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(74) Agent: **DANIELSSON, Helena**; BIOVITRUM AB,
S-112 76 STOCKHOLM (SE).

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(71) Applicant (*for all designated States except US*): **BIOVITRUM AB** [SE/SE]; S-112 76 STOCKHOLM (SE).

(72) Inventors; and

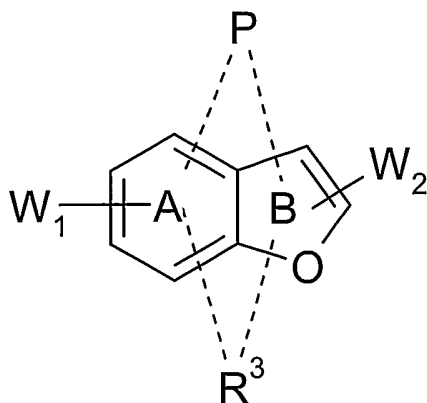
(75) Inventors/Applicants (*for US only*): **JOHANSSON, Gary** [SE/SE]; Albert Engströmsgatan 1, 2tr, S-754 30 UPPSALA (SE). **BRANDT, Peter** [SE/SE]; Barks väg 12, S-170 73 SOLNA (SE). **NILSSON, Björn M** [SE/SE]; Igeldammsvägen 20, 5tr, S-112 49 STOCKHOLM (SE).

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(54) Title: NOVEL BENZOFURAN DERIVATIVES, WHICH CAN BE USED IN PROPHYLAXIS OR TREATMENT OF 5-HT₆ RECEPTOR-RELATED DISORDER



(I)

(57) Abstract: The present invention relates to compounds of formula (I): wherein P, R³, W₁, and W₂ are as described herein, to pharmaceutical compositions comprising the compounds, to processes for their preparation, as well as to the use of the compounds for the preparation of a medicament against 5-HT₆ receptor-related disorders.

Novel benzofuran derivatives, which can be used in prophylaxis or treatment of 5-HT₆ receptor-related disorder

TECHNICAL FIELD

5 The present invention relates to novel compounds, to pharmaceutical compositions comprising the compounds, to processes for their preparation, as well as to the use of the compounds for the preparation of a medicament against 5-HT₆ receptor-related disorders.

BACKGROUND OF THE INVENTION

10

Obesity is a condition characterized by an increase in body fat content resulting in excess body weight above accepted norms. Obesity is the most important nutritional disorder in the western world and represents a major health problem in all industrialized countries. This disorder leads to increased mortality due to increased incidences of diseases
15 such as cardiovascular disease, digestive disease, respiratory disease, cancer and type 2 diabetes. Searching for compounds, which reduce body weight has been going on for many decades. One line of research has been activation of serotonergic systems, either by direct activation of serotonin receptor subtypes or by inhibiting serotonin reuptake. The exact receptor subtype profile required is however not known.

20 Serotonin (5-hydroxytryptamine or 5-HT), a key transmitter of the peripheral and central nervous system, modulates a wide range of physiological and pathological functions, including anxiety, sleep regulation, aggression, feeding and depression. Multiple serotonin receptor subtypes have been identified and cloned. One of these, the 5-HT₆ receptor, was cloned by several groups in 1993 (Ruat, M. et al. (1993) Biochem. Biophys. Res. Commun. 193: 268-276; Sebben, M. et al. (1994) NeuroReport 5: 2553-2557). This
25 receptor is positively coupled to adenylyl cyclase and displays affinity for antidepressants such as clozapine. Recently, the effect of 5-HT₆ antagonist and 5-HT₆ antisense oligonucleotides to reduce food intake in rats has been reported (Bentley, J.C. et al. (1999) Br J Pharmacol. Suppl. 126, P66; Bentley, J.C. et al. (1997) J. Psychopharmacol. Suppl. A64, 255; Woolley M.L. et al. (2001) Neuropharmacology 41: 210-219).
30

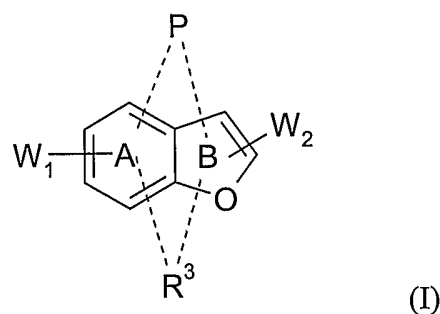
Compounds with enhanced affinity and selectivity for the 5-HT₆ receptor have been identified, e.g. in WO 00/34242 and by Isaac, M. et al. (2000) *6-Bicyclopiperazinyl-1-arylsulphonylindoles and 6-Bicyclopiperidinyl-1-arylsulphonylindoles derivatives as novel,*

potent and selective 5-HT₆ receptor antagonists. Bioorganic & Medicinal Chemistry Letters 10: 1719-1721 (2000), Bioorganic & Medicinal Chemistry Letters 13: 3355-3359 (2003), Expert Opinion Therapeutic Patents 12(4) 513-527 (2002).

It has surprisingly been found that the compounds according to the present invention show affinity for the 5-HT₆ receptor as antagonists at nanomolar range. Compounds according to the present invention and their pharmaceutically acceptable salts have 5-HT₆ receptor antagonist, agonist and partial agonist activity and are believed to be of potential use in the treatment or prophylaxis of obesity and type 2 diabetes, to achieve reduction of body weight and of body weight gain, as well as in the treatment or prophylaxis of disorders of the central nervous system such as anxiety, depression, panic attacks, memory disorders, cognitive disorders, epilepsy, sleep disorders, migraine, anorexia, bulimia, binge eating disorders, obsessive compulsive disorders, psychoses, Alzheimer's disease, Parkinson's disease, Huntington's chorea and/or schizophrenia, panic attacks, Attention Deficit Hyperactive Disorder (ADHD), withdrawal from drug abuse, neurodegenerative diseases characterized by impaired neuronal growth, and pain. The reduction of body weight and of body weight gain (e.g. treating body-weight disorders) is achieved *inter alia* by reduction of food intake. As used herein, the term "body weight disorders" refers to the disorders caused by an imbalance between energy intake and energy expenditure, resulting in abnormal (e.g., excessive) body weight. Such body weight disorders include obesity.

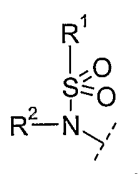
DISCLOSURE OF THE INVENTION

One object of the present invention is a compound of the Formula (I):

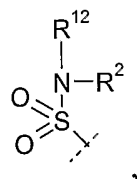


wherein:

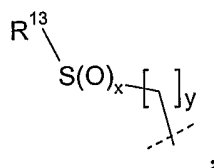
P is selected from a substituent of Formula (II)-(VII):



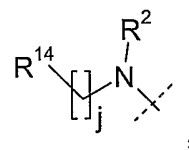
(II)



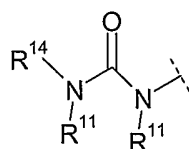
(III)



(IV)

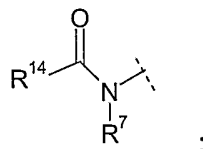


(V)



(VI)

or



(VII)

wherein:

x, y and j are each independently selected from 0, 1, and 2 ;

- wherein the dashed bonds denote that P and R³, respectively, may be attached to
 5 either the A or B ring at any carbon atom that allows the substitution, provided that P and
 R³ are not both simultaneously attached to ring B;

R¹ is selected from:

- (a) C₁₋₆-alkyl,
- (b) C₁₋₆-alkoxy-C₁₋₆-alkyl,
- 10 (c) C₃₋₆-alkenyl,
- (d) hydroxy-C₁₋₆-alkyl,
- (e) halo-C₁₋₆-alkyl,
- (f) aryl,
- (g) arylcarbonylmethyl,
- 15 (h) aryl-C₃₋₆-alkenyl,
- (i) aryl-C₁₋₆-alkyl,
- (j) C₃₋₇-cycloalkyl,
- (k) heteroaryl,
- (l) 4-piperidinyl,
- 20 (m) N-substituted 4-piperidinyl, wherein the substituents are selected from
 C₁₋₆-alkyl and aryl-C₁₋₆-alkyl,
- (o) heteroaryl-C₁₋₆-alkyl,

wherein any heteroaryl or aryl residue, alone or as part of another group may be
 substituted, independently, in one or more positions with a substituent selected from:

- 25 (a) hydrogen,

- (b) halogen,
 (c) C₁₋₆-alkyl,
 (d) hydroxy,
 (e) C₁₋₆-alkoxy,
 5 (f) C₂₋₆-alkenyl,
 (g) C₂₋₃-alkynyl,
 (h) phenyl,
 (i) phenoxy,
 (j) benzyloxy,
 10 (k) benzoyl,
 (l) benzyl,
 (m) -OCF₃,
 (n) -CN,
 (o) hydroxy-C₁₋₆-alkyl,
 15 (p) C₁₋₆-alkoxy-C₁₋₆-alkyl,
 (q) halo-C₁₋₆-alkyl,
 (r) -NR⁹R⁹,
 (s) -NO₂,
 (t) -CONR⁹R⁹,
 20 (u) -NR⁷COR¹⁰,
 (v) -C(=O)R¹⁰,
 (x) C₁₋₆-alkoxycarbonyl,
 (y) C₁₋₆-alkylthio,
 (z) -SCF₃,
 25 (aa) -CHF=CH₂,
 (ab) methylsulfonyl, or
 (ac) -COOH

with the proviso that when the substituent on the said aryl or heteroaryl residue is selected from phenyl, phenoxy, benzyloxy, benzoyl and benzyl, the phenyl ring thereof
 30 may be optionally substituted by one or more of halogen, C₁₋₄-alkyl, C₁₋₄-alkylthio, C₁₋₄-alkoxy, cyano, or trifluoromethyl;

R² is selected from:

- (a) hydrogen,

- (b) C₁₋₆-alkyl,
 (c) C₁₋₆-alkoxy-C₂₋₆ alkyl,
 (d) hydroxy-C₂₋₆ -alkyl,
 (e) -(CH₂)_m-CH₂-F, wherein m is 2-4,
 5 (f) 3,3,3-trifluoropropyl, or
 (g) C₁₋₄-alkylsulfonyl, provided that P is selected from a substituent of
 formula (V);

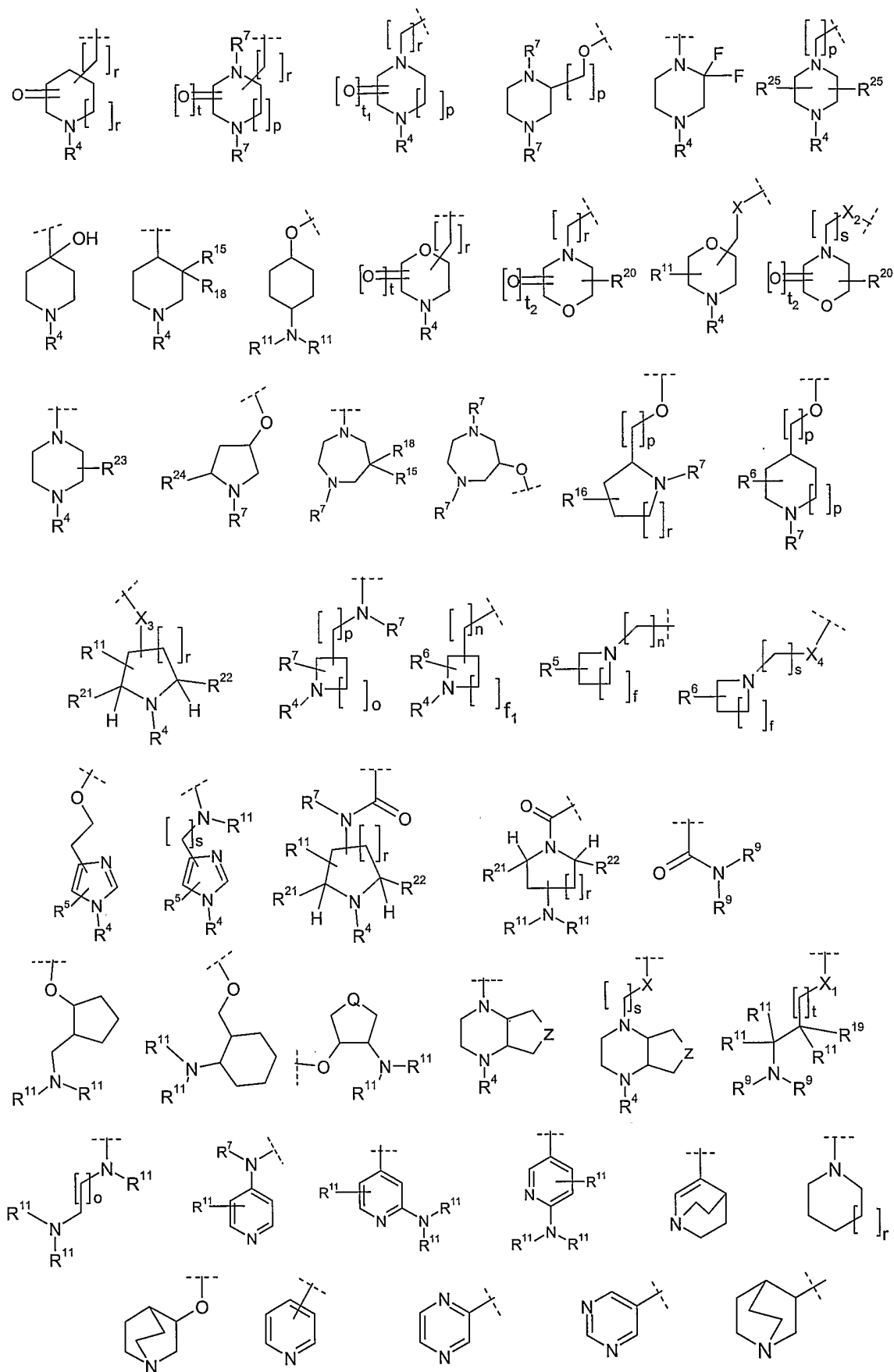
W₁ and W₂ are each independently selected from:

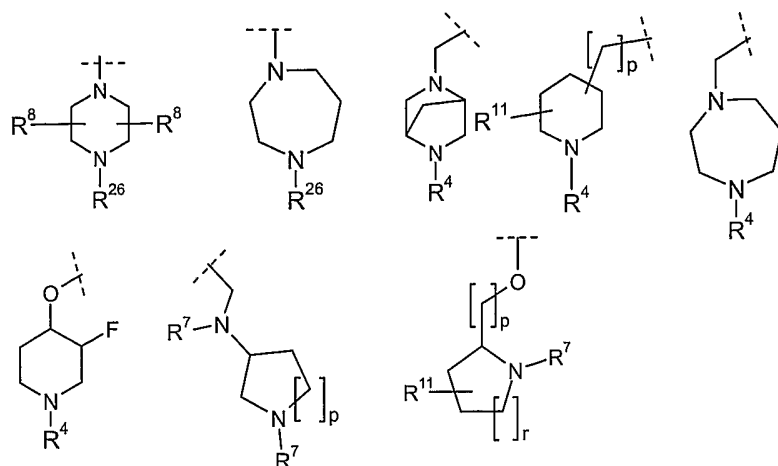
- (a) hydrogen,
 10 (b) halogen,
 (c) C₁₋₆-alkyl,
 (d) hydroxy,
 (e) C₁₋₆-alkoxy,
 (f) C₁₋₆-alkylthio,
 15 (g) C₂₋₆-alkenyl,
 (h) phenyl,
 (i) phenoxy,
 (j) benzyloxy,
 (k) benzoyl,
 20 (l) benzyl,
 (m) -OCF₃,
 (n) -CN,
 (o) hydroxy-C₁₋₆-alkyl,
 (p) C₁₋₆-alkoxy-C₁₋₆-alkyl,
 25 (q) halo-C₁₋₆-alkyl,
 (r) -CONR⁹R⁹,
 (s) -C(=O)R¹⁰,
 (t) C₁₋₆-alkoxycarbonyl,
 (u) -SCF₃, or
 30 (v) -CHF=CH₂,

with the proviso that when W₁ and W₂ are selected from phenyl, phenoxy, benzoyl, benzyloxy and benzyl, the phenyl ring thereof may be optionally substituted by one or more of halogen, C₁₋₄-alkyl, C₁₋₄-alkoxy, cyano, or trifluoromethyl, and with the further

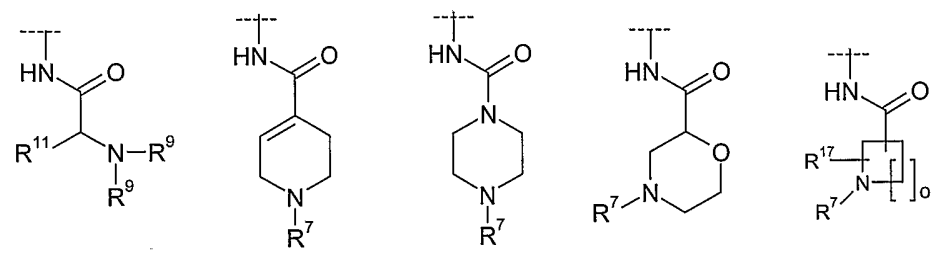
proviso that, when W_1 and W_2 are not selected from methoxy, methyl and halogen, at least one of W_1 and W_2 is selected from hydrogen;

R^3 is H when P is a substituent of Formula (II) wherein R^1 is N-substituted 4-piperidiny1, or R^3 is a group selected from:

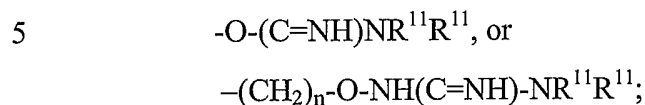




R^3 may also be a group selected from:



and further from a group selected from



wherein

$n = 0, 1, 2$ or 3

r is each independently $0, 1$ or 2 ,

10 $o = 1, 2$, or 3 ,

p is each independently 1 or 2 ,

$s = 2$ or 3 ,

$t = 0$ or 1 ,

$t_1 = 1$ or 2 ,

15 $t_2 = 0$ or 1 ,

$f = 1, 2, 3$ or 4 , and

$f_1 = 1, 2$ or 4 ;

with the proviso that when t_1 and p simultaneously are 1 , r is not 0 ;

X is selected from O , NR^7 and S ;

20 X_1 is selected from NR^7 and S ;

X_2 is selected from O, NR^7 and S, provided that X_2 is selected from NR^7 and S when $t_2 = 0$;

X_3 is selected from NR^7 and S, provided that X_3 is selected from S when $r = 1$;

X_4 is selected from O, NR^7 and S, provided that X_4 is selected from S and NR^7 when

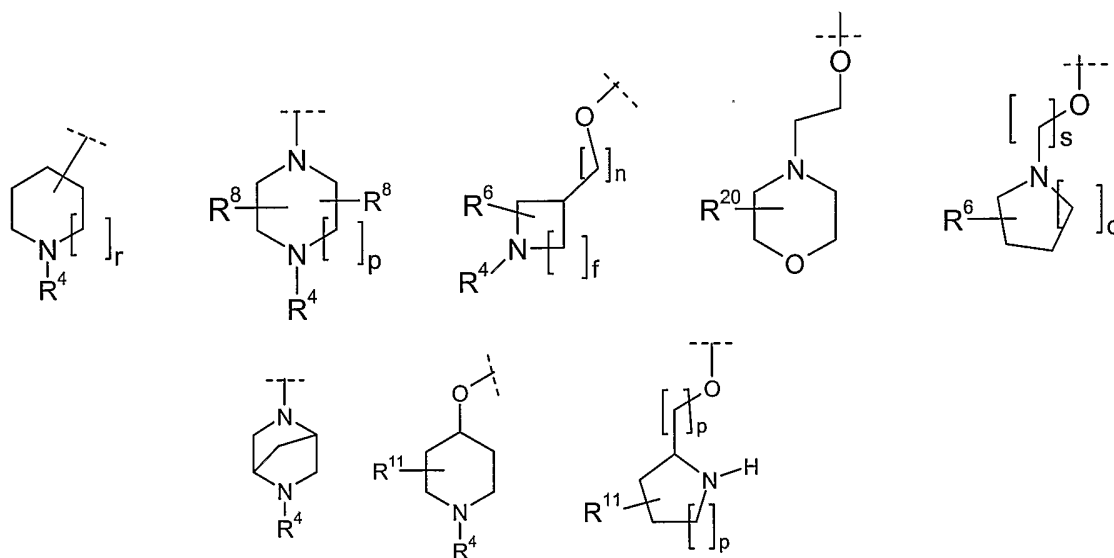
5 f is selected from 2, 3, and 4;

Q is selected from CH_2 , SO_2 and oxygen, provided that when Q is SO_2 or oxygen, p is 1;

Z is selected from SO_2 and oxygen;

when P is a group selected from a substituent of Formula (V) – (VII), R^3 is

10 additionally selected from the following groups:



wherein:

$n = 0, 1, 2$ or 3

15 $r = 0, 1$ or 2,

$o = 1, 2$, or 3,

$p = 1$ or 2,

$s = 2$ or 3, and

$f = 1, 2, 3$ or 4;

20 R^4 is a group selected from:

(a) hydrogen,

(b) C_{1-6} -alkyl,

(c) 2-cyanoethyl,

(d) hydroxy- C_{2-6} -alkyl,

25 (e) C_{3-6} -alkenyl,

- 5 (f) C₃₋₆-alkynyl,
 (g) C₃₋₇-cycloalkyl,
 (h) C₃₋₇-cycloalkyl-C₁₋₄-alkyl,
 (i) C₁₋₆-alkoxy-C₂₋₆-alkyl
 (j) -C(=NH)-N-R¹¹R¹¹,
 (k) -C(=O)-N-R¹¹R¹¹,
 (l) -CH₂-CO-N-R¹¹R¹¹, or
 (m) 3,3,3-trifluoropropyl;

R⁵ is selected from:

- 10 (a) hydrogen,
 (b) C₁₋₄-alkyl,
 (c) hydroxy-C₁₋₄-alkyl,
 (d) C₁₋₄-alkoxymethyl,
 (e) halo-C₁₋₄-alkyl,
 15 (f) -NR¹¹R¹¹,
 (g) -CO-NR¹¹R¹¹,
 (h) hydroxy, provided that the said hydroxy group is not attached to a carbon atom adjacent to a ring nitrogen atom, or

- (i) fluorine, provided that the said fluorine atom is not attached to a carbon atom adjacent to a ring nitrogen atom;

R⁶ is selected from:

- (a) hydrogen,
 (b) C₁₋₄-alkyl,
 (c) hydroxy-C₁₋₄-alkyl,
 25 (d) C₁₋₄-alkoxy-C₁₋₄-alkyl,
 (e) hydroxy, provided that the said hydroxy group is not attached to a carbon atom adjacent to a heterocyclic ring nitrogen atom, and further provided that the said heterocyclic ring is not substituted with oxo,
 (f) fluorine, provided that the said fluorine atom is not attached to a carbon atom adjacent to a ring nitrogen atom, or
 30 (g) halo-C₁₋₄-alkyl;

R⁷ is each independently selected from:

- (a) hydrogen, provided that R⁷ is not hydrogen when present simultaneously with r and said r is 1 or 2,

- (b) C₁₋₄-alkyl,
- (c) hydroxy-C₂₋₄-alkyl, or
- (d) methoxy-C₂₋₄-alkyl;

R⁸ is each independently selected from:

- 5 (a) hydrogen, or
 (b) C₁₋₄-alkyl, and

when both R⁸ simultaneously are selected from C₁₋₄-alkyl, said C₁₋₄-alkyls may be attached to the same or different carbon atoms, or when two groups are present at the same carbon atom they may together form a cyclopropane ring;

10 R⁹ is each independently selected from:

- (a) hydrogen,
- (b) C₁₋₆-alkyl
- (c) C₃₋₇-cycloalkyl, or

wherein the two R⁹ groups together with the nitrogen to which they are attached
15 form a heterocyclic ring; and provided that when the two R⁹ groups form a piperazine ring, the nitrogen of the said piperazine ring that allows the substitution is substituted with C₁₋₄-alkyl, and further provided that when the two R⁹ groups form a piperidine ring, any ring carbon atom in the said piperidine ring may be optionally substituted with methyl;

R¹⁰ is selected from:

- 20 (a) C₁₋₆-alkyl,
 (c) aryl, or
 (d) heteroaryl,

wherein heteroaryl or aryl may be substituted in one or more positions with substituents selected from halogen, C₁₋₄-alkyl, C₁₋₄-alkoxy, cyano, trifluoromethyl;

25 R¹¹ is each independently selected from:

- (a) hydrogen,
- (b) methyl, or
- (c) ethyl, provided that R¹¹ is present in a group R⁴ or R²⁶ selected from
-CH₂-CO-N-R¹¹R¹¹;

30 R¹² is selected from:

- (a) hydrogen,
- (b) C₁₋₆-alkyl,
- (c) aryl,
- (d) aryl-C₁₋₆-alkyl,

- (e) C₃₋₇-cycloalkyl,
- (f) C₃₋₇-cycloalkyl-C₁₋₄-alkyl,
- (g) heteroaryl, or
- (h) heteroaryl-C₁₋₆-alkyl,

5 wherein any heteroaryl or aryl residue, alone or as part of another group, is optionally substituted, independently, in one or more positions with substituents selected from:

- (a) hydrogen,
- (b) halogen,
- (c) C₁₋₆-alkyl,
- 10 (d) hydroxy,
- (e) C₁₋₆-alkoxy,
- (f) C₂₋₆-alkenyl,
- (g) C₂₋₆-alkynyl,
- (h) phenyl,
- 15 (i) phenoxy,
- (j) benzyloxy,
- (k) benzoyl,
- (l) benzyl,
- (m) -OCF₃,
- 20 (n) -CN,
- (o) hydroxy-C₁₋₆-alkyl,
- (p) C₁₋₆-alkoxy-C₁₋₆-alkyl,
- (q) halo-C₁₋₆-alkyl,
- (r) -NR⁹R⁹,
- 25 (s) -NO₂,
- (t) -CONR⁹R⁹,
- (u) -NR⁷COR¹⁰,
- (v) -C(=O)R¹⁰,
- (x) C₁₋₆-alkoxycarbonyl,
- 30 (y) C₁₋₆-alkylthio,
- (z) -SCF₃,
- (aa) -CHF=CH₂,
- (ab) methylsulfonyl, or

(ac) -COOH;

with the proviso that when the substituent on the said aryl or heteroaryl residue is selected from phenyl, phenoxy, benzyloxy, benzoyl, and benzyl, the phenyl ring thereof may be optionally substituted by one or more of halogen, C₁₋₄-alkyl, C₁₋₄-alkoxy, cyano, or trifluoromethyl;

R¹³ is selected from:

- (a) C₁₋₆-alkyl,
- (b) C₃₋₆-cycloalkyl,
- (c) aryl,
- (d) heteroaryl,
- (e) aryl-C₁₋₂-alkyl, or
- (f) heteroaryl-C₁₋₂-alkyl,

wherein any heteroaryl or aryl residue may be substituted in one or more positions with substituents selected from halogen, C₁₋₄-alkyl, C₁₋₄-alkoxy, cyano, trifluoromethyl, and acetyl;

R¹⁴ is selected from:

- (a) aryl,
- (b) heteroaryl,
- (c) aryl-C₁₋₃-alkyl, or
- (d) heteroaryl-C₁₋₃-alkyl,

wherein any heteroaryl or aryl residue may be substituted in one or more positions with substituents selected from halogen, C₁₋₄-alkyl, C₁₋₄-alkoxy, cyano, and trifluoromethyl;

R¹⁵ is selected from:

- (a) fluorine, or
- (b) hydroxy;

R¹⁶ is selected from:

- (a) hydrogen, provided that r = 0,
- (b) amino,
- (c) dimethylamino,
- (d) F, or
- (e) OH;

R¹⁷ is selected from:

- (a) hydrogen,

(b) C₁₋₄-alkyl,

(c) hydroxy, provided that the said hydroxy group is not attached to a carbon atom adjacent to a ring nitrogen atom;

R¹⁸ is selected from:

5 (a) hydrogen, or

(b) fluorine;

R¹⁹ is selected from:

(a) hydrogen,

(b) methyl,

10 (c) trifluoromethyl, or

(d) C₁₋₂-alkoxymethyl;

and provided that at least one of R¹⁹ and R¹¹, when present simultaneously, is selected from a non-hydrogen substituent, and further provided that when R¹⁹ is selected from trifluoromethyl or C₁₋₂-alkoxymethyl, each R¹¹ is selected from hydrogen;

15 R²⁰ is selected from:

(a) hydrogen,

(b) C₁₋₄-alkyl,

(c) hydroxy-C₁₋₄-alkyl,

(d) C₁₋₄-alkoxy-C₁₋₄-alkyl, or

20 (e) fluoromethyl;

with the proviso that when t₂ is 1, R²⁰ is H;

R²¹ and R²² are each independently selected from:

(a) hydrogen, or

(b) methyl,

25 provided that, when present at the same time as R¹¹, at least two of R¹¹, R²¹ and R²² are selected from hydrogen;

R²³ is selected from:

(a) hydroxy-C₁₋₄-alkyl,

(b) C₁₋₄-alkoxymethyl,

30 (c) halo-C₁₋₄-alkyl, or

(d) -CO-NR¹¹R¹¹, provided that R⁴ is not selected from -C(=NH)-N-R¹¹R¹¹, -C(=O)-N-R¹¹R¹¹, and -CH₂-CO-N-R¹¹R¹¹

;

R²⁴ is selected from:

- (a) hydroxymethyl,
- (b) methoxymethyl, or
- (c) fluoromethyl;

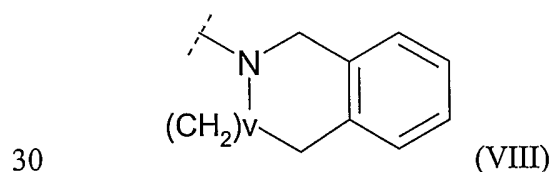
R^{25} is each independently selected from

- 5 (a) hydrogen,
 - (b) C_{1-4} -alkyl,
 - (c) hydroxy- C_{1-4} -alkyl,
 - (d) C_{1-4} -alkoxy- C_{1-4} -alkyl, or
 - (e) fluoromethyl;
- 10 with the proviso that when both R^{25} simultaneously are selected from C_{1-4} -alkyl, said C_{1-4} -alkyls may be attached to the same or different carbon atoms, and with the further proviso that when one R^{25} is selected from hydroxy- C_{1-4} -alkyl, C_{1-4} -alkoxy- C_{1-4} -alkyl, and fluoromethyl, the other R^{25} represents hydrogen; and

R^{26} is selected from

- 15 (a) 2-cyanoethyl,
- (b) C_{3-6} -alkenyl,
- (c) C_{3-6} -alkynyl,
- (d) C_{3-7} -cycloalkyl,
- (e) C_{3-7} -cycloalkyl- C_{1-4} -alkyl,
- 20 (f) $-\text{CH}_2\text{-CO-NR}^{11}\text{R}^{11}$, or
- (g) 3,3,3-trifluoropropyl;

- with the proviso that R^2 and R^{12} in Formula (III) are not simultaneously selected from hydrogen; and with the further proviso that the said R^2 and R^{12} together may form a heterocyclic ring selected from piperidine, pyrrolidine, morpholine, piperazine
- 25 thiomorpholine, and provided that when R^2 and R^{12} together form a piperazine ring, the distal piperazine nitrogen may be optionally substituted by C_{1-4} alkyl or aryl, and wherein said aryl is substituted in one or more positions with substituents selected from halogen, C_{1-4} -alkyl, C_{1-4} -alkoxy, cyano, trifluoromethyl; or R^2 and R^{12} together form a heteroaromatic ring of Formula (VIII):

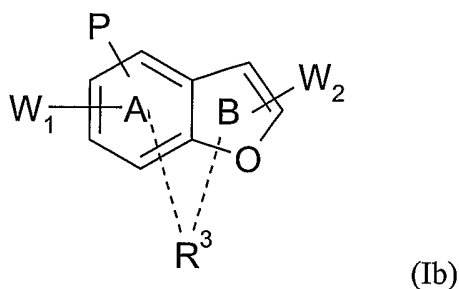


wherein v is 0, 1 or 2; and

further provided that when R^{15} is selected from hydroxy, R^{18} is selected from hydrogen; and

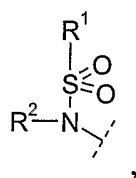
pharmaceutically acceptable salts, hydrates, solvates, geometrical isomers, tautomers, optical isomers, and prodrug forms thereof.

5 Preferred is a compound of the Formula (Ib):

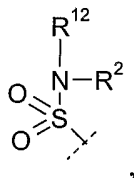


wherein:

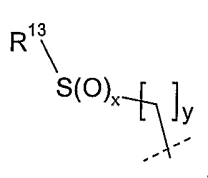
P is selected from a substituent of Formula (II)-(VII):



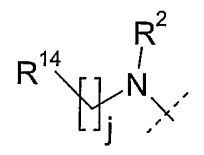
(II)



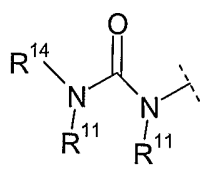
(III)



(IV)

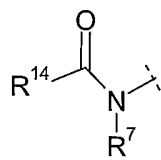


(V)



(VI)

or



(VII)

10 wherein:

x, y and j are each independently selected from 0, 1, and 2 ;

wherein the dashed bonds denote that R^3 may be attached to either the A or B ring at any carbon atom that allows the substitution;

R^1 is selected from:

- 15 (a) C_{1-6} -alkyl,
 (b) C_{1-6} -alkoxy- C_{2-6} -alkyl,
 (c) C_{3-6} -alkenyl,
 (d) hydroxy- C_{2-6} -alkyl,
 (e) halo- C_{1-6} -alkyl,
 20 (f) aryl,

- (g) arylcarbonylmethyl,
(h) aryl-C₃₋₆-alkenyl,
(i) aryl-C₁₋₆-alkyl,
(j) C₃₋₇-cycloalkyl,
5 (k) heteroaryl,
(o) heteroaryl-C₁₋₆-alkyl,

wherein any heteroaryl or aryl residue, alone or as part of another group may be optionally substituted, independently, in one or more positions with a substituent selected from

- 10 (b) halogen,
(c) C₁₋₆-alkyl,
(d) hydroxy,
(e) C₁₋₆-alkoxy,
(f) C₂₋₆-alkenyl,
15 (g) C₂₋₃-alkynyl,
(h) phenyl,
(i) phenoxy,
(j) benzyloxy,
(k) benzoyl,
20 (l) benzyl,
(m) -OCF₃,
(n) -CN,
(o) hydroxy-C₁₋₆-alkyl,
(p) C₁₋₆-alkoxy-C₁₋₆-alkyl,
25 (q) halo-C₁₋₆-alkyl,
(r) -NR⁹R⁹,
(s) -NO₂,
(t) -CONR⁹R⁹,
(u) -NR⁷COR¹⁰,
30 (v) -C(=O)R¹⁰,
(x) C₁₋₆-alkoxycarbonyl,
(y) C₁₋₆-alkylthio,
(z) -SCF₃,

- (aa) $-\text{CHF}=\text{CH}_2$,
- (ab) methylsulfonyl, or
- (ac) $-\text{COOH}$,

5 with the proviso that when the substituent on the said aryl or heteroaryl residue is selected from phenyl, phenoxy, benzyloxy, benzoyl and benzyl, the phenyl ring thereof may be optionally substituted by one or more of halogen, C_{1-4} -alkyl, C_{1-4} -alkylthio, C_{1-4} -alkoxy, cyano, or trifluoromethyl;

R^2 is selected from:

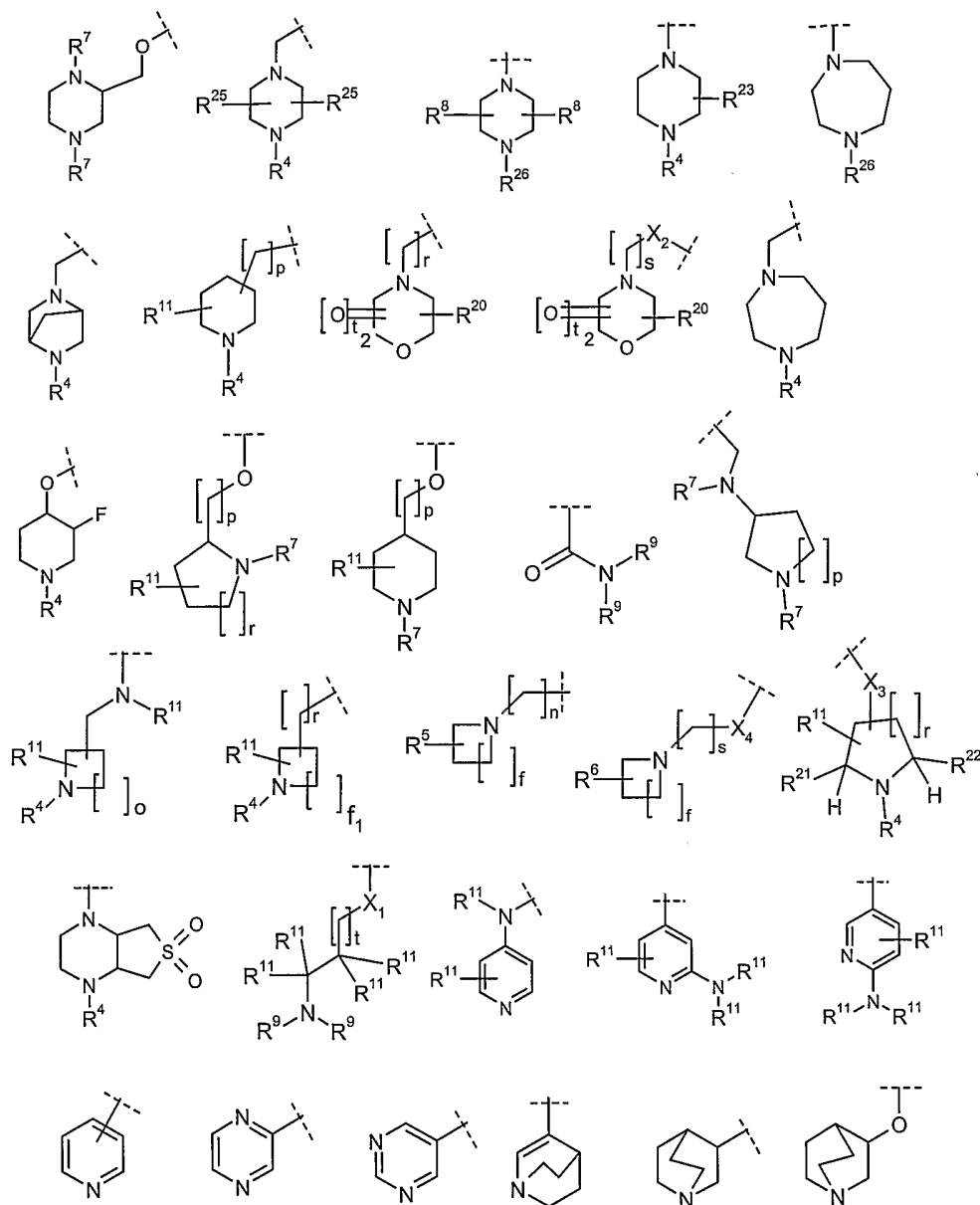
- (a) hydrogen,
- 10 (b) C_{1-6} -alkyl,
- (c) C_{1-6} -alkoxy- C_{2-6} alkyl,
- (d) hydroxy- C_{2-6} -alkyl,
- (e) $-(\text{CH}_2)_m-\text{CH}_2-\text{F}$, wherein m is 2-4, or
- (g) C_{1-4} -alkylsulfonyl, provided that P is selected from a substituent of
- 15 formula (V);

W_1 and W_2 are each independently selected from:

- (a) hydrogen,
- (b) halogen,
- (c) C_{1-6} -alkyl,
- 20 (d) hydroxy,
- (e) C_{1-6} -alkoxy,
- (f) C_{1-6} -alkylthio,
- (g) C_{2-6} -alkenyl,
- (m) $-\text{OCF}_3$,
- 25 (n) $-\text{CN}$,
- (o) hydroxy- C_{1-6} -alkyl,
- (p) C_{1-6} -alkoxy- C_{1-6} -alkyl,
- (q) halo- C_{1-6} -alkyl,
- (r) $-\text{CONR}^9\text{R}^9$,
- 30 (s) $-\text{C}(=\text{O})\text{R}^{10}$,
- (t) C_{1-6} -alkoxycarbonyl,
- (u) $-\text{SCF}_3$, or
- (v) $-\text{CHF}=\text{CH}_2$,

with the proviso that when W_1 and W_2 are not selected from hydroxy, methoxy, methyl and halogen, at least one of W_1 and W_2 is selected from hydrogen;

R^3 is a group selected from:



5 wherein

$n = 0, 1, 2$ or 3 ,

$r = 0, 1$ or 2 ,

$o = 1, 2$ or 3 ,

$p = 1$ or 2 ,

10 $s = 2$ or 3 ,

$t = 0$ or 1 ,

$t_2 = 0$ or 1 ,

$f = 1, 2, 3$ or 4 , and

$f_1 = 1, 2$ or 4 ;

X_1 is selected from NR^7 and S ;

X_2 is selected from O , NR^7 and S , provided that when $t_2 = 0$ and $s = 2$ then X_2 is

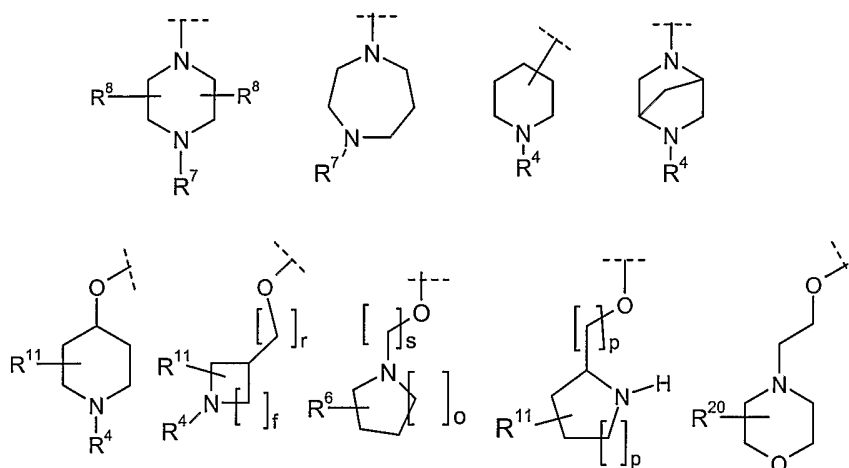
5 selected from NR^7 and S ;

X_3 is selected from NR^7 and S , provided that X_3 is selected from S when $r = 1$;

X_4 is selected from O , NR^7 and S , provided that X_4 is selected from S and NR^7 when f is selected from 2 and 3 , and R^6 simultaneously is selected from hydrogen and C_{1-4} alkyl;

when P is a group selected from a substituent of Formula (V) – (VII), R^3 is

10 additionally selected from the following groups:



wherein:

$r = 0, 1$ or 2 ,

$o = 1, 2$ or 3 ,

15 p is each independently 1 or 2 ,

$s = 2$ or 3 , and

$f = 1, 2, 3$ or 4 ;

R^4 is selected from:

(a) hydrogen,

20 (b) C_{1-6} -alkyl,

(c) 2-cyanoethyl,

(d) hydroxy- C_{2-6} -alkyl,

(e) C_{3-6} -alkenyl,

(f) C_{3-6} -alkynyl,

25 (g) C_{3-7} -cycloalkyl,

(h) C₃₋₇-cycloalkyl-C₁₋₄-alkyl,

(i) C₁₋₆-alkoxy-C₂₋₆-alkyl

(l) -CH₂-CO-N-R¹¹R¹¹, or

(m) 3,3,3-trifluoropropyl;

5 R⁵ is selected from:

(a) hydrogen,

(b) C₁₋₄-alkyl,

(c) hydroxy-C₁₋₄-alkyl,

(d) C₁₋₄-alkoxymethyl,

10 (e) halo-C₁₋₄-alkyl,

(f) -NR¹¹R¹¹,

(h) hydroxy, provided that the said hydroxy group is not attached to a carbon atom adjacent to a ring nitrogen atom, or

(i) fluorine, provided that the said fluorine atom is not attached to a carbon atom adjacent to a ring nitrogen atom;

15

R⁶ is selected from:

(a) hydrogen,

(b) C₁₋₄-alkyl,

(c) hydroxy-C₁₋₄-alkyl,

20 (d) C₁₋₄-alkoxy-C₁₋₄-alkyl,

(e) hydroxy, provided that the said hydroxy group is not attached to a carbon atom adjacent to a heterocyclic ring nitrogen atom,

(f) fluorine, provided that the said fluorine atom is not attached to a carbon atom adjacent to a ring nitrogen atom, or

25 (g) halo-C₁₋₄-alkyl;

R⁷ is each independently selected from:

(a) hydrogen, provided that R⁷ is not hydrogen when present simultaneously with r and said r is 1 or 2,

(b) C₁₋₄-alkyl,

30 (c) hydroxy-C₂₋₄-alkyl, or

(d) methoxy-C₂₋₄-alkyl;

R⁸ is each independently selected from:

(a) hydrogen, or

(b) C₁₋₄-alkyl, with the proviso that when both R⁸ simultaneously are selected from C₁₋₄-alkyl, said C₁₋₄-alkyl may be attached to the same or different carbon atoms, or when two groups are present at the same carbon atom they may together form a cyclopropane ring;

5 R⁹ is each independently selected from:

- (a) hydrogen,
- (b) C₁₋₆-alkyl
- (c) C₃₋₇-cycloalkyl, or

10 the two R⁹ groups together with the nitrogen to which they are attached form a heterocyclic ring; and provided that when the two R⁹ groups form a piperazine ring, the nitrogen of the said piperazine ring that allows the substitution may be optionally substituted with C₁₋₄-alkyl; and further provided that when the two R⁹ groups form a piperidine ring, any ring carbon atom in the said piperidine ring may be optionally substituted with methyl;

15 R¹⁰ is selected from:

- (a) C₁₋₆-alkyl,
- (c) aryl, or
- (d) heteroaryl,

20 wherein heteroaryl or aryl may be optionally substituted in one or more positions with substituents selected from halogen, C₁₋₄-alkyl, C₁₋₄-alkoxy, cyano, trifluoromethyl;

R¹¹ is each independently selected from:

- (a) hydrogen,
- (b) methyl, or
- (c) ethyl, provided that R¹¹ is present in a group R⁴ or R²⁶ selected from -CH₂-CO-N-R¹¹R¹¹;

25 R¹² is selected from:

- (a) hydrogen,
- (b) C₁₋₆-alkyl,
- (c) aryl,
- 30 (d) aryl-C₁₋₆-alkyl,
- (e) C₃₋₇-cycloalkyl,
- (f) C₃₋₇-cycloalkyl-C₁₋₄-alkyl,
- (g) heteroaryl, or
- (h) heteroaryl-C₁₋₆-alkyl,

wherein any heteroaryl or aryl residue, alone or as part of another group, may be optionally substituted, independently, in one or more positions with substituents selected from:

- (b) halogen,
- 5 (c) C₁₋₆-alkyl,
- (d) hydroxy,
- (e) C₁₋₆-alkoxy,
- (f) C₂₋₆-alkenyl,
- (g) C₂₋₃-alkynyl,
- 10 (h) phenyl,
- (i) phenoxy,
- (j) benzyloxy,
- (k) benzoyl,
- (l) benzyl,
- 15 (m) -OCF₃,
- (n) -CN,
- (o) hydroxy-C₁₋₆-alkyl,
- (p) C₁₋₆-alkoxy-C₁₋₆-alkyl,
- (q) halo-C₁₋₆-alkyl,
- 20 (r) -NR⁹R⁹,
- (s) -NO₂,
- (t) -CONR⁹R⁹,
- (u) -NR⁷COR¹⁰,
- (v) -C(=O)R¹⁰,
- 25 (x) C₁₋₆-alkoxycarbonyl,
- (y) C₁₋₆-alkylthio,
- (z) -SCF₃,
- (aa) -CHF=CH₂,
- (ab) methylsulfonyl, or
- 30 (ac) -COOH,

with the proviso that when the substituent on the said aryl or heteroaryl residue is selected from phenyl, phenoxy, benzyloxy, benzoyl, and benzyl, the phenyl ring thereof

may be optionally substituted by one or more of halogen, C₁₋₄-alkyl, C₁₋₄-alkoxy, cyano, or trifluoromethyl;

R¹³ is selected from:

- (a) C₁₋₆-alkyl,
- 5 (b) C₃₋₆-cycloalkyl,
- (c) aryl,
- (d) heteroaryl,
- (e) aryl-C₁₋₂-alkyl, or
- (f) heteroaryl-C₁₋₂-alkyl,

10 wherein any heteroaryl or aryl residue may be optionally substituted in one or more positions with substituents selected from halogen, C₁₋₄-alkyl, C₁₋₄-alkoxy, cyano, trifluoromethyl, and acetyl;

R¹⁴ is selected from:

- (a) aryl,
- 15 (b) heteroaryl,
- (c) aryl-C₁₋₃-alkyl, or
- (d) heteroaryl-C₁₋₃-alkyl,

wherein any heteroaryl or aryl residue may be substituted in one or more positions with substituents selected from halogen, C₁₋₄-alkyl, C₁₋₄-alkoxy, cyano, and
20 trifluoromethyl;

R²⁰ is each independently selected from:

- (a) hydrogen,
- (b) methyl,

with the proviso that when t₂ is 1, R²⁰ is H;

25 R²¹ and R²² are each independently selected from:

- (a) hydrogen, or
- (b) methyl,

provided that, when present simultaneously with R¹¹, at least two of R¹¹, R²¹ and R²² are selected from hydrogen;

30 R²³ is selected from:

- (a) hydroxy-C₁₋₄-alkyl,
- (b) C₁₋₄-alkoxymethyl, or
- (c) halo-C₁₋₄-alkyl;

R²⁵ is each independently selected from:

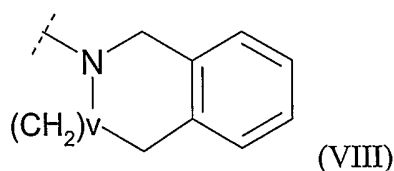
- (a) hydrogen,
- (b) C₁₋₄-alkyl,
- (c) hydroxy-C₁₋₄-alkyl,
- (d) C₁₋₄-alkoxy-C₁₋₄-alkyl, or
- 5 e) fluoromethyl,

with the proviso that when both R²⁵ simultaneously are selected from C₁₋₄-alkyl, said C₁₋₄-alkyl may be attached to the same or different carbon atoms, and with the further proviso that when one R²⁵ is selected from hydroxy-C₁₋₄-alkyl, C₁₋₄-alkoxy-C₁₋₄-alkyl, and fluoromethyl, the other R²⁵ represents hydrogen;

10 R²⁶ is selected from:

- (a) 2-cyanoethyl,
- (b) C₃₋₆-alkenyl,
- (c) C₃₋₆-alkynyl,
- (d) C₃₋₇-cycloalkyl,
- 15 (e) C₃₋₇-cycloalkyl-C₁₋₄-alkyl,
- (f) -CH₂-CO-NR¹¹R¹¹, or
- (g) 3,3,3-trifluoropropyl;

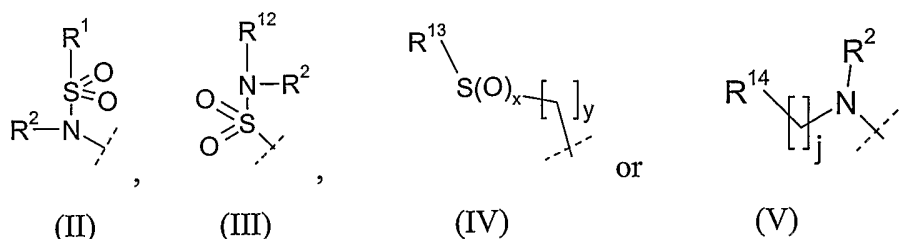
with the proviso that R² and R¹² in Formula (III) are not simultaneously selected from hydrogen; and with the further proviso that the said R² and R¹² together may form a
 20 heterocyclic ring selected from piperidine, pyrrolidine, morpholine, piperazine, thiomorpholine, and provided that when R² and R¹² together form a piperazine ring, the distal piperazine nitrogen may be optionally substituted by C₁₋₄ alkyl or aryl, and wherein said aryl may be optionally substituted in one or more positions with substituents selected from halogen, C₁₋₄-alkyl, C₁₋₄-alkoxy, cyano, trifluoromethyl; or R² and R¹² together form
 25 a heteroaromatic ring of Formula (VIII):



wherein v is 0 or 1.

It is further preferred that:

P is selected from a substituent of Formula (II)-(V)



wherein x is 2, y is 0 and j is 1;

R^1 is selected from:

- (f) aryl,
- (i) aryl- C_{1-3} -alkyl,
- (k) heteroaryl,
- (o) heteroaryl- C_{1-3} -alkyl,

wherein any heteroaryl or aryl residue, alone or as part of another group may be optionally substituted, independently, in one or more positions with a substituent selected from:

- (b) halogen,
- (c) C_{1-4} -alkyl,
- (d) hydroxy,
- (e) C_{1-4} -alkoxy,
- (m) $-\text{OCF}_3$,
- (n) $-\text{CN}$,
- (o) hydroxy- C_{1-4} -alkyl,
- (p) C_{1-2} -alkoxy- C_{1-2} -alkyl,
- (q) halo- C_{1-3} -alkyl,
- (r) $-\text{NR}^9\text{R}^9$,
- (t) $-\text{CONR}^9\text{R}^9$,
- (u) $-\text{NR}^7\text{COR}^{10}$,
- (v) $-\text{C}(=\text{O})\text{R}^{10}$,
- (x) C_{1-3} -alkoxycarbonyl,
- (y) C_{1-3} -alkylthio, or
- (ab) methylsulfonyl,

R^2 is selected from:

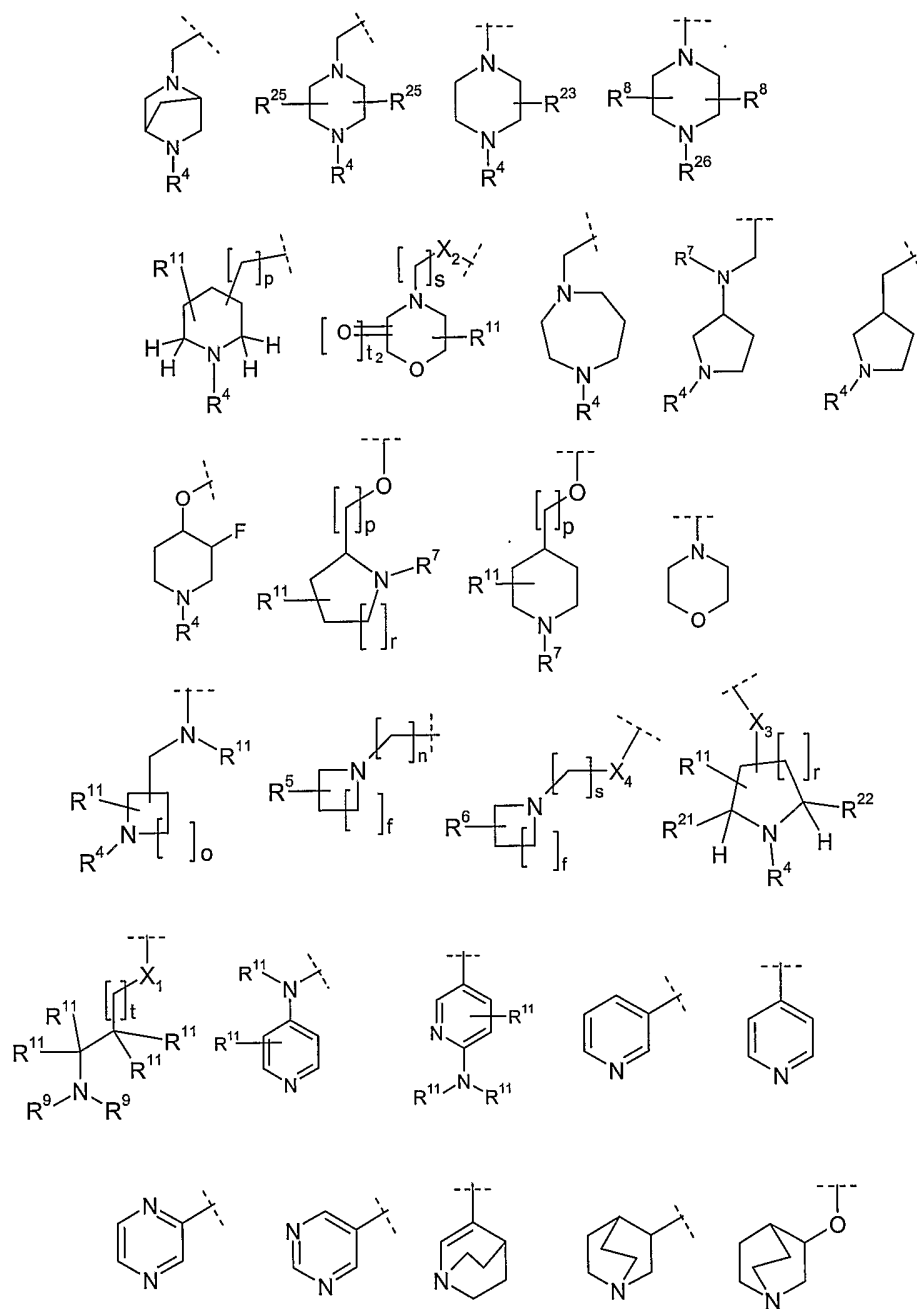
- (a) hydrogen,
- (b) C_{1-4} -alkyl,

W_1 and W_2 are each independently selected from:

- (a) hydrogen,
- (b) halogen,
- (c) C_{1-4} -alkyl,
- 5 (d) hydroxy,
- (e) C_{1-4} -alkoxy,
- (f) C_{1-4} -alkylthio,
- (m) $-OCF_3$,
- (n) $-CN$,
- 10 (o) hydroxy- C_{1-2} -alkyl,
- (p) C_{1-2} -alkoxy- C_{1-2} -alkyl,
- (q) $-CF_3$,
- (r) $-CONR^9R^9$,
- (s) acetyl,
- 15 (t) C_{1-4} -alkoxycarbonyl, or

with the proviso that when W_1 and W_2 are not selected from hydroxy, methoxy, methyl and halogen, at least one of W_1 and W_2 is selected from hydrogen;

R^3 is a group selected from:



wherein:

$$n = 0, 1, 2 \text{ or } 3$$

5 r is 0, 1 or 2,

$$o = 1, 2, \text{ or } 3,$$

p is 1 or 2,

 $s = 2 \text{ or } 3,$ $t = 0 \text{ or } 1,$

10 $t_2 = 0$ or 1, and

$f = 1, 2, 3$ or 4 ;

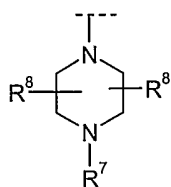
X_1 is selected from NR^7 and S ;

X_2 is selected from O , NR^7 and S , provided that X_2 is selected from NR^7 and S when $t = 0$ and $s = 2$;

5 X_3 is selected from NR^7 and S , provided that X_3 is selected from S when $r = 1$;

X_4 is selected from O , NR^7 and S , provided that X_4 is selected from S and NR^7 when f is selected from 2 and 3 , and R^6 simultaneously is selected from hydrogen and C_{1-4} alkyl; or;

10 when P is a group selected from formula (V) wherein $j = 1$, R^3 is additionally selected from the following group;



R^4 is selected from:

- (a) hydrogen,
- (b) C_{1-4} -alkyl,
- 15 (d) hydroxy- C_{2-4} -alkyl,
- (g) C_{3-6} -cycloalkyl,
- (h) C_{3-6} -cycloalkyl- C_{1-4} -alkyl,
- (i) C_{1-4} -alkoxy- C_{2-4} -alkyl
- (m) 3,3,3-trifluoropropyl;

20 R^5 is selected from:

- (a) hydrogen,
- (b) C_{1-4} -alkyl,
- (c) hydroxy- C_{1-4} -alkyl,
- (d) C_{1-4} -alkoxymethyl,
- 25 (e) halo- C_{1-4} -alkyl,
- (f) $-NR^{11}R^{11}$,
- (g) hydroxy, provided that the said hydroxy group is not attached to a carbon atom adjacent to a ring nitrogen atom, or
- (h) fluorine, provided that the said fluorine atom is not attached to a carbon
- 30 atom adjacent to a ring nitrogen atom;

R^6 is selected from:

- (a) hydrogen,
- (b) C₁₋₄-alkyl,
- (c) hydroxy-C₁₋₄-alkyl,
- (d) C₁₋₄-alkoxy-C₁₋₄-alkyl,

5 (e) hydroxy, provided that the said hydroxy group is not attached to a carbon atom adjacent to a heterocyclic ring nitrogen atom,

(f) fluorine, provided that the said fluorine atom is not attached to a carbon atom adjacent to a ring nitrogen atom, or

- (g) halo-C₁₋₄-alkyl;

10 R⁷ is each independently selected from:

(a) hydrogen, provided that R⁷ is not hydrogen when present simultaneously with r and said r is 1 or 2,

- (b) C₁₋₄-alkyl,
- (c) hydroxy-C₂₋₄-alkyl, or
- (d) methoxy-C₂₋₄-alkyl;

15

R⁸ is each independently selected from:

- (a) hydrogen, or
- (b) C₁₋₄-alkyl, with the proviso that when both R⁸ simultaneously are selected from C₁₋₄-alkyl, said C₁₋₄-alkyl may be attached to the same or different carbon atoms, or when two groups are present at the same carbon atom they may together form a cyclopropane ring;

20

R⁹ is each independently selected from:

- (a) hydrogen,
- (b) C₁₋₆-alkyl, or

25

the two R⁹ groups together with the nitrogen to which they are attached form a heterocyclic ring; and provided that when the two R⁹ groups form a piperazine ring, the nitrogen of the said piperazine ring that allows the substitution is optionally substituted with C₁₋₄-alkyl;

R¹⁰ is selected from:

30

- (a) C₁₋₆-alkyl,
- (c) aryl, or
- (d) heteroaryl,

wherein heteroaryl or aryl may be substituted in one or more positions with substituents selected from halogen, C₁₋₄-alkyl, C₁₋₄-alkoxy, cyano, trifluoromethyl;

R^{11} is each independently selected from:

- (a) hydrogen, or
- (b) methyl,
- (c) ethyl, provided that R^{11} is present in a group R^{26} selected from $-\text{CH}_2\text{-CO-}$

5 $\text{NR}^{11}\text{R}^{11}$;

R^{12} is selected from:

- (a) hydrogen,
- (c) aryl,
- (d) aryl- C_{1-3} -alkyl,
- 10 (g) heteroaryl, or
- (h) heteroaryl- C_{1-3} -alkyl,

wherein any heteroaryl or aryl residue, alone or as part of another group, may be optionally substituted, independently, in one or more positions with substituents selected from

- 15 (b) halogen,
- (c) C_{1-4} -alkyl,
- (d) hydroxy,
- (e) C_{1-4} -alkoxy,
- (m) $-\text{OCF}_3$,
- 20 (n) $-\text{CN}$,
- (o) hydroxy- C_{1-3} -alkyl,
- (p) C_{1-3} -alkoxy- C_{1-3} -alkyl,
- (q) halo- C_{1-4} -alkyl,
- (r) $-\text{NR}^9\text{R}^9$,
- 25 (t) $-\text{CONR}^9\text{R}^9$,
- (u) $-\text{NR}^7\text{COR}^{10}$,
- (v) $-\text{C}(=\text{O})\text{R}^{10}$,
- (x) C_{1-3} -alkylthio, or
- (ab) methylsulfonyl;

30 R^{13} is selected from:

- (c) aryl,
- (d) heteroaryl,
- (e) aryl- C_{1-2} -alkyl, or
- (f) heteroaryl- C_{1-2} -alkyl,

wherein any heteroaryl or aryl residue may be optionally substituted in one or more positions with substituents selected from halogen, C₁₋₄-alkyl, C₁₋₄-alkoxy, cyano, trifluoromethyl and acetyl;

R¹⁴ is selected from:

- 5 (a) aryl,
 (b) heteroaryl,
 (c) aryl-C₁₋₃-alkyl, or
 (d) heteroaryl-C₁₋₃-alkyl;

10 wherein any heteroaryl or aryl residue may be optionally substituted in one or more positions with substituents selected from halogen, C₁₋₄-alkyl, C₁₋₄-alkoxy, cyano, and trifluoromethyl;

R²⁰ is selected from:

- (a) hydrogen, or
 (b) methyl,
15 with the proviso that when t₂ is 1, R²⁰ is H;

R²¹ and R²² are each independently selected from:

- (a) hydrogen, or
 (b) methyl,

20 provided that, when present simultaneously with R¹¹, at least two of R¹¹, R²¹ and R²² are selected from hydrogen;

R²³ is selected from:

- (a) hydroxy-C₁₋₄-alkyl,
 (b) C₁₋₄-alkoxymethyl, or
 (c) halo-C₁₋₄-alkyl;

25 R²⁵ is selected from:

- (a) hydrogen,
 (b) C₁₋₄-alkyl,
 (c) hydroxy-C₁₋₄-alkyl,
 (d) C₁₋₄-alkoxy-C₁₋₄-alkyl, or
30 (e) fluoromethyl;

with the proviso that when both R²⁵ simultaneously are selected from C₁₋₄-alkyl, said C₁₋₄-alkyl may be attached to the same or different carbon atoms, and with the further proviso that when one R²⁵ is selected from hydroxy-C₁₋₄-alkyl, C₁₋₄-alkoxy-C₁₋₄-alkyl, and fluoromethyl; the other R²⁵ represents hydrogen;

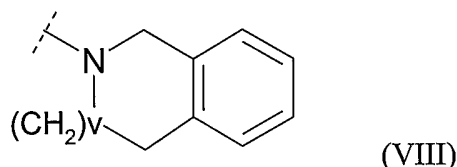
R^{26} is selected from:

(e) C_{3-7} -cycloalkyl- C_{1-4} -alkyl,

(f) $-CH_2-CO-NR^{11}R^{11}$, or

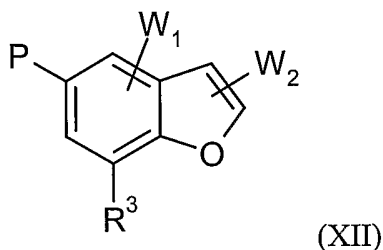
(g) 3,3,3-trifluoropropyl;

- 5 with the proviso that R^2 and R^{12} in Formula (III) are not simultaneously selected from hydrogen; and with the further proviso that the said R^2 and R^{12} together may form a heterocyclic ring selected from piperidine, pyrrolidine, morpholine, piperazine, thiomorpholine, and provided that when R^2 and R^{12} together form a piperazine ring, the distal piperazine nitrogen may be optionally substituted by C_{1-4} alkyl or aryl, and wherein
- 10 said aryl may be optionally substituted in one or more positions with substituents selected from halogen, C_{1-4} -alkyl, C_{1-4} -alkoxy, cyano, trifluoromethyl; or R^2 and R^{12} together form a heteroaromatic ring of Formula (VIII):



wherein v is 0 or 1.

