL, 2.84 mmol). The resulting solution was stirred 40 minutes. To this was added methyl iodide (0.16 mL, 2.58 mmol) dropwise at -78°C . The mixture was allowed to warm to room temperature, quenched with a sat. sodium bicarbonate solution and extracted several times with ethyl acetate. The combined organic layers were concentrated and flash column purification using a 0-10% ethyl acetate/ hexane gradient gave 2-bromo-3,5-difluoro-4-methylpyridine (**34b**). LRMS (ES) (M+H)⁺: observed = 209.9, calculated = 208.0.

Step 2-5: In an analogous manner to example 16-1, 2-bromo-3,5-difluoro-4-methylpyridine (**34b**) was used to prepare (2R,6R)-4-((R)-1-(3,5-difluoro-4-methylpyridin-2-yl)-3-methoxypropyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**34**) LRMS (ES) (M+H)⁺: observed = 581.4, calculated = 580.7.

EXAMPLE 35



Preparation of (2R,6R)-4-((R)-1-(3-fluoro-4,6-dimethylpyridin-2-yl)-3-methoxypropyl)-1-isobutyl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**35-1**)

5

Step 1: In an analogous manner to example **34b**, 2-bromo-3-fluoro-6-methylpyridine (**35a**) and methyl iodide was used to prepare 2-bromo-3-fluoro-4,6-dimethylpyridine (**35b**) LRMS (ES) (M+H)⁺: observed = 205.9, calculated = 204.0.

Step 2: Preparation of 1-(3-fluoro-4,6-dimethylpyridin-2-yl)-3-methoxypropan-1-ol (**35c**) To a stirred solution of 2-bromo-3-fluoro-4,6-dimethylpyridine (**35b**, 0.28 g, 1.37 mmol) in DCM (3.4 mL) chilled to -78°C was added n-butyl lithium (2.5M, 0.55 mL, 1.37 mmol). The resulting solution was stirred 15 minutes. To this was added 3-methoxypropanal (0.12 g, 1.37 mmol) dropwise at -78°C. The mixture was stirred at -78°C for 30min, quenched with a sat. ammonium chloride solution and extracted several times with DCM. The combined organic layers were concentrated and flash column purification using a 0-30% ethyl acetate/ hexane gradient gave 1-(3-fluoro-4,6-dimethylpyridin-2-yl)-3-methoxypropan-1-ol (**35c**). LRMS (ES) (M+H)⁺: observed = 214.0, calculated = 213.3.

10

15

Steps 3-5: In an analogous manner to example **16-1**, 1-(3-fluoro-4,6-dimethylpyridin-2-yl)-3-methoxypropan-1-ol (**35c**) was used to prepare (2R,6R)-4-((R)-1-(3-fluoro-4,6-dimethylpyridin-2-yl)-3-methoxypropyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**35-1**) LRMS (ES) (M+H)⁺: observed = 577.3, calculated = 576.7.

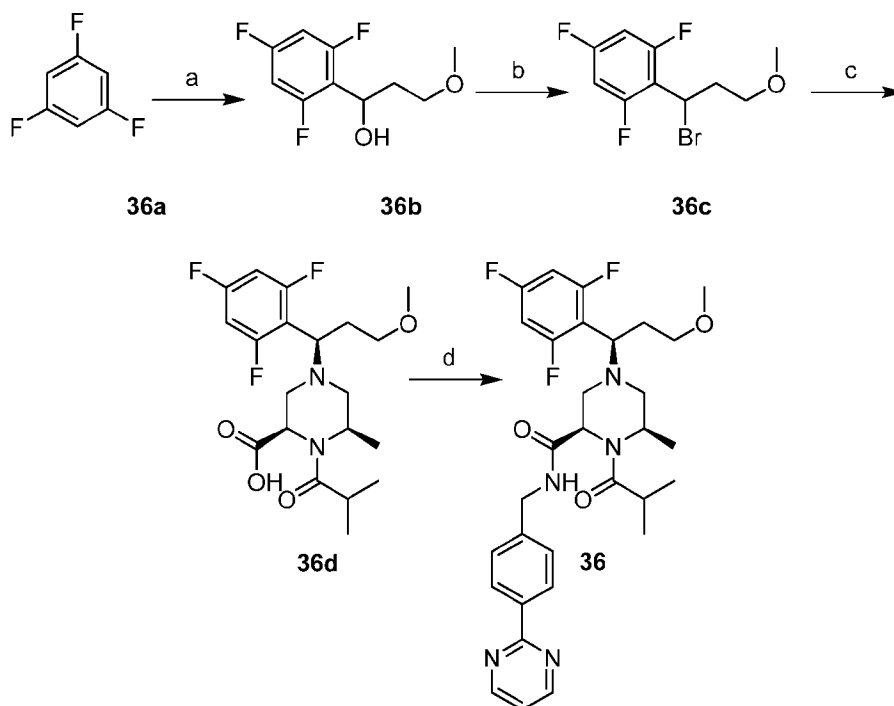
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The following compounds were prepared in an analogous manner to example **35-1** using the appropriately substituted aryl halide.

Example	Structure	Name	Calculated Mass	Observed Mass (M+H)
35-2		(2R,6R)-4-[(1R)-3-methoxy-1-(2,4,6-trifluorophenyl)propyl]-6-methyl-1-(2-methylpropanoyl)-N-[[4-(pyrimidin-2-yl)phenyl]methyl]piperazine-2-carboxamide	583.659	584.5
35-3		(2R,6R)-4-[(1R)-1-[3-fluoro-6-(trifluoromethyl)pyridin-2-yl]-3-methoxypropyl]-6-methyl-1-(2-methylpropanoyl)-N-[[4-(pyrimidin-2-yl)phenyl]methyl]piperazine-2-carboxamide	616.665	617.4

35-4		(2R,6R)-4-[(1R)-1-(5-fluoropyrimidin-2-yl)-3-methoxypropyl]-6-methyl-1-(2-methylpropanoyl)-N-{{[4-(pyrimidin-2-yl)phenyl]methyl}piperazine-2-carboxamide	549.654	550.4
35-5		(2R,6R)-4-[(1R)-3-methoxy-1-(pyrimidin-2-yl)propyl]-6-methyl-1-(2-methylpropanoyl)-N-{{[4-(pyrimidin-2-yl)phenyl]methyl}piperazine-2-carboxamide	531.663	532.5

EXAMPLE 36



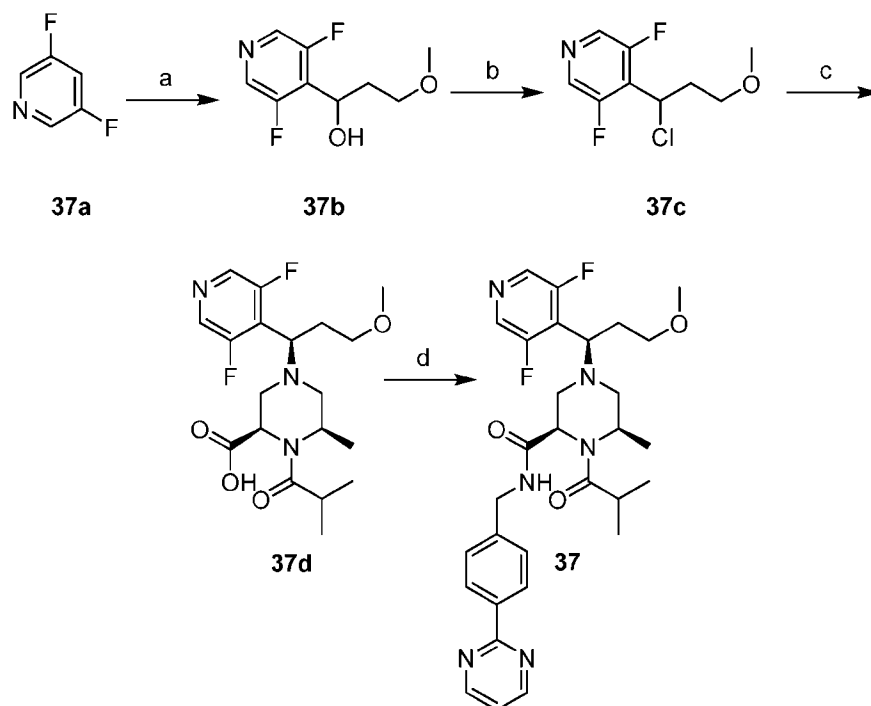
Preparation of (2R,6R)-1-isobutyryl-4-((R)-3-methoxy-1-(2,4,6-trifluorophenyl)propyl)-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**36**)

Step 1: Preparation of 3-methoxy-1-(2,4,6-trifluorophenyl)propan-1-ol (**36b**) To a stirred solution of 1,3,5-trifluorobenzene (**36a**, 1.0 g, 7.57 mmol) in THF (21.6 mL) chilled to -78°C was added n-butyl lithium (2.5M, 3.18 mL, 7.95 mmol). The resulting solution was stirred 1 hour. To this was added 3-methoxypropanal (0.67 g, 7.57 mmol) dissolved in THF (2mL) dropwise at -78°C. The mixture was allowed to warm to room temperature, quenched with a sat. ammonium chloride solution and extracted several times with ethyl acetate. The combined organic layers were concentrated and flash column purification using a 0-30% ethyl acetate/ hexane gradient gave 3-methoxy-1-(2,4,6-trifluorophenyl)propan-1-ol (**36b**, 55%).

Step 2: Preparation of 2-(1-bromo-3-methoxypropyl)-1,3,5-trifluorobenzene (**36c**) To a stirred solution of 3-methoxy-1-(2,4,6-trifluorophenyl)propan-1-ol (**36b**, 0.92 g, 4.18 mmol) in ethyl ether (1 mL) was added pyridine (0.135 mL, 1.67 mmol). The resulting mixture was chilled to 0°C in an ice bath and treated with PBr₃ (0.59 mL, 6.27 mmol) dissolved in ethyl ether (1 mL) dropwise. The mixture was allowed to stir at room temperature for 1 hour then chilled in an ice bath and quenched with ice. The mixture was extracted with ether and the combined organic phases were dried over sodium sulfite and concentrated to give 2-(1-bromo-3-methoxypropyl)-1,3,5-trifluorobenzene (**36c**, used crude)

Steps 3-4: In an analogous manner to example **16-1**, 2-(1-bromo-3-methoxypropyl)-1,3,5-trifluorobenzene (**36c**) was used to prepare (2R,6R)-1-isobutyryl-4-((R)-3-methoxy-1-(2,4,6-trifluorophenyl)propyl)-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**36**) LRMS (ES) (M+H)⁺: observed = 584.5, calculated = 583.6.

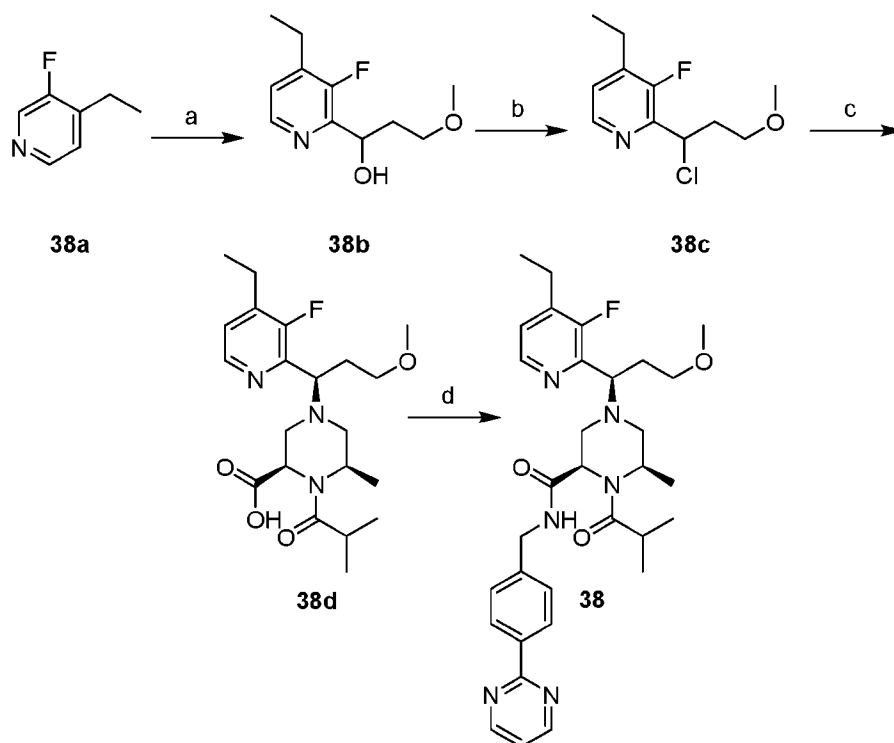
EXAMPLE 37



Preparation of (2R,6R)-4-((R)-1-(3,5-difluoropyridin-4-yl)-3-methoxypropyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**37**)

- 5 Step 1: Preparation of 1-(3,5-difluoropyridin-4-yl)-3-methoxypropan-1-ol (**37b**) To a stirred solution of 3,5-difluoropyridine (**37a**, 0.5 mL, 5.47 mmol) in THF (15.6 mL) chilled to -78°C was added LDA (2.0M, 3.01 mL, 6.02 mmol). The resulting solution was stirred 1 hour. To this was added 3-methoxypropanal (0.67 g, 7.57 mmol) dissolved in THF (2mL) dropwise at -78°C . The mixture was allowed to warm to room temperature, stirred 1 hr, quenched with a sat.
- 10 ammonium chloride solution and extracted several times with ethyl acetate. The combined organic layers were concentrated and flash column purification using a 0-50% ethyl acetate/hexane gradient gave 1-(3,5-difluoropyridin-4-yl)-3-methoxypropan-1-ol (**37b**, 66%). LRMS (ES) (M+H)⁺: observed = 204.1, calculated = 203.2.
- Steps 2-4: In an analogous manner to example **16-1**, 1-(3,5-difluoropyridin-4-yl)-3-methoxypropan-1-ol (**37b**) was used to prepare (2R,6R)-4-((R)-1-(3,5-difluoropyridin-4-yl)-3-methoxypropyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**37**) LRMS (ES) (M+H)⁺: observed = 567.0, calculated = 566.6.

EXAMPLE 38



Preparation of (2R,6R)-4-((R)-1-(4-ethyl-3-fluoropyridin-2-yl)-3-methoxypropyl)-1-isobutyl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**38**)

5

Step 1: Preparation of 1-(4-ethyl-3-fluoropyridin-2-yl)-3-methoxypropan-1-ol (**38b**) To a stirred solution of N,N-dimethylethanolamine (0.20 mL, 2.00 mmol) in Hexane (6.25 mL) chilled to 0°C was added n-butyl lithium (2.5M, 1.60 mL, 4.00 mmol). The resulting mixture was stirred for 20 minutes, then 4-ethyl-3-fluoropyridine (**38a**, 0.125 g, 1.00 mmol) in Hexane (1.2 mL) and the resulting solution was stirred 1 hour. The reaction was chilled to -78°C, and 3-methoxypropanal (0.22 g, 2.50 mmol) dissolved in THF (2mL) dropwise at -78°C. The mixture was allowed to warm to room temperature, quenched with a sat. sodium bicarbonate solution and extracted several times with ethyl acetate. The combined organic layers were concentrated and flash column purification using a 0-50% ethyl acetate/ hexane gradient gave 1-(4-ethyl-3-fluoropyridin-2-yl)-3-methoxypropan-1-ol (**38b**, 50%). LRMS (ES) (M+H)⁺: observed = 214.1, calculated = 213.3.

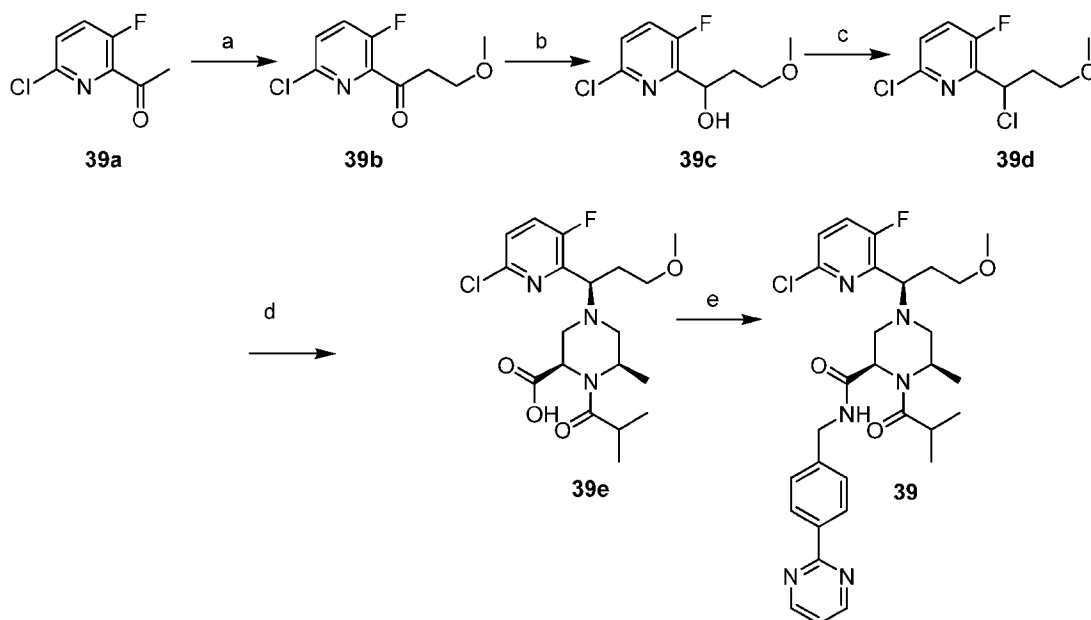
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Steps 2-4: In an analogous manner to example **16-1**, 1-(4-ethyl-3-fluoropyridin-2-yl)-3-methoxypropan-1-ol (**38b**) was used to prepare (2R,6R)-4-((R)-1-(4-ethyl-3-fluoropyridin-2-yl)-

3-methoxypropyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**38**) LRMS (ES) (M+H)⁺: observed = 577.3, calculated = 576.7.

EXAMPLE 39



- 5 Preparation of (2R,6R)-4-((R)-1-(6-chloro-3-fluoropyridin-2-yl)-3-methoxypropyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**39**)

Step 1: Preparation of 1-(6-chloro-3-fluoropyridin-2-yl)-3-methoxypropan-1-one (**39b**) To a stirred solution of 1-(6-chloro-3-fluoropyridin-2-yl)ethan-1-one (**39a**, 0.47 g, 2.71 mmol) in DCM (6.7 mL) chilled to 0°C in an ice bath was added Hunig's base (0.57 mL, 3.25 mmol). To this solution was added Trimethylsilyl trifluoromethanesulfonate (0.69 mL, 3.79 mmol) dropwise and the resulting solution was stirred 15 minutes at 0°C, then dimethoxymethane (0.264 mL, 2.98 mmol) was added and the mixture was allowed to warm to room temperature for 3 hours. The reaction was partitioned between water and dichloromethane. The organic phase was concentrated and extracted several times with ethyl acetate. The combined organic layers were concentrated and flash column purification using a 0-20% ethyl acetate/ hexane gradient gave 1-(6-chloro-3-fluoropyridin-2-yl)-3-methoxypropan-1-one (**39b**, 80%). LRMS (ES) (M+H)⁺: observed = 218.0, calculated = 217.6.

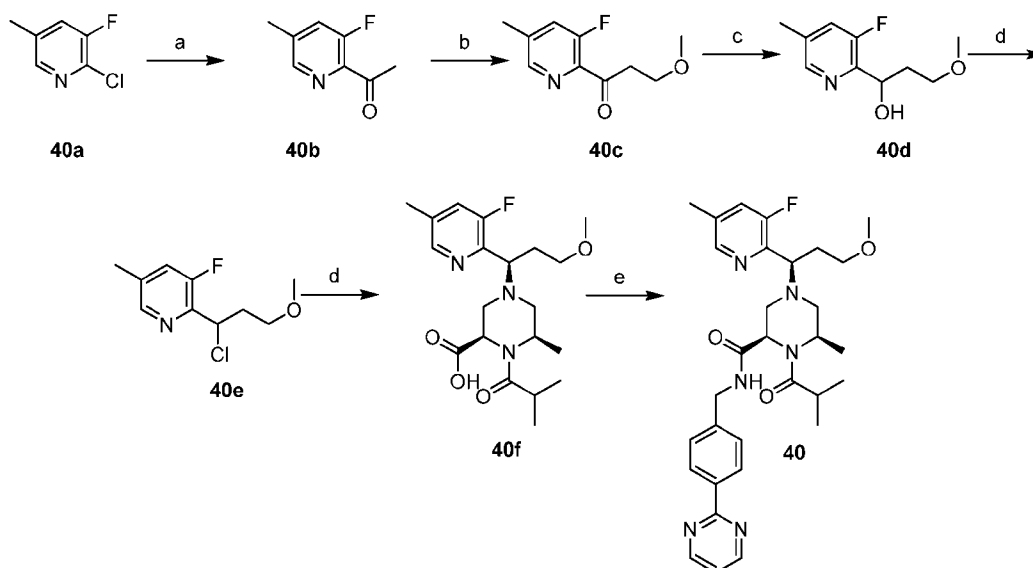
Step 2: Preparation of 1-(6-chloro-3-fluoropyridin-2-yl)-3-methoxypropan-1-ol (**39c**) To a stirred solution of 1-(6-chloro-3-fluoropyridin-2-yl)-3-methoxypropan-1-one (**39b**, 0.47 g, 2.16 mmol)

in THF (4 ml) and MeOH (0.5 mL) chilled to 0°C, was added sodium borohydride (0.08 g, 2.16 mmol) and the resulting mixture was stirred for 1 hour. Brine was added to the solution and the mixture was extracted with ethyl acetate. The organic phase was concentrated and flash column purification using a 0-30% ethyl acetate/ hexane gradient gave 1-(6-chloro-3-fluoropyridin-2-yl)-3-methoxypropan-1-ol (**39c**, 93%). LRMS (ES) (M+H)⁺: observed = 220.0, calculated = 219.6.

Steps 3-5: In an analogous manner to example **16-1**, 1-(6-chloro-3-fluoropyridin-2-yl)-3-methoxypropan-1-ol (**39c**) was used to prepare (2R,6R)-4-((R)-1-(6-chloro-3-fluoropyridin-2-yl)-3-methoxypropyl)-1-isobuteryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**39**) LRMS (ES) (M+H)⁺: observed = 583.3, calculated = 583.1.

10

EXAMPLE 40



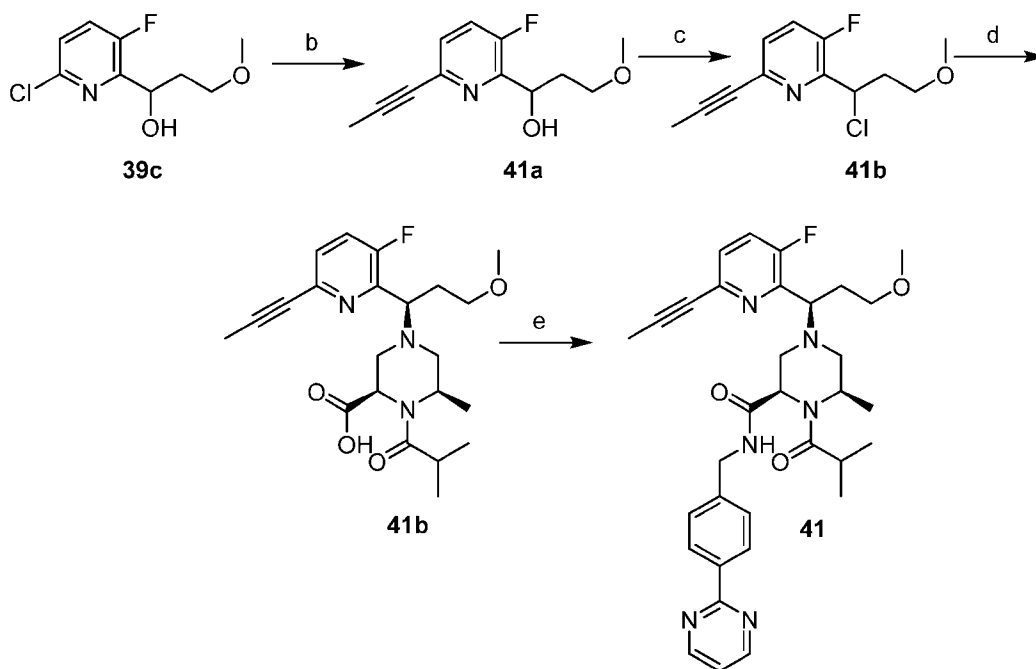
Preparation of (2R,6R)-4-((R)-1-(3-fluoro-5-methylpyridin-2-yl)-3-methoxypropyl)-1-isobuteryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**40**)

Step 1: Preparation of 1-(3-fluoro-5-methylpyridin-2-yl)ethan-1-one (**40b**) To a stirred solution of 2-chloro-3-fluoro-5-methylpyridine (**40a**, 0.50 g, 3.43 mmol) and Tetrakis(triphenylphosphine)palladium(0) (0.40 g, 0.34 mmol) under nitrogen was added Dioxane (8.5 mL) and tributyl(1-ethoxyvinyl)tin (1.39 mL, 4.12 mmol). The resulting solution was heated via microwave irradiation to 140°C for 1 hour. The mixture was allowed to cool to

room temperature and 1N HCl (7 mL) was added. The mixture was stirred overnight at room temperature, quenched with sat. sodium bicarbonate solution and extracted several times with ethyl acetate. The combined organic layers were filtered through celite and concentrated. Flash column purification using a 0-20% ethyl acetate/ hexane gradient gave 1-(3-fluoro-5-methylpyridin-2-yl)ethan-1-one (**40b**, used directly). LRMS (ES) (M+H)⁺: observed = 154.0, calculated = 153.1.

Steps 2-6: In an analogous manner to example **39**, 1-(3-fluoro-5-methylpyridin-2-yl)ethan-1-one (**40b**) was used to prepare (2R,6R)-4-((R)-1-(3-fluoro-5-methylpyridin-2-yl)-3-methoxypropyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**40**) LRMS (ES) (M+H)⁺: observed = 563.4, calculated = 562.7.

EXAMPLE 41



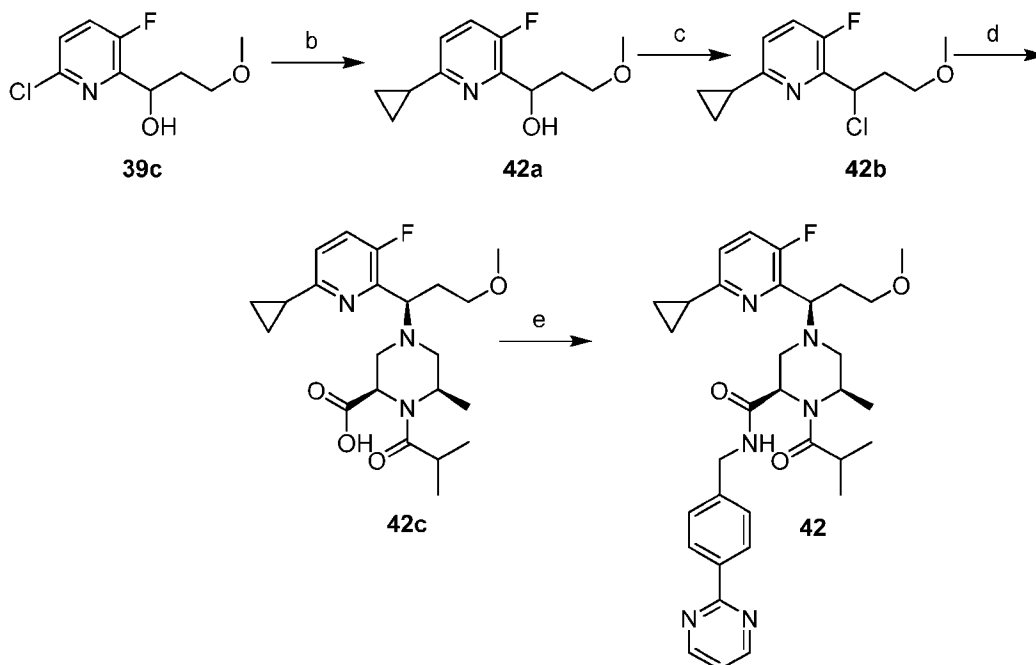
Preparation of (2R,6R)-4-((R)-1-(3-fluoro-6-(prop-1-yn-1-yl)pyridin-2-yl)-3-methoxypropyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**41**)

Step 1: In an analogous manner to example **28b**, 1-(6-chloro-3-fluoropyridin-2-yl)-3-methoxypropan-1-ol (**39c**) and tributyl(prop-1-yn-1-yl)stannane were used to prepare 1-(3-fluoro-6-(prop-1-yn-1-yl)pyridin-2-yl)-3-methoxypropan-1-ol (**41a**, used directly). LRMS (ES) (M+H)⁺: observed = 224.1, calculated = 223.2.

- 5 Steps 2-4: In an analogous manner to example **16-1**, 1-(3-fluoro-6-(prop-1-yn-1-yl)pyridin-2-yl)-3-methoxypropan-1-ol (**41a**) was used to prepare (2R,6R)-4-((R)-1-(3-fluoro-6-(prop-1-yn-1-yl)pyridin-2-yl)-3-methoxypropyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**41**) LRMS (ES) (M+H)⁺: observed = 587.4, calculated = 586.7.

10

EXAMPLE 42



Preparation of (2R,6R)-4-((R)-1-(6-cyclopropyl-3-fluoropyridin-2-yl)-3-methoxypropyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**42**)

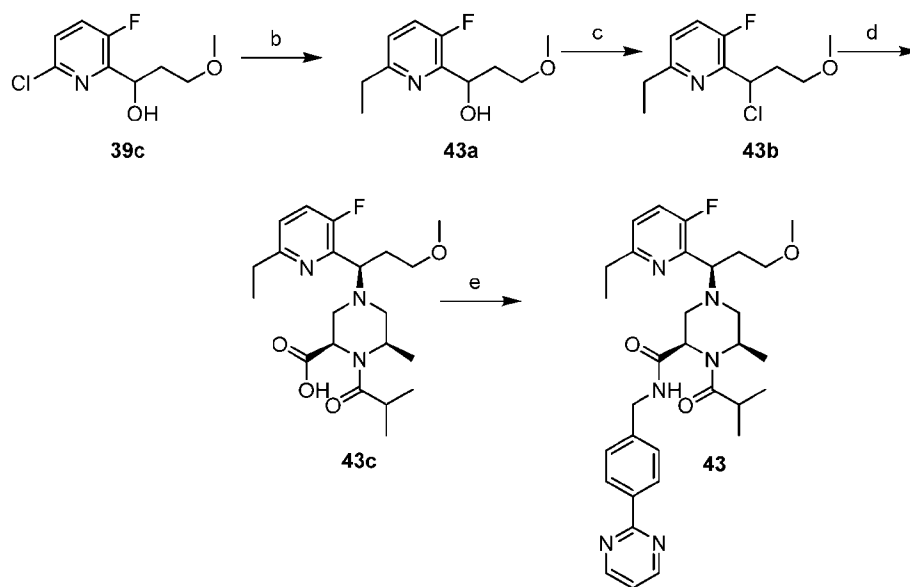
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Step 1: In an analogous manner to example **18a**, 1-(6-chloro-3-fluoropyridin-2-yl)-3-methoxypropan-1-ol (**39c**) and cyclopropyl boronic acid were used to prepare 1-(6-cyclopropyl-3-fluoropyridin-2-yl)-3-methoxypropan-1-ol (**42a**, 43%). LRMS (ES) (M+H)⁺: observed = 226.1, calculated = 225.3.