- 15 A set of preferred compounds within this invention are those of the general Formula (XII):



wherein W_1 , W_2 , P and R^3 are as defined for formula (Ib).

Further preferred compounds of Formula (XII) are compounds wherein

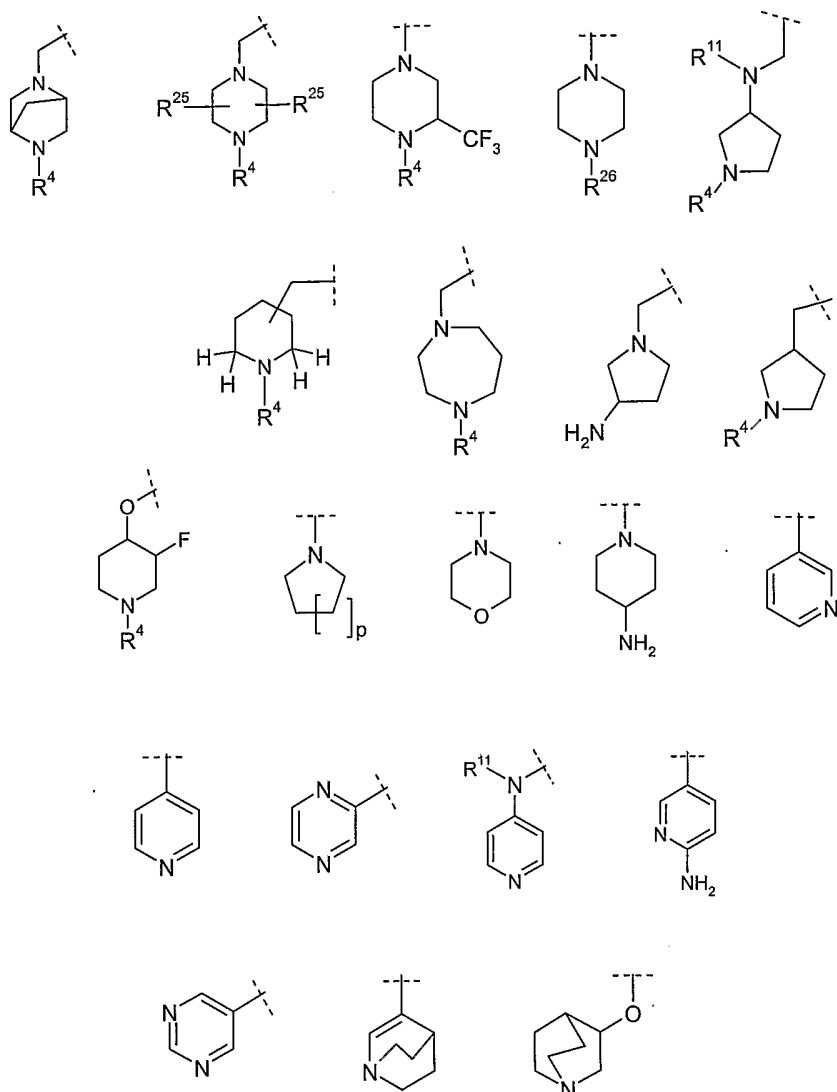
- 20 P is selected from a substituent of Formula (II) –(IV);
 x is 2 and y is 0;

R^1 is selected from aryl and heteroaryl, wherein any heteroaryl or aryl residue may be optionally substituted, independently, in one or more positions with a substituent selected from halogen, C_{1-4} -alkyl, C_{1-4} -alkoxy and trifluoromethyl;

- 25 R^2 is selected from hydrogen;

W_1 and W_2 are hydrogen;

R^3 is a group selected from



wherein

$p = 1$ or 2 ,

R^4 is selected from:

- 5 (a) hydrogen, or
- (b) C_{1-4} -alkyl;

R^{11} is each independently selected from:

- (a) hydrogen, or
- (b) methyl,
- 10 (c) ethyl, provided that R^{11} is present in a group R^{26} selected from $-CH_2-CO-NR^{11}R^{11}$;

R^{12} and R^{13} are each independently selected from aryl and heteroaryl,

wherein any heteroaryl or aryl residue may be optionally substituted, independently, in one or more positions with a substituent selected from halogen, C₁₋₄-alkyl, C₁₋₄-alkoxy, and CF₃;

R²⁵ is selected from:

- 5 (a) hydrogen, or
(b) C₁₋₄-alkyl;

R²⁶ is selected from:

- (e) C₃₋₇-cycloalkyl-C₁₋₄-alkyl,
(f) -CH₂-CO-NR¹¹R¹¹, or
10 (g) 3,3,3-trifluoropropyl.

In more preferred compounds of Formula (XII),

P is selected from a substituent of Formula (II) –(IV);

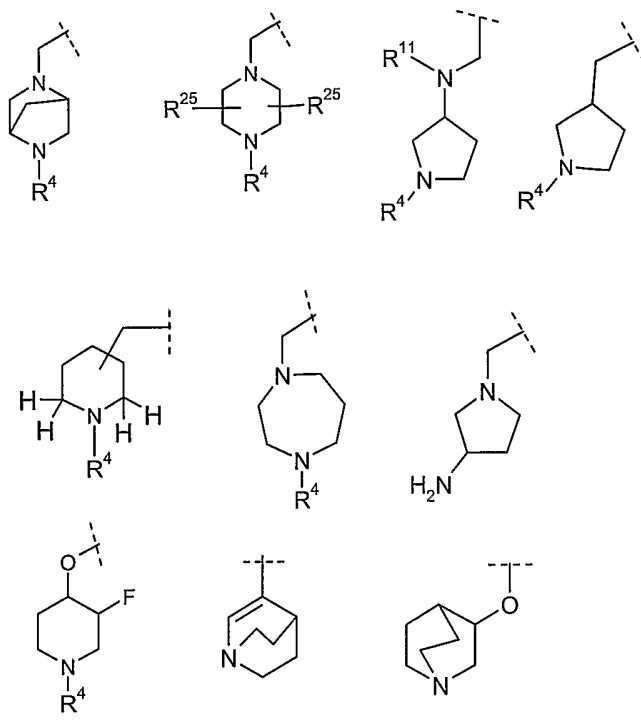
x is 2 and y is 0;

- R¹, R¹² and R¹³ are each independently selected from phenyl or substituted phenyl
15 selected from 2-methoxy-5-methylphenyl, 2-methylphenyl, 4-methylphenyl, 4-fluorophenyl, 3,4-dimethoxyphenyl, 2-chlorophenyl, 2-trifluoromethylphenyl, 2,6-dichlorophenyl, 3-chloro-4-methylphenyl, 3-methylphenyl, 3,6-dichloro-2-methylphenyl, and 2-chloro-5-fluorophenyl; or heteroaryl or substituted heteroaryl selected from 2-thienyl, 5-chloro-2-thienyl, 5-chloro-and 1,3-dimethyl-1H-pyrazol-4-yl;

- 20 R² is selected from hydrogen;

W₁ and W₂ are hydrogen;

R³ is a group selected from:



R⁴ is each independently selected from:

- (a) hydrogen, or
- (b) methyl,

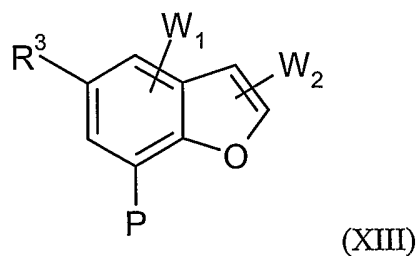
5 R¹¹ is each independently selected from:

- (a) hydrogen, or
- (b) methyl;

R²⁵ is each independently selected from:

- (a) hydrogen, or
- 10 (b) methyl.

A yet further set of preferred compounds within this invention are those of the general Formula (XIII):



wherein W₁, W₂, P and R³ are as defined for Formula (Ib).

15 Further preferred compounds of Formula (XIII) are compounds wherein:

P is selected from a substituent of Formula (II) –(IV);

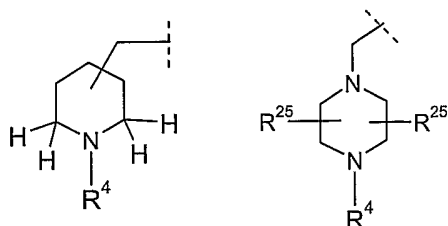
x is 2 and y is 0;

R^1 is selected from aryl and heteroaryl, wherein any heteroaryl or aryl residue may be optionally substituted, independently, in one or more positions with a substituent selected from halogen, C_{1-4} -alkyl, trifluoromethoxy, and C_{1-4} -alkoxy;

R^2 is selected from hydrogen;

5 W_1 and W_2 are hydrogen;

R^3 is a group selected from:



wherein:

R^4 is each independently selected from:

- 10 (a) hydrogen, or
(b) C_{1-4} -alkyl;

R^{25} is each independently selected from:

- (a) hydrogen, or
(b) C_{1-4} -alkyl, with the proviso that when both R^{25} represent C_{1-4} -alkyl, said C_{1-4} -alkyl may be attached to the same or different carbon atoms;
- 15

R^{12} and R^{13} are each independently selected from aryl and heteroaryl, wherein any heteroaryl or aryl residue may be optionally substituted, independently, in one or more positions with a substituent selected from halogen, C_{1-4} -alkyl, trifluoromethyl, and C_{1-4} -alkoxy.

20 In more preferred compounds of Formula (XIII),

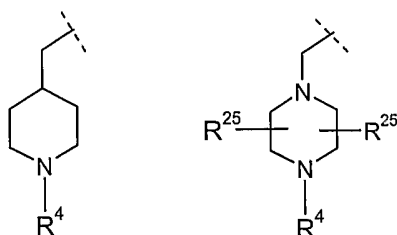
P is selected from a substituent of Formula (II);

R^1 is selected from 2-methoxy-5-methylphenyl;

R^2 is selected from hydrogen;

W_1 and W_2 are hydrogen;

25 R^3 is a group selected from:



R⁴ is each independently selected from

a) hydrogen, or

b) methyl;

R²⁵ is each independently selected from:

5 a) hydrogen, or

b) methyl.

Preferred compounds are

N-(7-{Methyl[3-(methylamino)propyl]amino}-1-benzofuran-5-yl)benzenesulfonamide hydrochloride,

10 N-(7-Piperidin-1-yl-1-benzofuran-5-yl)benzenesulfonamide,

4-Fluoro-N-(7-piperidin-1-yl-1-benzofuran-5-yl)benzenesulfonamide,

3,4-Dimethoxy-N-(7-piperidin-1-yl-1-benzofuran-5-yl)benzenesulfonamide hydrochloride,

3,4-Dimethoxy-N-(7-pyrrolidin-1-yl-1-benzofuran-5-yl)benzenesulfonamide,

15 N-(7-Pyrrolidin-1-yl-1-benzofuran-5-yl)benzenesulfonamide,

4-Fluoro-N-(7-pyrrolidin-1-yl-1-benzofuran-5-yl)benzenesulfonamide hydrochloride,

4-Fluoro-N-(7-morpholin-4-yl-1-benzofuran-5-yl)benzenesulfonamide

hydrochloride,

20 N-(7-Morpholin-4-yl-1-benzofuran-5-yl)benzenesulfonamide hydrochloride,

3,4-Dimethoxy-N-(7-morpholin-4-yl-1-benzofuran-5-yl)benzenesulfonamide,

2-Methoxy-5-methyl-N-(7-pyridin-4-yl-1-benzofuran-5-yl)benzenesulfonamide,

N-(7-Pyridin-3-yl-1-benzofuran-5-yl)benzenesulfonamide trifluoroacetate,

2-Methoxy-5-methyl-N-(7-pyridin-3-yl-1-benzofuran-5-yl)benzenesulfonamide

25 trifluoroacetate,

N-(7-Pyrazin-2-yl-1-benzofuran-5-yl)benzenesulfonamide trifluoroacetate,

N-(7-Pyrimidine-5-yl-1-benzofuran-5-yl)benzenesulfonamide hydrochloride, and,

N-[7-(1-Aza-bicyclo[2.2.2]oct-2-en-3-yl)-benzofuran-5-yl]-2-methoxy-5-methyl-benzenesulfonamide hydrochloride,

30 2-[4-(5-{[(2-Chlorophenyl)sulfonyl]amino}-1-benzofuran-7-yl)piperazin-1-yl]-

N,N-diethylacetamide hydrochloride,

N,N-diethyl-2-[4-(5-{[(2-methoxy-5-methylphenyl)sulfonyl]amino}-1-benzofuran-7-yl)piperazin-1-yl]acetamide hydrochloride,

- N-[7-(1-Azabicyclo[2.2.2.]oct-3-yloxy)-1-benzofuran-5-yl]benzenesulfonamide hydrochloride,
- N-[7-(1-Azabicyclo[2.2.2.]oct-3-yloxy)-1-benzofuran-5-yl]-2-chlorobenzenesulfonamide hydrochloride,
- 5 N-[7-(1-Azabicyclo[2.2.2.]oct-3-yloxy)-1-benzofuran-5-yl]-2-methoxy-5-benzenesulfonamide hydrochloride,
- N-{7-[(2-Morpholin-4-ylethyl)amino]-1-benzofuran-5-yl}benzenesulfonamide hydrochloride,
- 2-Methoxy-5-methyl-N-{7-[(2-morpholin-4-ylethyl)amino]-1-benzofuran-5-yl}benzenesulfonamide hydrochloride,
- 10 N-{7-[(2-Morpholin-4-ylethyl)amino]-1-benzofuran-5-yl}-2-(trifluoromethyl)benzenesulfonamide hydrochloride,
- 2,6-Dichloro-N-{7-[(2-morpholin-4-ylethyl)amino]-1-benzofuran-5-yl}benzenesulfonamide hydrochloride,
- 15 N-(7-{[2(Dimethylamino)ethyl]amino}-1-benzofuran-5-yl)-2-methoxy-5-benzenesulfonamide hydrochloride,
- 2-Chloro-N(7-{[2-(dimethylamino)}-1-benzofuran-5-yl)benzenesulfonamide hydrochloride,
- N-[7-(Pyridin-4-ylamino)-1-benzofuran-5-yl]benzenesulfonamide hydrochloride,
- 20 2-Chloro-N-[7-(pyridin-4-ylamino)-1-benzofuran-5-yl]benzenesulfonamide hydrochloride,
- 2-Methoxy-5-methyl-N-[7-(pyridin-4-ylamino)-1-benzofuran-5-yl]benzenesulfonamide hydrochloride,
- 2-Methoxy-5-methyl-N-[7-(piperazin-1-ylcarbonyl)-1-benzofuran-5-yl]benzenesulfonamide hydrochloride,
- 25 2-Methoxy-5-methyl-N-[7-(piperazin-1-ylmethyl)-1-benzofuran-5-yl]benzenesulfonamide hydrochloride,
- N-{7-[(3-Aminopyrrolidin-1-yl)methyl]-1-benzofuran-5-yl}-2-methoxy-5-methylbenzenesulfonamide hydrochloride,
- 30 N-[7(6,6-Dioxidohexahydrothieno[3,4-b]pyrazin-1(2H)-yl)-1-benzofuran-5-yl]-2-methoxy-5-methylbenzenesulfonamide hydrochloride,
- N-[7(6,6-Dioxidohexahydrothieno[3,4-b]pyrazin-1(2H)-yl)-1-benzofuran-5-yl]benzenesulfonamide hydrochloride,

N-{7-[(2-Pyrrolidin-1-ylethyl)amino]-1-benzofuran-5-yl} benzenesulfonamide hydrochloride,

2-Methoxy-5-methyl-N-{7-[(2-pyrrolidin-1-ylethyl)amino]-1-benzofuran-5-yl} benzenesulfonamide hydrochloride,

5 N-{7-[(2-Pyrrolidin-1-ylethyl)amino]-1-benzofuran-5-yl}-2-(trifluoromethyl)benzenesulfonamide hydrochloride,

3-Chloro-4-methyl-N-{7-[(2-pyrrolidin-1-ylethyl)amino]-1-benzofuran-5-yl} benzenesulfonamide hydrochloride,

10 2-Methoxy-5-methyl-N-{7-[(3-morpholin-4-ylpropyl)amino]-1-benzofuran-5-yl} benzenesulfonamide hydrochloride,

N-{7-[(3-Morpholin-4-ylpropyl)amino]-1-benzofuran-5-yl}-2-(trifluoromethyl)benzenesulfonamide hydrochloride,

3-Chloro-4-methyl-N-{7-[(3-morpholin-4-ylpropyl)amino]-1-benzofuran-5-yl} benzenesulfonamide hydrochloride,

15 N-[7-([(2R)-1-Ethylpyrrolidin-2-yl]methyl)amino]-1-benzofuran-5-yl] benzenesulfonamide hydrochloride,

N-[7-([(2R)-1-Ethylpyrrolidin-2-yl]methyl)amino]-1-benzofuran-5-yl]-2-methoxy-5-methylbenzenesulfonamide hydrochloride,

20 N-[7-([(2R)-1-Ethylpyrrolidin-2-yl]methyl)amino]-1-benzofuran-5-yl]-2-(trifluoromethyl)benzenesulfonamide hydrochloride,

N-[7-([(2R)-1-Ethylpyrrolidin-2-yl]methyl)amino]-1-benzofuran-5-yl]-3-methylbenzenesulfonamide hydrochloride,

N-[7-([(2R)-1-Ethylpyrrolidin-2-yl]methyl)amino]-1-benzofuran-5-yl]thiophene-2-sulfonamide hydrochloride,

25 5-Chloro-N-[7-([(2R)-1-ethylpyrrolidin-2-yl]methyl)amino]-1-benzofuran-5-yl]thiophene-2-sulfonamide hydrochloride,

5-Chloro-N-[7-([(2R)-1-ethylpyrrolidin-2-yl]methyl)amino]-1-benzofuran-5-yl]-1,3-dimethyl-1H-pyrazole-4-sulfonamide hydrochloride,

30 N-(7-{[3-(2-Methylpiperidin-1-yl)propyl]amino}-1-benzofuran-5-yl)benzenesulfonamide hydrochloride,

2-Methoxy-5-methyl-N-(7-{[3-(2-methylpiperidin-1-yl)propyl]amino}-1-benzofuran-5-yl)benzenesulfonamide hydrochloride,

N-(7-{[3-(2-Methylpiperidin-1-yl)propyl]amino}-1-benzofuran-5-yl)-2-(trifluoromethyl)benzenesulfonamide hydrochloride,

- 5-Chloro-1,3-dimethyl-N-(7-{[3-(2-methylpiperidin-1-yl)propyl]amino}-1-benzofuran-5-yl)-1H-pyrazole-4-sulfonamide hydrochloride,
N-[7-(6-Aminopyridin-3-yl)-1-benzofuran-5-yl]-2-methoxy-5-methylbenzenesulfonamide,
5 N-{7-[4-(Cyclopropylmethyl)piperazin-1-yl]-1-benzofuran-5-yl}-2-methoxy-5-methylbenzenesulfonamide hydrochloride,
2-Methoxy-5-methyl-N-{7-[4-(3,3,3-trifluoropropyl)piperazin-1-yl]-1-benzofuran-5-yl}benzenesulfonamide hydrochloride,
2-Methoxy-5-methyl-N-{7-[3-(trifluoromethyl)piperazin-1-yl]-1-benzofuran-5-yl}benzenesulfonamide hydrochloride,
10 N-[7-(Aminopiperidin-1-yl)-1-benzofuran-5-yl]-2-(trifluoromethyl)benzenesulfonamide hydrochloride,
N-[7-(Aminopiperidin-1-yl)-1-benzofuran-5-yl]-benzenesulfonamide hydrochloride,
15 N-[7-(Aminopiperidin-1-yl)-1-benzofuran-5-yl]-2-chlorobenzenesulfonamide hydrochloride,
N-[7-(Aminopiperidin-1-yl)-1-benzofuran-5-yl]-2-methoxy-5-methylbenzenesulfonamide hydrochloride,
N-(7-{[cis-3-Fluoropiperidin-4-yl]oxy}-1-benzofuran-5-yl)-2-methoxy-5-methylbenzenesulfonamide hydrochloride,
20 N-(7-{[trans-3-Fluoropiperidin-4-yl]oxy}-1-benzofuran-5-yl)-2-methoxy-5-methylbenzenesulfonamide hydrochloride ,
N-(7-{[cis-3-Fluoropiperidin-4-yl]oxy}-1-benzofuran-5-yl)-2-(trifluoromethyl)benzenesulfonamide hydrochloride,
25 N-(7-{[trans-3-Fluoropiperidin-4-yl]oxy}-1-benzofuran-5-yl)-2-(trifluoromethyl)benzenesulfonamide hydrochloride,
2-Chloro-N-(7-{[trans-3-fluoropiperidin-4-yl]oxy}-1-benzofuran-5-yl)benzenesulfonamide hydrochloride,
N-(7-{[trans-3-Fluoropiperidin-4-yl]oxy}-1-benzofuran-5-yl)-3-methylbenzenesulfonamide hydrochloride,
30 3,6-Dichloro-N-(7-{[trans-3-fluoropiperidin-4-yl]oxy}-1-benzofuran-5-yl)-2-methylbenzenesulfonamide hydrochloride,
2-Chloro-5-fluoro-N-(7-{[trans-3-fluoropiperidin-4-yl]oxy}-1-benzofuran-5-yl)benzenesulfonamide hydrochloride,

- N-(2-Methoxy-5-methylphenyl)-7-[(3-methylpiperazin-1-yl)methyl]-1-benzofuran-5-sulfonamide hydrochloride,
N-(2-Methylphenyl)-7-(piperazin-1-ylmethyl)-1-benzofuran-5-sulfonamide, trifluoroacetate,
5 7-[(3,5-Dimethylpiperazin-1-yl)methyl]-N-(2-methylphenyl)-1-benzofuran-5-sulfonamide, trifluoroacetate,
N-(2-Methylphenyl)-7-[(3-methylpiperazin-1-yl)methyl]-1-benzofuran-5-sulfonamide, trifluoroacetate,
7-(1,4-Diazepan-1-ylmethyl)-N-(2-methylphenyl)-1-benzofuran-5-sulfonamide,
10 trifluoroacetate,
7-[(trans-2,5-Dimethylpiperazin-1-yl)methyl]-N-(2-methylphenyl)-1-benzofuran-5-sulfonamide, trifluoroacetate,
N-(2-Methylphenyl)-7-[(2R)-2-methylpiperazin-1-ylmethyl]-1-benzofuran-5-sulfonamide, trifluoroacetate,
15 N-(2-Methoxy-5-methylphenyl)-7-[(3-methylpiperazin-1-yl)methyl]-1-benzofuran-5-sulfonamide, trifluoroacetate,
7-(1,4-Diazepan-1-ylmethyl)-N-(2-methoxy-5-methylphenyl)-1-benzofuran-5-sulfonamide, trifluoroacetate,
N-(2-Methoxy-5-methylphenyl)-7-(piperazin-1-ylmethyl)-1-benzofuran-5-sulfonamide, trifluoroacetate,
20 7-[(cis-3,5-Dimethylpiperazin-1-yl)methyl]-N-(2-methoxy-5-methylphenyl)-1-benzofuran-5-sulfonamide, trifluoroacetate,
7-[(trans-2,5-Dimethylpiperazin-1-yl)methyl]-N-(2-methoxy-5-methylphenyl)-1-benzofuran-5-sulfonamide, trifluoroacetate,,
25 7-[(1S,4S)-2,5-Diazabicyclo[2.2.1]hept-2-ylmethyl]-N-(2-methoxy-5-methylphenyl)-1-benzofuran-5-sulfonamide, trifluoroacetate,,
N-(2-Methoxy-5-methylphenyl)-7-[(2-methylpiperazin-1-yl)methyl]-1-benzofuran-5-sulfonamide, trifluoroacetate;
2-Chloro-N-[7-(piperazin-1-ylmethyl)-1-benzofuran-5-yl]benzenesulfonamide
30 dihydrochloride,
2-Methyl-N-[7-(piperazin-1-ylmethyl)-1-benzofuran-5-yl]benzenesulfonamide, dihydrochloride,
N-[7-(Piperazin-1-ylmethyl)-1-benzofuran-5-yl]thiophene-2-sulfonamide, dihydrochloride,

- 2-Chloro-N-[7-(1,4-diazepan-1-ylmethyl)-1-benzofuran-5-yl]benzenesulfonamide dihydrochloride,
- N-[7-(1,4-Diazepan-1-ylmethyl)-1-benzofuran-5-yl]-2-methylbenzenesulfonamide, dihydrochloride,
- 5 N-[7-(1,4-Diazepan-1-ylmethyl)-1-benzofuran-5-yl]thiophene-2-sulfonamide dihydrochloride,
- 2-Methoxy-5-methyl-N-{7-[(2-methylpiperazin-1-yl)methyl]-1-benzofuran-5-yl}benzenesulfonamide, dihydrochloride,
- 2-Methyl-N-{7-[(2-methylpiperazin-1-yl)methyl]-1-benzofuran-5-yl}benzenesulfonamide dihydrochloride,
- 10 2,5-Dichloro-N-{7-[(2-methylpiperazin-1-yl)methyl]-1-benzofuran-5-yl}thiophene-3-sulfonamide dihydrochloride,
- 2-Methoxy-5-methyl-N-{7-[(3-methylpiperazin-1-yl)methyl]-1-benzofuran-5-yl}benzenesulfonamide, dihydrochloride,
- 15 N-{7-[(3-Methylpiperazin-1-yl)methyl]-1-benzofuran-5-yl}-2-(trifluoromethyl)benzenesulfonamide, dihydrochloride,
- 2-Chloro-N-{7-[(3-methylpiperazin-1-yl)methyl]-1-benzofuran-5-yl}benzenesulfonamide, dihydrochloride,
- N-{7-[(1*S*,4*S*)-2,5-Diazabicyclo[2.2.1]hept-2-ylmethyl]-1-benzofuran-5-yl}-2-methoxy-5-methylbenzenesulfonamide, dihydrochloride,
- 20 N-{7-[(1*S*,4*S*)-2,5-Diazabicyclo[2.2.1]hept-2-ylmethyl]-1-benzofuran-5-yl}-2-(trifluoromethyl)benzenesulfonamide, dihydrochloride,
- N-{7-[(1*S*,4*S*)-2,5-Diazabicyclo[2.2.1]hept-2-ylmethyl]-1-benzofuran-5-yl}-2-methylbenzenesulfonamide, dihydrochloride,
- 25 2-Methoxy-5-methyl-N-{7-[(trans-2,5-dimethylpiperazin-1-yl)methyl]-1-benzofuran-5-yl}benzenesulfonamide, bistrifluoroacetate,
- 2-Methyl-N-{7-[(trans-2,5-dimethylpiperazin-1-yl)methyl]-1-benzofuran-5-yl}benzenesulfonamide, bistrifluoroacetate,
- 2-Chloro-N-{7-[(trans-2,5-dimethylpiperazin-1-yl)methyl]-1-benzofuran-5-yl}benzenesulfonamide, bistrifluoroacetate,
- 30 1-{5-[(2-Methoxy-5-methylphenyl)sulfonyl]-1-benzofuran-7-yl}methylpiperazine, trifluoroacetate,
- 1-{5-(Phenylsulfonyl)-1-benzofuran-7-yl}methylpiperazine, trifluoroacetate,

1-({5-[(4-Methylphenyl)sulfonyl]-1-benzofuran-7-yl}methyl)piperazine,
trifluoroacetate,
1-({5-[(2-Methoxy-5-methylphenyl)sulfonyl]-1-benzofuran-7-yl}methyl)-1,4-
diazepane, trifluoroacetate,
5 1-{[5-(Phenylsulfonyl)-1-benzofuran-7-yl]methyl}-1,4-diazepane, trifluoroacetate,
1-({5-[(4-Methylphenyl)sulfonyl]-1-benzofuran-7-yl}methyl)-1,4-diazepane,
trifluoroacetate,
1-({5-[(2-Methoxy-5-methylphenyl)sulfonyl]-1-benzofuran-7-yl}methyl)-2-
methylpiperazine, trifluoroacetate,
10 1-({5-[(2-Methoxy-5-methylphenyl)sulfonyl]-1-benzofuran-7-yl}methyl)-3-
methylpiperazine, trifluoroacetate,
N-(2-Methylphenyl)-7-[(3R)-pyrrolidin-3-ylamino]methyl-1-benzofuran-5-
sulfonamide, trifluoroacetate,
N-(2-Methylphenyl)-7-(piperidin-4-ylmethyl)-1-benzofuran-5-sulfonamide,
15 trifluoroacetate,
N-(2-Methylphenyl)-7-(pyrrolidin-3-ylmethyl)-1-benzofuran-5-sulfonamide,
trifluoroacetate,
N-(2-Methylphenyl)-7-(piperidin-3-ylmethyl)-1-benzofuran-5-sulfonamide,
trifluoroacetate,
20 2-Methoxy-5-methyl-N-[7-(piperidin-4-ylmethyl)-1-benzofuran-5-
yl]benzenesulfonamide, trifluoroacetate,
3-({5-[(4-Methylphenyl)sulfonyl]-1-benzofuran-7-yl}methyl)pyrrolidine,
trifluoroacetate,,
2-Methoxy-5-methyl-N-[5-(piperidin-4-ylmethyl)-1-benzofuran-7-
25 yl]benzenesulfonamide, trifluoroacetate,
2-Methoxy-5-methyl-N-{5-[(3-methylpiperazin-1-yl)methyl]-1-benzofuran-7-
yl}benzenesulfonamide, bis(trifluoroacetate,,
2-Methoxy-5-methyl-N-[5-(piperidin-4-ylmethyl)-1-benzofuran-7-
yl]benzenesulfonamide, trifluoroacetate.

30

Another object of the present invention is a process for the preparation of a compound as mentioned above, comprising the following steps:

(a) halogenation of 4-nitrophenol to give a dihalogenated 4-nitrophenol,

- (b) ring closure of a dihalogenated 4-nitrophenol using trimethylsilylacetylene to give a halogenated nitrobenzofuran,
- (c) nucleophilic displacement of a halogenated nitrobenzofuran with an amine to give an amine-substituted nitrobenzofuran,
- 5 (d) BOC-protection of an amine-substituted benzofuran to give a BOC-protected amine-substituted nitrobenzofuran,
- (e) reduction of a BOC-protected amine-substituted nitrobenzofuran to give a BOC-protected amine-substituted aminobenzofuran,
- (f) coupling of a halogenated nitrobenzofuran with a tributylstannylheterocycle,
- 10 tributylstannylheteroaryl compound, or heteroaryl boronic acid or heteroaryl boronic ester to give a heterocycle-substituted or heteroaryl-substituted nitrobenzofuran,
- (g) reduction of a heterocycle-substituted or aryl-substituted nitrobenzofuran to give a heterocycle-substituted or heteroaryl-substituted aminobenzofuran,
- (h) arylsulfonylation of a heterocycle-substituted or heteroaryl-substituted
- 15 aminobenzofuran to give a heterocycle-substituted or heteroaryl-substituted arylsulfonylaminobenzofuran,
- (i) arylsulfonylation of a BOC-protected amine-substituted aminobenzofuran to give a BOC-protected amine-substituted arylsulfonylaminobenzofuran,
- (j) removal of the BOC-protecting group from a BOC-protected amine-substituted
- 20 arylsulfonylaminobenzofuran,
- (k) benzylation of a BOC-protected amine-substituted aminobenzofuran to give a BOC-protected amine-substituted benzylaminobenzofuran,
- (l) removal of the BOC-protecting group from a BOC-protected amine-substituted benzylaminobenzofuran,
- 25 (m) benzoylation of a BOC-protected amine-substituted aminobenzofuran to give a BOC-protected amine-substituted benzoylaminobenzofuran,
- (n) removal of the BOC-protecting group from a BOC-protected amine-substituted benzoylaminobenzofuran,
- (o) reaction of a BOC-protected amine-substituted aminobenzofuran with an aryl
- 30 isocyanate to give a BOC-protected amine-substituted phenylaminocarbonylaminobenzofuran, and
- (p) removal of the BOC-protecting group from a BOC-protected amine-substituted phenylaminocarbonylaminobenzofuran.

Additional synthetic steps to reach the compounds of the present invention are outlined in Schemes 7-14.

Another object of the present invention is a compound as mentioned above for use in therapy, especially for use in the treatment or prophylaxis of a 5-HT₆ receptor-related disorder, to achieve reduction of body weight and of body weight gain.

Another object of the present invention is a pharmaceutical formulation comprising a compound as mentioned above as active ingredient, in combination with a pharmaceutically acceptable diluent or carrier, especially for use in the treatment or prophylaxis of a 5-HT₆ receptor-related disorder, to achieve reduction of body weight and of body weight gain.

Another object of the present invention is a method for treating a human or animal subject suffering from a 5-HT₆ receptor-related disorder, to achieve reduction of body weight and of body weight gain. The method can include administering to a subject (e.g., a human or an animal, dog, cat, horse, cow) in need thereof an effective amount of one or more compounds of any of the formulae herein, their salts, or compositions containing the compounds or salts.

The methods delineated herein can also include the step of identifying that the subject is in need of treatment of the 5-HT₆ receptor-related disorder, to achieve reduction of body weight and of body weight gain. Identifying a subject in need of such treatment can be in the judgment of a subject or a health care professional and can be subjective (e.g., opinion) or objective (e.g., measurable by a test or diagnostic method).

Another object of the present invention is a method for the treatment or prophylaxis of a 5-HT₆ receptor-related disorder, to achieve reduction of body weight and of body weight gain, which comprises administering to a subject in need of such treatment an effective amount of a compound as mentioned above.

Another object of the present invention is a method for modulating (e.g. inhibiting or promoting) 5-HT₆ receptor activity, which comprises administering to a subject in need of such treatment an effective amount of a compound as mentioned above.

Another object of the present invention is the use of a compound as mentioned above for the manufacture of a medicament for use in the prophylaxis or treatment of a 5-HT₆ receptor-related disorder, to achieve reduction of body weight and of body weight gain.

The compounds as mentioned above may be agonists, partial agonists or antagonists for the 5-HT₆ receptor. Preferably, the compounds act as partial agonists or antagonists for the 5-HT₆ receptor.

Another object of the present invention is a cosmetic composition comprising a compound as mentioned above as active ingredient, in combination with a cosmetically acceptable diluent or carrier, especially for use in the prophylaxis or treatment of a 5-HT₆ receptor-related disorder, to achieve reduction of body weight and of body weight gain.

Examples of 5-HT₆ receptor-related disorders are obesity; type II diabetes; disorders of the central nervous system such as anxiety, depression, panic attacks, memory disorders, cognitive disorders, epilepsy, sleep disorders, migraine, anorexia, bulimia, binge eating disorders, obsessive compulsive disorders, psychoses, Alzheimer's disease, Parkinson's disease, Huntington's chorea, schizophrenia, attention deficit hyperactive disorder (ADHD), withdrawal from drug abuse, neurodegenerative diseases characterized by impaired neuronal growth, and pain.

The compounds and compositions are useful for treating diseases, to achieve reduction of body weight and of body weight gain. The diseases include obesity; type II diabetes; disorders of the central nervous system such as anxiety, depression, panic attacks, memory disorders, cognitive disorders, epilepsy, sleep disorders, migraine, anorexia, bulimia, binge eating disorders, obsessive compulsive disorders, psychoses, Alzheimer's disease, Parkinson's disease, Huntington's chorea, schizophrenia, attention deficit hyperactive disorder (ADHD), withdrawal from drug abuse, neurodegenerative diseases characterized by impaired neuronal growth, and pain. In one aspect, the invention relates to a method for treating or preventing an aforementioned disease comprising administering to a subject in need of such treatment an effective amount or composition delineated herein.

Definitions

The following definitions shall apply throughout the specification and the appended claims.

Unless otherwise stated or indicated, the term "C₁₋₆-alkyl" denotes a straight or branched alkyl group having from 1 to 6 carbon atoms. Examples of said C₁₋₆-alkyl include methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, t-butyl and straight- and branched-chain pentyl and hexyl. For parts of the range "C₁₋₆-alkyl" all subgroups thereof

are contemplated such as C₁₋₅-alkyl, C₁₋₄-alkyl, C₁₋₃-alkyl, C₁₋₂-alkyl, C₂₋₆-alkyl, C₂₋₅-alkyl, C₂₋₄-alkyl, C₂₋₃-alkyl, C₃₋₆-alkyl, C₄₋₅-alkyl, etc. "Halo-C₁₋₆-alkyl" means a C₁₋₆-alkyl group substituted by one or more halogen atoms. Examples of said halo-C₁₋₆-alkyl include 2-fluoroethyl, fluoromethyl, trifluoromethyl and 2,2,2-trifluoroethyl. Likewise, "aryl-C₁₋₆-alkyl" means a C₁₋₆-alkyl group substituted by one or more aryl groups.

Unless otherwise stated or indicated, the term "hydroxy-C₁₋₆-alkyl" denotes a straight or branched alkyl group that has a hydrogen atom thereof replaced with OH. Examples of said hydroxy-C₁₋₆-alkyl include hydroxymethyl, 2-hydroxyethyl, 2-hydroxypropyl and 2-hydroxy-2-methylpropyl.

Unless otherwise stated or indicated, the term "C₁₋₆-alkoxy" denotes a straight or branched alkoxy group having from 1 to 6 carbon atoms. Examples of said C₁₋₆-alkoxy include methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy, iso-butoxy, sec-butoxy, t-butoxy and straight- and branched-chain pentoxy and hexoxy. For parts of the range "C₁₋₆-alkoxy" all subgroups thereof are contemplated such as C₁₋₅-alkoxy, C₁₋₄-alkoxy, C₁₋₃-alkoxy, C₁₋₂-alkoxy, C₂₋₆-alkoxy, C₂₋₅-alkoxy, C₂₋₄-alkoxy, C₂₋₃-alkoxy, C₃₋₆-alkoxy, C₄₋₅-alkoxy, etc.

Unless otherwise stated or indicated, the term C₁₋₆-alkoxy-C₁₋₆-alkyl denotes a straight or branched alkoxy group having from 1 to 6 carbon atoms connected to an alkyl group having from 1 to 6 carbon atoms. Examples of said C₁₋₆-alkoxy-C₁₋₆-alkyl include methoxymethyl, ethoxymethyl, iso-propoxymethyl, n-butoxymethyl, t-butoxymethyl and straight- and branched-chain pentoxymethyl. For parts of the range "C₁₋₆-alkoxy-C₁₋₆-alkyl" all subgroups thereof are contemplated such as C₁₋₅-alkoxy-C₁₋₆-alkyl, C₁₋₄-alkoxy-C₁₋₆-alkyl, C₁₋₃-alkoxy-C₁₋₆-alkyl, C₁₋₂-alkoxy-C₁₋₆-alkyl, C₂₋₆-alkoxy-C₁₋₆-alkyl, C₂₋₅-alkoxy-C₁₋₆-alkyl, C₂₋₄-alkoxy-C₁₋₆-alkyl, C₂₋₃-alkoxy-C₁₋₆-alkyl, C₃₋₆-alkoxy-C₁₋₆-alkyl, C₄₋₅-alkoxy-C₁₋₆-alkyl, C₁₋₆-alkoxy-C₁₋₅-alkyl, C₁₋₆-alkoxy-C₁₋₄-alkyl, etc.

Unless otherwise stated or indicated, the term "C₂₋₆-alkenyl" denotes a straight or branched alkenyl group having from 2 to 6 carbon atoms. Examples of said C₂₋₆-alkenyl include vinyl, allyl, 2,3-dimethylallyl, 1-butenyl, 1-pentenyl, and 1-hexenyl. For parts of the range "C₂₋₆-alkenyl" all subgroups thereof are contemplated such as C₂₋₅-alkenyl, C₂₋₄-alkenyl, C₂₋₃-alkenyl, C₃₋₆-alkenyl, C₄₋₅-alkenyl, etc. Likewise, "aryl-C₂₋₆-alkenyl" means a C₂₋₆-alkenyl group substituted by one or more aryl groups. Examples of said aryl-C₂₋₆-alkenyl include styryl and cinnamyl.

The term "oxo" denotes >C=O

Unless otherwise stated or indicated, the term "C₂₋₆-alkynyl" denotes a straight or branched alkynyl group having from 2 to 6 carbon atoms. Examples of said C₂₋₆-alkynyl include ethynyl, 1-propynyl, 1-butynyl, and 1-hexynyl. For parts of the range "C₂₋₆-alkynyl" all subgroups thereof are contemplated such as C₂₋₅-alkynyl, C₂₋₄-alkynyl, C₂₋₃-alkynyl, C₃₋₆-alkynyl, C₄₋₅-alkynyl, etc.

Unless otherwise stated or indicated, the term "C₃₋₇-cycloalkyl" denotes a cyclic alkyl group having a ring size from 3 to 7 carbon atoms. Examples of said cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, methylcyclohexyl, and cycloheptyl. For parts of the range "C₃₋₇-cycloalkyl" all subgroups thereof are contemplated such as C₃₋₆-cycloalkyl, C₃₋₅-cycloalkyl, C₃₋₄-cycloalkyl, C₄₋₇-cycloalkyl, C₄₋₆-cycloalkyl, C₄₋₅-cycloalkyl, C₅₋₇-cycloalkyl, C₆₋₇-cycloalkyl, etc.

Unless otherwise stated or indicated, the term "aryl" refers to a hydrocarbon ring system having at least one aromatic ring. Examples of aryls are phenyl, indenyl, indanyl, 1,2,3,4-tetrahydronaphthyl, 1-naphthyl, 2-naphthyl, and fluorenyl.

Likewise, aryloxy refers to an aryl group bonded to an oxygen atom.

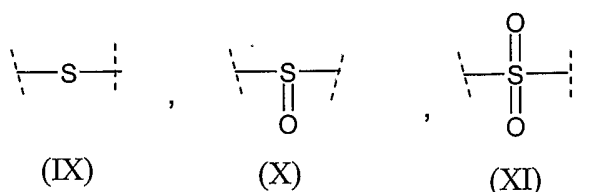
The term "heteroaryl" refers to a mono- or bicyclic aromatic ring system, only one ring need be aromatic, and the said heteroaryl moiety can be linked to the remainder of the molecule via a carbon or nitrogen atom in any ring, and having from 5 to 10 ring atoms (mono- or bicyclic), in which one or more of the ring atoms are other than carbon, such as nitrogen, sulphur, oxygen and selenium. Examples of such heteroaryl rings include furyl, pyrrolyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, thiazolyl, isothiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, chromanyl, quinazolinyl, indolyl, isoindolyl, indolinyl, isoindolinyl, indazolyl, pyrazolyl, pyridazinyl, quinolinyl, isoquinolinyl, benzofuranyl, 2,3-dihydrobenzofuranyl, 1,2,3,4-tetrahydroquinolinyl, 1,2,3,4-tetrahydroisoquinolinyl, benzodioxolyl, benzodioxinyl, benzothienyl, benzimidazolyl, benzothiazolyl, benzothiadiaazolyl, benzotriazolyl, and 2,1,3-benzoxadiazolyl groups. If a bicyclic heteroaryl ring is substituted, it may be substituted in any ring.

Unless otherwise stated or indicated, the term "heterocyclic" refers to a non-aromatic (i.e., partially or fully saturated) mono- or bicyclic ring system having 4 to 10 ring atoms with at least one heteroatom such as O, N, or S, and the remaining ring atoms are carbon. Examples of heterocyclic groups include piperidyl, tetrahydropyranyl, tetrahydrofuranyl, azepinyl, azetidyl, pyrrolidinyl, morpholinyl, imidazolinyl, thiomorpholinyl, pyranyl, dioxanyl, piperazinyl, octahydrofuro[3,4b]pyrazinyl, and 1-azabicyclo[2.2.2]oct-2-en-3-yl groups. When present, the sulfur atom may be in an oxidized form (i.e., S=O or O=S=O).

Examples of heterocyclic groups containing sulfur in oxidized form include octahydrothieno[3,4*b*]pyrazine 6,6-dioxide and thiomorpholine 1,1-dioxide.

Unless otherwise stated or indicated, the term “halogen” shall mean fluorine, chlorine, bromine or iodine.

- 5 The term $-S(O)_x$ in Formula (IV), wherein x is 0, 1 or 2, has the meaning as illustrated by Formula (IX) – (XI):



- The term “leaving group” refers to a group to be displaced from a molecule during a nucleophilic displacement reaction. Examples of leaving groups are iodide, bromide, chloride, methanesulphonate, hydroxy, methoxy, thiomethoxy, tosyl, or suitable protonated forms thereof (e.g., H_2O , $MeOH$), especially bromide and methanesulphonate.

“Optional” or “optionally” means that the subsequently described event or circumstance may but need not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not.

- 15 “Pharmaceutically acceptable” means being useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable and includes being useful for veterinary use as well as human pharmaceutical use.

- “Treatment” as used herein includes prophylaxis of the named disorder or condition, or amelioration or elimination of the disorder once it has been established.

“An effective amount” refers to an amount of a compound that confers a therapeutic effect on the treated subject. The therapeutic effect may be objective (i.e., measurable by some test or marker) or subjective (i.e., subject gives an indication of or feels an effect).

- The term “prodrug forms” means a pharmacologically acceptable derivative, such as an ester or an amide, which derivative is biotransformed in the body to form the active drug. Reference is made to Goodman and Gilman’s, *The Pharmacological basis of Therapeutics*, 8th ed., Mc-Graw-Hill, Int. Ed. 1992, “Biotransformation of Drugs”, p. 13-15; and “*The Organic Chemistry of Drug Design and Drug Action*” by Richard B. Silverman. Chapter 8, p 352. (Academic Press, Inc. 1992. ISBN 0-12-643730-0).

- 30 The following abbreviations have been used:

BINAP means 2,2'-bis(diphenylphosphino)1-1'-binaphthyl,

- BOC means tert-butyloxycarbonyl,
CV means Coefficient of Variation,
DCM means dichloromethane,
DME means 1,2-dimethoxyethane,
5 DMSO means dimethyl sulphoxide,
EDTA means ethylenediamine tetraacetic acid,
EtOH means ethanol,
EtOAc means ethyl acetate,
EGTA means ethylenebis(oxyethylenenitrilo)tetraacetic acid,
10 HEPES means 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid,
HPLC means high performance liquid chromatography,
LSD means lysergic acid, diethylamide,
MeCN means acetonitrile,
SPA means Scintillation Proximity Assay,
15 t-BuOK means potassium tert-butoxide,
TEA means triethylamine,
TFA means trifluoroacetic acid,
THF means tetrahydrofuran, and
Xantphos means 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene.
- 20 All isomeric forms possible (pure enantiomers, diastereomers, tautomers, racemic mixtures and unequal mixtures of two enantiomers) for the compounds delineated are within the scope of the invention. Such compounds can also occur as cis- or trans-, *E*- or *Z*-double bond isomer forms. All isomeric forms are contemplated.
- The compounds of the formula (I) may be used as such or, where appropriate, as
25 pharmacologically acceptable salts (acid or base addition salts) thereof. The pharmacologically acceptable addition salts mentioned above are meant to comprise the therapeutically active non-toxic acid and base addition salt forms that the compounds are able to form. Compounds that have basic properties can be converted to their
30 pharmaceutically acceptable acid addition salts by treating the base form with an appropriate acid. Exemplary acids include inorganic acids, such as hydrogen chloride, hydrogen bromide, hydrogen iodide, sulphuric acid, phosphoric acid; and organic acids such as formic acid, acetic acid, propanoic acid, hydroxyacetic acid, lactic acid, pyruvic acid, glycolic acid, maleic acid, malonic acid, oxalic acid, benzenesulphonic acid, toluenesulphonic acid, methanesulphonic acid, trifluoroacetic acid, fumaric acid, succinic

acid, malic acid, tartaric acid, citric acid, salicylic acid, p-aminosalicylic acid, pamoic acid, benzoic acid, ascorbic acid and the like. Exemplary base addition salt forms are the sodium, potassium, calcium salts, and salts with pharmaceutically acceptable amines such as, for example, ammonia, alkylamines, benzathine, and amino acids, such as, e.g. arginine and lysine.

For example, sulfonamide derivatives of Formula (I) wherein P is selected from a substituent of Formula (II) and (III) and wherein R² is hydrogen may be converted into their corresponding potassium, sodium or calcium salts, or salts of other alkali metals or alkaline earth metals. The term addition salt as used herein also comprises solvates which the compounds and salts thereof are able to form, such as, for example, hydrates, alcoholates and the like.

For clinical use, the compounds of the invention are formulated into pharmaceutical formulations for oral, rectal, parenteral or other mode of administration. Pharmaceutical formulations are usually prepared by mixing the active substance, or a pharmaceutically acceptable salt thereof, with conventional pharmaceutical excipients. Examples of excipients are water, gelatin, gum arabicum, lactose, microcrystalline cellulose, starch, sodium starch glycolate, calcium hydrogen phosphate, magnesium stearate, talcum, colloidal silicon dioxide, and the like. Such formulations may also contain other pharmacologically active agents, and conventional additives, such as stabilizers, wetting agents, emulsifiers, flavouring agents, buffers, and the like. Usually, the amount of active compounds is between 0.1-95% by weight of the preparation, preferably between 0.2-20% by weight in preparations for parenteral use and more preferably between 1-50% by weight in preparations for oral administration.

The formulations can be further prepared by known methods such as granulation, compression, microencapsulation, spray coating, etc. The formulations may be prepared by conventional methods in the dosage form of tablets, capsules, granules, powders, syrups, suspensions, suppositories or injections. Liquid formulations may be prepared by dissolving or suspending the active substance in water or other suitable vehicles. Tablets and granules may be coated in a conventional manner.

In a further aspect the invention relates to methods of making compounds of any of the formulae herein comprising reacting any one or more of the compounds of the formulae delineated herein, including any processes delineated herein. The compounds of the formula (I) above may be prepared by, or in analogy with, conventional methods.

The processes described above may be carried out to give a compound of the invention in the form of a free base or as an acid addition salt. A pharmaceutically acceptable acid addition salt may be obtained by dissolving the free base in a suitable organic solvent and treating the solution with an acid, in accordance with conventional procedures for preparing acid addition salts from base compounds. Examples of addition salt forming acids are mentioned above.

The compounds of formula (I) may possess one or more chiral carbon atoms, and they may therefore be obtained in the form of optical isomers, e.g. as a pure enantiomer, or as a mixture of enantiomers (racemate) or as a mixture containing diastereomers. The separation of mixtures of optical isomers to obtain pure enantiomers is well known in the art and may, for example, be achieved by fractional crystallization of salts with optically active (chiral) acids or by chromatographic separation on chiral columns.

The chemicals used in the synthetic routes delineated herein may include, for example, solvents, reagents, catalysts, and protecting group and deprotecting group reagents. The methods described above may also additionally include steps, either before or after the steps described specifically herein, to add or remove suitable protecting groups in order to ultimately allow synthesis of the compounds. In addition, various synthetic steps may be performed in an alternate sequence or order to give the desired compounds. Synthetic chemistry transformations and protecting group methodologies (protection and deprotection) useful in synthesizing applicable compounds are known in the art and include, for example, those described in R. Larock, *Comprehensive Organic Transformations*, VCH Publishers (1989); T.W. Greene and P.G.M. Wuts, *Protective Groups in Organic Synthesis*, 3rd Ed., John Wiley and Sons (1999); L. Fieser and M. Fieser, *Fieser and Fieser's Reagents for Organic Synthesis*, John Wiley and Sons (1994); and L. Paquette, ed., *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons (1995) and subsequent editions thereof.

The necessary starting materials for preparing the compounds of formula (I) are either known or may be prepared in analogy with the preparation of known compounds. The dose level and frequency of dosage of the specific compound will vary depending on a variety of factors including the potency of the specific compound employed, the metabolic stability and length of action of that compound, the patient's age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the condition to be treated, and the patient undergoing therapy. The daily dosage may, for example, range from about 0.001 mg to about 100 mg per kilo of body

weight, administered singly or multiply in doses, e.g. from about 0.01 mg to about 25 mg each. Normally, such a dosage is given orally but parenteral administration may also be chosen.

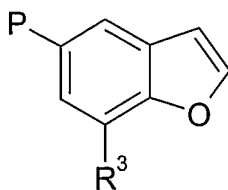
The invention will now be further illustrated by the following non-limiting Examples.

5 The specific examples below are to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever. Without further elaboration, it is believed that one skilled in the art can, based on the description herein, utilize the present invention to its fullest extent. All publications cited herein are hereby incorporated by reference in their entirety.

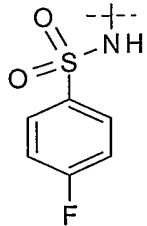
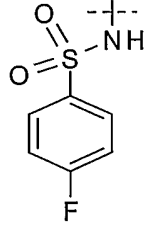
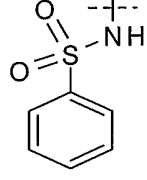
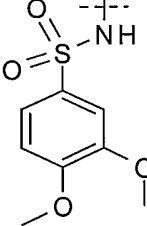
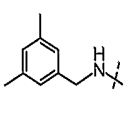
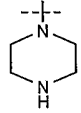
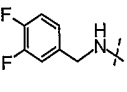
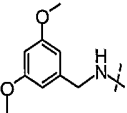
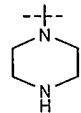
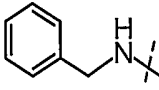
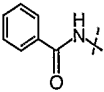
10 Methods

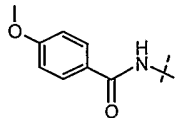
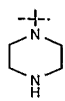
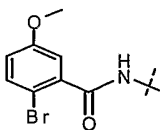
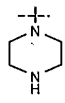
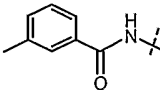
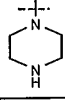
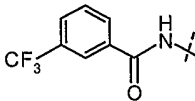
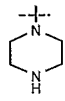
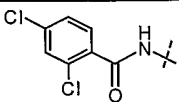
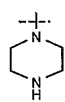
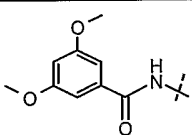
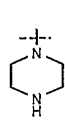
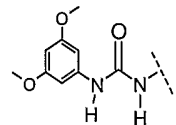
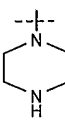
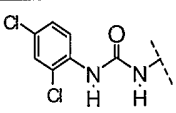
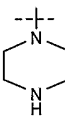
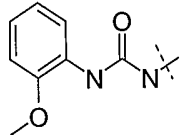
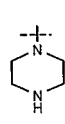
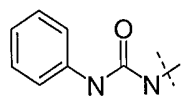
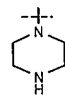
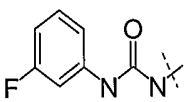
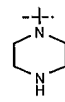
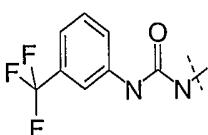
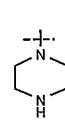
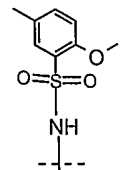
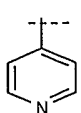
¹H nuclear magnetic resonance (NMR) and ¹³C NMR were recorded on Bruker Advance DPX 400, Bruker DRX-500, JEOL JNM-EX 270 or Varian MERCURY plus 400 MHz spectrometers. All spectra were recorded using residual solvent or tetramethylsilane (TMS) as internal standard. Ionspray mass spectrometry (MS) spectra were obtained on a Perkin-Elmer API 150EX mass spectrometer. Preparative HPLC/MS was performed on a Waters/Micromass Platform ZQ system equipped with System A: ACE 5 C8 column (19x50mm) or System B: Xterra MS C18, 5 µm column (19x50mm). The following HPLC setups have also been used: System C: Gilson/YMC AQ C18; 150x30 mm; System D: 15 Gilson Finnigan/YMC ODS AQ 5µm column (20x50mm); System E: Gyncotech HPLC-UV "SYS-2"; Ace C8, 5 µm column (21x50mm) and System F: Gyncotech HPLC-UV "SYS-2"; Ace C8, 5 µm column (30x150mm). Eluents used for System A, C-F: MeCN in milliQ-water with 0.1% TFA. Eluents used for System B: MilliQ water, MeCN and NH₄HCO₃ (100 mM). Analytical HPLC were performed on Agilent 1100, column: ACE 3 25 C8 (System A) or column: YMC ODS-AQ (System B) or column: Chromolith C18 (50x4.6mm) (System C), eluents: MilliQ/0.1%TFA and MeCN. Preparative flash chromatography was performed on Merck silica gel 60 (230-400 mesh). Reactions conducted under controlled microwave energy were performed with a Personal Chemistry Smith Creator using 0.5-2 mL, 2-5 mL or 20 mL Smith Process Vials fitted with 30 aluminium caps and septa.