Steps 2-4: In an analogous manner to example **16-1**, 1-(6-cyclopropyl-3-fluoropyridin-2-yl)-3-methoxypropan-1-ol (**42a**) was used to prepare (2R,6R)-4-((R)-1-(6-cyclopropyl-3-fluoropyridin-2-yl)-3-methoxypropyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**42**) LRMS (ES) (M+H)⁺: observed = 589.4, calculated = 588.7.

5

EXAMPLE 43

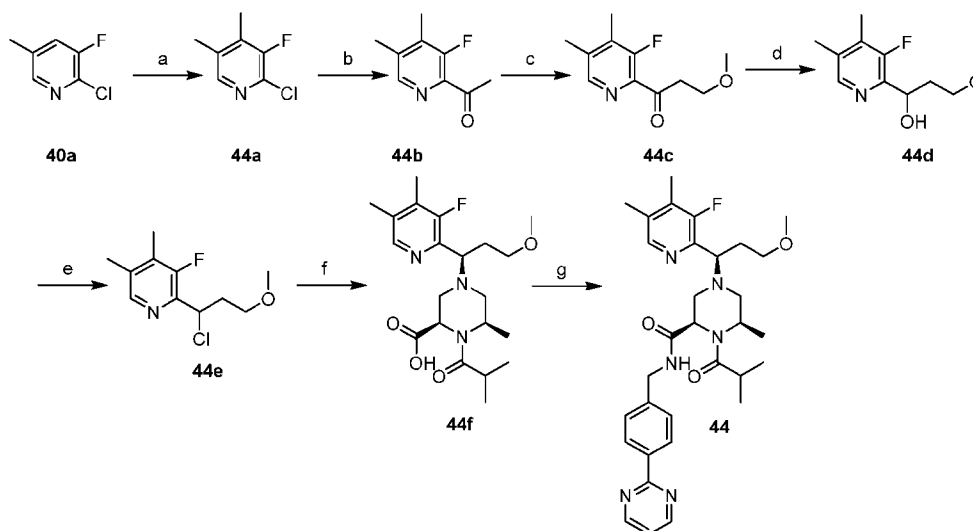


Preparation of (2R,6R)-4-((R)-1-(6-ethyl-3-fluoropyridin-2-yl)-3-methoxypropyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**43**)

- 10 Steps 1-4: In an analogous manner to example **42**, 1-(6-chloro-3-fluoropyridin-2-yl)-3-methoxypropan-1-ol (**39c**) and potassium ethyltrifluoroborate was used to prepare (2R,6R)-4-((R)-1-(6-ethyl-3-fluoropyridin-2-yl)-3-methoxypropyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**43**) LRMS (ES) (M+H)⁺: observed = 577.4, calculated = 576.7.

15

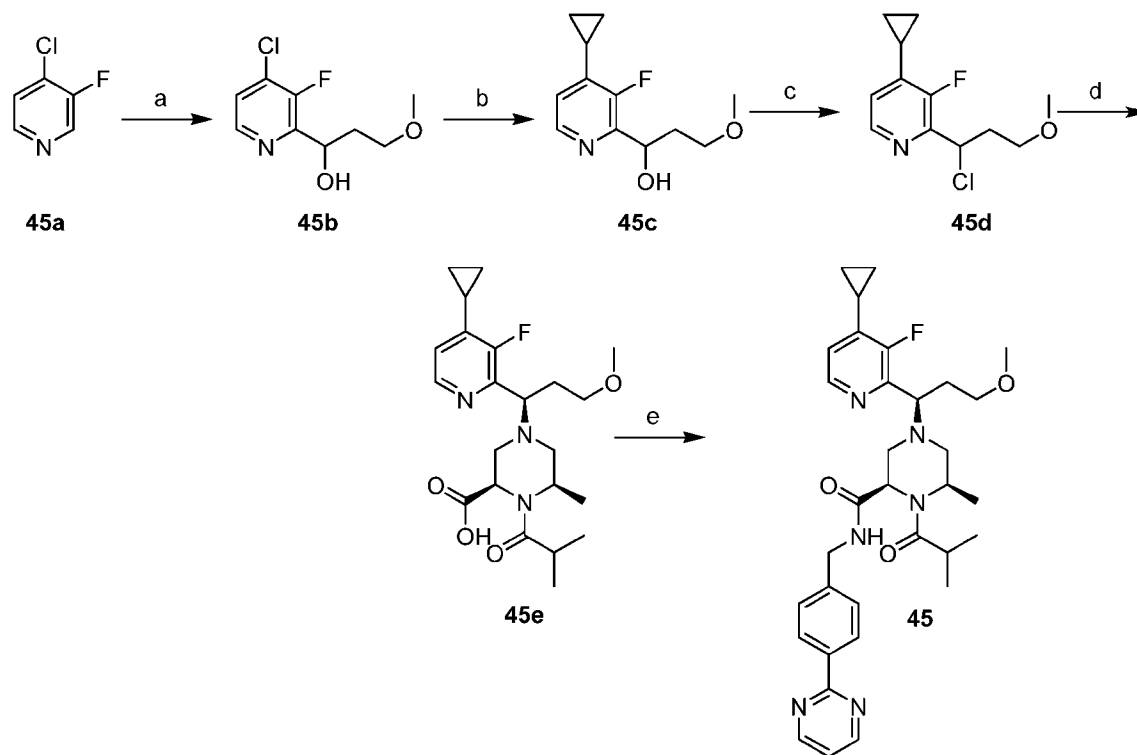
EXAMPLE 44



Preparation of (2R,6R)-4-((R)-1-(3-fluoro-4,5-dimethylpyridin-2-yl)-3-methoxypropyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**44**)

- 5 Step 1: Step 1: In an analogous manner to example **34b**, 2-chloro-3-fluoro-5-methylpyridine (**40a**) and methyl iodide was used to prepare 2-chloro-3-fluoro-4,5-dimethylpyridine (**44a**) LRMS (ES) (M+H)⁺: observed = 160.0, calculated = 159.6.
- Steps 2-7: In an analogous manner to example **40**, 2-chloro-3-fluoro-4,5-dimethylpyridine (**44a**) was used to prepare (2R,6R)-4-((R)-1-(3-fluoro-4,5-dimethylpyridin-2-yl)-3-methoxypropyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**44**) LRMS (ES)
- 10 (M+H)⁺: observed = 577.5, calculated = 576.7.

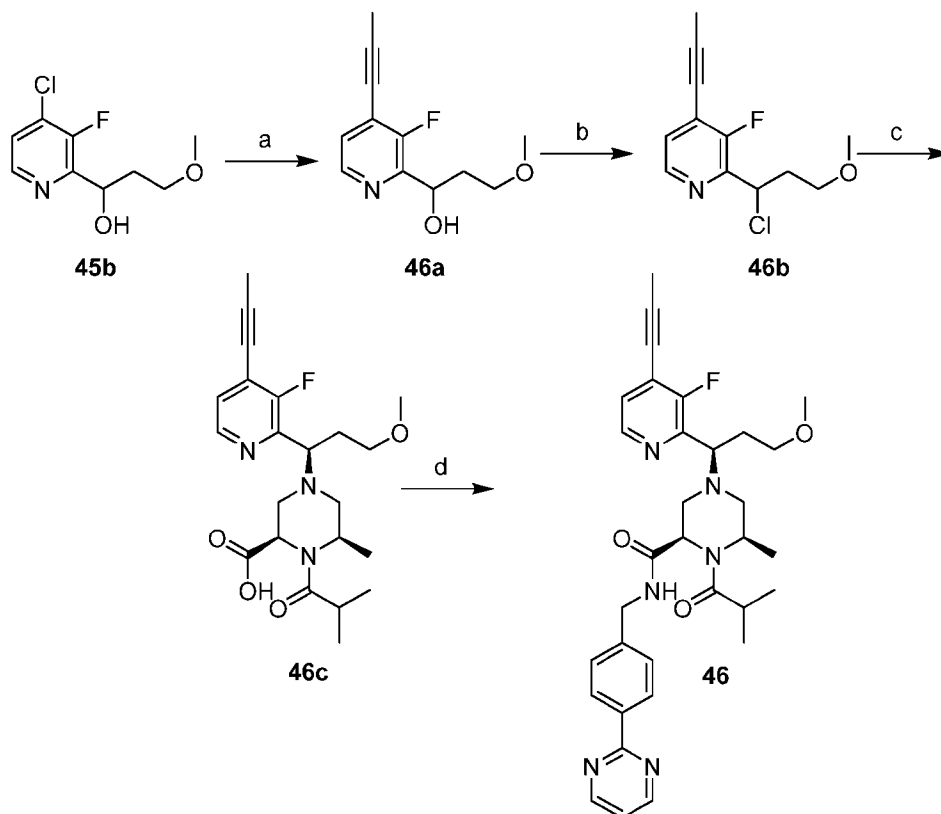
EXAMPLE 45



Preparation of (2R,6R)-4-((R)-1-(4-cyclopropyl-3-fluoropyridin-2-yl)-3-methoxypropyl)-1-isobutyl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**45**)

- 5 Step 1: In an analogous manner to example **37b**, 4-chloro-3-fluoropyridine (**45a**) and 3-methoxypropanal was used to prepare 1-(4-chloro-3-fluoropyridin-2-yl)-3-methoxypropan-1-ol (**45b**, 32%) LRMS (ES) (M+H)⁺: observed = 220.0, calculated = 219.6.
- Step 2: In an analogous manner to example **18a**, 1-(4-chloro-3-fluoropyridin-2-yl)-3-methoxypropan-1-ol (**45b**) and cyclopropyl boronic acid were used to prepare 1-(4-cyclopropyl-3-fluoropyridin-2-yl)-3-methoxypropan-1-ol (**45c**, 26%). LRMS (ES) (M+H)⁺: observed =
- 10 226.1, calculated = 225.3.
- Step 3-5: In an analogous manner to example **16-1**, 1-(4-cyclopropyl-3-fluoropyridin-2-yl)-3-methoxypropan-1-ol (**45c**) was used to prepare (2R,6R)-4-((R)-1-(4-cyclopropyl-3-fluoropyridin-2-yl)-3-methoxypropyl)-1-isobutyl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-
- 15 carboxamide (**45**) LRMS (ES) (M+H)⁺: observed = 589.3, calculated = 588.7.

EXAMPLE 46



Preparation of (2R,6R)-4-((R)-1-(3-fluoro-4-(prop-1-yn-1-yl)pyridin-2-yl)-3-methoxypropyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**46**)

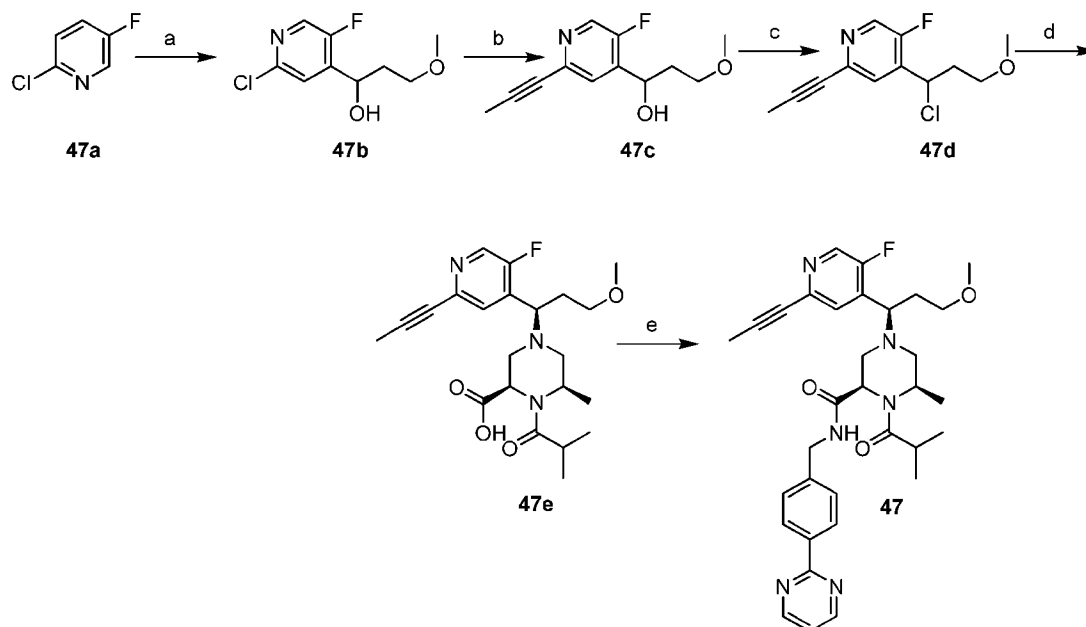
5

Step 1: In an analogous manner to example **28b**, 1-(4-chloro-3-fluoropyridin-2-yl)-3-methoxypropan-1-ol (**45b**) and tributyl(prop-1-yn-1-yl)stannane were used to prepare 1-(3-fluoro-4-(prop-1-yn-1-yl)pyridin-2-yl)-3-methoxypropan-1-ol (**46a**, 85%). LRMS (ES) (M+H)⁺: observed = 224.1, calculated = 223.2.

10 Steps 2-4: In an analogous manner to example **16-1**, 1-(3-fluoro-4-(prop-1-yn-1-yl)pyridin-2-yl)-3-methoxypropan-1-ol (**46a**) was used to prepare (2R,6R)-4-((R)-1-(3-fluoro-4-(prop-1-yn-1-yl)pyridin-2-yl)-3-methoxypropyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**46**) LRMS (ES) (M+H)⁺: observed = 587.3, calculated = 586.7.

15

EXAMPLE 47



Preparation of (2R,6R)-4-((R)-1-(5-fluoro-2-(prop-1-yn-1-yl)pyridin-4-yl)-3-methoxypropyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**47**)

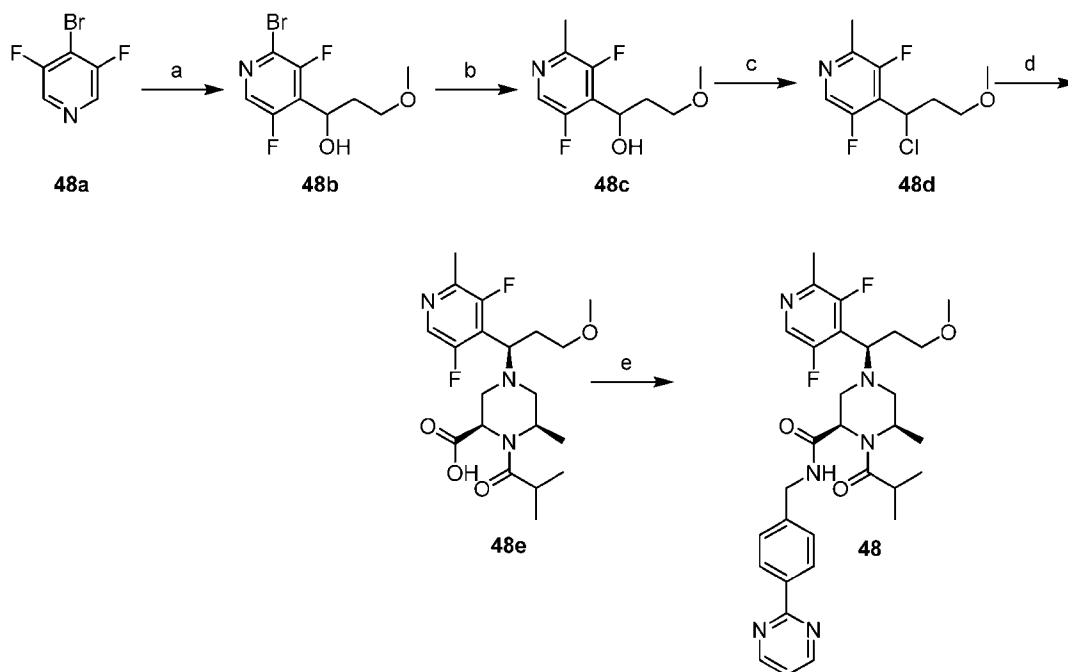
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Step 1: In an analogous manner to example **37b**, 2-chloro-5-fluoropyridine (**47a**) and 3-methoxypropanal was used to prepare 1-(2-chloro-5-fluoropyridin-4-yl)-3-methoxypropan-1-ol (**47b**, 54%) LRMS (ES) (M+H)⁺: observed = 220.0, calculated = 219.6.

Step 2: In an analogous manner to example **28b**, 1-(2-chloro-5-fluoropyridin-4-yl)-3-methoxypropan-1-ol (**47b**) and tributyl(prop-1-yn-1-yl)stannane were used to prepare 1-(5-fluoro-2-(prop-1-yn-1-yl)pyridin-4-yl)-3-methoxypropan-1-ol (**47c**, 91%). LRMS (ES) (M+H)⁺: observed = 224.1, calculated = 223.2.

Steps 2-4: In an analogous manner to example **16-1**, 1-(5-fluoro-2-(prop-1-yn-1-yl)pyridin-4-yl)-3-methoxypropan-1-ol (**47c**) was used to prepare (2R,6R)-4-((R)-1-(5-fluoro-2-(prop-1-yn-1-yl)pyridin-4-yl)-3-methoxypropyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**47**) LRMS (ES) (M+H)⁺: observed = 587.3, calculated = 586.7.

EXAMPLE 48



Preparation of (2R,6R)-4-((R)-1-(3,5-difluoro-2-methylpyridin-4-yl)-3-methoxypropyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**48**)

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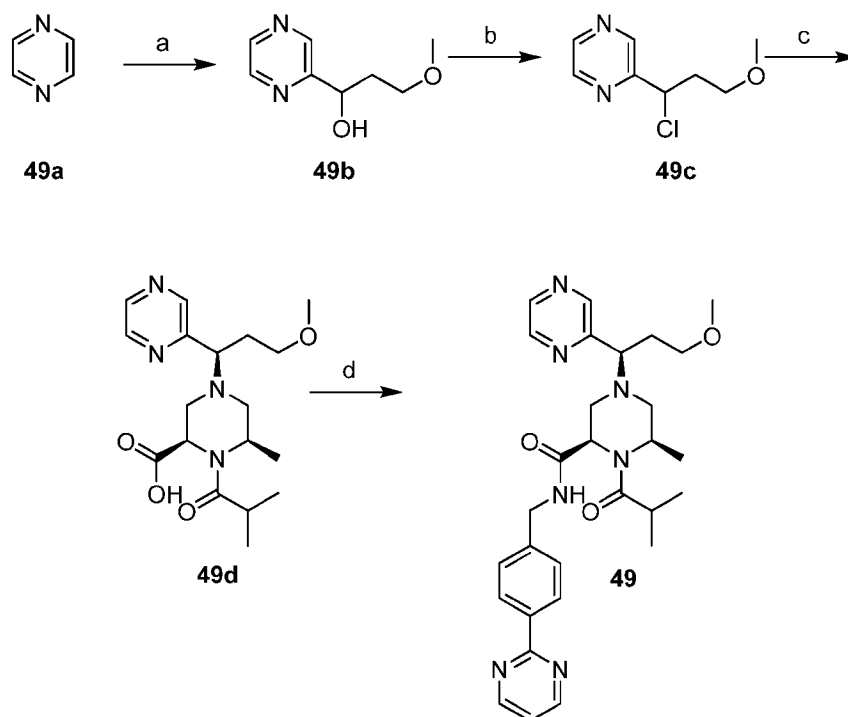
Step 1: In an analogous manner to example **37b**, 4-bromo-3,5-difluoropyridine (**48a**) and 3-methoxypropanal was used to prepare 1-(2-bromo-3,5-difluoropyridin-4-yl)-3-methoxypropan-1-ol (**48b**, 55%) LRMS (ES) (M+H)⁺: observed = 282.0, calculated = 282.0.

Step 2: In an analogous manner to example **20a**, 1-(2-bromo-3,5-difluoropyridin-4-yl)-3-methoxypropan-1-ol (**48b**) and methylboronic acid was used to prepare 1-(3,5-difluoro-2-methylpyridin-4-yl)-3-methoxypropan-1-ol (**48c**, 56%) LRMS (ES) (M+H)⁺: observed = 218.1, calculated = 217.2.

Steps 3-5: In an analogous manner to example **16-1**, 1-(3,5-difluoro-2-methylpyridin-4-yl)-3-methoxypropan-1-ol (**48c**) was used to prepare (2R,6R)-4-((R)-1-(3,5-difluoro-2-methylpyridin-4-yl)-3-methoxypropyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**48**) LRMS (ES) (M+H)⁺: observed = 581.3, calculated = 580.7.

15

EXAMPLE 49



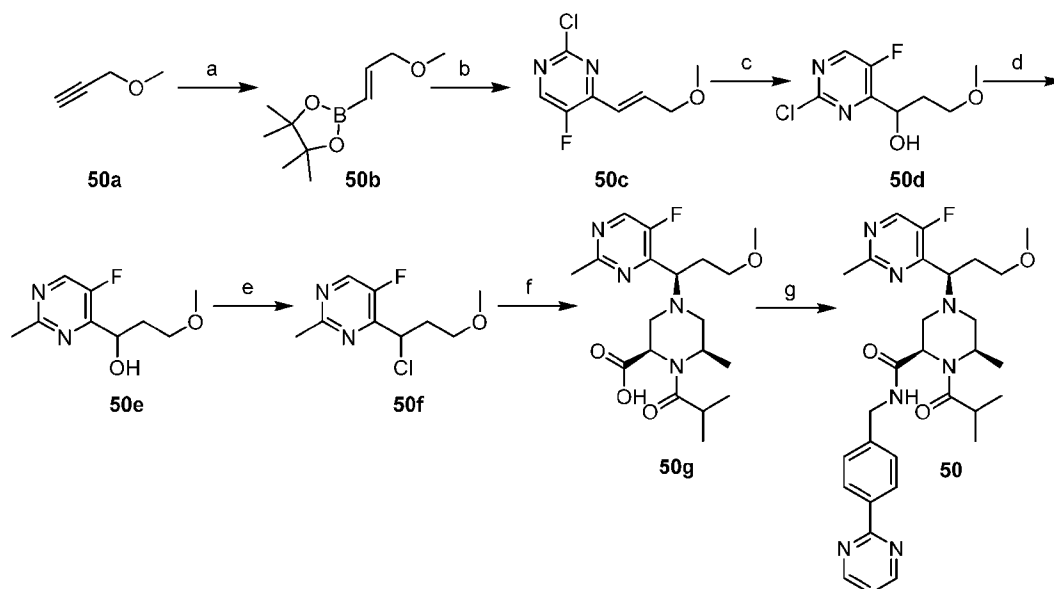
Preparation of (2R,6R)-1-isobutyryl-4-((R)-3-methoxy-1-(pyrazin-2-yl)propyl)-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**49**)

5

Step 1: To a solution of 2,2,6,6-tetramethylpiperidine (6.35 g, 45.0 mmol) in THF (150 mL) was added butyllithium (17.98 mL, 45.0 mmol) at -78 °C under N₂. The mixture was stirred at 0 °C for 30 mins. then the mixture was added pyrazine (**49a**, 3.0 g, 37.5 mmol) in THF (50 mL) at -78 °C and stirred the mixture was stirred at -78 °C for 20 minutes. Then to the mixture was added 3-methoxypropanal (6.60 g, 74.9 mmol) at -78 °C and stirred at -78 °C for 2 hours. The mixture was quenched with water (10 mL), which was extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine (10 mL), dried over Na₂SO₄ and filtered. The filtrate was concentrated in vacuo to give the crude, which was purified by Pre-TLC (SiO₂, EtOAc 100%) to give 3-methoxy-1-(pyrazin-2-yl)propan-1-ol (**49b**, 0.57 g, 8.7%)

15 Steps 2-4: In an analogous manner to example 16-1, 3-methoxy-1-(pyrazin-2-yl)propan-1-ol (**49b**) was used to prepare (2R,6R)-1-isobutyryl-4-((R)-3-methoxy-1-(pyrazin-2-yl)propyl)-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**49**) LRMS (ES) (M+H)⁺: observed = 532.3, calculated = 531.7.

EXAMPLE 50



Preparation of (2R,6R)-4-((R)-1-(5-fluoro-2-methylpyrimidin-4-yl)-3-methoxypropyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**50**)

5

Step 1: Preparation of 2-(3-methoxyprop-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**50b**) A mixture of K_2CO_3 (0.39 g, 2.85 mmol), $CuFe_2O_4$ (0.68 g, 2.85 mmol), 3-methoxyprop-1-yne (**50a**, 2.0 g, 28.5 mmol) and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (7.97 g, 31.4 mmol) in MeOH (20 mL) was stirred at 50 °C for 12 hours. The mixture was filtered and the filtrate was concentrated in vacuo. The mixture was quenched with water and extracted with EtOAc (3 x 30 mL). Filtered and concentrated in vacuo to give crude 2-(3-methoxyprop-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**50b**, 6.0 g, 85%). LRMS (ES) ($M+H$)⁺: observed = 199.1, calculated = 198.0.

10

Step 2: Preparation of 2-chloro-5-fluoro-4-(3-methoxyprop-1-en-1-yl)pyrimidine (**50c**) To a solution of 2,4-dichloro-5-fluoropyrimidine (2.0 g, 11.98 mmol) in Dioxane (50 mL) and Water (10 mL) were added 2-(3-methoxyprop-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**50b**, 2.97 g, 11.98 mmol), K_2CO_3 (3.31 g, 23.96 mmol) and $PdCl_2(dppf)$ (0.175 g, 0.240 mmol). The resulting mixture was stirred at 90 °C under N_2 protection for 15 hours. The reaction mixture was concentrated, 100 mL H_2O was added and extracted with EtOAc (50 mL x 3). The organic layer dried over Na_2SO_4 , filtered and concentrated. The crude product was purified by flash silica gel

20

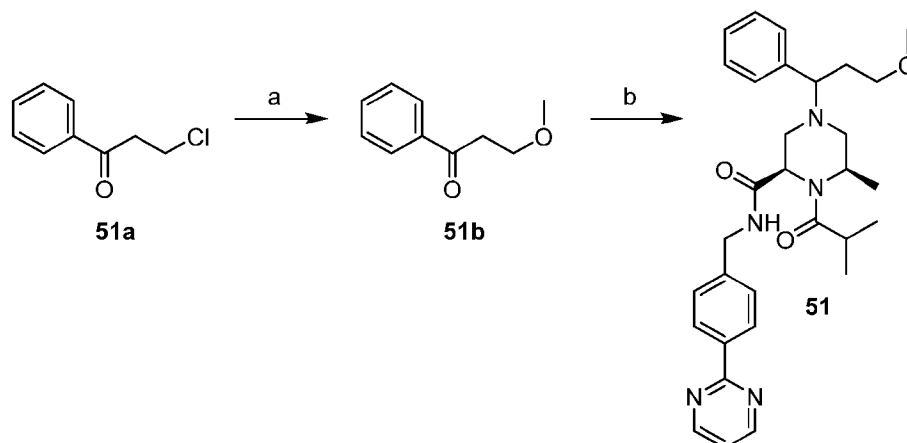
chromatography (ISCO®; 120 g Biotage® Silica Flash Column, Eluent of 0-18% EtOAc/PE gradient) to give 2-chloro-5-fluoro-4-(3-methoxyprop-1-en-1-yl)pyrimidine (**50c**, 2.3 g, 85%).

Step 3: Preparation of 1-(2-chloro-5-fluoropyrimidin-4-yl)-3-methoxypropan-1-ol (**50d**) A mixture of 2-chloro-5-fluoro-4-(3-methoxyprop-1-en-1-yl)pyrimidine (**50c**, 2.3 g, 11.35 mmol),
5 cobalt(ii) acetylacetonate hydrate (0.312 g, 1.135 mmol) and phenylsilane (2.457 g, 22.70 mmol) in THF (20 mL) was stirred at 25 °C under N₂ protection for 15 hours. The reaction was filtered and concentrated. The crude product was purified by column chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 50% EtOAc/ Petroleum ether gradient) to give 1-(2-chloro-5-fluoropyrimidin-4-yl)-3-methoxypropan-1-ol (**50d**, 1.7 g, 61%). LRMS (ES) (M+H)⁺:
10 observed = 221.0, calculated = 220.6.

Step 4: Preparation of 1-(5-fluoro-2-methylpyrimidin-4-yl)-3-methoxypropan-1-ol (**50e**) Na₂CO₃ (0.60 g, 5.67 mmol) and 1-(2-chloro-5-fluoropyrimidin-4-yl)-3-methoxypropan-1-ol (**50d**, 0.50 g, 2.27 mmol) were combined in a flask, 4-Dioxane (4 mL) / Water (1 mL). 2,4,6-trimethyl-1,3,5,2,4,6-trioxatriborinane (341 mg, 2.72 mmol) and PdCl₂(dppf) (166 mg, 0.227 mmol) were
15 added at 25 °C. Then the mixture was stirred at 90 °C under N₂ for 12 hours. The reaction was quenched with water and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with water (2 x 10 mL), brine (2 x 10 mL), dried (Na₂SO₄) and filtered. The filtrate was concentrated in vacuo to give crude product. The crude material was dissolved in EtOAc (10 mL) and aqueous HCl solution (1 M, 40 mL). The water was basified to pH= 7 with 1M aq. Na₂CO₃
20 and extracted with DCM: MeOH=10:1 (3 x 10 mL), dried (Na₂SO₄). Filtered and the filtrate was concentrated in vacuo. The crude product was purified by prep-TLC (Petroleum ether: EtOAc= 2:1) to give 1-(5-fluoro-2-methylpyrimidin-4-yl)-3-methoxypropan-1-ol (**50e**, 98%) LRMS (ES) (M+H)⁺: observed = 201.0, calculated = 200.2.

Steps 5-7: In an analogous manner to example **16-1**, 1-(5-fluoro-2-methylpyrimidin-4-yl)-3-methoxypropan-1-ol (**50e**) was used to prepare (2R,6R)-4-((R)-1-(5-fluoro-2-methylpyrimidin-4-yl)-3-methoxypropyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**50**) LRMS (ES) (M+H)⁺: observed = 564.3, calculated = 563.7.

EXAMPLE 51



Preparation of (2R,6R)-1-isobutyryl-4-(3-methoxy-1-phenylpropyl)-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**51**)

5

Step 1: Preparation of 3-methoxy-1-phenylpropan-1-one (**51b**) To a stirred solution of 3-chloro-1-phenylpropan-1-one (**51a**, 0.30 g, 1.78 mmol) in Methanol (6 mL) was added sodium iodide (0.267 g, 1.78 mmol) and the resulting mixture was heated overnight at 60°C. The mixture was allowed to cool to room temperature, filtered through celite and concentrated. Flash column purification using a 0-20% ethyl acetate/ hexane gradient gave 3-methoxy-1-phenylpropan-1-one (**51b**, 0.247 g, 85%).