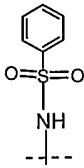
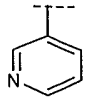
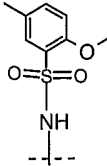
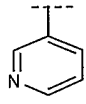
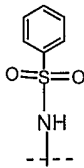
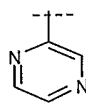
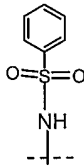
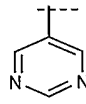
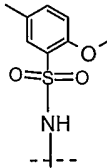
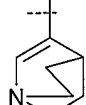
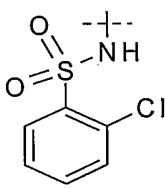
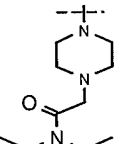
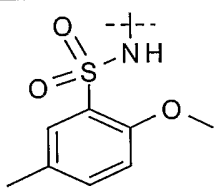
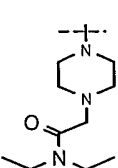
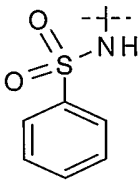
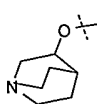
Table 1

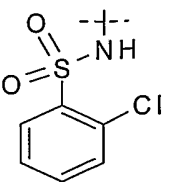
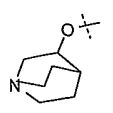
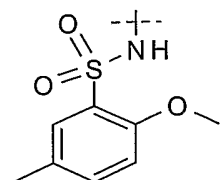
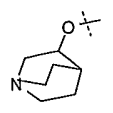
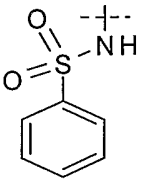
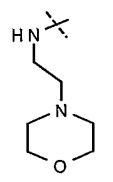
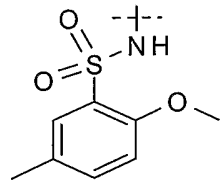
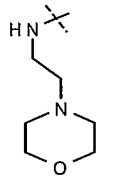
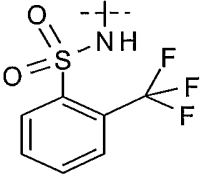
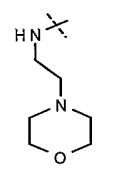
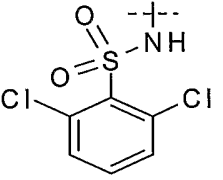
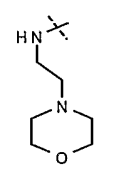
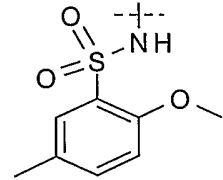
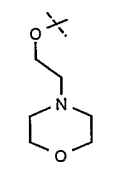
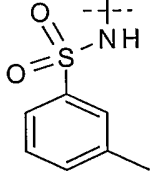
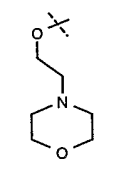


EXAMPLE		P	R3
1	N-(7-{Methyl[3-(methylamino)propyl]amino}-1-benzofuran-5-yl)benzenesulfonamide hydrochloride		
2	N-(7-Piperidin-1-yl-1-benzofuran-5-yl)benzenesulfonamide		
3	4-Fluoro-N-(7-piperidin-1-yl-1-benzofuran-5-yl)benzenesulfonamide		
4	3,4-Dimethoxy-N-(7-piperidin-1-yl-1-benzofuran-5-yl)benzenesulfonamide hydrochloride		
5	3,4-Dimethoxy-N-(7-pyrrolidin-1-yl-1-benzofuran-5-yl)benzenesulfonamide		
6	N-(7-Pyrrolidin-1-yl-1-benzofuran-5-yl)benzenesulfonamide		

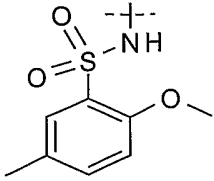
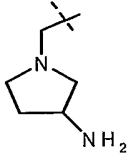
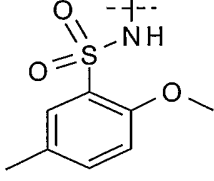
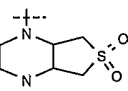
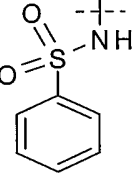
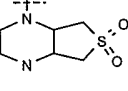
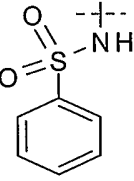
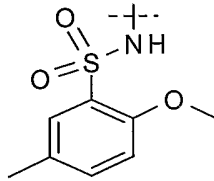
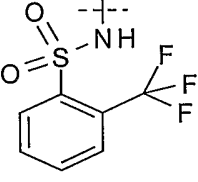
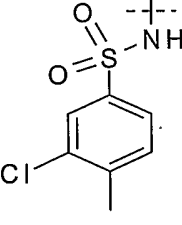
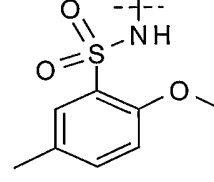
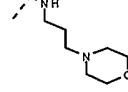
7	4-Fluoro-N-(7-pyrrolidin-1-yl-1-benzofuran-5-yl)benzenesulfonamide hydrochloride		
8	4-Fluoro-N-(7-morpholin-4-yl-1-benzofuran-5-yl)benzenesulfonamide hydrochloride		
9	N-(7-Morpholin-4-yl-1-benzofuran-5-yl)benzenesulfonamide hydrochloride		
10	3,4-Dimethoxy-N-(7-morpholin-4-yl-1-benzofuran-5-yl)benzenesulfonamide		
11	N-(3,5-Dimethylbenzyl)-7-piperazin-1-yl-1-benzofuran-5-amine hydrochloride		
12	N-(3,4-Difluorobenzyl)-7-piperazin-1-yl-1-benzofuran-5-amine hydrochloride		
13	N-(3,5-Dimethoxybenzyl)-7-piperazin-1-yl-1-benzofuran-5-amine hydrochloride		
14	N-Benzyl-7-piperazin-1-yl-1-benzofuran-5-amine hydrochloride		
15	N-(7-piperazin-1-yl-1-benzofuran-5-yl)benzamide hydrochloride		

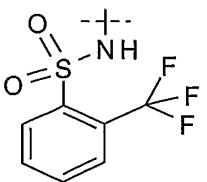
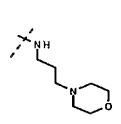
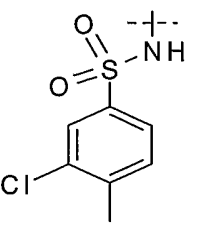
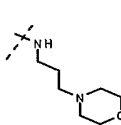
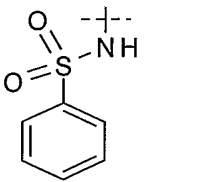
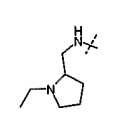
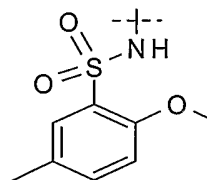
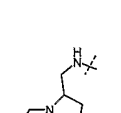
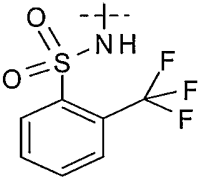
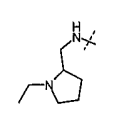
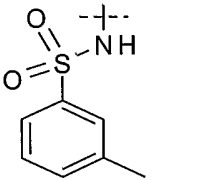
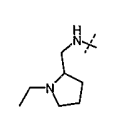
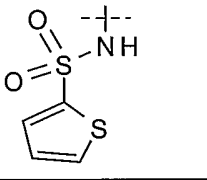
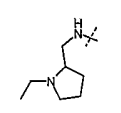
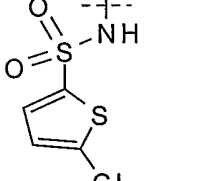
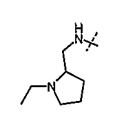
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17	2-Bromo-5-methoxy-N-(7-piperazin-1-yl-1-benzofuran-5-yl)benzamide hydrochloride		
18	3-Methyl-N-(7-piperazin-1-yl-1-benzofuran-5-yl)benzamide hydrochloride		
19	N-(7-Piperazin-1-yl-1-benzofuran-5-yl)-3-(trifluoromethyl)benzamide hydrochloride		
20	2,4-Dichloro-N-(7-piperazin-1-yl-1-benzofuran-5-yl)benzamide hydrochloride		
21	3,5-Dimethoxy-N-(7-piperazin-1-yl-1-benzofuran-5-yl)benzamide hydrochloride		
22	N-(3,5-Dimethoxyphenyl)-N'-(7-piperazin-1-yl-benzofuran-5-yl)urea hydrochloride		
23	N-(2,4-Dichlorophenyl)-N'-(7-piperazin-1-yl-benzofuran-5-yl)urea hydrochloride		
24	N-(2-Methoxyphenyl)-N'-(7-piperazin-1-yl-benzofuran-5-yl)urea hydrochloride		
25	N-Phenyl-N'-(7-piperazin-1-yl-1-benzofuran-5-yl)urea hydrochloride		
26	N-(3-Fluorophenyl)-N'-(7-piperazin-1-yl-benzofuran-5-yl)urea hydrochloride		
27	N-(7-Piperazin-1-yl-1-benzofuran-5-yl)-N'-(trifluoromethyl)phenyl]urea hydrochloride		
28	2-Methoxy-5-methyl-N-(7-pyridin-4-yl-1-benzofuran-5-yl)benzenesulfonamide		

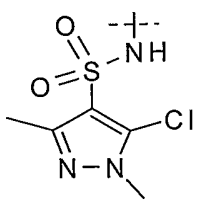
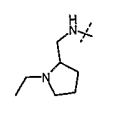
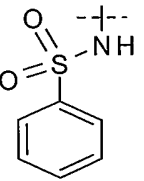
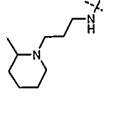
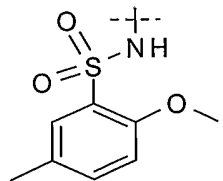
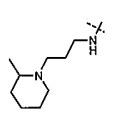
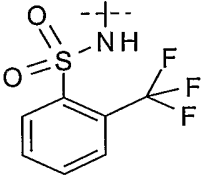
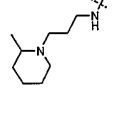
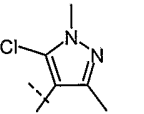
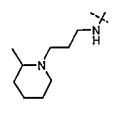
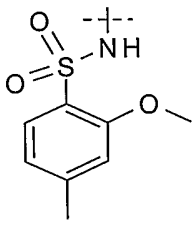
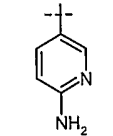
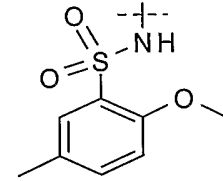
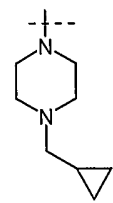
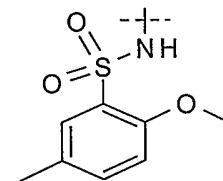
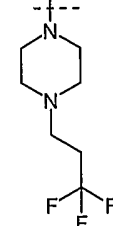
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30	2-Methoxy-5-methyl- <i>N</i> -(7-pyridin-3-yl-1-benzofuran-5-yl)benzenesulfonamide trifluoroacetate		
31	<i>N</i> -(7-Pyrazin-2-yl-1-benzofuran-5-yl)benzenesulfonamide trifluoroacetate		
32	<i>N</i> -(7-Pyrimidin-5-yl-1-benzofuran-5-yl)benzenesulfonamide hydrochloride		
33	<i>N</i> -[7-(1-Aza-bicyclo[2.2.2]oct-2-en-3-yl)-benzofuran-5-yl]-2-methoxy-5-methylbenzenesulfonamide hydrochloride		
34	2-[4-(5-[[2-(2-chlorophenyl)sulfonyl]amino]-1-benzofuran-7-yl)piperazin-1-yl]- <i>N,N</i> -diethylacetamide hydrochloride		
35	<i>N,N</i> -diethyl-2-[4-(5-[[2-(2-methoxy-5-methylphenyl)sulfonyl]amino]-1-benzofuran-7-yl)piperazin-1-yl]acetamide hydrochloride		
38	<i>N</i> -[7-(1-Azabicyclo[2.2.2]oct-3-yloxy)-1-benzofuran-5-yl]benzenesulfonamide hydrochloride		

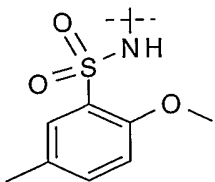
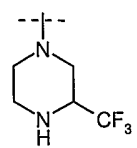
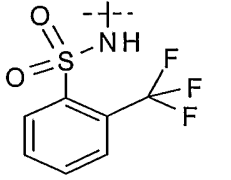
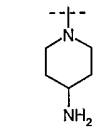
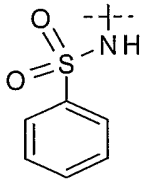
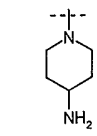
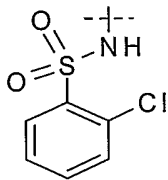
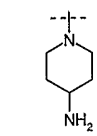
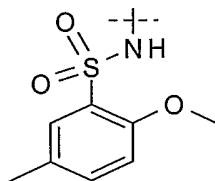
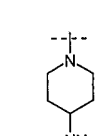
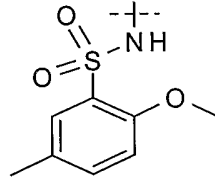
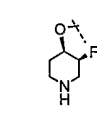
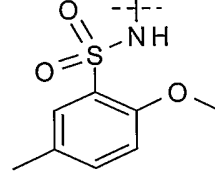
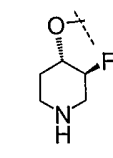
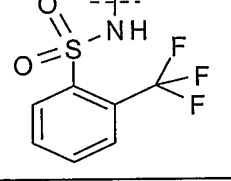
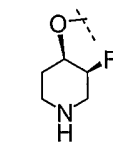
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40	N-[7-(1-Azabicyclo[2.2.2]oct-3-yloxy)-1-benzofuran-5-yl]-2-methoxy-5-benzenesulfonamide hydrochloride		
41	N-{7-[(2-Morpholin-4-ylethyl)amino]-1-benzofuran-5-yl} benzenesulfonamide hydrochloride		
42	2-Methoxy-5-methyl-N-{7-[(2-morpholin-4-ylethyl)amino]-1-benzofuran-5-yl} benzenesulfonamide hydrochloride		
43	N-{7-[(2-Morpholin-4-ylethyl)amino]-1-benzofuran-5-yl}-2-(trifluoromethyl)benzenesulfonamide hydrochloride		
44	2,6-Dichloro-N-{7-[(2-morpholin-4-ylethyl)amino]-1-benzofuran-5-yl} benzenesulfonamide hydrochloride		
45	2-Methoxy-5-methyl-N-[7-(2-morpholin-4-ylethoxy)-1-benzofuran-5-yl] benzenesulfonamide hydrochloride		
46	3-Methyl-N-[7-(2-morpholin-4-ylethoxy)-1-benzofuran-5-yl] benzenesulfonamide hydrochloride		

47	3-Chloro-4-methyl-N-[7-(2-morpholin-4-ylethoxy)-1-benzofuran-5-yl]benzenesulfonamide hydrochloride		
48	N-(7-{[2(Dimethylamino)ethyl]amino}-1-benzofuran-5-yl)-2-methoxy-5-benzenesulfonamide hydrochloride		
49	2-Chloro-N(7-{[2-(dimethylamino)]-1-benzofuran-5-yl})benzenesulfonamide hydrochloride		
50	N-[7-(Pyridin-4-ylamino)-1-benzofuran-5-yl]benzenesulfonamide hydrochloride		
51	2-Chloro-N[7-(pyridin-4-ylamino)-1-benzofuran-5-yl]benzenesulfonamide hydrochloride		
52	2-Methoxy-5-methyl-N-[7-(pyridin-4-ylamino)-1-benzofuran-5-yl]benzenesulfonamide hydrochloride		
53	2-Methoxy-5-methyl-N-[7-(piperazin-1-ylcarbonyl)-1-benzofuran-5-yl]benzenesulfonamide hydrochloride		
54	2-Methoxy-5-methyl-N-[7-(piperazin-1-ylmethyl)-1-benzofuran-5-yl]benzenesulfonamide hydrochloride		

55	N-{7-[(3-Aminopyrrolidin-1-yl)methyl]-1-benzofuran-5-yl}-2-methoxy-5-methylbenzenesulfonamide hydrochloride		
56	N-[7(6,6-Dioxidohexahydrothieno[3,4-b]pyrazin-1(2H)-yl)-1-benzofuran-5-yl]-2-methoxy-5-methylbenzenesulfonamide hydrochloride		
57	N-[7(6,6-Dioxidohexahydrothieno[3,4-b]pyrazin-1(2H)-yl)-1-benzofuran-5-yl]benzenesulfonamide hydrochloride		
58	N-{7-[(2-Pyrrolidin-1-ylethyl)amino]-1-benzofuran-5-yl}benzenesulfonamide hydrochloride		
59	2-Methoxy-5-methyl-N-{7-[(2-pyrrolidin-1-ylethyl)amino]-1-benzofuran-5-yl}benzenesulfonamide hydrochloride		
60	N-{7-[(2-Pyrrolidin-1-ylethyl)amino]-1-benzofuran-5-yl}-2-(trifluoromethyl)benzenesulfonamide hydrochloride		
61	3-Chloro-4-methyl-N-{7-[(2-pyrrolidin-1-ylethyl)amino]-1-benzofuran-5-yl}benzenesulfonamide hydrochloride		
62	2-Methoxy-5-methyl-N-{7-[(3-morpholin-4-ylpropyl)amino]-1-benzofuran-5-yl}benzenesulfonamide hydrochloride		

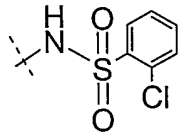
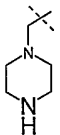
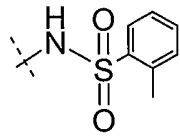
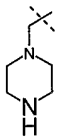
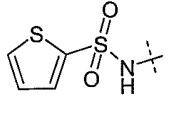
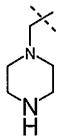
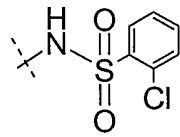
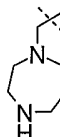
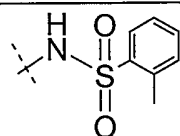
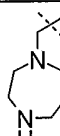
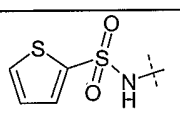
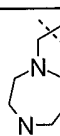
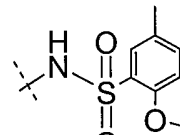
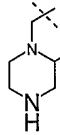
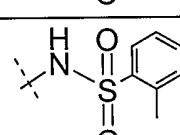
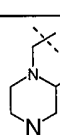
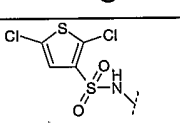
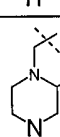
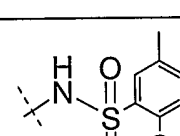
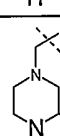
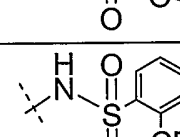
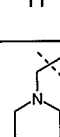
63	<i>N</i> -{7-[(3-Morpholin-4-ylpropyl)amino]-1-benzofuran-5-yl}-2-(trifluoromethyl)benzenesulfonamide hydrochloride		
64	3-Chloro-4-methyl- <i>N</i> -{7-[(3-morpholin-4-ylpropyl)amino]-1-benzofuran-5-yl}benzenesulfonamide hydrochloride		
65	<i>N</i> -[7-({[(2 <i>R</i>)-1-Ethylpyrrolidin-2-yl]methyl}amino)-1-benzofuran-5-yl]benzenesulfonamide hydrochloride		
66	<i>N</i> -[7-({[(2 <i>R</i>)-1-Ethylpyrrolidin-2-yl]methyl}amino)-1-benzofuran-5-yl]-2-methoxy-5-methylbenzenesulfonamide hydrochloride		
67	<i>N</i> -[7-({[(2 <i>R</i>)-1-Ethylpyrrolidin-2-yl]methyl}amino)-1-benzofuran-5-yl]-2-(trifluoromethyl)benzenesulfonamide hydrochloride		
68	<i>N</i> -[7-({[(2 <i>R</i>)-1-Ethylpyrrolidin-2-yl]methyl}amino)-1-benzofuran-5-yl]-3-methylbenzenesulfonamide hydrochloride		
69	<i>N</i> -[7-({[(2 <i>R</i>)-1-Ethylpyrrolidin-2-yl]methyl}amino)-1-benzofuran-5-yl]thiophene-2-sulfonamide hydrochloride		
70	5-Chloro- <i>N</i> -[7-({[(2 <i>R</i>)-1-ethylpyrrolidin-2-yl]methyl}amino)-1-benzofuran-5-yl]thiophene-2-sulfonamide hydrochloride		

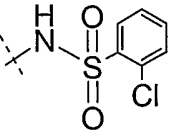
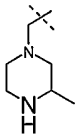
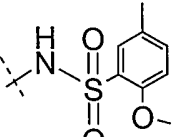
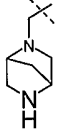
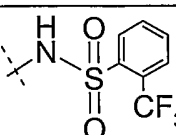
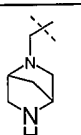
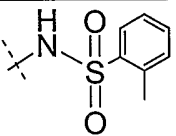
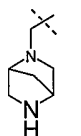
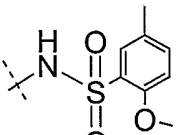
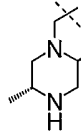
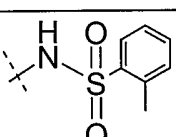
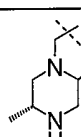
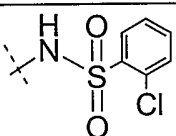
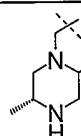
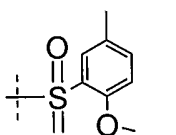
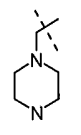
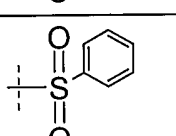
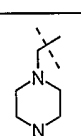
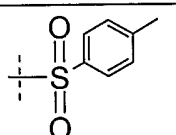
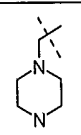
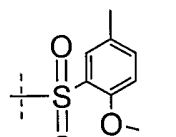
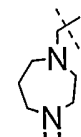
71	5-Chloro- <i>N</i> -[7-({[(2 <i>R</i>)-1-ethylpyrrolidin-2-yl]methyl}amino)-1-benzofuran-5-yl]-1,3-dimethyl-1 <i>H</i> -pyrazole-4-sulfonamide hydrochloride		
72	<i>N</i> -(7-{[3-(2-Methylpiperidin-1-yl)propyl]amino}-1-benzofuran-5-yl)benzenesulfonamide hydrochloride		
73	2-Methoxy-5-methyl- <i>N</i> -(7-{[3-(2-methylpiperidin-1-yl)propyl]amino}-1-benzofuran-5-yl)benzenesulfonamide hydrochloride		
74	<i>N</i> -(7-{[3-(2-Methylpiperidin-1-yl)propyl]amino}-1-benzofuran-5-yl)-2-(trifluoromethyl)benzenesulfonamide hydrochloride		
75	5-Chloro-1,3-dimethyl- <i>N</i> -(7-{[3-(2-methylpiperidin-1-yl)propyl]amino}-1-benzofuran-5-yl)-1 <i>H</i> -pyrazole-4-sulfonamide hydrochloride		
76	<i>N</i> -[7-(6-Aminopyridin-3-yl)-1-benzofuran-5-yl]-2-methoxy-5-methylbenzenesulfonamide		
77	<i>N</i> -{7-[4-(Cyclopropylmethyl)piperazin-1-yl]-1-benzofuran-5-yl}-2-methoxy-5-methylbenzenesulfonamide hydrochloride		
78	2-Methoxy-5-methyl- <i>N</i> -{7-[4-(3,3,3-trifluoropropyl)piperazin-1-yl]-1-benzofuran-5-yl}benzenesulfonamide hydrochloride		

79	2-Methoxy-5-methyl-N-{7-[3-(trifluoromethyl)piperazin-1-yl]-1-benzofuran-5-yl}benzenesulfonamide hydrochloride		
80	N-[7-(Aminopiperidin-1-yl)-1-benzofuran-5-yl]-2-(trifluoromethyl)benzenesulfonamide hydrochloride		
81	N-[7-(Aminopiperidin-1-yl)-1-benzofuran-5-yl]-benzenesulfonamide hydrochloride		
82	N-[7-(Aminopiperidin-1-yl)-1-benzofuran-5-yl]-2-chlorobenzenesulfonamide hydrochloride		
83	N-[7-(Aminopiperidin-1-yl)-1-benzofuran-5-yl]-2-methoxy-5-methylbenzenesulfonamide hydrochloride		
84	N-(7-{[<i>cis</i> -3-Fluoropiperidin-4-yl]oxy}-1-benzofuran-5-yl)-2-methoxy-5-methylbenzenesulfonamide hydrochloride		
85	N-(7-{[<i>trans</i> -3-Fluoropiperidin-4-yl]oxy}-1-benzofuran-5-yl)-2-methoxy-5-methylbenzenesulfonamide hydrochloride		
86	N-(7-{[<i>cis</i> -3-Fluoropiperidin-4-yl]oxy}-1-benzofuran-5-yl)-2-(trifluoromethyl)benzenesulfonamide hydrochloride		

87	<i>N</i> -(7-{{ <i>trans</i> -3-Fluoropiperidin-4-yl}oxy}-1-benzofuran-5-yl)-2-(trifluoromethyl)benzenesulfonamide hydrochloride		
88	2-Chloro- <i>N</i> -(7-{{ <i>trans</i> -3-fluoropiperidin-4-yl}oxy}-1-benzofuran-5-yl)benzenesulfonamide hydrochloride		
89	<i>N</i> -(7-{{ <i>trans</i> -3-Fluoropiperidin-4-yl}oxy}-1-benzofuran-5-yl)-3-methylbenzenesulfonamide hydrochloride		
90	3,6-Dichloro- <i>N</i> -(7-{{ <i>trans</i> -3-fluoropiperidin-4-yl}oxy}-1-benzofuran-5-yl)-2-methylbenzenesulfonamide hydrochloride		
91	2-Chloro-5-fluoro- <i>N</i> -(7-{{ <i>trans</i> -3-fluoropiperidin-4-yl}oxy}-1-benzofuran-5-yl)benzenesulfonamide hydrochloride		
92	<i>N</i> -(2-Methoxy-5-methylphenyl)-7-[(3-methylpiperazin-1-yl)methyl]-1-benzofuran-5-sulfonamide hydrochloride		
93	<i>N</i> -(2-Methylphenyl)-7-(piperazin-1-ylmethyl)-1-benzofuran-5-sulfonamide, trifluoroacetate		
94	7-[(3,5-Dimethylpiperazin-1-yl)methyl]- <i>N</i> -(2-methylphenyl)-1-benzofuran-5-sulfonamide, trifluoroacetate		
95	<i>N</i> -(2-Methylphenyl)-7-[(3-methylpiperazin-1-yl)methyl]-1-benzofuran-5-sulfonamide, trifluoroacetate		

96	7-(1,4-Diazepan-1-ylmethyl)-N-(2-methylphenyl)-1-benzofuran-5-sulfonamide, trifluoroacetate		
97	7-{{(trans-2,5-Dimethylpiperazin-1-yl)methyl}-N-(2-methylphenyl)-1-benzofuran-5-sulfonamide, trifluoroacetate		
98	N-(2-Methylphenyl)-7-{{(2R)-2-methylpiperazin-1-yl)methyl}-1-benzofuran-5-sulfonamide, trifluoroacetate		
99	N-(2-Methoxy-5-methylphenyl)-7-[(3-methylpiperazin-1-yl)methyl]-1-benzofuran-5-sulfonamide, trifluoroacetate		
100	7-(1,4-Diazepan-1-ylmethyl)-N-(2-methoxy-5-methylphenyl)-1-benzofuran-5-sulfonamide, trifluoroacetate		
101	N-(2-Methoxy-5-methylphenyl)-7-(piperazin-1-ylmethyl)-1-benzofuran-5-sulfonamide, trifluoroacetate		
102	7-{{(cis-3,5-Dimethylpiperazin-1-yl)methyl}-N-(2-methoxy-5-methylphenyl)-1-benzofuran-5-sulfonamide, trifluoroacetate		
103	7-{{[trans-2,5-Dimethylpiperazin-1-yl)methyl]-N-(2-methoxy-5-methylphenyl)-1-benzofuran-5-sulfonamide, trifluoroacetate		
104	7-(2,5-Diazabicyclo[2.2.1]hept-2-ylmethyl)-N-(2-methoxy-5-methylphenyl)-1-benzofuran-5-sulfonamide, trifluoroacetate		
105	N-(2-Methoxy-5-methylphenyl)-7-[(2-methylpiperazin-1-yl)methyl]-1-benzofuran-5-sulfonamide, trifluoroacetate		

106	2-Chloro-N-[7-(piperazin-1-ylmethyl)-1-benzofuran-5-yl]benzenesulfonamide dihydrochloride		
107	2-Methyl-N-[7-(piperazin-1-ylmethyl)-1-benzofuran-5-yl]benzenesulfonamide, dihydrochloride		
108	N-[7-(Piperazin-1-ylmethyl)-1-benzofuran-5-yl]thiophene-2-sulfonamide, dihydrochloride		
109	2-Chloro-N-[7-(1,4-diazepan-1-ylmethyl)-1-benzofuran-5-yl]benzenesulfonamide dihydrochloride		
110	N-[7-(1,4-Diazepan-1-ylmethyl)-1-benzofuran-5-yl]-2-methylbenzenesulfonamide, dihydrochloride		
111	N-[7-(1,4-Diazepan-1-ylmethyl)-1-benzofuran-5-yl]thiophene-2-sulfonamide dihydrochloride		
112	2-Methoxy-5-methyl-N-{7-[(2-methylpiperazin-1-yl)methyl]-1-benzofuran-5-yl}benzenesulfonamide, dihydrochloride		
113	2-Methyl-N-{7-[(2-methylpiperazin-1-yl)methyl]-1-benzofuran-5-yl}benzenesulfonamide dihydrochloride		
114	2,5-Dichloro-N-{7-[(2-methylpiperazin-1-yl)methyl]-1-benzofuran-5-yl}thiophene-3-sulfonamide dihydrochloride		
115	2-Methoxy-5-methyl-N-{7-[(3-methylpiperazin-1-yl)methyl]-1-benzofuran-5-yl}benzenesulfonamide, dihydrochloride		
116	N-{7-[(3-Methylpiperazin-1-yl)methyl]-1-benzofuran-5-yl}-2-(trifluoromethyl)benzenesulfonamide, dihydrochloride		

117	2-Chloro-N-{7-[(3-methylpiperazin-1-yl)methyl]-1-benzofuran-5-yl}benzenesulfonamide, dihydrochloride		
118	N-[7-(2,5-Diazabicyclo[2.2.1]hept-2-ylmethyl)-1-benzofuran-5-yl]-2-methoxy-5-methylbenzenesulfonamide, dihydrochloride		
119	N-[7-(2,5-Diazabicyclo[2.2.1]hept-2-ylmethyl)-1-benzofuran-5-yl]-2-(trifluoromethyl)benzenesulfonamide, dihydrochloride		
120	N-[7-(2,5-Diazabicyclo[2.2.1]hept-2-ylmethyl)-1-benzofuran-5-yl]-2-methylbenzenesulfonamide, dihydrochloride		
121	2-Methoxy-5-methyl-N-{7-[(trans-2,5-dimethylpiperazin-1-yl)methyl]-1-benzofuran-5-yl}benzenesulfonamide, bistrifluoroacetate		
122	2-Methyl-N-{7-[(trans-2,5-dimethylpiperazin-1-yl)methyl]-1-benzofuran-5-yl}benzenesulfonamide, bistrifluoroacetate		
123	2-Chloro-N-{7-[(trans-2,5-dimethylpiperazin-1-yl)methyl]-1-benzofuran-5-yl}benzenesulfonamide, bistrifluoroacetate		
124	1-({5-[(2-Methoxy-5-methylphenyl)sulfonyl]-1-benzofuran-7-yl}methyl)piperazine, trifluoroacetate		
125	1-({5-[(Phenylsulfonyl)-1-benzofuran-7-yl]methyl}piperazine, trifluoroacetate		
126	1-({5-[(4-Methylphenyl)sulfonyl]-1-benzofuran-7-yl}methyl)piperazine, trifluoroacetate		
127	1-({5-[(2-Methoxy-5-methylphenyl)sulfonyl]-1-benzofuran-7-yl}methyl)-1,4-diazepane, trifluoroacetate		

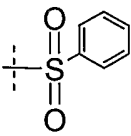
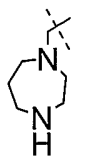
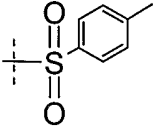
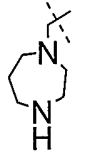
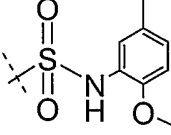
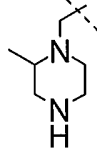
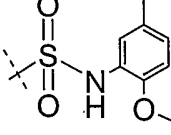
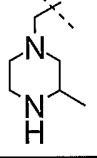
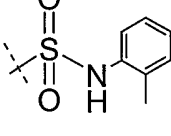
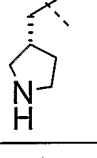
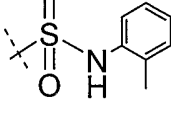
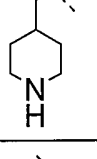
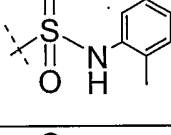
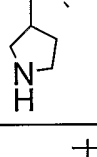
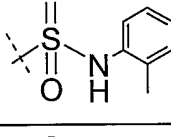
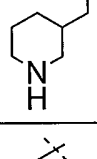
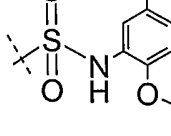
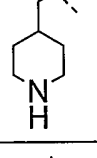
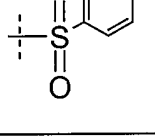
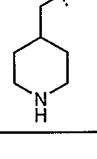
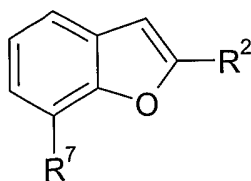
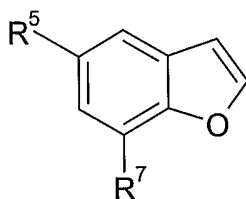
128	1-([5-(Phenylsulfonyl)-1-benzofuran-7-yl]methyl)-1,4-diazepane, trifluoroacetate		
129	1-([5-[(4-Methylphenyl)sulfonyl]-1-benzofuran-7-yl]methyl)-1,4-diazepane, trifluoroacetate		
130	1-([5-[(2-Methoxy-5-methylphenyl)sulfonyl]-1-benzofuran-7-yl]methyl)-2-methylpiperazine, trifluoroacetate		
131	1-([5-[(2-Methoxy-5-methylphenyl)sulfonyl]-1-benzofuran-7-yl]methyl)-3-methylpiperazine, trifluoroacetate		
134	N-(2-Methylphenyl)-7-[(3R)-pyrrolidin-3-ylamino]methyl-1-benzofuran-5-sulfonamide, trifluoroacetate		
135	N-(2-Methylphenyl)-7-(piperidin-4-ylmethyl)-1-benzofuran-5-sulfonamide, trifluoroacetate		
136	N-(2-Methylphenyl)-7-(pyrrolidin-3-ylmethyl)-1-benzofuran-5-sulfonamide, trifluoroacetate		
137	N-(2-Methylphenyl)-7-(piperidin-3-ylmethyl)-1-benzofuran-5-sulfonamide, trifluoroacetate		
138	2-Methoxy-5-methyl-N-[7-(piperidin-4-ylmethyl)-1-benzofuran-5-yl]benzenesulfonamide, trifluoroacetate		
139	3-([5-[(4-Methylphenyl)sulfonyl]-1-benzofuran-7-yl]methyl)pyrrolidine, trifluoroacetate		

Table 2



EXAMPLE		R7	R2
36	N-[2-(1-Azabicyclo[2.2.2]oct-2-en-3-yl)-1-benzofuran-7-yl]benzenesulfonamide hydrochloride		
37	N-[2-(1-Azabicyclo[2.2.2]oct-2-en-3-yl)-1-benzofuran-7-yl]-2-methoxy-5-methylbenzenesulfonamide hydrochloride		

Table 3



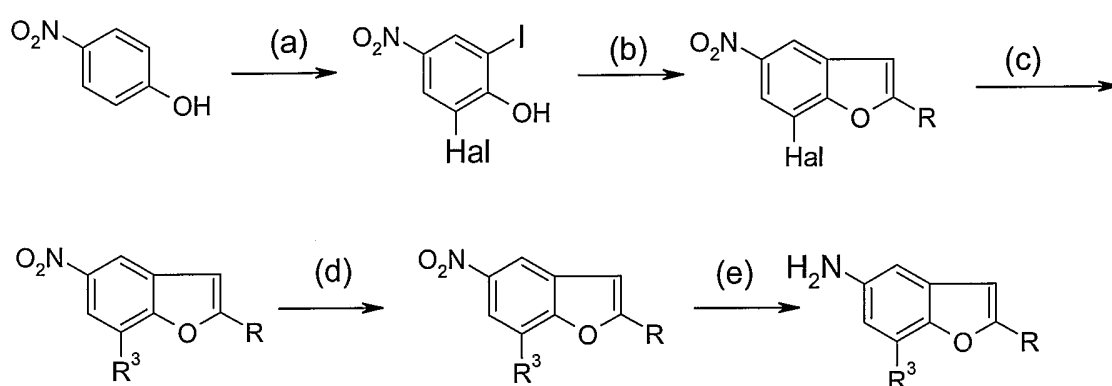
EXAMPLE		R7	R5
132	2-Methoxy-5-methyl-N-[5-(piperidin-4-ylmethyl)-1-benzofuran-7-yl]benzenesulfonamide, trifluoroacetate		
133	2-Methoxy-5-methyl-N-{5-[(3-methylpiperazin-1-yl)methyl]-1-benzofuran-7-yl}benzenesulfonamide, bis(trifluoroacetate)		
140	2-Methoxy-5-methyl-N-[5-(piperidin-4-ylmethyl)-1-benzofuran-7-yl]benzenesulfonamide, trifluoroacetate		

5

The preparation of the compounds of Formula (I) according to the Examples may in particular be illuminated by the following Schemes 1-6, wherein steps (a) to (s) are detailed below.

The experimental details are given for each of the specific synthetic examples. Schemes 1-6 are merely illustrative of some methods by which the compounds of the present invention may be synthesized, and various modifications to these synthetic reaction schemes may be made. Any primary or secondary amine nitrogen, if present, in R³ may optionally be protected with a nitrogen protecting group, such as tert-butoxycarbonyl (t-BOC) or benzyl, in reactions targeting a compound of Formula (I). Subsequent N-deprotection is carried out by conventional methods such as those described in Protective Groups in Organic Synthesis, John Wiley & Sons, 1991.

10 Scheme 1



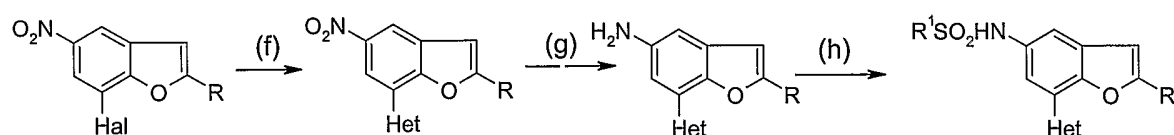
R = H or SiMe₃

Hal = Cl, Br, or I

R³ is as defined for Formula (I).

15

Scheme 2



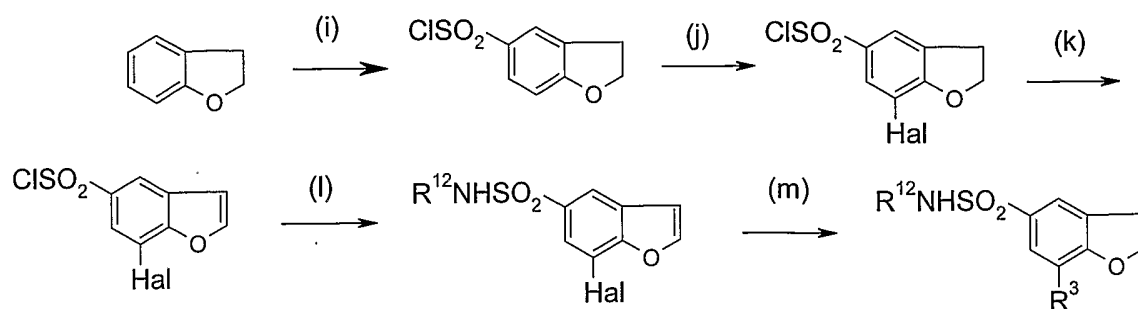
R = H or SiMe₃

20

Hal = Cl, Br, or I

Het = a heteroaryl group or a heterocyclic group within the scope of R³ as defined for Formula (I). Exemplary heteroaryl or heterocyclic groups are selected from 3-pyridyl, 4-pyridyl, pyrazinyl, 5-pyrimidyl, and 1-azabicyclo[2.2.2]oct-3-en-2-yl

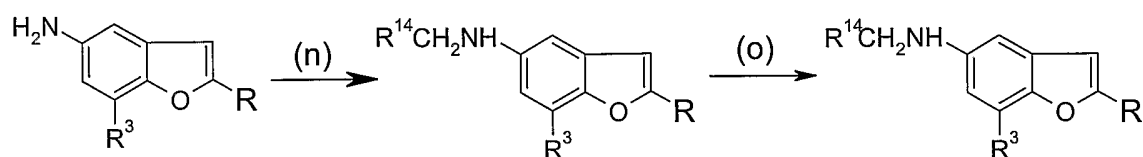
R¹ is as defined for Formula (I).

Scheme 3

Hal = Cl, Br, or I

R^3 and R^{12} are as defined for Formula (I)

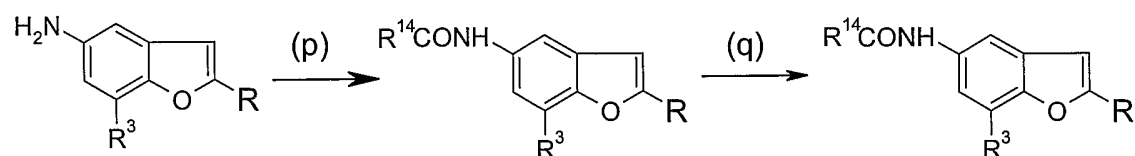
5

Scheme 4

$R = H$ or $SiMe_3$

R^3 and R^{14} are as defined for Formula (I).

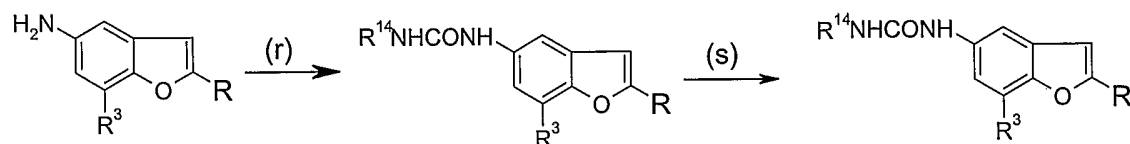
10

Scheme 5

$R = H$ or $SiMe_3$

R^3 and R^{14} are as defined for Formula (I).

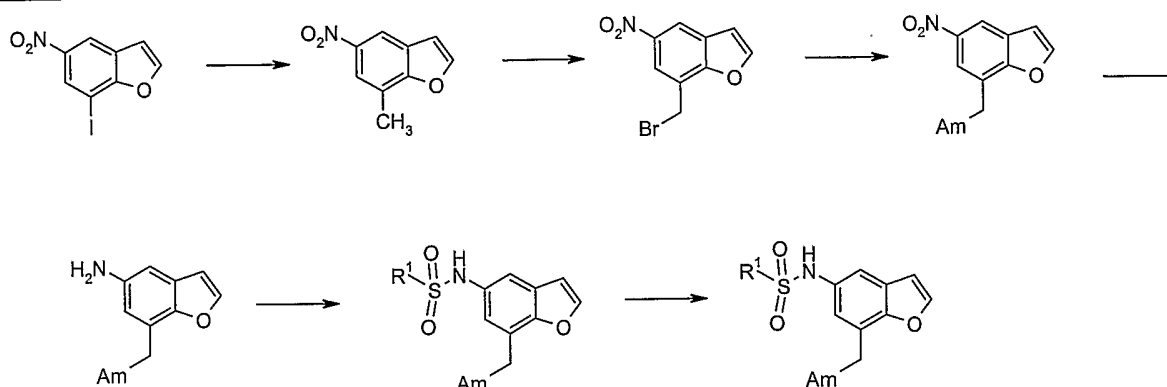
15

Scheme 6

$R = H$ or $SiMe_3$

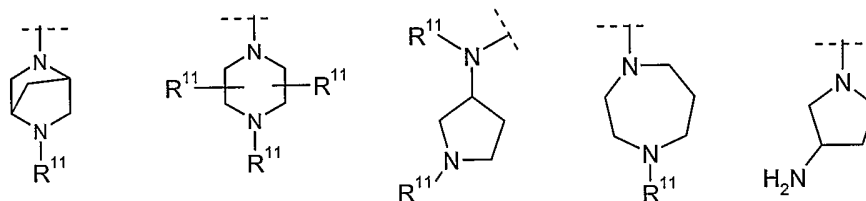
R^3 and R^{14} are as defined for Formula (I).

20

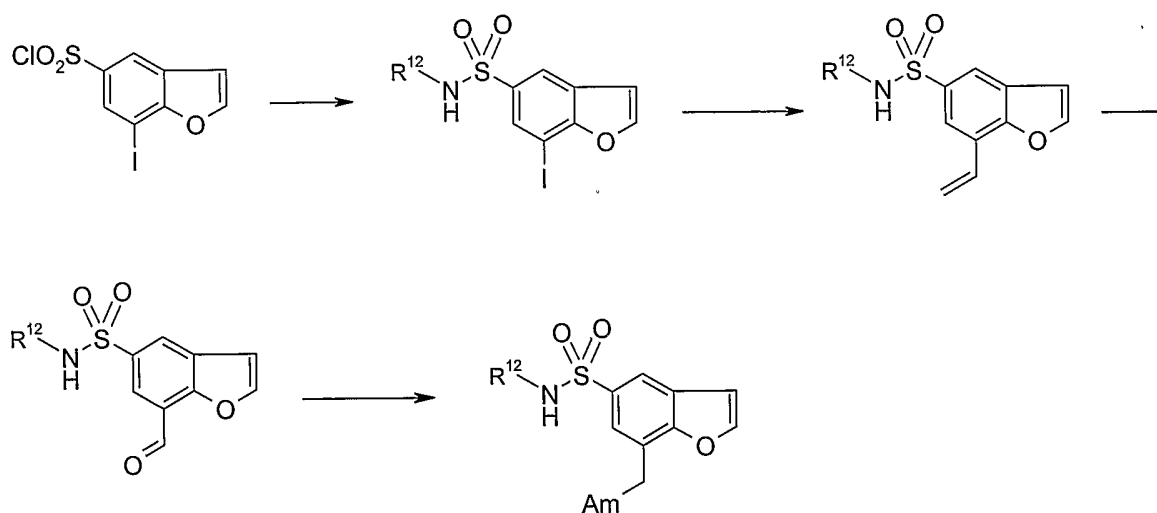
Scheme 7

R¹ is as defined for formula (I) and Am is attached to the remainder of the molecule via a nitrogen atom. Exemplary Am groups are depicted in Figure 1.

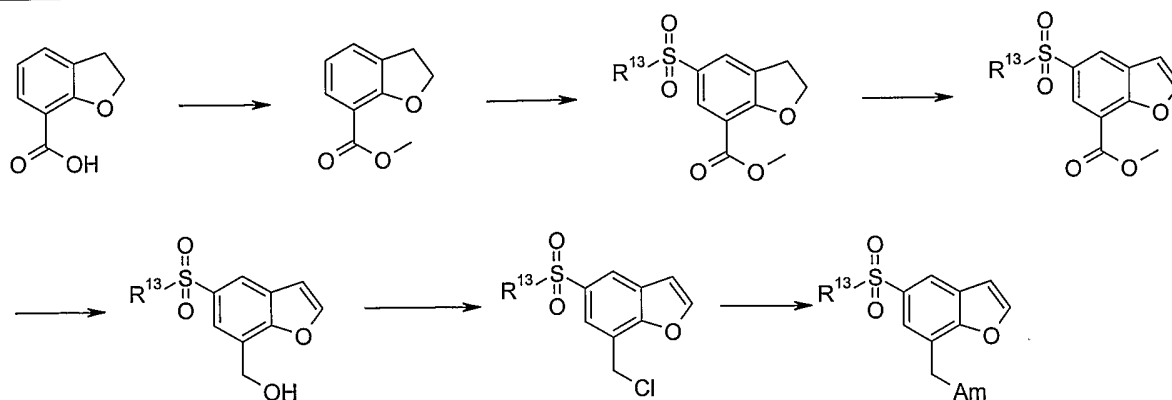
5

Figure 1

wherein R¹¹ is each independently selected from hydrogen or methyl.

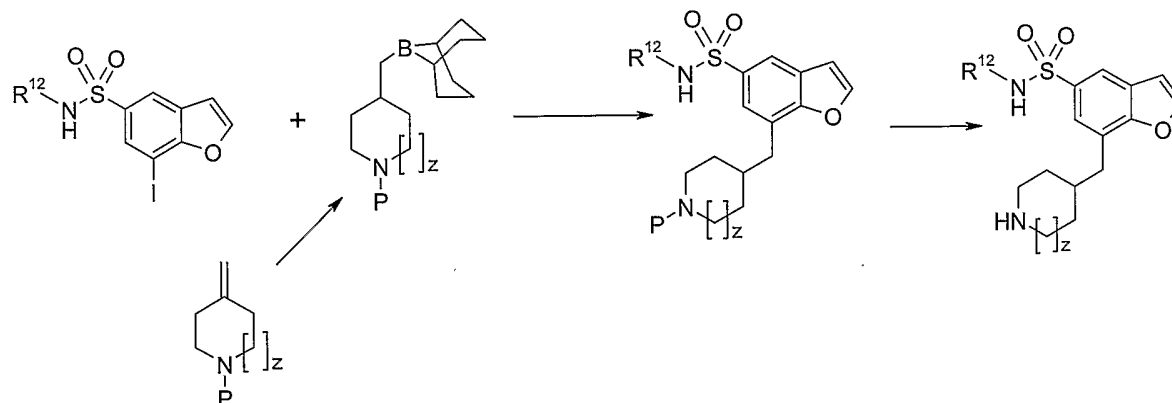
10 **Scheme 8**

R¹² is as defined for formula (I) and Am is attached to the remainder of the molecule via a nitrogen atom. Exemplary Am groups are shown in Figure 1.

Scheme 9

R^{12} is as defined for formula (I) and Am is attached to the remainder of the molecule via a nitrogen atom. Exemplary Am groups are shown in Figure 1.

5

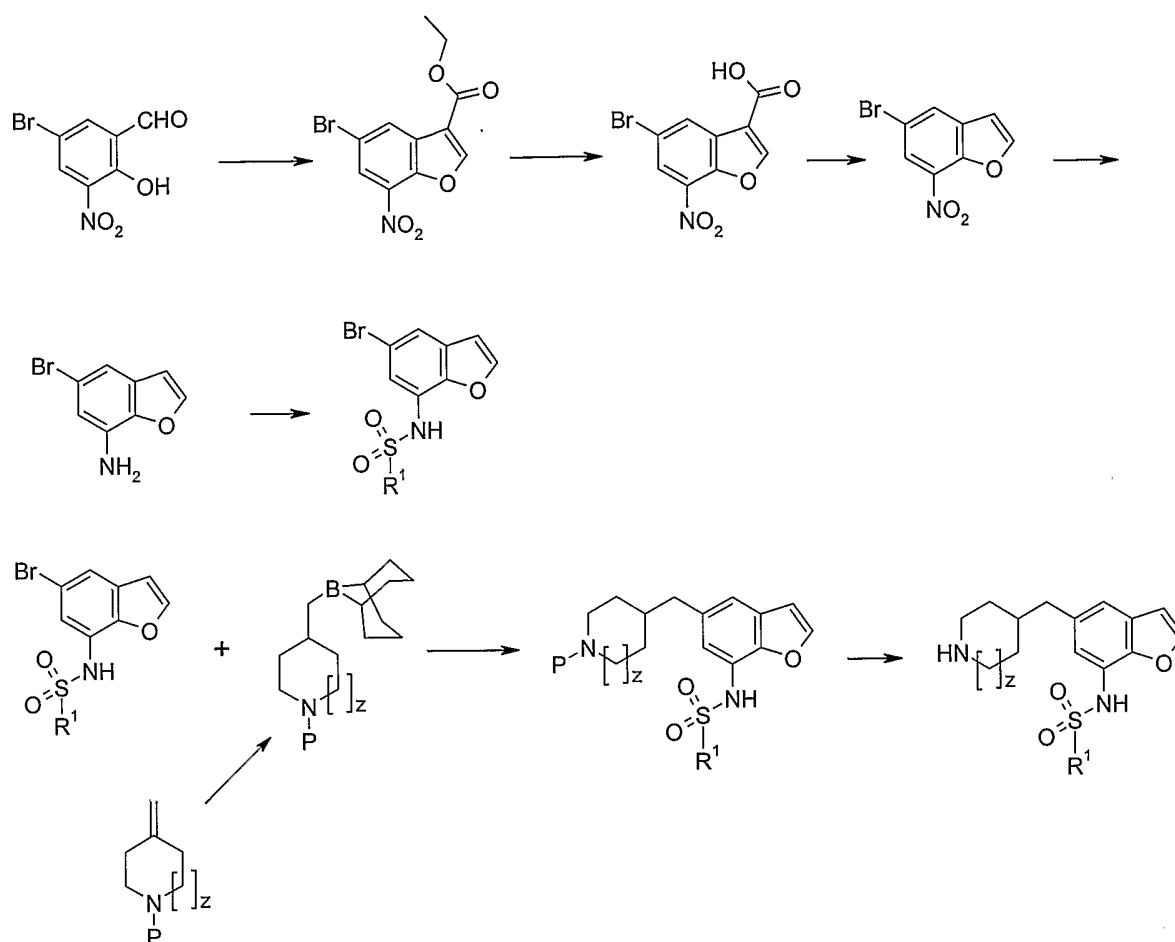
Scheme 10

R^{12} is as defined for formula (I);

P is a suitable protecting group such as t-BOC

and $z = 0, 1$ or 2

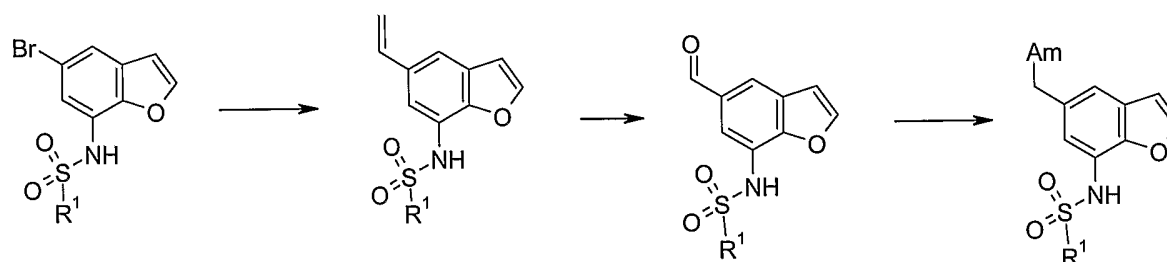
10

Scheme 11

R^1 is as defined for formula (I);

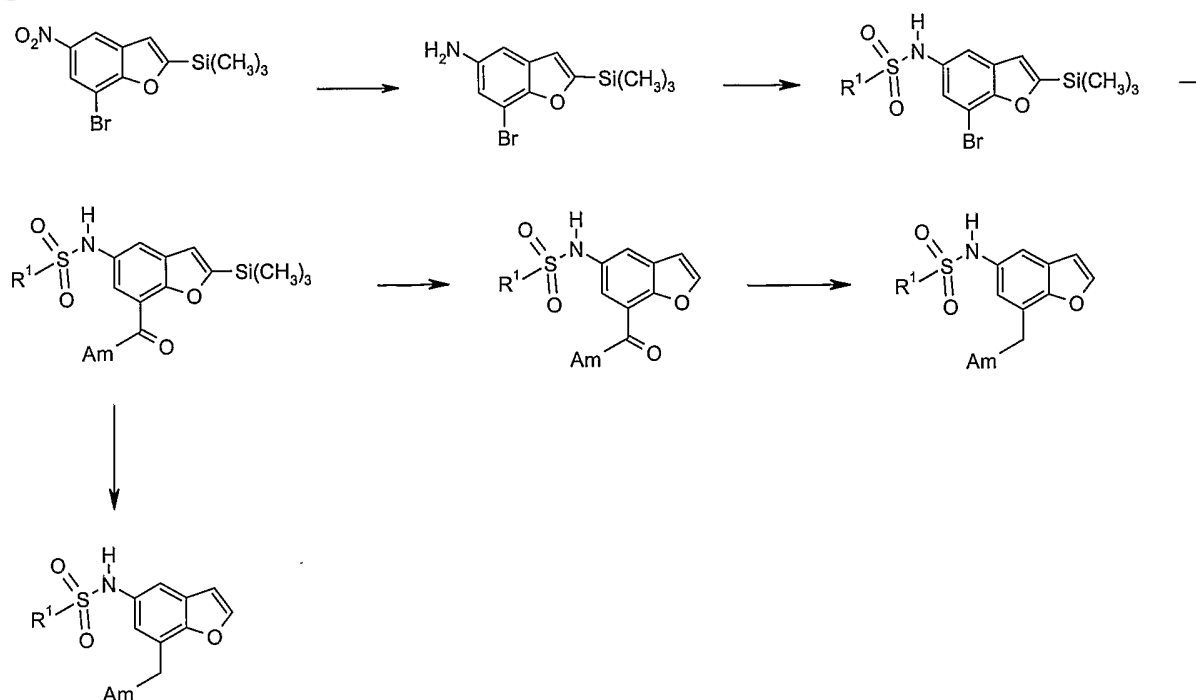
P is a suitable protecting group such as t-BOC; and

$z = 0, 1$ or 2

Scheme 12

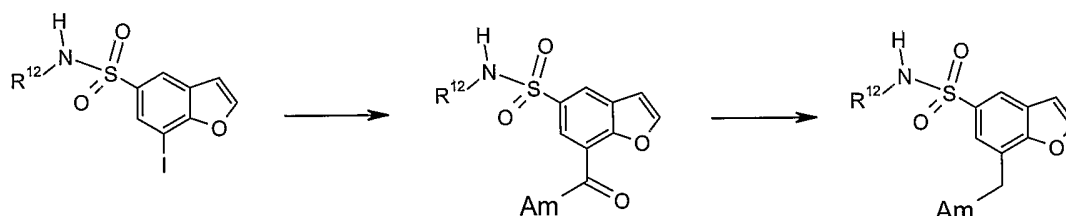
R^1 is as defined for formula (I) and Am is attached to the remainder of the molecule

via a nitrogen atom. Exemplary Am groups are shown in Figure 1.

Scheme 13

R^1 is as defined for formula (I) and Am is attached to the remainder of the molecule via a nitrogen atom. Exemplary Am groups are shown in Figure 1.

5

Scheme 14

R^{12} is as defined for formula (I) and Am is attached to the remainder of the molecule via a nitrogen atom. Exemplary Am groups are shown in Figure 1.

10

INTERMEDIATE 1**N,N'-Dimethyl-N-(5-nitro-1-benzofuran-7-yl)-propyl-1,3-diamine**

To a mixture of 7-iodo-5-nitro-1-benzofuran (prepared according to the following procedures Castro, C. E.; Stephens, R. D. *J. Org. Chem.* **1963**, 28, 2163 and Doad, G. J. S.; Barltrop, J. A.; Petty, C. M.; Owen, T. C. *Tetrahedron Lett.* **1989**, 30, 1597-1598) (300 mg, 1.0 mmol), Xantphos (60 mg, 0.1 mmol), $Pd_2(dba)_3$ (23 mg, 25 μ mol), sodium tert-butoxide (125 mg, 1.3 mmol) in xylene (10 mL) was added N,N'-dimethylpropane-1,3-diamine (540 μ L, 5 mmol). The mixture was stirred at 120 °C for 2 h, allowed to cool and

15

filtered through a Celite pad. The filtrate was concentrated in vacuo to give the crude title compound. MS m/z 264 (M+H)⁺.

INTERMEDIATE 2

5 **tert-Butyl 3-[(5-amino-1-benzofuran-7-yl)(methyl)amino]propyl(methyl)carbamate**

The crude N,N'-dimethyl-N-(5-nitro-1-benzofuran-7-yl)propyl-1,3-diamine (Intermediate 1) was dissolved in DCM (10 mL) and di-tert-butyl dicarbonate (327 mg, 1.5 mmol) in DCM (5 mL) was added at 0 °C. The mixture was stirred at 0 °C for 15 min, after which time the ice-bath was removed and the mixture was stirred for 2 h at room temperature.

- 10 Water was added. The organic material was extracted with chloroform (2x), the combined organic layers were dried (MgSO₄) and filtered. The volatiles were evaporated to give a yellow oil which was filtered through silica gel eluting with EtOAc. The volatiles were evaporated and the crude material of tert-butyl methyl[3-(methyl{5-nitro-1-benzofuran-7-yl}amino)]propyl]carbamate was dissolved in EtOH and an excess of Raney Ni as a
- 15 suspension in EtOH (4 mL) was added followed by the addition of hydrazine hydrate (300 µL, 6 mmol). The reaction mixture was stirred at room temperature for 2 h followed by filtration through a Celite pad pre-treated with water. The Celite pad was washed with MeOH and the filtrate was concentrated in vacuo to give the title compound (250 mg) as a crude, which was used directly in the next step.

20

INTERMEDIATE 3

tert-Butyl methyl[3-(methyl{5-[(phenylsulfonyl)amino]-1-benzofuran-7-yl}amino)propyl]carbamate

- 25 Benzenesulfonyl chloride (115 µL, 0.9 mmol) was added to a mixture of tert-butyl 3-[(5-amino-1-benzofuran-7-yl)(methyl)amino]propyl(methyl)carbamate (Intermediate 2; 250 mg, 0.75 mmol) in DCM (2 mL) followed by addition of pyridine (1 mL). The reaction mixture was stirred at room temperature for 4 h. The volatiles were evaporated in vacuo and the residue obtained was purified using RP-HPLC (Gilson/YMC AQ C18; 150x30 mm) to give the title compound as a beige oil (202 mg, 43% over 4 steps); HPLC 93%, R_T:
- 30 2.49 min (System A); 95%, R_T: 2.27 min (System B); ¹H NMR (CDCl₃) δ ppm 1.41 (s, 9H), 1.60-1.75 (m, 2H), 2.74 (s, 3H), 2.93 (s, 3H), 3.13-3.25 (m, 2H), 3.42-3.53 (m, 2H), 6.19-6.69 (m, 2H), 6.87-7.06 (m, 1H), 7.33-7.58 (m, 4H), 7.71-7.79 (m, 2H); MS m/z 474 (M+H)⁺.

EXAMPLE 1

N-(7-{Methyl[3-(methylamino)propyl]amino}-1-benzofuran-5-yl)benzenesulfonamide hydrochloride

5 tert-Butyl methyl[3-(methyl{5-[(phenylsulfonyl)amino]-1-benzofuran-7-yl}amino)propyl]carbamate (Intermediate 3; 202 mg, 0.43 mmol) in DCM (2 mL) was treated with TFA (2 mL) at 0 °C for 10 min and was stirred for an additional 30 min at room temperature. After concentration in vacuo, the residue was re-dissolved in MeOH and treated with an excess of 1M HCl in diethyl ether. Removal of the solvents gave the
10 title compound (173 mg, 98%) as a white solid; HPLC 100%, R_T : 1.65 min (System A); 100%, R_T : 0.630 min (System B); ^1H NMR (methanol- d_4) δ ppm 1.85-2.00 (m, 2H), 2.67 (s, 3H), 3.04-3.17 (m, 5H), 3.64-3.73 (m, 2H), 6.81-6.84 (m, 1H), 6.95-6.98 (m, 1H), 7.06-7.09 (m, 1H), 7.43-7.60 (m, 3H), 7.72-7.78 (m, 2H), 7.81-7.85 (m, 1H); MS m/z 374 (M+H) $^+$.

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INTERMEDIATE 4

1-(5-Nitro-1-benzofuran-7-yl)piperidine

Step 1. 2-Bromo-6-iodo-4-nitrophenol. A solution of 4-nitrophenol (130 g, 0.96 mol) in acetonitrile (500 mL) was cooled to 0 °C. While keeping the temperature below 5 °C,
20 chlorosulfonic acid (120 g, 1.03 mol) was added. The resulting mixture was stirred for 30 min at 0-5 °C. N-bromosuccinimide (181 g, 1.01 mol) was added portionwise to the mixture during 7 h, while keeping the temperature below 8 °C. The reaction was then quenched by addition of a solution of NaHSO₃ (250 g, 2.4 mol) in water (600 mL) while the temperature was kept below 20 °C. The water phase was removed and the remaining
25 organic phase was concentrated to 300 mL by distillation. The residue was diluted with acetic acid (381 mL, 6.6 mol) and potassium acetate (212 g, 2.16 mol) was added. The temperature was adjusted to 50 °C and ICl (152 g, 0.936 mol) was added while the temperature was maintained between 50 and 80 °C. When the addition was completed, the product was precipitated by addition of water (1000 mL). After cooling to 10 °C, the
30 product was isolated by filtration, to yield 290 g (90%) of 2-bromo-6-iodo-4-nitrophenol. ^1H NMR (270 MHz, CDCl₃) δ ppm 6.53 (s, 1 H) 8.42 (d, $J=2.72$ Hz, 1 H) 8.58 (d, $J=2.72$ Hz, 1 H).

Step 2. 7-Bromo-5-nitro-2-(trimethylsilyl)benzofuran. To a solution of 2-bromo-6-iodo-4-nitrophenol (200 g, 581.56 mmol; obtained in Step 1) in acetonitrile (2800 mL) were added CuI (2.22 g, 11.63 mmol) and Et₃N (117.70 g, 1163.12 mmol). N₂ atmosphere was established and PdCl₂(PPh₃)₂ (4.08 g, 5.82 mmol) was added followed by slow addition of (trimethylsilyl)acetylene (59.98 g, 610.64 mmol) during 2 h. The reaction mixture was stirred overnight until complete formation of intermediate 2-bromo-4-nitro-6-[(trimethylsilyl)ethynyl]phenol and then heated to 85 °C for 8 h. The mixture was diluted with acetonitrile (1500 mL) and activated carbon (6 g) was added followed by water (600 mL). The resulting suspension was heated to 85 °C and the carbon was removed by filtration. The volume was adjusted to 1950 mL by distillation followed by the addition of water (1600 mL). The product was obtained as an oily precipitation that solidified upon cooling. The liquid was decanted off and the solid residue was dissolved in acetonitrile (500 mL). The volatiles were eliminated to give 149.7 g (82%) of 7-bromo-5-nitro-2-(trimethylsilyl)-benzofuran. ¹H NMR (270 MHz, CDCl₃) δ ppm 0.39 (s, 9 H) 7.12 (s, 1 H) 8.38 (d, J=2.23 Hz, 1 H) 8.42 (d, J=2.23 Hz, 1 H).

Step 3. 1-(5-Nitro-1-benzofuran-7-yl)piperidine. A mixture of 7-bromo-5-nitro-2-(trimethylsilyl)benzofuran (1.57 g, 5 mmol; obtained in Step 2), piperidine (0.47 g, 5.5 mmol), Pd(OAc)₂ (56 mg, 0.25 mmol), BINAP (0.31 g, 0.5 mmol) and NaOtBu (0.96 g, 10 mmol) in xylene (15 mL) was stirred at 110 °C for 6 h. The cooled mixture was filtered through Celite and concentrated to give an oil that was put on a SiO₂-column and eluted with EtOAc/hexane (25:75) to give 1-(5-nitro-1-benzofuran-7-yl)piperidine. Yield: 650 mg (53%). ¹H NMR (400 MHz, CDCl₃) δ ppm 1.62-1.70 (m, 2 H), 1.77-1.85 (m, 4 H), 3.36 (t, 4 H), 6.86 (d, 1 H), 7.64 (d, 1 H), 7.73 (d, 1 H), 8.09 (d, 1 H); GC-MS (EI+) for C₁₃H₁₄N₂O₃ m/z 246 M⁺.

INTERMEDIATE 5

4-(5-Nitro-1-benzofuran-7-yl)morpholine

Prepared according to the procedure of Intermediate 4 (Step 3) starting from morpholine. Yield: 460 mg (37%); ¹H NMR (400 MHz, CDCl₃) δ ppm 3.40-3.45 (m, 4 H), 3.94-3.98 (m, 4 H), 6.90 (d, 1 H), 7.64 (d, 1 H), 7.74 (d, 1 H), 8.15 (d, 1 H); GC-MS (EI+) for C₁₂H₁₂N₂O₄ m/z 248 (M)⁺.

INTERMEDIATE 6

7-Piperidin-1-yl-1-benzofuran-5-amine

1-(5-Nitro-1-benzofuran-7-yl)piperidine (630 mg, 2.56 mmol; Intermediate 4) was dissolved in EtOAc (50 mL), PtO₂ added and the mixture stirred under H₂ for 36 h.

Filtration through Celite and concentration of the filtrate furnished 7-piperidin-1-yl-1-

5 benzofuran-5-amine. Yield: 540 mg (98%). ¹H NMR (400 MHz, CDCl₃) δ ppm 1.59-1.65 (m, 2 H), 1.71-1.83 (m, 4 H), 3.21-3.26 (m, 4 H), 3.55 (br s, 2 H), 6.19 (d, 1 H), 6.45 (d, 1 H), 6.56 (d, 1 H), 7.51 (d, 1 H); GC-MS (EI⁺) for C₁₃H₁₆N₂O *m/z* 216 M⁺.

INTERMEDIATE 7**10 7-Morpholin-4-yl-1-benzofuran-5-amine**

Prepared according to the procedure of Intermediate 6 starting from 4-(5-nitro-1-benzofuran-7-yl)morpholine (Intermediate 5). Yield: 520 mg (98%); ¹H NMR (400 MHz, CDCl₃) δ ppm 3.28-3.32 (m, 4 H), 3.56 (br s, 2 H), 3.91-3.95 (m, 4 H), 6.17 (d, 1 H), 6.50 (d, 1 H), 6.58 (d, 1 H), 7.50 (d, 1 H); GC-MS (EI⁺) for C₁₂H₁₄N₂O₂ *m/z* 218 (M)⁺.

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EXAMPLE 2**N-(7-Piperidin-1-yl-1-benzofuran-5-yl)benzenesulfonamide**

The synthesis was performed according to the procedure of Intermediate 3 starting from 7-piperidin-1-yl-1-benzofuran-5-amine (Intermediate 6). Yield: 70 mg (39%). ¹H NMR (400
20 MHz, CDCl₃) δ ppm 1.57-1.62 (m, 2 H), 1.70-1.78 (m, 4 H), 3.16 (t, 4 H), 6.39 (br s, 1 H), 6.41 (d, 1 H), 6.63 (d, 1 H), 6.83 (d, 1 H), 7.37-7.43 (m, 2 H), 7.49-7.54 (m, 1 H), 7.57 (d, 1 H), 7.68-7.72 (m, 2 H); MS (ESI⁺) for C₁₉H₂₀N₂O₃S *m/z* 357 (M+H)⁺; HPLC 97% (System A).

25 EXAMPLE 3**4-Fluoro-N-(7-piperidin-1-yl-1-benzofuran-5-yl)benzenesulfonamide**

The synthesis was performed according to the procedure of Intermediate 3 starting from 7-piperidin-1-yl-1-benzofuran-5-amine (Intermediate 6). Yield: 55 mg (29%). ¹H NMR (400
30 MHz, CDCl₃) δ ppm 1.56-1.65 (m, 2 H), 1.70-1.79 (m, 4 H), 3.19 (t, 4 H), 6.43 (d, 1 H), 6.48 (br s, 1 H), 6.63 (d, 1 H), 6.81 (d, 1 H), 7.04-7.10 (m, 2 H), 7.58 (d, 1 H), 7.68-7.74 (m, 2 H); ¹³C NMR (100 MHz, CDCl₃) δ 24.30, 25.88, 50.90, 107.00, 108.11, 108.42, 115.96, 116.19, 128.67, 130.01, 131.52, 134.89, 138.76, 144.80, 145.16, 163.85, 166.39; MS (ESI⁺) for C₁₉H₁₉FN₂O₃S *m/z* 375 (M+H)⁺. HPLC 100% (System A).

EXAMPLE 4

3,4-Dimethoxy-N-(7-piperidin-1-yl-1-benzofuran-5-yl)benzenesulfonamide hydrochloride

- 5 The synthesis was performed according to the procedure of Intermediate 3 starting from 7-piperidin-1-yl-1-benzofuran-5-amine (Intermediate 6). Yield: 100 mg (48%). ¹H NMR (400 MHz, CDCl₃) δ ppm 1.52-1.57 (m, 2 H), 1.62-1.66 (m, 4 H), 3.09-3.15 (m, 4 H), 3.69 (s, 3 H), 3.75 (s, 3 H), 6.50-6.55 (m, 1 H), 6.82 (d, 1 H), 6.88 (d, 1 H), 7.01 (d, 1 H), 7.20-7.26 (m, 2 H), 7.87 (d, 1 H), 9.80 (br s, 1 H); MS (ESI+) for C₂₁H₂₄N₂O₅S m/z 417 (M+H)⁺;
- 10 HPLC 100% (System A).

INTERMEDIATE 8

1-(5-Nitro-1-benzofuran-7-yl)pyrrolidine

- The synthesis was performed as described for Intermediate 4 (Step 3). Yield 26%. ¹H
- 15 NMR (400 MHz, CDCl₃) δ ppm 2.03-2.08 (m, 4 H), 3.66-3.72 (m, 4 H), 6.82 (d, 1 H), 7.23 (d, 1 H), 7.67 (d, 1 H), 7.81 (d, 1 H); GC-MS (EI+) for C₁₂H₁₂N₂O₃ m/z 232 M⁺.

INTERMEDIATE 9

7-Pyrrolidin-1-yl-1-benzofuran-5-amine

- 20 The synthesis was performed as described for Intermediate 6. Yield 48%. MS (ESI+) for C₁₂H₁₄N₂O m/z 203 (M+H)⁺.

EXAMPLE 5

3,4-Dimethoxy-N-(7-pyrrolidin-1-yl-1-benzofuran-5-yl)benzenesulfonamide

- 25 The title compound was prepared according to the procedure of Intermediate 3 starting from 7-pyrrolidin-1-yl-1-benzofuran-5-amine (Intermediate 9). Yield: 70 mg (43%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.88-1.93 (m, 4 H), 3.38-3.43 (m, 4 H), 3.71 (s, 3 H), 3.75 (s, 3 H), 6.16 (d, 1 H), 6.60 (d, 1 H), 6.75 (d, 1 H), 7.01 (d, 1 H), 7.24-7.29 (m, 2 H), 7.80 (d, 1 H), 9.71 (s, 1 H); ¹³C NMR (100 MHz, DMSO-*d*₆) δ 24.72, 48.82, 55.62, 55.71,
- 30 100.66, 101.57, 106.96, 109.54, 110.91, 120.58, 128.29, 131.10, 134.01, 134.58, 140.65, 145.37, 148.33, 151.89; MS (ESI+) for C₂₀H₂₂N₂O₅S m/z 403 (M+H)⁺; HPLC 98% (System A).

EXAMPLE 6

N-(7-Pyrrolidin-1-yl-1-benzofuran-5-yl)benzenesulfonamide

The title compound was prepared according to the procedure of Intermediate 3 starting from 7-pyrrolidin-1-yl-1-benzofuran-5-amine (Intermediate 9). Yield: 30 mg (22%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.86-1.93 (m, 4 H), 3.36-3.43 (m, 4 H), 6.13 (br s, 1 H), 6.59 (br s, 1 H), 6.73 (d, 1 H), 7.45-7.60 (m, 3 H), 7.73 (d, 2 H), 7.79 (d, 1 H), 9.92 (s, 1 H); ¹³C NMR (100 MHz, DMSO-*d*₆) δ ppm 24.73, 48.79, 100.68, 101.51, 106.97, 126.74, 128.33, 129.05, 132.58, 133.70, 134.62, 139.67, 140.68, 145.40; MS (ESI+) for C₁₈H₁₈N₂O₃S *m/z* 343 (M+H)⁺; HPLC 95% (System A).

10

EXAMPLE 7

4-Fluoro-N-(7-pyrrolidin-1-yl-1-benzofuran-5-yl)benzenesulfonamide hydrochloride

The title compound was prepared according to the procedure of Intermediate 3 starting from 7-pyrrolidin-1-yl-1-benzofuran-5-amine (Intermediate 9). Yield: 65 mg (41%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.87-1.94 (m, 4 H), 3.38-3.44 (m, 4 H), 6.13 (d, 1 H), 6.58 (d, 1 H), 6.75 (d, 1 H), 7.34-7.40 (m, 2 H), 7.74-7.80 (m, 2 H), 7.81 (d, 1 H), 9.94 (s, 1 H); ¹³C NMR (100 MHz, DMSO-*d*₆) δ ppm 24.73, 48.85, 100.97, 101.73, 106.99, 116.13, 116.36, 128.38, 129.71, 1129.80, 133.51, 134.59, 135.99, 140.77, 145.48, 162.88, 165.38; MS (ESI+) for C₁₈H₁₇FN₂O₃S *m/z* 361.0 (M+H)⁺; HPLC 98%.

20

EXAMPLE 8

4-Fluoro-N-(7-morpholin-4-yl-1-benzofuran-5-yl)benzenesulfonamide hydrochloride

The title compound was prepared according to the procedure of Intermediate 3 starting from Intermediate 7. Yield: 100 mg (53%); ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 3.08-3.14 (m, 4 H), 3.72-3.78 (m, 4 H), 6.47 (d, 1 H), 6.83 (d, 1 H), 6.88 (d, 1 H), 7.32-7.40 (m, 2 H), 7.74-7.78 (m, 2 H), 7.88 (d, 1 H), 10.07 (s, 1 H); ¹³C NMR (100 MHz, DMSO-*d*₆) δ ppm 49.31, 65.98, 105.45, 106.13, 107.14, 116.20, 116.43, 128.52, 129.85, 133.24, 135.70, 137.00, 143.09, 145.74, 162.96, 165.46; MS (ESI+) for C₁₈H₁₇FN₂O₄S *m/z* 377.2 (M+H)⁺; HPLC 100 %.

30

EXAMPLE 9

N-(7-Morpholin-4-yl-1-benzofuran-5-yl)benzenesulfonamide hydrochloride,

The title compound was prepared according to the procedure of Intermediate 3 starting from Intermediate 7. Yield: 75 mg (42%); ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 3.06-3.12 (m, 4 H), 3.71-3.78 (m, 4 H), 6.46 (d, 1 H), 6.82 (d, 1 H), 6.88 (d, 1 H), 7.48-7.54 (m, 2 H), 7.54-7.60 (m, 1 H), 7.71 (d, 2 H), 7.87 (d, 1 H), 10.03 (s, 1 H); ¹³C NMR (100 MHz, DMSO-*d*₆) δ 49.29, 65.98, 105.30, 105.90, 107.10, 126.75, 128.46, 129.11, 132.71, 133.40, 136.93, 139.37, 142.99, 145.67; MS (ESI+) for C₁₈H₁₈N₂O₄S *m/z* 359.2 (M+H)⁺; HPLC 97 %.

EXAMPLE 10

10 **3,4-Dimethoxy-N-(7-morpholin-4-yl-1-benzofuran-5-yl)benzenesulfonamide**

The title compound was prepared according to the procedure of Intermediate 3 starting from Intermediate 7. Yield: 45 mg (21%); ¹H NMR (400 MHz, CDCl₃) δ ppm 3.23-3.28 (m, 4 H), 3.75 (s, 3 H), 3.89 (s, 3 H), 3.89-3.93 (m, 4 H), 6.53 (br s, 1 H), 6.65 (d, 1 H), 6.76 (br s, 1 H), 6.82 (d, 1 H), 6.89 (br s, 1 H), 7.18 (d, 1 H), 7.35 (dd, 1 H), 7.57 (d, 1 H); MS (ESI+) for C₂₀H₂₂N₂O₆S *m/z* 419.0 (M+H)⁺; HPLC 88 %.

INTERMEDIATE 10

***tert*-Butyl 4-(5-amino-1-benzofuran-7-yl)piperazine-1-carboxylate**

tert-Butyl 4-(5-nitro-1-benzofuran-7-yl)piperazine-1-carboxylate* (1 g, 2.9 mmol) was dissolved in THF/EtOH (1:4). An excess of Raney-Ni (slurry in ethanol) was added followed by hydrazine-hydrate (0.58 g, 11.5 mmol). The reaction mixture was stirred at room temperature overnight. Filtration and evaporation afforded 1.19 g of the title product that was used in the next step without further purification. HPLC purity 93%, R_T=1.71 min (System A; 10-97% MeCN over 3 min). *Previously described in WO 2002100822.

25

General procedure A: Alkylation of *tert*-butyl 4-(5-amino-1-benzofuran-7-yl)piperazine-1-carboxylate.

A stock solution of *tert*-butyl 4-(5-amino-1-benzofuran-7-yl)piperazine-1-carboxylate (0.12 g, 0.378 mmol; Intermediate 10) in acetonitrile was added together with K₂CO₃ (52 mg, 0.378 mmol) to respective benzyl bromide (0.378 mmol). The mixtures were shaken at room temperature for 3 h. The reaction progress was controlled with LC-MS. Workup: filtration and purification by preparative HPLC using acetonitrile-water gradients containing 0.1% trifluoroacetic acid. *N*-deprotection was carried out according to the procedure of Example

1 and the target hydrochloride salt was obtained following treatment with 2 M HCl in ether.

EXAMPLE 11

5 **N-(3,5-Dimethylbenzyl)-7-piperazin-1-yl-1-benzofuran-5-amine hydrochloride**

Prepared by general procedure A from 1-(bromomethyl)-3,5-dimethylbenzene (75 mg, 0.378 mmol). Yield: 8 mg (6%). HPLC 93%, R_T : 1.240 (System A; 10-97% MeCN over 3 min). ^1H NMR (270 MHz, methanol- d_4) δ ppm 2.30 (s, 6 H) 3.47-3.64 (m, 8 H) 4.52 (s, 2 H) 6.86-6.95 (m, 2 H) 7.08-7.09 (m, 3 H) 7.32 (s, 1 H) 7.93 (s, 1 H). LC-MS 336 (M+H) $^+$.

10

EXAMPLE 12

N-(3,4-Difluorobenzyl)-7-piperazin-1-yl-1-benzofuran-5-amine hydrochloride

Prepared by general procedure A from 4-(bromomethyl)-1,2-difluorobenzene (78 mg, 0.378 mmol). Yield: 6 mg (5%). HPLC 97%, R_T : 1.499 (System A; 10-97% MeCN over 3 min). ^1H NMR (270 MHz, methanol- d_4) δ ppm 3.46-3.63 (m, 8 H) 4.73 (s, 2 H) 6.86-6.94 (m, 2 H) 7.36 (s, 1 H) 7.49-7.64 (m, 2 H) 7.91-8.00 (m, 2 H). LC-MS 344 (M+H) $^+$.

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EXAMPLE 13

N-(3,5-Dimethoxybenzyl)-7-piperazin-1-yl-1-benzofuran-5-amine hydrochloride

20 Prepared by general procedure A from 1-(bromomethyl)-3,5-dimethoxybenzene (87 mg, 0.378 mmol). Yield: 8 mg (6%). HPLC 93%, R_T : 1.355 (System A; 10-97% MeCN over 3 min). ^1H NMR (270 MHz, methanol- d_4) δ ppm 3.47-3.65 (m, 8 H) 3.76 (s, 6H) 4.56 (s, 2 H) 6.54 (s, 1H) 6.64 (s, 2H) 6.89 (s, 1H) 6.95 (s, 1H) 7.35 (s, 1 H) 7.92 (s, 1 H). LC-MS 368 (M+H) $^+$.

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EXAMPLE 14

N-Benzyl-7-piperazin-1-yl-1-benzofuran-5-amine hydrochloride

A stock solution of *tert*-butyl 4-(5-amino-1-benzofuran-7-yl)piperazine-1-carboxylate (0.12 g, 0.378 mmol; Intermediate 10) in acetonitrile was added, together with K_2CO_3 (52 mg, 0.378 mmol), to benzyl bromide (65 mg, 0.378 mmol). The mixture was shaken at room temperature for 3 h. The product was controlled with LC-MS, filtered and purified by preparative HPLC using acetonitrile-water gradients containing 0.1% trifluoroacetic acid. N-deprotection and conversion into the hydrochloride salt was performed by treatment

30

with with 2 M HCl in ether. Yield: 19 mg (16.4%). HPLC 92%, R_T : 1.240 (System A; 10-97% MeCN over 3 min). ^1H NMR (270 MHz, methanol- d_4) δ ppm 3.56 (d, 8 H) 4.65 (s, 2 H) 6.94 (s, 2 H) 7.43 (s, 6 H) 7.92 (s, 1 H). LC-MS 308 (M+H) $^+$.

5 **General procedure B:** Amidation of *tert*-butyl 4-(5-amino-1-benzofuran-7-yl)piperazine-1-carboxylate.

Pyridine (274 μL , 3.40 mmol) and a stock solution of *tert*-butyl 4-(5-amino-1-benzofuran-7-yl)piperazine-1-carboxylate (0.12 g, 0.378 mmol; Intermediate 10) in DCM (2 mL) were added to the respective benzoyl chloride (0.454 mmol). The mixtures were shaken at room
10 temperature for 2 h. The products were controlled with LC-MS and the solvent was removed. Purification of the products was done by preparative HPLC using acetonitrile-water gradients containing 0.1% trifluoroacetic acid. The final products were obtained following *N*-deprotection according to the procedure of Example 1 and conversion into the corresponding hydrochloride salt by treatment with 2 M HCl in ether.

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EXAMPLE 15

N-(7-Piperazin-1-yl-1-benzofuran-5-yl)benzamide hydrochloride

Prepared by general procedure B from *tert*-butyl 4-(5-amino-1-benzofuran-7-yl)piperazine-1-carboxylate (64 mg, 0.454 mmol; Intermediate 10). Yield: 3 mg (3%). HPLC 94%, R_T :
20 1.534 (System A; 10-97% MeCN over 3 min). ^1H NMR (270 MHz methanol- d_4) δ ppm 3.46-3.61 (m, 8 H) 6.85 (d, $J=2.23$ Hz, 1 H) 7.28 (d, $J=1.24$ Hz, 1 H) 7.52-7.59 (m, 4 H) 7.78 (d, $J=1.98$ Hz, 1 H) 7.95 (d, $J=6.68$ Hz, 2 H). LC-MS 322 (M+H) $^+$.

EXAMPLE 16

25 **4-Methoxy-N-(7-piperazin-1-yl-1-benzofuran-5-yl)benzamide hydrochloride**

Prepared by general procedure B from 4-methoxybenzoyl chloride (77 mg, 0.454 mmol). Yield: 2 mg (1.5%). HPLC 99%, R_T : 1.568 (System A; 10-97% MeCN over 3 min). ^1H
NMR (270 MHz, methanol- d_4) δ ppm 3.44-3.61 (m, 8 H) 3.87 (s, 2 H) 6.84 (d, $J=2.23$ Hz, 1 H) 7.04 (d, $J=8.91$ Hz, 2 H) 7.27 (d, $J=1.48$ Hz, 1 H) 7.52 (d, $J=1.73$ Hz, 1 H) 7.77 (d,
30 $J=1.98$ Hz, 1 H) 7.93 (d, $J=8.91$ Hz, 2 H). LC-MS 352 (M+H) $^+$.

EXAMPLE 17

2-Bromo-5-methoxy-N-(7-piperazin-1-yl-1-benzofuran-5-yl)benzamide hydrochloride

Prepared by general procedure B from 2-bromo-5-methoxybenzoyl chloride (113 mg, 0.454 mmol). Yield: 10 mg (6.2%). HPLC 85%, R_T : 1.685 (System A; 10-97% MeCN over 3 min). ^1H NMR (270 MHz, methanol- d_4) δ ppm 3.46-3.48 (m, 4 H) 3.59-3.61 (m, 4 H) 3.84 (s, 3 H) 6.84 (d, $J=1.98$ Hz, 1 H) 6.97 (dd, $J=8.66, 2.72$ Hz, 1 H) 7.10 (d, $J=2.97$ Hz, 1 H) 7.23 (s, 1 H) 7.54-7.59 (m, 2 H) 7.78 (d, $J=1.98$ Hz, 1 H). LC-MS 430 (M+H) $^+$.

EXAMPLE 18

3-Methyl-N-(7-piperazin-1-yl-1-benzofuran-5-yl)benzamide hydrochloride

Prepared by general procedure B from 3-methylbenzoyl chloride (70 mg, 0.454 mmol). Yield: 14 mg (11.1%). HPLC 93%, R_T : 1.666 (System A; 10-97% MeCN over 3 min). ^1H NMR (270 MHz, methanol- d_4) δ ppm 2.43 (s, 3 H) 3.46-3.62 (m, 8 H) 6.84 (d, $J=1.73$ Hz, 1 H) 7.39 (d, $J=4.21$ Hz, 2 H) 7.76 (d, $J=10.14$ Hz, 3 H). LC-MS 336 (M+H) $^+$.

EXAMPLE 19

N-(7-Piperazin-1-yl-1-benzofuran-5-yl)-3-(trifluoromethyl)benzamide hydrochloride

Prepared by general procedure B from 3-(trifluoromethyl)benzoyl chloride (95 mg, 0.454 mmol). Yield: 12 mg (8.2%). HPLC 88%, R_T : 1.779 (System A; 10-97% MeCN over 3 min). ^1H NMR (270 MHz, methanol- d_4) δ ppm 3.45-3.63 (m, 8 H) 6.86 (d, $J=2.23$ Hz, 1 H) 7.31 (d, $J=1.73$ Hz, 1 H) 7.58 (s, 1 H) 7.75-7.79 (m, 2 H) 7.92 (s, 1 H) 8.24 (m, 2 H). LC-MS 390.1 (M+H) $^+$.

EXAMPLE 20

2,4-Dichloro-N-(7-piperazin-1-yl-1-benzofuran-5-yl)benzamide hydrochloride

Prepared by general procedure B from 2,4-dichlorobenzoyl chloride (95 mg, 0.454 mmol). Yield: 19 mg (12.9%). HPLC 93%, R_T : 1.803 (System A; 10-97% MeCN over 3 min). ^1H NMR (270 MHz, methanol- d_4) δ ppm 3.47-3.62 (m, 8 H) 6.84 (d, $J=2.23$ Hz, 1 H) 7.21 (d, $J=2.23$ Hz, 1 H) 7.44-7.78 (m, 5 H). LC-MS 390 (M+H) $^+$.

EXAMPLE 21

3,5-Dimethoxy-N-(7-piperazin-1-yl-1-benzofuran-5-yl)benzamide hydrochloride

Prepared by general procedure B from 3,5-dimethoxybenzoyl chloride (91 mg, 0.454 mmol). Yield: 18.3 mg (12.7%). HPLC 91%, R_T : 1.666 (System A; 10-97% MeCN over 3 min). ^1H NMR (270 MHz, methanol- d_4) δ ppm 2.76-7.82 (m, 8 H) 3.04 (s, 6 H) 5.87 (s, 1

H) 6.02 (d, $J=1.57$ Hz, 1 H) 6.30 (d, $J=1.57$ Hz, 2 H) 6.41-6.49 (m, 1 H) 6.78-6.79 (m, 1 H) 6.98-6.69 (m, 1 H). LC-MS 382 ($M+H$)⁺.

General procedure C: Synthesis of urea derivatives from *tert*-butyl 4-(5-amino-1-

5 benzofuran-7-yl)piperazine-1-carboxylate. **Method A.**

A stock solution of *tert*-butyl 4-(5-amino-1-benzofuran-7-yl)piperazine-1-carboxylate (0.12 g, 0.378 mmol; Intermediate 10) in acetonitrile (2 mL) and pyridine (274 μ L, 3.4 mmol) were added to the respective aryl isocyanate (0.416 mmol). The mixtures were shaken at room temperature over night. The reaction progress was controlled with LC-MS.

10 Workup: filtration and purification by preparative HPLC using acetonitrile-water gradients containing 0.1% trifluoroacetic acid. The final products were obtained following *N*-deprotection according to the procedure of Example 1 and conversion into the hydrochloride salt by treatment with 2 M HCl in ether.

15 **EXAMPLE 22**

N-(3,5-Dimethoxyphenyl)-N'-(7-piperazin-1-yl-benzofuran-5-yl)urea hydrochloride.

Prepared by general procedure C (method A) from 1-isocyanato-3,5-dimethoxybenzene (75 mg, 0.416 mmol). Yield: 11 mg (8 %). HPLC 100%, R_T : 1.673 (System A; 10-97% MeCN over 3 min). ¹H NMR (270 MHz, methanol-*d*₄) δ ppm 3.44-3.46 (m, 4 H) 3.56-3.57 (m, 4 H) 3.75 (s, 6 H) 6.78 (d, $J=1.98$ Hz, 2 H) 7.03 (s, 2 H) 7.27 (d, $J=1.48$ Hz, 1 H) 7.72 (d, $J=1.98$ Hz, 2 H). LC-MS 397 ($M+H$)⁺.

EXAMPLE 23

N-(2,4-Dichlorophenyl)-N'-(7-piperazin-1-yl-benzofuran-5-yl)urea hydrochloride.

25 Prepared by general procedure C (method A) from 2,4-dichloro-1-isocyanatobenzene (78 mg, 0.416 mmol). Yield: 9 mg (6%). HPLC 100%, R_T : 1.775 (System A; 10-97% MeCN over 3 min). ¹H NMR (270 MHz, methanol-*d*₄) δ ppm 3.46-3.47 (m, 4 H) 3.58-3.59 (m, 4H) 6.80 (d, $J=1.98$ Hz, 1 H) 7.06-7.07 (m, 1 H) 7.26 (d, $J=2.23$ Hz, 1 H) 7.29 (d, $J=2.47$ Hz, 1 H) 7.46 (d, $J=2.47$ Hz, 1 H) 7.74 (d, $J=1.98$ Hz, 1 H) 8.13 (d, $J=8.91$ Hz, 1 H). LC-
30 MS 405 ($M+H$)⁺.

General procedure C: Synthesis of urea derivatives from *tert*-butyl 4-(5-amino-1-benzofuran-7-yl)piperazine-1-carboxylate. **Method B.**

A stock solution of *tert*-butyl 4-(5-amino-1-benzofuran-7-yl)piperazine-1-carboxylate (0.12 g, 0.378 mmol; Intermediate 10) in acetonitrile was added, together with triethylamine (158 μ L, 1.13 mmol), to respective isocyanate (0.416 mmol). The mixtures were shaken at room temperature overnight. The reaction progress was controlled with LC-MS. Workup: filtration and purification by preparative HPLC using acetonitrile-water gradients containing 0.1% trifluoroacetic acid. The final products were obtained following *N*-deprotection according to the procedure of Example 1 and conversion into the corresponding hydrochloride salt by treatment with 2 M HCl in ether.

10 EXAMPLE 24

N-(2-Methoxyphenyl)-N'-(7-piperazin-1-yl-1-benzofuran-5-yl)urea hydrochloride

Prepared by the general procedure above (Method B) from 1-isocyanato-2-methoxybenzene (60 mg, 0.416 mmol). Yield: 33 mg (23.8%). HPLC 93%, R_T : 1.673 (System A; 10-97% MeCN over 3 min). ^1H NMR (270 MHz, methanol- d_4) δ ppm 3.44-3.60 (m, 8 H) 3.92 (s, 3 H) 6.79-6.99 (m, 5 H) 7.12-7.21 (m, 1 H) 7.73 (d, $J=2.23$ Hz, 1 H) 8.05 (d, $J=7.67$ Hz, 1 H). LC-MS 367.1 (M+H) $^+$.

EXAMPLE 25

N-Phenyl-N'-(7-piperazin-1-yl-1-benzofuran-5-yl)urea hydrochloride

20 Prepared by the general procedure above (Method B) from isocyanatobenzene (50 mg, 0.416 mmol). Yield: 31 mg (24.4%). HPLC 93%, R_T : 1.583 (System A; 10-97% MeCN over 3 min). ^1H NMR (270 MHz, methanol- d_4) δ ppm 3.43-3.47 (m, 4 H) 3.56-3.60 (m, 4 H) 6.80 (d, $J=2.23$ Hz, 1 H) 7.09-7.21 (m, 2 H) 7.22-7.31 (m, 3 H) 7.43 (d, $J=8.41$ Hz, 2 H) 7.74 (d, $J=2.23$ Hz, 1 H). LC-MS 337 (M+H) $^+$.

25

EXAMPLE 26

N-(3-Fluorophenyl)-N'-(7-piperazin-1-yl-1-benzofuran-5-yl)urea hydrochloride

Prepared by the general procedure above (Method B) from 1-fluoro-3-isocyanatobenzene (57 mg, 0.416 mmol). Yield: 5 mg (3.7%). HPLC 93%, R_T : 1.700 (System A; 10-97% MeCN over 3 min). ^1H NMR (270 MHz, methanol- d_4) δ ppm 3.46-3.47 (m, 4 H) 3.57-3.60 (m, 4 H) 6.77-6.81 (m, 2 H) 7.08-7.09 (m, 2 H) 7.22-7.28 (m, 2 H) 7.42-7.47 (m, 1 H) 7.74 (d, $J=1.98$ Hz, 1 H). LC-MS 355 (M+H) $^+$.

30

EXAMPLE 27

N-(7-Piperazin-1-yl-1-benzofuran-5-yl)-N'-(trifluoromethyl)phenyl]urea hydrochloride

Prepared by the general procedure above (Method B) from 1-isocyanato-3-(trifluoromethyl)benzene (78 mg, 0.416 mmol). Yield: 27 mg (17.7%). HPLC 91%, R_T : 1.932 (System A; 10-97% MeCN over 3 min). ^1H NMR (270 MHz, methanol- d_4) δ ppm 3.44-3.47 (m, 4 H) 3.57-3.61 (m, 4 H) 6.81 (d, $J=2.23$ Hz, 1 H) 7.12-7.30 (m, 3 H) 7.51 (m, 2 H) 7.74 (d, $J=2.23$ Hz, 1 H) 7.96 (s, 1 H). LC-MS 405 (M+H) $^+$.

INTERMEDIATE 11

4-(5-Nitro-1-benzofuran-7-yl)pyridine

7-Iodo-5-nitrobenzofuran (2.00 g, 0.00692 mol), 4-tributylstannylpyridine (2.80 g, 0.00761 mol), copper(I)iodide (132 mg, 0.692 mmol) and dichlorobis(triphenylphosphine)palladium(II) (49 mg, 0.0692 mmol) were added to a 50 mL test tube followed by DMF (20 mL). The mixture was heated at 100 °C overnight in a StemBlock. After cooling to room temperature, aqueous sodium hydroxide (2 M; 4 mL) was added and the solution was stirred for 15 min. Chloroform (20 mL) was added and the mixture was filtered through Celite. The aqueous layer was then extracted with chloroform (3x) and the combined organic phases were evaporated. The residue was then triturated with ether and the precipitate was dried in vacuo overnight to yield a light brown solid. Yield: 686 mg (41%); HLPC (System A) purity = 99%, m/z = 241 (M+H) $^+$, ^1H NMR (270 MHz, DMSO- d_6) δ ppm 7.33 (d, $J=2.23$ Hz, 1 H) 7.98 (m, 2 H) 8.38 (d, $J=2.23$ Hz, 1 H) 8.50 (d, $J=2.47$ Hz, 1 H) 8.75 (d, $J=2.23$ Hz, 1 H) 8.79 (m, 2 H).

INTERMEDIATE 12

3-(5-Nitro-1-benzofuran-7-yl)pyridine

The title compound was prepared according to the procedure described for Intermediate 11 using 3-tributylstannylpyridine. Yield: 145 mg (35%); HLPC (System A) purity = 97%, m/z = 241 (M+H) $^+$, ^1H NMR (270 MHz, DMSO- d_6) δ ppm 7.32 (d, $J=2.23$ Hz, 1 H) 7.63 (dd, $J=7.79, 4.82$ Hz, 1 H) 8.33 (m, 1 H) 8.36 (d, $J=2.23$ Hz, 1 H) 8.44 (d, $J=2.47$ Hz, 1 H) 8.72 (m, 2 H) 9.14 (d, $J=1.73$ Hz, 1 H).

INTERMEDIATE 13

2-(5-Nitro-1-benzofuran-7-yl)pyridine

The title compound was prepared according to the procedure described for Intermediate 11 using 2-tributylstannylpyridine.. Yield: 282 mg (42%); HPLC (System A) purity = 98%,
5 $m/z = 241$ (M+H)⁺, ¹H NMR (270 MHz, DMSO-*d*₆) δ ppm 7.33 (d, J=2.23 Hz, 1 H) 7.53 (m, 1 H) 8.06 (m, 1 H) 8.41 (m, 2 H) 8.72 (d, J=2.47 Hz, 1 H) 8.84 (m, 1 H) 8.99 (d, J=2.47 Hz, 1 H).

INTERMEDIATE 14

10 **2-(5-Nitro-1-benzofuran-7-yl)pyrazine**

The title compound was prepared according to the procedure described for Intermediate 11 using 2-tributylstannylpyrazine. Yield: 238 mg (57%); HPLC (System A) purity = 97%,
 $m/z = 242$ (M+H)⁺, ¹H NMR (270 MHz, DMSO-*d*₆) δ ppm 7.35 (d, J=2.23 Hz, 1 H) 8.43 (d, J=2.23 Hz, 1 H) 8.78 (m, 2 H) 8.92 (m, 2 H) 9.58 (s, 1 H).

15

INTERMEDIATE 15

2-(5-Nitro-1-benzofuran-7-yl)pyrimidine

The title compound was prepared according to the procedure described for Intermediate 11 using 2-tributylstannylpyrimidine. Yield: 219 mg (52%); HPLC (System A) purity = 97%,
20 $m/z = 242$ (M+H)⁺, ¹H NMR (270 MHz, DMSO-*d*₆) δ ppm 7.32 (d, J=2.23 Hz, 1 H) 7.61 (t, J=4.95 Hz, 1 H) 8.40 (d, J=2.23 Hz, 1 H) 8.81 (d, J=2.47 Hz, 1 H) 9.07 (m, 3 H).

INTERMEDIATE 16

4-(5-Amino-1-benzofuran-7-yl)pyridine

25 4-(5-Nitro-1-benzofuran-7-yl)pyridine (125 mg, 0.520 mmol; Intermediate 11) was dissolved in 1,4-dioxane (15 mL). After addition of ethanol (20 mL), Raney-nickel (slurry in ethanol; 2 mL) and hydrazine hydrate (4 mL) were added and the mixture was left stirring at room temperature overnight. The product was used directly in the subsequent reaction after filtration through Celite and evaporation of solvent.

30

EXAMPLE 28

2-Methoxy-5-methyl-N-(7-pyridin-4-yl-1-benzofuran-5-yl)benzenesulfonamide

4-(5-Amino-1-benzofuran-7-yl)pyridine (55 mg, 0.260 mmol; Intermediate 16) and 6-methoxy-m-toluenesulfonyl chloride (69 mg, 0.312 mmol) was dissolved in dichloromethane (5 mL). Triethylamine (73 μ L, 0.520 mmol) was added and the mixture was shaken for 2 h. After concentration, the residue was triturated with cold acetonitrile and the precipitate was collected and dried in vacuo. Yield: 56 mg (55%); HPLC (System A) purity = 98%, m/z = 395 ($M+H$)⁺, ¹H NMR (270 MHz, DMSO-*d*₆) δ ppm 2.21 (s, 3 H) 3.87 (s, 3 H) 7.09 (m, 2 H) 7.35 (dd, J =8.54, 2.10 Hz, 1 H) 7.56 (m, 2 H) 8.14 (d, J =2.23 Hz, 1 H) 8.25 (d, J =6.68 Hz, 2 H) 8.98 (d, J =6.68 Hz, 2 H) 10.13 (s, 1 H).

10 EXAMPLE 29

N-(7-Pyridin-3-yl-1-benzofuran-5-yl)benzenesulfonamide trifluoroacetate

The title compound was prepared according to the procedure described for Example 28 using 3-(5-amino-1-benzofuran-7-yl)pyridine* and purified by preparative HPLC. Yield: 63 mg (51%); HPLC (System A) purity = 95%, m/z = 351 ($M+H$)⁺, ¹H NMR (270 MHz, methanol-*d*₄) δ ppm 6.90 (d, J =2.23 Hz, 1 H) 7.49 (m, 5 H) 7.74 (m, 2 H) 7.89 (d, J =2.23 Hz, 1 H) 8.01 (m, 1 H) 8.77 (m, 2 H) 9.19 (d, J =1.73 Hz, 1 H). *Prepared according to the procedure of Intermediate 16 using 3-(5-nitro-1-benzofuran-7-yl)pyridine (Intermediate 12).

20 EXAMPLE 30

2-Methoxy-5-methyl-N-(7-pyridin-3-yl-1-benzofuran-5-yl)benzenesulfonamide trifluoroacetate

The title compound was prepared according to the procedure described for Example 28, using 3-(5-amino-1-benzofuran-7-yl)pyridine* and purified by preparative HPLC (System D). Yield: 67 mg (50%); HPLC (System A) purity = 97%, m/z = 395 ($M+H$)⁺, ¹H NMR (270 MHz, methanol-*d*₄) δ ppm 2.17 (s, 3 H) 3.95 (s, 3 H) 6.88 (d, J =2.23 Hz, 1 H) 7.01 (d, J =8.41 Hz, 1 H) 7.29 (m, 1 H) 7.48 (d, J =2.23 Hz, 2 H) 7.54 (m, 1 H) 7.86 (d, J =2.23 Hz, 1 H) 8.10 (m, 1 H) 8.84 (m, 2 H) 9.24 (d, J =1.98 Hz, 1 H). *Prepared according to the procedure of Intermediate 16 using 3-(5-nitro-1-benzofuran-7-yl)pyridine (Intermediate 12).

EXAMPLE 31

N-(7-Pyrazin-2-yl-1-benzofuran-5-yl)benzenesulfonamide trifluoroacetate

The title compound was prepared according to the procedure described for Example 28 using 2-(5-amino-1-benzofuran-7-yl)pyrazine* and purified by preparative HPLC (System D). Yield: 20 mg (17%), HLPC (System A) purity = 98%, $m/z = 352$ (M+H)⁺, ¹H NMR (270 MHz, DMSO-*d*₆) δ ppm 7.07 (d, J=2.23 Hz, 1 H) 7.53 (m, 3 H) 7.76 (m, 2 H) 7.91 (d, J=1.98 Hz, 1 H) 8.14 (d, J=2.23 Hz, 1 H) 8.67 (d, J=2.47 Hz, 1 H) 8.82 (m, 1 H) 9.45 (d, J=1.73 Hz, 1 H) 10.39 (s, 1 H). *Prepared according to the procedure of Intermediate 16 using 2-(5-nitro-1-benzofuran-7-yl)pyrazine (Intermediate 14).

10 INTERMEDIATE 17

5-(5-Nitro-1-benzofuran-7-yl)pyrimidine

Pd(PPh₃)₄ (240 mg, 209 mmol) was added to 7-iodo-5-nitro-1-benzofurane (1.00 g, 3.45 mmol) in DME (11 mL) and the resulting mixture was stirred for 10 min. The color went from dark red to mustard yellow. Pyrimidine-5-boronic acid (0.24 g, 0.21 mmol) and 1 M Na₂CO₃ (5 mL) were added and the reaction mixture was refluxed at 100 °C for 2.5 h. The mixture was concentrated *in vacuo* and the residue was dissolved in 1 M HCl (50 mL) and washed with diethyl ether (50 mL). The aqueous layer was made basic (pH 8), by addition of K₂CO₃, and extracted with chloroform (3x). The combined organic layers were dried with K₂CO₃, filtered and concentrated to afford 0.455 g (55%) of a yellow solid. HPLC 100%, R_T: 1.870 min (System A; 10-97% over 3 min). ¹H NMR (270 MHz, CDCl₃) δ ppm 7.06 (d, J=2.47 Hz, 1 H) 7.90 (d, J=2.23 Hz, 1 H) 8.45 (d, J=2.23 Hz, 1 H) 8.63 (d, J=2.23 Hz, 1 H) 9.28-9.31 (m, 3 H). LC-MS 242 (M+H)⁺.

INTERMEDIATE 18

25 **7-Pyrimidin-5-yl-1-benzofuran-5-amine**

Raney-nickel (slurry in ethanol; 2 mL) and hydrazine (0.378 g, 7.55 mmol) were added to 5-(5-nitro-1-benzofuran-7-yl)pyrimidine (0.455 g, 1.87 mmol, Intermediate 17) in ethanol/THF (100 mL:25 mL). The mixture was stirred at room temperature for 3 h, filtered through Celite and concentrated *in vacuo* to afford 0.317 g (80%) of the title compound as a yellow solid. HPLC 100%, R_T: 0.957 min (System A; 10-97% over 3 min). ¹H NMR (270 MHz, methanol-*d*₄) δ ppm 6.77 (d, J=2.23 Hz, 1 H) 7.05 (q, J=2.23 Hz, 2 H) 7.76 (d, J=2.23 Hz, 1 H) 9.14 (s, 1 H) 9.26 (s, 2 H). LC-MS 212 (M+H)⁺.

EXAMPLE 32

N-(7-Pyrimidin-5-yl-1-benzofuran-5-yl)benzenesulfonamide hydrochloride

Benzenesulfonyl chloride (0.093 g, 0.524 mmol) and pyridine (347 μ L, 430 mmol) were added to 7-pyrimidin-5-yl-1-benzofuran-5-amine (0.100 g, 0.473 mmol; Intermediate 18) in dichloromethane (2 mL). The mixture was shaken at room temperature for 1 h and the solvent was removed. The crude product was purified by preparative HPLC using acetonitrile-water gradients containing 0.1% trifluoroacetic acid and then converted into the hydrochloride salt by treatment with 2 M HCL in diethyl ether. This gave 0.071 g (43%) of the title compound as a yellow solid. HPLC 97%, R_T : 1.863 min (System A; 10-97% over 3 min). ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ ppm 6.98 (d, $J=2.20$ Hz, 1 H) 7.34 (d, $J=2.20$ Hz, 1 H) 7.50-7.54 (m, 3 H) 7.58-7.60 (m, 1 H) 7.80-7.82 (m, 1 H) 7.97 (d, $J=2.20$ Hz, 1 H) 9.10 (s, 2 H) 9.20 (s, 1 H) 9.87 (s, 1 H). GC-MS 351 (M^+).

EXAMPLE 33

N-[7-(1-Aza-bicyclo[2.2.2]oct-2-en-3-yl)-benzofuran-5-yl]-2-methoxy-5-methyl-benzenesulfonamide hydrochloride

3-Tributylstannanyl-1-aza-bicyclo[2.2.2]oct-2-ene (2.14 g, 5.36 mmol; prepared according to *Bioorg. Med. Chem. Lett.* **1994**, 4, 2837-2840) was added to a mixture of 7-iodo-5-nitro-benzofuran (0.52 g, 1.79 mmol), $\text{Pd}(\text{PPh}_3)_4$ (0.206 g, 0.17 mmol) in DMF (10 mL). The mixture was heated at 160 $^\circ\text{C}$ for 10 min in a sealed reaction vessel using controlled microwave energy. The reaction mixture was diluted with CHCl_3 and then filtered through a pad of Celite and concentrated under reduced pressure. The residue was purified by repetitive chromatography on silica using gradient elution, ($\text{CHCl}_3 \rightarrow \text{CHCl}_3 + 10\% \text{ MeOH} + 0.4\% \text{ NH}_3$) followed by $\text{CHCl}_3 + 10\% \text{ MeOH} + 0.4\% \text{ NH}_3$ to give 399.5 mg of 3-(5-nitro-benzofuran-7-yl)-1-aza-bicyclo[2.2.2]oct-2-ene. This intermediate was dissolved in a solvent system of EtOH:THF (4:1; 20 mL) and Raney-Ni (~ 1.0 mL suspension in EtOH) was added followed by hydrazine monohydrate (6 equiv). The mixtures are stirred vigorously for 3 h and then filtered through Celite pre-treated with water. The filtrate was concentrated, followed by the addition of toluene and re-evaporation to yield 340 mg of the crude intermediate (7-(1-aza-bicyclo[2.2.2]oct-2-en-3-yl)-benzofuran-5-ylamine). Most of this material (325 mg; 1.35 mmol) was dissolved in DCM (5 mL). Pyridine (1.05 mL) was added followed by 2-methoxy-5-methyl-benzenesulfonyl chloride (267 mg, 1.20 mmol). The resultant mixture was stirred at room temperature for 16 h and then concentrated under

reduced pressure. The residue was purified by column chromatography on silica using gradient elution ($\text{CHCl}_3 \rightarrow \text{CHCl}_3 + 10\% \text{ MeOH} + 0.4\% \text{ NH}_3$) to give 230 mg of the free base of the title compound. The free base was dissolved in MeOH and 1 M HCl in ether was added to the solution. More ether was added and the precipitate was collected by filtration to give 182 mg of the HCl-salt. The product was dissolved in $\text{CH}_3\text{CN}:\text{MeOH}$ (2:1) and then purified by preparative reversed phase HPLC. The pure HPLC fractions were pooled and then concentrated to give the TFA-salt of the final product. The TFA-salt was converted to the HCl-salt: yield 100 mg of *N*-[7-(1-aza-bicyclo[2.2.2]oct-2-en-3-yl)-benzofuran-5-yl]-2-methoxy-5-methyl-benzenesulfonamide hydrochloride; ^1H NMR (270 MHz, $\text{DMSO}-d_6$) δ ppm 1.57-1.76 (m, 2H), 2.00-2.20 (m, 3H), 2.21 (s, 3H), 3.00-3.17 (m, 2H), 3.27-3.66 (m, obscured in part by solvent signal, 3H), 3.86 (s, 3H), 6.99-7.09 (m, 2H), 7.20-7.42 (m, 4H), 7.53-7.60 (m, 1H), 8.05-8.10 (m, 1H), 9.98 (m, s, 1H); GC-MS (EI+) for $\text{C}_{23}\text{H}_{24}\text{N}_2\text{O}_4\text{S}$ m/z 425 (M) $^+$.

15 INTERMEDIATE 19

***tert*-Butyl 4-(5-[(2-chlorophenyl)sulfonyl]amino)-1-benzofuran-7-yl)piperazine-1-carboxylate**

tert-Butyl 4-(5-amino-1-benzofuran-7-yl)piperazine-1-carboxylate (0.59 g, 1.87 mmol; Intermediate 10) was dissolved in DCM. 2-Chlorobenzenesulfonyl chloride (0.59 g, 2.8 mmol) was added followed by pyridine (0.45 mL, 5.6 mmol). The reaction mixture was stirred at room temperature overnight. Filtration through a silica plug afforded 0.66 g (72%) of the title product. HPLC purity 92%, $R_T=2.56$ min (System A; 10-97% MeCN over 3 min). ^1H NMR (400 MHz, CDCl_3) δ ppm 1.48 (s, 9 H) 3.07 - 3.21 (m, 4 H) 3.51 - 3.65 (m, 4 H) 6.51 (d, $J=2.0$ Hz, 1 H) 6.62 (d, $J=2.3$ Hz, 1 H) 6.93 (d, $J=2.0$ Hz, 1 H) 7.00 (s, 1 H) 7.18 - 7.31 (m, 2 H) 7.36 - 7.47 (m, 1 H) 7.47 - 7.57 (m, 2 H) 7.90 (dd, $J=7.9, 1.6$ Hz, 1 H). MS (ESI+) m/z 492.2 ($\text{M}+\text{H}$) $^+$.

INTERMEDIATE 20

2-Chloro-*N*-(7-piperazin-1-yl-1-benzofuran-5-yl)benzenesulfonamide

tert-Butyl 4-(5-[(2-chlorophenyl)sulfonyl]amino)-1-benzofuran-7-yl)piperazine-1-carboxylate (0.66 g, 1.34 mmol; Intermediate 19) was dissolved in DCM (5 mL) and TFA was added (30% solution of TFA in DCM; 5 mL) and the mixture was stirred for 30 min. The solvents were evaporated. The residue was dissolved in water, pH adjusted to pH 8

and extracted with EtOAc. The organic layer was dried and evaporated to give 0.41 g (80%) of the title product that was used in the next step without further purification. HPLC purity 93%, $R_T=1.61$ min (System A; 10-97% MeCN over 3 min).

5 INTERMEDIATE 21

1-(5-Nitro-1-benzofuran-7-yl)piperazine

Removal of the N-t-BOC group in *tert*-butyl 4-(5-nitro-1-benzofuran-7-yl)piperazine-1-carboxylate* was performed according to the procedure of Intermediate 20 giving 2.3 g (80%) of the title compound as a yellow solid. HPLC purity 94%, $R_T=1.37$ min (System A; 10-97% MeCN over 3 min). *Previously described in WO 2002100822.

INTERMEDIATE 22

N,N-Diethyl-2-[4-(5-nitro-1-benzofuran-7-yl)piperazin-1-yl]acetamide

A mixture of 1-(5-nitro-1-benzofuran-7-yl)piperazine (0.4 g, 1.6 mmol; Intermediate 21) and 2-chloro-*N,N*-diethylacetamide (0.48 g, 3.2 mmol) in the presence of K_2CO_3 (0.45 g, 3.2 mmol) in DMF was heated at 225 °C for 5 min using controlled microwave energy. The solvent was evaporated and the residue triturated with MeCN to give 0.31 g (54%) of the title compound as a yellow solid. HPLC purity 80%, $R_T=1.63$ min (System A; 10-97% MeCN over 3 min). ^1H NMR (400 MHz, $DMSO-d_6$) δ ppm 1.02 (t, $J=7.0$ Hz, 3 H) 1.14 (t, $J=7.0$ Hz, 3 H) 2.58 - 2.77 (m, 4 H) 3.14 - 3.50 (m, 10 H) 7.14 (d, $J=2.3$ Hz, 1 H) 7.53 (d, $J=2.3$ Hz, 1 H) 8.18 (dd, $J=12.5, 2.3$ Hz, 2 H).

INTERMEDIATE 23

2-[4-(5-Amino-1-benzofuran-7-yl)piperazin-1-yl]-*N,N*-diethylacetamide

Reduction of the nitro group in *N,N*-diethyl-2-[4-(5-nitro-1-benzofuran-7-yl)piperazin-1-yl]acetamide (0.3 g, 0.83 mmol; Intermediate 22) was performed according to the procedure of Intermediate 10. Yield: 0.19 g (70%). This material was used in the next step without further purification. MS (ESI+) m/z 331.2 ($M+H$)⁺.

30 EXAMPLE 34

2-[4-(5-[(2-Chlorophenyl)sulfonyl]amino)-1-benzofuran-7-yl)piperazin-1-yl]-*N,N*-diethylacetamide hydrochloride

2-[4-(5-Amino-1-benzofuran-7-yl)piperazin-1-yl]-*N,N*-diethylacetamide (0.095 g, 0.29 mmol; Intermediate 23) was reacted with 2-chlorobenzenesulfonyl chloride according to

the procedure of Intermediate 19. Yield: 0.06 g (41%) after purification by preparative HPLC (System E; 20-50% MeCN). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.08 (t, *J*=6.9 Hz, 3 H) 1.15 (t, *J*=6.9 Hz, 3 H) 3.09 - 3.43 (m, 7 H) 3.55 - 3.65 (m, 2 H) 3.67 - 3.76 (m, 2 H) 4.39 (s, 2 H) 6.62 (d, *J*=1.0 Hz, 1 H) 6.86 (d, *J*=1.3 Hz, 1 H) 6.93 (d, *J*=1.5 Hz, 1 H) 7.47 (t, *J*=7.0 Hz, 1 H) 7.60 (q, *J*=7.7 Hz, 2 H) 7.91 (d, *J*=1.3 Hz, 1 H) 8.01 (d, *J*=7.8 Hz, 1 H) 10.08 (s, 1 H) 10.46 (s, 1 H). HPLC purity 92%, *R*_T=1.85 min (System A; 10-97% MeCN over 3 min). MS (ESI+) *m/z* 505.2 (M+H)⁺.

EXAMPLE 35

10 **N,N-Diethyl-2-[4-(5-[(2-methoxy-5-methylphenyl)sulfonyl]amino)-1-benzofuran-7-yl)piperazin-1-yl]acetamide hydrochloride**

2-[4-(5-Amino-1-benzofuran-7-yl)piperazin-1-yl]-N,N-diethylacetamide (0.095 g, 0.29 mmol; Intermediate 23) was reacted with 2-methoxy-5-methylphenylsulfonyl chloride according to the procedure of Intermediate 19. Yield: 0.05 g (33%) after preparative HPLC (System F; 10-50% MeCN). HPLC purity 93%, *R*_T=1.87 min (System A; 10-97% MeCN over 3 min). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.08 (t, *J*=7.0 Hz, 3 H) 1.16 (t, *J*=7.0 Hz, 3 H) 2.20 (s, 3 H) 3.08 - 3.45 (m, 7 H) 3.58-3.73 (m, 4 H) 3.87 (s, 3 H) 4.40 (s, 2 H) 6.61 (d, *J*=1.8 Hz, 1 H) 6.85 (d, *J*=2.0 Hz, 1 H) 6.93 (d, *J*=1.8 Hz, 1 H) 7.04 (d, *J*=8.5 Hz, 1 H) 7.32 (dd, *J*=8.8, 2.0 Hz, 1 H) 7.52 (d, *J*=1.8 Hz, 1 H) 7.89 (d, *J*=2.3 Hz, 1 H) 9.75 (s, 1 H) 10.07 (s, 1 H) MS (ESI+) *m/z* 515.4 (M+H)⁺.

INTERMEDIATE 24

3-(7-Bromo-1-benzofuran-2-yl)quinuclidin-3-ol

Step 1. 3-[(Trimethylsilyl)ethynyl]quinuclidin-3-ol.

25 A mixture of 3-quinuclidinone hydrochloride (24.12 g, 0.149 mol) and Na₂CO₃ (27 g, 0.25 mol), in water (500 mL) was extracted with dichloromethane (500 mL). The organic phase was evaporated to dryness. The residue was dissolved in THF (200 g) and slowly added to a solution of TMS-Li-acetylide (1.1 equiv) in THF (200 g) at 0-5 °C. When the addition was completed, a solution of NaHCO₃ in water (500 mL) was added. The organic phase
30 was washed with additional water (500 mL) and evaporated to dryness to yield 20.89 g (63%) of the title compound as a white solid. ¹H NMR (270 MHz, CDCl₃) δ ppm 0.15 (s, 9 H) 1.27 - 1.46 (m, 1 H) 1.47 - 1.73 (m, 1 H) 1.80 - 2.14 (m, 3 H) 2.61 - 3.02 (m, 5 H) 3.17 (dd, *J*=13.86, 1.73 Hz, 1 H) 4.14 (br s, 1 H).

Step 2. 3-(7-Bromo-1-benzofuran-2-yl)quinuclidin-3-ol.

2,6-Dibromonitrophenol (3.0 g, 0.0119 mol), 3-[(trimethylsilyl)ethynyl]quinuclidin-3-ol (2.66 g, 0.0119 mol; obtained in Step 1), Cu₂O (1.70 g, 0.0119 mol) and pyridine (200 mL) were added to a round bottom flask. The resulting mixture was heated at reflux overnight, filtered through Celite, and the solvent was evaporated. The residue was purified by chromatography on silica gel using ethyl acetate (250 mL) and methanol (500 mL) as eluents. The methanol fraction was evaporated to yield 1.12 g (29%) of the title compound. HPLC purity = 90%, m/z = 322 (M+H)⁺.

10

INTERMEDIATE 25

3-(7-Bromo-1-benzofuran-2-yl)-1-azabicyclo[2.2.2]oct-2-ene

3-(7-Bromo-1-benzofuran-2-yl)quinuclidin-3-ol (600 mg, 1.86 mmol; Intermediate 24, Step 2) was dissolved in methanol (2 mL) and formic acid (40 mL) was added to the flask. The resulting mixture was heated at reflux overnight. Concentration in vacuo furnished 562 mg (99%) of the title product. HPLC purity = 90%, m/z = 305 (M+H)⁺.