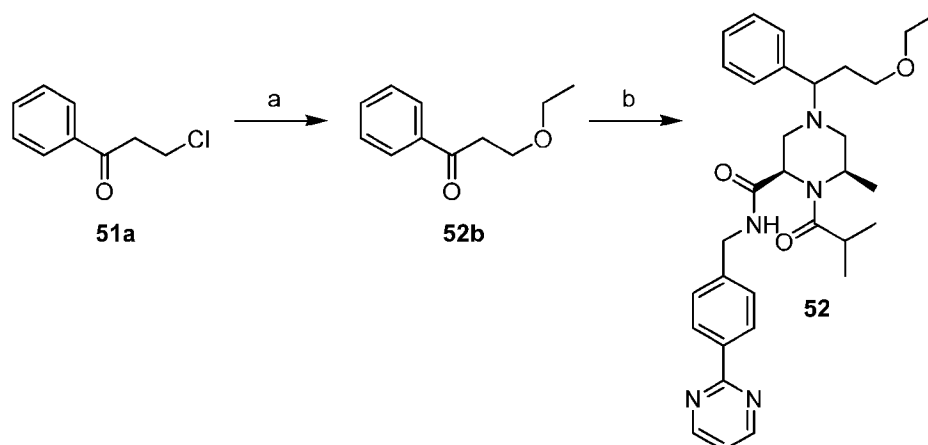
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Step 2: Preparation of (2R,6R)-1-isobutyryl-4-(3-methoxy-1-phenylpropyl)-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**51**) To a stirred solution of (2R,6R)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**12g**, 0.024 g, 0.063 mmol) and 3-methoxy-1-phenylpropan-1-one (**51b**, 0.041 g, 0.252 mmol) in dichloroethane (0.42 mL) was added solid supported sodium cyanoborohydride 2.51 mmol/g (0.08 g) and acetic acid (0.022 mL). The resulting mixture was heated via microwave irradiation to 100°C for 2 hours. The mixture was filtered through celite and concentrated. The crude material was purified by reverse phase purification to give (2R,6R)-1-isobutyryl-4-(3-methoxy-1-phenylpropyl)-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**51**, 0.007 g, 17%). LRMS (ES) (M+H)⁺: observed = 530.4, calculated = 529.7.

15

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EXAMPLE 52



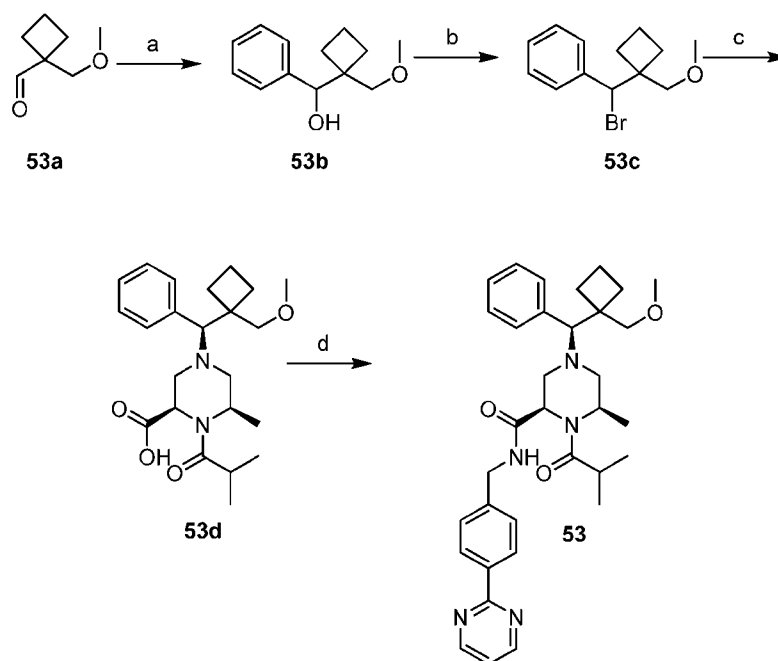
Preparation of (2R,6R)-4-(3-ethoxy-1-phenylpropyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**52**)

5

Steps 1-2: In an analogous manner to example **51**, 3-chloro-1-phenylpropan-1-one (**51a**) and ethanol were used to prepare (2R,6R)-4-(3-ethoxy-1-phenylpropyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**52**) LRMS (ES) (M+H)⁺: observed = 544.4, calculated = 543.7.

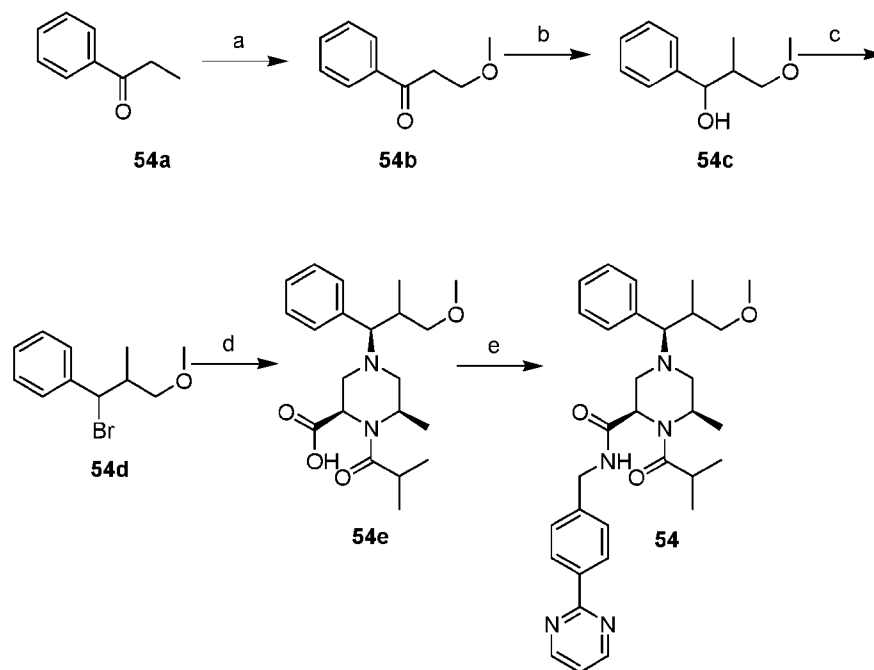
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EXAMPLE 53



Preparation of (2R,6R)-1-isobutyryl-4-((S)-(1-(methoxymethyl)cyclobutyl)(phenyl)methyl)-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**53**)

- Step 1: Preparation of (1-(methoxymethyl)cyclobutyl)(phenyl)methanol (**53b**) To a stirred solution of 1-(methoxymethyl)cyclobutanecarbaldehyde (**53a**, 0.40 g, 3.12 mmol) in THF (10 mL) chilled in an ice bath under N₂ was added phenyl magnesium bromide solution (1M, 4.68 mL, 4.68 mmol) and the resulting mixture was at 0°C for 90 minutes. The mixture was poured into saturated ammonium chloride solution and extracted several times with ethyl acetate. The combined organic layers were concentrated. Flash column purification using a 0-10% ethyl acetate/ hexane gradient gave (1-(methoxymethyl)cyclobutyl)(phenyl)methanol (**53b**, 0.547 g, 85%).
- Step 2: Preparation of (bromo(1-(methoxymethyl)cyclobutyl)methyl)benzene (**53c**) To a stirred solution of (1-(methoxymethyl)cyclobutyl)(phenyl)methanol (**53b**, 0.540 g, 2.62 mmol) in ethyl ether (4 mL) was added pyridine (0.085 mL, 1.05 mmol) and the resulting mixture was chilled in an ice bath. To this was added PBr₃ (0.37 mL, 3.93 mmol) dissolved in ethyl ether (3mL) dropwise over 5 minutes. The resulting solution was stirred 30 minutes and allowed to warm to room temperature. The mixture was chilled to 0°C and quenched with ice. The mixture was extracted with ethyl ether, dried over sodium sulfate and concentrated to give (bromo(1-(methoxymethyl)cyclobutyl)methyl)benzene (**53c**, 0.568 g, 81%)
- Steps 3-4: In an analogous manner to example **16-1**, (bromo(1-(methoxymethyl)cyclobutyl)methyl)benzene (**53c**) was used to prepare (2R,6R)-1-isobutyryl-4-((S)-(1-(methoxymethyl)cyclobutyl)(phenyl)methyl)-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**53**) LRMS (ES) (M+H)⁺: observed = 570.5, calculated = 569.7.



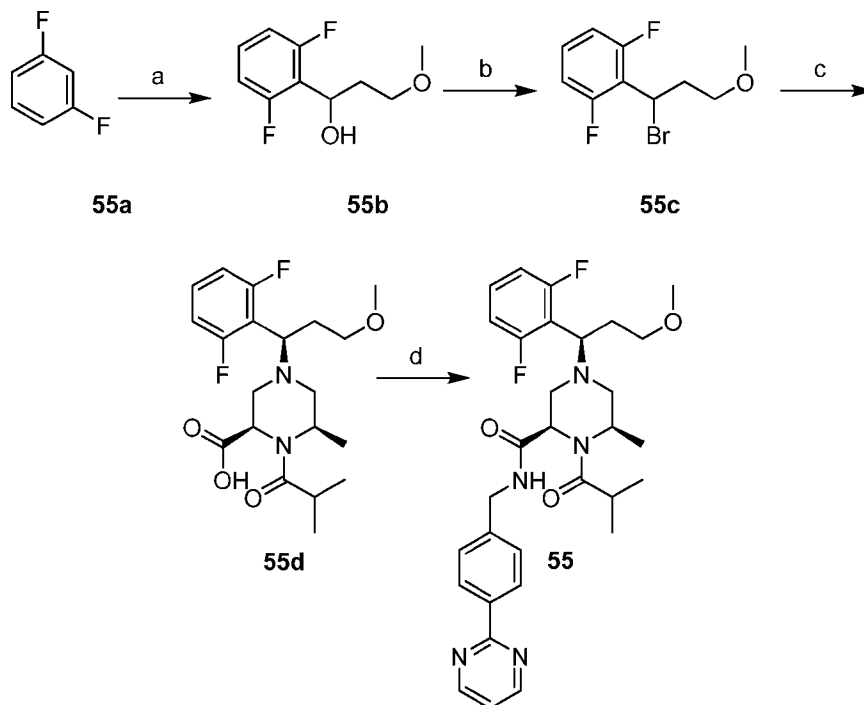
Preparation of (2R,6R)-1-isobutyl-4-((1R)-3-methoxy-2-methyl-1-phenylpropyl)-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**54**)

- 5 Step 1: Preparation of 3-methoxy-1-phenylpropan-1-one (**54b**) To a stirred solution of propiophenone (**54a**, 0.66 g, 4.93 mmol) in methanol (3 mL) was added potassium carbonate (0.068 g, 0.493 mmol) and formaldehyde (0.367 mL, 4.93 mmol) and the resulting mixture was stirred 10 days at room temperature. The mixture was concentrated and flash column purification using a 0-10% ethyl acetate/ hexane gradient gave 3-methoxy-1-phenylpropan-1-one (**54b**, 0.624 g, 71%).
- 10 Step 2: Preparation of 3-methoxy-2-methyl-1-phenylpropan-1-ol (**54c**) To a stirred solution of 3-methoxy-1-phenylpropan-1-one (**54b**, 0.818 g, 4.59 mmol) in THF (15 mL) and Methanol (1 mL) chilled in an ice bath was added sodium borohydride (0.174 g, 4.59 mmol) and the mixture was stirred for 3 hours. The mixture was diluted with ethyl acetate and washed with brine. The organic phase was concentrated and flash column purification using a 0-30% ethyl acetate/ hexane gradient gave 3-methoxy-2-methyl-1-phenylpropan-1-ol (**54c**, 0.627 g, 76%).
- 15 Step 3: In an analogous manner to example **53c**, 3-methoxy-2-methyl-1-phenylpropan-1-ol (**54c**) was used to prepare (1-bromo-3-methoxy-2-methylpropyl)benzene (**54d**).

Steps 4-5: In an analogous manner to example **16-1**, (1-bromo-3-methoxy-2-methylpropyl)benzene (**54d**) was used to prepare (2R,6R)-1-isobutyryl-4-((1R)-3-methoxy-2-methyl-1-phenylpropyl)-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**54**) LRMS (ES) (M+H)⁺: observed = 544.5, calculated = 543.7.

5

EXAMPLE 55

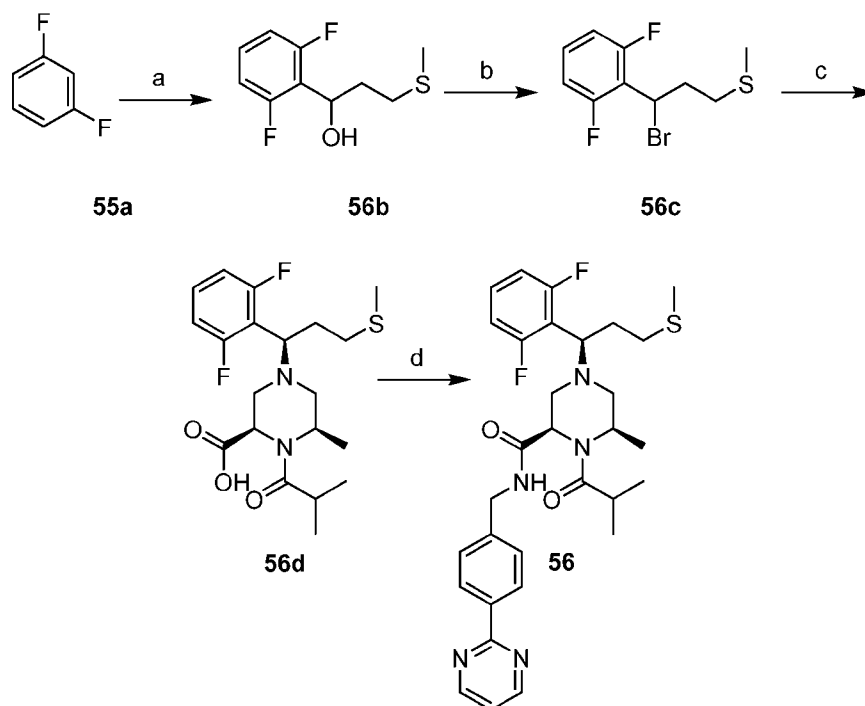


Preparation of (2R,6R)-4-((R)-1-(2,6-difluorophenyl)-3-methoxypropyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**55**)

10 Steps 1-4: In an analogous manner to example **36**, 1,3-difluorobenzene (**55a**) was used to prepare (2R,6R)-4-((R)-1-(2,6-difluorophenyl)-3-methoxypropyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**55**) LRMS (ES) (M+H)⁺: observed = 566.4, calculated = 565.6.

EXAMPLE 56

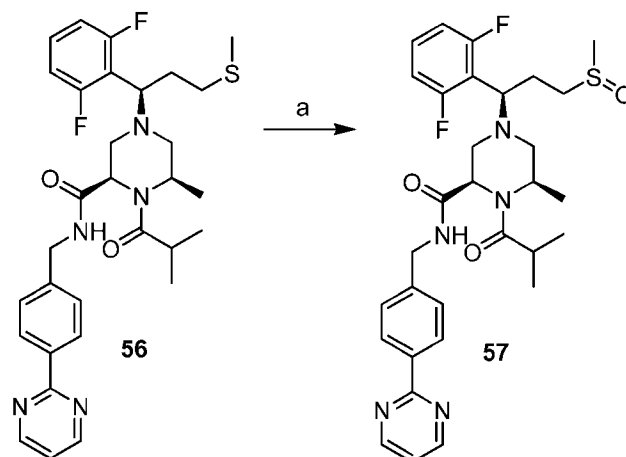
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Preparation of (2R,6R)-4-((R)-1-(2,6-difluorophenyl)-3-(methylthio)propyl)-1-isobutyl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**56**)

- 5 Steps 1-4: In an analogous manner to example **36**, 1,3-difluorobenzene (**55a**) and 3-(methylthio)propanal was used to prepare (2R,6R)-4-((R)-1-(2,6-difluorophenyl)-3-(methylthio)propyl)-1-isobutyl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**56**) LRMS (ES) (M+H)⁺: observed = 582.4, calculated = 581.7.

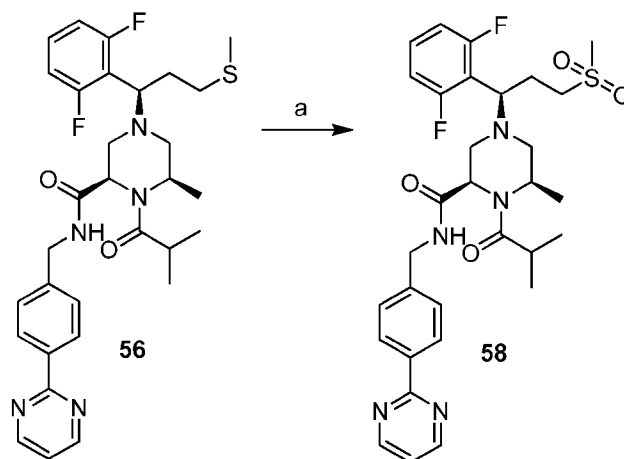
EXAMPLE 57



Preparation of (2R,6R)-4-((1R)-1-(2,6-difluorophenyl)-3-(methylsulfinyl)propyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**57**)

Step 1: To a stirred solution of (2R,6R)-4-((R)-1-(2,6-difluorophenyl)-3-(methylthio)propyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**56**, 0.025 g, 0.036 mmol) in dichloromethane (0.30 mL) was added mCPBA (0.009 g, 0.036 mmol) and the resulting solution was stirred 20 min and concentrated. The crude material was purified by reverse phase purification to give (2R,6R)-4-((1R)-1-(2,6-difluorophenyl)-3-(methylsulfinyl)propyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**57**, 0.014 g, 55%). LRMS (ES) (M+H)⁺: observed = 598.4, calculated = 597.7.

EXAMPLE 58



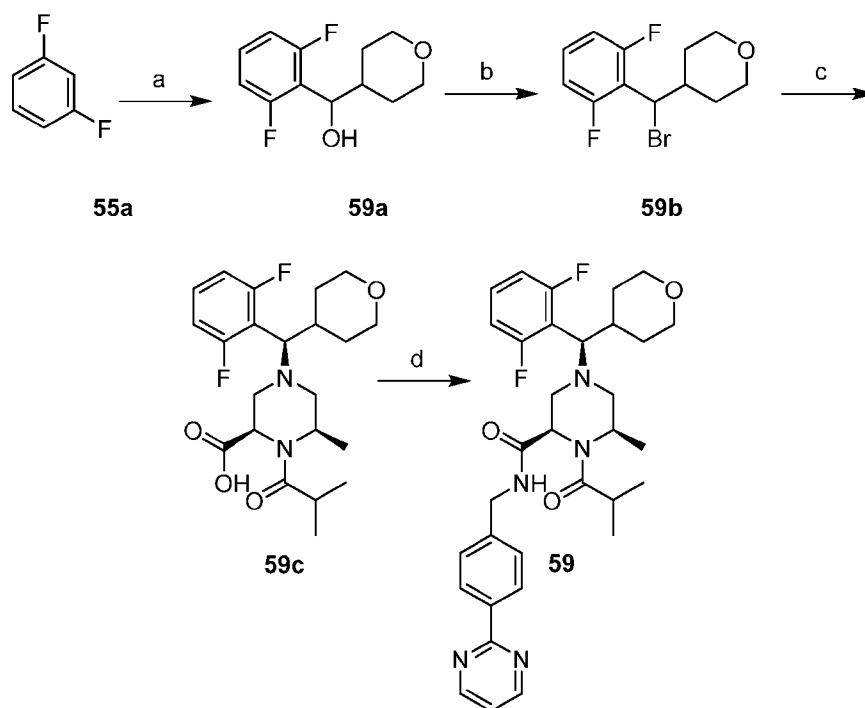
Preparation of (2R,6R)-4-((R)-1-(2,6-difluorophenyl)-3-(methylsulfonyl)propyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**58**)

15

Step 1: To a stirred solution of (2R,6R)-4-((R)-1-(2,6-difluorophenyl)-3-(methylthio)propyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**56**, 0.020 g, 0.036 mmol) in dichloromethane (0.30 mL) was added mCPBA (0.014 g, 0.057 mmol) and the resulting solution was stirred 20 min and concentrated. The crude material was purified by reverse phase purification to give (2R,6R)-4-((R)-1-(2,6-difluorophenyl)-3-(methylsulfonyl)propyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**58**, 0.010 g, 48%). LRMS (ES) (M+H)⁺: observed = 614.5, calculated = 613.7.

20

EXAMPLE 59



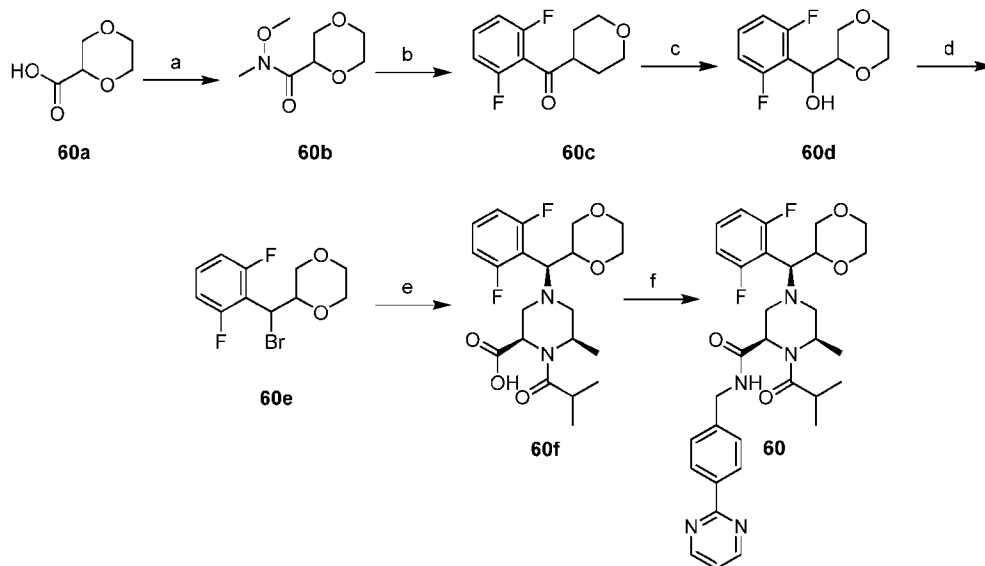
Preparation of (2R,6R)-4-((R)-(2,6-difluorophenyl)(tetrahydro-2H-pyran-4-yl)methyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**59**)

5

Steps 1-4: In an analogous manner to example **36**, 1,3-difluorobenzene (**55a**) and tetrahydro-2H-pyran-4-carbaldehyde was used to prepare (2R,6R)-4-((R)-(2,6-difluorophenyl)(tetrahydro-2H-pyran-4-yl)methyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**59**) LRMS (ES) (M+H)⁺: observed = 592.5, calculated = 591.7.

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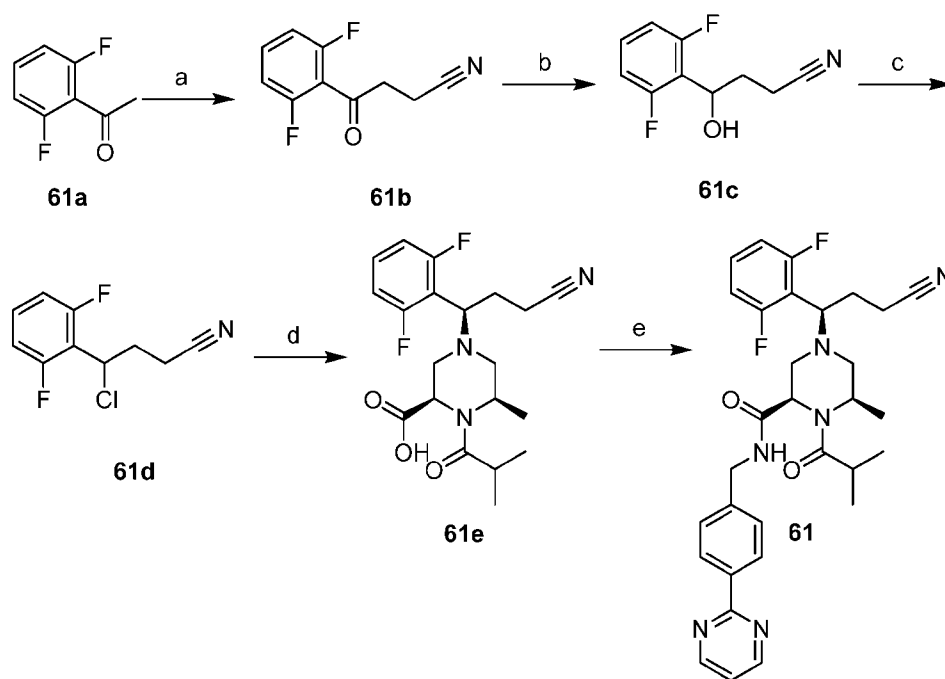
EXAMPLE 60



Preparation of (2R,6R)-4-((1S)-(2,6-difluorophenyl)(1,4-dioxan-2-yl)methyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**60**)

- 5 Step 1: Preparation of N-methoxy-N-methyl-1,4-dioxane-2-carboxamide (**60b**) To a stirred solution of 1,4-dioxane-2-carboxylic acid (**60a**, 3.0 g, 22.71 mmol), N,O-dimethylhydroxylamine HCl (2.66 g, 27.2 mmol) and DMAP (0.277 g, 2.27 mmol) in Dichloromethane (65 mL) was added EDC (5.22 g, 27.2 mmol) and triethylamine (3.8 mL, 27.2 mmol). The resulting solution was stirred 4 hours, quenched with 1N HCl solution and extracted with dichloromethane, and
- 10 ethyl acetate. The combined organic layers were concentrated. Flash column purification using a 0-100% ethyl acetate/ hexane gradient gave N-methoxy-N-methyl-1,4-dioxane-2-carboxamide (**60b**, 2.95 g, 74%). LRMS (ES) (M+H)⁺: observed = 175.1, calculated = 176.1.
- Step 2: In an analogous manner to example **36**, 1,3-difluorobenzene (**55a**) and N-methoxy-N-methyl-1,4-dioxane-2-carboxamide (**60b**) were used to prepare (2,6-difluorophenyl)(tetrahydro-
- 15 2H-pyran-4-yl)methanone (**60c**) LRMS (ES) (M+H)⁺: observed = 229.1, calculated = 228.1.
- Step 3: In an analogous manner to example **54c**, (2,6-difluorophenyl)(tetrahydro-2H-pyran-4-yl)methanone (**60c**) and sodium borohydride were used to prepare (2,6-difluorophenyl)(1,4-dioxan-2-yl)methanol (**60d**) LRMS (ES) (M+H)⁺: observed = 231.1, calculated = 230.2.
- Steps 4-6: In an analogous manner to example **36**, (2,6-difluorophenyl)(1,4-dioxan-2-yl)methanol (**60d**) was used to prepare (2R,6R)-4-((1S)-(2,6-difluorophenyl)(1,4-dioxan-2-yl)methyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**60**)
- 20 LRMS (ES) (M+H)⁺: observed = 594.7, calculated = 593.6.

EXAMPLE 61



Preparation of (2R,6R)-4-((R)-3-cyano-1-(2,6-difluorophenyl)propyl)-1-isobutyl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**61**)

5

Step 1: Preparation of 4-(2,6-difluorophenyl)-4-oxobutanenitrile (**61b**) To a stirred solution of 1-(2,6-difluorophenyl)ethan-1-one (**61a**, 0.7 mL, 5.37 mmol) in THF (16.7 mL) chilled in an ice bath to 0°C was added LDA (2.0M, 2.68 mL, 5.37 mmol) dropwise. The resulting solution was stirred for 20 minutes and then bromoacetonitrile (0.41 mL, 5.90 mmol) was added. The reaction was stirred for 90 minutes then quenched with saturated ammonium chloride solution and extracted with ethyl acetate. The organic layer was concentrated and flash column purification using a 0-30% ethyl acetate/ hexane gradient gave 4-(2,6-difluorophenyl)-4-oxobutanenitrile (**61b**, 0.35 g, 33%).

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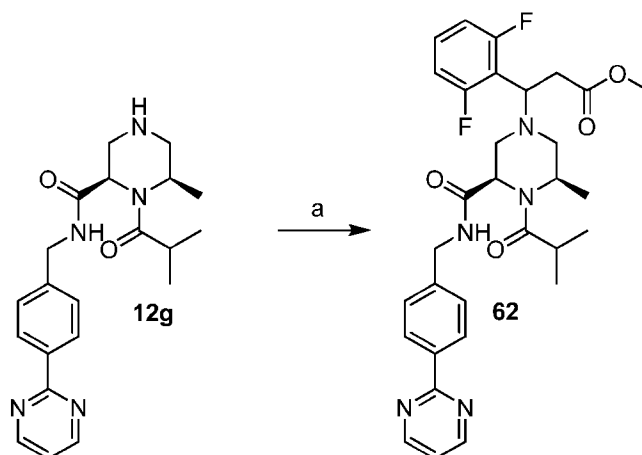
Step 2: In an analogous manner to example **54c**, 4-(2,6-difluorophenyl)-4-oxobutanenitrile (**61b**) and sodium borohydride were used to prepare 4-(2,6-difluorophenyl)-4-hydroxybutanenitrile (**61c**) LRMS (ES) (M+H)⁺: observed = 198.0, calculated = 197.1.

15

Steps 3-5: In an analogous manner to example **16-1**, 4-(2,6-difluorophenyl)-4-hydroxybutanenitrile (**61c**) was used to prepare (2R,6R)-4-((R)-3-cyano-1-(2,6-

difluorophenyl)propyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**61**) LRMS (ES) (M+H)⁺: observed = 561.2, calculated = 560.6.

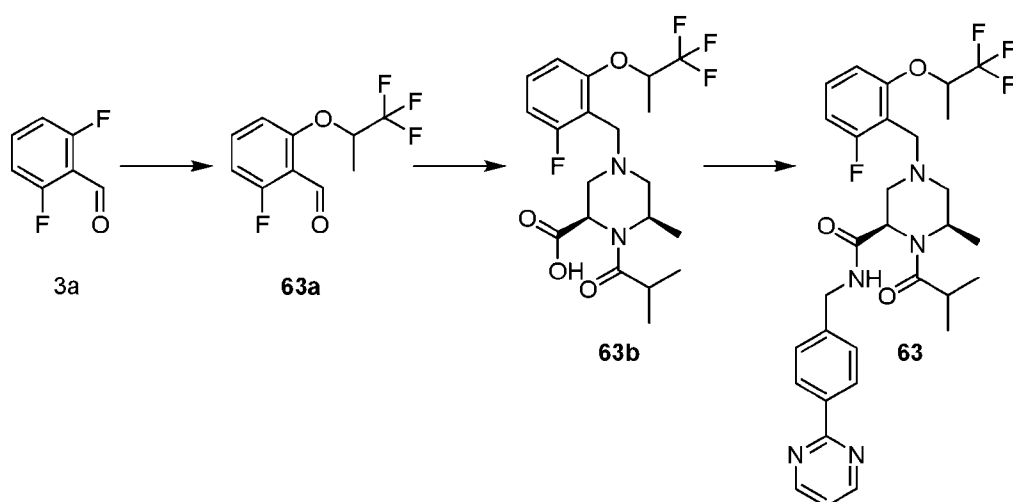
EXAMPLE 62



- 5 Preparation of methyl 3-(2,6-difluorophenyl)-3-((3R,5R)-4-isobutyryl-3-methyl-5-((4-(pyrimidin-2-yl)benzyl)carbamoyl)piperazin-1-yl)propanoate (**62**)

Step 1: To a stirred solution of (2R,6R)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**12g**, 0.04 g, 0.105 mmol) in DCM (0.24 mL) under nitrogen was added triethylamine (0.03 mL, 0.215 mmol), followed by addition of trimethylsilyl chloride (0.02 mL, 0.156 mmol). The resulting solution was stirred at room temperature for 1
 10 hour 30 minutes and concentrated under nitrogen. The mixture was dissolved in THF (0.24 mL) under nitrogen. To this was added 2,6-difluorobenzaldehyde (0.02 mL, 0.185 mmol) and trimethylsilyl chloride (0.02 mL, 0.156 mmol). The resulting mixture was stirred 30 minutes then
 15 concentrated under nitrogen. To the mixture was added THF (0.24 mL) and 1-(tertbutyldimethylsilyloxy)-1-methoxyethene (0.046 mL, 0.21 mmol) under nitrogen. Upon completion of reaction the mixture was concentrated and purified by reverse phase purification to give methyl 3-(2,6-difluorophenyl)-3-((3R,5R)-4-isobutyryl-3-methyl-5-((4-(pyrimidin-2-yl)benzyl)carbamoyl)piperazin-1-yl)propanoate (**62**, 0.012 g, 17%). LRMS (ES) (M+H)⁺:
 20 observed = 580.7, calculated = 579.6.

EXAMPLE 63



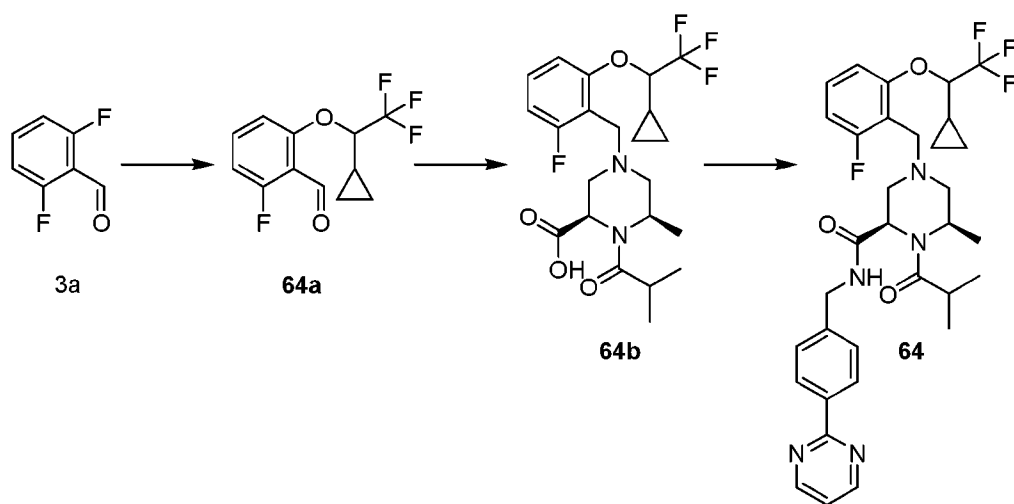
Preparation of (2R,6R)-4-(2-fluoro-6-((1,1,1-trifluoropropan-2-yl)oxy)benzyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**63**)

Step 1: In an analogous manner to example **13a**, 2,6-difluorobenzaldehyde (**3a**) and 1,1,1-trifluoropropan-2-ol was used to prepare 2-fluoro-6-((1,1,1-trifluoropropan-2-yl)oxy)benzaldehyde (**63a**, 65%) LRMS (ES) (M+H)⁺: observed = 237.0, calculated = 236.1.

Step 2: In an analogous manner to example **1-1**, (2R,6R)-1-isobutyryl-6-methylpiperazine-2-carboxylic acid (**16a**) and 2-fluoro-6-((1,1,1-trifluoropropan-2-yl)oxy)benzaldehyde (**63a**) were used to prepare (2R,6R)-4-(2-fluoro-6-((1,1,1-trifluoropropan-2-yl)oxy)benzyl)-1-isobutyryl-6-methylpiperazine-2-carboxylic acid (**63b**, 76%). LRMS (ES) (M+H)⁺: observed = 435.3, calculated = 434.4.

Step 3: In an analogous manner to example **16-1**, (2R,6R)-4-(2-fluoro-6-((1,1,1-trifluoropropan-2-yl)oxy)benzyl)-1-isobutyryl-6-methylpiperazine-2-carboxylic acid (**63b**) and (4-(pyrimidin-2-yl)phenyl)methanamine, HCl were used to prepare (2R,6R)-4-(2-fluoro-6-((1,1,1-trifluoropropan-2-yl)oxy)benzyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**63**, 68%). LRMS (ES) (M+H)⁺: observed = 602.3, calculated = 601.6.

EXAMPLE 64



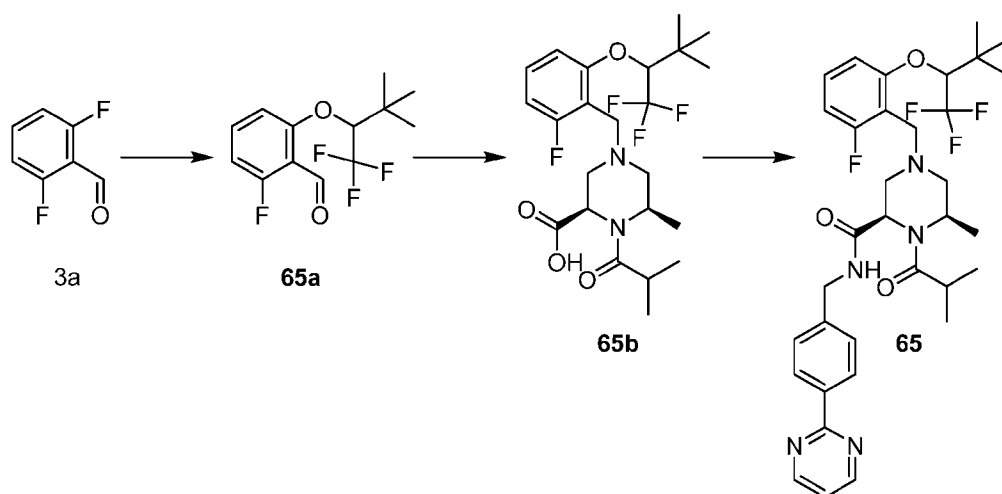
Preparation of (2R,6R)-4-(2-(1-cyclopropyl-2,2,2-trifluoroethoxy)-6-fluorobenzyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**64**)

5

Steps 1-3: In an analogous manner to example **63**, 2,6-difluorobenzaldehyde (**3a**) and 1-cyclopropyl-2,2,2-trifluoroethan-1-ol were used to prepare (2R,6R)-4-(2-(1-cyclopropyl-2,2,2-trifluoroethoxy)-6-fluorobenzyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**64**) LRMS (ES) (M+H)⁺: observed = 628.3, calculated = 627.6.

10

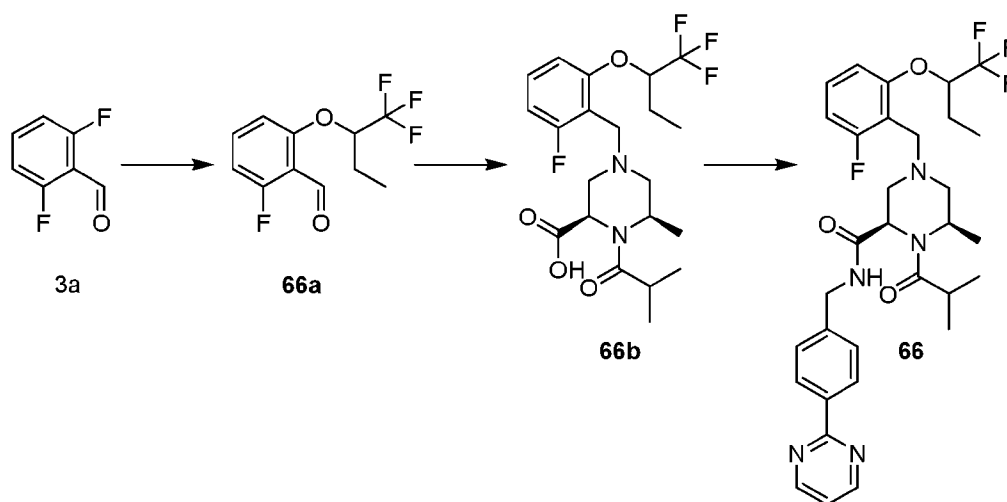
EXAMPLE 65



Preparation of (2R,6R)-4-(2-fluoro-6-((1,1,1-trifluoro-3,3-dimethylbutan-2-yl)oxy)benzyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**65**)

Steps 1-3: In an analogous manner to example **63**, 2,6-difluorobenzaldehyde (**3a**) and 1,1,1-trifluoro-3,3-dimethylbutan-2-ol were used to prepare (2R,6R)-4-(2-fluoro-6-((1,1,1-trifluoro-3,3-dimethylbutan-2-yl)oxy)benzyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**65**) LRMS (ES) (M+H)⁺: observed = 644.3, calculated = 643.7.

EXAMPLE 66



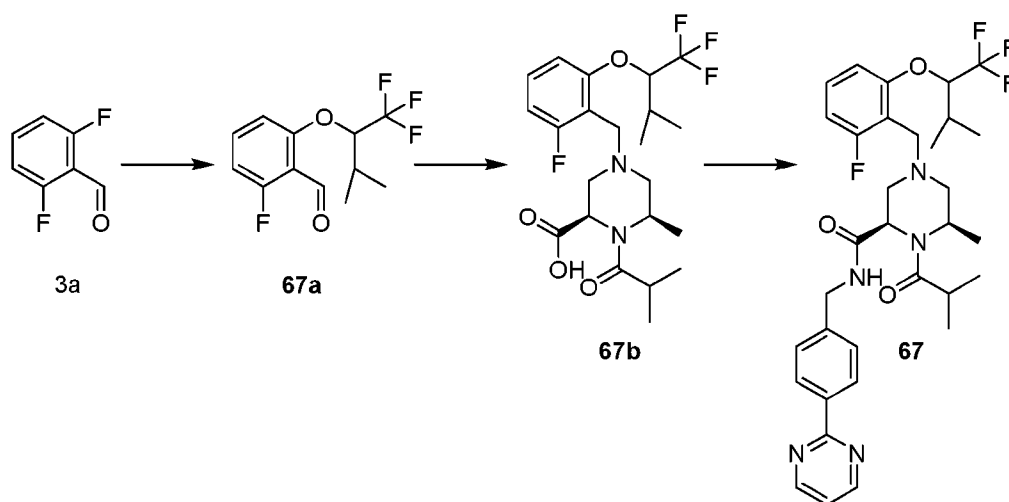
10

Preparation of (2R,6R)-4-(2-fluoro-6-((1,1,1-trifluorobutan-2-yl)oxy)benzyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**66**)

Steps 1-3: In an analogous manner to example **63**, 2,6-difluorobenzaldehyde (**3a**) and 1,1,1-trifluorobutan-2-ol were used to prepare (2R,6R)-4-(2-fluoro-6-((1,1,1-trifluorobutan-2-yl)oxy)benzyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**66**) LRMS (ES) (M+H)⁺: observed = 616.3, calculated = 615.6.

15

EXAMPLE 67



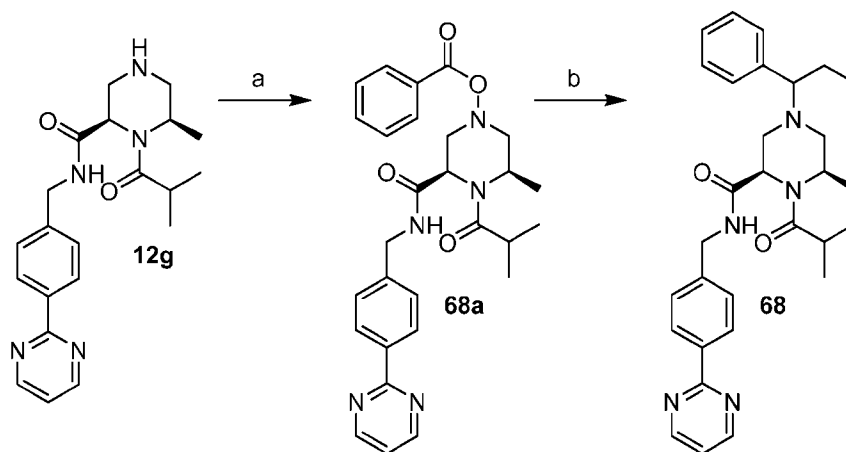
Preparation of (2R,6R)-4-(2-fluoro-6-((1,1,1-trifluoro-3-methylbutan-2-yl)oxy)benzyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**67**)

5

Steps 1-3: In an analogous manner to example **63**, 2,6-difluorobenzaldehyde (**3a**) and 1,1,1-trifluoro-3-methylbutan-2-ol were used to prepare (2R,6R)-4-(2-fluoro-6-((1,1,1-trifluoro-3-methylbutan-2-yl)oxy)benzyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**67**) LRMS (ES) (M+H)⁺: observed = 630.3, calculated = 629.7.

10

EXAMPLE 68



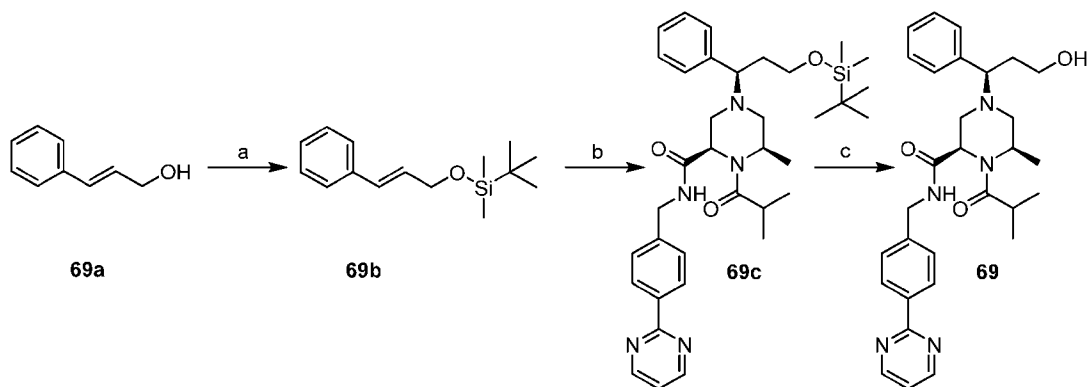
Preparation of (2R,6R)-1-isobutyryl-6-methyl-4-(1-phenylpropyl)-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**68**)

Step 1: Preparation of (3R,5R)-4-isobutyryl-3-methyl-5-((4-(pyrimidin-2-yl)benzyl)carbamoyl)piperazin-1-yl benzoate (**68a**). To a stirred solution of (2R,6R)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide HCl (**12g**, 1.11 g, 2.66 mmol) in DMF (20.0 mL) under nitrogen was added K₂HPO₄ (2.32 g, 13.32 mmol),
5 followed by addition of benzoyl peroxide (0.71 g, 2.93 mmol). The resulting solution was stirred at room temperature overnight. Additional K₂HPO₄ (2.32 g, 13.32 mmol) and benzoyl peroxide (0.71 g, 2.93 mmol) were added and stirred for 3 hours under nitrogen. The mixture was diluted with water and extracted several times with ethyl acetate. The combined organic layers were washed with brine, dried over magnesium sulfate and concentrated. Flash column purification
10 using a 0-100% ethyl acetate/ heptane gradient gave (3R,5R)-4-isobutyryl-3-methyl-5-((4-(pyrimidin-2-yl)benzyl)carbamoyl)piperazin-1-yl benzoate (**68a**, 0.389 g, 29%). LRMS (ES) (M+H)⁺: observed = 502.3, calculated = 501.5.

Step 2: Preparation of (2R,6R)-1-isobutyryl-6-methyl-4-(1-phenylpropyl)-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**68**). To a solution of (3R,5R)-4-isobutyryl-3-methyl-5-((4-(pyrimidin-2-yl)benzyl)carbamoyl)piperazin-1-yl benzoate (**68a**, 0.045 g, 0.090 mmol) dissolved
15 in THF (0.3 mL) under nitrogen was added (E)-prop-1-en-1-ylbenzene (15.0 uL, 0.116 mmol). To this mixture was added a catalyst solution prepared by combining Cu(OAc)₂ (1 mg, 5.51 uM), DTBM-SEGPHOS (6.5 mg, 5.51 uM) in THF (0.3 mL) under nitrogen followed by addition of
20 methyldiethoxysilane (29uL, 0.181 mmol). After addition of the catalyst solution, the reaction was heated overnight at 40°C. The reaction was concentrated and flash column purification using a 0-100% ethyl acetate/ heptane gradient gave (2R,6R)-1-isobutyryl-6-methyl-4-(1-phenylpropyl)-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**68**, 0.015 g, 33%).
LRMS (ES) (M+H)⁺: observed = 500.3, calculated = 499.6.

25

EXAMPLE 69

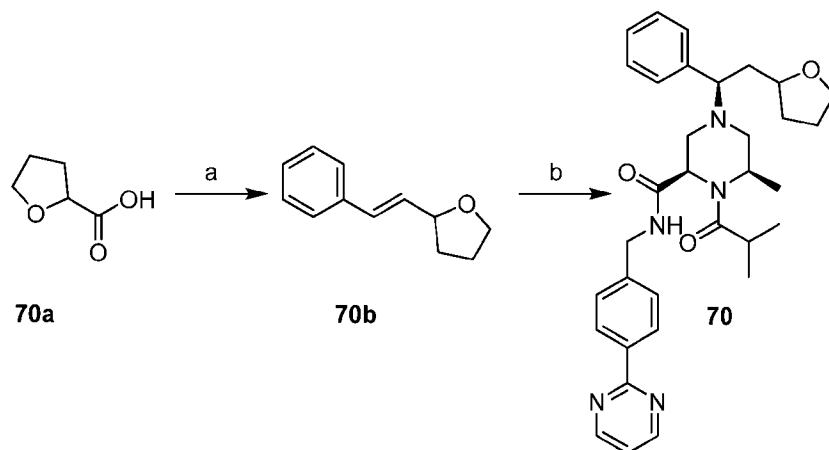


Preparation of (2R,6R)-4-((R)-3-hydroxy-1-phenylpropyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**69**)

- 5 Step 1: Preparation of tert-butyl(cinnamyloxy)dimethylsilane (**69b**). To a stirred solution of (E)-3-phenylprop-2-en-1-ol (**69a**, 0.25 g, 1.86 mmol) in DCM (10.0 mL) was added imidazole (0.19 g, 2.79 mmol), followed by addition of TBDMS-Cl (0.42 g, 2.79 mmol). The resulting solution was stirred at room temperature overnight. The solution was filtered through celite and concentrated. Flash column purification using a 0-25% ethyl acetate/ heptane gradient gave tert-
- 10 butyl(cinnamyloxy)dimethylsilane (**69b**, 0.423 g, 91%).
- Step 2: In an analogous manner to example **68**, (3R,5R)-4-isobutyryl-3-methyl-5-((4-(pyrimidin-2-yl)benzyl)carbamoyl)piperazin-1-yl benzoate (**68a**), tert-butyl(cinnamyloxy)dimethylsilane (**69b**) and R-DTBM-SEGPPOS were used to prepare (2R,6R)-4-((R)-3-((tert-
- 15 butyldimethylsilyl)oxy)-1-phenylpropyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**69c**) LRMS (ES) (M+H)⁺: observed = 630.4, calculated = 629.9.
- Step 3: Preparation of (2R,6R)-4-((R)-3-hydroxy-1-phenylpropyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**69**). To a stirred solution of (2R,6R)-4-((R)-3-((tert-
- 20 butyldimethylsilyl)oxy)-1-phenylpropyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**69c**, 0.032 g, 0.051 mmol) in THF (0.5 mL) was added TBAF (1M, 0.16 mL, 0.16 mmol) and the resulting mixture was stirred at room temperature for 4 hours and concentrated. Flash column purification using a 0-100% ethyl acetate/ heptane gradient gave (2R,6R)-4-((R)-3-hydroxy-1-phenylpropyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**69**, 0.021 g, 80%).

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EXAMPLE 70



Preparation of (2R,6R)-1-isobutyl-6-methyl-4-((1R)-1-phenyl-2-(tetrahydrofuran-2-yl)ethyl)-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**70**)

5

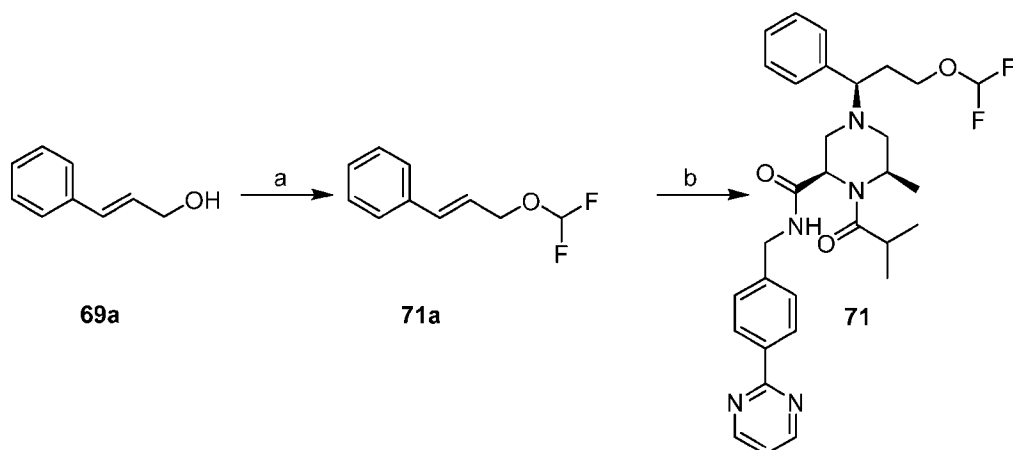
Step 1: Preparation of (E)-2-styryltetrahydrofuran (**70b**) To a stirred solution of tetrahydrofuran-2-carboxylic acid (**70a**, 0.24 mL, 2.50 mmol) and cesium bicarbonate (0.794 g, 4.09 mmol) in dioxane (4 mL) under nitrogen was added (E)-(2-(phenylsulfonyl)vinyl)benzene (0.20 g, 0.819 mmol) and [IR(DTBPPY)(PPY)₂PF₆] (0.004 g, 4.38 μM). The resulting mixture was irradiated with 450nm 100% blue LED in an integrated photoreactor with fan cooling overnight. The crude reaction was diluted with ethyl acetate, filtered through celite and concentrated. Flash column purification using a 0-25% ethyl acetate/ heptane gradient gave (E)-2-styryltetrahydrofuran (**70b**, 0.021 g, 14%).

10

Step 2: In an analogous manner to example **68**, (3R,5R)-4-isobutyl-3-methyl-5-((4-(pyrimidin-2-yl)benzyl)carbamoyl)piperazin-1-yl benzoate (**68a**), (E)-2-styryltetrahydrofuran (**70b**) and R-DTBM-SEGPPOS were used to prepare (2R,6R)-1-isobutyl-6-methyl-4-((1R)-1-phenyl-2-(tetrahydrofuran-2-yl)ethyl)-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**70**) LRMS (ES) (M+H)⁺: observed = 556.4, calculated = 555.7.

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EXAMPLE 71



Preparation of (2R,6R)-4-((R)-3-(difluoromethoxy)-1-phenylpropyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**71**)

5

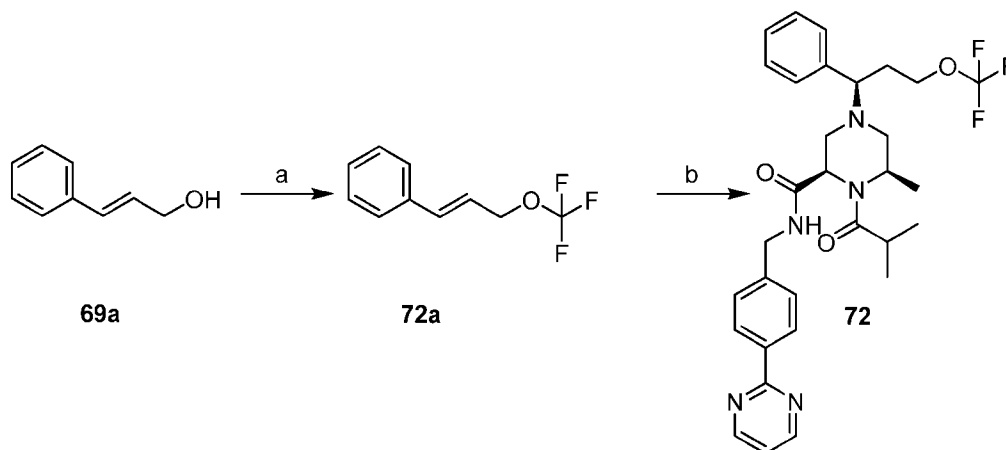
Step 1: Preparation of (E)-3-(difluoromethoxy)prop-1-en-1-ylbenzene (**71a**) To a stirred solution of (E)-3-phenylprop-2-en-1-ol (**69a**, 0.25 g, 1.86 mmol) in DCM (1.2 mL) under nitrogen was added potassium hydrogen fluoride (0.58 g, 7.45 mmol) and water (1.2 mL). This mixture was degassed with nitrogen and added to this was (bromodifluoromethyl)trimethylsilane (0.58 mL, 3.74 mmol) dropwise. The resulting mixture was stirred at room temperature overnight, diluted with DCM, filtered through celite and concentrated. Flash column purification using a 100% hexanes gave (E)-3-(difluoromethoxy)prop-1-en-1-ylbenzene (**71a**, 0.281 g, 82%).

10

Step 2: In an analogous manner to example **68**, (3R,5R)-4-isobutyryl-3-methyl-5-((4-(pyrimidin-2-yl)benzyl)carbamoyl)piperazin-1-yl benzoate (**68a**), (E)-3-(difluoromethoxy)prop-1-en-1-ylbenzene (**71a**) and R-DTBM-SEPHOS were used to prepare (2R,6R)-4-((R)-3-(difluoromethoxy)-1-phenylpropyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**71**) LRMS (ES) (M+H)⁺: observed = 566.3, calculated = 565.6.

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EXAMPLE 72



Preparation of (2R,6R)-1-isobutyl-6-methyl-4-((R)-1-phenyl-3-(trifluoromethoxy)propyl)-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**72**)

5

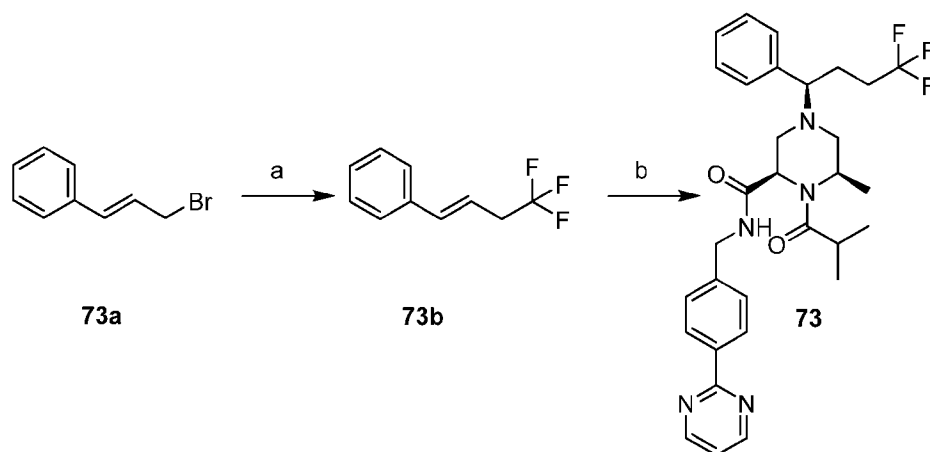
Step 1: Preparation of (E)-3-(trifluoromethoxy)prop-1-en-1-yl)benzene (**72a**) To a microwave vial containing (E)-3-phenylprop-2-en-1-ol (**69a**, 0.25 g, 1.86 mmol), silver trifluoromethanesulfonate (0.957 mg, 3.73 mmol), Selectfluor (990 mg, 2.79 mmol), and potassium fluoride (325 mg, 5.59mmol) was added ethyl acetate (8 mL) under nitrogen. After one minute was added 2-fluoropyridine (0.32 mL, 3.73 mmol) and TMS-CF₃ (0.55 mL, 3.72 mmol). This mixture was degassed with nitrogen and was stirred at room temperature overnight, diluted with ethyl acetate, filtered through celite and concentrated. Flash column purification using a 100% hexanes gave (E)-3-(trifluoromethoxy)prop-1-en-1-yl)benzene (**72a**, 0.211 g, 56%).

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Step 2: In an analogous manner to example **68**, (3R,5R)-4-isobutyl-3-methyl-5-((4-(pyrimidin-2-yl)benzyl)carbamoyl)piperazin-1-yl benzoate (**68a**), (E)-3-(trifluoromethoxy)prop-1-en-1-yl)benzene (**72a**) and R-DTBM-SEGPPOS were used to prepare (2R,6R)-1-isobutyl-6-methyl-4-((R)-1-phenyl-3-(trifluoromethoxy)propyl)-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**72**) LRMS (ES) (M+H)⁺: observed = 584.3, calculated = 583.6.

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EXAMPLE 73



Preparation of (2R,6R)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)-4-((R)-4,4,4-trifluoro-1-phenylbutyl)piperazine-2-carboxamide (**73**)

5

Step 1: Preparation of (E)-(4,4,4-trifluorobut-1-en-1-yl)benzene (**73b**) To a stirred solution of copper (I) thiophene-2-carboxylate (0.005 g, 0.026 mmol) and potassium fluoride (0.223 g, 3.85 mmol) in THF (6 mL) under nitrogen was added cinnamyl bromide (0.19 mL, 1.28 mmol) and TMS-CF₃ (0.57 mL, 3.86 mmol). The resulting mixture was heated to 60°C overnight, diluted with ethyl acetate, filtered through celite and concentrated. Flash column purification using a 100% hexanes gave (E)-(4,4,4-trifluorobut-1-en-1-yl)benzene (**73b**, 0.130 g, 54%).