15

INTERMEDIATE 26

[2-(1-Azabicyclo[2.2.2]oct-2-en-3-yl)-1-benzofuran-7-yl]amine

3-(7-Bromo-1-benzofuran-2-yl)-1-azabicyclo[2.2.2]oct-2-ene (300 mg, 0.986 mmol; Intermediate 25) was dissolved in methanol (2 mL). A solution of concentrated aqueous ammonia (25%; 10 mL) and CuCl₂ (15 mg) were added and the resulting mixture was heated at 120 °C for 48 h. The mixture was run through a silica plug using methanol/ammonia solution (9:1) as eluent. Concentration in vacuo furnished 236 mg of the crude title product. This material was used directly in subsequent experiments.

25

EXAMPLE 36

N-[2-(1-Azabicyclo[2.2.2]oct-2-en-3-yl)-1-benzofuran-7-yl]benzenesulfonamide hydrochloride

[2-(1-Azabicyclo[2.2.2]oct-2-en-3-yl)-1-benzofuran-7-yl]amine (118 mg, 0.493 mmol; Intermediate 26), benzenesulfonyl chloride (104 mg, 0.592 mmol) and triethylamine (137 µl, 0.986 mmol) were dissolved in ethanol (5 mL). The mixture was shaken for 2 hours. Purification was carried out by preparative HPLC (20-90% acetonitrile/TFA-water gradient). Evaporated to yield 47 mg TFA salt, which was converted to the HCl salt by

30

stirring it in HCl/ether. Yield: 37 mg (18%), HPLC purity = 99%, m/z = 381 (M+H)⁺, ¹H NMR (270 MHz, methanol-*d*₄) δ ppm 1.74 - 1.91 (m, 2 H) 2.10 - 2.26 (m, 2 H) 3.15 - 3.29 (m, 2 H) 3.49 - 3.57 (m, 1 H) 3.64 - 3.78 (m, 2 H) 6.97 - 7.01 (m, 1 H) 7.13 - 7.28 (m, 3 H) 7.38 - 7.57 (m, 4 H) 7.70 - 7.76 (m, 2 H).

5

EXAMPLE 37

***N*-[2-(1-Azabicyclo[2.2.2]oct-2-en-3-yl)-1-benzofuran-7-yl]-2-methoxy-5-methylbenzenesulfonamide hydrochloride**

The title compound was prepared according to the same procedure as Example 36. Yield:

10 56 mg (25%), HPLC purity = 99%, m/z = 425 (M+H)⁺, ¹H NMR (270 MHz, CDCl₃) δ ppm 1.77 - 1.96 (m, 2 H) 2.06 - 2.20 (m, 2 H) 2.22 (s, 3 H) 3.14 - 3.32 (m, 2 H) 3.39 - 3.48 (m, 1 H) 3.55 - 3.71 (m, 2 H) 3.97 (s, 3 H) 6.89 - 6.95 (m, 2 H) 7.06 - 7.29 (m, 5 H) 7.41 (dd, J =7.92, 0.99 Hz, 1 H).

15 EXAMPLE 38

***N*-[7-(1-Azabicyclo[2.2.2.]oct-3-yloxy)-1-benzofuran-5-yl]benzenesulfonamide hydrochloride**

Step 1. 3-[(5-nitro-1-benzofuran-7-yl)oxy]quinuclidine.

7-Iodo-5-nitro-1-benzofuran (1.00 g, 3.46 mmol), quinuclidin-3-ol (1.10 g, 8.65 mmol),
20 1,10-phenanthroline (0.25 g, 1.38 mmol), CuI (0.13 g, 0.69 mmol) and toluene (20 mL) were mixed together and heated at 140 °C overnight. The solvent was removed in vacuo and the crude product was purified by flash chromatography (eluent: hexane and chloroform:MeOH:triethylamine; 9:0.9:0.1) to give 3-[(5-nitro-1-benzofuran-7-yl)oxy]quinuclidine (3.46 mmol).

25

Step 2. 7-(1-Azabicyclo[2.2.2]oct-3-yloxy)-1-benzofuran-5-amine.

3-[(5-Nitro-1-benzofuran-7-yl)oxy]quinuclidine (1.38 g, 4.79 mmol; obtained in Step1) was dissolved in ethanol:THF (100 mL: 25 mL) and Raney-nickel (slurry in ethanol; 6 mL) and hydrazine (891 μ L, 0.18 mmol) were added. The mixture was stirred at room
30 temperature for 3 h and then filtered through Celite and the solvent was removed in vacuo. The crude product was purified by flash chromatography [eluent: DCM:methanol (6:1) and chloroform:MeOH:triethylamine (9:1:0.1)] to give 7-(1-azabicyclo[2.2.2]oct-3-yloxy)-1-benzofuran-5-amine (500 mg; 40%).

Step 3. N-[7-(1-Azabicyclo[2.2.2]oct-3-yloxy)-1-benzofuran-5-yl]benzenesulfonamide hydrochloride.

Benzenesulfonyl chloride (30 μ L, 0.232 mmol) and pyridine (141 μ L, 1.74 mmol) were added to 7-(1-azabicyclo[2.2.2]oct-3-yloxy)-1-benzofuran-5-amine (0.50 g, 0.194 mmol; obtained in Step 2) in DCM (2 mL). The mixture was shaken at room temperature for 2 h and then the solvent was removed in vacuo. Purification of the product was done by preparative HPLC using acetonitrile-water gradients containing 0.1% trifluoroacetic acid. The obtained TFA salt was converted into the hydrochloride salt by treatment with 2 M HCl in ether. Yield: 11.0 mg (11.8%). HPLC 100%, R_T : 1.680 (System B; 10-97% MeCN over 3 min). ^1H NMR (270 MHz, methanol- d_4) δ ppm 0.91 (t, $J=7.05$ Hz, 1 H) 1.31 (m, 1 H) 1.89-2.36 (m, 5 H) 3.32-3.46 (m, 4 H) 3.77-3.87 (m, 1 H) 6.68-6.74 (m, 2 H) 6.94 (s, 1 H) 7.43-7.56 (m, 3 H) 7.68-7.73 (m, 3 H). LC-MS 399 (M+H) $^+$.

EXAMPLE 39

N-[7-(1-Azabicyclo[2.2.2]oct-3-yloxy)-1-benzofuran-5-yl]-2-chlorobenzenesulfonamide hydrochloride

The title compound was prepared according to the procedure of Example 38, Step 3, starting from 7-(1-azabicyclo[2.2.2]oct-3-yloxy)-1-benzofuran-5-amine (obtained in Example 38, Step 2) and 2-chlorobenzenesulfonyl chloride (0.49 g, 0.232 mmol). Yield: 55 mg (54%). HPLC 100%, R_T : 1.760 (System B; 10-97% MeCN over 3 min). ^1H NMR (270 MHz, methanol- d_4) δ ppm 1.80-2.35 (m, 5 H) 2.18 (d, $J=7.42$ Hz, 1 H) 2.25 (s, 1 H) 3.29-3.30 (m, 2 H) 3.41 (t, $J=8.04$ Hz, 2 H) 3.83 (dd, $J=13.61, 7.92$ Hz, 1 H) 3.97 (s, 1 H) 6.73-6.76 (m, 2 H) 6.99-7.05 (m, 2 H) 7.33-7.36 (m, 1 H) 7.50-7.54 (m, 1 H) 7.70 (t, $J=2.60$ Hz, 1 H) 7.96 (d, $J=7.67$ Hz, 1 H). LC-MS 433 (M+H) $^+$.

EXAMPLE 40

N-[7-(1-Azabicyclo[2.2.2]oct-3-yloxy)-1-benzofuran-5-yl]-2-methoxy-5-methylbenzenesulfonamide hydrochloride

The title compound was prepared according to the procedure of Example 38, Step 3, starting from 7-(1-azabicyclo[2.2.2]oct-3-yloxy)-1-benzofuran-5-amine (obtained in Example 38, Step 2) and 2-methoxy-5-methylbenzenesulfonyl chloride (0.51 g, 0.232 mmol). Yield: 80 mg (77%). HPLC 100%, R_T : 1.794 (System B; 10-97% MeCN over 3

min). ^1H NMR (270 MHz, methanol- d_4) δ ppm 0.92 (d, $J=7.92$ Hz, 1 H) 1.28-1.37 (m, 1 H) 1.99 (d, $J=11.13$ Hz, 3 H) 2.21 (s, 3 H) 2.36 (s, 1 H) 3.46-3.48 (m, 4 H) 3.85 (d, $J=7.18$ Hz, 1 H) 3.96 (s, 3 H) 5.02-5.04 (m, 1 H) 6.73-6.77 (m, 2 H) 6.96 (s, 1 H) 7.03 (d, $J=8.41$ Hz, 1 H) 7.32 (d, $J=7.42$ Hz, 1 H) 7.49 (s, 1 H) 7.70 (d, $J=1.48$ Hz, 1 H). LC-MS 443
5 (M+H) $^+$.

INTERMEDIATE 27

(2-Morpholin-4-ylethyl)(5-nitro-1-benzofuran-7-yl)amine

7-Iodo-5-nitrobenzofuran (1.00 g, 3.46 mmol), 4-(2-aminoethyl)morpholine (0.54 g, 4.15
10 mmol), NaOt-Bu (0.47 g, 0.00484 mol), Xantphos (0.20 g, 0.346 mmol) and Pd_2dba_3 (80 mg, 0.0865 mol) were heated in xylene (20 mL) at 120 °C for 1.5 hours. The reaction mixture was filtered through Celite and the solvent evaporated. The residue was run through a silica plug using dichloromethane (DCM) and then a 90:9:1 mixture of DCM/MeOH/ NH_3 (aqueous 25%) as eluents. The product-containing fractions were
15 concentrated to yield 0.978 g (97%) of the title compound as a dark yellow oil. HPLC purity = 97 %, $m/z = 292$ (M+H) $^+$, ^1H NMR (270 MHz, CDCl_3) δ ppm 2.44 - 2.61 (m, 4 H) 2.75 (t, $J=5.81$ Hz, 2 H) 3.31 - 3.43 (m, 2 H) 3.69 - 3.82 (m, 4 H) 6.85 (d, $J=1.98$ Hz, 1 H) 7.36 (d, $J=1.98$ Hz, 1 H) 7.70 (d, $J=1.98$ Hz, 1 H) 7.90 (d, $J=2.23$ Hz, 1 H).

20 INTERMEDIATE 28

 N^7 -(2-Morpholin-4-ylethyl)-1-benzofuran-5,7-diamine

(2-Morpholin-4-ylethyl)(5-nitro-1-benzofuran-7-yl)amine (450 mg, 1.545 mmol; Intermediate 27) was dissolved in THF (5 mL). After addition of ethanol (100 mL), Raney-nickel (cat.) and hydrazine hydrate (2 mL), the mixture was left stirring at room
25 temperature for 2 h. The product was used directly in the subsequent reaction after filtration through Celite and evaporation of solvent.

INTERMEDIATE 29

4-{2-[(5-Nitro-1-benzofuran-7-yl)oxy]ethyl}morpholine

30 To a test tube was added 7-iodo-5-nitrobenzofuran (1.0 g, 0.00346 mol), 4-(2-hydroxyethyl)morpholine (0.91 g, 0.00692 mol), cesium carbonate (2.25 g, 0.00692 mol), 1,10-phenanthroline (0.25 g, 0.00138 mol) and CuI (130 mg, 0.692 mmol). Toluene (15 mL) was added and the solution was heated in a StemBlock for 72 h. After filtration

through Celite, the crude material was purified by flash chromatography (EtOAc/DCM; 1:1). Yield: 32%, HPLC purity = 90%, m/z = 293 (M+H)⁺.

INTERMEDIATE 30

5 [7-(2-Morpholin-4-ylethoxy)-1-benzofuran-5-yl]amine

The title compound was prepared according to the same procedure as Intermediate 28 starting from Intermediate 29. The product was used directly in the subsequent reaction (Example 45).

10 EXAMPLE 41

N-{7-[(2-Morpholin-4-ylethyl)amino]-1-benzofuran-5-yl}benzenesulfonamide hydrochloride

To a solution of *N*⁷-(2-Morpholin-4-ylethyl)-1-benzofuran-5,7-diamine (58 mg, 0.221 mmol; Intermediate 28) in dichloromethane (2 mL) were added triethylamine (62 µL, 0.442 mmol) and benzenesulfonyl chloride (39 mg, 0.221 mmol). The mixture was stirred at room temperature for 1 h and evaporated. The residue was purified by preparative HPLC (System D), evaporated pure fractions, and converted the resulting TFA salt to a HCl salt. Yield: 32%, HPLC purity = 100%, m/z = 402 (M+H)⁺, ¹H NMR (270 MHz, methanol-*d*₄) δ ppm 3.43 (t, *J*=6.06 Hz, 2 H) 3.40 - 3.61 (m, *J*=6.06, 6.06 Hz, 4 H) 3.68 (t, *J*=6.06 Hz, 2 H) 3.75 - 4.14 (m, 4 H) 6.48 - 6.55 (m, 2 H) 6.64 (d, *J*=2.23 Hz, 1 H) 7.41 - 7.59 (m, 3 H) 7.65 - 7.74 (m, 3 H).

EXAMPLE 42

25 2-Methoxy-5-methyl-*N*-{7-[(2-morpholin-4-ylethyl)amino]-1-benzofuran-5-yl}benzenesulfonamide hydrochloride

The title compound was prepared according to the procedure of Example 41. Yield: 37%, HPLC purity = 100%, m/z = 446 (M+H)⁺, ¹H NMR (270 MHz, methanol-*d*₄) δ ppm 2.18 - 2.24 (s, 3 H) 3.35 - 3.60 (m, 4 H) 3.43 (t, *J*=5.94 Hz, 2 H) 3.67 (t, *J*=5.94 Hz, 2 H) 3.74 - 4.07 (m, 4 H) 3.94 - 3.99 (m, 3 H) 6.51 (d, *J*=1.98 Hz, 1 H) 6.63 (dd, *J*=4.08, 2.10 Hz, 2 H) 7.03 (d, *J*=8.41 Hz, 1 H) 7.32 (dd, *J*=8.78, 2.60 Hz, 1 H) 7.49 (d, *J*=2.23 Hz, 1 H) 7.64 (d, *J*=2.23 Hz, 1 H).

EXAMPLE 43

***N*-{7-[(2-Morpholin-4-ylethyl)amino]-1-benzofuran-5-yl}-2-(trifluoromethyl)benzenesulfonamide hydrochloride**

The title compound was prepared according to the procedure of Example 41. Yield: 38%, HPLC purity = 100%, $m/z = 470$ (M+H)⁺, ¹H NMR (270 MHz, methanol-*d*₄) δ ppm 3.15 - 3.63 (m, 4 H) 3.43 (t, $J=5.94$ Hz, 2 H) 3.67 (t, $J=6.06$ Hz, 2 H) 3.72 - 4.14 (m, 4 H) 6.49 (d, $J=1.73$ Hz, 1 H) 6.64 (dd, $J=7.42$, 1.98 Hz, 2 H) 7.60 - 7.75 (m, 3 H) 7.88 - 7.94 (m, 1 H) 8.00 - 8.04 (m, 1 H).

EXAMPLE 44

10 2,6-Dichloro-*N*-{7-[(2-morpholin-4-ylethyl)amino]-1-benzofuran-5-yl}benzenesulfonamide hydrochloride

The title compound was prepared according to the procedure of Example 41. Yield: 19%, HPLC purity = 100%, $m/z = 470$ (M+H)⁺, ¹H NMR (270 MHz, methanol-*d*₄) δ ppm 3.22 - 3.60 (m, 4 H) 3.45 (t, $J=5.94$ Hz, 2 H) 3.69 (t, $J=5.94$ Hz, 2 H) 3.72 - 4.13 (m, 4 H) 6.58 (d, $J=1.98$ Hz, 1 H) 6.67 (dd, $J=9.65$, 1.98 Hz, 2 H) 7.33 - 7.41 (m, 1 H) 7.45 - 7.52 (m, 2 H) 7.66 (d, $J=1.98$ Hz, 1 H).

EXAMPLE 45

20 2-Methoxy-5-methyl-*N*-[7-(2-morpholin-4-ylethoxy)-1-benzofuran-5-yl]benzenesulfonamide hydrochloride

The title compound was prepared according to the procedure of Example 41 starting from [7-(2-morpholin-4-ylethoxy)-1-benzofuran-5-yl]amine (Intermediate 30). Yield: 32%, HPLC purity = 99%, $m/z = 447$ (M+H)⁺, ¹H NMR (270 MHz, methanol-*d*₄) δ ppm 2.20 (s, 3 H) 3.26 - 3.74 (m, 4 H) 3.66 - 3.72 (m, 2 H) 3.75 - 4.15 (m, 4 H) 3.96 (s, 3 H) 4.49 - 4.57 (m, 2 H) 6.73 (d, $J=2.23$ Hz, 1 H) 6.85 (d, $J=1.98$ Hz, 1 H) 6.96 (d, $J=1.98$ Hz, 1 H) 6.99 - 7.04 (m, 1 H) 7.27 - 7.34 (m, 1 H) 7.51 (d, $J=2.23$ Hz, 1 H) 7.70 (d, $J=2.23$ Hz, 1 H).

EXAMPLE 46

30 3-Methyl-*N*-[7-(2-morpholin-4-ylethoxy)-1-benzofuran-5-yl]benzenesulfonamide hydrochloride

The title compound was prepared according to the procedure of Example 41 starting from [7-(2-morpholin-4-ylethoxy)-1-benzofuran-5-yl]amine (Intermediate 30). Yield: 28%, HPLC purity = 98%, $m/z = 417$ (M+H)⁺, ¹H NMR (270 MHz, methanol-*d*₄) δ ppm 2.28 -

2.36 (m, 3 H) 3.24 - 3.69 (m, 4 H) 3.67 - 3.73 (m, 2 H) 3.76 - 4.17 (m, 4 H) 4.51 - 4.59 (m, 2 H) 6.74 (d, $J=2.23$ Hz, 1 H) 6.82 (d, $J=1.98$ Hz, 1 H) 6.89 (d, $J=1.98$ Hz, 1 H) 7.27 - 7.40 (m, 2 H) 7.46 - 7.57 (m, 2 H) 7.73 (d, $J=2.23$ Hz, 1 H).

5 EXAMPLE 47

3-Chloro-4-methyl-N-[7-(2-morpholin-4-ylethoxy)-1-benzofuran-5-yl]benzenesulfonamide hydrochloride

The title compound was prepared according to the procedure of Example 41 starting from [7-(2-morpholin-4-ylethoxy)-1-benzofuran-5-yl]amine (Intermediate 30). Yield: 11%,

10 HPLC purity = 99%, $m/z = 451$ ($M+H$)⁺, ¹H NMR (270 MHz, methanol-*d*₄) δ ppm 2.36 - 2.39 (m, 3 H) 3.31 - 3.71 (m, 4 H) 3.68 - 3.74 (m, 2 H) 3.75 - 4.22 (m, 4 H) 4.54 - 4.61 (m, 2 H) 6.77 (d, $J=1.98$ Hz, 1 H) 6.87 (q, $J=1.98$ Hz, 2 H) 7.35 - 7.40 (m, 1 H) 7.48 - 7.54 (m, 1 H) 7.66 (d, $J=1.73$ Hz, 1 H) 7.75 (d, $J=1.98$ Hz, 1 H).

15 INTERMEDIATE 31

[2-(Dimethylamino)ethyl](5-nitro-1-benzofuran-7-yl)amine

Xylene (75 mL) was added to 7-iodo-5-nitro-1-benzofuran (1.00 g, 3.46 mmol), *N,N*-dimethylethane-1,2-diamine (0.37 g, 4.15 mmol), Pd₂(dba)₃ (0.08 g, 0.87 mmol), Xantphos (0.20 g, 0.35 mmol) and Cs₂CO₃ (1.59 g, 4.84 mmol). The mixture was stirred at 120 °C

20 overnight, filtered through Celite and the solvent was removed in vacuo. The crude product was purified by flash chromatography [eluent: DCM:MeOH (6:1) and DCM:MeOH:Et₃N (9:1:0.1)] to afford 0.378 g (44%) of the title compound. HPLC 90%, R_T : 1.430 (System A; 10-97% MeCN over 3 min). ¹H NMR (270 MHz, methanol-*d*₄) δ ppm 2.44 (d, $J=3.22$ Hz, 6 H) 2.81 (t, $J=6.56$ Hz, 2 H) 3.52 (t, $J=6.56$ Hz, 2 H) 6.97 (d, $J=2.23$ Hz, 1 H) 7.40 (d, $J=2.23$ Hz, 1 H) 7.89 (t, $J=1.98$ Hz, 2 H). LC-MS 250 ($M+H$)⁺.

EXAMPLE 48

N-(7-{[2-(Dimethylamino)ethyl]amino}-1-benzofuran-5-yl)-2-methoxy-5-benzenesulfonamide

30 *Step 1. N⁷-[2-(Dimethylamino)ethyl]-1-benzofuran-5,7-diamine.*

Raney-nickel (slurry in ethanol; 2 mL) and hydrazine (295 μ L, 6.08 mmol) were added to [2-(dimethylamino)ethyl](5-nitro-1-benzofuran-7-yl)amine (0.378 g, 1.52 mmol; Intermediate 31) in a mixture of ethanol (100 mL) and THF (25 mL). The reaction mixture

was stirred at room temperature for 2 h. Additional Raney-nickel (slurry in ethanol; 2 mL) and hydrazine (295 μ L, 6.08 mmol) were added and stirring was continued overnight. The mixture was filtered through Celite and the solvent was removed. The crude product was used in the next step without further purification.

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Step 2. N-(7-{[2(Dimethylamino)ethyl]amino}-1-benzofuran-5-yl)-2-methoxy-5-benzenesulfonamide.

2-methoxy-5-methylbenzenesulfonyl chloride (0.145 g, 0.657 mmol) and pyridine (398 μ L, 4.93 mmol) were added to *N*⁷-[2-(dimethylamino)ethyl]-1-benzofuran-5,7-diamine (0.120 g, 0.547 mmol; from Step 1) in DCM (1 mL). The mixture was shaken at room temperature for 1 h, solvent was removed in vacuo and the product was purified by preparative HPLC using acetonitrile-water gradients containing 0.1% trifluoroacetic acid. The obtained TFA salt was converted into the hydrochloride salt by treatment with 2 M HCl in ether to afford 13.3 mg (6%) of the title product. HPLC 99%, *R*_T: 1.692 (System A; 10-97% MeCN over 3 min). ¹H NMR (270 MHz, methanol-*d*₄) δ ppm 2.21 (s, 3 H) 2.94 (s, 6 H) 3.40 (t, *J*=5.69 Hz, 2 H) 3.60-3.64 (m, 2 H) 3.97 (s, 3 H) 6.52 (s, 1 H) 6.64 (t, *J*=2.10 Hz, 1 H) 7.03 (d, *J*=8.41 Hz, 1 H) 7.32 (d, *J*=6.19 Hz, 1 H) 7.50 (d, *J*=1.98 Hz, 1 H) 7.65 (d, *J*=2.23 Hz, 2 H). LC-MS 404 (M+H)⁺.

20 EXAMPLE 49

2-Chloro-N-(7-{[2-(dimethylamino)}-1-benzofuran-5-yl)benzenesulfonamide hydrochloride

2-Chlorobenzenesulfonyl chloride (0.139 g, 0.657 mmol) and pyridine (398 μ L, 4.93 mmol) were added to *N*⁷-[2-(dimethylamino)ethyl]-1-benzofuran-5,7-diamine (0.120 g, 0.547 mmol; Example 48, Step 1) in DCM (1 mL). The mixture was shaken at room temperature for 1 h, solvent removed in vacuo, and the product was purified by preparative HPLC using acetonitrile-water gradients containing 0.1% trifluoroacetic acid. The obtained TFA salt was converted into the hydrochloride salt by treatment with 2 M HCl in ether to afford 22.8 mg (10%) of the title product. HPLC 99%, *R*_T: 1.651 (System A; 10-97% MeCN over 3 min). ¹H NMR (270 MHz, methanol-*d*₄) δ ppm 2.94 (s, 6 H) 3.40 (s, 2 H) 3.65 (d, *J*=1.48 Hz, 2 H) 6.65 (d, *J*=1.73 Hz, 1 H) 7.36 (t, *J*=7.18 Hz, 2 H) 7.50-7.56 (m, 3 H) 7.66 (d, *J*=1.73 Hz, 1 H) 7.97 (d, *J*=7.67 Hz, 1 H). LC-MS 394 (M+H)⁺.

INTERMEDIATE 32

N-(5-Nitro-1-benzofuran-7-yl)pyridin-4-yl-amine

A mixture of 7-iodo-5-nitro-1-benzofuran (1.00 g, 3.46 mmol), 4-aminopyridine (0.39 g, 4.15 mmol), Xantphos (0.20 g, 0.36 mmol), Pd₂(dba)₃ (0.08 g, 0.09 mmol), NaOtBu (0.47 g, 4.84 mmol) in xylene (200 mL) was heated at 120 °C overnight. The reaction mixture was filtered through Celite and a yellow precipitate was formed which was collected by filtration to yield 0.52 g (60%) of the title product. HPLC 96%, R_T: 1.344 (System A; 10-97% MeCN over 3 min). ¹H NMR (270 MHz, methanol-*d*₄) δ ppm 6.91-7.12 (m, 4 H) 8.00 (d, *J*=2.23 Hz, 1 H) 8.15-8.24 (m, 2 H) 8.37 (d, *J*=2.23 Hz, 1 H). LC-MS 256 (M+H)⁺.

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INTERMEDIATE 33

5-Amino-1-benzofuran-7-yl)pyridin-4-yl-amine

Raney-nickel (slurry in ethanol; 2 mL) and hydrazine (404 μL, 8.33 mmol) were added to N-(5-nitro-1-benzofuran-7-yl)pyridin-4-yl-amine (0.52 g, 2.08 mmol; Intermediate 32) in ethanol (40 mL) and THF (10 mL). The mixture was stirred at room temperature for 3 h, filtered through Celite and the solvent was removed in vacuo to yield 0.27 g (53%) of the title product. HPLC 96%, R_T: 0.964 (System A; 10-97% MeCN over 3 min). ¹H NMR (270 MHz, methanol-*d*₄) δ ppm 6.69 (d, *J*=2.23 Hz, 1 H) 6.72 (d, *J*=2.23 Hz, 1 H) 6.77 (d, *J*=1.98 Hz, 1 H) 6.83 (dd, *J*=4.95, 1.48 Hz, 2 H) 7.62 (d, *J*=1.98 Hz, 1 H) 8.08 - 8.10 (m, 2 H). LC-MS 226 (M+H)⁺.

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EXAMPLE 50

N-[7-(Pyridin-4-ylamino)-1-benzofuran-5-yl]benzenesulfonamide hydrochloride

Benzenesulfonyl chloride (65 μL, 0.48 mmol) and pyridine (289 μL, 3.58 mmol) were added to (5-amino-1-benzofuran-7-yl)pyridin-4-yl-amine (90 mg, 0.40 mmol; Intermediate 33) in DCM (2 mL). The mixture was heated at 40 °C for 10 min, shaken at room temperature for 1 h, and solvent was removed in vacuo. The residue was purified by preparative HPLC using acetonitrile-water gradients containing 0.1% trifluoroacetic acid. The obtained TFA salt was converted into the hydrochloride salt by treatment with 2 M HCl in ether to afford 78.7 mg (45%) of the title product. HPLC 100%, R_T: 1.560 (System A; 10-97% MeCN over 3 min). ¹H NMR (270 MHz, methanol-*d*₄) δ ppm 6.91 (s, 1 H) 7.04 (d, *J*=2.23 Hz, 2 H) 7.36 (d, *J*=1.98 Hz, 1 H) 7.51-7.65 (m, 3 H) 7.74-7.77 (m, 2 H) 8.03

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(d, $J=1.98$ Hz, 1 H) 8.32 (d, $J=6.93$ Hz, 2 H) 10.43 (s, 1 H) 10.84 (s, 1 H). LC-MS 366 (M+H)⁺.

EXAMPLE 51

5 **2-Chloro-N-[7-(pyridin-4-ylamino)-1-benzofuran-5-yl]benzenesulfonamide hydrochloride**

Prepared by the same method as for N-[7-(pyridin-4-ylamino)-1-benzofuran-5-yl]benzenesulfonamide hydrochloride (Example 50) from 2-chlorobenzenesulfonyl chloride (101 mg, 0.48 mmol). This furnished 60.3 mg (32%) of 2-chloro-N-[7-(pyridin-4-ylamino)-1-benzofuran-5-yl]benzenesulfonamide hydrochloride. HPLC 100%, R_T: 1.639 (System A; 10-97% MeCN over 3 min). ¹H NMR (270 MHz, methanol-*d*₄) δ ppm 6.92 (s, 1 H) 7.03 (d, $J=2.23$ Hz, 1 H) 7.09 (d, $J=1.98$ Hz, 1 H) 7.36 (d, $J=2.23$ Hz, 1 H) 7.48-7.53 (m, 1 H) 7.60-7.68 (m, 2 H) 8.02-8.06 (m, 2 H) 8.33 (d, $J=7.18$ Hz, 2 H) 10.74 (s, 1 H) 10.86 (s, 1 H). LC-MS 400 (M+H)⁺.

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EXAMPLE 52

2-Methoxy-5-methyl-N-[7-(pyridin-4-ylamino)-1-benzofuran-5-yl]benzenesulfonamide hydrochloride

Prepared by the same method as for N-[7-(pyridin-4-ylamino)-1-benzofuran-5-yl]benzenesulfonamide hydrochloride (Example 50) from 2-methoxy-5-methylbenzenesulfonyl chloride (105 mg, 0.48 mmol). This furnished 50.9 mg (26%) of 2-methoxy-5-methyl-N-[7-(pyridin-4-ylamino)-1-benzofuran-5-yl]benzenesulfonamide hydrochloride. HPLC 100%, R_T: 1.692 (System A; 10-97% MeCN over 3 min). ¹H NMR (270 MHz, methanol-*d*₄) δ ppm 2.21 (s, 3 H) 3.86 (s, 3 H) 6.91 (s, 1 H) 7.02-7.09 (m, 3 H) 7.33-7.38 (m, 2 H) 7.55 (d, $J=1.73$ Hz, 1 H) 8.00 (d, $J=1.98$ Hz, 1 H) 8.32 (d, $J=6.93$ Hz, 2 H) 10.04 (s, 1 H) 10.78 (s, 1 H). LC-MS 410 (M+H)⁺.

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EXAMPLE 53

2-Methoxy-5-methyl-N-[7-(piperazin-1-ylcarbonyl)-1-benzofuran-5-yl]benzenesulfonamide hydrochloride

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Step 1. 7-Bromo-2-trimethylsilylbenzofuran-5-ylamine.

7-Bromo-5-nitro-2-trimethylsilylbenzofuran (5.0 g, 15.9 mmol; Intermediate 4, Step 2) was reduced with PtO₂ (363 mg, 1.6 mmol) in EtOAc (100 mL) over 2.5 bar H₂ overnight. The

resulting mixture was filtered through wetted Celite to yield 4.5 g (quantitative) of 7-bromo-2-trimethylsilanyl-benzofuran-5-ylamine.

Step 2. *N*-(7-Bromo-2-trimethylsilanyl-benzofuran-5-yl)-2-methoxy-5-methylbenzenesulfonamide.

Coupling of the amine (4.5 g, 15.9 mmol) from Step 1 with 2-methoxy-5-methylphenylsulfonyl chloride (3.5 g, 15.9 mmol) in dichloromethane (200 mL) using pyridine as a base (3.2 mL, 40 mmol) required 2.5 hours at ambient temperature. Washing the resulting mixture with water, drying and concentration yielded 7.4 g (100%) of *N*-(7-bromo-2-trimethylsilanyl-benzofuran-5-yl)-2-methoxy-5-methylbenzenesulfonamide as a dark orange solid.

Step 3. 4-[5-(2-Methoxy-5-methylbenzenesulfonylamino)-benzofuran-7-carbonyl]-piperazine-1-carboxylic acid *tert*-butyl ester.

The Heck carbonylation was performed under controlled microwave heating at 150°C/15 min by mixing the above bromide (168 mg, 0.36 mmol) from Step 2, (*tert*-butoxycarbonyl)piperazine (134 mg, 0.72 mmol), Mo(CO)₆ (48 mg, 0.18 mmol), trans-di(acetato)bis[o-(di-*o*-tolylphosphino)benzyl]dipalladium (II) (Herrmann's catalyst, 36 mg, 0.04 mmol), aqueous K₂CO₃ (4 M; 300 µL, 1.3 mmol) and diglyme (1 mL). This yielded about 50% of product with TMS remaining (4-[5-(2-methoxy-5-methylbenzenesulfonylamino)-2-trimethylsilanyl-benzofuran-7-carbonyl]-piperazine-1-carboxylic acid *tert*-butyl ester) and about 7% product with TMS absent, i.e., the title product. Both products were isolated pure by preparative HPLC (Gilson; using a gradient of 30-70% MeCN). Yield TMS product: 53 mg (24%) yellow oil. HPLC 100% R_T=2.06 (System C; 2-95% MeCN over 2 min). The TMS group was removed by allowing to stir in *t*-BuN⁺F⁻ (0.5 mL, 1 M in THF) in THF (3 mL) at ambient temperature for 1 h 20 min. Purification using preparative HPLC (gradient of 30-70% MeCN) gave additional material of the title product as a yellow oil.

Step 4. 2-Methoxy-5-methyl-*N*-[7-(piperazin-1-ylcarbonyl)-1-benzofuran-5-yl]benzenesulfonamide hydrochloride. Deprotection of the *N*-*t*-BOC group in 4-[5-(2-methoxy-5-methylbenzenesulfonylamino)-benzofuran-7-carbonyl]-piperazine-1-carboxylic acid *tert*-butyl ester (Step 3) was performed by adding HCl/ether to a solution of the said substrate in ethyl acetate and allowed to stir overnight at ambient temperature.

Concentration of the solution gave the title product as a white solid. Yield: 31 mg. HPLC 96% $R_T=2.73$ min (System A; 30-80% MeCN over 3 min), 1.05 min (System C; 2-95% MeCN over 2 min). ^1H NMR (400 Mz, methanol- d_4) δ ppm 2.17 (s, 3H), 3.19 (m, 2H), 3.34 (m, 2H), 3.49 (m, 2H), 3.91 (s, 3H), 4.01 (m, 2H), 6.80 (d, $J=2.2$ Hz, 1H), 6.99 (d, $J=8.6$ Hz, 1H), 7.20 (d, $J=2.2$ Hz, 1H), 7.28 (dd, $J=8.6$, 2.0 Hz, 1H), 7.45 (d, $J=2.2$ Hz, 1H), 7.49 (d, $J=2.0$ Hz, 1H), 7.76 (d, $J=2.0$ Hz, 1H). ^{13}C NMR (400 Mz, MeOH- d_4) δ ppm 19.15, 55.60, 94.55, 106.86, 112.31, 116.62, 118.32, 118.44, 125.90, 129.07, 129.89, 130.51, 133.47, 135.37, 140.33, 147.22, 147.92, 154.75, 166.24 (C=O). MS (ESI) for $\text{C}_{21}\text{H}_{23}\text{N}_3\text{O}_5\text{S}$ m/z 430 (M+H).

EXAMPLE 54

2-Methoxy-5-methyl-N-[7-(piperazin-1-ylmethyl)-1-benzofuran-5-yl]benzenesulfonamide hydrochloride

To a solution of 4-[5-(2-methoxy-5-methyl-benzenesulfonylamino)-2-trimethylsilanyl-benzofuran-7-carbonyl]-piperazine-1-carboxylic acid tert-butyl ester (94 mg, 0.16 mmol; obtained in Example 53, Step 3) in THF was added LiAlH_4 (22 mg, 0.56 mmol) and allowed to stir overnight at 80 °C (only 50% conversion to t-BOC- and TMS-deprotected bisamine product after 3 hours). The solution was made neutral by addition of aqueous 1 M HCl and extracted with ethyl acetate, but little product in organic phase. The resulting aqueous phase was therefore made acidic, and then concentrated. Purification by preparative HPLC (Gilson; gradient of 20-50% MeCN) gave 14 mg of pure product as the TFA salt. Conversion to the HCl salt was done with aqueous 6 M HCl. Concentration gave the final product as a white solid. Yield: 15 mg. HPLC 100% $R_T=2.51$ min (System A; 30-80% MeCN over 3 min), 0.94 min (System C; 2-95% MeCN over 2 min). ^1H NMR (400 Mz, MeOH- d_4) δ ppm 2.14 (s, 3H), 2.98 (s, 3H), 3.66 (br m, 9H), 4.69 (s, 2H), 6.80 (d, $J=8.3$ Hz, 1H), 6.82 (d, $J=2.2$ Hz, 1H), 7.14 (dd, $J=8.3$, 2.2 Hz, 1H), 7.38 (d, $J=2.0$ Hz, 1H), 7.40 (d, $J=2.0$ Hz, 1H), 7.52 (d, $J=2.2$ Hz, 1H), 7.82 (d, $J=2.2$ Hz, 1H). MS(ESI) for $\text{C}_{21}\text{H}_{25}\text{N}_3\text{O}_4\text{S}$ m/z 416 (M+H).

EXAMPLE 55

N-{7-[(3-Aminopyrrolidin-1-yl)methyl]-1-benzofuran-5-yl}-2-methoxy-5-methylbenzenesulfonamide hydrochloride

To a solution of {1-[5-(2-methoxy-5-methyl-benzenesulfonylamino)-2-trimethylsilyl-benzofuran-7-carbonyl]-pyrrolidin-3-yl}-carbamic acid tert-butyl ester* (84 mg, 0.14 mmol) in THF was added LiAlH₄ (22 mg, 0.56 mmol) and the resulting mixture was allowed to stir for 4 h at 80 °C. Ethyl acetate was added and the mixture was washed with 1 M aqueous HCl and then with water, dried and concentrated to yield 37 mg of the mono
5 boc-protected diamine. (According to HPLC, 34% was reduced at the furan ring). Purification by preparative HPLC (Gilson; gradient of 40-80% MeCN) gave pure boc-protected diamine. N-Deprotection was performed cleanly overnight in 6 M aqueous HCl (attempts with HCl/ether at 60 °C overnight gave only 25% product and some biproducts)
10 to give the product after evaporation as a yellow solid. Yield: 16 mg. HPLC 92% R_T=1.30 min (System A; 30-80% MeCN over 3 min), 1.03 min (System C; 2-95% MeCN over 2 min). The peaks in the proton NMR spectrum are broad due to the conformational flexibility of the pyrrolidine ring. ¹H NMR (400 Mz, methanol-*d*₄) δ ppm 1.44 (br s, 1H), 2.17 (s, 3H), 2.38 (br s, 1H), 3.37-3.83 (br m, 4H), 3.97 (s, 3H), 4.08-4.73 (br m, 3H), 6.82
15 (br s, 1H), 7.03 (m, 1H), 7.22-7.34 (br m, 5H), 7.48 (m, 3H), 7.81 (br s, 1H). MS(ESI) for C₂₁H₂₅N₃O₄S m/z 416 (M+H). *Prepared from pyrrolidin-3-yl-carbamic acid tert-butyl ester according to the procedure of Example 53 (Step 3).

INTERMEDIATE 34

20 Octahydrothieno[3,4-b]pyrazine 6,6-dioxide*

cis-3,4-Dichlorotetrahydrothiophene 1,1-dioxide (5.0 g, 26.0 mmol) in dioxane (40 mL) was added dropwise to ethane-1,2-diamine (10.4 g, 173.0 mmol) in dioxane (25 mL) at 0 °C. The mixture was heated at 100 °C for 3 h, followed by cooling to room temperature and continued stirring overnight. The two layers were separated and the bottom layer,
25 containing ethylene diamine and amine salt, was washed twice with dioxane. The dioxane layers were combined and the solvent was removed in vacuo. The crude product was recrystallized from toluene to afford 2.7 g (59%) of the title compound as white crystals. HPLC 98%, R_T: 0.292 (System B; 10-97% MeCN over 3 min). ¹H NMR (270 MHz, methanol-*d*₄) δ ppm 2.67-2.76 (m, 2 H) 2.86-2.96 (m, 2 H) 3.13-3.20 (m, 2 H) 3.33-3.44
30 (m, 2 H) 3.63-3.70 (m, 2 H). LC-MS 177 (M+H)⁺. *Previously described in U.S. Patent 3,882,122.

INTERMEDIATE 35

1-(5-Nitro-1-benzofuran-7-yl)octahydrothieno[3,4-b]pyrazine 6,6-dioxide

Xylene (150 mL) was added to 7-iodo-5-nitro-1-benzofuran (1.00 g, 3.46 mmol), octahydrothieno[3,4-b]pyrazine 6,6-dioxide (0.73 g, 4.15 mmol; Intermediate 34), Pd₂(dba)₃ (0.08 g, 0.87 mmol), Xantphos (0.20 g, 0.35 mmol) and Cs₂CO₃ (1.59 g, 4.84 mmol). The resulting mixture was stirred at 120 °C overnight, filtered through Celite and the solvent was removed in vacuo. The crude product was purified by flash chromatography [eluent: DCM and DCM:MeOH (1:1)] and then recrystallized from MeOH to afford 0.354 g (8%) of the title product. HPLC 90%, R_T: 1.390 (System A; 10-97% MeCN over 3min). ¹H NMR (270 MHz, CDCl₃) δ ppm 2.85 (dd, J=12.62, 7.42 Hz, 1 H) 3.16-3.49 (m, 6 H) 3.71 (t, J=11.63 Hz, 1 H) 4.02-4.05 (m, 1 H) 5.17-5.25 (m, 1 H) 6.93 (d, J=2.23 Hz, 1 H) 7.62 (t, J=2.72 Hz, 1 H) 7.77 (d, J=1.98 Hz, 1 H) 8.19 (d, J=1.98 Hz, 1 H). LC-MS 338 (M+H)⁺.

INTERMEDIATE 36**7-(6,6-Dioxidohexahydrothieno[3,4-b]pyrazine-1(2H)-yl)-1-benzofuran-5-amine**

Raney-nickel (slurry in ethanol; 2 mL) and hydrazine (204 mL, 4.20 mmol) were added to 1-(5-nitro-1-benzofuran-7-yl)octahydrothieno[3,4-b]pyrazine 6,6-dioxide (0.354 g, 1.05 mmol; Intermediate 35) in a mixture of THF (20 mL) and EtOH (80 mL). The resulting mixture was stirred at room temperature overnight and then more Raney-nickel (slurry in ethanol; 2 mL) and hydrazine (204 mL, 4.20 mmol) were added and stirring was continued overnight. The mixture was filtered through Celite and the solvent was removed in vacuo to afford 0.338 g (quantitative). HPLC 90%, R_T: 0.782 (System A; 10-97% MeCN over 3 min). ¹H NMR (270 MHz, methanol-d₄) δ ppm 2.79 (dd, J=12.49, 7.30 Hz, 1 H) 2.90-3.25 (m, 4 H) 3.43-3.64 (m, 3 H) 3.91-3.94 (m, 1 H) 5.01-5.07 (m, 1 H) 6.33 (d, J=1.98 Hz, 1 H) 6.61 (dd, J=12.99, 2.10 Hz, 2 H) 7.62 (d, J=1.98 Hz, 1 H). LC-MS 308 (M+H)⁺.

EXAMPLE 56**N-[7(6,6-Dioxidohexahydrothieno[3,4-b]pyrazin-1(2H)-yl)-1-benzofuran-5-yl]-2-methoxy-5-methylbenzenesulfonamide hydrochloride**

2-Methoxy-5-methylbenzenesulfonyl chloride (0.094 g, 0.428 mmol) and pyridine (259 μL, 3.21 mmol) were added to 7-(6,6-dioxidohexahydrothieno[3,4-b]pyrazine-1(2H)-yl)-1-benzofuran-5-amine (0.110 g, 0.357 mmol; Intermediate 36) in DCM (1 mL). The mixture was shaken at room temperature for 1 h, solvent removed in vacuo, and the residue was

purified by preparative HPLC using acetonitrile-water gradients containing 0.1% trifluoroacetic acid. The obtained TFA salt was converted into the hydrochloride salt by treatment with 2 M HCl in ether to afford 20.0 mg (11%) of the title product. HPLC 98%, R_T : 1.483 (System A; 10-97% MeCN over 3 min). ^1H NMR (270 MHz, methanol- d_4) δ ppm 3.08-3.12 (m, 2 H) 3.37-3.79 (m, 6 H) 3.96 (s, 3 H) 4.55 (d, $J=3.96$ Hz, 1 H) 6.77 (d, $J=2.23$ Hz, 1 H) 6.84 (d, $J=1.98$ Hz, 1 H) 7.03 (d, $J=8.41$ Hz, 1 H) 7.12 (d, $J=1.98$ Hz, 1 H) 7.31 (dd, $J=8.78$, 1.86 Hz, 1 H) 7.51 (d, $J=1.73$ Hz, 1 H) 7.74 (d, $J=2.23$ Hz, 1 H). LC-MS 492 (M+H) $^+$.

10 EXAMPLE 57

N-[7(6,6-Dioxidohexahydrothieno[3,4-b]pyrazin-1(2H)-yl)-1-benzofuran-5-yl]benzenesulfonamide hydrochloride

Benzenesulfonyl chloride (0.076 g, 0.428 mmol) and pyridine (259 mL, 3.21 mmol) were added to 7-(6,6-dioxidohexahydrothieno[3,4-b]pyrazine-1(2H)-yl)-1-benzofuran-5-amine (0.110 g, 0.357 mmol; Intermediate 36) in DCM (1 mL). The mixture was shaken at room temperature for 1 h, solvent removed in vacuo, and the residue was purified by preparative HPLC using acetonitrile-water gradients containing 0.1% trifluoroacetic acid. The obtained TFA salt was converted into the hydrochloride salt by treatment with 2 M HCl in ether to afford 27.0 mg (17%) of the title product. HPLC 99%, R_T : 1.556 (System A; 10-97% MeCN over 3 min). ^1H NMR (270 MHz, methanol- d_4) δ ppm 3.17 (d, $J=6.68$ Hz, 2 H) 3.47-3.85 (m, 6 H) 4.52-4.56 (m, 1 H) 4.95-4.99 (m, 1 H) 6.77-6.79 (m, 2 H) 7.07 (d, $J=1.98$ Hz, 1 H) 7.42-7.54 (m, 3 H) 7.69-7.77 (m, 3 H). LC-MS 448 (M+H) $^+$.

EXAMPLE 58

25 **N-{7-[(2-Pyrrolidin-1-ylethyl)amino]-1-benzofuran-5-yl}benzenesulfonamide hydrochloride**

To a test tube containing benzenesulfonyl chloride (42 mg, 0.235 mmol) was added a solution of N^7 -(2-pyrrolidin-1-ylethyl)-1-benzofuran-5,7-diamine* (48 mg, 0.195 mmol) in dichloromethane (3 mL). After addition of triethylamine (55 μL , 0.391 mmol), the mixture was shaken for 1 h and then concentrated. The residue was purified by preparative HPLC. The resulting TFA-salt was treated with HCl/ether and evaporated to provide the title compound. Yield: 5%, HPLC purity = 99%, m/z = 386 (M+H) $^+$, ^1H NMR (270 MHz, methanol- d_4) δ ppm 1.95 - 2.26 (m, 4 H) 3.03 - 3.24 (m, 2 H) 3.38 - 3.47 (m, 2 H) 3.58 -

- 3.65 (m, 2 H) 3.64 - 3.77 (m, 2 H) 6.45 - 6.48 (m, 1 H) 6.55 - 6.57 (m, 1 H) 6.65 (d, $J=2.23$ Hz, 1 H) 7.40 - 7.59 (m, 3 H) 7.67 (d, $J=2.23$ Hz, 1 H) 7.68 - 7.73 (m, 2 H). *Prepared in two steps starting from 2-pyrrolidin-1-yl-ethylamine: i) Pd-catalysed amination of 7-iodo-5-nitro-benzofuran according to the procedure of Intermediate 31 to provide (5-nitro-benzofuran-7-yl)-(2-pyrrolidin-1-yl-ethyl)-amine and ii) reduction of the nitro group of (5-nitro-benzofuran-7-yl)-(2-pyrrolidin-1-yl-ethyl)-amine to provide N^7 -(2-pyrrolidin-1-ylethyl)-1-benzofuran-5,7-diamine according to the procedure of Example 48 (Step 1).

EXAMPLE 59

- 10 **2-Methoxy-5-methyl- N -{7-[(2-pyrrolidin-1-ylethyl)amino]-1-benzofuran-5-yl}benzenesulfonamide hydrochloride**

The title compound was prepared according to the procedure described for Example 58.

- Yield: 18%, HPLC purity = 98%, $m/z = 430$ (M+H)⁺, ¹H NMR (500 MHz, DMSO- d_6) δ ppm 1.81 - 1.92 (m, 2 H) 1.96 - 2.08 (m, 2 H) 2.18 - 2.22 (m, 3 H) 3.00 - 3.12 (m, 2 H) 15 3.31 - 3.37 (m, 2 H) 3.39 - 3.45 (m, 2 H) 3.55 - 3.63 (m, 2 H) 3.87 - 3.90 (m, 3 H) 6.34 - 6.37 (m, 1 H) 6.59 - 6.63 (m, 1 H) 6.77 (d, $J=2.20$ Hz, 1 H) 7.03 - 7.07 (m, 1 H) 7.32 (m, 1 H) 7.48 - 7.50 (m, 1 H) 7.83 (d, $J=1.88$ Hz, 1 H).

EXAMPLE 60

- 20 **N -{7-[(2-Pyrrolidin-1-ylethyl)amino]-1-benzofuran-5-yl}-2-(trifluoromethyl)benzenesulfonamide hydrochloride**

The title compound was prepared according to the procedure described for Example 58.

- Yield: 31%, HPLC purity = 99%, $m/z = 454$ (M+H)⁺, ¹H NMR (270 MHz, methanol- d_4) δ ppm 1.92 - 2.26 (m, 4 H) 3.07 - 3.22 (m, 2 H) 3.39 - 3.48 (m, 2 H) 3.56 - 3.64 (m, 2 H) 3.61 - 3.75 (m, 2 H) 6.49 (d, $J=1.98$ Hz, 1 H) 6.63 (d, $J=1.98$ Hz, 1 H) 6.66 (d, $J=2.23$ Hz, 25 1 H) 7.60 - 7.76 (m, 3 H) 7.88 - 7.95 (m, 1 H) 7.99 - 8.05 (m, 1 H).

EXAMPLE 61

- 30 **3-Chloro-4-methyl- N -{7-[(2-pyrrolidin-1-ylethyl)amino]-1-benzofuran-5-yl}benzenesulfonamide hydrochloride**

The title compound was prepared according to the procedure described for Example 58.

- Yield: 32%, HPLC purity = 99%, $m/z = 433$ (M+H)⁺, ¹H NMR (270 MHz, methanol- d_4) δ ppm 1.93 - 2.25 (m, 4 H) 2.35 - 2.40 (m, 3 H) 3.11 - 3.24 (m, 2 H) 3.42 - 3.50 (m, 2 H) 3.61 - 3.68 (m, 2 H) 3.65 - 3.76 (m, 2 H) 6.47 - 6.50 (m, 1 H) 6.56 - 6.60 (m, 1 H) 6.67 (d,

$J=2.23$ Hz, 1 H) 7.35 - 7.40 (m, 1 H) 7.48 - 7.54 (m, 1 H) 7.67 (d, $J=1.98$ Hz, 1 H) 7.68 (d, $J=1.98$ Hz, 1 H).

EXAMPLE 62

5 **2-Methoxy-5-methyl-N-{7-[(3-morpholin-4-ylpropyl)amino]-1-benzofuran-5-yl}benzenesulfonamide hydrochloride**

The title compound was prepared according to the procedure described for Example 58 using N⁷-(3-morpholin-4-yl-propyl)-benzofuran-5,7-diamine.* Yield: 5%, HPLC purity = 98%, $m/z = 460$ (M+H)⁺, ¹H NMR (270 MHz, methanol-*d*₄) δ ppm 1.99 - 2.15 (m, 2 H)
10 2.18 - 2.27 (m, 3 H) 3.17 - 3.40 (m, 6 H) 3.61 - 4.05 (m, 6 H) 3.94 - 3.98 (m, 3 H) 6.46 (d, $J=1.73$ Hz, 1 H) 6.53 - 6.57 (m, 1 H) 6.61 (d, $J=2.23$ Hz, 1 H) 6.99 - 7.06 (m, 1 H) 7.27 - 7.34 (m, 1 H) 7.47 - 7.52 (m, 1 H) 7.60 (d, $J=2.23$ Hz, 1 H). * Prepared in two steps starting from 3-morpholin-4-yl-propylamine: i) Pd-catalysed amination of 7-iodo-5-nitro-benzofuran according to the procedure of Intermediate 31 to provide (3-morpholin-4-yl-propyl)-(5-nitro-benzofuran-7-yl)-amine and ii) reduction of the nitro group of (3-morpholin-4-yl-propyl)-(5-nitro-benzofuran-7-yl)-amine to provide N⁷-(3-morpholin-4-yl-propyl)-benzofuran-5,7-diamine according to the procedure of Example 48 (Step 1).
15

EXAMPLE 63

20 **N-{7-[(3-Morpholin-4-ylpropyl)amino]-1-benzofuran-5-yl}-2-(trifluoromethyl)benzenesulfonamide hydrochloride**

The title compound was prepared according to the procedure described for Example 58 using N⁷-(3-morpholin-4-yl-propyl)-benzofuran-5,7-diamine. Yield: 13%, HPLC purity = 99%, $m/z = 484$ (M+H)⁺, ¹H NMR (270 MHz, methanol-*d*₄) δ ppm 1.99 - 2.15 (m, 2 H)
25 3.03 - 3.38 (m, 6 H) 3.38 - 3.57 (m, 2 H) 3.62 - 3.85 (m, 2 H) 3.89 - 4.14 (m, 2 H) 6.44 (d, $J=1.98$ Hz, 1 H) 6.53 (d, $J=1.98$ Hz, 1 H) 6.62 (d, $J=2.23$ Hz, 1 H) 7.60 - 7.75 (m, 3 H) 7.89 - 7.94 (m, 1 H) 7.99 - 8.05 (m, 1 H).

EXAMPLE 64

30 **3-Chloro-4-methyl-N-{7-[(3-morpholin-4-ylpropyl)amino]-1-benzofuran-5-yl}benzenesulfonamide hydrochloride**

The title compound was prepared according to the procedure described for Example 58 using N⁷-(3-morpholin-4-yl-propyl)-benzofuran-5,7-diamine. Yield: 15%, HPLC purity =

99%, $m/z = 464$ ($M+H$)⁺, ¹H NMR (270 MHz, methanol-*d*₄) δ ppm 2.04 - 2.18 (m, 2 H) 2.35 - 2.40 (m, 3 H) 3.06 - 3.24 (m, 2 H) 3.27 - 3.41 (m, 4 H) 3.44 - 3.57 (m, 2 H) 3.65 - 3.81 (m, 2 H) 3.98 - 4.13 (m, 2 H) 6.43 - 6.49 (m, 2 H) 6.63 (d, $J=1.98$ Hz, 1 H) 7.34 - 7.40 (m, 1 H) 7.47 - 7.52 (m, 1 H) 7.65 (d, $J=1.98$ Hz, 1 H) 7.66 (d, $J=1.98$ Hz, 1 H).

5

INTERMEDIATE 37

{{(2*R*)-1-Ethylpyrrolidin-2-yl)methyl}(5-nitro-1-benzofuran-7-yl)amine

The title compound was prepared according to the procedure described for Intermediate 27 using (R)-2-aminomethyl-1-ethylpyrrolidine. Yield: 100%, HPLC purity = 90%, $m/z = 290$ ($M+H$)⁺.

10

INTERMEDIATE 38

***N*⁷-{{(2*R*)-1-Ethylpyrrolidin-2-yl)methyl}-1-benzofuran-5,7-diamine**

The title compound was prepared according to the procedure described for Intermediate 28 using {{(2*R*)-1-ethylpyrrolidin-2-yl)methyl}(5-nitro-1-benzofuran-7-yl)amine (Intermediate 37). The obtained product was used directly in the subsequent reaction.

15

EXAMPLE 65

***N*-[7-({{(2*R*)-1-Ethylpyrrolidin-2-yl)methyl}amino)-1-benzofuran-5-yl]benzenesulfonamide hydrochloride**

20

The title compound was prepared according to the procedure of Example 41 using *N*⁷-{{(2*R*)-1-ethylpyrrolidin-2-yl)methyl}-1-benzofuran-5,7-diamine. Yield: 7 mg (8%), HPLC purity = 95%, $m/z = 400$ ($M+H$)⁺, ¹H NMR (270 MHz, methanol-*d*₄) δ ppm 1.29 (t, $J=7.30$ Hz, 3 H) 1.83 - 2.39 (m, 4 H) 3.05 - 3.28 (m, 2 H) 3.37 - 3.54 (m, 1 H) 3.54 - 3.61 (m, $J=6.06$, 3.34 Hz, 2 H) 3.63 - 3.77 (m, 2 H) 6.47 (d, $J=1.73$ Hz, 1 H) 6.57 (d, $J=1.98$ Hz, 1 H) 6.65 (d, $J=2.23$ Hz, 1 H) 7.39 - 7.59 (m, 3 H) 7.65 - 7.73 (m, 3 H).

25

EXAMPLE 66

***N*-[7-({{(2*R*)-1-Ethylpyrrolidin-2-yl)methyl}amino)-1-benzofuran-5-yl]-2-methoxy-5-methylbenzenesulfonamide hydrochloride**

30

The title compound was prepared according to the procedure of Example 41 using *N*⁷-{{(2*R*)-1-ethylpyrrolidin-2-yl)methyl}-1-benzofuran-5,7-diamine. Yield: 16 mg (17%), HPLC purity = 97%, $m/z = 444$ ($M+H$)⁺, ¹H NMR (270 MHz, methanol-*d*₄) δ ppm 1.27 (t,

$J=7.18$ Hz, 3 H) 1.85 - 2.20 (m, 2 H) 2.19 - 2.23 (s, 3 H) 2.24 - 2.42 (m, 1 H) 3.01 - 3.28 (m, 3 H) 3.38 - 3.53 (m, 1 H) 3.54 - 3.60 (m, 2 H) 3.63 - 3.81 (m, 2 H) 3.94 - 3.98 (s, 3 H) 6.53 (d, $J=1.73$ Hz, 1 H) 6.64 (dd, $J=3.84$, 1.86 Hz, 2 H) 7.00 - 7.06 (m, 1 H) 7.28 - 7.35 (m, 1 H) 7.45 - 7.51 (m, 1 H) 7.64 (d, $J=1.98$ Hz, 1 H).

5

EXAMPLE 67

***N*-[7-({[(2*R*)-1-Ethylpyrrolidin-2-yl]methyl}amino)-1-benzofuran-5-yl]-2-(trifluoromethyl)benzenesulfonamide hydrochloride**

The title compound was prepared according to the procedure of Example 41 using *N*⁷-
10 {[(2*R*)-1-ethylpyrrolidin-2-yl]methyl}-1-benzofuran-5,7-diamine. Yield: 21 mg (21%),
HPLC purity = 99%, $m/z = 468$ (M+H)⁺, ¹H NMR (270 MHz, methanol-*d*₄) δ ppm 1.29 (t,
 $J=7.30$ Hz, 3 H) 1.82 - 2.39 (m, 4 H) 3.05 - 3.28 (m, 2 H) 3.40 - 3.53 (m, 1 H) 3.53 - 3.61
(m, 2 H) 3.63 - 3.78 (m, 2 H) 6.50 (d, $J=1.98$ Hz, 1 H) 6.66 (dd, $J=5.57$, 2.10 Hz, 2 H) 7.58
- 7.77 (m, 3 H) 7.88 - 7.95 (m, 1 H) 7.97 - 8.05 (m, 1 H).

15

EXAMPLE 68

***N*-[7-({[(2*R*)-1-Ethylpyrrolidin-2-yl]methyl}amino)-1-benzofuran-5-yl]-3-methylbenzenesulfonamide hydrochloride**

The title compound was prepared according to the procedure of Example 41 using *N*⁷-
20 {[(2*R*)-1-ethylpyrrolidin-2-yl]methyl}-1-benzofuran-5,7-diamine. Yield: 15 mg (16%),
HPLC purity = 96%, $m/z = 414$ (M+H)⁺, ¹H NMR (270 MHz, methanol-*d*₄) δ ppm 1.29 (t,
 $J=7.30$ Hz, 3 H) 1.81 - 2.38 (m, 4 H) 2.30 - 2.34 (s, 3 H) 3.02 - 3.27 (m, 2 H) 3.39 - 3.54
(m, 1 H) 3.54 - 3.61 (m, 2 H) 3.64 - 3.79 (m, 2 H) 6.47 (d, $J=1.98$ Hz, 1 H) 6.57 (d, $J=1.73$
Hz, 1 H) 6.66 (d, $J=2.23$ Hz, 1 H) 7.26 - 7.41 (m, 2 H) 7.44 - 7.55 (m, 2 H) 7.67 (d, $J=1.98$
25 Hz, 3 H).

EXAMPLE 69

***N*-[7-({[(2*R*)-1-Ethylpyrrolidin-2-yl]methyl}amino)-1-benzofuran-5-yl]thiophene-2-sulfonamide hydrochloride**

The title compound was prepared according to the procedure of Example 41 using *N*⁷-
30 {[(2*R*)-1-ethylpyrrolidin-2-yl]methyl}-1-benzofuran-5,7-diamine. Yield: 17 mg (19%),
HPLC purity = 99%, $m/z = 406$ (M+H)⁺, ¹H NMR (270 MHz, methanol-*d*₄) δ ppm 1.30 (t,
 $J=7.30$ Hz, 3 H) 1.82 - 2.42 (m, 4 H) 3.02 - 3.28 (m, 2 H) 3.39 - 3.57 (m, 1 H) 3.57 - 3.64

(m, 2 H) 3.64 - 3.82 (m, 2 H) 6.49 - 6.54 (m, $J=1.98$ Hz, 1 H) 6.64 (d, $J=1.98$ Hz, 1 H) 6.69 (d, $J=1.98$ Hz, 1 H) 7.04 (dd, $J=4.95, 3.71$ Hz, 1 H) 7.43 (dd, $J=3.71, 1.24$ Hz, 1 H) 7.63 - 7.72 (m, 2 H).