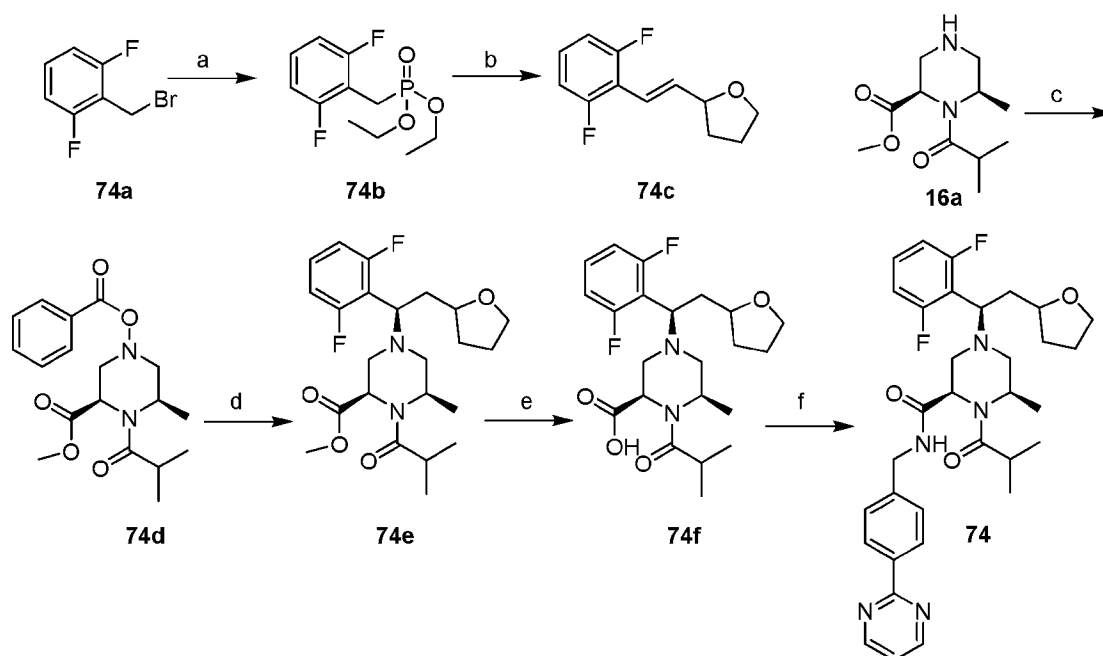
10

Step 2: In an analogous manner to example **68**, (3R,5R)-4-isobutyryl-3-methyl-5-((4-(pyrimidin-2-yl)benzyl)carbamoyl)piperazin-1-yl benzoate (**68a**), (E)-(4,4,4-trifluorobut-1-en-1-yl)benzene (**73b**) and R-DTBM-SEGPHOS were used to prepare (2R,6R)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)-4-((R)-4,4,4-trifluoro-1-phenylbutyl)piperazine-2-carboxamide (**73**)

15

LRMS (ES) (M+H)⁺: observed = 568.3, calculated = 567.6.

EXAMPLE 74



Preparation of (2R,6R)-4-((1R)-1-(2,6-difluorophenyl)-2-(tetrahydrofuran-2-yl)ethyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**74**)

5

Step 1: Preparation of diethyl (2,6-difluorobenzyl)phosphonate (**74b**) 2-(bromomethyl)-1,3-difluorobenzene (**74a**, 500 mg, 2.415 mmol) and triethyl phosphite (1.3 mL, 7.43 mmol) were combined neat then heated to 130 °C overnight. The mixture was allowed to cool and flash column purification using a 0-50% ethyl acetate/ heptane gradient gave diethyl (2,6-difluorobenzyl)phosphonate (**74b**, 0.693 g, Quan).

10

Step 2: Preparation of (E)-2-(2,6-difluorostyryl)tetrahydrofuran (**74c**) A solution of diethyl (2,6-difluorobenzyl)phosphonate (**74b**, 165 mg, 0.624 mmol) in 4 mL THF was cooled to 0 °C. To this was added 1M NaHMDS (0.625 ml, 0.625 mmol) in THF slowly. After 15 minutes, a solution of tetrahydrofuran-2-carbaldehyde (50 mg, 0.499 mmol) in 1 mL THF was added slowly. After 2 hr the mixture was diluted with saturated aqueous NH₄Cl and extracted with EtOAc (3x). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated. Flash column purification using a 0-10% EtOAc/heptane gradient gave (E)-2-(2,6-difluorostyryl)tetrahydrofuran. (**74c**, 0.015 g, 15%).

15

Step 3: In an analogous manner to example **68a**, methyl (2R,6R)-1-isobutyryl-6-methylpiperazine-2-carboxylate (**16a**), and benzoyl peroxide were used to prepare methyl

20

(2R,6R)-4-(benzyloxy)-1-isobutyryl-6-methylpiperazine-2-carboxylate (**74d**) LRMS (ES) (M+H)⁺: observed = 349.2, calculated = 348.4.

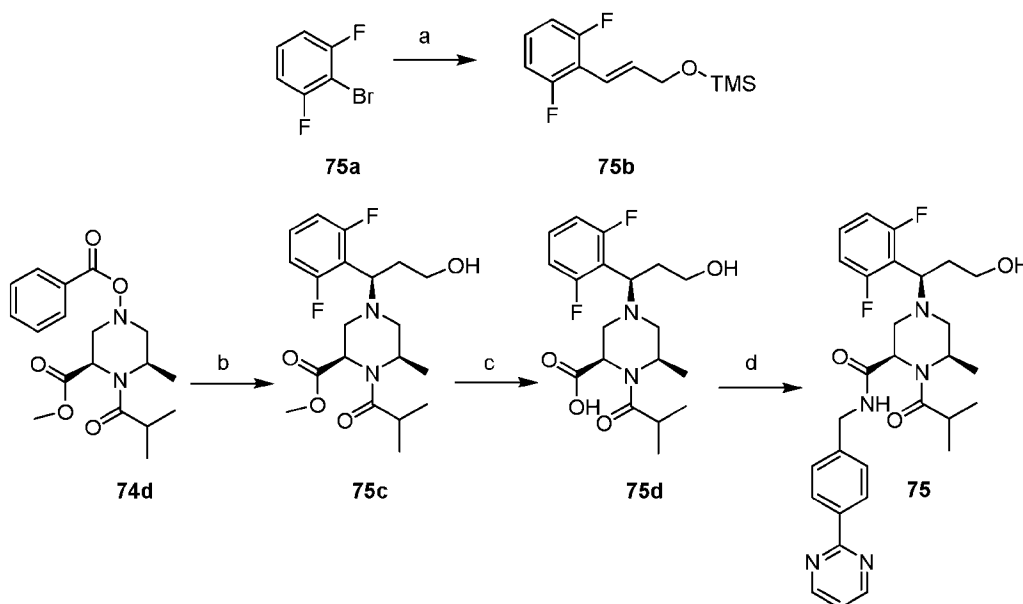
Step 4: In an analogous manner to example **68**, methyl (2R,6R)-4-(benzyloxy)-1-isobutyryl-6-methylpiperazine-2-carboxylate (**74d**), (E)-2-(2,6-difluorostyryl)tetrahydrofuran (**74c**) and S-DTBM-SEGPHOS were used to prepare methyl (2R,6R)-4-((1R)-1-(2,6-difluorophenyl)-2-(tetrahydrofuran-2-yl)ethyl)-1-isobutyryl-6-methylpiperazine-2-carboxylate (**74e**) LRMS (ES) (M+H)⁺: observed = 439.3, calculated = 438.5.

Step 5: In an analogous manner to example **1f**, methyl (2R,6R)-4-((1R)-1-(2,6-difluorophenyl)-2-(tetrahydrofuran-2-yl)ethyl)-1-isobutyryl-6-methylpiperazine-2-carboxylate (**74e**) and potassium trimethylsilylanolate were used to prepare (2R,6R)-4-((1R)-1-(2,6-difluorophenyl)-2-(tetrahydrofuran-2-yl)ethyl)-1-isobutyryl-6-methylpiperazine-2-carboxylic acid (**74f**). LRMS (ES) (M+H)⁺: observed = 425.3, calculated = 424.5.

Step 6: In an analogous manner to example **12f**, (2R,6R)-4-((1R)-1-(2,6-difluorophenyl)-2-(tetrahydrofuran-2-yl)ethyl)-1-isobutyryl-6-methylpiperazine-2-carboxylic acid (**74f**) and (4-(pyrimidin-2-yl)phenyl)methanamine were used to prepare (2R,6R)-4-((1R)-1-(2,6-difluorophenyl)-2-(tetrahydrofuran-2-yl)ethyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**74**). LRMS (ES) (M+H)⁺: observed = 592.4, calculated = 591.7.

20

EXAMPLE 75



Preparation of (2R,6R)-4-((R)-1-(2,6-difluorophenyl)-3-hydroxypropyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**75**)

Step 1: Preparation of (E)-((3-(2,6-difluorophenyl)allyl)oxy)trimethylsilane (**75b**)

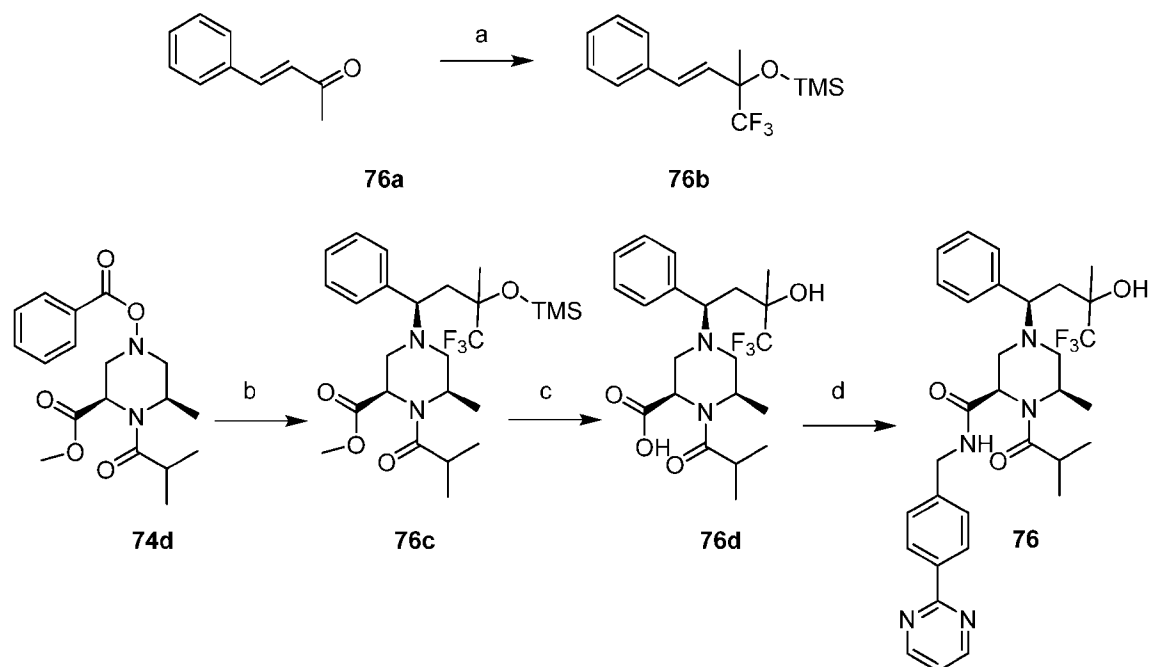
- 5 To a vial charged with 2-bromo-1,3-difluorobenzene (**75a**, 250 mg, 1.295 mmol), (E)-trimethyl((3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)allyl)oxy)silane (431 mg, 1.684 mmol), and Pd(Ph₃P)₄ (150 mg, 0.130 mmol), was added DME (10 ml) and 2M K₂CO₃ (1.3 ml, 2.60 mmol). The vial was sealed then degassed (3xpump/N₂). The gas inlet was removed and the mixture heated to 80 °C overnight. The mixture was allowed to cool, diluted with EtOAc, filtered
10 through a pad of Celite and concentrated. Flash column purification using a 0-25% EtOAc/heptane gradient gave (E)-((3-(2,6-difluorophenyl)allyl)oxy)trimethylsilane (**75b**, 0.137 g, 44%).

- Step 2: In an analogous manner to example **68**, methyl (2R,6R)-4-(benzoyloxy)-1-isobutyryl-6-methylpiperazine-2-carboxylate (**74d**), (E)-((3-(2,6-difluorophenyl)allyl)oxy)trimethylsilane
15 (**75b**) and S-DTBM-SEGPHOS were used to prepare methyl (2R,6R)-4-((R)-1-(2,6-difluorophenyl)-3-hydroxypropyl)-1-isobutyryl-6-methylpiperazine-2-carboxylate (**75c**) LRMS (ES) (M+H)⁺: observed = 399.4, calculated = 398.4.

- Step 3: In an analogous manner to example **1f**, methyl (2R,6R)-4-((R)-1-(2,6-difluorophenyl)-3-hydroxypropyl)-1-isobutyryl-6-methylpiperazine-2-carboxylate (**75c**) and potassium
20 trimethylsilanolate were used to prepare (2R,6R)-4-((R)-1-(2,6-difluorophenyl)-3-hydroxypropyl)-1-isobutyryl-6-methylpiperazine-2-carboxylic acid (**75d**). LRMS (ES) (M+H)⁺: observed = 385.3, calculated = 384.4.

- Step 4: In an analogous manner to example **12f**, (2R,6R)-4-((R)-1-(2,6-difluorophenyl)-3-hydroxypropyl)-1-isobutyryl-6-methylpiperazine-2-carboxylic acid (**75d**) and (4-(pyrimidin-2-yl)phenyl)methanamine were used to prepare (2R,6R)-4-((R)-1-(2,6-difluorophenyl)-3-hydroxypropyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide
25 (**75**). LRMS (ES) (M+H)⁺: observed = 552.4, calculated = 551.6.

EXAMPLE 76



Preparation of (2R,6R)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)-4-((1R)-4,4,4-trifluoro-3-hydroxy-3-methyl-1-phenylbutyl)piperazine-2-carboxamide (**76**)

5

Step 1: Preparation of (E)-trimethyl((1,1,1-trifluoro-2-methyl-4-phenylbut-3-en-2-yl)oxy)silane (**76b**) A vial was charged with CsF (12 mg, 0.079 mmol), DME (7 ml), and (E)-4-phenylbut-3-en-2-one (225 mg, 1.539 mmol). The vial was sealed with a septum cap then TMS-CF₃ (0.28 ml, 1.894 mmol) was added via syringe at room temperature. After 3 hr the mixture was concentrated. Flash column purification using a 100% hexanes gave (E)-trimethyl((1,1,1-trifluoro-2-methyl-4-phenylbut-3-en-2-yl)oxy)silane (**76b**, 0.402 g, 91%).

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Step 2: In an analogous manner to example **68**, methyl (2R,6R)-4-(benzoyloxy)-1-isobutyryl-6-methylpiperazine-2-carboxylate (**74d**), (E)-trimethyl((1,1,1-trifluoro-2-methyl-4-phenylbut-3-en-2-yl)oxy)silane (**76b**) and S-DTBM-SEPHOS were used to prepare methyl (2R,6R)-1-isobutyryl-6-methyl-4-((1R)-4,4,4-trifluoro-3-methyl-1-phenyl-3-((trimethylsilyl)oxy)butyl)piperazine-2-carboxylate (**76c**) LRMS (ES) (M+H)⁺: observed = 517.4, calculated = 516.6.

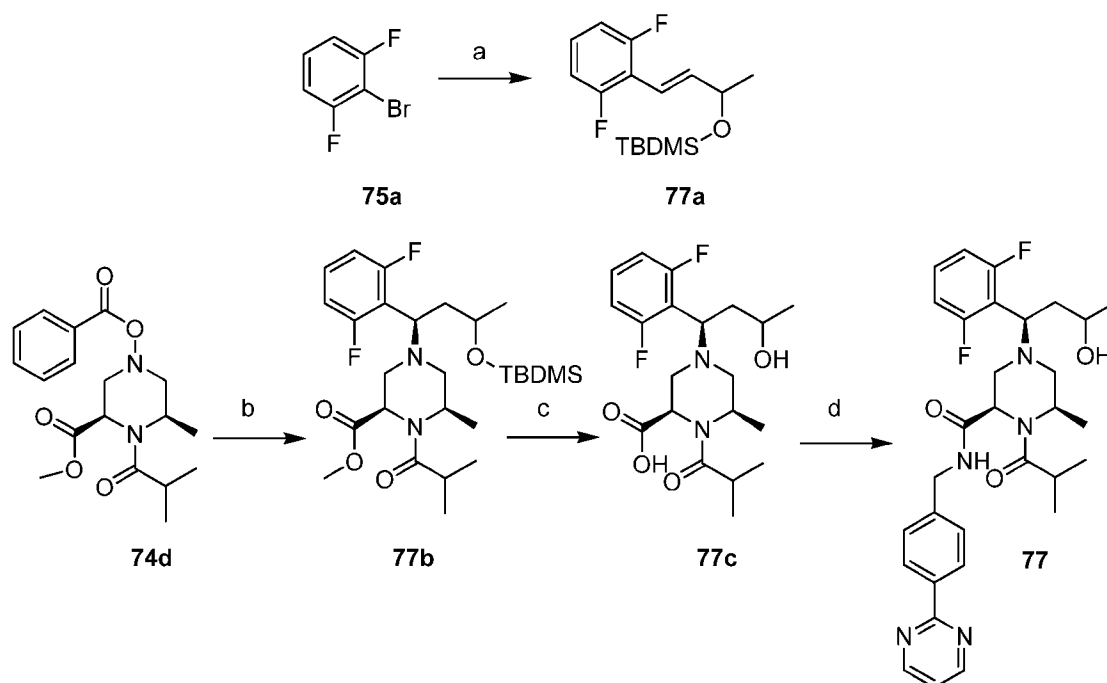
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Step 3: In an analogous manner to example **1f**, methyl (2R,6R)-1-isobutyryl-6-methyl-4-((1R)-4,4,4-trifluoro-3-methyl-1-phenyl-3-((trimethylsilyl)oxy)butyl)piperazine-2-carboxylate (**76c**)

and potassium trimethylsilanolate were used to prepare (2R,6R)-1-isobutyryl-6-methyl-4-((1R)-4,4,4-trifluoro-3-hydroxy-3-methyl-1-phenylbutyl)piperazine-2-carboxylic acid (**76d**). LRMS (ES) (M+H)⁺: observed = 431.3, calculated = 430.4.

Step 4: In an analogous manner to example **12f**, (2R,6R)-1-isobutyryl-6-methyl-4-((1R)-4,4,4-trifluoro-3-hydroxy-3-methyl-1-phenylbutyl)piperazine-2-carboxylic acid (**76d**) and (4-(pyrimidin-2-yl)phenyl)methanamine were used to prepare (2R,6R)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)-4-((1R)-4,4,4-trifluoro-3-hydroxy-3-methyl-1-phenylbutyl)piperazine-2-carboxamide (**76**). LRMS (ES) (M+H)⁺: observed = 598.4, calculated = 597.6.

EXAMPLE 77



Preparation of (2R,6R)-4-((1R)-1-(2,6-difluorophenyl)-3-hydroxybutyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**77**)

Step 1: Preparation of (E)-tert-butyl((4-(2,6-difluorophenyl)but-3-en-2-yl)oxy)dimethylsilane (**77a**) To a vial charged with 2-bromo-1,3-difluorobenzene (**75a**, 100 mg, 0.518 mmol), (E)-tert-butyl dimethyl((4-(tributylstannyl)but-3-en-2-yl)oxy)silane (296 mg, 0.622 mmol), and Pd(Ph3P)₄ (60 mg, 0.052 mmol), was added toluene (4 ml). The vial was sealed then degassed (3x pump/N₂). The gas inlet was removed and the mixture heated to 100 °C overnight. The mixture was allowed to cool and concentrated. Flash column purification using a 0-10%

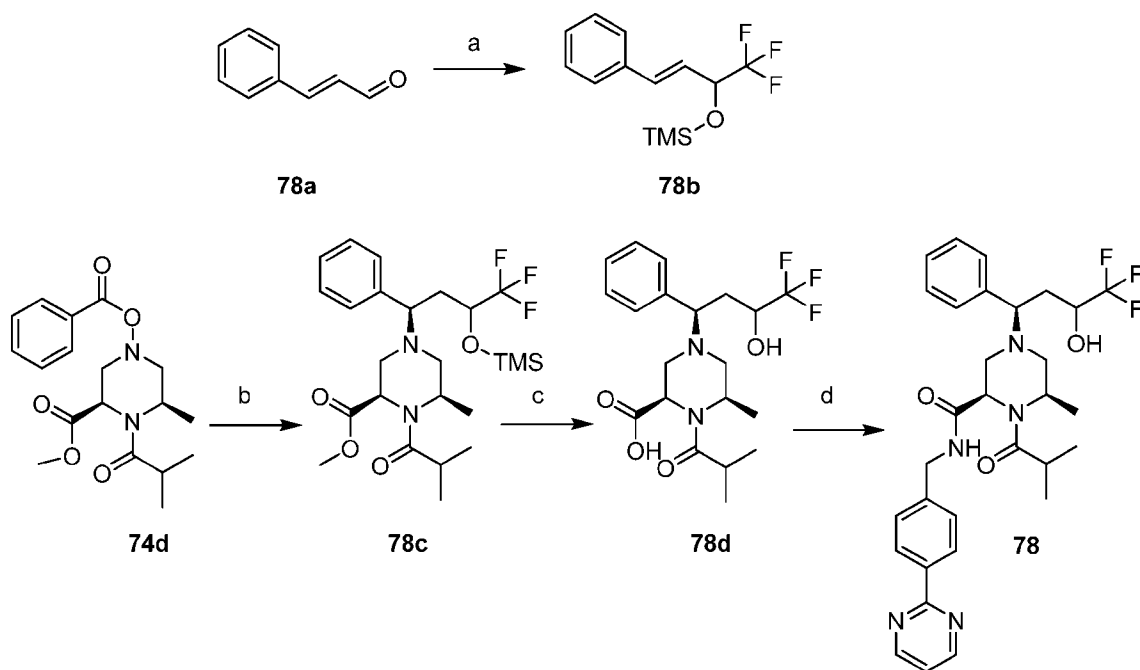
EtOAc/heptane gradient gave (E)-tert-butyl((4-(2,6-difluorophenyl)but-3-en-2-yl)oxy)dimethylsilane (**77a**, 0.086 g, 55%).

Step 2: In an analogous manner to example **68**, methyl (2R,6R)-4-(benzoyloxy)-1-isobutyryl-6-methylpiperazine-2-carboxylate (**74d**), (E)-tert-butyl((4-(2,6-difluorophenyl)but-3-en-2-yl)oxy)dimethylsilane (**77a**) and S-DTBM-SEGPHOS were used to prepare methyl (2R,6R)-4-((1R)-3-((tert-butyldimethylsilyl)oxy)-1-(2,6-difluorophenyl)butyl)-1-isobutyryl-6-methylpiperazine-2-carboxylate (**77b**) LRMS (ES) (M+H)⁺: observed = 527.5, calculated = 526.7.

Step 3: In an analogous manner to example **1f**, methyl (2R,6R)-4-((1R)-3-((tert-butyldimethylsilyl)oxy)-1-(2,6-difluorophenyl)butyl)-1-isobutyryl-6-methylpiperazine-2-carboxylate (**77b**) and potassium trimethylsilanolate were used to prepare (2R,6R)-4-((1R)-1-(2,6-difluorophenyl)-3-hydroxybutyl)-1-isobutyryl-6-methylpiperazine-2-carboxylic acid (**77c**). LRMS (ES) (M+H)⁺: observed = 399.3, calculated = 398.4.

Step 4: In an analogous manner to example **12f**, (2R,6R)-4-((1R)-1-(2,6-difluorophenyl)-3-hydroxybutyl)-1-isobutyryl-6-methylpiperazine-2-carboxylic acid (**77c**) and (4-(pyrimidin-2-yl)phenyl)methanamine were used to prepare (2R,6R)-4-((1R)-1-(2,6-difluorophenyl)-3-hydroxybutyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**77**). LRMS (ES) (M+H)⁺: observed = 566.4, calculated = 565.6.

EXAMPLE 78

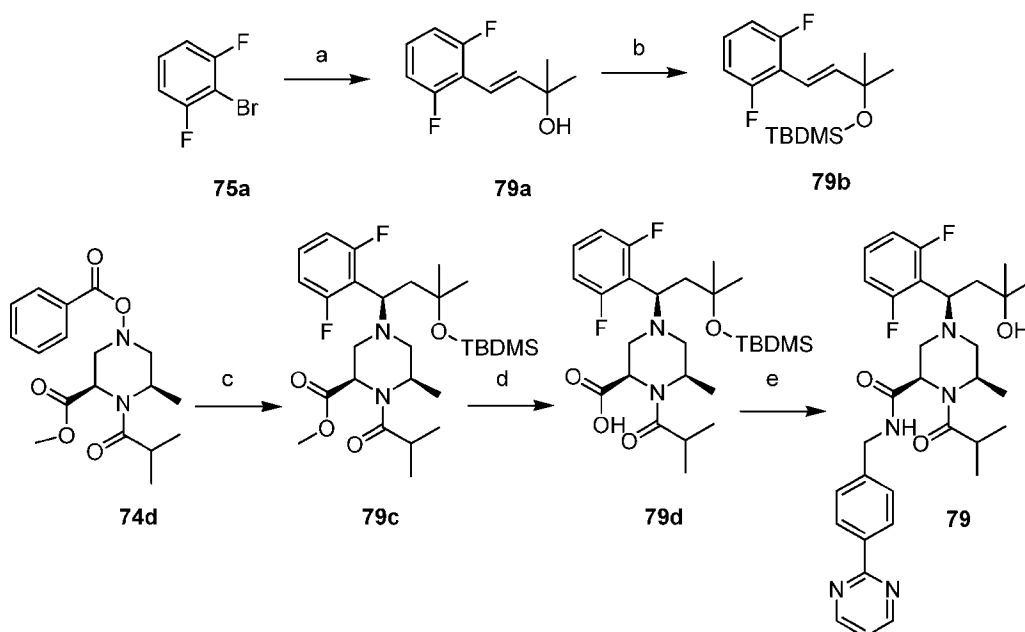


Preparation of (2R,6R)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)-4-((1R)-4,4,4-trifluoro-3-hydroxy-1-phenylbutyl)piperazine-2-carboxamide (**78**)

- Step 1: Preparation of (E)-trimethyl((1,1,1-trifluoro-4-phenylbut-3-en-2-yl)oxy)silane (**78b**) A vial was charged with CsF (12 mg, 0.079 mmol), DME (7 ml), and cinnamaldehyde (**78a**, 0.190 ml, 1.513 mmol). The vial was sealed with a septum cap then TMS-CF₃ (0.27 ml, 1.827 mmol) was added vial syringe at room temperature. After 3 hr the mixture was concentrated. Flash column purification using a 100% hexanes gave (E)-trimethyl((1,1,1-trifluoro-4-phenylbut-3-en-2-yl)oxy)silane (**78b**, 0.379 g, 91%).
- Step 2: In an analogous manner to example **68**, methyl (2R,6R)-4-(benzoyloxy)-1-isobutyryl-6-methylpiperazine-2-carboxylate (**74d**), (E)-trimethyl((1,1,1-trifluoro-4-phenylbut-3-en-2-yl)oxy)silane (**78b**) and S-DTBM-SEGPPOS were used to prepare methyl (2R,6R)-1-isobutyryl-6-methyl-4-((1R)-4,4,4-trifluoro-1-phenyl-3-((trimethylsilyl)oxy)butyl)piperazine-2-carboxylate (**78c**) LRMS (ES) (M+H)⁺: observed = 503.4, calculated = 502.6.
- Step 3: In an analogous manner to example **1f**, methyl (2R,6R)-1-isobutyryl-6-methyl-4-((1R)-4,4,4-trifluoro-1-phenyl-3-((trimethylsilyl)oxy)butyl)piperazine-2-carboxylate (**78c**) and potassium trimethylsilanolate were used to prepare (2R,6R)-1-isobutyryl-6-methyl-4-((1R)-4,4,4-trifluoro-3-hydroxy-1-phenylbutyl)piperazine-2-carboxylic acid (**78d**). LRMS (ES) (M+H)⁺: observed = 417.3, calculated = 416.4.
- Step 4: In an analogous manner to example **12f**, (2R,6R)-1-isobutyryl-6-methyl-4-((1R)-4,4,4-trifluoro-3-hydroxy-1-phenylbutyl)piperazine-2-carboxylic acid (**78d**) and (4-(pyrimidin-2-yl)phenyl)methanamine were used to prepare (2R,6R)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)-4-((1R)-4,4,4-trifluoro-3-hydroxy-1-phenylbutyl)piperazine-2-carboxamide (**78**). LRMS (ES) (M+H)⁺: observed = 584.4, calculated = 583.6.

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EXAMPLE 79



Preparation of (2R,6R)-4-((R)-1-(2,6-difluorophenyl)-3-hydroxy-3-methylbutyl)-1-isobutyl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**79**)

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Step 1: Preparation of (E)-4-(2,6-difluorophenyl)-2-methylbut-3-en-2-ol (**79a**)

To a vial charged with 2-bromo-1,3-difluorobenzene (**75a**, 200 mg, 1.036 mmol), (E)-2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-3-en-2-ol (275 mg, 1.295 mmol), and PdCl₂(dppf) (76 mg, 0.104 mmol), was added DME (10 ml) and 2M K₂CO₃ (1.04 ml, 2.08 mmol). The vial was sealed then degassed (3xpump/N₂). The gas inlet was removed and the mixture heated to 80 °C overnight. The mixture was allowed to cool, diluted with EtOAc, filtered through a pad of Celite and concentrated. Flash column purification using a 0-25% EtOAc/heptane gradient gave (E)-4-(2,6-difluorophenyl)-2-methylbut-3-en-2-ol (**79a**, 0.156 g, 76%).

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Step 2: Preparation of (E)-tert-butyl((4-(2,6-difluorophenyl)-2-methylbut-3-en-2-

yl)oxy)dimethylsilane (**79b**) A solution of (E)-4-(2,6-difluorophenyl)-2-methylbut-3-en-2-ol (**79a**, 156 mg, 0.787 mmol) in DCM (4 mL) was cooled to 0 °C. To this was added 2,6-lutidine (0.37 mL, 3.18 mmol) then tert-butyldimethylsilyl trifluoromethanesulfonate (0.365 mL, 1.588 mmol). Additional 2,6-lutidine and tert-butyldimethylsilyl trifluoromethanesulfonate were added as needed until reaction completion. The mixture was concentrated. Flash column purification

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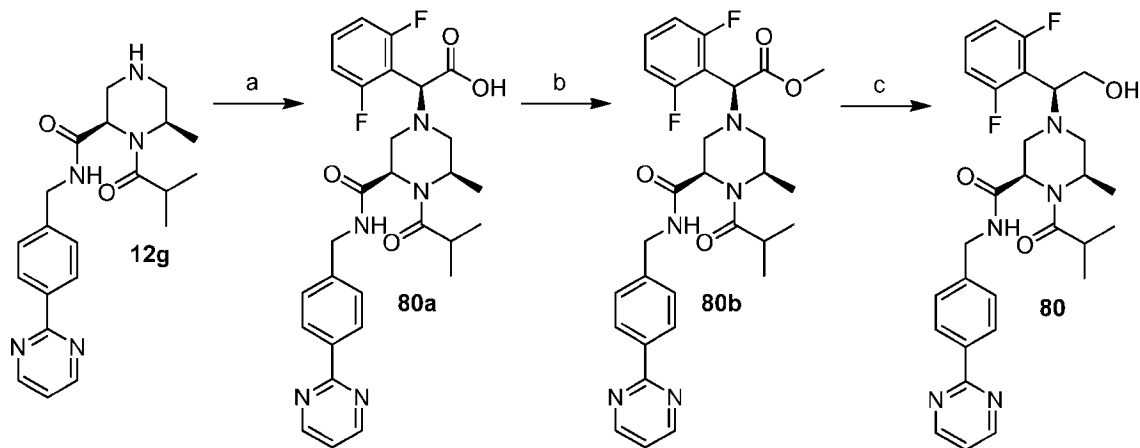
using a 0-10% EtOAc/heptane gradient gave (E)-tert-butyl((4-(2,6-difluorophenyl)-2-methylbut-3-en-2-yl)oxy)dimethylsilane (**79b**, 0.122 g, 50%).