5 EXAMPLE 70

5-Chloro-*N*-[7-({[(2*R*)-1-ethylpyrrolidin-2-yl]methyl}amino)-1-benzofuran-5-yl]thiophene-2-sulfonamide hydrochloride

The title compound was prepared according to the procedure of Example 41 using *N*⁷-{[(2*R*)-1-ethylpyrrolidin-2-yl]methyl}-1-benzofuran-5,7-diamine. Yield: 5 mg (5%),

- 10 HPLC purity = 99%, $m/z = 440$ (M+H)⁺, ¹H NMR (270 MHz, methanol-*d*₄) δ ppm 1.32 (t, $J=7.30$ Hz, 3 H) 1.84 - 2.42 (m, 4 H) 3.06 - 3.28 (m, 2 H) 3.44 - 3.58 (m, 1 H) 3.59 - 3.65 (m, 2 H) 3.65 - 3.82 (m, 2 H) 6.52 (d, $J=1.73$ Hz, 1 H) 6.68 (d, $J=1.98$ Hz, 1 H) 6.73 (d, $J=2.23$ Hz, 1 H) 6.95 - 6.99 (m, 1 H) 7.22 - 7.26 (m, 1 H) 7.72 (d, $J=2.23$ Hz, 1 H).

15 EXAMPLE 71

5-Chloro-*N*-[7-({[(2*R*)-1-ethylpyrrolidin-2-yl]methyl}amino)-1-benzofuran-5-yl]-1,3-dimethyl-1*H*-pyrazole-4-sulfonamide hydrochloride

The title compound was prepared according to the procedure of Example 41 using *N*⁷-{[(2*R*)-1-ethylpyrrolidin-2-yl]methyl}-1-benzofuran-5,7-diamine. Yield: 12 mg (12%),

- 20 HPLC purity = 98%, $m/z = 452$ (M+H)⁺, ¹H NMR (270 MHz, methanol-*d*₄) δ ppm 1.33 (t, $J=7.30$ Hz, 3 H) 1.87 - 2.41 (m, 4 H) 2.17 - 2.20 (m, 3 H) 3.07 - 3.28 (m, 2 H) 3.44 - 3.65 (m, 3 H) 3.66 - 3.82 (m, 2 H) 3.70 - 3.73 (m, 3 H) 6.53 (d, $J=1.98$ Hz, 1 H) 6.64 (d, $J=1.98$ Hz, 1 H) 6.70 (d, $J=1.98$ Hz, 1 H) 7.70 (d, $J=2.23$ Hz, 1 H).

25 EXAMPLE 72

***N*-(7-{[3-(2-Methylpiperidin-1-yl)propyl]amino}-1-benzofuran-5-yl)benzenesulfonamide hydrochloride**

The title compound was prepared according to the procedure described for Example 58 using *N*⁷-[3-(2-methylpiperidin-1-yl)-propyl]-benzofuran-5,7-diamine.* Yield: 9%, HPLC

- 30 purity = 97%, $m/z = 428$ (M+H)⁺, ¹H NMR (270 MHz, methanol-*d*₄) δ ppm 1.29 (d, $J=6.43$ Hz, 0.3 H, rotamers) 1.32 (d, $J=6.43$ Hz, 3 H) 1.45 - 2.17 (m, 8 H) 2.91 - 3.07 (m, 1 H) 3.13 - 3.27 (m, 3 H) 3.35 (t, $J=6.43$ Hz, 2 H) 3.39 - 3.56 (m, 1 H) 6.43 - 6.49 (m, 2 H) 6.61 (d, $J=2.23$ Hz, 1 H) 7.40 - 7.58 (m, 3 H) 7.63 (d, $J=1.98$ Hz, 1 H) 7.68 - 7.74 (m, 2

- H). *Prepared in two steps starting from 3-(2-methyl-piperidin-1-yl)-propylamine: i) Pd-catalysed amination of 7-iodo-5-nitro-benzofuran according to the procedure of Intermediate 31 to provide [3-(2-methyl-piperidin-1-yl)-propyl]-(5-nitro-benzofuran-7-yl)-amine, and ii) reduction of the nitro group of (3-morpholin-4-yl-propyl)-(5-nitro-benzofuran-7-yl)-amine to provide N⁷-[3-(2-methyl-piperidin-1-yl)-propyl]-benzofuran-5,7-diamine according to the procedure of Example 48 (Step 1).

EXAMPLE 73

2-Methoxy-5-methyl-N-(7-{[3-(2-methylpiperidin-1-yl)propyl]amino}-1-benzofuran-5-yl)benzenesulfonamide hydrochloride

- The title compound was prepared according to the procedure described for Example 58 using N⁷-[3-(2-methyl-piperidin-1-yl)-propyl]-benzofuran-5,7-diamine. Yield: 7%, HPLC purity = 98%, m/z = 472 (M+H)⁺, ¹H NMR (270 MHz, methanol-d₄) δ ppm 1.29 (d, J=6.43 Hz, 0.3 H, rotamers) 1.31 (d, J=6.43 Hz, 3 H) 1.48 - 2.16 (m, 8 H) 2.18 - 2.22 (m, 3 H) 2.88 - 3.05 (m, 1 H) 3.11 - 3.27 (m, 3 H) 3.31 - 3.39 (m, 2 H) 3.38 - 3.55 (m, 1 H) 3.94 - 3.98 (m, 3 H) 6.46 - 6.49 (m, 1 H) 6.58 (d, J=1.98 Hz, 1 H) 6.61 (d, J=1.98 Hz, 1 H) 6.99 - 7.05 (m, 1 H) 7.27 - 7.34 (m, 1 H) 7.48 - 7.52 (m, 1 H) 7.60 (d, J=1.98 Hz, 1 H).

EXAMPLE 74

N-(7-{[3-(2-Methylpiperidin-1-yl)propyl]amino}-1-benzofuran-5-yl)-2-(trifluoromethyl)benzenesulfonamide hydrochloride

- The title compound was prepared according to the procedure described for Example 58 using N⁷-[3-(2-methyl-piperidin-1-yl)-propyl]-benzofuran-5,7-diamine. Yield: 1%, HPLC purity = 97%, m/z = 496 (M+H)⁺, ¹H NMR (270 MHz, methanol-d₄) δ ppm 1.29 (d, J=6.43 Hz, 0.3 H, rotamers) 1.33 (d, J=6.43 Hz, 3 H) 1.45 - 2.20 (m, 8 H) 2.94 - 3.08 (m, 1 H) 3.12 - 3.28 (m, 3 H) 3.32 - 3.39 (m, 2 H) 3.44 - 3.59 (m, 1 H) 6.46 - 6.49 (m, 1 H) 6.53 (d, J=1.98 Hz, 1 H) 6.63 (d, J=2.23 Hz, 1 H) 7.60 - 7.76 (m, 3 H) 7.88 - 7.94 (m, 1 H) 7.99 - 8.06 (m, 1 H).

EXAMPLE 75

5-Chloro-1,3-dimethyl-N-(7-{[3-(2-methylpiperidin-1-yl)propyl]amino}-1-benzofuran-5-yl)-1H-pyrazole-4-sulfonamide hydrochloride

The title compound was prepared according to the procedure described for Example 58 using N⁷-[3-(2-methyl-piperidin-1-yl)-propyl]-benzofuran-5,7-diamine. Yield: 10%, HPLC

purity = 97%, $m/z = 480$ ($M+H$)⁺, ¹H NMR (270 MHz, methanol-*d*₄) δ ppm 1.30 (d, $J=6.43$ Hz, 0.4 H, rotamers) 1.35 (d, $J=6.43$ Hz, 3 H) 1.50 - 2.16 (m, 8 H) 2.17 - 2.21 (m, 3 H) 2.93 - 3.08 (m, 1 H) 3.15 - 3.27 (m, 3 H) 3.38 (t, $J=6.43$ Hz, 2 H) 3.41 - 3.58 (m, 1 H) 3.70 - 3.73 (m, 3 H) 6.46 - 6.49 (m, 1 H) 6.56 (d, $J=1.73$ Hz, 1 H) 6.66 (d, $J=1.98$ Hz, 1 H) 7.66 (d, $J=1.98$ Hz, 1 H).

INTERMEDIATE 39

5-(5-Nitro-benzofuran-7-yl)-pyridin-2-ylamine

7-Iodo-5-nitrobenzofuran (289 mg, 1.0 mmol), pinacolborane (192 mg, 1.5 mmol) and PdCl₂(dppf)·DCM were added to a test tube together with dioxane (4 mL). Triethylamine (304 mg, 3.0 mmol) was added carefully to the solution, and the mixture was heated in a StemBlock at 70 °C overnight to form 5-nitro-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-benzofuran in situ. Then 2-amino-5-iodopyridine (220 mg, 1.0 mmol) and aqueous barium hydroxide (1 mL; 2 M) were added. The resulting mixture was stirred at 70 °C overnight and then filtered through Celite and evaporated. The residue was extracted with chloroform/water and evaporated to give the title product. Yield: 82%, HPLC purity = 82%, $m/z = 256$ ($M+H$)⁺.

INTERMEDIATE 40

5-(5-Amino-1-benzofuran-7-yl)pyridin-2-amine

The title compound was prepared from 5-(5-nitro-benzofuran-7-yl)-pyridin-2-ylamine (Intermediate 39) according to the procedure of Intermediate 28. The product was used directly in the subsequent reaction.

EXAMPLE 76

***N*-[7-(6-Aminopyridin-3-yl)-1-benzofuran-5-yl]-2-methoxy-5-methylbenzenesulfonamide**

The title compound was prepared from 5-(5-amino-1-benzofuran-7-yl)pyridin-2-amine (Intermediate 40) according to the procedure of Example 41, except the purification step where flash chromatography (eluent: 30% EtOAc in hexane) was employed. Yield: 7%, HPLC purity = 93%, $m/z = 410$ ($M+H$)⁺, ¹H NMR (270 MHz, methanol-*d*₄) δ ppm 2.20 (s, 3 H) 3.96 (s, 3 H) 6.84 (d, $J=2.23$ Hz, 1 H) 6.99 - 7.05 (m, $J=8.41$ Hz, 1 H) 7.10 - 7.17 (m, $J=9.90$ Hz, 1 H) 7.27 - 7.36 (m, 3 H) 7.51 - 7.55 (m, 1 H) 7.82 (d, $J=2.23$ Hz, 1 H) 8.27 - 8.34 (m, 2 H).

INTERMEDIATE 41

2-Methoxy-5-methyl-N-(7-piperazin-1-yl-1-benzofuran-5-yl)benzenesulfonamide

tert-Butyl 4-(5-{{[(2-methoxy-5-methylphenyl)sulfonyl]amino}-1-benzofuran-7-

- 5 yl)piperazine-1-carboxylate* (1.5 g, 2.99 mmol) was reacted according to the procedure of Intermediate 20 and the product was used in the next step without further purification. Yield: 1.2 g (100%). HPLC purity 99%, R_T =1.60 min (System A; 10-97% MeCN over 3 min). *Prepared from *tert*-butyl 4-(5-amino-1-benzofuran-7-yl)piperazine-1-carboxylate (Intermediate 10) according to the procedure of Intermediate 19.

10

EXAMPLE 77

N-{7-[4-(Cyclopropylmethyl)piperazin-1-yl]-1-benzofuran-5-yl}-2-methoxy-5-methylbenzenesulfonamide hydrochloride

- Cyclopropanecarbaldehyde (0.087 g, 1.25 mmol) was added to a solution of 2-methoxy-5-methyl-N-(7-piperazin-1-yl-1-benzofuran-5-yl)benzenesulfonamide (0.1 g, 0.25 mmol; Intermediate 41) in methanol. After being stirred at room temperature for 5 min, sodium cyanoborohydride (0.156 g, 2.5 mmol) was added and the resulting mixture was stirred at room temperature for 5 days. Precipitation from the reaction mixture was collected by filtration giving the free base of the title compound (0.063 g; 55%). The free base was dissolved in MeOH and treated with HCl/ether 1 M to give the title compound. Yield: 0.029 g (43%). HPLC 100%, R_T =1.82 min (System A; 10-97% MeCN over 3 min). ^1H NMR (400 MHz, DMSO- d_6) δ ppm 0.37 - 0.48 (m, 2 H) 0.59 - 0.72 (m, 2 H) 1.09 - 1.22 (m, 1 H) 2.20 (s, 3 H) 3.03 (dd, J =6.7, 5.4 Hz, 2 H) 3.12 - 3.26 (m, 4 H) 3.59 - 3.75 (m, 4 H) 3.87 (s, 3 H) 6.59 (d, J =1.8 Hz, 1 H) 6.85 (d, J =2.0 Hz, 1 H) 6.95 (d, J =1.8 Hz, 1 H) 7.03 (d, J =8.5 Hz, 1 H) 7.32 (dd, J =8.4, 2.1 Hz, 1 H) 7.51 (d, J =2.0 Hz, 1 H) 7.89 (d, J =2.3 Hz, 1 H) 9.74 (s, 1 H). MS (ESI+) for $\text{C}_{24}\text{H}_{29}\text{N}_3\text{O}_4\text{S}$ m/z 456.2 ($\text{M}+\text{H}$) $^+$.

25

EXAMPLE 78

2-Methoxy-5-methyl-N-{7-[4-(3,3,3-trifluoropropyl)piperazin-1-yl]-1-benzofuran-5-yl}benzenesulfonamide hydrochloride

30

The title compound was prepared from 2-methoxy-5-methyl-N-(7-piperazin-1-yl-1-benzofuran-5-yl)benzenesulfonamide (0.1 g, 0.25 mmol; Intermediate 41) and 3,3,3-trifluoropropanal according to the procedure of Example 77. Precipitation from the reaction mixture was collected by filtration giving the free base of the title compound

(0.075 g; 60%). The free base was dissolved in MeOH and treated with HCl/ether 1 M to give the title compound. Yield: 0.078 g (96%). HPLC 98%, R_T =1.84 min (System A; 10-97% MeCN over 3 min). ^1H NMR (400 MHz, DMSO- d_6) δ ppm 2.20 (s, 3 H) 2.93 - 3.10 (m, 2 H) 3.15 (s, 2 H) 3.16 - 3.30 (m, 4 H) 3.36 - 3.50 (m, 2 H) 3.60 - 3.77 (m, 3 H) 3.87 (s, 3 H) 6.58 (d, J =1.8 Hz, 1 H) 6.85 (d, J =2.3 Hz, 1 H) 6.95 (d, J =1.8 Hz, 1 H) 7.03 (d, J =8.5 Hz, 1 H) 7.25 (s, 2 H) 7.31 (dd, J =8.5, 2.3 Hz, 1 H) 7.38 (s, 2 H) 7.51 (s, 3 H) 7.89 (d, J =2.3 Hz, 1 H) 9.74 (s, 1 H). MS (ESI+) for $\text{C}_{23}\text{H}_{26}\text{F}_3\text{N}_3\text{O}_4\text{S}$ m/z 498.2 ($\text{M}+\text{H}$) $^+$.

INTERMEDIATE 42

10 **3,3-Dibromo-1,1,1-trifluoroacetone***

1,1,1-Trifluoropropanone (50.0 g, 446.2 mmol) was dissolved in concentrated sulphuric acid (250 g). Br_2 (81.69 g, 510.1 mmol) was added dropwise, at room temperature, during 2 h and the mixture was stirred overnight. After this time, additional Br_2 (40.85 g, 255.6 mmol) was added and the mixture stirred overnight. Separated the two phases formed when allowed to stand and distilled the bottom layer to yield 3,3-dibromo-1,1,1-trifluoroacetone as a yellow oil (10.37 g, 8.6 %). ^1H NMR (270 MHz, CDCl_3) δ ppm 6.23 (s, 1 H). *Previously described in Rec. Trav. Chim. Pays-Bas 1995, 114, 97-102.

INTERMEDIATE 43

20 **3,3,3-Trifluoro-2-oxopropanal***

3,3-Dibromo-1,1,1-trifluoroacetone (10.37 g, 38.43 mmol; Intermediate 42) was dissolved in water (51.85 g). NaOAc (12.61 g, 153.72 mmol) was added and the resulting mixture was stirred at 100 °C overnight. Extracted the mixture with EtOAc (50 mL) and evaporated the solvents from the organic phase. The residue was redissolved in EtOAc (20 mL) and filtration yielded 3,3,3-trifluoro-2-oxopropanal (1.35 g, 24 %). *Previously described in Rec. Trav. Chim. Pays-Bas 1995, 114, 97-102.

INTERMEDIATE 44

1-Benzyl-3-(trifluoromethyl)piperazine*

30 A solution of 3,3,3-trifluoro-2-oxopropanal (0.31 g, 2.3 mmol; Intermediate 43) in DMF (10 mL) was cooled to 0 °C and a solution of N-benzylethane-1,2-diamine (0.37 g, 2.72 mmol) in DMF (10 mL) was added. After being stirred at room temperature overnight, the mixture was concentrated in vacuo. The residue was redissolved in THF (5 mL) and citrate

buffer (5.3 mL; 0.4 M), followed by NaBH₃CN (0.31 g, 4.9 mmol), were added. The resulting mixture was stirred at room temperature overnight. The mixture was made basic (pH 8) with aqueous NaOH (8 mL; 1 M) and the aqueous layer was extracted twice with DCM (15 mL). The combined organic layers were dried (Na₂SO₄) and concentrated. The residue was purified by LC-MS prep to give 1-benzyl-3-(trifluoromethyl)piperazine (66 mg, 12 %). HPLC 94 %, RT= 1.25 min (System A; 10-97 % MeCN over 3 min). ¹H NMR (270 MHz, CDCl₃) δ ppm 2.77 (s, 2 H) 3.17 - 3.31 (m, 1 H) 3.32 - 3.64 (m, 3 H) 3.83 - 4.02 (m, 1 H) 4.13 - 4.31 (m, 2 H) 6.68 (s, 1 H) 7.30 - 7.55 (m, 5 H). MS (ESI+) m/z 245. *Previously described in Rec. Trav. Chim. Pays-Bas 1995, 114, 97-102.

10

INTERMEDIATE 45

2-(Trifluoromethyl)piperazine*

1-Benzyl-3-(trifluoromethyl)piperazine (0.74 g, 3.0 mmol; Intermediate 44) was dissolved in acetic acid (70 mL) and water (5 mL). Pd, 5 % on carbon, (0.074 g) was added and hydrogenation was performed at 3 bar and 70 °C overnight. The reaction mixture was filtered through Celite and the pad was rinsed with water (5 mL). Solvents were removed in vacuo, toluene (20 mL) added to the residue, followed by re-concentration in vacuo to remove residual water. The desired product sublimated on the evaporator and 0.15 g (32 %) was collected as a white powder. ¹H NMR (270 MHz, methanol-*d*₄) δ ppm 2.67 - 2.87 (m, 3 H) 2.91 - 3.05 (m, 2 H) 3.12 - 3.21 (m, 1 H). MS (ESI+) m/z 155. *Previously described in Rec. Trav. Chim. Pays-Bas 1995, 114, 97-102.

20

INTERMEDIATE 46

1-(5-Nitro-1-benzofuran-7-yl)-3-(trifluoromethyl)piperazine

To 7-iodo-5-nitro-1-benzofuran (231.4 mg, 0.08 mmol) the following was added:

Xantphos (92.6 mg, 0.16 mmol), Pd₂dba₃ (36.6 mg, 0.04 mmol), sodium tert-butoxide (215.4 mg, 2.24 mmol), 2-(trifluoromethyl)piperazine (148.1 mg, 0.96 mmol; Intermediate 45) and xylene (23 mL). The resulting mixture was stirred at 100 °C for 3 days. Filtration through Celite and purification by flash chromatography, using EtOAc:heptane (1:1) as eluent, furnished 1-(5-nitro-1-benzofuran-7-yl)-3-(trifluoromethyl)piperazine (112 mg, 44 % yield). HPLC 90 %, RT=1.648 min (System A; 10-97 % MeCN over 3 min), MS (ESI+) m/z 316 (M+H)⁺.

30

INTERMEDIATE 47

7-[3-(Trifluoromethyl)piperazin-1-yl]-1-benzofuran-5-amine

1-(5-Nitro-1-benzofuran-7-yl)-3-(trifluoromethyl)piperazine (96.6 mg, 0.31 mmol; Intermediate 46) was dissolved in THF (6 mL) and EtOH (25 mL). Raney nickel (slurry in ethanol; 1 mL) and H₂NNH₂ (61.4 mg, 1.23 mmol) were added and the mixture was stirred at room temperature overnight. Filtration through Celite and concentration gave 7-[3-(trifluoromethyl)piperazin-1-yl]-1-benzofuran-5-amine (55 mg, 63 %). This material was used in the next reaction step without further purification.

10 EXAMPLE 79

2-Methoxy-5-methyl-N-{7-[3-(trifluoromethyl)piperazin-1-yl]-1-benzofuran-5-yl}benzenesulfonamide hydrochloride

A mixture of 7-[3-(trifluoromethyl)piperazin-1-yl]-1-benzofuran-5-amine (59 mg, 0.19 mmol; Intermediate 47), pyridine (155 μ L, 1.93 mmol) and 6-methoxy-m-toluene-sulfonyl chloride (42.6 mg, 0.19 mmol) in DCM (2 mL) was stirred at room temperature overnight. Volatiles were removed in vacuo. The residue was redissolved in MeOH (1.5 mL) and the solution was filtered. Addition of MeOH (100 μ L), HCl in ether (500 μ L) and ether (500 μ L), followed by removal of solvents in vacuo furnished 2-methoxy-5-methyl-N-{7-[3-(trifluoromethyl)piperazin-1-yl]-1-benzofuran-5-yl}benzenesulfonamide hydrochloride as a brown oil (44.1 mg, 47 %). HPLC 100 %, RT= 1.861 min (System A; 10-97 % MeCN over 3 min). ¹H NMR (270 MHz, methanol-*d*₄) δ ppm 2.23 (s, 3 H) 2.28 (s, 1 H) 2.98 - 3.24 (m, 1 H) 3.46 - 3.71 (m, 2 H) 3.85 (s, 1 H) 3.96 (s, 3 H) 4.09 - 4.19 (m, 1 H) 4.56 - 4.70 (m, 1 H) 6.75 (d, *J*=1.98 Hz, 2 H) 6.98 (d, *J*=1.73 Hz, 1 H) 7.02 (s, 1 H) 7.05 (s, 1 H) 7.33 (dd, *J*=8.04, 2.60 Hz, 1 H) 7.52 (d, *J*=1.73 Hz, 1 H) 7.73 (d, *J*=2.23 Hz, 1 H) 8.10 - 8.19 (m, 1 H) 8.64 - 8.74 (m, 1 H) 8.90 (d, *J*=5.20 Hz, 1 H). MS (ESI+) *m/z* 470 (M+H)⁺.

INTERMEDIATE 48

***tert*-Butyl [1-(5-nitro-1-benzofuran-7-yl)piperidin-4-yl]carbamate**

Xylene (200 mL) was added to 7-iodo-5-nitro-1-benzofuran (2.78 g, 9.61 mmol), *tert*-butyl piperidin-4-ylcarbamate (2.31 g, 12.0 mmol), Pd₂(dba)₃ (0.22 g, 0.24 mmol), Xantphos (0.56 g, 0.96 mmol) and sodium *tert*-butoxide (1.29 g, 13.0 mmol). The mixture was heated at 120 °C with stirring for 16 h. The reaction mixture was allowed to reach room temperature, filtered through a pad of Celite, and concentrated in vacuo. The crude

product was purified by flash chromatography, using DCM as eluent, to afford 1.03 g (84%) of the title product. HPLC 94%, R_T : 2.770 (System B; 10-97% MeCN over 3min).

^1H NMR (270 MHz, methanol- d_4) δ ppm 1.45 (s, 9 H) 1.62 - 1.72 (m, 2 H) 1.75 - 2.03 (m, 2 H) 2.94 - 3.02 (m, 2 H) 3.55 - 3.57 (m, 1 H) 3.88 - 3.93 (m, 2 H) 7.01 (d, $J=2.23$ Hz, 1 H) 7.64 (d, $J=2.23$ Hz, 1 H) 7.93 (d, $J=2.23$ Hz, 1 H) 8.13 (d, $J=2.23$ Hz, 1 H). LC-MS 362 (M+H) $^+$.

INTERMEDIATE 49

***tert*-Butyl [1-(5-amino-1-benzofuran-7-yl)piperidin-4-yl]carbamate**

Hydrazine (1.038 mL, 28 mmol) and raney-nickel (slurry in ethanol; 10 mL) were added to *tert*-butyl [1-(5-nitro-1-benzofuran-7-yl)piperidine-4-yl]carbamate (1.03 g, 2.85 mmol; Intermediate 48) in a mixture of THF (50 mL) and ethanol (150 mL). The mixture was stirred at room temperature for 16 h, filtered through a pad of Celite and concentrated in vacuo to afford 1.02 g (quantitative) of the title product. HPLC 95%, R_T : 1.746 (System A; 10-97% MeCN over 3 min). ^1H NMR (270 MHz, methanol- d_4) δ ppm 1.45 (s, 9 H) 1.65 - 1.69 (m, 2 H) 1.72 - 1.96 (m, 2 H) 2.76 - 2.85 (m, 2 H) 3.50 - 3.54 (m, 1 H) 3.76 (d, $J=12.62$ Hz, 2 H) 6.33 (d, $J=1.98$ Hz, 1 H) 6.54 (d, $J=1.98$ Hz, 1 H) 6.60 (d, $J=2.23$ Hz, 1 H) 7.59 (d, $J=1.98$ Hz, 1 H). LC-MS 332 (M+H) $^+$.

EXAMPLE 80

N-[7-(Aminopiperidin-1-yl)-1-benzofuran-5-yl]-2-(trifluoromethyl)-benzenesulfonamide hydrochloride

2-(Trifluoromethyl)benzenesulfonyl chloride (89.0 mg, 0.36 mmol) and pyridine (219 mL) were added to *tert*-butyl [1-(5-amino-1-benzofuran-7-yl)piperidin-4-yl]carbamate (100.0 mg, 0.30 mmol; Intermediate 49) in DCM (1 mL). The mixture was shaken at room temperature for 1 h, solvent removed in vacuo and the residue was purified by preparative HPLC using acetonitrile-water gradients containing 0.1% trifluoroacetic acid. N-deprotection and conversion into the hydrochloride salt was performed by treatment with 2 M HCl in ether. This furnished 76.1 mg (57%) of the title product. HPLC 100%, R_T : 1.834 (System A; 10-97% MeCN over 3 min). ^1H NMR (500 MHz, DMSO- d_6) δ ppm 1.70 - 1.72 (m, 2 H) 2.00-2.02 (m, 2 H) 2.78 (t, $J=11.30$ Hz, 2 H) 3.21 (s, 1 H) 3.71 (d, $J=12.56$ Hz, 2 H) 6.60 (d, $J=1.88$ Hz, 1 H) 6.83 (d, $J=2.20$ Hz, 1 H) 6.85 - 6.91 (m, $J=1.88$ Hz, 1 H) 7.80 - 7.81 (m, 2 H) 7.88 - 7.89 (m, 1 H) 7.96 - 7.98 (m, 1 H) 8.08 - 8.10 (m, 4 H) 10.40 (s, 1 H). LC-MS 440 (M+H) $^+$.

EXAMPLE 81

N-[7-(Aminopiperidin-1-yl)-1-benzofuran-5-yl]-benzenesulfonamide hydrochloride

Benzenesulfonyl chloride (64.0 mg, 0.36 mmol) and pyridine (219 μ L) were added to *tert*-butyl [1-(5-amino-1-benzofuran-7-yl)piperidin-4-yl]carbamate (100.0 mg, 0.30 mmol; Intermediate 49) in DCM (1 mL). The mixture was shaken at room temperature for 1 h, solvent was removed in vacuo and the residue was purified by preparative HPLC using acetonitrile-water gradients containing 0.1% trifluoroacetic acid. N-deprotection and conversion into the hydrochloride salt was performed by treatment with 2 M HCl in ether. This furnished 31.3 mg (28%) of the title product. HPLC 100%, R_T : 1.612 (System A; 10-97% MeCN over 3 min). ^1H NMR (500 MHz, DMSO- d_6) δ ppm 1.69 - 1.70 (m, 2 H) 2.00 - 2.01 (m, 2 H) 2.76 (t, $J=11.30$ Hz, 2 H) 3.18 - 3.26 (m, 1 H) 6.54 (d, $J=1.88$ Hz, 1 H) 6.82 (d, $J=2.20$ Hz, 1 H) 6.86 (d, $J=1.88$ Hz, 1 H) 7.52 (t, $J=7.54$ Hz, 2 H) 7.57 - 7.68 (m, 1 H) 7.71 - 7.72 (m, 2 H) 7.88 (d, $J=2.20$ Hz, 1 H) 8.14 (s, 3 H) 10.03 (s, 1 H). LC-MS 372 (M+H) $^+$.

EXAMPLE 82

N-[7-(Aminopiperidin-1-yl)-1-benzofuran-5-yl]-2-chlorobenzenesulfonamide hydrochloride

2-Chlorobenzenesulfonyl chloride (76.0 mg, 0.36 mmol) and pyridine (219 mL) were added to *tert*-butyl [1-(5-amino-1-benzofuran-7-yl)piperidin-4-yl]carbamate (100.0 mg, 0.30 mmol; Intermediate 49) in DCM (1 mL). The mixture was shaken at room temperature for 1 h, solvent was removed in vacuo and the residue was purified by preparative HPLC using acetonitrile-water gradients containing 0.1% trifluoroacetic acid. N-deprotection and conversion into the hydrochloride salt was performed by treatment with 2 M HCl in ether. This furnished to 60.6 mg (50%) of the title product. HPLC 100%, R_T : 1.702 (System A; 10-97% MeCN over 3 min). ^1H NMR (500 MHz, DMSO- d_6) δ ppm 1.69 - 1.72 (m, 2 H) 2.01 - 2.02 (m, 2 H) 2.76 (t, $J=11.62$ Hz, 2 H) 3.21 (s, 1 H) 3.68 (d, $J=12.56$ Hz, 2 H) 6.58 (s, 1 H) 6.82 (d, $J=2.20$ Hz, 1 H) 6.88 (s, 1 H) 7.47 (t, $J=7.54$ Hz, 1 H) 7.62 - 7.63 (m, 2 H) 7.87 (d, $J=1.88$ Hz, 1 H) 7.99 (d, $J=7.54$ Hz, 1 H) 8.23 (s, 3 H) 10.33 (s, 1 H). LC-MS 406 (M+H) $^+$.

EXAMPLE 83

N-[7-(Aminopiperidin-1-yl)-1-benzofuran-5-yl]-2-methoxy-5-methylbenzenesulfonamide hydrochloride

2-Methoxy-5-methylbenzenesulfonyl chloride (80.0 mg, 0.36 mmol) and pyridine (219 mL) were added to *tert*-butyl [1-(5-amino-1-benzofuran-7-yl)piperidin-4-yl]carbamate (100.0 mg, 0.30 mmol; Intermediate 49) in DCM (1 mL). The mixture was shaken at room temperature for 1 h, solvent was removed in vacuo and the residue was purified by preparative HPLC using acetonitrile-water gradients containing 0.1% trifluoroacetic acid. N-deprotection and conversion into the hydrochloride salt was performed by treatment with 2 M HCl in ether. This furnished 59.0 mg (47%) of the title product. HPLC 100%, R_T : 1.731 (System A; 10-97% MeCN over 3 min). ^1H NMR (500 MHz, DMSO- d_6) δ ppm 1.70 - 1.76 (m, 2 H) 2.05 (d, $J=10.05$ Hz, 2 H) 2.20 (s, 3 H) 2.76 (t, $J=11.46$ Hz, 2 H) 3.19- 3.21 (m, 1 H) 3.65 (d, $J=12.56$ Hz, 2 H) 3.87 (s, 3 H) 6.58 (d, $J=1.88$ Hz, 1 H) 6.81 (d, $J=2.20$ Hz, 1 H) 6.89 (d, $J=1.88$ Hz, 1 H) 7.04 (d, $J=8.48$ Hz, 1 H) 7.32 (dd, $J=8.48, 2.20$ Hz, 1 H) 7.51 (d, $J=2.20$ Hz, 1 H) 7.86 (d, $J=1.88$ Hz, 1 H) 8.35 (d, $J=3.45$ Hz, 3 H) 9.65 (s, 1 H). LC-MS 416 (M+H) $^+$.

INTERMEDIATE 50

***tert*-Butyl *cis*-3-fluoro-4-[(5-nitro-1-benzofuran-7-yl)oxy]piperidine-1-carboxylate**
and

INTERMEDIATE 51

***tert*-Butyl *trans*-3-fluoro-4-[(5-nitro-1-benzofuran-7-yl)oxy]piperidine-1-carboxylate**
7-Iodo-5-nitrobenzofuran (2.0 g, 6.9 mmol), *tert*-butyl 3-fluoro-4-hydroxypiperidine-1-carboxylate* (3.8 g, 17.3 mmol; mixture of *cis/trans* isomers), 1,10-phenanthroline (0.50 g, 2.8 mmol), CuI (0.26 g, 1.4 mmol) and Cs₂CO₃ (4.5 g, 13.8 mmol) were heated in toluene (20 mL) at 120 °C for 72 h. The reaction mixture was filtered through Celite and evaporated. The resulting diastereomers were separated by flash chromatography using heptane/EtOAc [(4:1) → (2:1)] to yield 255 mg of the *cis*-isomer and 919 mg of the *trans*-isomer.

cis-isomer (Intermediate 50): Yield: 10%, HPLC purity = 70%, m/z = 381 (M+H) $^+$.
trans-isomer (Intermediate 51): Yield: 35%, HPLC purity = 94%, m/z = 381 (M+H) $^+$.

*Prepared according to the procedure described in WO2001085728.

INTERMEDIATE 52

***tert*-Butyl *cis*-4-[(5-amino-1-benzofuran-7-yl)oxy]-3-fluoropiperidine-1-carboxylate**

To a solution of *tert*-butyl *cis*-3-fluoro-4-[(5-nitro-1-benzofuran-7-yl)oxy]piperidine-1-carboxylate (200 mg, 0.526 mmol; Intermediate 50) dissolved in THF (10 mL) and ethanol (40 mL), was added Raney-nickel (as a slurry in ethanol) and hydrazine hydrate (0.2 mL). The mixture was stirred at room temperature for 30 min and then filtered through Celite
5 and evaporated. The residue was re-dissolved in toluene and evaporated again. This material was used directly in the subsequent experiment.

INTERMEDIATE 53

***tert*-Butyl *trans*-4-[(5-amino-1-benzofuran-7-yl)oxy]-3-fluoropiperidine-1-carboxylate**

10 The title compound was prepared from Intermediate 51 according to the procedure of Intermediate 52 and was used directly in the subsequent experiment.

EXAMPLE 84

***N*-(7-[(*cis*-3-Fluoropiperidin-4-yl)oxy]-1-benzofuran-5-yl)-2-methoxy-5-methylbenzenesulfonamide hydrochloride**
15

To a solution of *tert*-butyl *cis*-4-[(5-amino-1-benzofuran-7-yl)oxy]-3-fluoropiperidine-1-carboxylate (92 mg, 0.263 mmol; Intermediate 52) in dichloromethane (3 mL) was added 6-methoxy-*m*-toluenesulfonyl chloride (70 mg, 0.315 mmol) and triethylamine (73 μ L, 0.525 mmol). The mixture was shaken at room temperature for 1 h and then evaporated.
20 Purified by preparative HPLC (gradient 50-85% MeCN in TFA/water). The residue was dissolved in methanol (0.5 mL) and HCl/ether (2 mL). After the solution had been stirred for 2 h, the solvent was evaporated to furnish the title compound. Yield: 25 mg (20%),
HPLC purity = 95%, m/z = 435 ($M+H$)⁺, ¹H NMR (270 MHz, methanol-*d*₄) δ ppm 1.90 - 2.37 (m, 2 H) 2.16 - 2.26 (m, 3 H) 3.14 - 3.46 (m, 2 H) 3.48 - 3.74 (m, 2 H) 3.92 - 3.98 (m,
25 3 H) 4.73 - 4.88 (m, 1 H) 4.89 - 5.12 (m, 1 H) 6.72 (d, J =2.23 Hz, 0.2 H, rotamers) 6.75 (d, J =1.98 Hz, 1 H) 6.80 (d, J =1.98 Hz, 0.2 H, rotamers) 6.87 (d, J =1.98 Hz, 1 H) 6.95 (d, J =1.98 Hz, 0.2 H, rotamers) 6.98 - 7.05 (m, 2 H) 7.27 - 7.35 (m, 1 H) 7.50 - 7.53 (m, 1 H) 7.72 (d, J =2.23 Hz, 1 H).

30 EXAMPLE 85

***N*-(7-[(*trans*-3-Fluoropiperidin-4-yl)oxy]-1-benzofuran-5-yl)-2-methoxy-5-methylbenzenesulfonamide hydrochloride**

The title compound was prepared according to the same procedure as Example 84 starting from *tert*-butyl *trans*-4-[(5-amino-1-benzofuran-7-yl)oxy]-3-fluoropiperidine-1-

carboxylate (Intermediate 53) and 6-methoxy-*m*-toluenesulfonyl chloride. Yield: 8 mg (5%), HPLC purity = 92%, $m/z = 435$ ($M+H$)⁺, ¹H NMR (270 MHz, methanol-*d*₄) δ ppm 2.12 - 2.30 (m, 2 H) 2.21 (s, 3 H) 3.14 - 3.34 (m, 2 H) 3.37 - 3.53 (m, 1 H) 3.63 - 3.79 (m, 1 H) 3.95 (s, 3 H) 4.72 - 4.83 (m, 1 H) 4.95 - 5.20 (m, 1 H) 6.73 (d, $J=2.23$ Hz, 1 H) 6.84 (d, $J=1.73$ Hz, 1 H) 6.99 (d, $J=1.98$ Hz, 1 H) 7.00 - 7.05 (m, 1 H) 7.28 - 7.35 (m, 1 H) 7.50 (d, $J=1.98$ Hz, 1 H) 7.70 (d, $J=1.98$ Hz, 1 H).

EXAMPLE 86

***N*-(7-{[*cis*-3-Fluoropiperidin-4-yl]oxy}-1-benzofuran-5-yl)-2-(trifluoromethyl)benzenesulfonamide hydrochloride**

The title compound was prepared according to the procedure described for Example 84 using 2-(trifluoromethyl)benzenesulfonyl chloride. Yield: 27 mg (21%), HPLC purity = 100%, $m/z = 459$ ($M+H$)⁺, ¹H NMR (270 MHz, methanol-*d*₄) δ ppm 1.94 - 2.37 (m, 2 H) 3.14 - 3.49 (m, 3 H) 3.53 - 3.70 (m, 1 H) 4.78 - 5.16 (m, 2 H) 6.74 (d, $J=2.23$ Hz, 0.3 H, rotamers) 6.77 (d, $J=2.23$ Hz, 1 H) 6.79 (d, $J=1.98$ Hz, 0.3 H, rotamers) 6.87 (d, $J=1.98$ Hz, 1 H) 6.95 (d, $J=1.98$ Hz, 0.3 H, rotamers) 7.02 (d, $J=1.98$ Hz, 1 H) 7.61 - 7.74 (m, 3 H) 7.75 (d, $J=2.23$ Hz, 1 H) 7.88 - 7.95 (m, 1 H) 7.98 - 8.06 (m, 1 H).

EXAMPLE 87

***N*-(7-{[*trans*-3-Fluoropiperidin-4-yl]oxy}-1-benzofuran-5-yl)-2-(trifluoromethyl)benzenesulfonamide hydrochloride**

The title compound was prepared according to the procedure described for Example 84 starting from *tert*-butyl *trans*-4-[(5-amino-1-benzofuran-7-yl)oxy]-3-fluoropiperidine-1-carboxylate (Intermediate 53) and 2-(trifluoromethyl)benzenesulfonyl chloride. Yield: 49 mg (25%), HPLC purity = 100%, $m/z = 459$ ($M+H$)⁺, ¹H NMR (270 MHz, methanol-*d*₄) δ ppm 2.13 - 2.31 (m, 2 H) 3.15 - 3.56 (m, 3 H) 3.64 - 3.79 (m, 1 H) 4.77 - 4.97 (m, 1 H) 5.00 - 5.24 (m, 1 H) 6.75 (d, $J=1.98$ Hz, 1 H) 6.81 - 6.84 (m, 1 H) 6.99 (d, $J=1.73$ Hz, 1 H) 7.60 - 7.77 (m, 3 H) 7.87 - 7.95 (m, 1 H) 7.98 - 8.05 (m, 1 H).

EXAMPLE 88

2-Chloro-*N*-(7-{[*trans*-3-fluoropiperidin-4-yl]oxy}-1-benzofuran-5-yl)benzenesulfonamide hydrochloride

The title compound was prepared according to the procedure described for Example 84 starting from *tert*-butyl *trans*-4-[(5-amino-1-benzofuran-7-yl)oxy]-3-fluoropiperidine-1-

carboxylate (Intermediate 53) and 2-chlorobenzenesulfonyl chloride. Yield: 40 mg (22%), HPLC purity = 100%, $m/z = 425$ ($M+H$)⁺, ¹H NMR (270 MHz, methanol-*d*₄) δ ppm 2.09 - 2.35 (m, 2 H) 3.10 - 3.57 (m, 3 H) 3.62 - 3.79 (m, 1 H) 4.73 - 4.96 (m, 1 H) 4.97 - 5.23 (m, 1 H) 6.74 (d, $J=2.23$ Hz, 1 H) 6.85 (d, $J=1.98$ Hz, 1 H) 7.05 (d, $J=1.73$ Hz, 1 H) 7.31 - 7.40 (m, 1 H) 7.45 - 7.58 (m, 2 H) 7.71 (d, $J=2.23$ Hz, 1 H) 7.96 (dd, $J=7.79$, 1.61 Hz, 1 H).

EXAMPLE 89

***N*-(7-{{*trans*-3-Fluoropiperidin-4-yl}oxy}-1-benzofuran-5-yl)-3-methylbenzenesulfonamide hydrochloride**

The title compound was prepared according to the procedure described for Example 84 starting from *tert*-butyl *trans*-4-[(5-amino-1-benzofuran-7-yl)oxy]-3-fluoropiperidine-1-carboxylate (Intermediate 53) and 3-methylbenzenesulfonyl chloride. Yield: 47 mg (27%), HPLC purity = 100%, $m/z = 405$ ($M+H$)⁺, ¹H NMR (270 MHz, methanol-*d*₄) δ ppm 2.12 - 2.34 (m, 2 H) 2.28 - 2.34 (m, 3 H) 3.15 - 3.57 (m, 3 H) 3.64 - 3.78 (m, 1 H) 4.73 - 4.97 (m, 1 H) 4.98 - 5.21 (m, 1 H) 6.71 - 6.79 (m, 2 H) 7.25 - 7.57 (m, 4 H) 7.70 - 7.74 (m, 1 H).

EXAMPLE 90

3,6-Dichloro-*N*-(7-{{*trans*-3-fluoropiperidin-4-yl}oxy}-1-benzofuran-5-yl)-2-methylbenzenesulfonamide hydrochloride

The title compound was prepared according to the procedure described for Example 84 starting from *tert*-butyl *trans*-4-[(5-amino-1-benzofuran-7-yl)oxy]-3-fluoropiperidine-1-carboxylate (Intermediate 53) and 3,6-dichloro-2-methylbenzenesulfonyl chloride. Yield: 39 mg (19%), HPLC purity = 98%, $m/z = 473$ ($M+H$)⁺, ¹H NMR (270 MHz, methanol-*d*₄) δ ppm 2.11 - 2.34 (m, 2 H) 2.47 - 2.54 (m, 3 H) 3.14 - 3.56 (m, 3 H) 3.63 - 3.79 (m, 1 H) 4.76 - 4.97 (m, 1 H) 4.97 - 5.22 (m, 1 H) 6.77 (d, $J=1.98$ Hz, 1 H) 6.83 (d, $J=1.73$ Hz, 1 H) 7.06 (d, $J=1.98$ Hz, 1 H) 7.26 (d, $J=1.98$ Hz, 1 H) 7.50 (d, $J=1.98$ Hz, 1 H) 7.74 (d, $J=2.23$ Hz, 1 H).

EXAMPLE 91

2-Chloro-5-fluoro-*N*-(7-{{*trans*-3-fluoropiperidin-4-yl}oxy}-1-benzofuran-5-yl)benzenesulfonamide hydrochloride

The title compound was prepared according to the procedure described for Example 84 starting from *tert*-butyl *trans*-4-[(5-amino-1-benzofuran-7-yl)oxy]-3-fluoropiperidine-1-

carboxylate (Intermediate 53) and 2-chloro-5-fluorobenzenesulfonyl chloride. Yield: 34 mg (18%), HPLC purity = 100%, $m/z = 443$ ($M+H$)⁺, ¹H NMR (270 MHz, methanol-*d*₄) δ ppm 2.11 - 2.36 (m, 2 H) 3.15 - 3.58 (m, 3 H) 3.63 - 3.81 (m, 1 H) 4.77 - 4.98 (m, 1 H) 5.00 - 5.24 (m, 1 H) 6.75 (d, $J=2.23$ Hz, 1 H) 6.85 (d, $J=1.98$ Hz, 1 H) 7.05 (d, $J=1.98$ Hz, 1 H) 7.09 - 7.20 (m, 1 H) 7.42 (dd, $J=8.66, 2.47$ Hz, 1 H) 7.72 (d, $J=2.23$ Hz, 1 H) 7.97 - 8.06 (m, 1 H).

INTERMEDIATE 54

2,3-Dihydro-benzofuran-5-sulfonyl chloride

Chlorosulphonic acid (43.4 g, 0.366 mol) in DCM (10 mL) was added to a cold solution (5 °C) of 2,3-dihydrobenzofuran (20 g, 0.166 mol) in DCM (200 mL). After the addition the reaction was left with stirring at room temperature overnight. The reaction mixture was quenched with water (150 mL) keeping the temperature below 10 °C. The organic phase was separated and washed with an aqueous solution of NaHCO₃ (13.9 g dissolved in 150 mL of water). The organic solvents were evaporated to yield the title compound as a solid residue 3.3 g (23 %). ¹H NMR 270 MHz (CDCl₃) δ ppm 3.32 (t, $J=8.91$ Hz, 2 H) 4.75 (t, $J=8.91$ Hz, 2 H) 6.90 (d, $J=9.15$ Hz, 1 H) 7.78 - 7.90 (m, 2 H)

INTERMEDIATE 55

7-Iodo-2,3-dihydro-benzofuran-5-sulfonyl chloride

A solution of ICl (7.7 g, 47 mmol) in DCM (100 mL) was added dropwise to a solution of 2,3-dihydro-benzofuran-5-sulfonyl chloride (5 g, 23 mmol; Intermediate 54) in DCM (100 mL) at reflux temperature under nitrogen atmosphere. The reaction was heated at reflux overnight. The reaction mixture was cooled at room temperature and acetonitrile (50 mL) was added. The resultant mixture was washed with a saturated solution of NaHCO₃ and the organic phase was separated followed by elimination of the volatiles under vacuum to give 8 g of brown oil which was used to the next step without further purification. ¹H NMR 270 MHz (CDCl₃) δ ppm 3.45 (t, $J=8.91$ Hz, 2 H) 4.82 (t, $J=8.91$ Hz, 2 H) 7.79 (d, $J=1.48$ Hz, 1 H) 8.16 (d, $J=1.98$ Hz, 1 H).

INTERMEDIATE 56

7-Iodo-benzofuran-5-sulfonyl chloride

AIBN (270 mg, 1.3 mmol) and NBS (2.5 g, 14 mmol) were added to 7-iodo-2,3-dihydro-benzofuran-5-sulfonyl chloride (4.4 g, 13 mmol; Intermediate 55) in chlorobenzene (30 mL) at 70 °C. The heating was turned off one hour after the addition. Acetonitrile (30 mL) was added and the organic phase was washed with sodium sulphite in water. The organic phase was separated and the volatiles were evaporated to give 4 g (90%) of the title compound as yellow crystals. ¹H NMR 270 MHz (CDCl₃) δ ppm 7.07 (d, *J*=2.23 Hz, 1 H) 7.90 (d, *J*=2.23 Hz, 1 H) 8.29 - 8.37 (m, 1 H).

INTERMEDIATE 57

10 **7-Iodo-N-(2-methoxy-5-methylphenyl)-1-benzofuran-5-sulfonamide**

To a solution of 7-iodo-1-benzofuran-5-sulfonyl chloride (10.75 g, 31 mmol; Intermediate 56) in dichloromethane (200 mL) was added 5-methyl-2-methoxyaniline (4.25 g, 31 mmol) and pyridine (7.4 mL, 93 mmol) and allowed to stir at ambient temperature overnight. The dark red solution was washed with water, separated, dried and filtered through a plug of silica to remove most of the red impurity, and finally concentrated. Yield: 13.51 g (99%) red solid. HPLC 90% R_T=2.58 min (System A; 30-80% MeCN over 3 min), 1.75 min (System C; 2-95% MeCN over 2 min). ¹H NMR (400 MHz, CDCl₃) δ ppm 2.23 (m, 3 H) 3.52 (s, 3 H) 6.54 (d, *J*=8.30 Hz, 1 H) 6.79 (dd, *J*=8.42, 1.59 Hz, 1 H) 6.86 (d, *J*=2.20 Hz, 1 H) 6.96 (s, 1 H) 7.31 (d, *J*=1.71 Hz, 1 H) 7.71 (d, *J*=2.20 Hz, 1 H) 7.95 (d, *J*=1.71 Hz, 1 H) 8.04 (d, *J*=1.71 Hz, 1 H). MS(ESI) for C₁₆H₁₄INO₄S m/z 444 (M+H).

EXAMPLE 92

N-(2-Methoxy-5-methylphenyl)-7-[(3-methylpiperazin-1-yl)methyl]-1-benzofuran-5-sulfonamide hydrochloride

25 *Step 1. 7-(3-Methyl-piperazin-1-carbonyl)-benzofuran-5-sulfonic acid (2-methoxy-5-methyl-phenyl)-amide.*

To 7-iodo-N-(2-methoxy-5-methylphenyl)-1-benzofuran-5-sulfonamide (100 mg, 0.23 mmol; Intermediate 57) was added 2-methylpiperazine (45 mg, 0.46 mmol), Herrmann's catalyst (25 mg, 0.02 mmol), Mo(CO)₆ (30 mg, 0.12 mmol) and K₂CO₃ (112 mg, 0.81 mmol) in diglyme (3 mL) and warmed in the StemBlock at 120 °C. After 20 minutes, the mixture was filtered, diluted with ethyl acetate and washed with water. After concentration, the crude mixture was purified by preparative HPLC (Gilson; gradient 30-70% MeCN) to give, after making basic with NaOH and washing with water, the title

amide product. Yield: 36 mg (36%). HPLC 88% $R_T=1.09$ (System C; 2-95% MeCN over 2 min). MS(ESI) for $C_{22}H_{25}N_3O_5S$ m/z 444 (M+H).

5 *Step 2. N-(2-Methoxy-5-methylphenyl)-7-[(3-methylpiperazin-1-yl)methyl]-1-benzofuran-5-sulfonamide hydrochloride.*

To the obtained 7-(3-methyl-piperazin-1-carbonyl)-benzofuran-5-sulfonic acid (2-methoxy-5-methyl-phenyl)-amide (30 mg, 0.07 mmol; Step 1) was added $LiAlH_4$ (9.0 mg, 0.24 mmol) in dry THF (4 mL) and the mixture was warmed to reflux. After 1 h, HPLC analysis showed 15% product and the remaining impurities. Added mixture to 2 M HCl, concentrated and purified by preparative HPLC (Gilson; gradient of 30-70% MeCN). The pure fractions were stripped, HCl/ether added and concentrated to give the title compound as a colourless solid. Yield: 1.3 mg (5%). HPLC 90% $R_T=1.17$ min (System A; 30-80% MeCN over 3 min), 1.13 min (System C; 2-95% MeCN over 2 min). ^1H NMR (400 MHz, methanol- d_4) δ ppm 1.29 (d, $J=7.0$ Hz, 2 H) 2.21 (s, 3 H) 2.72 (m, 1 H) 2.86 (m, 1 H) 3.38 (s, 4 H) 3.43-3.64 (m, 4 H) 4.30 (d, $J=6.59$ Hz, 2 H) 6.62 (d, $J=8.30$ Hz, 1 H) 6.81 - 6.88 (m, 1 H) 6.99 (d, $J=2.44$ Hz, 1 H) 7.25 (d, $J=1.95$ Hz, 1 H) 7.76 (br s, 1 H) 7.94 (d, $J=2.20$ Hz, 1 H) 8.08 (d, $J=1.71$ Hz, 1 H). MS (ESI) for $C_{22}H_{27}N_3O_4S$ m/z 430 (M+H).

INTERMEDIATE 58

20 **7-Iodo-N-(2-methylphenyl)-1-benzofuran-5-sulfonamide**

7-Iodo-1-benzofuran-5-sulfonyl chloride (10 g, 29.2 mmol; Intermediate 56) and 2-methyl aniline (3.43 mL, 32.1 mmol) were dissolved in dichloromethane (150 mL) and pyridine (3.53 mL, 43.8 mmol) was added. The solution was stirred overnight and washed with 1 M HCl (2 x 100 mL), dried over sodium sulfate and evaporated to give the crude solid product that was recrystallized from methanol. Yield: 5.32 g (44%) of a beige solid. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 2.05 (s, 3 H) 6.36 (s, 1 H) 6.95 (d, $J=2.3$ Hz, 1 H) 7.11 - 7.19 (m, 3 H) 7.28 (d, $J=7.5$ Hz, 1 H) 7.81 (d, $J=2.3$ Hz, 1 H) 7.99 (d, $J=1.8$ Hz, 1 H) 8.08 (d, $J=1.8$ Hz, 1 H).

30 INTERMEDIATE 59

N-(2-Methylphenyl)-7-vinyl-1-benzofuran-5-sulfonamide

7-Iodo-N-(2-methylphenyl)-1-benzofuran-5-sulfonamide (0.41 g, 1 mmol; Intermediate 58), tributylvinyltin (0.32 mL, 1.1 mmol), bis(triphenylphosphine)palladium diacetate (10

mg) and acetonitrile (3 mL) were heated under microwave irradiation to 180 °C for 5 min. The mixture was cooled, filtered and evaporated. The resulting oil was washed with hexane (2 x 50 mL), dissolved in diethyl ether (50 mL), filtered and evaporated to give the crude product which was crystallized from ethanol:water (3:1). Yield 0.19 g (61%) of an off white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.93 (s, 3 H) 5.57 (dd, *J*=11.3, 1.0 Hz, 1 H) 6.12 (dd, *J*=17.8, 1.0 Hz, 1 H) 6.84 - 7.07 (m, 6 H) 7.62 (d, *J*=1.8 Hz, 1 H) 7.84 (d, *J*=1.8 Hz, 1 H) 8.14 (d, *J*=2.3 Hz, 1 H) 9.43 (s, 1 H).

INTERMEDIATE 60

10 **7-Formyl-*N*-(2-methylphenyl)-1-benzofuran-5-sulfonamide**

N-(2-Methylphenyl)-7-vinyl-1-benzofuran-5-sulfonamide (1.03 g, 3.3 mmol; Intermediate 59) was dissolved in dioxane (30 mL) and 2,6-lutidine (0.8 mL). Osmium tetroxide (84 mg, 0.33 mmol) was added with stirring followed by a solution of sodium periodate (2.82 g, 13.2 mmol) in water (10 mL). After stirring for 90 minutes, 1 M HCl (40 mL) was added followed by water (200 mL). The precipitated product was collected by filtration, washed with water and dried under vacuo. Yield: 0.95 g (91%) of an off white solid.

¹H NMR (400 MHz, CDCl₃) δ ppm 2.05 (s, 3 H) 6.38 (s, 1 H) 6.95 (d, *J*=2.3 Hz, 1 H) 7.11 (dd, *J*=5.1, 1.1 Hz, 2 H) 7.13 - 7.19 (m, 2 H) 7.91 (d, *J*=2.3 Hz, 1 H) 8.25 (dd, *J*=15.8, 1.8 Hz, 2 H) 10.42 (s, 1 H).

20

EXAMPLE 93

***N*-(2-Methylphenyl)-7-(piperazin-1-ylmethyl)-1-benzofuran-5-sulfonamide, trifluoroacetate**

7-Formyl-*N*-(2-methylphenyl)-1-benzofuran-5-sulfonamide (20 mg, 0.06 mmol; Intermediate 60), *N*-(*tert*-butoxycarbonyl)piperazine (13 mg, 0.07 mmol), acetic acid (36 μL, 0.63 mmol), sodium triacetoxyborohydride (27 mg, 0.13 mmol) were combined with dry THF (3 mL) and heated under microwave irradiation to 130 °C for 5 min. The solution was cooled, filtered and evaporated. The residue was dissolved in methanol (3 mL) and treated with concentrated hydrochloric acid (0.3 mL). This solution was heated under microwave irradiation to 100 °C for 5 min. The solvent was evaporated to give the crude product which was purified by preparative HPLC (Gilson system equipped with an ACE 5 C8 column (30x150 mm), Flow: 35 mL/min. Eluent: gradient 15-40% MeCN in 0.1% TFA in MilliQ water. Yield: 16 mg (50%). Analytical HPLC were performed on Agilent 1100,

column: ACE 3 C8 (system A) or column: YMC-Pack (system B), eluents:

MilliQ/0.1%TFA and MeCN. HPLC 99% $R_T=1.48$ (System A; 10-97% MeCN over 3 min) 99% $R_T=1.31$ (System B; 10-90% MeCN over 3 min). MS (ESI+) for $C_{20}H_{23}N_3O_3S$ m/z 386 (M+1). ^1H NMR (400 MHz, methanol- d_4) δ ppm 1.89 (s, 3 H) 2.65 - 2.72 (m, 4 H) 3.10 - 3.17 (m, 4 H) 3.95 (s, 2 H) 6.92 (d, $J=2.3$ Hz, 1 H) 6.96 - 6.99 (m, 2 H) 6.99 - 7.02 (m, $J=3.2, 1.8, 1.8$ Hz, 2 H) 7.51 (d, $J=1.8$ Hz, 1 H) 7.87 (d, $J=2.3$ Hz, 1 H) 7.96 (d, $J=1.8$ Hz, 1 H).

EXAMPLE 94

10 7-[(3,5-Dimethylpiperazin-1-yl)methyl]-N-(2-methylphenyl)-1-benzofuran-5-sulfonamide, trifluoroacetate

The title compound was prepared according to the procedure described for Example 93, using 7-formyl-N-(2-methylphenyl)-1-benzofuran-5-sulfonamide (40 mg, 0.12 mmol; Intermediate 60) and 3,5-dimethylpiperazine (16 mg, 0.14 mmol) [Note: no HCl deprotection step]. Yield: 21.5 mg (40%). HPLC 97% $R_T=1.57$ (System A; 10-97% MeCN over 3 min) 99% $R_T=1.39$ (System B; 10-90% MeCN over 3 min). MS (ESI+) for $C_{22}H_{27}N_3O_3S$ m/z 414 (M+1). ^1H NMR (400 MHz, methanol- d_4) δ ppm 1.19 (d, $J=6.8$ Hz, 6 H) 1.91 (s, 3 H) 2.11 (dd, $J=12.7, 11.4$ Hz, 2 H) 2.96 (dd, $J=12.9, 2.4$ Hz, 2 H) 3.27 (ddd, $J=11.1, 6.7, 3.3$ Hz, 2 H) 3.91 (s, 2 H) 6.90 (d, $J=2.3$ Hz, 1 H) 6.95 - 7.03 (m, 4 H) 7.57 (d, $J=1.5$ Hz, 1 H) 7.86 (d, $J=2.3$ Hz, 1 H) 7.91 (d, $J=1.8$ Hz, 1 H).

EXAMPLE 95

N-(2-Methylphenyl)-7-[(3-methylpiperazin-1-yl)methyl]-1-benzofuran-5-sulfonamide, trifluoroacetate

25 The title compound was prepared according to the procedure described for Example 93, using 7-formyl-N-(2-methylphenyl)-1-benzofuran-5-sulfonamide (40 mg, 0.12 mmol; Intermediate 60) and 2-methylpiperazine (14 mg, 0.14 mmol). [Note: no HCl deprotection step]. Yield: 31.6 mg (59%). HPLC 99% $R_T=1.50$ (System A; 10-97% MeCN over 3 min) 99% $R_T=1.33$ (System B; 10-90% MeCN over 3 min). MS (ESI+) for $C_{21}H_{25}N_3O_3S$ m/z 400 (M+1). ^1H NMR (400 MHz, methanol- d_4) δ ppm 1.20 (d, $J=6.8$ Hz, 3 H) 1.90 (s, 3 H) 2.33 (dd, $J=12.7, 10.7$ Hz, 1 H) 2.47 (td, $J=12.4, 3.1$ Hz, 1 H) 2.87 - 2.94 (m, $J=12.8$ Hz, 1 H) 3.00 - 3.09 (m, 2 H) 3.26 - 3.34 (m, $J=10.0, 6.8, 6.8, 3.0$ Hz, 2 H) 3.94 - 4.04 (m, 2 H)

6.92 (d, $J=2.3$ Hz, 1 H) 6.97 (dt, $J=5.0, 2.2$ Hz, 2 H) 7.01 (td, $J=3.6, 2.0$ Hz, 2 H) 7.55 (d, $J=1.8$ Hz, 1 H) 7.87 (d, $J=2.0$ Hz, 1 H) 7.95 (d, $J=1.8$ Hz, 1 H).

EXAMPLE 96

5 **7-(1,4-Diazepan-1-ylmethyl)-N-(2-methylphenyl)-1-benzofuran-5-sulfonamide, trifluoroacetate**

The title compound was prepared according to the procedure described for Example 93, using 7-formyl-*N*-(2-methylphenyl)-1-benzofuran-5-sulfonamide (40 mg, 0.12 mmol; Intermediate 60) and *N*-(*tert*-butoxycarbonyl)homopiperazine (28 mg, 0.14 mmol). Yield: 10 21.0 mg (31%). HPLC 99% $R_T=1.34$ (System A; 10-97% MeCN over 3 min) 99% $R_T=1.18$ (System B; 10-90% MeCN over 3 min). MS (ESI+) for $C_{21}H_{25}N_3O_3S$ m/z 400 (M+1). ^1H NMR (400 MHz, methanol- d_4) δ ppm 1.94 (s, 3 H) 2.10 - 2.17 (m, 2 H) 3.28 - 3.35 (m, 4 H) 3.49 - 3.59 (m, 4 H) 4.60 (s, 2 H) 6.92 - 7.04 (m, 5 H) 7.72 (d, $J=1.8$ Hz, 1 H) 7.94 (d, $J=2.3$ Hz, 1 H) 8.09 (d, $J=1.8$ Hz, 1 H).

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EXAMPLE 97

7-[(*trans*-2,5-Dimethylpiperazin-1-yl)methyl]-N-(2-methylphenyl)-1-benzofuran-5-sulfonamide, trifluoroacetate

The title compound was prepared according to the procedure described for Example 93, using 7-formyl-*N*-(2-methylphenyl)-1-benzofuran-5-sulfonamide (80 mg, 0.24 mmol; Intermediate 60) and *trans*-2,5-dimethylpiperazine (58 mg, 0.48 mmol). [Note: no HCl deprotection step]. Yield: 20 32.2 mg (30%). HPLC 99% $R_T=1.58$ (System A; 10-97% MeCN over 3 min) 99% $R_T=1.40$ (System B; 10-90% MeCN over 3 min). MS (ESI+) for $C_{22}H_{27}N_3O_3S$ m/z 414 (M+1). ^1H NMR (400 MHz, methanol- d_4) δ ppm 1.12 (d, $J=6.5$ Hz, 3 H) 1.22 (d, $J=5.8$ Hz, 3 H) 1.91 (s, 3 H) 2.23 (dd, $J=13.1, 11.3$ Hz, 1 H) 2.75 - 2.86 (m, 3 H) 3.14 - 3.21 (m, 1 H) 3.27 (dd, $J=12.2, 2.4$ Hz, 1 H) 3.72 (d, $J=14.3$ Hz, 1 H) 4.37 (d, $J=14.3$ Hz, 1 H) 6.91 (d, $J=2.3$ Hz, 1 H) 6.97 - 7.03 (m, 4 H) 7.58 (d, $J=1.8$ Hz, 1 H) 7.86 (d, $J=2.3$ Hz, 1 H) 7.91 (d, $J=1.8$ Hz, 1 H).

30 EXAMPLE 98

N-(2-Methylphenyl)-7-[(*2R*)-2-methylpiperazin-1-yl]methyl]-1-benzofuran-5-sulfonamide, trifluoroacetate

The title compound was prepared according to the procedure described for Example 93, using 7-formyl-*N*-(2-methylphenyl)-1-benzofuran-5-sulfonamide (40 mg, 0.12 mmol; Intermediate 60) and (3*R*)-3-methyl-1-tritylpiperazine (48 mg, 0.14 mmol). Yield: 22.8 mg (35%). HPLC 96% R_T =1.49 (System A; 10-97% MeCN over 3 min) 96% R_T =1.31

- 5 (System B; 10-90% MeCN over 3 min). MS (ESI+) for $C_{21}H_{25}N_3O_3S$ m/z 400 ($M+1$).
 ^1H NMR (400 MHz, methanol- d_4) δ ppm 1.32 (d, J =6.3 Hz, 3 H) 1.90 (s, 3 H) 2.58 - 2.66 (m, 1 H) 2.87 - 2.97 (m, 2 H) 2.99 - 3.08 (m, 2 H) 3.24 - 3.27 (m, 1 H) 3.33 (dt, J =11.9, 1.8 Hz, 1 H) 3.91 (d, J =14.1 Hz, 1 H) 4.50 (d, J =14.1 Hz, 1 H) 6.94 (d, J =2.3 Hz, 1 H) 6.96 - 6.99 (m, 2 H) 7.01 (dd, J =4.0, 2.8 Hz, 2 H) 7.56 (d, J =1.8 Hz, 1 H) 7.88 (d, J =2.0 Hz, 1 H)
10 7.99 (d, J =1.8 Hz, 1 H).

INTERMEDIATE 61

***N*-(2-Methoxy-5-methylphenyl)-7-vinyl-1-benzofuran-5-sulfonamide**

- Five batches each consisting of a mixture of *N*-(2-methoxy-5-methylphenyl)-7-iodo-1-benzofuran-5-sulfonamide (443 mg, 1.0 mmol; Intermediate 57), tributyl(vinyl)tin (350
15 mg, 1.1 mmol) and bis(triphenylphosphine)palladium diacetate (15 mg, 0.02 mmol) in acetonitrile (3 mL) was heated in a Smith Creator microwave oven to 180 °C for 5 min. The combined reaction mixtures were filtered and concentrated to give 2.0 g of crystalline crude material that was put through a SiO_2 column using EtOAc/hexane (gradient 5:95→
20 25:75) as eluent giving 1.3 g (75 %) of off-white crystalline product. ^1H NMR (400 MHz, $CDCl_3$) δ 2.26 (s, 3 H), 3.53 (s, 3 H), 5.56 (dd, 1 H), 6.16 (dd, 1 H), 6.57 (d, 1 H), 6.79-6.98 (m, 4 H), 7.38 (d, 1 H), 7.71-7.74 (m, 2 H), 7.94 (d, 1 H); MS (ESI+) for $C_{18}H_{17}NO_4S$ m/z 344 ($M+H$)⁺.

25 INTERMEDIATE 62

7-Formyl-*N*-(2-methoxy-5-methylphenyl)-1-benzofuran-5-sulfonamide

- Osmium tetroxide (84 mg, 0.33 mmol) was added to a solution of *N*-(2-methoxy-5-methylphenyl)-7-vinyl-1-benzofuran-5-sulfonamide (1.25 g, 3.3 mmol; Intermediate 61) and lutidine (0.71 g, 6.6 mmol) in dioxane (30 mL). A solution of sodium periodate (2.82
30 g, 13.2 mmol) in water (10 mL) was added under stirring. After 90 min, aqueous HCl (2 M; 40 mL) was added to give a clear solution. Addition of water (200 mL) gave a precipitate that was collected by filtration. This material was washed with water and dried to give 1.12 g (88 %) of the title product. ^1H NMR (400 MHz, $CDCl_3$) δ 2.27 (s, 3 H), 3.55

(s, 3 H), 6.57 (d, 1 H), 6.80-6.85 (m, 1 H), 6.92 (d, 1 H), 7.02 (br s, 1 H), 7.38 (d, 1 H), 7.85 (d, 1 H), 8.22 (d, 1 H), 8.28 (d, 1 H), 10.38 (s, 1 H).

EXAMPLE 99

5 **N-(2-Methoxy-5-methylphenyl)-7-[(3-methylpiperazin-1-yl)methyl]-1-benzofuran-5-sulfonamide, trifluoroacetate**

A mixture of 7-formyl-*N*-(2-methoxy-5-methylphenyl)-1-benzofuran-5-sulfonamide (100 mg, 0,29 mmol; Intermediate 62), 2-methylpiperazine (32 mg, 0,32 mmol) and sodium triacetoxyborohydride (245 mg, 1,16 mmol) in 1,2-dichloroethane (3 mL) was stirred
10 overnight. Filtration and concentration provided 100 mg of crude material that was purified by preparative HPLC to after concentration give 30 mg (19 %) of the title product. ¹H NMR (400 MHz, methanol-*d*₄) δ 1.27 (d, 3 H), 2.24 (s, 3 H), 2.33-2.40 (m, 1 H), 2.46-2.55 (m, 1 H), 2.91-2.98 (m, 1 H), 3.05-3.17 (m, 2 H), 3.32-3.38 (m, 1 H), 3.39 (s, 3 H), 3.96-4.08 (m, 2 H), 6.64 (d, 1 H), 6.87 (dd, 1 H), 6.97 (d, 1 H), 7.28 (d, 1 H), 7.66 (d, 1 H), 7.91
15 (d, 1 H), 8.04 (d, 1 H); MS (ESI+) for C₂₂H₂₇N₃O₄S *m/z* 430 (M+H)⁺; HPLC 99 %, R_T=1.66 in (System A; 10-97% MeCN over 3 min), 99% R_T=1.46 (System B; 10-97% MeCN over 3 min).

EXAMPLE 100

20 **7-(1,4-Diazepan-1-ylmethyl)-N-(2-methoxy-5-methylphenyl)-1-benzofuran-5-sulfonamide, trifluoroacetate**

The title product was prepared according to the procedure of Example 99. Yield: 55 mg (69%). ¹H NMR (400 MHz, methanol-*d*₄) δ 2.16-2.23 (m, 2 H), 2.23 (s, 3 H), 3.35-3.42 (m, 4 H), 3.39 (s, 3 H), 3.58-3.67 (m, 4 H), 4.66 (s, 2 H), 6.64 (d, 1 H), 6.88 (dd, 1 H), 7.05
25 (d, 1 H), 7.28 (d, 1 H), 7.84 (d, 1 H), 7.98 (d, 1 H), 8.18 (d, 1 H); MS (ESI+) for C₂₂H₂₇N₃O₄S *m/z* 430 (M+H)⁺; HPLC 99 %, R_T=1.50 in (System A; 10-97% MeCN over 3 min), 99% R_T=1.33 (System B; 10-97% MeCN over 3 min).

EXAMPLE 101

30 **N-(2-Methoxy-5-methylphenyl)-7-(piperazin-1-ylmethyl)-1-benzofuran-5-sulfonamide, trifluoroacetate**

The title product was prepared according to the procedure of Example 99. Yield:

26 mg (34%). ¹H NMR (400 MHz, methanol-*d*₄) δ 2.24 (s, 3 H), 2.91-2.96 (m, 4 H), 3.26-3.32 (m, 4 H), 3.38 (s, 3 H), 4.17 (s, 2 H), 6.63 (d, 1 H), 6.87 (dd, 1 H), 6.99 (d, 1 H), 7.28 (d, 1 H), 7.68 (d, 1 H), 7.92 (d, 1 H), 8.08 (d, 1 H); MS (ESI+) for C₂₁H₂₅N₃O₄S *m/z* 416 (M+H)⁺; HPLC 99 %, R_T=1.58 in (System A; 10-97% MeCN over 3 min), 99% R_T=1.39 (System B; 10-97% MeCN over 3 min).

EXAMPLE 102

7-[(*cis*-3,5-Dimethylpiperazin-1-yl)methyl]-N-(2-methoxy-5-methylphenyl)-1-benzofuran-5-sulfonamide, trifluoroacetate

10 The title product was prepared according to the procedure of Example 99. Yield: 39 mg (48%). ¹H NMR (400 MHz, methanol-*d*₄) δ 1.26 (d, 6 H), 2.20-2.28 (m, 2 H), 2.23 (s, 3 H), 3.03-3.08 (m, 2 H), 3.32-3.39 (m, 2 H), 3.41 (s, 3 H), 4.01 (s, 2 H), 6.65 (d, 1 H), 6.86 (dd, 1 H), 6.96 (d, 1 H), 7.27 (d, 1 H), 7.69 (d, 1 H), 7.90 (d, 1 H), 8.02 (d, 1 H); MS (ESI+) for C₂₃H₂₉N₃O₄S *m/z* 444 (M+H)⁺; HPLC 99 %, R_T=1.70 in (System A; 10-97% MeCN over 3 min), 99% R_T=1.50 (System B; 10-97% MeCN over 3 min).

EXAMPLE 103

7-[(*trans*-2,5-Dimethylpiperazin-1-yl)methyl]-N-(2-methoxy-5-methylphenyl)-1-benzofuran-5-sulfonamide, trifluoroacetate.

20 The title product was prepared according to the procedure of Example 99. Yield: 11 mg (13%). ¹H NMR (400 MHz, methanol-*d*₄) δ 1.17 (d, 3 H), 1.26 (d, 3 H), 2.16-2.24 (m, 1 H), 2.24 (s, 3 H), 2.72-2.78 (m, 1 H), 2.82-2.91 (m, 2 H), 3.19-3.25 (m, 1 H), 3.30-3.35 (m, 1 H), 3.41 (s, 3 H), 3.71 (d, 1 H), 4.36 (d, 1 H), 6.66 (d, 1 H), 6.87 (dd, 1 H), 6.97 (d, 1 H), 7.29 (d, 1 H), 7.67 (d, 1 H), 7.91 (d, 1 H), 8.02 (d, 1 H); MS (ESI+) for C₂₃H₂₉N₃O₄S *m/z* 444 (M+H)⁺; HPLC 99 %, R_T=1.70 in (System A; 10-97% MeCN over 3 min), 99% R_T=1.49 (System B; 10-97% MeCN over 3 min).

EXAMPLE 104

7-[(1*S*,4*S*)-2,5-Diazabicyclo[2.2.1]hept-2-ylmethyl]-N-(2-methoxy-5-methylphenyl)-1-benzofuran-5-sulfonamide, trifluoroacetate

30 The title product was prepared according to the procedure of Example 99. Yield: 46 mg (73%). ¹H NMR (400 MHz, CD₃OD) δ 2.20 (d, 1 H), 2.23 (s, 3 H), 2.54 (d, 1 H), 3.38 (s, 3 H), 3.44-3.50 (m, 2 H), 3.56 (dd, 1 H), 3.78 (dd, 1 H), 4.28 (br s, 1 H), 4.54 (br s, 1 H),

4.61 (d, 1 H), 4.71 (d, 1 H), 6.64 (d, 1 H), 6.88 (dd, 1 H), 7.04 (d, 1 H), 7.28 (d, 1 H), 7.83 (d, 1 H), 7.97 (d, 1 H), 8.16 (d, 1 H); MS (ESI+) for $C_{22}H_{25}N_3O_4S$ m/z 428 (M+H)⁺; HPLC 99 %, $R_T=1.50$ in (System A; 10-97% MeCN over 3 min), 99% $R_T=1.32$ (System B; 10-97% MeCN over 3 min).

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EXAMPLE 105**N-(2-Methoxy-5-methylphenyl)-7-[(2-methylpiperazin-1-yl)methyl]-1-benzofuran-5-sulfonamide, trifluoroacetate**

The title product was prepared according to the procedure of Example 99. Yield: 31 mg (49%). ¹H NMR (400 MHz, methanol-*d*₄) δ 1.35 (d, 3 H), 2.24 (s, 3 H), 2.56-2.65 (m, 1 H), 2.87-3.11 (overlapping m, 4 H), 3.25-3.28 (m, 1 H), 3.33-3.37 (m, 1 H), 3.38 (s, 3 H), 3.88 (d, 1 H), 3.48 (d, 1 H), 6.64 (d, 1 H), 6.87 (dd, 1 H), 6.98 (d, 1 H), 7.29 (d, 1 H), 7.66 (d, 1 H), 7.92 (d, 1 H), 8.07 (d, 1 H); MS (ESI+) for $C_{22}H_{27}N_3O_4S$ m/z 430 (M+H)⁺; HPLC 99 %, $R_T=1.58$ in (System A; 10-97% MeCN over 3 min), 99% $R_T=1.40$ (System B; 10-97% MeCN over 3 min).

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INTERMEDIATE 63**7-Methyl-5-nitro-1-benzofuran**

7-Iodo-5-nitro-benzofuran (6.5 g, 22.1 mmol), Pd(OAc)₂ (1 g, 3.9 mmol), P(*o*-tolyl)₃ (5.5 g, 18.2 mmol), Me₄Sn (8.05 g, 42 mmol), and Et₃N (3.16 mL, 20.4 mmol) were dissolved in DMF (40 mL) and portioned out in 13 tubes and heated at 100 °C for 10 min each using controlled microwave energy. The reaction mixtures were combined and filtered and the solvent was evaporated. The crude material was purified using flash chromatography (using a gradient of *isohexane* – 10% EtOAc in *isohexane*). Yield: 2.82 g (70%) of 7-methyl-5-nitro-1-benzofuran. ¹H NMR (400 MHz, CDCl₃) δ ppm 2.51 - 2.64 (m, 3 H) 6.90 (d, $J=2.3$ Hz, 1 H) 7.77 (d, $J=2.3$ Hz, 1 H) 8.04 (d, $J=1.3$ Hz, 1 H) 8.37 (d, $J=2.3$ Hz, 1 H); HPLC 96% $R_t=2.31$ min (System A; 10-97% in 3 min ACE column). MS (ESI+) for $C_9H_7NO_3$ m/z 178 (M+H)⁺.

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INTERMEDIATE 64**7-(Bromomethyl)-5-nitro-benzofuran**

7-Methyl-5-nitro-1-benzofuran (2.1 g, 12 mmol; Intermediate 63) was dissolved in CCl₄ and heated to 80 °C. Benzoyl peroxide (0.43 g, 1.6 mmol) was added followed by NBS

(2.1 g, 12 mmol) that was added in small portions. The reaction mixture was heated at reflux overnight with stirring. Additional benzoyl peroxide (0.08 mmol) and NBS (0.2 mmol) were added and the reaction mixture was stirred for one additional night. After this time, the mixture was filtered and concentrated. The crude was redissolved in DCM and washed with water. The organic solvent was dried (MgSO₄) and evaporated. The residue was purified using preparative HPLC with a gradient of 45-70% MeCN. This afforded 0.7 g (22%) of 7-(bromomethyl)-5-nitro-benzofuran as a solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 4.78 (s, 2 H) 6.96 (d, *J*=2.3 Hz, 1 H) 7.84 (d, *J*=2.3 Hz, 1 H) 8.28 (d, *J*=2.3 Hz, 1 H) 8.49 (d, *J*=2.3 Hz, 1 H). HPLC Rt=1.9 min (System A; 30-80% MeCN over 3 min ACE column).

EXAMPLE 106

2-Chloro-N-[7-(piperazin-1-ylmethyl)-1-benzofuran-5-yl]benzenesulfonamide dihydrochloride

Step 1: *tert*-Butyl 4-[(5-nitro-1-benzofuran-7-yl)methyl]piperazine-1-carboxylate
7-(Bromomethyl)-5-nitro-1-benzofuran (145 mg, 70 mol % pure, 0.44 mmol; Intermediate 64), K₂CO₃ (181 mg, 1.31 mmol) and 1-boc-piperazine (98 mg, 0.53 mmol) were mixed in dry MeCN (5 mL) and heated to 80 °C while stirring for 2 h using a StemBlock. The solvent was evaporated under reduced pressure and the residue was partitioned between water and DCM (x2). The organic layers were combined, dried (Na₂SO₄) and purified using flashtube (10% MeOH in DCM). This afforded the title product (123 mg, 78%) as a light yellow solid. HPLC 98%, R_T=1.70 min (System A; 10-97% MeCN over 3 min), 99%, R_T=1.55 min (System B; 10-97% MeCN over 3 min). MS (ESI+) for C₁₈H₂₃N₃O₅ *m/z* 362 (M+H)⁺.

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Step 2: 4-(5-Amino-benzofuran-7-ylmethyl)-piperazine-1-carboxylic acid *tert*-butyl ester

Raney nickel (slurry in ethanol) and hydrazine hydrate (66 µL, 1.36 mmol) were added to *tert*-butyl 4-[(5-nitro-1-benzofuran-7-yl)methyl]piperazine-1-carboxylate (123 mg, 0.34 mmol; obtained in Step 1) in ethanol:THF (4:1; 10 mL). The mixture was stirred at room temperature for 1 h. Unreacted starting material was still present and additional Raney nickel and hydrazine hydrate (33 µL, 0.68 mmol) were added with continuous stirring for 1 h. The mixture was filtered through a pad of Celite, which was rinsed several times with

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ethanol. Evaporation of the solvent gave 119 mg (quantitative) of the title amine as a green sticky oil which was used directly in the next step.

Step 3: 2-Chloro-N-[7-(piperazin-1-ylmethyl)-1-benzofuran-5-yl]benzenesulfonamide dihydrochloride

Dry pyridine (20 μ L, 0.24 mmol) and 2-chlorobenzenesulfonyl chloride (25 μ L, 0.18 mmol) were added to a solution of 4-(5-amino-benzofuran-7-ylmethyl)-piperazine-1-carboxylic acid *tert*-butyl ester (40 mg, 0.12 mmol; obtained in Step 2) in a mixture of dry DCM:THF (2:1; 3 mL). The resulting mixture was stirred for 3 h and volatiles were then evaporated. The product was purified using flashtube (15% MeOH in DCM). The residue was dissolved in TFA:water (9:1; 2 mL) and the mixture was stirred at room temperature for 30 min to accomplish removal of the N-t-BOC group. The reaction mixture was made basic by addition of saturated aqueous Na₂CO₃ (pH 8-9) and extracted with DCM (x2). The organic layers were combined, dried (Na₂SO₄) and concentrated. The crude product was purified with preparative HPLC (System A; 10-40% MeCN). Pure fractions were combined and concentrated. The obtained TFA salt was dissolved in MeOH and 1 M HCl in ether was added, followed by concentration to give the title compound (10 mg, 18%) as a light yellow solid. HPLC 100%, R_T=1.38 min (System A; 10-97% MeCN over 3 min), 100%, R_T=1.23 min (System B; 10-97% MeCN over 3 min). ¹H NMR (400 MHz, methanol-*d*₄) δ ppm 2.86 - 2.92 (m, 4 H) 3.25 - 3.28 (m, 4 H) 4.04 - 4.08 (m, 2 H) 6.73 (d, *J*= 2.26 Hz, 1 H) 7.15 (d, *J*=2.01 Hz, 1 H) 7.26 - 7.31 (m, 1 H) 7.32 (d, *J*=2.26 Hz, 1 H) 7.42 - 7.47 (m, 1 H) 7.47 - 7.52 (m, 1 H) 7.70 (d, *J*=2.26 Hz, 1 H) 7.90 (dd, *J*=8.03, 1.51 Hz, 1 H). MS (ESI+) for C₁₉H₂₀ClN₃O₃S *m/z* 406 (M+H).

EXAMPLE 107

2-Methyl-N-[7-(piperazin-1-ylmethyl)-1-benzofuran-5-yl]benzenesulfonamide, dihydrochloride

The title compound was prepared according to the procedure of Example 106, Step 3, starting from 4-(5-amino-benzofuran-7-ylmethyl)-piperazine-1-carboxylic acid *tert*-butyl ester (40 mg, 0.12 mmol; obtained in Example 106, Step 2) and 2-methylbenzenesulfonyl chloride (26 μ L, 0.18 mmol). The crude product was purified with preparative HPLC (System B; 10-40% MeCN). The title compound (10 mg, 19%) was obtained as a colorless solid. HPLC 99%, R_T=1.41 min (System A; 10-97% MeCN over 3 min), 99%, R_T=1.26

min (System B; 10-97% MeCN over 3 min). ¹H NMR (400 MHz, methanol-*d*₄) δ ppm 2.66 (s, 3 H) 3.50 - 3.65 (m, 8 H) 4.67 (s, 2 H) 6.86 (d, *J*=2.01 Hz, 1 H) 7.22 - 7.29 (m, 1 H) 7.30 - 7.37 (m, 2 H) 7.40 - 7.48 (m, 2 H) 7.81 - 7.90 (m, 2 H). MS (ESI+) for C₂₀H₂₃N₃O₃S *m/z* 386 (M+H)⁺.

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EXAMPLE 108

N-[7-(Piperazin-1-ylmethyl)-1-benzofuran-5-yl]thiophene-2-sulfonamide, dihydrochloride

The title compound was prepared according to the procedure of Example 106, Step 3, starting from 4-(5-amino-benzofuran-7-ylmethyl)-piperazine-1-carboxylic acid *tert*-butyl ester (40 mg, 0.12 mmol; obtained in Example 106, Step 2) and 2-thiophenesulfonyl chloride (33 mg, 0.18 mmol). Additional 2-thiophenesulfonyl chloride (10 mg, 0.05 mmol) was added with continued stirring for 1 h. The crude product was purified with preparative HPLC (System B; 10-40% MeCN). The title compound (3 mg, 6%) was obtained as a colorless solid. HPLC 95%, *R*_T=1.25 min (System A; 10-97% MeCN over 3 min), 95%, *R*_T=1.11 min (System B; 10-97% MeCN over 3 min). ¹H NMR (400 MHz, methanol-*d*₄) δ ppm 3.43 - 3.49 (m, 4 H) 3.50 - 3.57 (m, 4 H) 4.59 (s, 2 H) 6.90 (d, *J*=2.26 Hz, 1 H) 7.05 (dd, *J*=5.02, 3.76 Hz, 1 H) 7.35 (d, *J*=2.26 Hz, 1 H) 7.45 - 7.50 (m, 2 H) 7.70 (dd, *J*=5.02, 1.51 Hz, 1 H) 7.88 (d, *J*=2.26 Hz, 1 H). MS (ESI+) for C₁₇H₁₉N₃O₃S₂ *m/z* 378 (M+H)⁺.

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EXAMPLE 109

2-Chloro-N-[7-(1,4-diazepan-1-ylmethyl)-1-benzofuran-5-yl]benzenesulfonamide dihydrochloride**Step 1: *tert*-Butyl 4-[(5-nitro-1-benzofuran-7-yl)methyl]-1,4-diazepane-1-carboxylate**

The title product, obtained as a light yellow solid, was prepared according to the procedure of Example 106, Step 1, starting from 1-boc-homopiperazine (103 μL, 0.53 mmol). Yield: 109 mg (66%). HPLC 98%, *R*_T=1.73 min (System A; 10-97% MeCN over 3 min), 100%, *R*_T=1.57 min (System B; 10-97% MeCN over 3 min). MS (ESI+) for C₁₉H₂₅N₃O₅ *m/z* 376 (M+H)⁺.

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Step 2: 4-(5-Amino-benzofuran-7-ylmethyl)-1,4-diazepane-1-carboxylic acid *tert*-butyl ester

The title compound was prepared according to the procedure of Example 106, Step 2, starting from *tert*-butyl 4-[(5-nitro-1-benzofuran-7-yl)methyl]-1,4-diazepane-1-carboxylate (obtained in Step 1).

5 **Step 3: 2-Chloro-N-[7-(1,4-diazepan-1-ylmethyl)-1-benzofuran-5-yl]benzenesulfonamide dihydrochloride**

The title compound was prepared according to the procedure of Example 106, Step 3, starting from 4-(5-amino-benzofuran-7-ylmethyl)-1,4-diazepane-1-carboxylic acid *tert*-butyl ester (36 mg, 0.10 mmol; obtained in Step 2) and 2-chlorobenzenesulfonyl chloride
10 (21 μ L, 0.16 mmol). The crude material was purified with preparative HPLC (System B; 10-40% MeCN). The title compound (16 mg, 33%) was obtained as a colorless solid. HPLC 95%, R_T =1.31 min (System A; 10-97% MeCN over 3 min), 96%, R_T =1.17 min (System B; 10-97% MeCN over 3 min). ^1H NMR (400 MHz, methanol- d_4) δ ppm 2.25 - 2.37 (m, 2 H) 3.41 - 3.48 (m, 2 H) 3.48 - 3.59 (m, J =4.52 Hz, 2 H) 3.69 - 3.75 (m, J =3.51
15 Hz, 2 H) 3.74 - 3.83 (m, 2 H) 4.70 (s, 2 H) 6.86 (d, J =2.26 Hz, 1 H) 7.36 - 7.41 (m, 1 H) 7.42 (d, J =2.01 Hz, 1 H) 7.51 - 7.59 (m, 3 H) 7.85 (d, J =2.01 Hz, 1 H) 8.00 - 8.04 (m, J =7.91, 1.13 Hz, 1 H). MS (ESI+) for $\text{C}_{20}\text{H}_{22}\text{ClN}_3\text{O}_3\text{S}$ m/z 420 ($\text{M}+\text{H}$) $^+$.

EXAMPLE 110

20 **N-[7-(1,4-Diazepan-1-ylmethyl)-1-benzofuran-5-yl]-2-methylbenzenesulfonamide, dihydrochloride**

The title compound was prepared according to the procedure of Example 106, Step 3, starting from 4-(5-amino-benzofuran-7-ylmethyl)-1,4-diazepane-1-carboxylic acid *tert*-butyl ester (36 mg, 0.10 mmol; obtained in Example 109, Step 2) and 2-
25 methylbenzenesulfonyl chloride (23 μ L, 0.16 mmol). The title compound (13 mg, 28%) was obtained as a colorless solid. HPLC 99%, R_T =1.35 min (System A; 10-97% MeCN over 3 min), 100%, R_T =1.22 min (System B; 10-97% MeCN over 3 min). ^1H NMR (400 MHz, methanol- d_4) δ ppm 2.26 - 2.32 (m, 2 H) 2.66 (s, 3 H) 3.40 - 3.60 (m, 4 H) 3.69 - 3.83 (m, 4 H) 4.69 (s, 2 H) 6.86 (d, J =2.26 Hz, 1 H) 7.23 - 7.29 (m, 1 H) 7.32 - 7.38 (m, 2
30 H) 7.41 - 7.46 (m, 1 H) 7.47 (d, J =2.26 Hz, 1 H) 7.84 - 7.90 (m, 2 H). MS (ESI+) for $\text{C}_{21}\text{H}_{25}\text{N}_3\text{O}_3\text{S}$ m/z 400 ($\text{M}+\text{H}$) $^+$.

EXAMPLE 111

N-[7-(1,4-Diazepan-1-ylmethyl)-1-benzofuran-5-yl]thiophene-2-sulfonamide dihydrochloride

The title compound was prepared according to the procedure of Example 106, Step 3, starting from 4-(5-amino-benzofuran-7-ylmethyl)-1,4-diazepane-1-carboxylic acid tert-butyl ester (36 mg, 0.10 mmol; obtained in Example 109, Step 2) and 2-thiophenesulfonyl chloride (29 mg, 0.16 mmol). Additional 2-thiophenesulfonyl chloride (10 mg, 0.06 mmol) was added with continuous stirring for 1 h. The title compound (10 mg, 22%) was obtained as a colorless solid. HPLC 100%, $R_T=1.20$ min (System A; 10-97% MeCN over 3 min), 100%, $R_T=1.06$ min (System B; 10-97% MeCN over 3 min). ^1H NMR (400 MHz, methanol- d_4) δ ppm 2.20 - 2.29 (m, 2 H) 3.34 - 3.41 (m, 2 H) 3.41 - 3.55 (m, 2 H) 3.63 - 3.69 (m, 2 H) 3.69 - 3.77 (m, 2 H) 4.66 (s, 2 H) 6.84 (d, $J=2.26$ Hz, 1 H) 6.98 (dd, $J=5.02$, 3.76 Hz, 1 H) 7.32 (d, $J=2.01$ Hz, 1 H) 7.42 (dd, $J=3.76$, 1.25 Hz, 1 H) 7.47 (d, $J=2.26$ Hz, 1 H) 7.63 (dd, $J=5.02$, 1.25 Hz, 1 H) 7.82 (d, $J=2.26$ Hz, 1 H). MS (ESI+) for $\text{C}_{18}\text{H}_{21}\text{N}_3\text{O}_3\text{S}_2$ m/z 392 ($\text{M}+\text{H}$) $^+$.

EXAMPLE 112

2-Methoxy-5-methyl-N-{7-[(2-methylpiperazin-1-yl)methyl]-1-benzofuran-5-yl}benzenesulfonamide, dihydrochloride

Step 1: tert-Butyl 3-methyl-4-[(5-nitro-1-benzofuran-7-yl)methyl]piperazine-1-carboxylate

A mixture of 7-(bromomethyl)-5-nitro-1-benzofuran (120 mg, 70 mol %, 0.39 mmol; Intermediate 64), K_2CO_3 (162 mg, 1.17 mmol) and tert-butyl 3-methylpiperazine-1-carboxylate (94 mg, 0.47 mmol) in dry MeCN (5 mL) was heated at 80 °C while stirring for 1 h 45 min using a StemBlock. The solvent was evaporated under reduced pressure and the residue was partitioned between water and DCM (x2). The organic layers were combined, dried (Na_2SO_4) and purified using flashtube (10% MeOH in DCM). This afforded the title product (115 mg, 78%) as a light yellow sticky oil. HPLC 99%, $R_T=2.47$ min (System A; 5-60% MeCN over 3 min), 99%, $R_T=2.27$ min (System B; 5-60% MeCN over 3 min). MS (ESI+) for $\text{C}_{19}\text{H}_{25}\text{N}_3\text{O}_5$ m/z 376 ($\text{M}+\text{H}$) $^+$.

Step 2: tert-Butyl 4-[(5-amino-1-benzofuran-7-yl)methyl]-3-methylpiperazine-1-carboxylate

Raney nickel (slurry in ethanol) and hydrazine hydrate (97 μ L, 2.0 mmol) were added to tert-butyl 3-methyl-4-[(5-nitro-1-benzofuran-7-yl)methyl]piperazine-1-carboxylate (115 mg, 0.31 mmol; obtained in Step 1) in ethanol:THF (4:1; 5 mL). The resulting mixture was stirred at room temperature for 1.5 h, followed by filtration through Celite. The Celite pad was rinsed several times with ethanol. The solvent was evaporated to give the crude product (136 mg) as a light green solid. This material was used in the next step without further purification. HPLC 98%, R_T =1.77 min (System A; 5-60% MeCN over 3 min), 100%, R_T =1.50 min (System B; 5-60% MeCN over 3 min). MS (ESI+) for $C_{19}H_{27}N_3O_3$ m/z 346 (M+H)⁺.

Step 3: 2-Methoxy-5-methyl-N-{7-[(2-methylpiperazin-1-yl)methyl]-1-benzofuran-5-yl}benzenesulfonamide, dihydrochloride

Pyridine (17 μ L, 0.20 mmol) and 6-methoxy-m-toluenesulfonyl chloride (34 mg, 0.15 mmol) were added to a solution of tert-butyl 4-[(5-amino-1-benzofuran-7-yl)methyl]-3-methylpiperazine-1-carboxylate (45 mg crude material, 0.10 mmol; obtained in Step 2) in dry DCM:THF (2:1; 3 mL). The reaction mixture was stirred at room temperature for 2 h and the solvent was evaporated under reduced pressure followed by purification by flashtube (15% MeOH in DCM). The residue was dissolved in TFA:water (9:1; 4.5 mL) and the mixture was stirred at room temperature for 1 h to accomplish removal of the N-t-BOC group. The reaction mixture was diluted with DCM (10 mL) and saturated aqueous Na_2CO_3 was added to reach pH 8-9 (~15 mL). The phases were separated using "phase separator" filters and the organic phase was concentrated. The crude product was purified by preparative HPLC (System B; 10-40% MeCN). Pure fractions were combined and concentrated to give the product as the free base, which was dissolved in MeOH and 1 M HCl in ether (200 μ L, 0.2 mmol) was added. The solvent was evaporated to give the title compound (19 mg, 38%) as an off-white solid. HPLC 99%, R_T =1.46 min (System A; 10-97% MeCN over 3 min), 100%, R_T =1.29 min (System B; 10-97% MeCN over 3 min). ¹H NMR (400 MHz, methanol-*d*₄) δ ppm 1.72 (d, J =6.53 Hz, 3 H) 2.20 (s, 3 H) 3.39 - 3.62 (m, 5 H) 3.67 - 3.74 (m, 1 H) 3.87 - 3.96 (m, 1 H) 3.98 (s, 3 H) 4.60 (d, J =13.55 Hz, 1 H) 4.93 (d, J =13.80 Hz, 1 H) 6.87 (d, J =2.26 Hz, 1 H) 7.04 (d, J =8.53 Hz, 1 H) 7.28 - 7.37 (m, 2 H) 7.52 (d, J =2.26 Hz, 1 H) 7.54 (d, J =2.01 Hz, 1 H) 7.85 (d, J =2.01 Hz, 1 H). MS (ESI+) for $C_{22}H_{27}N_3O_4S$ m/z 430 (M+H)⁺.

EXAMPLE 113

2-Methyl-N-{7-[(2-methylpiperazin-1-yl)methyl]-1-benzofuran-5-yl}benzenesulfonamide dihydrochloride

The title product was prepared according to the procedure of Example 112, Step 3, starting from tert-butyl 4-[(5-amino-1-benzofuran-7-yl)methyl]-3-methylpiperazine-1-carboxylate (45 mg crude material, 0.10 mmol; obtained in Example 112, Step 2) and o-toluenesulfonyl chloride (22 μ L, 0.15 mmol). The title compound (17 mg, 35%) was obtained as an off-white solid. HPLC 99%, R_T =1.42 min (System A; 10-97% MeCN over 3 min), 100%, R_T =1.26 min (System B; 10-97% MeCN over 3 min). ^1H NMR (400 MHz, methanol- d_4) δ ppm 1.69 - 1.74 (m, 3 H) 2.67 (s, 3 H) 3.37 - 3.62 (m, 5 H) 3.67 - 3.75 (m, 1 H) 3.84 - 3.95 (m, 1 H) 4.57 - 4.65 (m, 1 H) 4.90 - 4.97 (m, J =13.55 Hz, 1 H) 6.86 (d, J =2.26 Hz, 1 H) 7.23 - 7.29 (m, J =7.65, 7.65 Hz, 1 H) 7.31 (d, J =2.01 Hz, 1 H) 7.32 - 7.36 (m, 1 H) 7.40 - 7.46 (m, 1 H) 7.50 (d, J =2.01 Hz, 1 H) 7.85 - 7.90 (m, 2 H). MS (ESI+) for $\text{C}_{21}\text{H}_{25}\text{N}_3\text{O}_3\text{S}$ m/z 400 ($\text{M}+\text{H}$) $^+$.

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EXAMPLE 114

2,5-Dichloro-N-{7-[(2-methylpiperazin-1-yl)methyl]-1-benzofuran-5-yl}thiophene-3-sulfonamide dihydrochloride

The title product was prepared according to the procedure of Example 112, Step 3, starting from tert-butyl 4-[(5-amino-1-benzofuran-7-yl)methyl]-3-methylpiperazine-1-carboxylate (45 mg crude material, 0.10 mmol; obtained in Example 112, Step 2) and 2,5-dichlorothiophene-3-sulphonyl chloride (38 mg, 0.15 mmol). The title compound (23 mg, 43%) was obtained as an off-white solid. HPLC 98%, R_T =1.61 min (System A; 10-97% MeCN over 3 min), 100%, R_T =1.43 min (System B; 10-100% MeCN over 3 min). ^1H NMR (400 MHz, methanol- d_4) δ ppm 1.53 (d, J =6.27 Hz, 3 H) 2.87 - 3.02 (m, 1 H) 3.14 - 3.27 (m, 2 H) 3.39 - 3.47 (m, 1 H) 3.47 - 3.54 (m, 1 H) 4.12 - 4.24 (m, 1 H) 4.62 - 4.71 (m, 1 H) 6.89 (d, J =2.26 Hz, 1 H) 7.13 (s, 1 H) 7.30 - 7.32 (m, J =1.76 Hz, 1 H) 7.45 (d, J =2.26 Hz, 1 H) 7.85 (d, J =2.26 Hz, 1 H). *Two hydrogens are not visible in the spectrum. Probably "hidden" behind the H_2O - and the MeOH signals. MS (ESI+) for $\text{C}_{18}\text{H}_{19}\text{Cl}_2\text{N}_3\text{O}_3\text{S}_2$ m/z 460 ($\text{M}+\text{H}$) $^+$.

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EXAMPLE 115

2-Methoxy-5-methyl-N-{7-[(3-methylpiperazin-1-yl)methyl]-1-benzofuran-5-yl}benzenesulfonamide, dihydrochloride

Step 1: 3-Methyl-1-[(5-nitro-1-benzofuran-7-yl)methyl]piperazine

The title compound was prepared according to the procedure of Example 112, Step 1, starting from 7-(bromomethyl)-5-nitro-1-benzofuran (120 mg, 70 mol%, 0.39 mmol; Intermediate 64) and 2-methylpiperazine (196 mg, 1.95 mmol). The crude product was purified by flash chromatography (eluent: 4% MeOH, 1% NEt₃ in DCM). The title compound (102 mg, 87%) was obtained as a light yellow sticky oil. HPLC 99%, R_T=1.60 min (System A; 5-60% MeCN over 3 min), 100%, R_T=1.40 min (System B; 5-60% MeCN over 3 min). MS (ESI+) for C₁₄H₁₇N₃O₃ *m/z* 276 (M+H)⁺.

Step 2: *tert*-Butyl 2-methyl-4-[(5-nitro-1-benzofuran-7-yl)methyl]piperazine-1-carboxylate

Di-*tert*-butyl dicarbonate (89 mg, 0.41 mmol) in dry DCM (2 mL) was added, with a syringe, under N₂ to 3-methyl-1-[(5-nitro-1-benzofuran-7-yl)methyl]piperazine (102 mg, 0.37 mmol; obtained in Step 1) and NEt₃ (77 µL, 0.77 mmol) in dry DCM (5 mL) at 0 °C. The resulting mixture was allowed to attain room temperature and stirred for 1.5 h. The reaction mixture was diluted with DCM and saturated aqueous Na₂CO₃ was added. The organic layer was dried (Na₂SO₄) and concentrated followed by purification with flash chromatography (eluent: 1.5% MeOH in DCM). This gave the title compound (124 mg, 89%) as a white foam. HPLC 90%, R_T=2.53 min (System A; 5-60% MeCN over 3 min), 90%, R_T=2.35 min (System B; 5-60% MeCN over 3 min). MS (ESI+) for C₁₉H₂₅N₃O₅ *m/z* 376 (M+H)⁺.

Step 3: *tert*-Butyl 4-[(5-amino-1-benzofuran-7-yl)methyl]-2-methylpiperazine-1-carboxylate

The title compound was prepared according to the procedure of Example 112, Step 2, using *tert*-butyl 2-methyl-4-[(5-nitro-1-benzofuran-7-yl)methyl]piperazine-1-carboxylate (124 mg, 0.33 mmol; obtained in Step 2). The crude title compound (124 mg) was obtained as a light green solid. This material was used in the next step without further purification. HPLC 100%, R_T=1.82 min (System A; 5-60% MeCN over 3 min), 100%, R_T=1.57 min (System B; 5-60% MeCN over 3 min). MS (ESI+) for C₁₉H₂₇N₃O₃ *m/z* 346 (M+H)⁺.

Step 4: 2-Methoxy-5-methyl-N-{7-[(3-methylpiperazin-1-yl)methyl]-1-benzofuran-5-yl}benzenesulfonamide, dihydrochloride

tert-Butyl 4-[(5-amino-1-benzofuran-7-yl)methyl]-2-methylpiperazine-1-carboxylate (41 mg crude starting material, 0.11 mmol; obtained in Step 3) was dissolved in dry DCM:THF (2:1; 3 mL). Pyridine (18 μ L, 0.22 mmol) and 6-methoxy-m-toluenesulfonyl chloride (36 mg, 0.17 mmol) were added. The resultant mixture was stirred at room temperature for 2 h and the solvent was evaporated under reduced pressure followed by purification by flashtube (11% MeOH in DCM). The residue was dissolved in TFA:water (9:1; 4.5 mL) and the mixture was stirred at room temperature for 1 h to accomplish removal of the N-t-BOC group. The reaction mixture was diluted with DCM (10 mL) and saturated aqueous Na₂CO₃ was added to reach pH 8-9 (~15 mL). The phases were separated using "phase separator" filters and the organic phase was concentrated. The crude product was purified by preparative HPLC (System B; 10-40% MeCN). Pure fractions were combined and concentrated to give the product as the free base, which was dissolved in MeOH and 1 M HCl in ether (200 μ L, 0.2 mmol) was added. The solvent was evaporated to give the title compound (16 mg, 29%) as an off-white solid. HPLC 99%, R_T=1.48 min (System A; 10-97% MeCN over 3 min), 100%, R_T=1.30 min (System B; 10-97% MeCN over 3 min). ¹H NMR (400 MHz, methanol-*d*₄) δ ppm 1.38 - 1.45 (m, *J*=6.53 Hz, 3 H) 2.20 (s, 3 H) 3.34 - 3.42 (m, *J*=13.30 Hz, 1 H) 3.46 - 3.78 (m, 5 H) 3.79 - 3.91 (m, 1 H) 3.98 (s, 3 H) 4.71 (s, 2 H) 6.87 (d, *J*=2.26 Hz, 1 H) 7.04 (d, *J*=8.53 Hz, 1 H) 7.29 - 7.34 (m, *J*=8.78, 2.01 Hz, 1 H) 7.37 (d, *J*=2.26 Hz, 1 H) 7.51 - 7.53 (m, *J*=2.01 Hz, 1 H) 7.54 (d, *J*=2.26 Hz, 1 H) 7.85 (d, *J*=2.01 Hz, 1 H). MS (ESI+) for C₂₂H₂₇N₃O₄S *m/z* 430 (M+H)⁺.

EXAMPLE 116

25 N-{7-[(3-Methylpiperazin-1-yl)methyl]-1-benzofuran-5-yl}-2-(trifluoromethyl)benzenesulfonamide, dihydrochloride

The title compound was prepared according to the procedure of Example 115, Step 4, starting from tert-butyl 4-[(5-amino-1-benzofuran-7-yl)methyl]-2-methylpiperazine-1-carboxylate (41 mg crude starting material, 0.11 mmol; obtained in Example 115, Step 3) and 2-(trifluoromethyl)benzenesulfonyl chloride (25 μ L, 0.17 mmol). The title compound (24 mg, 44%) was obtained as an off-white solid. HPLC 98%, R_T=1.56 min (System A; 10-97% MeCN over 3 min), 97%, R_T=1.37 min (System B; 10-97% MeCN over 3 min). ¹H NMR (400 MHz, methanol-*d*₄) δ ppm 1.41 (d, *J*=6.53 Hz, 3 H) 3.36 - 3.44 (m, *J*=13.30,

12.05 Hz, 1 H) 3.47 - 3.78 (m, 5 H) 3.81 - 3.94 (m, 1 H) 4.74 (s, 2 H) 6.88 (d, $J=2.26$ Hz, 1 H) 7.41 (d, $J=2.01$ Hz, 1 H) 7.53 (d, $J=2.26$ Hz, 1 H) 7.68 - 7.76 (m, 2 H) 7.88 (d, $J=2.01$ Hz, 1 H) 7.90 - 7.95 (m, $J=6.90, 2.13$ Hz, 1 H) 8.09 - 8.13 (m, 1 H). MS (ESI+) for $C_{21}H_{22}F_3N_3O_3S$ m/z 454 (M+H)⁺.

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EXAMPLE 117

2-Chloro-N-{7-[(3-methylpiperazin-1-yl)methyl]-1-benzofuran-5-yl}benzenesulfonamide, dihydrochloride

The title compound was prepared according to the procedure of Example 115, Step 4, starting from tert-butyl 4-[(5-amino-1-benzofuran-7-yl)methyl]-2-methylpiperazine-1-carboxylate (41 mg crude starting material, 0.11 mmol; obtained in Example 115, Step 3) and 2-chlorobenzenesulfonyl chloride (22 μ L, 0.17 mmol). The title compound (21 mg, 39%) was obtained as an off-white solid. HPLC 100%, $R_T=1.42$ min (System A; 10-97% MeCN over 3 min), 100%, $R_T=1.26$ min (System B; 10-97% MeCN over 3 min). ¹H NMR (400 MHz, methanol- d_4) δ ppm 1.41 (d, $J=6.53$ Hz, 3 H) 3.32 - 3.37 (m, 1 H) 3.45 - 3.59 (m, 2 H) 3.63 - 3.76 (m, 3 H) 3.78 - 3.89 (m, 1 H) 4.70 (s, 2 H) 6.86 (d, $J=2.26$ Hz, 1 H) 7.36 - 7.41 (m, 1 H) 7.42 (d, $J=2.01$ Hz, 1 H) 7.49 - 7.54 (m, 1 H) 7.54 - 7.58 (m, 2 H) 7.86 (d, $J=2.01$ Hz, 1 H) 8.02 (dd, $J=7.91, 1.63$ Hz, 1 H). MS (ESI+) for $C_{20}H_{22}ClN_3O_3S$ m/z 420 (M+H)⁺.

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EXAMPLE 118

N-{7-[(1S,4S)-2,5-Diazabicyclo[2.2.1]hept-2-ylmethyl]-1-benzofuran-5-yl}-2-methoxy-5-methylbenzenesulfonamide, dihydrochloride**Step 1: tert-Butyl (1S,4S)-5-[(5-nitro-1-benzofuran-7-yl)methyl]-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate**

The title compound was prepared according to the procedure of Example 112, Step 1, starting from 7-(bromomethyl)-5-nitro-1-benzofuran (120 mg, 70 mol%, 0.39 mmol; Intermediate 64) and tert-butyl (1S,4S)-(-)-2,5-diazabicyclo-(2.2.1)heptane-2-carboxylate (93 mg, 0.47 mmol). The title compound (115 mg, 79%) was obtained as a light yellow sticky oil. HPLC 99%, $R_T=2.34$ min (System A; 5-60% MeCN over 3 min), 99%, $R_T=2.15$ min (System B; 5-60% MeCN over 3 min). MS (ESI+) for $C_{19}H_{23}N_3O_5$ m/z 374 (M+H)⁺.

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Step 2: tert-Butyl (1S,4S)-5-[(5-amino-1-benzofuran-7-yl)methyl]-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate

The title compound was prepared according to the procedure of Example 112, Step 2, using using *tert*-butyl (1*S*,4*S*)-5-[(5-nitro-1-benzofuran-7-yl)methyl]-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (116 mg, 0.31 mmol; obtained in Step 1). The title compound (133 mg) was obtained as a light green solid.. This material was used in the next step without further purification. HPLC 99%, R_T =1.69 min (System A; 5-60% MeCN over 3 min), 100%, R_T =1.45 min (System B; 5-60% MeCN over 3 min). MS (ESI+) for $C_{19}H_{25}N_3O_3$ m/z 344 (M+H)⁺.

Step 3: *N*-{7-[(1*S*,4*S*)-2,5-Diazabicyclo[2.2.1]hept-2-ylmethyl]-1-benzofuran-5-yl}-2-methoxy-5-methylbenzenesulfonamide, dihydrochloride

The title compound was prepared according to the procedure of Example 112, Step 3, starting from *tert*-butyl (1*S*,4*S*)-5-[(5-amino-1-benzofuran-7-yl)methyl]-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (44 mg crude starting material, 0.10 mmol; obtained in Step 2) and 6-methoxy-*m*-toluenesulfonyl chloride (34 mg, 0.15 mmol). The title compound (11 mg, 20%) was obtained as an off-white solid. HPLC 100%, R_T =1.39 min (System A; 10-97% MeCN over 3 min), 100%, R_T =1.24 min (System B; 10-97% MeCN over 3 min). ¹H NMR (400 MHz, methanol-*d*₄) δ ppm 2.20 (s, 3 H) 2.28 - 2.34 (m, J =12.80 Hz, 1 H) 2.61 - 2.70 (m, 1 H) 3.52 - 3.58 (m, J =13.80, 2.76 Hz, 1 H) 3.64 - 3.72 (m, J =13.30, 2.51 Hz, 1 H) 3.85 - 3.93 (m, 1 H) 3.98 (s, 3 H) 4.48 (s, 1 H) 4.65 (s, 1 H) 4.70 - 4.76 (m, 1 H) 4.77 - 4.82 (m, 2 H) 6.87 (d, J =2.01 Hz, 1 H) 7.04 (d, J =8.53 Hz, 1 H) 7.30 - 7.34 (m, J =8.53, 2.26 Hz, 1 H) 7.41 (d, J =2.26 Hz, 1 H) 7.50 (d, J =2.01 Hz, 1 H) 7.51 - 7.53 (m, J =2.26 Hz, 1 H) 7.85 (d, J =2.26 Hz, 1 H). MS (ESI+) for $C_{22}H_{25}N_3O_4S$ m/z 428 (M+H)⁺.

EXAMPLE 119

***N*-{7-[(1*S*,4*S*)-2,5-Diazabicyclo[2.2.1]hept-2-ylmethyl]-1-benzofuran-5-yl}-2-(trifluoromethyl)benzenesulfonamide, dihydrochloride**

The title compound was prepared according to the procedure of Example 112, Step 3, starting from *tert*-butyl (1*S*,4*S*)-5-[(5-amino-1-benzofuran-7-yl)methyl]-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (44 mg crude starting material, 0.10 mmol; obtained in Example 118, Step 2) and 2-(trifluoromethyl)benzenesulfonyl chloride (24 μ L, 0.15 mmol). The title compound (18 mg, 34%) was obtained as an off-white solid. HPLC 99%, R_T =1.46 min (System A; 10-97% MeCN over 3 min), 100%, R_T =1.29 min (System

B; 10-97% MeCN over 3 min). ¹H NMR (400 MHz, methanol-*d*₄) δ ppm 2.31 - 2.37 (m, *J*=13.05 Hz, 1 H) 2.65 - 2.78 (m, *J*=6.27 Hz, 1 H) 3.53 - 3.60 (m, *J*=13.43, 2.89 Hz, 1 H) 3.67 - 3.76 (m, 1 H) 3.88 - 3.96 (m, *J*=12.80 Hz, 1 H) 4.51 (s, 1 H) 4.66 (s, 1 H) 4.72 - 4.79 (m, 1 H) 4.84 (d, 2 H) 6.88 (d, *J*=2.01 Hz, 1 H) 7.46 (d, *J*=2.01 Hz, 1 H) 7.51 (d, *J*=2.01 Hz, 1 H) 7.68 - 7.75 (m, 2 H) 7.88 (d, *J*=2.26 Hz, 1 H) 7.89 - 7.94 (m, 1 H) 8.09 - 8.13 (m, 1 H). MS (ESI+) for C₂₁H₂₀F₃N₃O₃S *m/z* 452 (M+H)⁺.

EXAMPLE 120

***N*-{7-[(1*S*,4*S*)-2,5-Diazabicyclo[2.2.1]hept-2-ylmethyl]-1-benzofuran-5-yl}-2-methylbenzenesulfonamide, dihydrochloride**

The title compound was prepared according to the procedure of Example 112, Step 3, starting from *tert*-butyl (1*S*,4*S*)-5-[(5-amino-1-benzofuran-7-yl)methyl]-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (44 mg crude starting material, 0.10 mmol; obtained in Example 118, Step 2) and *o*-toluenesulfonyl chloride (22 μL, 0.15 mmol). The title compound (15 mg, 31%) was obtained as an off-white solid. HPLC 98%, *R*_T=1.37 min (System A; 10-97% MeCN over 3 min), 97%, *R*_T=1.21 min (System B; 10-97% MeCN over 3 min). ¹H NMR (400 MHz, methanol-*d*₄) δ ppm 2.28 - 2.34 (m, 1 H) 2.66 (s, 3 H) 2.67 - 2.72 (m, 1 H) 3.52 - 3.59 (m, *J*=13.68, 2.64 Hz, 1 H) 3.63 - 3.76 (m, 1 H) 3.85 - 3.93 (m, *J*=12.80 Hz, 1 H) 4.45 - 4.51 (m, 1 H) 4.65 (s, 1 H) 4.69 - 4.78 (m, 1 H) 4.78 - 4.83 (m, 2 H) 6.86 (d, *J*=2.26 Hz, 1 H) 7.23 - 7.29 (m, 1 H) 7.31 - 7.36 (m, *J*=7.53 Hz, 1 H) 7.37 - 7.46 (m, 2 H) 7.48 (d, *J*=2.26 Hz, 1 H) 7.84 - 7.88 (m, 2 H). MS (ESI+) for C₂₁H₂₃N₃O₃S *m/z* 398 (M+H)⁺.

EXAMPLE 121

2-Methoxy-5-methyl-*N*-{7-[(*trans*-2,5-dimethylpiperazin-1-yl)methyl]-1-benzofuran-5-yl}benzenesulfonamide, bis(trifluoroacetate)

Step 1: *trans*-2,5-Dimethyl-1-[(5-nitro-1-benzofuran-7-yl)methyl]piperazine

The title compound was prepared according to the procedure of Example 112, Step 1, starting from 7-(bromomethyl)-5-nitro-1-benzofuran (0.16 g, 0.6 mmol) and *trans*-2,5-dimethylpiperazine (0.36 g, 3.1 mmol). This afforded the title product (0.11 g, 60%) as a light yellow solid. HPLC 98% *R*_T=1.26 min (System A; 10-97% MeCN over 3 min). ¹H NMR (400 MHz, CDCl₃) δ ppm 0.93 (d, *J*=6.3 Hz, 3 H) 1.17 (d, *J*=6.0 Hz, 3 H) 1.48 (br s, 1H) 1.79 (dd, *J*=11.0, 10.3 Hz, 1 H) 2.29 - 2.41 (m, 1 H) 2.63 - 2.75 (m, 2 H) 2.80 - 2.89 (m, 1 H) 2.93 (dd, *J*=12.0, 3.3 Hz, 1 H) 3.61 (d, *J*=14.6 Hz, 1 H) 4.28 (d, *J*=14.3 Hz, 1 H)

6.91 (d, $J=2.3$ Hz, 1 H) 7.76 (d, $J=2.3$ Hz, 1 H) 8.29 (d, $J=2.3$ Hz, 1 H) 8.41 (d, $J=2.3$ Hz, 1 H). MS (ESI+) m/z 290.1 (M+H)⁺.

Step 2: *tert*-Butyl *trans*-2,5-dimethyl-4-[(5-nitro-1-benzofuran-7-yl)methyl]piperazine-

5 1-carboxylate

trans-2,5-Dimethyl-1-[(5-nitro-1-benzofuran-7-yl)methyl]piperazine (0.11 g, 0.4 mmol; obtained in Step 1) was dissolved in MeOH. Boc-anhydride (0.114 g, 0.5 mmol) was added and the reaction was stirred at ambient temperature overnight. The solvent was evaporated and the residue was dissolved in DCM and washed with citric acid. The organic layer was
10 dried (MgSO₄) and evaporated to give 0.135 g (91%) of the title product. HPLC 96% $R_t=1.79$ min (System A; 10-97% MeCN over 3 min). ¹H NMR (400 MHz, CDCl₃) δ ppm 1.07 (d, $J=6.5$ Hz, 3 H) 1.27 (d, $J=6.8$ Hz, 3 H) 1.46 (s, 9 H) 2.18 - 2.27 (m, 1 H) 2.82 (dd, $J=11.5, 4.3$ Hz, 1 H) 2.98 - 3.06 (m, 1 H) 3.37 (dd, $J=13.1, 3.5$ Hz, 1 H) 3.65 - 3.75 (d, $J=13.1$ Hz, 1 H) 3.83 - 3.95 (m, 2 H) 4.16 - 4.27 (m, 1 H) 6.91 (d, $J=2.3$ Hz, 1 H) 7.76 (d, $J=2.3$ Hz, 1 H) 8.25 - 8.55 (m, 2 H). MS (ESI+) m/z 390.2 (M+H)⁺.
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Step 3: *tert*-Butyl *trans*-4-[(5-amino-1-benzofuran-7-yl)methyl]-2,5-dimethylpiperazine-1-carboxylate

tert-Butyl *trans*-2,5-dimethyl-4-[(5-nitro-1-benzofuran-7-yl)methyl]piperazine-1-carboxylate (0.14 g, 0.35 mmol; obtained in Step 2) was dissolved in THF/EtOH (4:1; 5
25 mL). Excess Raney-Ni (slurry in EtOH) was added followed by hydrazine hydrate (0.07 g, 1.39 mmol). The reaction mixture was stirred overnight at ambient temperature. After filtration and evaporation of solvent, a crude oil (0.11 g, 87%) was obtained that was used in the next step without further purification. HPLC 86% $R_t=1.15$ min (System B; 10-97%
30 MeCN over 3 min). MS (ESI+) m/z 360.2 (M+H)⁺.

Step 4: *tert*-Butyl *trans*-4-[(5-{[(2-methoxy-5-methylphenyl)sulfonyl]amino}-1-benzofuran-7-yl)methyl]-2,5-dimethylpiperazine-1-carboxylate

tert-Butyl *trans*-4-[(5-amino-1-benzofuran-7-yl)methyl]-2,5-dimethylpiperazine-1-carboxylate (0.037 g, 0.1 mmol; obtained in Step 3) was dissolved in DCM and reacted
35 with 2-methoxy-5-methylbenzenesulfonyl chloride (0.045 g, 0.2 mmol) and pyridine

(0.024 g, 0.3 mmol) overnight. The mixture was washed with 1 M HCl and the organic layer was dried (MgSO₄) and evaporated. The crude was purified using flashtube (10% MeOH in DCM) and afforded the title product (0.026 g, 48%). HPLC 93% R_T=2.01 min (System A; 10-97% MeCN over 3 min), 93% R_T=1.85 min (System B; 10-97% MeCN over 3 min). MS (ESI+) *m/z* 544.2 (M+H)⁺.

Step 5: 2-Methoxy-5-methyl-N-{7-[(*trans*-2,5-dimethylpiperazin-1-yl)methyl]-1-benzofuran-5-yl}benzenesulfonamide, bis(trifluoroacetate)

A solution of *tert*-butyl *trans*-4-[(5-{[(2-methoxy-5-methylphenyl)sulfonyl]amino}-1-benzofuran-7-yl)methyl]-2,5-dimethylpiperazine-1-carboxylate (0.026 g, 0.047 mmol; obtained in Step 4) in TFA:water (9:1) was stirred at ambient temperature for 1 h. The solvent was evaporated and the residue was purified by preparative HPLC (System A; 20-40% MeCN). Pure fractions were combined and concentrated to give the title compound as a colorless TFA-salt (0.020 mg, 63%). HPLC 100%, R_T=1.52 min (System A; 10-97% MeCN over 3 min), 100%, R_T=1.25 min (System B; 10-97% MeCN over 3 min). ¹H NMR (400 MHz, methanol-*d*₄) δ ppm 1.24 (d, *J*=6.53 Hz, 3 H) 1.48 (d, *J*=6.27 Hz, 3 H) 2.20 (s, 3 H) 2.61 (dd, *J*=13.30, 11.54 Hz, 1 H) 3.05 - 3.23 (m, 3 H) 3.39 - 3.47 (m, 1 H) 3.50 (dd, *J*=12.92, 2.64 Hz, 1 H) 3.97 (s, 3 H) 4.07 (d, *J*=13.80 Hz, 1 H) 4.60 (d, *J*=13.80 Hz, 1 H) 6.80 (d, *J*=2.26 Hz, 1 H) 7.03 (d, *J*=8.53 Hz, 1 H) 7.24 (d, *J*=2.01 Hz, 1 H) 7.29 - 7.33 (m, *J*=8.78, 2.01 Hz, 1 H) 7.35 (d, *J*=2.01 Hz, 1 H) 7.48 - 7.51 (m, *J*=1.51 Hz, 1 H) 7.76 (d, *J*=2.01 Hz, 1 H). MS (ESI+) for C₂₃H₂₉N₃O₄S *m/z* 444 (M+H)⁺.