Step 3: In an analogous manner to example **68**, methyl (2R,6R)-4-(benzoyloxy)-1-isobutyryl-6-methylpiperazine-2-carboxylate (**74d**), (E)-tert-butyl((4-(2,6-difluorophenyl)-2-methylbut-3-en-2-yl)oxy)dimethylsilane (**79b**) and S-DTBM-SEGPHOS were used to prepare methyl (2R,6R)-4-((R)-3-((tert-butyldimethylsilyl)oxy)-1-(2,6-difluorophenyl)-3-methylbutyl)-1-isobutyryl-6-methylpiperazine-2-carboxylate (**79c**) LRMS (ES) (M+H)⁺: observed = 541.5, calculated = 540.7.

Step 4: In an analogous manner to example **1f**, methyl (2R,6R)-4-((R)-3-((tert-butyldimethylsilyl)oxy)-1-(2,6-difluorophenyl)-3-methylbutyl)-1-isobutyryl-6-methylpiperazine-2-carboxylate (**79c**) and potassium trimethylsilanolate were used to prepare (2R,6R)-4-((R)-3-((tert-butyldimethylsilyl)oxy)-1-(2,6-difluorophenyl)-3-methylbutyl)-1-isobutyryl-6-methylpiperazine-2-carboxylic acid (**79d**). LRMS (ES) (M+H)⁺: observed = 528.5, calculated = 526.7.

Step 5: Preparation of (2R,6R)-4-((R)-1-(2,6-difluorophenyl)-3-hydroxy-3-methylbutyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**79**) To a stirred solution of (2R,6R)-4-((R)-3-((tert-butyldimethylsilyl)oxy)-1-(2,6-difluorophenyl)-3-methylbutyl)-1-isobutyryl-6-methylpiperazine-2-carboxylic acid (**79d**, 0.032 g, 0.061 mmol) and (4-(pyrimidin-2-yl)phenyl)methanamine, HCl (0.018 g, 0.08 mmol) in DMF (0.5 mL) was added HATU (0.030 g, 0.079 mmol) and triethylamine (0.034 mL, 0.244 mmol). The resulting mixture was stirred at room temperature for 3 hours. To this was added HF-pyridine (0.03 mL, 0.333 mmol) and the mixture was heated to 50°C for 30 minutes. The solution was allowed to cool, concentrated, and purified by prep-HPLC to give (2R,6R)-4-((R)-1-(2,6-difluorophenyl)-3-hydroxy-3-methylbutyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**79**, 0.011 g, 26%). LRMS (ES) (M+H)⁺: observed = 580.5, calculated = 579.6.

EXAMPLE 80



Preparation of (2R,6R)-4-((S)-1-(2,6-difluorophenyl)-2-hydroxyethyl)-1-isobutyryl-6-methyl-N-
5 (4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**80**)

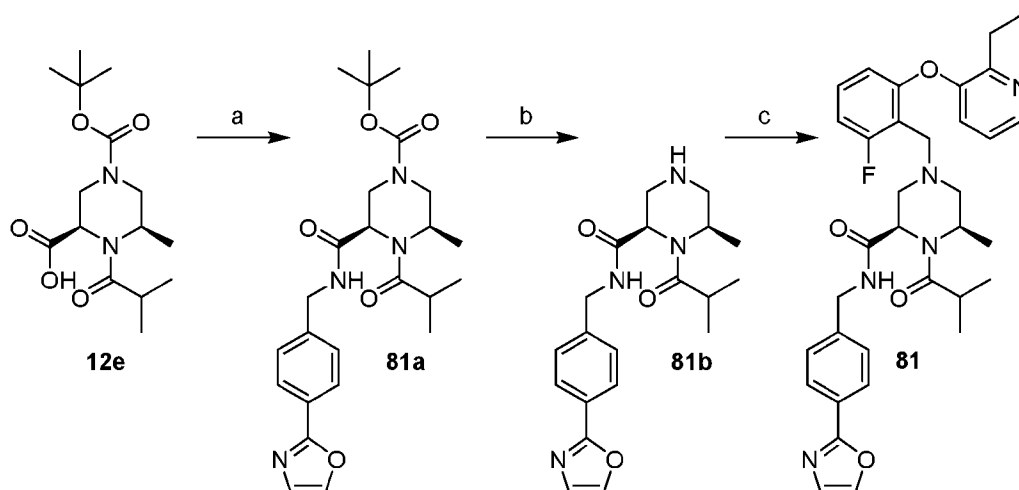
Step 1: Preparation of (S)-2-(2,6-difluorophenyl)-2-((3R,5R)-4-isobutyryl-3-methyl-5-((4-
(pyrimidin-2-yl)benzyl)carbamoyl)piperazin-1-yl)acetic acid (**80a**) (2R,6R)-1-isobutyryl-6-
methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**12g**, 300 mg, 0.786 mmol)
10 dissolved in CH₂Cl₂ (1.5 ml) was added to a 2 mL microwave vial containing solid (2,6-
difluorophenyl)boronic acid (248 mg, 1.573 mmol). 2-oxoacetic acid (0.084 ml, 1.573 mmol)
was added. The vial was sealed and heated to 120 °C for 10 min. LCMS analysis showed
formation of the desired product. The reaction was concentrated and purified by prep-HPLC to
give (S)-2-(2,6-difluorophenyl)-2-((3R,5R)-4-isobutyryl-3-methyl-5-((4-(pyrimidin-2-
15 yl)benzyl)carbamoyl)piperazin-1-yl)acetic acid (**80a**, 0.012 g, 3%). LRMS (ES) (M+H)⁺:
observed = 552.4, calculated = 551.1.

Step 2: Preparation of methyl (S)-2-(2,6-difluorophenyl)-2-((3R,5R)-4-isobutyryl-3-methyl-5-
(4-(pyrimidin-2-yl)benzyl)carbamoyl)piperazin-1-yl)acetate (**80b**) (S)-2-(2,6-difluorophenyl)-2-
20 ((3R,5R)-4-isobutyryl-3-methyl-5-((4-(pyrimidin-2-yl)benzyl)carbamoyl)piperazin-1-yl)acetic
acid (**80a**, 12 mg, 0.022 mmol) was dissolved in DCM (290 µl) and MeOH (145 µl). The solution
was cooled to 0 °C and (trimethylsilyl)diazomethane (32.6 µl, 0.065 mmol) was added. Reaction
was stirred 1 hr and concentrated to give crude methyl (S)-2-(2,6-difluorophenyl)-2-((3R,5R)-4-

isobutyryl-3-methyl-5-((4-(pyrimidin-2-yl)benzyl)carbamoyl)piperazin-1-yl)acetate (**80b**) LRMS (ES) (M+H)⁺: observed = 566.5, calculated = 565.6.

Step 3: Preparation of (2R,6R)-4-((S)-1-(2,6-difluorophenyl)-2-hydroxyethyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**80**) methyl 2-(2,6-difluorophenyl)-2-((3R,5R)-4-isobutyryl-3-methyl-5-((4-(pyrimidin-2-yl)benzyl)carbamoyl)piperazin-1-yl)acetate (**80b**, 12 mg, 0.021 mmol) was dissolved in THF (450 μ l) and MeOH (50 μ l). Lithium tetrahydroborate (106 μ l, 0.212 mmol) was added and the reaction was allowed to stir at rt for 30 min. The reaction was quenched with water (5 mL) and extracted with CH₂Cl₂ (3 x 5 mL). The combined organic layers were washed with water (5 mL), dried (MgSO₄) and concentrated. Purification by prep-HPLC to gave (2R,6R)-4-((S)-1-(2,6-difluorophenyl)-2-hydroxyethyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**80**, 0.0075 g, 46%). LRMS (ES) (M+H)⁺: observed = 538.1, calculated = 537.6.

EXAMPLE 81



Preparation of (2R,6R)-4-(2-((2-ethylpyridin-3-yl)oxy)-6-fluorobenzyl)-1-isobutyryl-6-methyl-N-(4-(oxazol-2-yl)benzyl)piperazine-2-carboxamide (**81**)

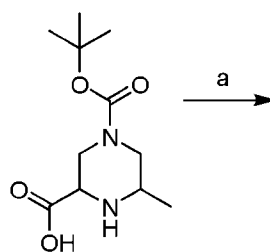
Step 1: In an analogous manner to example **12f**, (2R,6R)-4-(tert-butoxycarbonyl)-1-isobutyryl-6-methylpiperazine-2-carboxylic acid (**12e**) and (4-(oxazol-2-yl)phenyl)methanamine were used to prepare tert-butyl (3R,5R)-4-isobutyryl-3-methyl-5-((4-(oxazol-2-yl)benzyl)carbamoyl)piperazine-1-carboxylate (**81a**). LRMS (ES) (M+H)⁺: observed = 471.3, calculated = 470.5.

Step 2: In an analogous manner to example **12g**, tert-butyl (3R,5R)-4-isobutyryl-3-methyl-5-((4-(oxazol-2-yl)benzyl)carbamoyl)piperazine-1-carboxylate (**81a**) and HCl were used to prepare (2R,6R)-1-isobutyryl-6-methyl-N-(4-(oxazol-2-yl)benzyl)piperazine-2-carboxamide (**81b**).

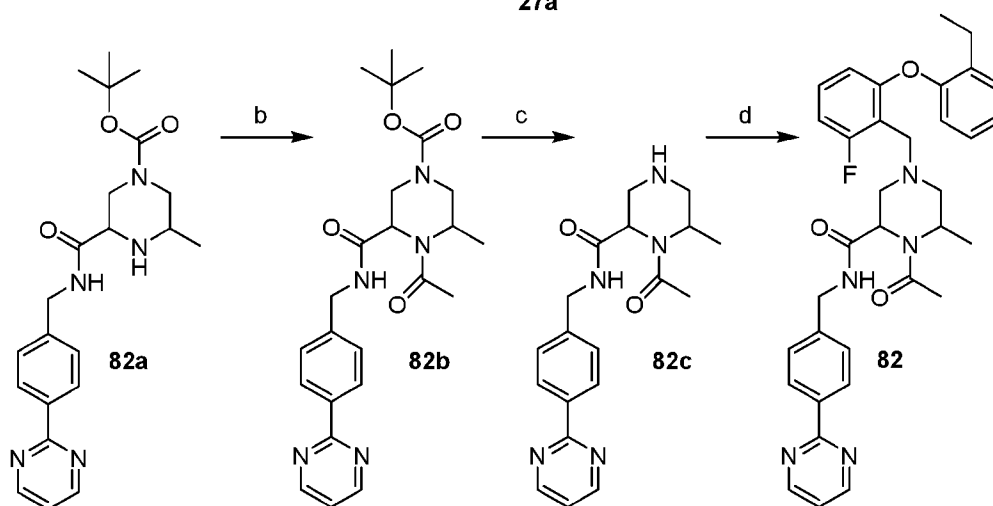
LRMS (ES) (M+H)⁺: observed = 371.3, calculated = 370.4.

- 5 Step 3: In an analogous manner to example **13-5**, (2R,6R)-1-isobutyryl-6-methyl-N-(4-(oxazol-2-yl)benzyl)piperazine-2-carboxamide (**81b**) was used to prepare (2R,6R)-4-(2-((2-ethylpyridin-3-yl)oxy)-6-fluorobenzyl)-1-isobutyryl-6-methyl-N-(4-(oxazol-2-yl)benzyl)piperazine-2-carboxamide (**81**). LRMS (ES) (M+H)⁺: observed = 600.4, calculated = 599.7.

EXAMPLE 82



27a



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Preparation of 1-acetyl-4-(2-(2-ethylphenoxy)-6-fluorobenzyl)-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (**82**)

- 15 Step 1: In an analogous manner to example 12f, 4-(tert-butoxycarbonyl)-6-methylpiperazine-2-carboxylic acid (**27a**) and (4-(pyrimidin-2-yl)phenyl)methanamine were used to prepare tert-

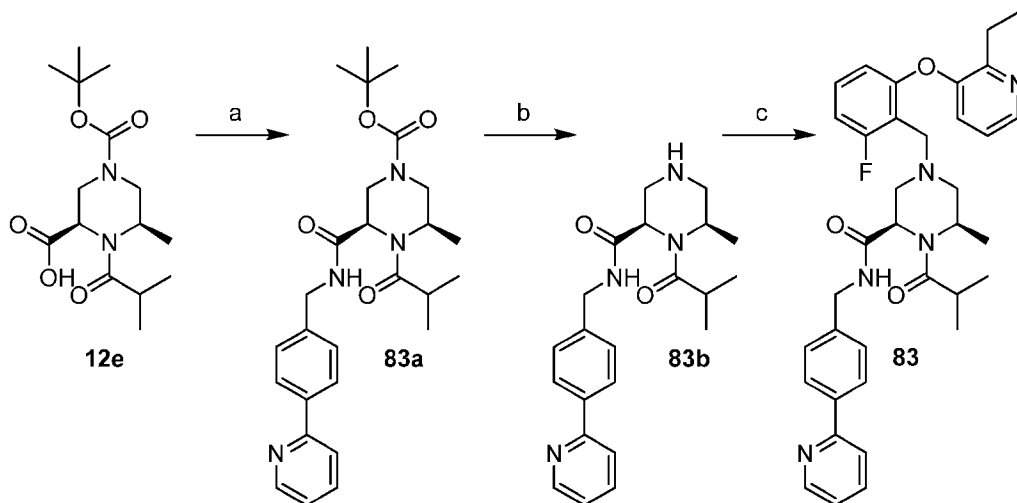
butyl 3-methyl-5-((4-(pyrimidin-2-yl)benzyl)carbamoyl)piperazine-1-carboxylate (82a). LRMS (ES) (M+H)⁺: observed = 412.3, calculated = 411.5.

Step 2: In an analogous manner to example 1e, tert-butyl 3-methyl-5-((4-(pyrimidin-2-yl)benzyl)carbamoyl)piperazine-1-carboxylate (82a) and acetic anhydride were used to prepare tert-butyl 4-acetyl-3-methyl-5-((4-(pyrimidin-2-yl)benzyl)carbamoyl)piperazine-1-carboxylate (82b). LRMS (ES) (M+H)⁺: observed = 454.3, calculated = 453.5.

Step 3: In an analogous manner to example 1h tert-butyl 4-acetyl-3-methyl-5-((4-(pyrimidin-2-yl)benzyl)carbamoyl)piperazine-1-carboxylate (82b) and HCl were used to prepare 1-acetyl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (82c). LRMS (ES) (M+H)⁺: observed = 354.3, calculated = 353.4.

Step 4: In an analogous manner to example 13-1, 1-acetyl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (82c) was used to prepare 1-acetyl-4-(2-(2-ethylphenoxy)-6-fluorobenzyl)-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (82). LRMS (ES) (M+H)⁺: observed = 582.4, calculated = 581.6.

EXAMPLE 83



Preparation of (2R,6R)-4-(2-((2-ethylpyridin-3-yl)oxy)-6-fluorobenzyl)-1-isobutyryl-6-methyl-N-(4-(pyridin-2-yl)benzyl)piperazine-2-carboxamide (**83**)

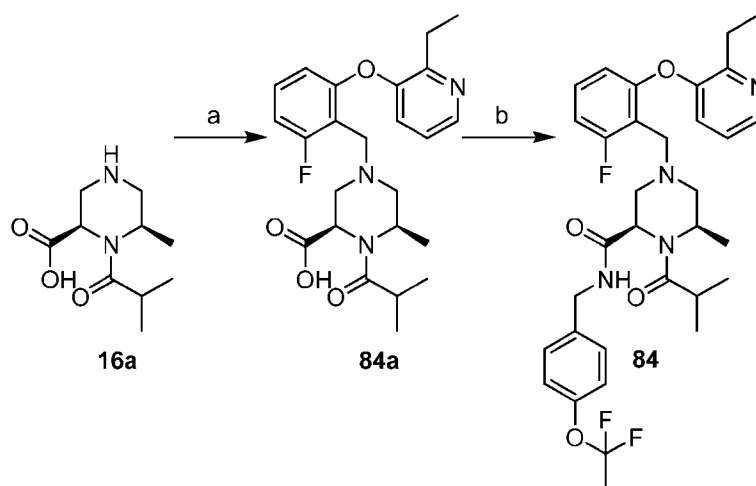
Step 1: In an analogous manner to example 12f, (2R,6R)-4-(tert-butoxycarbonyl)-1-isobutyryl-6-methylpiperazine-2-carboxylic acid (**12e**) and (4-(pyridin-2-yl)phenyl)methanamine were used to

prepare tert-butyl (3R,5R)-4-isobutyryl-3-methyl-5-((4-(pyridin-2-yl)benzyl)carbamoyl) piperazine-1-carboxylate (**83a**). LRMS (ES) (M+H)⁺: observed = 481.4, calculated = 480.6.

Step 2: In an analogous manner to example **12g**, tert-butyl (3R,5R)-4-isobutyryl-3-methyl-5-((4-(pyridin-2-yl)benzyl)carbamoyl)piperazine-1-carboxylate (**83a**) and HCl were used to prepare (2R,6R)-1-isobutyryl-6-methyl-N-(4-(pyridin-2-yl)benzyl)piperazine-2-carboxamide (**83b**). LRMS (ES) (M+H)⁺: observed = 381.3, calculated = 380.5.

Step 3: In an analogous manner to example **13-5**, (2R,6R)-1-isobutyryl-6-methyl-N-(4-(pyridin-2-yl)benzyl)piperazine-2-carboxamide (**83b**) was used to prepare (2R,6R)-4-(2-((2-ethylpyridin-3-yl)oxy)-6-fluorobenzyl)-1-isobutyryl-6-methyl-N-(4-(pyridin-2-yl)benzyl)piperazine-2-carboxamide (**83**). LRMS (ES) (M+H)⁺: observed = 610.5, calculated = 609.8.

EXAMPLE 84

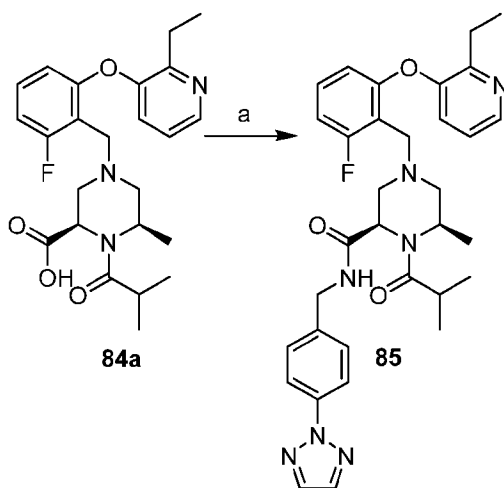


Preparation of (2R,6R)-N-(4-(1,1-difluoroethoxy)benzyl)-4-(2-((2-ethylpyridin-3-yl)oxy)-6-fluorobenzyl)-1-isobutyryl-6-methylpiperazine-2-carboxamide (**84**)

Step 1: In an analogous manner to example **13-5**, (2R,6R)-1-isobutyryl-6-methylpiperazine-2-carboxylic acid (**16a**) was used to prepare (2R,6R)-4-(2-((2-ethylpyridin-3-yl)oxy)-6-fluorobenzyl)-1-isobutyryl-6-methylpiperazine-2-carboxylic acid (**84a**). LRMS (ES) (M+H)⁺: observed = 444.4, calculated = 443.5.

Step 2: In an analogous manner to example **16-1**, (2R,6R)-4-(2-((2-ethylpyridin-3-yl)oxy)-6-fluorobenzyl)-1-isobutyryl-6-methylpiperazine-2-carboxylic acid (**84a**) and (4-(1,1-difluoroethoxy)phenyl)methanamine was used to prepare (2R,6R)-N-(4-(1,1-difluoroethoxy)benzyl)-4-(2-((2-ethylpyridin-3-yl)oxy)-6-fluorobenzyl)-1-isobutyryl-6-methylpiperazine-2-carboxamide (**84**). LRMS (ES) (M+H)⁺: observed = 613.5, calculated = 612.7.

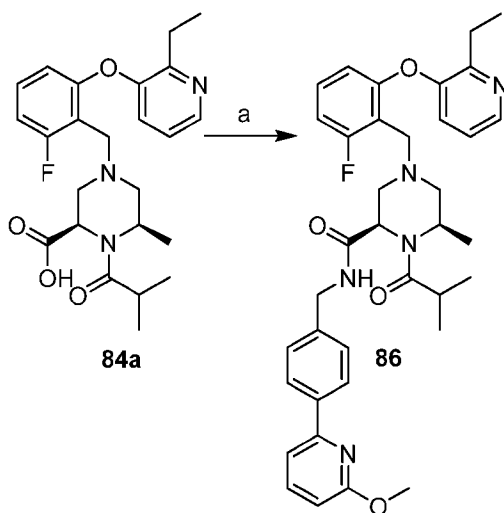
EXAMPLE 85



Preparation of (2R,6R)-N-(4-(2H-1,2,3-triazol-2-yl)benzyl)-4-(2-((2-ethylpyridin-3-yl)oxy)-6-fluorobenzyl)-1-isobutyryl-6-methylpiperazine-2-carboxamide (**85**)

In an analogous manner to example **16-1**, (2R,6R)-4-(2-((2-ethylpyridin-3-yl)oxy)-6-fluorobenzyl)-1-isobutyryl-6-methylpiperazine-2-carboxylic acid (**84a**) and (4-(2H-1,2,3-triazol-2-yl)phenyl)methanamine was used to prepare (2R,6R)-N-(4-(2H-1,2,3-triazol-2-yl)benzyl)-4-(2-((2-ethylpyridin-3-yl)oxy)-6-fluorobenzyl)-1-isobutyryl-6-methylpiperazine-2-carboxamide (**85**). LRMS (ES) (M+H)⁺: observed = 600.5, calculated = 599.7.

EXAMPLE 86



Preparation of (2R,6R)-4-(2-((2-ethylpyridin-3-yl)oxy)-6-fluorobenzyl)-1-isobutyryl-N-(4-(6-methoxypyridin-2-yl)benzyl)-6-methylpiperazine-2-carboxamide (**86**)

5

In an analogous manner to example **16-1**, (2R,6R)-4-(2-((2-ethylpyridin-3-yl)oxy)-6-fluorobenzyl)-1-isobutyryl-6-methylpiperazine-2-carboxylic acid (**84a**) and (4-(6-methoxypyridin-2-yl)phenyl)methanamine was used to prepare (2R,6R)-4-(2-((2-ethylpyridin-3-yl)oxy)-6-fluorobenzyl)-1-isobutyryl-N-(4-(6-methoxypyridin-2-yl)benzyl)-6-methylpiperazine-2-carboxamide (**86**). LRMS (ES) (M+H)⁺: observed = 640.0, calculated = 639.8.

10

The following table shows data for representative compounds of the Examples as orexin receptor agonists as determined by assays described herein. Emax (%) represents percent activity at maximum tested concentration.

15

Example	hOX2R_IP IC ₅₀ (nM)	Emax (%)
1-1	2499	70.53
1-2	204.4	99.31
1-3	270.5	97.91
1-4	271.1	88.98
1-5	328.8	90.45
1-6	357.1	98.94

1-7	362.2	99.67
1-8	401.4	99.35
1-9	510.4	98.05
1-10	584.5	98.7
1-11	612.2	97.49
1-12	754.9	97.1
1-13	766.5	97.3
1-14	885.7	89.35
1-15	993.2	79.92
1-16	1157	100.6
1-17	1607	55.05
1-18	1797	72.73
1-19	1859	45.77
1-20	1962	96.36
1-21	1992	100.8
1-22	2017	95.08
1-23	2052	90.95
1-24	2087	98.31
1-25	2102	49.54
1-26	2175	95.28
1-27	2214	84.63
1-28	2276	86.96
1-29	2295	106.1
1-30	2303	94.87
1-31	2362	86.16
1-32	2536	76
1-33	2538	81.46
1-34	2806	91.14
1-35	2810	86.35
1-36	2856	109.3
1-37	2859	65.11

1-38	2969	61.9
1-39	3128	51.65
1-40	3445	94.95
1-41	3449	83.08
1-42	3992	77.6
1-43	3998	82.75
1-44	4078	83.98
1-45	4198	98.34
1-46	4503	90.26
1-47	4692	30.33
1-48	5194	40
1-49	5781	51.75
1-50	5784	83.27
1-51	5932	77.61
1-52	5938	81.44
1-53	5981	70.39
1-54	6289	83.66
1-55	6892	28.85
1-56	6957	80.35
1-57	6981	82.85
1-58	7024	33.95
1-59	7092	82.08
1-60	8610	88.85
1-61	9705	38.59
1-62	9802	84.82
1-63	10430	86.1
1-64	10590	56.47
1-65	11270	53.88
1-66	11420	64.87
1-67	12490	75.74
1-68	14350	45.45

1-69	16340	47.71
1-70	18210	84.3
1-71	18950	79.53
1-72	33920	66.52
1-73	54930	48.43
1-74	84920	26.22
1-75	92800	42.04
1-76	100200	47.02
1-77	100200	40.27
1-78	100200	17.62
1-79	100200	13.14
1-80	100200	27.1
1-81	100200	21
2-1	3754	93.2
2-2	206.6	97.78
2-3	511.9	71.2
2-4	512.2	96.64
2-5	1131	98.32
2-6	1550	93.68
2-7	2243	97.55
2-8	2874	58.09
2-9	6763	41.9
2-10	21780	75.68
2-11	100200	22.68
3	147.5	99.6
4	549.1	98.86
5	1147	84.92
6	3546	60.29
7	8789	98.75
8	1049	94.48
9	2436	92.59

10	835.2	101.7
11	871.7	102.2
12	430.1	98.32
13-1	9.475	98.46
13-2	5.825	101.3
13-3	6.177	98.43
13-4	8.292	99.8
13-5	9.482	98.56
13-6	9.573	96.47
13-7	9.627	96.15
13-8	12.46	101.2
13-9	13.36	98.79
13-10	18.42	100.6
13-11	18.82	100.1
13-12	21.78	99.1
13-13	23.82	98.13
13-14	25.26	99.17
13-15	26.84	100.8
13-16	35.34	100
13-17	36.26	99.64
13-18	43.69	98.39
13-19	44.19	105.1
13-20	57.14	97.1
13-21	70.24	100.5
13-22	73.72	100.5
13-23	77.63	100.8
13-24	89.83	99.01
13-25	96.83	100.6
13-26	105.2	99.67
13-27	105.6	100.8
13-28	107.6	100.1

13-29	112.3	98.87
13-30	114.8	100.7
13-31	117	100.5
13-32	129.4	100.5
13-33	133.8	99.47
13-34	156.4	99.54
13-35	171	98.36
13-36	187.7	100.8
14	32.68	99.7
15	153.9	98.24
16-1	19.2	101.6
16-2	9.493	101
16-3	10.54	101.7
16-4	26.67	100.7
16-5	29.29	99.95
16-6	47.53	99.8
16-7	161.4	100.7
16-8	237.1	101.2
16-9	336.7	100.1
16-10	418.6	99.51
16-11	11.77	100.5
16-12	39.2	100.4
16-13	53.27	99.99
17	4.611	101.2
18	5.02	101.7
19	3.124	101.5
20-1	3.309	101.8
20-2	2.682	101.1
20-3	4.848	100.5
20-4	6.728	101.5
20-5	8.261	101.2

20-6	9.251	101.3
20-7	12.91	100.3
20-8	15.45	101.5
20-9	17.16	100.2
20-10	21.38	100.3
20-11	33.88	101.6
20-12	42.75	98.63
20-13	43.4	100
20-14	47.55	101
20-15	215.4	100.7
20-16	10130	14.89
20-17	5.53	101.3
21	20.02	101.5
22	6.854	100.8
23	24.46	100.1
24	52.85	99.71
25	3.008	102.2
26	7.489	100.2
27	1095	29
28	8.37	101
29	4.397	100.4
30	88.14	96.96
31	173.7	100.1
32	6.901	101.7
33	23.17	101.4
34	377.7	99.57
35-1	12.87	101.3
35-2	195.8	100.7
35-3	282.9	100.4
35-4	326.9	100.4
36	31.67	100

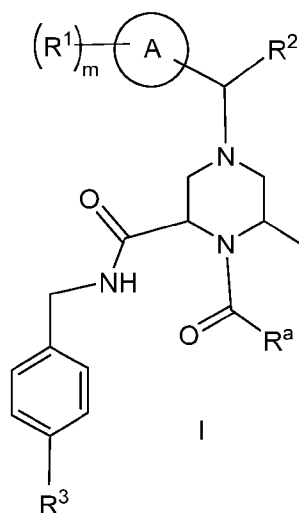
37	464	100.3
38	454.4	100.2
39	103.5	101.8
40	212.8	99.19
41	22.11	101.5
42	25.17	101.4
43	62.14	99.65
44	183.6	100
45	342.8	99.56
46	2138	93.44
47	136.8	100.6
48	620.6	98.83
49	4818	82.13
50	435.6	100.8
51	469.5	98.84
52	1368	100.4
53	282.1	100.8
54	259.8	99.83
55	22.91	100.5
56	270.5	100.1
57	623.9	100.8
58	592.2	100.2
59	455.8	100.3
60	319.2	99.74
61	292.6	99.19
62	39.44	100.9
63	130	99.69
64	24.49	101.6
65	16.66	100.5
66	13.55	100.9
67	12.96	100.9

68	6260	93.41
69	26.2	99.42
70	70.29	100.6
71	647.4	100.4
72	3982	97.07
73	923.4	99.42
74	25.65	99.51
75	10.99	100.1
76	4566	96.5
77	25.92	101.5
78	388.8	99.53
79	765.4	102.8
80	71.25	98.98
81	7.639	99.66
82	64	97.3
83	12.38	98.27
84	8.97	93.62
85	8.62	93.29
86	5.17	99.19

While the invention has been described and illustrated with reference to certain particular embodiments thereof, those skilled in the art will appreciate that various adaptations, changes, modifications, substitutions, deletions, or additions of procedures and protocols may be made
5 without departing from the spirit and scope of the invention.

WHAT IS CLAIMED IS:

1. A compound of formula I:



wherein:

- 5 Ring A is selected from aryl and heteroaryl;

R is independently selected from H, -C₁₋₆alkyl, O-C₁₋₆alkyl, CF₃, CHF₂, CH₂F, and C₃₋₆ cycloalkyl;

- 10 R^a is selected from -C₁₋₆alkyl and -C₃₋₆ cycloalkyl;

R¹ is independently selected from:

- (1) -(CR₂)_n-heteroaryl, where the heteroaryl is unsubstituted or substituted with one to six substituents independently selected from R⁴,
- 15 (2) -(CR₂)_n-heterocyclyl, where the heterocyclyl is unsubstituted or substituted with one to six substituents independently selected from R⁴,
- (3) -(CR₂)_n- C₃₋₆ cycloalkyl, where the cycloalkyl is unsubstituted or substituted with one to six substituents independently selected from R⁴,
- (4) -C₁₋₆ alkyl, where the alkyl is unsubstituted or substituted with one to six
- 20 substituents independently selected from R⁴,
- (5) -O(CR₂)_pR⁴,

- (6) -OR,
 (7) halo,
 (8) -OCR₂C(O)NR₂,
 (9) -OCR₂CF₃,
 5 (10) -O(CR₂)_tOCR₃,
 (11) -(CR₂)_nCN
 (12) -(CR₂)_nNR₂,
 (13) -O(CR₂)_tNR₂
 (14) -C₂-C₆ alkenyl, where the alkenyl is unsubstituted or substituted with one to six
 10 substituents independently selected from R⁴, and
 (15) -C₂-C₆ alkynyl, where the alkynyl is unsubstituted or substituted with one to six
 substituents independently selected from R⁴;

R² is selected from:

- 15 (1) H,
 (2) -C₁-6alkyl, where the alkyl is unsubstituted or substituted with one to three
 substituents selected from R⁵,
 (3) halo,
 (4) -(CR₂)_sOR,
 20 (5) -(CR₂)_sCN
 (6) -(CR₂)_sS(O)_zR,
 (7) -(CR₂)_sC(O)OR,
 (8) aryl, where the aryl is unsubstituted or substituted with one to three substituents
 selected from R⁵; and
 25 (9) -(CR₂)_s-heterocyclyl, where the heterocyclyl is unsubstituted or substituted with
 one to three substituents selected from R⁵;

R³ is independently selected from:

- (1) -C₁-6alkyl, where the alkyl is unsubstituted or substituted with one to four
 30 substituents independently selected from R⁷,

- (2) -C₃₋₆ cycloalkyl, where the cycloalkyl is unsubstituted or substituted with one to four substituents independently selected from R⁷,
- (3) aryl, where the aryl is unsubstituted or substituted with one to four substituents independently selected from R⁷,
- 5 (4) heteroaryl, where the heteroaryl is unsubstituted or substituted with one to four substituents independently selected from R⁷,
- (5) -(CH₂)_x-C₂-C₆ alkenyl, where the alkenyl is unsubstituted or substituted with one to four substituents independently selected from R⁷,
- (6) -(CH₂)_x-C₂-C₆ alkynyl, where the alkynyl is unsubstituted or substituted with one
10 to four substituents independently selected from R⁷, and
- (7) -OCF₂CH₃;

R⁴ is independently selected from:

- (1) hydrogen,
- 15 (2) -C₁₋₆alkyl, which is unsubstituted or substituted with one to six substituents independently selected from R⁶,
- (3) aryl, which is unsubstituted or substituted with one to six substituents independently selected from R⁶,
- (4) heteroaryl, which is unsubstituted or substituted with one to six substituents
20 independently selected from R⁶,
- (5) heterocyclyl, which is unsubstituted or substituted with one to six substituents independently selected from R⁶,
- (6) halo,
- (7) -OR,
- 25 (8) -CN,
- (9) -S(O)_zR, and
- (10) -C(O)OR;

R⁵ is independently selected from:

- 30 (1) halo,
- (2) -OR,

- (3) -CN,
 (4) -S(O)_zR,
 (5) -C(O)OR,
 (6) -CF₃,
 5 (7) heterocyclyl, and
 (8) -C₁₋₆alkyl;

R⁶ is independently selected from: H, halo, -OR, -NR₂, -CF₃, and -C₁₋₆ alkyl;

- 10 R⁷ is independently selected from: halo, -OR, C₃₋₆ cycloalkyl, -CF₃, -CHF₂, -CH₂F, and -C₁₋₆ alkyl;

m is independently selected from 0, 1, 2, 3 and 4;

n is independently selected from 0, 1 and 2;

- 15 p is independently selected from 0, 1 and 2;

s is independently selected from 0, 1, 2 and 3;

t is independently selected from 1, 2, 3 and 4;

x is independently selected from 0, 1, and 2; and

z is independently selected from 0, 1 and 2;

20

or a pharmaceutically acceptable salt thereof.

2. A compound of Claim 1, wherein:

- 25 Ring A is selected from pyrazinyl, naphthyl, pyrimidinyl, thiazolyl, oxazolyl, pyrazolyl, triazolyl, imidazolyl, quinolinyl, pyradazinyl, phenyl and pyridinyl;

R^a is -C₁₋₆alkyl;

R¹ is independently selected from:

- 30 (1) -(CR₂)_n-heteroaryl, where the heteroaryl is unsubstituted or substituted with one to six substituents independently selected from R⁴,

- (2) $-(\text{CR}_2)_n$ -heterocyclyl, where the heterocyclyl is unsubstituted or substituted with one to six substituents independently selected from R^4 ,
- (3) $-\text{C}_{1-6}$ alkyl, where the alkyl is unsubstituted or substituted with one to six substituents independently selected from R^4 ,
- 5 (4) $-\text{O}(\text{CR}_2)_p\text{R}^4$,
- (5) $-\text{OR}$,
- (6) halo,
- (7) $-\text{OCR}_2\text{C}(\text{O})\text{NR}_2$,
- (8) $-\text{OCR}_2\text{CF}_3$,
- 10 (9) $-\text{O}(\text{CR}_2)_t\text{OCR}_3$,
- (10) $-(\text{CR}_2)_n\text{CN}$
- (11) $-(\text{CR}_2)_n\text{NR}_2$, and
- (12) $-\text{O}(\text{CR}_2)_t\text{NR}_2$;

15 R^2 is selected from:

- (1) H,
- (2) $-\text{C}_{1-6}$ alkyl, where the alkyl is unsubstituted or substituted with one to three substituents selected from R^5 ,
- (3) halo,
- 20 (4) $-(\text{CR}_2)_s\text{OR}$, and
- (5) $-(\text{CR}_2)_s\text{C}(\text{O})\text{OR}$;

R^3 is independently selected from:

- (1) $-\text{C}_{1-6}$ alkyl, where the alkyl is unsubstituted or substituted with one to four substituents independently selected from R^7 ,
- 25 (2) aryl, where the aryl is unsubstituted or substituted with one to four substituents independently selected from R^7 ,
- (3) heteroaryl, where the heteroaryl is unsubstituted or substituted with one to four substituents independently selected from R^7 , and
- 30 (4) $-\text{OCF}_2\text{CH}_3$;

R⁴ is independently selected from:

- (1) -C₁₋₆alkyl, which is unsubstituted or substituted with one to six substituents independently selected from R⁶,
- (2) aryl, which is unsubstituted or substituted with one to six substituents independently selected from R⁶,
- (3) heteroaryl, which is unsubstituted or substituted with one to six substituents independently selected from R⁶,
- (4) heterocyclyl, which is unsubstituted or substituted with one to six substituents independently selected from R⁶
- (5) halo, and
- (6) -OR;

R⁵ is independently selected from:

- (1) halo,
- (2) -OR,
- (3) -CN,
- (4) -S(O)₂R,
- (5) -C(O)OR,
- (6) -CF₃,
- (7) heterocyclyl, and
- (8) -C₁₋₆alkyl;

R⁶ is independently selected from: H, halo, -OR, -NR₂, -CF₃, and -C₁₋₆ alkyl;

R⁷ is independently selected from: halo, -OR, C₃₋₆ cycloalkyl, -CF₃, -CHF₂, -CH₂F, and -C₁₋₆ alkyl;

m is independently selected from 0, 1, 2 and 3;

n is independently selected from 0, 1 and 2;

p is independently selected from 0, 1 and 2;

s is independently selected from 0, 1, 2 and 3;

t is independently selected from 1, 2, 3 and 4;
x is independently selected from 0, 1, and 2; and
z is independently selected from 0, 1 and 2;

5 or a pharmaceutically acceptable salt thereof.

3. A compound of Claim 1, wherein:

Ring A is selected from phenyl and pyridinyl;

10

R^a is -C₁₋₆alkyl;

R¹ is independently selected from:

- (1) -C₁₋₆ alkyl, where the alkyl is unsubstituted or substituted with one to six substituents independently selected from R⁴,
- 15 (2) -O(CR₂)_pR⁴,
- (3) -OR, and
- (4) Halo;

R² is selected from:

- 20 (1) H,
- (2) -C₁₋₆alkyl, where the alkyl is unsubstituted or substituted with one to three substituents selected from R⁵,
- (3) -(CR₂)_sOR, and
- (4) -(CR₂)_sC(O)OR;

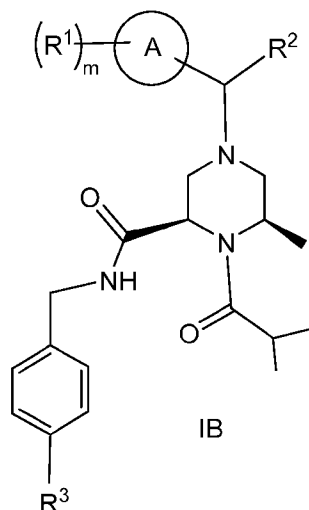
25

R³ is independently selected from:

- (1) Heteroaryl which is selected from pyrimidinyl, pyridinyl, or oxazolyl, where the heteroaryl is unsubstituted or substituted with one to four substituents independently selected from R⁷, and
- 30 (2) -OCF₂CH₃;

or a pharmaceutically acceptable salt thereof.

4. A compound of Claim 1, as depicted in Formula IB:



wherein:

Ring A is selected from aryl and heteroaryl;

5

R is independently selected from H, -C₁₋₆alkyl, -O-C₁₋₆alkyl, -CF₃, -CHF₂, -CH₂F, and -C₃₋₆ cycloalkyl;

R¹ is independently selected from:

- 10 (1) -(CR₂)_n-heteroaryl, where the heteroaryl is unsubstituted or substituted with one to six substituents independently selected from R⁴,
- (2) -(CR₂)_n-heterocyclyl, where the heterocyclyl is unsubstituted or substituted with one to six substituents independently selected from R⁴,
- (3) -(CR₂)_n- C₃₋₆ cycloalkyl, where the cycloalkyl is unsubstituted or substituted with
- 15 one to six substituents independently selected from R⁴,
- (4) -C₁₋₆ alkyl, where the alkyl is unsubstituted or substituted with one to six substituents independently selected from R⁴,
- (5) -O(CR₂)_pR⁴,
- (6) -OR,
- 20 (7) halo,
- (8) -OCR₂C(O)NR₂,
- (9) -OCR₂CF₃,

- (10) $-\text{O}(\text{CR}_2)_t\text{OCR}_3$,
 (11) $-(\text{CR}_2)_n\text{CN}$
 (12) $-(\text{CR}_2)_n\text{NR}_2$,
 (13) $-\text{O}(\text{CR}_2)_t\text{NR}_2$
 5 (14) $\text{C}_2\text{-C}_6$ alkenyl, where the alkenyl is unsubstituted or substituted with one to six substituents independently selected from R^4 , and
 (15) $\text{C}_2\text{-C}_6$ alkynyl, where the alkynyl is unsubstituted or substituted with one to six substituents independently selected from R^4 ;

10 R^2 is selected from:

- (1) H,
 (2) -C_{1-6} alkyl, where the alkyl is unsubstituted or substituted with one to three substituents selected from R^5 ,
 (3) halo,
 15 (4) $-(\text{CR}_2)_s\text{OR}$,
 (5) $-(\text{CR}_2)_s\text{CN}$
 (6) $-(\text{CR}_2)_s\text{S}(\text{O})_z\text{R}$,
 (7) $-(\text{CR}_2)_s\text{C}(\text{O})\text{OR}$,
 (8) aryl, where the aryl is unsubstituted or substituted with one to three substituents
 20 selected from R^5 ; and
 (9) $-(\text{CR}_2)_s$ -heterocyclyl, where the heterocyclyl is unsubstituted or substituted with one to three substituents selected from R^5 ;

R^3 is independently selected from:

- 25 (1) -C_{1-6} alkyl, where the alkyl is unsubstituted or substituted with one to four substituents independently selected from R^7 ,
 (2) -C_{3-6} cycloalkyl, where the cycloalkyl is unsubstituted or substituted with one to four substituents independently selected from R^7 ,
 (3) aryl, where the aryl is unsubstituted or substituted with one to four substituents
 30 independently selected from R^7 ,

- (4) heteroaryl, where the heteroaryl is unsubstituted or substituted with one to four substituents independently selected from R^7 ,
- (5) $-(CH_2)_x-C_2-C_6$ alkenyl, where the alkenyl is unsubstituted or substituted with one to four substituents independently selected from R^7 ,
- 5 (6) $-(CH_2)_x-C_2-C_6$ alkynyl, where the alkynyl is unsubstituted or substituted with one to four substituents independently selected from R^7 , and
- (8) $-OCF_2CH_3$;

R^4 is independently selected from:

- 10 (1) hydrogen,
- (2) $-C_{1-6}$ alkyl, which is unsubstituted or substituted with one to six substituents independently selected from R^6 ,
- (3) aryl, which is unsubstituted or substituted with one to six substituents independently selected from R^6 ,
- 15 (4) heteroaryl, which is unsubstituted or substituted with one to six substituents independently selected from R^6 ,
- (5) heterocyclyl, which is unsubstituted or substituted with one to six substituents independently selected from R^6 ,
- (6) halo,
- 20 (7) $-OR$,
- (8) $-CN$,
- (9) $-S(O)_zR$, and
- (10) $-C(O)OR$;

25 R^5 is independently selected from:

- (1) halo,
- (2) $-OR$,
- (3) $-CN$,
- (4) $-S(O)_zR$,
- 30 (5) $-C(O)OR$,
- (6) $-CF_3$,
- (7) heterocyclyl, and

(8) -C₁₋₆alkyl;

R⁶ is independently selected from: H, halo, -OR, -NR₂, -CF₃, and -C₁₋₆ alkyl;

5 R⁷ is independently selected from: halo, -OR, C₃₋₆ cycloalkyl, -CF₃, -CHF₂, -CH₂F, and -C₁₋₆ alkyl;

m is independently selected from 0, 1, 2, 3 and 4;

n is independently selected from 0, 1 and 2;

10 p is independently selected from 0, 1 and 2;

s is independently selected from 0, 1, 2 and 3;

t is independently selected from 1, 2, 3 and 4;

x is independently selected from 0, 1, and 2; and

z is independently selected from 0, 1 and 2;

15

or a pharmaceutically acceptable salt thereof.

5. The compound of any of Claims 1-4, or a pharmaceutically acceptable salt thereof, wherein Ring A is selected from: pyrazinyl, naphthyl, pyrimidinyl, thiazolyl, oxazolyl,
20 pyrazolyl, triazolyl, imidazolyl, quinoliny, pyradaziny, phenyl and pyridinyl.

6. The compound of any of Claims 1-5, or a pharmaceutically acceptable salt thereof, wherein R¹ is selected from:

- 25 (1) -(CR₂)_n-heteroaryl, where the heteroaryl is unsubstituted or substituted with one to six substituents independently selected from R⁴,
- (2) -(CR₂)_n-heterocyclyl, where the heterocyclyl is unsubstituted or substituted with one to six substituents independently selected from R⁴,
- (3) -C₁₋₆ alkyl, where the alkyl is unsubstituted or substituted with one to six substituents independently selected from R⁴,
- 30 (4) -O(CR₂)_pR⁴,
- (5) -OR,
- (6) halo,

- (7) $-\text{OCR}_2\text{C}(\text{O})\text{NR}_2$,
 (8) $-\text{OCR}_2\text{CF}_3$,
 (9) $-\text{O}(\text{CR}_2)_t\text{OCR}_3$,
 (10) $-(\text{CR}_2)_n\text{CN}$,
 5 (11) $-(\text{CR}_2)_n\text{NR}_2$, and
 (12) $-\text{O}(\text{CR}_2)_t\text{NR}_2$.

7. The compound of any of Claims 1-6, or a pharmaceutically acceptable salt thereof, wherein R^2 is selected from H, $-(\text{CR}_2)_s\text{OR}$, $-\text{C}_{1-6}\text{alkyl}$, where the alkyl is unsubstituted
 10 or substituted with one to three substituents selected from R^5 , $-(\text{CR}_2)_s\text{C}(\text{O})\text{OR}$, and $-\text{CF}_3$.

8. The compound of any of Claims 1-7, or a pharmaceutically acceptable salt thereof, wherein R^3 is selected from
 (1) $-\text{C}_{1-6}\text{alkyl}$, where the alkyl is unsubstituted or substituted with one to four
 15 substituents independently selected from R^7 ,
 (2) aryl, where the aryl is unsubstituted or substituted with one to four substituents independently selected from R^7 ,
 (3) heteroaryl, where the heteroaryl is unsubstituted or substituted with one to four substituents independently selected from R^7 , and
 20 (4) $-\text{OCF}_2\text{CH}_3$.

9. The compound of any of Claims 1-8, or a pharmaceutically acceptable salt thereof, wherein R^4 is selected from $-\text{OR}$, halo, $-\text{C}_{1-6}\text{alkyl}$, aryl, heteroaryl, and heterocyclyl, where said alkyl, aryl, heteroaryl or heterocyclyl is unsubstituted or substituted with one to six
 25 substituents independently selected from R^6 .

10. A compound which is selected from:
 cis-4-benzyl-N-(4-(furan-2-yl)benzyl)-1-isobutyryl-6-methylpiperazine-2-carboxamide (1-1);
 (2R,6R)-N- $\{[4-(\text{furan-2-yl})\text{phenyl}]\text{methyl}\}$ -6-methyl-1-(2-methylpropanoyl)-4- $\{[2-(\text{morpholin-4-yl})\text{phenyl}]\text{methyl}\}$ piperazine-2-carboxamide (1-2);
 30 N- $\{[4-(\text{furan-2-yl})\text{phenyl}]\text{methyl}\}$ -6-methyl-1-(2-methylpropanoyl)-4- $\{[2-(\text{phenoxyphenyl})\text{methyl}]\text{piperazine-2-carboxamide (1-3)}$;

- 4-[(2,6-difluorophenyl)methyl]-N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (1-4);
N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)-4-({2-[(pyridin-3-yl)oxy]phenyl}methyl)piperazine-2-carboxamide (1-5);
- 5 4-{[2-(2-amino-2-oxoethoxy)phenyl]methyl}-N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (1-6);
4-{[2-fluoro-6-(morpholin-4-yl)phenyl]methyl}-N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (1-7);
N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)-4-{[2-(morpholin-4-yl)phenyl]methyl}piperazine-2-carboxamide (1-8);
- 10 N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)-4-({2-[(1H-pyrazol-1-yl)methyl]phenyl}methyl)piperazine-2-carboxamide (1-9);
4-[(3-fluoropyridin-2-yl)methyl]-N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (1-10);
- 15 4-[(2-fluoro-6-methoxyphenyl)methyl]-N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (1-11);
N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)-4-({2-[(pyrazin-2-yl)oxy]phenyl}methyl)piperazine-2-carboxamide (1-12);
4-[(2-fluoro-5-methylphenyl)methyl]-N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (1-13);
- 20 N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)-4-({2-[(pyridin-2-yl)oxy]phenyl}methyl)piperazine-2-carboxamide (1-14);
4-[(2-fluorophenyl)methyl]-N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (1-15);
- 25 N-{[4-(furan-2-yl)phenyl]methyl}-4-{[2-(2-methoxyethoxy)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (1-16);
N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)-4-{[2-(2,2,2-trifluoroethoxy)phenyl]methyl}piperazine-2-carboxamide (1-17);
N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)-4-({2-[(oxolan-2-yl)methoxy]phenyl}methyl)piperazine-2-carboxamide (1-18);
- 30 4-[(2-chloro-6-fluorophenyl)methyl]-N-{[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (1-19);

- N- {[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)-4-[(pyrimidin-2-yl)methyl]piperazine-2-carboxamide (1-20);
- N- {[4-(furan-2-yl)phenyl]methyl}-4- {[2-(4-hydroxypiperidin-1-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (1-21);
- 5 N- {[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)-4-[(4-methyl-1,3-thiazol-2-yl)methyl]piperazine-2-carboxamide (1-22);
- N- {[4-(furan-2-yl)phenyl]methyl}-4-[(2-methoxyphenyl)methyl]-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (1-23);
- 4- {[2-(difluoromethoxy)phenyl]methyl}-N- {[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (1-24);
- 10 4-[(2-ethoxyphenyl)methyl]-N- {[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (1-25);
- N- {[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)-4- {[4-(propan-2-yl)-1,3-thiazol-2-yl]methyl}piperazine-2-carboxamide (1-26);
- 15 4-[(2-cyanophenyl)methyl]-N- {[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (1-27);
- 4-[(3-cyanophenyl)methyl]-N- {[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (1-28);
- N- {[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)-4- {[2-(pyridin-4-yl)phenyl]methyl}piperazine-2-carboxamide (1-29);
- 20 N- {[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)-4-[(pyridin-2-yl)methyl]piperazine-2-carboxamide (1-30);
- N- {[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)-4-[(pyridin-3-yl)methyl]piperazine-2-carboxamide (1-31);
- 25 4-[(2,3-difluorophenyl)methyl]-N- {[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (1-32);
- 4-[(2-fluoro-3-methoxyphenyl)methyl]-N- {[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (1-33);
- 4-[(2-fluoro-5-methoxyphenyl)methyl]-N- {[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (1-34);
- 30 N- {[4-(furan-2-yl)phenyl]methyl}-6-methyl-4-[(3-methylphenyl)methyl]-1-(2-methylpropanoyl)piperazine-2-carboxamide (1-35);

- N- {[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)-4- {[2-(1H-1,2,4-triazol-1-yl)phenyl]methyl} piperazine-2-carboxamide (1-36);
- N- {[4-(furan-2-yl)phenyl]methyl}-4-[(3-methoxyphenyl)methyl]-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (1-37);
- 5 4-[(3-fluorophenyl)methyl]-N- {[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (1-38);
- 4-[(4-fluorophenyl)methyl]-N- {[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (1-39);
- N- {[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)-4- {[2-
- 10 (trifluoromethoxy)phenyl]methyl} piperazine-2-carboxamide (1-40);
- N- {[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)-4- {[2-(pyridin-3-yl)phenyl]methyl} piperazine-2-carboxamide (1-41);
- 4-[(2-fluoro-6-hydroxyphenyl)methyl]-N- {[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (1-42);
- 15 4-[(3-chloro-2-fluorophenyl)methyl]-N- {[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (1-43);
- 4-[(2-cyclopropylphenyl)methyl]-N- {[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (1-44);
- 4- {[2-(cyanomethyl)phenyl]methyl}-N- {[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-
- 20 methylpropanoyl)piperazine-2-carboxamide (1-45);
- N- {[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)-4- {[2-(pyrimidin-5-yl)phenyl]methyl} piperazine-2-carboxamide (1-46);
- N- {[4-(furan-2-yl)phenyl]methyl}-4-[(2-hydroxyphenyl)methyl]-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (1-47);
- 25 N- {[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)-4-[(5-methyl-1,3-thiazol-2-yl)methyl]piperazine-2-carboxamide (1-48);
- 4- {[3-(dimethylamino)phenyl]methyl}-N- {[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (1-49);
- 4-[(3-fluoropyridin-4-yl)methyl]-N- {[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-
- 30 methylpropanoyl)piperazine-2-carboxamide (1-50);
- 4- {[2-fluoro-5-(trifluoromethyl)phenyl]methyl}-N- {[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (1-51);

- N- {[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)-4- {[2-(1H-pyrazol-1-yl)phenyl]methyl} piperazine-2-carboxamide (1-52);
- 4- {[2-(difluoromethyl)phenyl]methyl}-N- {[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (1-53);
- 5 N- {[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)-4- {[2-(piperidin-1-yl)phenyl]methyl} piperazine-2-carboxamide (1-54);
- N- {[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)-4- {[2-(pyrrolidin-1-yl)phenyl]methyl} piperazine-2-carboxamide (1-55);
- N- {[4-(furan-2-yl)phenyl]methyl}-6-methyl-4-[(3-methyl-1,2-oxazol-5-yl)methyl]-1-(2-methylpropanoyl)piperazine-2-carboxamide (1-56);
- 10 N- {[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)-4-[(5-methyl-1H-pyrazol-3-yl)methyl]piperazine-2-carboxamide (1-57);
- N- {[4-(furan-2-yl)phenyl]methyl}-6-methyl-4-[(2-methylphenyl)methyl]-1-(2-methylpropanoyl)piperazine-2-carboxamide (1-58);
- 15 N- {[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)-4- {[2-[(morpholin-4-yl)methyl]phenyl]methyl} piperazine-2-carboxamide (1-59);
- 4- {[2-[2-(dimethylamino)ethoxy]phenyl]methyl}-N- {[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (1-60);
- N- {[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)-4- [(2-methyl-1,3-thiazol-5-yl)methyl]piperazine-2-carboxamide (1-61);
- 20 N- {[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)-4- {[2-(1H-1,2,3-triazol-1-yl)phenyl]methyl} piperazine-2-carboxamide (1-62);
- N- {[4-(furan-2-yl)phenyl]methyl}-6-methyl-4- {[2-(4-methylpiperazin-1-yl)phenyl]methyl}-1-(2-methylpropanoyl)piperazine-2-carboxamide (1-63);
- 25 4-[(2-ethylphenyl)methyl]-N- {[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (1-64);
- 4- {[2-fluoro-3-(trifluoromethyl)phenyl]methyl}-N- {[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (1-65);
- N- {[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)-4- {[2-(trifluoromethyl)phenyl]methyl} piperazine-2-carboxamide (1-66);
- 30 N- {[4-(furan-2-yl)phenyl]methyl}-4-[(3-hydroxypyridin-2-yl)methyl]-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (1-67);

- 4-[(5-cyano-2-fluorophenyl)methyl]-N-{[4-(furan-2-yl)phenyl)methyl]-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (1-68);
- N-{[4-(furan-2-yl)phenyl)methyl]-6-methyl-1-(2-methylpropanoyl)-4-[(pyridin-4-yl)methyl]piperazine-2-carboxamide (1-69);
- 5 4-{[2-(dimethylamino)phenyl)methyl]-N-{[4-(furan-2-yl)phenyl)methyl]-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (1-70);
- 4-[(1,3-dimethyl-1H-pyrazol-5-yl)methyl]-N-{[4-(furan-2-yl)phenyl)methyl]-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (1-71);
- N-{[4-(furan-2-yl)phenyl)methyl]-6-methyl-1-(2-methylpropanoyl)-4-[(1-methyl-1H-pyrazol-5-yl)methyl]piperazine-2-carboxamide (1-72);
- 10 N-{[4-(furan-2-yl)phenyl)methyl]-6-methyl-4-[(1-methyl-1H-imidazol-5-yl)methyl]-1-(2-methylpropanoyl)piperazine-2-carboxamide (1-73);
- 4-[(4-cyanophenyl)methyl]-N-{[4-(furan-2-yl)phenyl)methyl]-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (1-74);
- 15 4-({2-[(dimethylamino)methyl]phenyl)methyl}-N-{[4-(furan-2-yl)phenyl)methyl]-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (1-75);
- N-{[4-(furan-2-yl)phenyl)methyl]-6-methyl-4-[(4-methyl-1H-imidazol-2-yl)methyl]-1-(2-methylpropanoyl)piperazine-2-carboxamide (1-76);
- N-{[4-(furan-2-yl)phenyl)methyl]-6-methyl-4-[(2-methyl-1H-imidazol-4-yl)methyl]-1-(2-methylpropanoyl)piperazine-2-carboxamide (1-77);
- 20 N-{[4-(furan-2-yl)phenyl)methyl]-6-methyl-1-(2-methylpropanoyl)-4-[(4-methyl-4H-1,2,4-triazol-3-yl)methyl]piperazine-2-carboxamide (1-78);
- 4-{[4-(dimethylamino)phenyl)methyl]-N-{[4-(furan-2-yl)phenyl)methyl]-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (1-79);
- 25 N-{[4-(furan-2-yl)phenyl)methyl]-4-[(4-methoxyphenyl)methyl]-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (1-80);
- N-{[4-(furan-2-yl)phenyl)methyl]-6-methyl-4-[(4-methylphenyl)methyl]-1-(2-methylpropanoyl)piperazine-2-carboxamide (1-81);
- cis-N-(4-(furan-2-yl)benzyl)-1-isobutyryl-6-methyl-4-(quinolin-8-ylmethyl)piperazine-2-carboxamide (2-1);
- 30 4-[(2,6-difluoro-3-methylphenyl)methyl]-N-{[4-(furan-2-yl)phenyl)methyl]-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (2-2);

- N- {[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)-4-[(2,4,6-trifluorophenyl)methyl]piperazine-2-carboxamide (2-3);
- N- {[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)-4-[(2,3,5,6-tetrafluorophenyl)methyl]piperazine-2-carboxamide (2-4);
- 5 N- {[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)-4-[(1,3-thiazol-2-yl)methyl]piperazine-2-carboxamide (2-5);
- N- {[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)-4-(pent-2-yn-1-yl)piperazine-2-carboxamide (2-6);
- 4-(but-2-yn-1-yl)-N- {[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (2-7);
- 10 4-[(2-bromo-6-fluorophenyl)methyl]-N- {[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (2-8);
- 4-[(2-chlorophenyl)methyl]-N- {[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (2-9);
- 15 N- {[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)-4-[(pyridazin-3-yl)methyl]piperazine-2-carboxamide (2-10);
- N- {[4-(furan-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)-4-[(naphthalen-1-yl)methyl]piperazine-2-carboxamide (2-11);
- cis-4-(2-fluoro-6-phenoxybenzyl)-N-(4-(furan-2-yl)benzyl)-1-isobutyryl-6-methylpiperazine-2-carboxamide (3);
- 20 cis-4-(2-(benzyloxy)-6-fluorobenzyl)-N-(4-(furan-2-yl)benzyl)-1-isobutyryl-6-methylpiperazine-2-carboxamide (4);
- cis-4-(2-ethoxy-6-fluorobenzyl)-N-(4-(furan-2-yl)benzyl)-1-isobutyryl-6-methylpiperazine-2-carboxamide (5);
- 25 cis-4-(2-fluoro-6-hydroxybenzyl)-N-(4-(furan-2-yl)benzyl)-1-isobutyryl-6-methylpiperazine-2-carboxamide (6);
- cis-N-(4-(furan-2-yl)benzyl)-1-isobutyryl-6-methyl-4-(2-(pyridin-4-yloxy)benzyl)piperazine-2-carboxamide (7);
- cis-N-(4-(furan-2-yl)benzyl)-1-isobutyryl-6-methyl-4-(2-(pyridin-4-yloxy)benzyl)piperazine-2-carboxamide (8);
- 30 cis-N-(4-(furan-2-yl)benzyl)-1-isobutyryl-6-methyl-4-(2-(oxazol-2-ylmethyl)benzyl)piperazine-2-carboxamide (9);

- cis-4-(2-((4H-1,2,4-triazol-4-yl)methyl)benzyl)-N-(4-(furan-2-yl)benzyl)-1-isobutyryl-6-methylpiperazine-2-carboxamide (10);
- cis-N-(4-(furan-2-yl)benzyl)-1-isobutyryl-6-methyl-4-(2-(tetrahydro-2H-pyran-4-yl)benzyl)piperazine-2-carboxamide (11);
- 5 (2R,6R)-4-(2,6-difluorobenzyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (12);
- (2R,6R)-4-(2-fluoro-6-(2-methoxyphenoxy)benzyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (13-1)
- (2R,6R)-4-({2-[(2-ethyl-5-methylpyridin-3-yl)oxy]-6-fluorophenyl}methyl)-6-methyl-1-(2-methylpropanoyl)-N-{{4-(pyrimidin-2-yl)phenyl}methyl}piperazine-2-carboxamide (13-2);
- 10 (2R,6R)-4-({2-[2-(dimethylamino)phenoxy]-6-fluorophenyl}methyl)-6-methyl-1-(2-methylpropanoyl)-N-{{4-(pyrimidin-2-yl)phenyl}methyl}piperazine-2-carboxamide (13-3);
- (2R,6R)-4-{{2-(2-ethylphenoxy)-6-fluorophenyl}methyl}-6-methyl-1-(2-methylpropanoyl)-N-{{4-(pyrimidin-2-yl)phenyl}methyl}piperazine-2-carboxamide (13-4);
- 15 (2R,6R)-4-({2-[(2-ethylpyridin-3-yl)oxy]-6-fluorophenyl}methyl)-6-methyl-1-(2-methylpropanoyl)-N-{{4-(pyrimidin-2-yl)phenyl}methyl}piperazine-2-carboxamide (13-5);
- (2R,6R)-4-({2-fluoro-6-[2-(trifluoromethyl)phenoxy]phenyl}methyl)-6-methyl-1-(2-methylpropanoyl)-N-{{4-(pyrimidin-2-yl)phenyl}methyl}piperazine-2-carboxamide (13-6);
- (2R,6R)-4-({2-fluoro-6-[(imidazo[1,2-a]pyridin-8-yl)oxy]phenyl}methyl)-6-methyl-1-(2-methylpropanoyl)-N-{{4-(pyrimidin-2-yl)phenyl}methyl}piperazine-2-carboxamide (13-7);
- 20 (2R,6R)-4-({2-[(2,6-dimethylpyridin-3-yl)oxy]-6-fluorophenyl}methyl)-6-methyl-1-(2-methylpropanoyl)-N-{{4-(pyrimidin-2-yl)phenyl}methyl}piperazine-2-carboxamide (13-8);
- (2R,6R)-4-{{2-(2,6-dimethylphenoxy)-6-fluorophenyl}methyl}-6-methyl-1-(2-methylpropanoyl)-N-{{4-(pyrimidin-2-yl)phenyl}methyl}piperazine-2-carboxamide (13-9);
- 25 (2R,6R)-4-({2-fluoro-6-[(2-methylpyridin-3-yl)oxy]phenyl}methyl)-6-methyl-1-(2-methylpropanoyl)-N-{{4-(pyrimidin-2-yl)phenyl}methyl}piperazine-2-carboxamide (13-10);
- (2R,6R)-4-({2-fluoro-6-[(3-methoxy-2-methylpyridin-4-yl)oxy]phenyl}methyl)-6-methyl-1-(2-methylpropanoyl)-N-{{4-(pyrimidin-2-yl)phenyl}methyl}piperazine-2-carboxamide (13-11);
- (2R,6R)-4-{{2-fluoro-6-(2-methylphenoxy)phenyl}methyl}-6-methyl-1-(2-methylpropanoyl)-N-{{4-(pyrimidin-2-yl)phenyl}methyl}piperazine-2-carboxamide (13-12);
- 30 (2R,6R)-4-({2-fluoro-6-[2-(trifluoromethoxy)phenoxy]phenyl}methyl)-6-methyl-1-(2-methylpropanoyl)-N-{{4-(pyrimidin-2-yl)phenyl}methyl}piperazine-2-carboxamide (13-13);

- (2R,6R)-4-{[2-(2-chlorophenoxy)-6-fluorophenyl]methyl}-6-methyl-1-(2-methylpropanoyl)-N-{[4-(pyrimidin-2-yl)phenyl]methyl}piperazine-2-carboxamide (13-14);
- (2R,6R)-4-({2-[(6-ethylpyridin-3-yl)oxy]-6-fluorophenyl}methyl)-6-methyl-1-(2-methylpropanoyl)-N-{[4-(pyrimidin-2-yl)phenyl]methyl}piperazine-2-carboxamide (13-15);
- 5 (2R,6R)-4-({2-[(2-chloro-6-methylpyridin-3-yl)oxy]-6-fluorophenyl}methyl)-6-methyl-1-(2-methylpropanoyl)-N-{[4-(pyrimidin-2-yl)phenyl]methyl}piperazine-2-carboxamide (13-16);
- (2R,6R)-4-({2-fluoro-6-[(4-methylpyridin-3-yl)oxy]phenyl}methyl)-6-methyl-1-(2-methylpropanoyl)-N-{[4-(pyrimidin-2-yl)phenyl]methyl}piperazine-2-carboxamide (13-17);
- (2R,6R)-4-{[2-fluoro-6-(2-methoxy-6-methylphenoxy)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)-N-{[4-(pyrimidin-2-yl)phenyl]methyl}piperazine-2-carboxamide (13-18);
- 10 (2R,6R)-4-({2-[(6-chloropyridin-3-yl)oxy]-6-fluorophenyl}methyl)-6-methyl-1-(2-methylpropanoyl)-N-{[4-(pyrimidin-2-yl)phenyl]methyl}piperazine-2-carboxamide (13-19);
- (2R,6R)-4-[(2-fluoro-6-phenoxyphenyl)methyl]-6-methyl-1-(2-methylpropanoyl)-N-{[4-(pyrimidin-2-yl)phenyl]methyl}piperazine-2-carboxamide (13-20);
- 15 (2R,6R)-4-({2-[(2,6-dichloropyridin-3-yl)oxy]-6-fluorophenyl}methyl)-6-methyl-1-(2-methylpropanoyl)-N-{[4-(pyrimidin-2-yl)phenyl]methyl}piperazine-2-carboxamide (13-21);
- (2R,6R)-4-({2-fluoro-6-[(4-methoxypyridin-3-yl)oxy]phenyl}methyl)-6-methyl-1-(2-methylpropanoyl)-N-{[4-(pyrimidin-2-yl)phenyl]methyl}piperazine-2-carboxamide (13-22);
- (2R,6R)-4-({2-[(2-chloropyrimidin-5-yl)oxy]-6-fluorophenyl}methyl)-6-methyl-1-(2-methylpropanoyl)-N-{[4-(pyrimidin-2-yl)phenyl]methyl}piperazine-2-carboxamide (13-23);
- 20 (2R,6R)-4-({2-fluoro-6-[(6-methylpyridin-3-yl)oxy]phenyl}methyl)-6-methyl-1-(2-methylpropanoyl)-N-{[4-(pyrimidin-2-yl)phenyl]methyl}piperazine-2-carboxamide (13-24);
- (2R,6R)-4-({2-fluoro-6-[(6-fluoropyridin-3-yl)oxy]phenyl}methyl)-6-methyl-1-(2-methylpropanoyl)-N-{[4-(pyrimidin-2-yl)phenyl]methyl}piperazine-2-carboxamide (13-25);
- 25 (2R,6R)-4-({2-fluoro-6-[(2-fluoropyridin-3-yl)oxy]phenyl}methyl)-6-methyl-1-(2-methylpropanoyl)-N-{[4-(pyrimidin-2-yl)phenyl]methyl}piperazine-2-carboxamide (13-26);
- (2R,6R)-4-({2-fluoro-6-[(2-fluoro-6-methylpyridin-3-yl)oxy]phenyl}methyl)-6-methyl-1-(2-methylpropanoyl)-N-{[4-(pyrimidin-2-yl)phenyl]methyl}piperazine-2-carboxamide (13-27);
- (2R,6R)-4-({2-fluoro-6-[(4-methylpyridin-2-yl)oxy]phenyl}methyl)-6-methyl-1-(2-methylpropanoyl)-N-{[4-(pyrimidin-2-yl)phenyl]methyl}piperazine-2-carboxamide (13-28);
- 30 (2R,6R)-4-({2-fluoro-6-[(5-methoxypyridin-2-yl)oxy]phenyl}methyl)-6-methyl-1-(2-methylpropanoyl)-N-{[4-(pyrimidin-2-yl)phenyl]methyl}piperazine-2-carboxamide (13-29);

- (2R,6R)-4-({2-fluoro-6-[(2-methoxypyridin-4-yl)oxy]phenyl}methyl)-6-methyl-1-(2-methylpropanoyl)-N-{{4-(pyrimidin-2-yl)phenyl}methyl}piperazine-2-carboxamide (13-30);
(2R,6R)-4-({2-fluoro-6-[(pyridin-3-yl)oxy]phenyl}methyl)-6-methyl-1-(2-methylpropanoyl)-N-{{4-(pyrimidin-2-yl)phenyl}methyl}piperazine-2-carboxamide (13-31);
5 (2R,6R)-4-({2-fluoro-6-[(6-methylpyridin-2-yl)oxy]phenyl}methyl)-6-methyl-1-(2-methylpropanoyl)-N-{{4-(pyrimidin-2-yl)phenyl}methyl}piperazine-2-carboxamide (13-32);
(2R,6R)-4-({2-fluoro-6-[(5-methylpyridin-2-yl)oxy]phenyl}methyl)-6-methyl-1-(2-methylpropanoyl)-N-{{4-(pyrimidin-2-yl)phenyl}methyl}piperazine-2-carboxamide (13-33);
(2R,6R)-4-({2-fluoro-6-[(5-methylpyridin-3-yl)oxy]phenyl}methyl)-6-methyl-1-(2-methylpropanoyl)-N-{{4-(pyrimidin-2-yl)phenyl}methyl}piperazine-2-carboxamide (13-34);
10 (2R,6R)-4-({2-fluoro-6-[(2-methoxypyrimidin-5-yl)oxy]phenyl}methyl)-6-methyl-1-(2-methylpropanoyl)-N-{{4-(pyrimidin-2-yl)phenyl}methyl}piperazine-2-carboxamide (13-35);
(2R,6R)-4-({2-fluoro-6-[(pyridin-2-yl)oxy]phenyl}methyl)-6-methyl-1-(2-methylpropanoyl)-N-{{4-(pyrimidin-2-yl)phenyl}methyl}piperazine-2-carboxamide (13-36);
15 (2R,6R)-4-(2-fluoro-6-(2-methoxyphenoxy)benzyl)-1-isobutyl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (14);
(2R,6R)-1-isobutyl-6-methyl-4-(2-phenoxybenzyl)-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (15);
(2R,6R)-4-(1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl)-1-isobutyl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (16-1);
20 (2R,6R)-4-[(1R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl]-6-methyl-1-(2-methylpropanoyl)-N-{{4-(1,3-thiazol-2-yl)phenyl}methyl}piperazine-2-carboxamide (16-2);
(2R,6R)-N-{{4-(1,1-difluoroethoxy)phenyl}methyl}-4-[(1R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl]-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (16-3);
25 (2R,6R)-4-[(1R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl]-6-methyl-1-(2-methylpropanoyl)-N-{{4-(1,3-oxazol-2-yl)phenyl}methyl}piperazine-2-carboxamide (16-4);
(2R,6R)-4-[(1R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl]-6-methyl-1-(2-methylpropanoyl)-N-{{4-(2H-1,2,3-triazol-2-yl)phenyl}methyl}piperazine-2-carboxamide (16-5);
(2R,6R)-4-[(1R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl]-6-methyl-1-(2-methylpropanoyl)-N-[(4-propylphenyl)methyl]piperazine-2-carboxamide (16-6);
30 (2R,6R)-N-[(4-cyclopropylphenyl)methyl]-4-[(1R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl]-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (16-7);

- (2R,6R)-N-[(4-tert-butylphenyl)methyl]-4-[(1R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl]-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (16-8);
- (2R,6R)-4-[(1R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl]-6-methyl-1-(2-methylpropanoyl)-N-{[4-(propan-2-yl)phenyl]methyl} piperazine-2-carboxamide (16-9);
- 5 (2R,6R)-N-[(4-ethylphenyl)methyl]-4-[(1R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl]-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (16-10);
- (2R,6R)-4-[(1R)-1-(3-fluoro-6-methylpyridin-2-yl)-3-methoxypropyl]-6-methyl-1-(2-methylpropanoyl)-N-{[4-(pyrimidin-2-yl)phenyl]methyl} piperazine-2-carboxamide (16-11);
- (2R,6R)-4-[(1R)-1-(3-fluoropyridin-2-yl)-3-methoxypropyl]-6-methyl-1-(2-methylpropanoyl)-N-{[4-(pyrimidin-2-yl)phenyl]methyl} piperazine-2-carboxamide (16-12);
- 10 (2R,6R)-4-[(1R)-1-(3,5-difluoropyridin-2-yl)-3-methoxypropyl]-6-methyl-1-(2-methylpropanoyl)-N-{[4-(pyrimidin-2-yl)phenyl]methyl} piperazine-2-carboxamide (16-13);
- (2R,6R)-N-(4-(5-chloro-6-methoxypyridin-2-yl)benzyl)-4-((R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl)-1-isobutyl-6-methylpiperazine-2-carboxamide (17);
- 15 (2R,6R)-N-(4-(5-cyclopropyl-6-methoxypyridin-2-yl)benzyl)-4-((R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl)-1-isobutyl-6-methylpiperazine-2-carboxamide (18);
- (2R,6R)-4-((R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl)-1-isobutyl-N-(4-(6-methoxy-5-methylpyridin-2-yl)benzyl)-6-methylpiperazine-2-carboxamide (19);
- (2R,6R)-4-((R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl)-N-(4-(5-fluoro-6-methoxypyridin-2-yl)benzyl)-1-isobutyl-6-methylpiperazine-2-carboxamide (20-1);
- 20 (2R,6R)-N-{[4-(4,6-dimethoxypyridin-2-yl)phenyl]methyl}-4-[(1R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl]-6-methyl-1-(2-methylpropanoyl) piperazine-2-carboxamide (20-2);
- (2R,6R)-4-[(1R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl]-N-{[4-(6-methoxy-4-methylpyridin-2-yl) phenyl]methyl}-6-methyl-1-(2-methylpropanoyl) piperazine-2-carboxamide (20-3);
- 25 (2R,6R)-4-[(1R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl]-N-{[4-(4-methoxypyrimidin-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (20-4);
- 30 (2R,6R)-4-[(1R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl]-N-({4-[6-methoxy-4-(trifluoromethyl)pyridin-2-yl]phenyl} methyl)-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (20-5);

- (2R,6R)-N-{[4-(6-ethoxypyridin-2-yl)phenyl]methyl}-4-[(1R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl]-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (20-6);
- (2R,6R)-N-{[4-(3,6-dimethoxypyridin-2-yl)phenyl]methyl}-4-[(1R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl]-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (20-7);
- (2R,6R)-N-({4-[6-(difluoromethyl)pyridin-2-yl]phenyl}methyl)-4-[(1R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl]-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (20-8);
- (2R,6R)-N-[(2'-fluoro-3'-methoxy[1,1'-biphenyl]-4-yl)methyl]-4-[(1R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl]-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (20-9);
- (2R,6R)-4-[(1R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl]-N-{[4-(5-fluoropyrimidin-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (20-10);
- (2R,6R)-4-[(1R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl]-6-methyl-1-(2-methylpropanoyl)-N-{[4-(thieno[2,3-b]pyridin-6-yl)phenyl]methyl}piperazine-2-carboxamide (20-11);
- (2R,6R)-N-({4-[6-(difluoromethoxy)pyridin-2-yl]phenyl}methyl)-4-[(1R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl]-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (20-12);
- (2R,6R)-4-[(1R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl]-N-{[4-(6-methoxypyrazin-2-yl)phenyl]methyl}-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (20-13);
- (2R,6R)-4-[(1R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl]-6-methyl-1-(2-methylpropanoyl)-N-{[4-(1-methyl-1H-pyrrolo[2,3-b]pyridin-6-yl)phenyl]methyl}piperazine-2-carboxamide (20-14);
- (2R,6R)-4-[(1R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl]-6-methyl-1-(2-methylpropanoyl)-N-({4-[6-(trifluoromethoxy)pyridin-2-yl]phenyl}methyl)piperazine-2-carboxamide (20-15);
- (2R,6R)-4-[(1R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl]-6-methyl-N-{[4-(1-methyl-6-oxo-1,6-dihydro-2H-pyridin-2-yl)phenyl]methyl}-1-(2-methylpropanoyl)piperazine-2-carboxamide (20-16);
- (2R,6R)-N-{[4-(3-fluoro-6-methoxypyridin-2-yl)phenyl]methyl}-4-[(1R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl]-6-methyl-1-(2-methylpropanoyl)piperazine-2-carboxamide (20-17);

- (2R,6R)-4-((R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl)-1-isobutyl-6-methyl-N-(4-(pyridin-2-yl)benzyl)piperazine-2-carboxamide (21);
- (2R,6R)-N-(4-(4-cyclopropyl-6-methoxy pyridin-2-yl)benzyl)-4-((R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl)-1-isobutyl-6-methylpiperazine-2-carboxamide (22);
- 5 (2R,6R)-4-((R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl)-N-((2'-fluoro-5'-methoxy-[1,1'-biphenyl]-4-yl)methyl)-1-isobutyl-6-methylpiperazine-2-carboxamide (23);
- (2R,6R)-N-(4-(6-cyclopropoxy pyridin-2-yl)benzyl)-4-((R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl)-1-isobutyl-6-methylpiperazine-2-carboxamide (24);
- (2R,6R)-4-((R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl)-1-isobutyl-N-(4-(6-methoxy pyridin-2-yl)benzyl)-6-methylpiperazine-2-carboxamide (25);
- 10 (2R,6R)-4-((R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl)-1-isobutyl-N-(4-(3-methoxy pyridin-2-yl)benzyl)-6-methylpiperazine-2-carboxamide (26);
- 1-(cyclopropanecarbonyl)-4-(2,6-difluorobenzyl)-N-(4-(furan-2-yl)benzyl)-6-methylpiperazine-2-carboxamide (27);
- 15 (2R,6R)-4-((R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl)-1-isobutyl-6-methyl-N-(4-(prop-1-yn-1-yl)benzyl)piperazine-2-carboxamide (28);
- (2R,6R)-N-(4-(cyclopropylethynyl)benzyl)-4-((R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl)-1-isobutyl-6-methylpiperazine-2-carboxamide (29);
- (2R,6R)-4-((R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl)-1-isobutyl-6-methyl-N-
- 20 (4-(3,3,3-trifluoroprop-1-yn-1-yl)benzyl)piperazine-2-carboxamide (30);
- (2R,6R)-N-(4-(but-2-yn-1-yl)benzyl)-4-((R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl)-1-isobutyl-6-methylpiperazine-2-carboxamide (31);
- (2R,6R)-4-((R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl)-1-isobutyl-6-methyl-N-(4-(4-methyl-2H-1,2,3-triazol-2-yl)benzyl)piperazine-2-carboxamide (32);
- 25 (2R,6R)-N-(4-(4,5-dimethyl-2H-1,2,3-triazol-2-yl)benzyl)-4-((R)-1-(3-fluoro-4-methylpyridin-2-yl)-3-methoxypropyl)-1-isobutyl-6-methylpiperazine-2-carboxamide (33);
- (2R,6R)-4-((R)-1-(3,5-difluoro-4-methylpyridin-2-yl)-3-methoxypropyl)-1-isobutyl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (34);
- (2R,6R)-4-((R)-1-(3-fluoro-4,6-dimethylpyridin-2-yl)-3-methoxypropyl)-1-isobutyl-6-methyl-
- 30 N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (35-1);
- (2R,6R)-4-[(1R)-3-methoxy-1-(2,4,6-trifluorophenyl)propyl]-6-methyl-1-(2-methylpropanoyl)-N-{[4-(pyrimidin-2-yl)phenyl]methyl}piperazine-2-carboxamide (35-2);

- (2R,6R)-4-[(1R)-1-[3-fluoro-6-(trifluoromethyl)pyridin-2-yl]-3-methoxypropyl]-6-methyl-1-(2-methylpropanoyl)-N-[[4-(pyrimidin-2-yl)phenyl]methyl]piperazine-2-carboxamide (35-3);
- (2R,6R)-4-[(1R)-1-(5-fluoropyrimidin-2-yl)-3-methoxypropyl]-6-methyl-1-(2-methylpropanoyl)-N-[[4-(pyrimidin-2-yl)phenyl]methyl]piperazine-2-carboxamid (35-4);
- 5 (2R,6R)-4-[(1R)-3-methoxy-1-(pyrimidin-2-yl)propyl]-6-methyl-1-(2-methylpropanoyl)-N-[[4-(pyrimidin-2-yl)phenyl]methyl]piperazine-2-carboxamide (35-5);
- (2R,6R)-1-isobutyryl-4-((R)-3-methoxy-1-(2,4,6-trifluorophenyl)propyl)-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (36);
- (2R,6R)-4-((R)-1-(3,5-difluoropyridin-4-yl)-3-methoxypropyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (37);
- 10 (2R,6R)-4-((R)-1-(4-ethyl-3-fluoropyridin-2-yl)-3-methoxypropyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (38);
- (2R,6R)-4-((R)-1-(6-chloro-3-fluoropyridin-2-yl)-3-methoxypropyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (39);
- 15 (2R,6R)-4-((R)-1-(3-fluoro-5-methylpyridin-2-yl)-3-methoxypropyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (40);
- (2R,6R)-4-((R)-1-(3-fluoro-6-(prop-1-yn-1-yl)pyridin-2-yl)-3-methoxypropyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (41);
- (2R,6R)-4-((R)-1-(6-cyclopropyl-3-fluoropyridin-2-yl)-3-methoxypropyl)-1-isobutyryl-6-methyl-
- 20 N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (42);
- (2R,6R)-4-((R)-1-(6-ethyl-3-fluoropyridin-2-yl)-3-methoxypropyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (43);
- (2R,6R)-4-((R)-1-(3-fluoro-4,5-dimethylpyridin-2-yl)-3-methoxypropyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (44);
- 25 (2R,6R)-4-((R)-1-(4-cyclopropyl-3-fluoropyridin-2-yl)-3-methoxypropyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (45);
- (2R,6R)-4-((R)-1-(3-fluoro-4-(prop-1-yn-1-yl)pyridin-2-yl)-3-methoxypropyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (46);
- (2R,6R)-4-((R)-1-(5-fluoro-2-(prop-1-yn-1-yl)pyridin-4-yl)-3-methoxypropyl)-1-isobutyryl-6-
- 30 methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (47);
- (2R,6R)-4-((R)-1-(3,5-difluoro-2-methylpyridin-4-yl)-3-methoxypropyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (48);

- (2R,6R)-1-isobutyryl-4-((R)-3-methoxy-1-(pyrazin-2-yl)propyl)-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (49);
- (2R,6R)-4-((R)-1-(5-fluoro-2-methylpyrimidin-4-yl)-3-methoxypropyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (50);
- 5 (2R,6R)-1-isobutyryl-4-(3-methoxy-1-phenylpropyl)-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (51);
- (2R,6R)-4-(3-ethoxy-1-phenylpropyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (52);
- (2R,6R)-1-isobutyryl-4-((S)-(1-(methoxymethyl)cyclobutyl)(phenyl)methyl)-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (53);
- 10 (2R,6R)-1-isobutyryl-4-((1R)-3-methoxy-2-methyl-1-phenylpropyl)-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (54);
- (2R,6R)-4-((R)-1-(2,6-difluorophenyl)-3-methoxypropyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (55);
- 15 (2R,6R)-4-((R)-1-(2,6-difluorophenyl)-3-(methylthio)propyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (56);
- (2R,6R)-4-((1R)-1-(2,6-difluorophenyl)-3-(methylsulfinyl)propyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (57);
- (2R,6R)-4-((R)-1-(2,6-difluorophenyl)-3-(methylsulfonyl)propyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (58);
- 20 (2R,6R)-4-((R)-(2,6-difluorophenyl)(tetrahydro-2H-pyran-4-yl)methyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (59);
- (2R,6R)-4-((1S)-(2,6-difluorophenyl)(1,4-dioxan-2-yl)methyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (60);
- 25 (2R,6R)-4-((R)-3-cyano-1-(2,6-difluorophenyl)propyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (61);
- methyl 3-(2,6-difluorophenyl)-3-((3R,5R)-4-isobutyryl-3-methyl-5-((4-(pyrimidin-2-yl)benzyl)carbamoyl)piperazin-1-yl)propanoate (62);
- (2R,6R)-4-(2-fluoro-6-((1,1,1-trifluoropropan-2-yl)oxy)benzyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (63);
- 30 (2R,6R)-4-(2-(1-cyclopropyl-2,2,2-trifluoroethoxy)-6-fluorobenzyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (64);

- (2R,6R)-4-(2-fluoro-6-((1,1,1-trifluoro-3,3-dimethylbutan-2-yl)oxy)benzyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (65);
- (2R,6R)-4-(2-fluoro-6-((1,1,1-trifluorobutan-2-yl)oxy)benzyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (66);
- 5 (2R,6R)-4-(2-fluoro-6-((1,1,1-trifluoro-3-methylbutan-2-yl)oxy)benzyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (67);
- (2R,6R)-1-isobutyryl-6-methyl-4-(1-phenylpropyl)-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (68);
- (2R,6R)-4-((R)-3-hydroxy-1-phenylpropyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (69);
- 10 (2R,6R)-1-isobutyryl-6-methyl-4-((1R)-1-phenyl-2-(tetrahydrofuran-2-yl)ethyl)-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (70);
- (2R,6R)-4-((R)-3-(difluoromethoxy)-1-phenylpropyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (71);
- 15 (2R,6R)-1-isobutyryl-6-methyl-4-((R)-1-phenyl-3-(trifluoromethoxy)propyl)-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (72);
- (2R,6R)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)-4-((R)-4,4,4-trifluoro-1-phenylbutyl)piperazine-2-carboxamide (73);
- (2R,6R)-4-((1R)-1-(2,6-difluorophenyl)-2-(tetrahydrofuran-2-yl)ethyl)-1-isobutyryl-6-methyl-N-
- 20 (4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (74);
- (2R,6R)-4-((R)-1-(2,6-difluorophenyl)-3-hydroxypropyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (75);
- (2R,6R)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)-4-((1R)-4,4,4-trifluoro-3-hydroxy-3-methyl-1-phenylbutyl)piperazine-2-carboxamide (76);
- 25 (2R,6R)-4-((1R)-1-(2,6-difluorophenyl)-3-hydroxybutyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (77);
- (2R,6R)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)-4-((1R)-4,4,4-trifluoro-3-hydroxy-1-phenylbutyl)piperazine-2-carboxamide (78);
- 30 (2R,6R)-4-((R)-1-(2,6-difluorophenyl)-3-hydroxy-3-methylbutyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (79);
- (2R,6R)-4-((S)-1-(2,6-difluorophenyl)-2-hydroxyethyl)-1-isobutyryl-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (80);

- (2R,6R)-4-(2-((2-ethylpyridin-3-yl)oxy)-6-fluorobenzyl)-1-isobutyl-6-methyl-N-(4-(oxazol-2-yl)benzyl)piperazine-2-carboxamide (81);
1-acetyl-4-(2-(2-ethylphenoxy)-6-fluorobenzyl)-6-methyl-N-(4-(pyrimidin-2-yl)benzyl)piperazine-2-carboxamide (82);
- 5 (2R,6R)-4-(2-((2-ethylpyridin-3-yl)oxy)-6-fluorobenzyl)-1-isobutyl-6-methyl-N-(4-(pyridin-2-yl)benzyl)piperazine-2-carboxamide (83);
(2R,6R)-N-(4-(1,1-difluoroethoxy)benzyl)-4-(2-((2-ethylpyridin-3-yl)oxy)-6-fluorobenzyl)-1-isobutyl-6-methylpiperazine-2-carboxamide (84);
(2R,6R)-N-(4-(2H-1,2,3-triazol-2-yl)benzyl)-4-(2-((2-ethylpyridin-3-yl)oxy)-6-fluorobenzyl)-1-isobutyl-6-methylpiperazine-2-carboxamide (85); and
- 10 (2R,6R)-4-(2-((2-ethylpyridin-3-yl)oxy)-6-fluorobenzyl)-1-isobutyl-N-(4-(6-methoxypyridin-2-yl)benzyl)-6-methylpiperazine-2-carboxamide (86);
or a pharmaceutically acceptable salt thereof.
- 15 11. A pharmaceutical composition which comprises an inert carrier and a compound of any of Claims 1-10 or a pharmaceutically acceptable salt thereof.
- 20 12. A compound of any of Claims 1-10 or a pharmaceutically acceptable salt thereof for use in therapy.
13. A compound of any of Claims 1-10, or a pharmaceutically acceptable salt thereof, for use in the treatment or prevention of a sleep disorder.
- 25 14. A method for treating narcolepsy in a mammalian subject which comprises administering to the patient an effective amount of the compound of any of Claims 1-10 or a pharmaceutically acceptable salt thereof.
- 30 15. A method for treating hypersomnia in a mammalian subject which comprises administering to the patient an effective amount of the compound of any of Claims 1-10 or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 23/79457

A. CLASSIFICATION OF SUBJECT MATTER

IPC - INV. A61K 31/395, A61K 31/496, A61K 31/495 (2024.01)

ADD. A61K 31/33 (2024.01)

CPC - INV. A61K 31/395, A61K 31/496, A61K 31/495

ADD. A61K 31/33

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

See Search History document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2007/0142391 A1 (PAGE, et.al.) 21 June 2007 (21.06.2007) para [0413]	1-5; 10
A	US 2011/0183955 A1 (ECKL, et.al.) 28 July 2011 (28.07.2011) para [0119]	1-5; 10
A	US 2005/0277649 A1 (DEGRAFFENREID, et.al.) 15 December 2005 (15.12.2005) para [0186]; pg. 19	1-5; 10
A	CHENG, et.al. Design and Synthesis of Piperazine-based Matrix Metalloproteinase Inhibitors in Journal of Medicinal Chemistry, 2000, Vol. 43, pp. 369-380. pg. 371, Table 3	1-5; 10

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"D" document cited by the applicant in the international application

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

24 JANUARY 2024

Date of mailing of the international search report

MAR 13 2024

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 23/79457

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☒ Claims Nos.: 6-9; 11-15
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.