EXAMPLE 122

2-Methyl-N-{7-[(*trans*-2,5-dimethylpiperazin-1-yl)methyl]-1-benzofuran-5-yl}benzenesulfonamide, bis(trifluoroacetate)

Step 1: *tert*-Butyl *trans*-2,5-dimethyl-4-[(5-{[(2-methylphenyl)sulfonyl]amino}-1-benzofuran-7-yl)methyl]piperazine-1-carboxylate

The title product was prepared according to the procedure of Example 121, Step 4, starting from *tert*-butyl *trans*-4-[(5-amino-1-benzofuran-7-yl)methyl]-2,5-dimethylpiperazine-1-carboxylate (obtained in Example 121, Step 3) and 2-methylbenzenesulfonyl chloride (0.039 g, 0.2 mmol). Yield: 0.022 g (43%). HPLC 95% R_T=1.99 min (System A; 10-97% MeCN over 3 min), 93% R_T=1.85 min (System B; 10-97% MeCN over 3 min). MS (ESI+) *m/z* 514.2(M+H)⁺.

Step 2: 2-Methyl-N-{7-[(*trans*-2,5-dimethylpiperazin-1-yl)methyl]-1-benzofuran-5-yl}benzenesulfonamide, bis(trifluoroacetate)

The title product was prepared according to the procedure of Example 121, Step 5, starting from *tert*-butyl *trans*-2,5-dimethyl-4-[(5-{[(2-methylphenyl)sulfonyl]amino}-1-

- 5 benzofuran-7-yl)methyl]piperazine-1-carboxylate (0.022 g, 0.043 mmol; obtained in Step 1). Yield: 0.017 g (62%). HPLC 100%, R_T =1.49 min (System A; 10-97% MeCN over 3 min), 100%, R_T =1.22 min (System B; 10-97% MeCN over 3 min). ^1H NMR (400 MHz, methanol- d_4) δ ppm 1.20 - 1.27 (m, 3 H) 1.43 - 1.51 (m, 3 H) 2.51 - 2.65 (m, 1 H) 2.63 (s, 3 H) 3.02 - 3.25 (m, 3 H) 3.38 - 3.45 (m, 1 H) 3.45 - 3.53 (m, 1 H) 4.00 - 4.11 (m, 1 H)
10 4.53 - 4.64 (m, 1 H) 6.79 (d, J =2.26 Hz, 1 H) 7.15 - 7.35 (m, 4 H) 7.40 - 7.46 (m, 1 H) 7.75 - 7.80 (m, 1 H) 7.82 - 7.87 (m, J =8.03, 1.25 Hz, 1 H). MS (ESI+) for $\text{C}_{22}\text{H}_{27}\text{N}_3\text{O}_3\text{S}$ m/z 414 (M+H) $^+$.

EXAMPLE 123

- 15 **2-Chloro-N-{7-[(*trans*-2,5-dimethylpiperazin-1-yl)methyl]-1-benzofuran-5-yl}benzenesulfonamide, bis(trifluoroacetate)**

Step 1: *tert*-Butyl *trans*-4-[(5-{[(2-chlorophenyl)sulfonyl]amino}-1-benzofuran-7-yl)methyl]-2,5-dimethylpiperazine-1-carboxylate

- The title product was prepared according to the procedure of Example 121, Step 4, starting
20 from *tert*-butyl *trans*-4-[(5-amino-1-benzofuran-7-yl)methyl]-2,5-dimethylpiperazine-1-carboxylate (obtained in Example 121, Step 3) and 2-chlorobenzenesulfonyl chloride (0.043 g, 0.2 mmol). Yield: 0.017 g (26%). HPLC 94% R_T =2.01 min (System A; 10-97% MeCN over 3 min), 98% R_T =1.85 min (System B; 10-97% MeCN over 3 min). MS (ESI+) m/z 534.2 (M+H) $^+$.

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Step 2: 2-Chloro-N-{7-[(*trans*-2,5-dimethylpiperazin-1-yl)methyl]-1-benzofuran-5-yl}benzenesulfonamide, bis(trifluoroacetate)

- The title compound was prepared according to the procedure of Example 121, Step 5, starting from *tert*-butyl *trans*-4-[(5-{[(2-chlorophenyl)sulfonyl]amino}-1-benzofuran-7-yl)methyl]-2,5-dimethylpiperazine-1-carboxylate (0.017 g, 0.032 mmol; obtained in Step
30 1). Yield: 0.016 g (76%). HPLC 99%, R_T =1.47 min (System A; 10-97% MeCN over 3 min), 100%, R_T =1.20 min (System B; 10-97% MeCN over 3 min). ^1H NMR (400 MHz, methanol- d_4) δ ppm 1.23 (d, J =6.53 Hz, 3 H) 1.43 (d, J =5.77 Hz, 3 H) 2.48 (dd, J =13.18, 11.42 Hz, 1 H) 3.00 - 3.06 (m, 2 H) 3.10 (dd, J =13.30, 3.26 Hz, 1 H) 3.34 - 3.42 (m, 1 H)

3.42 - 3.47 (m, 1 H) 3.96 (d, $J=14.05$ Hz, 1 H) 4.51 (d, $J=14.05$ Hz, 1 H) 6.79 (d, $J=2.01$ Hz, 1 H) 7.24 (d, $J=2.01$ Hz, 1 H) 7.33 - 7.39 (m, 2 H) 7.47 - 7.53 (m, 1 H) 7.53 - 7.57 (m, 1 H) 7.76 (d, $J=2.26$ Hz, 1 H) 7.94 - 7.99 (m, $J=7.78$, 1.51 Hz, 1 H). MS (ESI+) for $C_{21}H_{24}ClN_3O_3S$ m/z 434 (M+H)⁺.

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INTERMEDIATE 65

Methyl 2,3-dihydro-1-benzofuran-7-carboxylate

2,3-Dihydrobenzofuran-7-carboxylic acid (8 g, 48.7 mmol) was dissolved in methanol (39.6 mL, 975 mmol) and concentrated sulfuric acid (2.6 mL, 48.7 mmol) was slowly added. The mixture was refluxed at 80 °C for 17 h. The solvent was evaporated and the residue was dissolved in ethyl acetate and washed with brine. The organic layer was evaporated to give the title compound as a beige solid. Yield: 8.6 g (99%). HPLC purity 93%, $R_T=1.72$ min (System A; 10-97% MeCN over 3 min); 96%, $R_T=1.67$ min (System B; 10-97% MeCN over 3 min). MS (ESI+) for $C_{10}H_{10}O_3$ m/z 179 (M+H)⁺.

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INTERMEDIATE 66

Methyl 5-[(2-methoxy-5-methylphenyl)sulfonyl]-2,3-dihydro-1-benzofuran-7-carboxylate

To methyl 2,3-dihydro-1-benzofuran-7-carboxylate (1 g, 5.6 mmol; Intermediate 65) were 2-methoxy-5-methylbenzenesulfonic acid (1.13 g, 5.6 mmol) and phosphorus pentoxide-methanesulfonic acid solution (1:10; 13.5 mL) added. The mixture was stirred at room temperature for 48 h. Additional 2-methoxy-5-methylbenzenesulfonic acid (0.56 g, 2.8 mmol) was added and the reaction mixture was stirred at 50 °C for 15 h. The mixture was poured onto water/ice and the formed precipitate was filtrated off, dissolved in DCM and evaporated. The crude product was purified using flash chromatography (eluent: isohexane:EtOAc 1:1) yielding the title compound. Yield: 1.07 g (53%). MS (ESI+) for $C_{18}H_{18}O_6S$ m/z 363 (M+H)⁺.

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INTERMEDIATE 67

30 **Methyl 5-[(2-methoxy-5-methylphenyl)sulfonyl]-1-benzofuran-7-carboxylate**

Methyl 5-[(2-methoxy-5-methylphenyl)sulfonyl]-2,3-dihydro-1-benzofuran-7-carboxylate (879 mg, 2.4 mmol; Intermediate 66) was dissolved in chlorobenzene (6 mL). N-bromosuccinimide (432 mg, 2.4 mmol) and benzoyl peroxide (58 mg, 0.24 mmol) were added and the mixture was stirred at 100 °C for 17 h. The mixture was washed with

saturated aqueous NaHCO₃ and the organic layer was concentrated. Yield: 405 mg (46%) after purification by preparative HPLC (System F; 40-60% MeCN). MS (ESI+) for C₁₈H₁₆O₆S *m/z* 361 (M+H)⁺.

5 INTERMEDIATE 68

{5-[(2-Methoxy-5-methylphenyl)sulfonyl]-1-benzofuran-7-yl}methanol

Methyl 5-[(2-methoxy-5-methylphenyl)sulfonyl]-1-benzofuran-7-carboxylate (400 mg, 1.1 mmol; Intermediate 67) was dissolved in dry THF (3 mL) and 1 M lithium aluminiumhydride in THF (0.3 mL) was slowly added. The mixture was stirred at room
10 temperature overnight. After this time, water (0.15 mL) was added and stirring was continued for 10 min, followed by the addition of 2 M aqueous NaOH (0.15 mL) and water (0.45 mL). The precipitate formed was filtered off and the solvent was evaporated. The crude product was used in the next step without further purification. MS (ESI+) for C₁₇H₁₆O₅S *m/z* 333 (M+H)⁺.

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INTERMEDIATE 69

7-(Chloromethyl)-5-[(2-methoxy-5-methylphenyl)sulfonyl]-1-benzofuran

Oxalyl chloride (0.1 mL, 1.1 mmol) was dissolved in dry DCM (2 mL) and DMF (0.9 mL, 1.1 mmol) was added (very exothermic reaction). {5-[(2-Methoxy-5-
20 methylphenyl)sulfonyl]-1-benzofuran-7-yl}methanol (370 mg, 1.1 mmol; Intermediate 68) was added and the resultant mixture was stirred at room temperature for 17 h. The mixture was washed with 2 M NaOH (2x) and the organic layer was concentrated yielding the crude product. This material was used in the next step without further purification. MS (ESI+) for C₁₇H₁₅ClO₄S *m/z* 351 (M+H)⁺.

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EXAMPLE 124

1-({5-[(2-Methoxy-5-methylphenyl)sulfonyl]-1-benzofuran-7-yl}methyl)piperazine, trifluoroacetate

7-(Chloromethyl)-5-[(2-methoxy-5-methylphenyl)sulfonyl]-1-benzofuran (35 mg, 0.1 mmol; Intermediate 69) was dissolved in ethanol (2 mL) and N-t-Boc-piperazine (28 mg, 0.1 mmol) and sodium bicarbonate (13 mg, 0.1 mmol) were added. The mixture was heated at 80 °C in a StemBlock overnight. The mixture was extracted with chloroform (x2) and the chloroform-layers were evaporated. Purification was done by preparative HPLC/MS (System A; 10-40% MeCN). The obtained N-t-BOC derivative of the title
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compound was dissolved in DCM (1 mL) and TFA (1 mL) was added. After being stirred at room temperature overnight, the solvent was evaporated to provide the title compound. Yield: 11 mg (27%) after purification by preparative HPLC/MS (System A; 10-40% MeCN). HPLC purity 98%, $R_T=1.50$ min (System A; 10-97% MeCN over 3 min); 99%, $R_T=1.30$ min (System B; 10-90% MeCN over 3 min). ^1H NMR (400 MHz, CDCl_3) δ ppm 2.35 (s, 3 H) 3.26 - 3.46 (m, 8 H) 3.70 (s, 3 H) 4.34 (s, 2 H) 6.78 (d, $J=8.53$ Hz, 1 H) 6.90 (d, $J=2.01$ Hz, 1 H) 7.32 (dd, $J=8.41, 1.63$ Hz, 1 H) 7.75 (d, $J=1.25$ Hz, 1 H) 7.89 - 7.98 (m, 2 H) 8.30 (d, $J=1.25$ Hz, 1 H). MS (ESI+) for $\text{C}_{21}\text{H}_{24}\text{N}_2\text{O}_4\text{S}$ m/z 401 ($\text{M}+\text{H}$) $^+$.

10 EXAMPLE 125

1-{[5-(Phenylsulfonyl)-1-benzofuran-7-yl]methyl}piperazine, trifluoroacetate

Step 1: Methyl 5-(phenylsulfonyl)-2,3-dihydro-1-benzofuran-7-carboxylate

The title compound was prepared according to the procedure of Intermediate 66 starting from methyl 2,3-dihydro-1-benzofuran-7-carboxylate (1 g, 5.6 mmol; Intermediate 65) and benzenesulfonic acid (0.89 g, 5.6 mmol). Yield: 882 mg (49%). MS (ESI+) for $\text{C}_{16}\text{H}_{14}\text{O}_5\text{S}$ m/z 319 ($\text{M}+\text{H}$) $^+$.

Step 2: Methyl 5-(phenylsulfonyl)-1-benzofuran-7-carboxylate

The title compound was prepared according to the procedure of Intermediate 67 starting from methyl 5-(phenylsulfonyl)-2,3-dihydro-1-benzofuran-7-carboxylate (198 mg, 0.6 mmol; obtained in Step 1). Yield: 80 mg (41%) after purification by preparative HPLC (System F; 40-70% MeCN). MS (ESI+) for $\text{C}_{16}\text{H}_{14}\text{O}_5\text{S}$ m/z 317 ($\text{M}+\text{H}$) $^+$.

Step 3: [5-(Phenylsulfonyl)-1-benzofuran-7-yl]methanol

The title compound was prepared according to the procedure of Intermediate 68 starting from methyl 5-(phenylsulfonyl)-1-benzofuran-7-carboxylate (80 mg, 0.25 mmol; obtained in Step 2). The crude material was used directly in the subsequent reaction. MS (ESI+) for $\text{C}_{15}\text{H}_{12}\text{O}_4\text{S}$ m/z 289 ($\text{M}+\text{H}$) $^+$.

Step 4: 7-(Chloromethyl)-5-(phenylsulfonyl)-1-benzofuran

The title compound was prepared according to the procedure of Intermediate 69 starting from [5-(phenylsulfonyl)-1-benzofuran-7-yl]methanol (73 mg, 0.3 mmol; obtained in Step 3). The crude material was used directly in the subsequent reaction. MS (ESI+) for $\text{C}_{15}\text{H}_{11}\text{ClO}_3\text{S}$ m/z 307 ($\text{M}+\text{H}$) $^+$.

Step 5: 1-{{5-(Phenylsulfonyl)-1-benzofuran-7-yl}methyl}piperazine, trifluoroacetate

N-t-BOC-piperazine (24 mg, 0.13 mmol) and sodium bicarbonate (11 mg, 0.13 mmol) were added to a solution of 7-(chloromethyl)-5-(phenylsulfonyl)-1-benzofuran (26 mg, 0.08 mmol; obtained in Step 4) in ethanol (2 mL). The mixture was stirred at 80 °C in a STEM-block overnight and the solvent was evaporated. The obtained N-t-BOC derivative of the title compound was dissolved in DCM (1 mL) and TFA (1 mL) was added. After the mixture had been stirred at room temperature for 2 h, the solvent was evaporated to provide the title compound. Yield: 6.1 mg (12%) after purification by preparative HPLC/MS (System A; 10-40% MeCN). HPLC purity 99%, R_T =1.39 min (System A; 10-97% MeCN over 3 min); 96%, R_T =1.16 min (System B; 10-90% MeCN over 3 min). ^1H NMR (400 MHz, CDCl_3) δ ppm 3.10 - 3.17 (m, 4 H) 3.34 - 3.39 (m, 4 H) 4.20 (s, 2 H) 6.87 - 6.92 (m, 1 H) 7.46 - 7.58 (m, 3 H) 7.75 (d, J =2.26 Hz, 1 H) 7.92 - 7.97 (m, 3 H) 8.26 (d, J =1.76 Hz, 1 H). MS (ESI+) for $\text{C}_{19}\text{H}_{20}\text{N}_2\text{O}_3\text{S}$ m/z 357 ($\text{M}+\text{H}$) $^+$.

EXAMPLE 126**1-{{5-[(4-Methylphenyl)sulfonyl]-1-benzofuran-7-yl}methyl}piperazine, trifluoroacetate****Step 1: Methyl 5-[(4-methylphenyl) sulfonyl]-2,3-dihydro-1-benzofuran-7-carboxylate**

The title compound was prepared according to the procedure of Intermediate 66 starting from methyl 2,3-dihydro-1-benzofuran-7-carboxylate (1 g, 5.6 mmol; Intermediate 65) and 4-methylbenzenesulfonic acid (0.97 g, 5.6 mmol). Yield: 405 mg (22%). MS (ESI+) for $\text{C}_{17}\text{H}_{16}\text{O}_5\text{S}$ m/z 333 ($\text{M}+\text{H}$) $^+$.

Step 2: Methyl 5-[(4-methylphenyl)sulfonyl]-1-benzofuran-7-carboxylate

The title compound was prepared according to the procedure of Intermediate 67 starting from methyl 5-[(4-methylphenyl) sulfonyl]-2,3-dihydro-1-benzofuran-7-carboxylate (117 mg, 0.4 mmol; obtained in Step 1). Yield: 62 mg (53%) after purification by preparative HPLC (System F; 40-60% MeCN). MS (ESI+) for $\text{C}_{17}\text{H}_{16}\text{O}_5\text{S}$ m/z 331 ($\text{M}+\text{H}$) $^+$.

Step 3: {5-[(4-Methylphenyl)sulfonyl]-1-benzofuran-7-yl}methanol

The title compound was prepared according to the procedure of Intermediate 68 starting from methyl 5-[(4-methylphenyl)sulfonyl]-1-benzofuran-7-carboxylate (62 mg, 0.19 mmol; obtained in Step 2). MS (ESI+) for $\text{C}_{16}\text{H}_{14}\text{O}_4\text{S}$ m/z 303 ($\text{M}+\text{H}$) $^+$.

Step 4: 7-(Chloromethyl)-5-[(4-methylphenyl)sulfonyl]-1-benzofuran

The title compound was prepared according to the procedure of Intermediate 69 starting from {5-[(4-methylphenyl)sulfonyl]-1-benzofuran-7-yl}methanol (57 mg, 0.2 mmol; obtained in Step 3). MS (ESI+) for C₁₆H₁₃ClO₃S *m/z* 321 (M+H)⁺.

Step 5: 1-({5-[(4-Methylphenyl)sulfonyl]-1-benzofuran-7-yl}methyl)piperazine, trifluoroacetate

The title compound was prepared according to the procedure of Example 125, Step 5, starting from 7-(chloromethyl)-5-[(4-methylphenyl)sulfonyl]-1-benzofuran (20 mg, 0.06 mmol; obtained in Step 4). Yield: 5.8 mg (15%) after purification by preparative HPLC/MS (System A; 5-20% MeCN). HPLC purity 99%, R_T=1.52 min (System A; 10-97% MeCN over 3 min); 99%, R_T=1.28 min (System B; 10-90% MeCN over 3 min). ¹H NMR (400 MHz, CHLOROFORM-D) δ ppm 2.37 (s, 3 H) 3.33 - 3.37 (m, 4 H) 3.44 - 3.50 (m, 4 H) 4.37 (s, 2 H) 6.90 (d, *J*=2.26 Hz, 1 H) 7.28 (d, *J*=8.03 Hz, 2 H) 7.75 (d, *J*=2.26 Hz, 1 H) 7.81 (d, *J*=8.28 Hz, 2 H) 7.97 (d, *J*=1.51 Hz, 1 H) 8.26 (d, *J*=1.76 Hz, 1 H). MS (ESI+) for C₂₀H₂₂N₂O₃S *m/z* 371 (M+H)⁺.

EXAMPLE 127**1-({5-[(2-Methoxy-5-methylphenyl)sulfonyl]-1-benzofuran-7-yl}methyl)-1,4-diazepane, trifluoroacetate**

7-(Chloromethyl)-5-[(2-methoxy-5-methylphenyl)sulfonyl]-1-benzofuran (66 mg, 0.19 mmol; Intermediate 69) was dissolved in ethanol (2 mL) and 1-boc-homopiperazine (57 mg, 0.28 mmol) and sodium bicarbonate (24 mg, 0.28 mmol) were added. The mixture was heated to 80 °C in a StemBlock overnight. The mixture was extracted with chloroform (x2) and the chloroform-layers were evaporated. The obtained N-t-BOC derivative of the title compound was dissolved in DCM (1 mL) and TFA (1 mL) was added. After being stirred at room temperature for 2 h, the solvent evaporated to provide the title compound. Yield: 39 mg (32%) after purification by preparative HPLC/MS (System A; 10-40% MeCN). HPLC purity 99%, R_T=1.41 min (System A; 10-97% MeCN over 3 min); 99%, R_T=1.19 min (System B; 10-90% MeCN over 3 min). ¹H NMR (400 MHz, CDCl₃) δ ppm 2.16 (bs, 2 H) 2.24 (s, 3 H) 3.30 (bs, 2 H) 3.39 (bs, 2 H) 3.54 (bs, 2 H) 3.57 - 3.67 (m, 5 H) 4.50 (s,

2 H) 6.69 (d, $J=8.78$ Hz, 1 H) 6.81 (d, $J=1.76$ Hz, 1 H) 7.23 (d, $J=8.53$ Hz, 1 H) 7.66 (s, 1 H) 7.81 (s, 1 H) 7.94 (s, 1 H) 8.22 (s, 1 H). MS (ESI+) for $C_{22}H_{26}N_2O_4S$ m/z 415 (M+H)⁺.

EXAMPLE 128

5 1-{{5-(Phenylsulfonyl)-1-benzofuran-7-yl}methyl}-1,4-diazepane, trifluoroacetate

The title compound was prepared according to the procedure of Example 127 starting from 7-(chloromethyl)-5-(phenylsulfonyl)-1-benzofuran (37 mg, 0.12 mmol; obtained in Example 125, Step 4). Yield: 9.4 mg (13%) after purification by preparative HPLC/MS (System A; 10-40% MeCN). HPLC purity 99%, $R_T=1.29$ min (System A; 10-97% MeCN over 3 min); 99%, $R_T=1.16$ min (System B; 10-90% MeCN over 3 min). ¹H NMR (400 MHz, CDCl₃) δ ppm 2.28 - 2.35 (m, 2 H) 3.42 - 3.52 (m, 4 H) 3.65 - 3.77 (m, 4 H) 4.60 (s, 2 H) 6.93 (d, $J=2.26$ Hz, 1 H) 7.46 - 7.53 (m, 2 H) 7.53 - 7.59 (m, 1 H) 7.77 (d, $J=2.26$ Hz, 1 H) 7.92 - 7.97 (m, 2 H) 8.09 (d, $J=1.76$ Hz, 1 H) 8.32 (d, $J=1.76$ Hz, 1 H). MS (ESI+) for $C_{20}H_{22}N_2O_3S$ m/z 371 (M+H)⁺.

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EXAMPLE 129

1-{{5-[(4-Methylphenyl)sulfonyl]-1-benzofuran-7-yl}methyl}-1,4-diazepane, trifluoroacetate

The title compound was prepared according to the procedure of Example 127 starting from 7-(chloromethyl)-5-[(4-methylphenyl)sulfonyl]-1-benzofuran (32 mg, 0.10 mmol; obtained in Example 126, Step 4). Yield: 8.1 mg (13%) after purification by preparative HPLC/MS (System A; 10-40% MeCN). HPLC purity 99%, $R_T=1.42$ min (System A; 10-97% MeCN over 3 min); 99%, $R_T=2.94$ min (System B; 10-90% MeCN over 3 min). ¹H NMR (400 MHz, CDCl₃) δ ppm 2.31 (bs, 2 H) 2.37 (s, 3 H) 3.41 - 3.54 (m, 4 H) 3.66 - 3.79 (m, 4 H) 4.61 (s, 2 H) 6.91 (d, $J=2.26$ Hz, 1 H) 7.26 - 7.31 (m, 2 H) 7.75 (d, $J=2.26$ Hz, 1 H) 7.81 (d, $J=8.28$ Hz, 2 H) 8.07 (d, $J=1.51$ Hz, 1 H) 8.29 (d, $J=1.76$ Hz, 1 H). MS (ESI+) for $C_{21}H_{24}N_2O_3S$ m/z 385 (M+H)⁺.

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EXAMPLE 130

30 1-{{5-[(2-Methoxy-5-methylphenyl)sulfonyl]-1-benzofuran-7-yl}methyl}-2-methylpiperazine, trifluoroacetate

7-(Chloromethyl)-5-[(2-methoxy-5-methylphenyl)sulfonyl]-1-benzofuran (60 mg, 0.17 mmol; Intermediate 69) was dissolved in ethanol (2 mL) and tert-butyl 3-methylpiperazine-1-carboxylate (41 mg, 0.21 mmol) and sodium bicarbonate (22 mg, 0.26

mmol) were added. The resulting mixture was heated at 80 °C in a StemBlock overnight. The mixture was extracted with chloroform (x2) and the chloroform layers were concentrated. The obtained N-t-BOC derivative of the title compound was dissolved in DCM (1 mL) and TFA (1 mL) was added. After the mixture had been stirred at room temperature for 2 h, the solvent was evaporated. Yield: 33 mg (36%) after purification by preparative HPLC/MS (System A; 10-40% MeCN). HPLC purity 99%, R_T =1.55 min (System A; 10-97% MeCN over 3 min); 99%, R_T =1.37 min (System B; 10-97% MeCN over 3 min). ^1H NMR (400 MHz, CDCl_3) δ ppm 1.65 (d, J =6.27 Hz, 3 H) 2.34 (s, 3 H) 3.35 - 3.61 (m, 6 H) 3.68 (s, 3 H) 3.90 - 3.99 (m, 1 H) 4.46 (d, J =13.55 Hz, 1 H) 4.82 (d, J =13.55 Hz, 1 H) 6.77 (d, J =8.53 Hz, 1 H) 6.92 (d, J =2.26 Hz, 1 H) 7.32 (dd, J =8.53, 1.76 Hz, 1 H) 7.75 (d, J =2.26 Hz, 1 H) 7.87 (d, J =2.01 Hz, 1 H) 7.97 (d, J =1.25 Hz, 1 H) 8.34 (d, J =1.51 Hz, 1 H). MS (ESI+) for $\text{C}_{22}\text{H}_{26}\text{N}_2\text{O}_4\text{S}$ m/z 414 ($\text{M}+\text{H}$) $^+$.

EXAMPLE 131

1-({5-[(2-Methoxy-5-methylphenyl)sulfonyl]-1-benzofuran-7-yl}methyl)-3-methylpiperazine, trifluoroacetate
7-(Chloromethyl)-5-[(2-methoxy-5-methylphenyl)sulfonyl]-1-benzofuran (60 mg, 0.17 mmol; Intermediate 69) was dissolved in ethanol (2 mL) and 2-methylpiperazine (21 mg, 0.21 mmol) and sodium bicarbonate (22 mg, 0.26 mmol) were added. The mixture was heated at 80 °C in a StemBlock overnight. The mixture was extracted with chloroform (x2) and the chloroform layers were evaporated. The obtained N-t-BOC derivative of the title compound was dissolved in DCM (1 mL) and TFA (1 mL) was added. After the mixture had been stirred at room temperature for 2 h, the solvent was evaporated. Yield: 28 mg (31%) after purification by preparative HPLC/MS (System A; 10-40% MeCN). HPLC purity 99%, R_T =1.57 min (System A; 10-97% MeCN over 3 min); 99%, R_T =1.35 min (System B; 10-97% MeCN over 3 min). ^1H NMR (400 MHz, CDCl_3) δ ppm 0.80 - 0.90 (m, 2 H) 1.30 (d, J =6.27 Hz, 3 H) 2.35 (s, 3 H) 3.14 (t, J =12.05 Hz, 1 H) 3.27 - 3.45 (m, 4 H) 3.70 (s, 3 H) 4.40 (s, 2 H) 6.78 (d, J =8.53 Hz, 1 H) 6.91 (d, J =2.26 Hz, 1 H) 7.32 (dd, J =8.41, 1.88 Hz, 1 H) 7.76 (d, J =2.01 Hz, 1 H) 7.88 - 7.99 (m, 2 H) 8.32 (d, J =1.51 Hz, 1 H). MS (ESI+) for $\text{C}_{22}\text{H}_{26}\text{N}_2\text{O}_4\text{S}$ m/z 414 ($\text{M}+\text{H}$) $^+$.

INTERMEDIATE 70

(5-Bromo-1-benzofuran-7-yl)amine

Step 1: Ethyl 5-bromo-7-nitro-1-benzofuran-3-carboxylate

A mixture of 5-bromo-2-hydroxy-3-nitrobenzaldehyde (8.9 g, 36.2 mmol), diethyl bromomalonate (6.3 mL, 37.3 mmol) and potassium carbonate (4.6 g) in butanone (50 mL) was heated a reflux for 4 h. The mixture was cooled, filtered and evaporated to give the crude product which was recrystallized from ethanol. Yield: 6.6 g (58%) of a pale yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.29 (t, *J*=7.0 Hz, 3 H) 4.35 (q, *J*=7.1 Hz, 2 H) 7.83 (s, 1 H) 8.39 (d, *J*=2.0 Hz, 1 H) 8.43 (d, *J*=2.0 Hz, 1 H).

Step 2: 5-Bromo-7-nitro-1-benzofuran-3-carboxylic acid

Ethyl 5-bromo-7-nitro-1-benzofuran-3-carboxylate (5.5 g, 17.5 mmol; obtained in Step 1) was suspended in ethanol (20 mL). 2 M NaOH (20 mL) was added and the mixture was heated at reflux for 2 h. The ethanol was removed by evaporation and the remaining solution acidified with concentrated HCl (4 mL), diluted with water and the product collected by filtration, washed with water and dried in a vacuum oven. Yield: 4.65 g (93%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.43 (s, 1 H) 8.26 (d, *J*=1.8 Hz, 1 H) 8.34 (d, *J*=2.0 Hz, 1 H).

Step 3: 5-Bromo-7-nitro-1-benzofuran

5-Bromo-7-nitro-1-benzofuran-3-carboxylic acid (4.65 g, 16 mmol; obtained in Step 2) was suspended in quinoline (25 mL), 0.1 g CuO was added and the mixture heated to 190 °C for 30 minutes. The warm reaction mixture was diluted with hot toluene (100 mL), filtered and the filter cake washed with hot toluene (total 400 mL). The combined toluene extracts were washed with 1 M HCl (2x100 mL) and brine, evaporated and the solid product washed with hexane, collected by filtration and dried. Yield: 1.9 g (48%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.13 (d, *J*=2.3 Hz, 1 H) 8.20 (d, *J*=2.0 Hz, 1 H) 8.28 (d, *J*=2.3 Hz, 1 H) 8.32 (d, *J*=2.0 Hz, 1 H).

Step 4: (5-Bromo-1-benzofuran-7-yl)amine

A mixture of 5-bromo-7-nitro-1-benzofuran (1.9 g, 7.9 mmol; obtained in Step 3), iron powder (2.3 g) methanol (20 mL), 1,4-dioxane (20 mL) and ammonium chloride (2.3 g dissolved in 10 mL of water), was refluxed overnight. The warm mixture was filtered through wetted Celite, which was further washed with hot methanol and the solvents were evaporated. The crude product was dissolved in hot ethanol/water (100 mL) and then water

added so that product began to crystallize out. The product was collected by filtration, washed with water and dried in a vacuum oven. Yield: 1.1 g (65%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 5.63 (s, 2 H) 6.68 (d, *J*=2.0 Hz, 1 H) 6.81 (d, *J*=2.3 Hz, 1 H) 6.96 (d, *J*=2.0 Hz, 1 H) 7.92 (d, *J*=2.3 Hz, 1 H).

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EXAMPLE 132

2-Methoxy-5-methyl-N-[5-(piperazin-1-ylmethyl)-1-benzofuran-7-yl]benzenesulfonamide, bis(trifluoroacetate)**Step 1: N-(5-Bromo-1-benzofuran-7-yl)-2-methoxy-5-methylbenzenesulfonamide**

- 10 A mixture of (5-bromo-1-benzofuran-7-yl)amine (500 mg, 2.4 mmol; Intermediate 70, Step 4), pyridine (0.38 mL, 4.7 mmol) and 6-methoxy-*m*-toluenesulfonyl chloride (0.78 g, 3.5 mmol) in dry DCM (20 mL) was stirred at room temperature for 2.5 h. Additional 6-methoxy-*m*-toluenesulfonyl chloride (0.26 g, 1.2 mmol) was added with continuous stirring over night. The reaction mixture was diluted with DCM and extracted with water. The
- 15 organic layer was concentrated. The product precipitated from a mixture of DCM/isohexane/MeOH (80:20:20) and was collected by filtration to give the title compound 580 mg (61%) as a light brown solid. HPLC 94%, *R*_T=2.32 min (System A; 30-80% MeCN over 3 min). MS (ESI+) for C₁₆H₁₄BrNO₄S *m/z* 396 (monoisotop.mass+H)⁺.

20 **Step 2: 2-Methoxy-5-methyl-N-[5-(piperazin-1-ylmethyl)-1-benzofuran-7-yl]benzenesulfonamide, bis(trifluoroacetate)**

- Pd(PPh₃)₂OAc₂ (189 mg, 0.25 mmol) and vinyltributyltin (295 μL, 1.01 mmol) were added to *N*-(5-bromo-1-benzofuran-7-yl)-2-methoxy-5-methylbenzenesulfonamide (200 mg, 0.51 mmol; obtained in Step 1) in dry toluene under argon. The mixture was stirred at 110 °C
- 25 over weekend (62 h). The reaction mixture was filtered and concentrated. The crude mixture was stirred with isohexane for 10 min. The isohexane was decanted off and the residue was dried under reduced pressure. The alkene intermediate was dissolved in dioxane (6 mL) and lutidine (120 μL, 1.0 mmol). Osmium tetroxide (26 mg, 0.10 mmol) was added and a color change from light brown to dark brown/black was noticed. Sodium
- 30 periodate (432 mg, 2.02 mmol) in water (1.5 mL, warmed to dissolve) was added while stirring. A light brown precipitation was formed after 1 min. The mixture was stirred for 2 h, and partitioned between 2 M aqueous HCl and DCM. The organic layer was dried (Na₂SO₄), filtered and concentrated to give the crude aldehyde as a black solid. Half of the

material was suspended in dry THF (4 mL) and N-t-BOC-piperazine (50 mg, 0.27 mmol), acetic acid (140 μ L, 2.5 mmol) and sodium triacetoxyborohydride (104 mg, 0.49 mmol) were added. The reaction mixture was irradiated using microwaves, 300 s at 130 °C. The mixture was filtered, dissolved in MeOH (2 mL) and concentrated HCl (0.5 mL) and irradiated using microwaves, 300 s 100 °C. The solvent was evaporated, the residue dissolved in MeOH and purified by preparative HPLC (System A; 19-40% MeCN). Pure fractions were combined and concentrated to give the title compound (31 mg, 20%) as a brown gum. HPLC 100%, R_T =1.35 min (System A; 10-97% MeCN over 3 min), 99%, R_T =1.15 min (System B; 10-97% MeCN over 3 min). ^1H NMR (400 MHz, methanol- d_4) δ ppm 2.22 (s, 3 H) 3.30 - 3.36 (m, 4 H) 3.43 - 3.50 (m, 4 H) 3.81 (s, 3 H) 4.29 (s, 2 H) 6.82 (d, J =2.26 Hz, 1 H) 6.95 (d, J =8.53 Hz, 1 H) 7.28 - 7.33 (m, J =8.53, 2.26 Hz, 1 H) 7.43 (d, J =1.51 Hz, 1 H) 7.48 (d, J =1.51 Hz, 1 H) 7.56 - 7.59 (m, J =2.26 Hz, 1 H) 7.77 (d, J =2.26 Hz, 1 H). MS (ESI+) for $\text{C}_{21}\text{H}_{25}\text{N}_3\text{O}_4\text{S}$ m/z 416 ($\text{M}+\text{H}$) $^+$.

15 EXAMPLE 133

2-Methoxy-5-methyl-N-{5-[(3-methylpiperazin-1-yl)methyl]-1-benzofuran-7-yl}benzenesulfonamide, bis(trifluoroacetate)

The title compound was prepared according to the procedure of Example 132, Step 2, using 2-methylpiperazine (27 mg, 0.27 mmol). The title compound (18 mg, 11%) was obtained as a brown gum. HPLC 97%, R_T =1.38 min (System A; 10-97% MeCN over 3 min), 98%, R_T =1.18 min (System B; 10-97% MeCN over 3 min). ^1H NMR (400 MHz, methanol- d_4) δ ppm 1.33 (d, J =6.53 Hz, 3 H) 2.22 (s, 3 H) 2.82 (dd, J =13.18, 11.42 Hz, 1 H) 2.94 - 3.04 (m, 1 H) 3.31 - 3.44 (m, 2 H) 3.51 - 3.59 (m, 2 H) 3.79 - 3.87 (m, 1 H) 3.81 (s, 3 H) 4.18 (s, 2 H) 6.81 (d, J =2.01 Hz, 1 H) 6.95 (d, J =8.53 Hz, 1 H) 7.27 - 7.32 (m, J =8.53, 2.26 Hz, 1 H) 7.41 (d, J =1.76 Hz, 1 H) 7.45 (d, J =1.76 Hz, 1 H) 7.55 - 7.58 (m, J =1.51 Hz, 1 H) 7.75 (d, J =2.26 Hz, 1 H). MS (ESI+) for $\text{C}_{22}\text{H}_{27}\text{N}_3\text{O}_4\text{S}$ m/z 430 ($\text{M}+\text{H}$) $^+$.

EXAMPLE 134

30 N-(2-Methylphenyl)-7-[(3R)-pyrrolidin-3-ylamino]methyl-1-benzofuran-5-sulfonamide, trifluoroacetate

The title compound was prepared according to the procedure of Example 93 starting from 7-formyl-N-(2-methylphenyl)-1-benzofuran-5-sulfonamide (80 mg, 0.24 mmol; Intermediate 60) and (R)-(+)-3-aminopyrrolidine (50 mg, 0.6 mmol). [Note: no HCl deprotection step]. Yield: 17.8 mg (28%). HPLC 97% R_T =1.39 (System A; 10-97%

MeCN over 3 min) 98% $R_T=1.22$ (System B; 10-90% MeCN over 3 min). MS (ESI+) for $C_{20}H_{23}N_3O_3S$ m/z 386 (M+1). ^1H NMR (400 MHz, methanol- d_4) δ ppm 1.94 (s, 3 H) 2.02 - 2.12 (m, 1 H) 2.44 - 2.54 (m, 1 H) 3.24 - 3.31 (m, 1 H) 3.40 - 3.52 (m, 2 H) 3.72 (dd, $J=12.8, 8.3$ Hz, 1 H) 4.04 (tt, $J=8.3, 5.5$ Hz, 1 H) 4.68 (d, $J=2.5$ Hz, 2 H) 6.92 - 7.03 (m, 5 H) 7.73 (d, $J=1.5$ Hz, 1 H) 7.94 (d, $J=2.3$ Hz, 1 H) 8.08 (d, $J=1.8$ Hz, 1 H).

EXAMPLE 135

N-(2-Methylphenyl)-7-(piperidin-4-ylmethyl)-1-benzofuran-5-sulfonamide, trifluoroacetate

- 10 9-Borabicyclo[3.3.1]-nonane (9-BBN; 0.5 M in THF, 2.2 mL, 2.2 mmol) was added to a solution of 1-(4-methylidenepiperidino)ethan-1-one (Maybridge Chemical Company, 140 mg, 1 mmol) in dry THF (2 mL) under a nitrogen atmosphere at 0 °C. After stirring for 1 h at 0 °C, the solution was allowed to warm to room temperature for 3 h. Next, a microwave reaction tube was charged with 7-iodo-N-(2-methylphenyl)-1-benzofuran-5-sulfonamide
- 15 (40 mg, 0.1 mmol; Intermediate 58), Herrmann's catalyst (5 mg), dry THF (3 mL), 4 M aqueous NaOH (0.1 mL) and the above solution of in situ generated 1-[4-(9-borabicyclo[3.3.1]non-9-ylmethyl)-piperidin-1-yl]-ethanone (0.75 mL, 0.17 mmol). The mixture was heated under microwave irradiation to 140 °C for 5 minutes. This reaction mixture and three similar mixtures were combined, filtered and evaporated. The residue
- 20 was dissolved in DCM (20 mL) and washed with 1 M HCl. After evaporation of the solvent, the crude acetylated derivative of the title product was purified by preparative HPLC-MS (System A 30-60% MeCN 0.1% TFA). The purified material was N-deprotected by dissolving in methanol (3 mL), adding concentrated aqueous HCl (1 mL) and heating under microwave irradiation to 120 °C for 1 hour. The final product was
- 25 purified by preparative HPLC-MS (System A 30-60% MeCN 0.1% TFA) to give 5.9 mg (3%) of the title compound. HPLC 95% $R_T=1.75$ (System A; 10-97% MeCN over 3 min) 95% $R_T=1.58$ (System B; 10-90% MeCN over 3 min). MS (ESI+) for $C_{21}H_{24}N_2O_3S$ m/z 385 (M+1). ^1H NMR (400 MHz, methanol- d_4) δ ppm 1.26 - 1.38 (m, 2 H) 1.60 - 1.71 (m, $J=14.1$ Hz, 2 H) 1.87 (s, 2 H) 1.89 - 1.97 (m, 2 H) 2.76 - 2.85 (m, 4 H) 3.11 - 3.19 (m, 1 H)
- 30 3.26 - 3.30 (m, 2 H) 6.88 (d, $J=2.3$ Hz, 1 H) 6.96 - 7.03 (m, 4 H) 7.27 (d, $J=1.5$ Hz, 1 H) 7.83 (d, $J=2.3$ Hz, 1 H) 7.86 (d, $J=1.8$ Hz, 1 H).

INTERMEDIATE 71

tert*-Butyl 4-methylenepiperidine-1-carboxylate

To a solution of methyl triphenylphosphonium bromide (2.69 g, 7.5 mmol) in THF (20 mL) was *n*-butyllithium (1.8 M; 4.2 mL, 7.5 mmol) in hexane slowly added at -78°C . The mixture was stirred for 1 h. After this time, a solution of *tert*-butyl 4-oxopiperidine-1-carboxylate (1 g, 5.0 mmol) in THF (10 mL) was added dropwise to the mixture. The resultant mixture was stirred at room temperature overnight. The reaction mixture was quenched with water and extracted with isohexane (x3). The combined isohexane layers were evaporated and filtrated through a silica-plug. The crude product was purified using flash chromatography with DCM as eluent yielding 0.58 g (59%) of the title compound. HPLC purity 91%, $R_T=2.47$ min (System A; 10-97% MeCN over 3 min); 86%, $R_T=2.43$ min (System B; 10-97% MeCN over 3 min). ^1H NMR (400 MHz, CDCl_3) δ ppm 1.46 (s, 9 H) 2.12 - 2.22 (m, 4 H) 3.35 - 3.46 (m, 4 H) 4.73 (s, 2 H). MS (ESI+) for $\text{C}_{11}\text{H}_{19}\text{NO}_2$ m/z 142 ($\text{M}-\text{C}_4\text{H}_8$) $^+$.

*Previously reported in J. Med. Chem. 2002, 45, 3143-3160.

INTERMEDIATE 72

tert*-Butyl 3-methylenepyrrolidine-1-carboxylate

The title compound was prepared according to the procedure of Intermediate 71 starting from *tert*-butyl 3-oxopyrrolidine-1-carboxylate (0.8 g, 4.3 mmol), triphenylphosphonium bromide (2.31 g, 6.5 mmol) and *n*-BuLi (1.8 M; 2.4 mL, 6.5 mmol). Yield: 0.23 g (29%) after purification by flash chromatography with DCM as eluent. HPLC purity 99%, $R_T=2.28$ min (System A; 10-97% MeCN over 3 min); 99%, $R_T=2.21$ min (System B; 10-97% MeCN over 3 min). ^1H NMR (400 MHz, CDCl_3) δ ppm 1.23 - 1.40 (m, 9 H) 2.42 (t, $J=6.78$ Hz, 2 H) 3.31 (t, $J=7.40$ Hz, 2 H) 3.71 - 3.85 (m, 2 H) 4.74 - 4.91 (m, 2 H). MS (ESI+) for $\text{C}_{10}\text{H}_{17}\text{NO}_2$ m/z 128 ($\text{M}-\text{C}_4\text{H}_8$) $^+$.

*Previously reported in Tetrahedron 1997, 53, 539-556.

INTERMEDIATE 73

***tert*-Butyl 3-methylenepiperidine-1-carboxylate**

The title compound was prepared according to the procedure of Intermediate 71 starting from *tert*-butyl 3-oxopiperidine-1-carboxylate (1 g, 5.0 mmol), triphenylphosphonium bromide (2.69 g, 7.5 mmol) and *n*-BuLi (1.8 M; 4.2 mL, 7.5 mmol). Yield: 0.28 g (28%) after purification by flash chromatography with 10% isohexane in DCM as eluent. HPLC

purity 95%, $R_T=2.43$ min (System A; 10-97% MeCN over 3 min); 90%, $R_T=2.38$ min (System B; 10-97% MeCN over 3 min). ^1H NMR (400 MHz, CDCl_3) δ ppm 1.41 - 1.48 (m, 9 H) 1.56 - 1.65 (m, 2 H) 2.20 - 2.30 (m, 2 H) 3.38 - 3.47 (m, 2 H) 3.86 (s, 2 H) 4.74 (s, 1 H) 4.80 (s, 1 H). MS (ESI+) for $\text{C}_{11}\text{H}_{19}\text{NO}_2$ m/z 142 ($\text{M}-\text{C}_4\text{H}_8$)⁺.

5 *Previously reported in Tetrahedron 2002, 58, 7165-7175.

EXAMPLE 136

N-(2-Methylphenyl)-7-(pyrrolidin-3-ylmethyl)-1-benzofuran-5-sulfonamide, trifluoroacetate

10 9 BBN (0.5 M in THF; 1.5 mL, 0.75 mmol) was added to a solution of *tert*-butyl 3-methylenepyrrolidine-1-carboxylate (110 mg, 0.6 mmol; Intermediate 72) in dry THF (1 mL) under a nitrogen atmosphere at 0 °C. After stirring for 1 h at 0 °C, the solution was allowed to warm to room temperature for 3 h. A microwave reaction tube was charged with 7-iodo-*N*-(2-methylphenyl)-1-benzofuran-5-sulfonamide (90 mg, 0.2 mmol;

15 Intermediate 58), Herrmann's catalyst (10 mg), dry THF (2.5 mL), 4 M aqueous NaOH (0.2 mL) and half of the above solution of in situ generated 3-(9-borabicyclo[3.3.1]non-9-ylmethyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (1.1 mL, 0.3 mmol). The mixture was heated under microwave irradiation at 140 °C for 5 min. This reaction mixture and a similar mixture were combined, filtered and evaporated. The residue was dissolved in

20 methanol (3 mL), concentrated HCl (0.5 mL) was added and the mixture heated under microwave irradiation at 100 °C for 5 min to accomplish deprotection of the N-*t*-BOC group. Purification by preparative HPLC (System F 20-45% MeCN 0.1% TFA) provided 31 mg (13%) of the title compound. HPLC 98% $R_T=1.69$ (System A; 10-97% MeCN over 3 min) 98% $R_T=1.53$ (System B; 10-90% MeCN over 3 min). MS (ESI+) for

25 $\text{C}_{20}\text{H}_{22}\text{N}_2\text{O}_3\text{S}$ m/z 371 ($\text{M}+1$). ^1H NMR (400 MHz, methanol- d_4) δ ppm 1.57 (dq, $J=13.3$, 8.8 Hz, 1 H) 1.87 (s, 3 H) 1.88 - 1.95 (m, 1 H) 2.58 - 2.70 (m, 1 H) 2.81 (dd, $J=11.4$, 8.9 Hz, 1 H) 2.96 (ddd, $J=18.1$, 14.0, 7.5 Hz, 2 H) 3.10 - 3.21 (m, 2 H) 3.30 (ddd, $J=11.9$, 8.2, 4.3 Hz, 1 H) 6.89 (d, $J=2.3$ Hz, 1 H) 6.97 - 7.02 (m, 4 H) 7.32 (d, $J=1.8$ Hz, 1 H) 7.85 (d, $J=2.0$ Hz, 1 H) 7.87 (d, $J=1.8$ Hz, 1 H).

30

EXAMPLE 137

N-(2-Methylphenyl)-7-(piperidin-3-ylmethyl)-1-benzofuran-5-sulfonamide, trifluoroacetate

The title compound was prepared according to the procedure of Example 136 starting from from *tert*-butyl 3-methylenepiperidine-1-carboxylate (120 mg, 0.6 mmol; Intermediate 73) and 7-iodo-*N*-(2-methylphenyl)-1-benzofuran-5-sulfonamide (180 mg, 0.4 mmol; Intermediate 58). Yield: 40 mg (21%). HPLC 99% $R_T=1.74$ (System A; 10-97% MeCN

5 over 3 min) 100% $R_T=1.58$ (System B; 10-90% MeCN over 3 min). MS (ESI+) for $C_{21}H_{24}N_2O_3S$ m/z 385 (M+1). ^1H NMR (400 MHz, methanol- d_4) δ ppm 1.60 - 1.72 (m, 3 H) 1.85 - 1.95 (m, 2 H) 1.99 (s, 3 H) 2.15 - 2.26 (m, $J=11.3$, 7.6, 7.6, 3.8, 3.8 Hz, 1 H) 2.73 (t, $J=12.3$ Hz, 1 H) 2.86 - 2.97 (m, 3 H) 3.24 (dd, $J=12.5$, 3.5 Hz, 1 H) 3.34 - 3.37 (m, 1 H) 6.98 (d, $J=2.3$ Hz, 1 H) 7.05 - 7.09 (m, 2 H) 7.09 - 7.12 (m, 2 H) 7.41 (d, $J=1.8$ Hz, 1 H) 7.94 (d, $J=2.3$ Hz, 1 H) 7.96 (d, $J=1.8$ Hz, 1 H).

INTERMEDIATE 74

7-Iodo-1-benzofuran-5-amine

7-Iodo-5-nitro-1-benzofuran (2.5 g, 8.6 mmol) and iron (2.51 g, 45.0 mmol) were added to
15 a round bottom flask. Methanol (25 mL), 1,4-dioxane (25 mL) and ammonium chloride (2.5 g, 46.7 mmol), dissolved in water (50 mL), were added and the mixture was heated at 100 °C for 16 h. The reaction mixture was filtered through Celite and volatiles were evaporated off. The residue was dissolved in a mixture of methanol (10 mL) and DCM (90 mL). This mixture was filtered through a silica plug and the solvent was evaporated
20 yielding 2.22 g (99%) of the title compound as a brown oil. HPLC purity 70%, $R_T=1.26$ min (System A; 10-97% MeCN over 3 min). MS (ESI+) for C_8H_6INO m/z 260 (M+H) $^+$.

INTERMEDIATE 75

N-(7-Iodo-1-benzofuran-5-yl)-2-methoxy-5-methylbenzenesulfonamide

25 To a mixture of 7-iodo-1-benzofuran-5-amine (2.22 g, 8.6 mmol; Intermediate 74) in dry DCM/THF (5:1; 50 mL, starting material partly dissolved), were added pyridine (1.43 mL, 17.1 mmol) and 6-methoxy-*m*-toluenesulfonyl chloride (2.64 g, 12.8 mmol). The resultant mixture was stirred at ambient temperature overnight for 21 h. The solvent was evaporated under reduced pressure and the crude product was purified using flash chromatography
30 (eluent: 20% isohexane in DCM). Pure fractions were combined and concentrated to give the product (1.62 g, 42%) as a light brown fluffy solid. HPLC 81%, $R_T=2.26$ min (System A; 30-80% MeCN over 3 min), 86%, $R_T=2.27$ min (System B; 10-97% MeCN over 3 min). ^1H NMR (400 MHz, $CDCl_3$) δ ppm 2.22 (s, 3 H) 4.04 (s, 3 H) 6.77 (d, $J=2.01$ Hz, 1 H)

6.92 (d, $J=8.28$ Hz, 1 H) 7.25 - 7.29 (m, 1 H) 7.32 (d, $J=2.01$ Hz, 1 H) 7.36 (d, $J=2.01$ Hz, 1 H) 7.53 - 7.55 (m, $J=2.26$ Hz, 1 H) 7.62 (d, $J=2.26$ Hz, 1 H). MS (ESI+) for $C_{16}H_{14}INO_4$ m/z 444 (M+H)⁺.

5 **EXAMPLE 138**

2-Methoxy-5-methyl-N-[7-(piperidin-4-ylmethyl)-1-benzofuran-5-yl]benzenesulfonamide, trifluoroacetate

The title compound was prepared according to the procedure of Example 136 starting from *tert*-butyl 4-methylenepiperidine-1-carboxylate (120 mg, 0.6 mmol; Intermediate 71) and
10 *N*-(7-iodo-1-benzofuran-5-yl)-2-methoxy-5-methylbenzenesulfonamide (180 mg, 0.42 mmol; Intermediate 75). Yield: 69 mg (33%). HPLC 96% $R_T=1.75$ (System A; 10-97% MeCN over 3 min) 99% $R_T=1.58$ (System B; 10-90% MeCN over 3 min). MS (ESI+) for $C_{22}H_{26}N_2O_4S$ m/z 415 (M+1). ¹H NMR (400 MHz, methanol-*d*₄) δ ppm 1.22 - 1.34 (m, 2 H) 1.61 (d, $J=13.6$ Hz, 2 H) 1.80 - 1.91 (m, $J=11.3, 7.6, 7.6, 3.6, 3.6$ Hz, 1 H) 2.10 (s, 3 H)
15 2.69 (d, $J=7.3$ Hz, 2 H) 2.78 (td, $J=12.9, 2.6$ Hz, 2 H) 3.24 (d, $J=2.0$ Hz, 2 H) 3.87 (s, 3 H) 6.62 (d, $J=2.3$ Hz, 1 H) 6.79 (d, $J=2.0$ Hz, 1 H) 6.93 (d, $J=8.5$ Hz, 1 H) 7.10 (d, $J=2.0$ Hz, 1 H) 7.21 (dd, 1 H) 7.38 (d, $J=2.0$ Hz, 1 H) 7.58 (d, $J=2.3$ Hz, 1 H).

INTERMEDIATE 76

20 **2-(2,6-Dibromophenoxy)ethyl bromide***

A mixture of 2,6-dibromophenol (10.2 g, 40 mmol), 1,2-dibromoethane (7.6 g, 40 mmol) and NaOH (1.76 g, 44 mmol) in water was heated at reflux overnight under stirring. The mixture was cooled, extracted with diethyl ether (2x100 mL), the extract washed with aqueous NaOH, brine, dried (MgSO₄) and concentrated to give the product as a pale
25 yellow oil. Yield: 10.0 g (70 %). ¹H NMR (400 MHz, CDCl₃) δ 3.73 (t, 2 H), 4.31 (t, 2 H), 6.88 (t, 1 H), 7.50 (d, 2 H).

*Previously reported in Tetrahedron Lett. 1998, 39, 2219-2222.

INTERMEDIATE 77

30 **7-Bromo-2,3-dihydrobenzofuran***

A solution of 2-(2,6-dibromophenoxy)ethyl bromide (1.08 g, 3 mmol; Intermediate 76) in a mixture of THF (12 mL) and hexane (3 mL) was cooled in a ethanol/dry ice bath for 30 min. *n*-BuLi in hexane (2 mL of 1.5 M solution) was added dropwise over 15 min. The

reaction mixture was stirred at -78°C for another 30 min after which time the bath was allowed to slowly warm to 0°C . The mixture was poured onto water and extracted with diethyl ether (2x100 mL). The combined extract was dried and concentrated to give a pale brown oil (0.5 g) containing the product contaminated with approximately 25 % 2,3-dihydrobenzofuran. This material was used as such for further synthesis but could if necessary be purified by flash chromatography [eluent: hexane $\rightarrow$ EtOAc/hexane (5:95)]. ^1H NMR (400 MHz, CDCl_3) δ 3.30 (t, 2 H), 4.65 (t, 2 H), 6.71 (t, 1 H), 7.11 (dd, 1 H), 7.25 (dd, 1 H).

*Previously reported in Tetrahedron Lett. 1998, 39, 2219-2222.

10

INTERMEDIATE 78

7-Bromo-5-[(4-methylphenyl)sulfonyl]-2,3-dihydro-1-benzofuran

7-Bromo-1,2-dihydrobenzofuran (64 mg, 0.3 mmol; Intermediate 77) and para-toluensulfonic acid monohydrate (62 mg, 0.3 mmol) were mixed and then a 1:10 mixture (by weight) of methanesulfonic and phosphorous pentoxide (1 mL) was added. The resultant mixture was stirred over night at room temperature and was then poured onto ice/water. The obtained crystalline material was filtered and dried to give 120 mg of the title product. ^1H NMR (400 MHz, CDCl_3) δ 2.40 (s, 3 H), 3.33 (t, 2 H), 4.73 (t, 2 H), 7.29 (d, 2 H), 7.65 (d, 1 H), 7.79 (d, 2 H), 7.89 (d, 1 H); GC-MS (EI+) for $\text{C}_{15}\text{H}_{13}\text{BrSO}_3$ m/z 354 (M+H) $^+$.

20

INTERMEDIATE 79

7-Bromo-5-[(4-methylphenyl)sulfonyl]-1-benzofuran

A mixture of 7-bromo-5-[(4-methylphenyl)sulfonyl]-2,3-dihydro-1-benzofuran (353 mg, 1 mmol; Intermediate 78), NBS (178 mg, 1 mmol) and dibenzoylperoxide (24 mg, 0.1 mmol) in carbon tetrachloride (20 mL) was heated to 80°C for 2 h. TEA (2 mL) was added and the mixture was heated for another 2 h. Flash chromatography using EtOAc/hexane 10:90 $\rightarrow$ 25:75 as eluent gave the title product as a white crystalline material. Yield: 130 mg (37%). ^1H NMR (400 MHz, CDCl_3) δ 2.39 (s, 3 H), 6.93 (d, 1 H), 7.30 (d, 2 H), 7.78 (d, 1 H), 7.84 (d, 2 H), 8.02 (d, 1 H), 8.19 (d, 1 H).

30

EXAMPLE 139

**3-({5-[(4-Methylphenyl)sulfonyl]-1-benzofuran-7-yl}methyl)pyrrolidine,
trifluoroacetate**

The title compound was prepared according to the procedure of Example 136 starting from *tert*-butyl 3-methylenepiperidine-1-carboxylate (60 mg, 0.3 mmol; Intermediate 73) and 7-bromo-5-[(4-methylphenyl)sulfonyl]-1-benzofuran (70 mg, 0.21 mmol; Intermediate 79). Yield: 3 mg (3%). HPLC 97% $R_T=1.79$ (System A; 10-97% MeCN over 3 min) 97% $R_T=1.61$ (System B; 10-90% MeCN over 3 min). MS (ESI+) for $C_{21}H_{23}NO_3S$ m/z 356 (M+1).

10 **EXAMPLE 140**

2-Methoxy-5-methyl-N-[5-(piperidin-4-ylmethyl)-1-benzofuran-7-yl]benzenesulfonamide, trifluoroacetate

The title compound was prepared according to the procedure of Example 136 starting from *tert*-butyl 4-methylenepiperidine-1-carboxylate (120 mg, 0.6 mmol; Intermediate 71) and *N*-(5-bromo-1-benzofuran-7-yl)-2-methoxy-5-methylbenzenesulfonamide (150 mg, 0.42 mmol; obtained in Example 132, Step 1). Yield: 27 mg (12%). HPLC 97% $R_T=1.68$ (System A; 10-97% MeCN over 3 min) 97% $R_T=1.52$ (System B; 10-90% MeCN over 3 min). MS (ESI+) for $C_{22}H_{26}N_2O_4S$ m/z 415 (M+1). ^1H NMR (400 MHz, methanol- d_4) δ ppm 1.22 - 1.33 (m, 2 H) 1.62 - 1.73 (m, 3 H) 2.13 (s, 3 H) 2.51 (d, $J=7.0$ Hz, 2 H) 2.80 (td, $J=12.7, 2.4$ Hz, 2 H) 3.24 - 3.28 (m, 2 H) 3.77 (s, 3 H) 6.63 (d, $J=2.0$ Hz, 1 H) 6.87 (d, $J=8.5$ Hz, 1 H) 6.98 (d, $J=1.5$ Hz, 1 H) 7.05 (d, $J=1.5$ Hz, 1 H) 7.21 (dd, $J=8.2, 1.9$ Hz, 1 H) 7.46 (d, $J=2.3$ Hz, 1 H) 7.59 (d, $J=2.3$ Hz, 1 H).

25 **BIOLOGICAL TESTS**

The ability of a compound according to the invention to bind to the human 5-HT₆ receptor, and to be pharmaceutically useful, can be determined using *in vivo* and *in vitro* assays known in the art.

30

(a) 5-HT₆ binding Assay

Binding affinity experiment for the 5-HT₆ receptor are performed in HEK293 cells transfected with the human 5-HT₆ receptor using [^3H]-LSD as labeled ligand according to

the general method as described by Boess F.G et al. Neuropharmacology 36(4/5) 713-720, 1997.

Materials

5 Cell culture

The HEK-293 cell line transfected with the human 5-HT₆ receptor was cultured in Dulbeccos Modified Eagles Medium containing 5 % dialyzed foetal bovine serum, (Gibco BRL 10106-169), 0.5 mM sodium pyruvate and 400 µg/mL Geneticin (G-418) (Gibco BRL10131-019). The cells were passaged 1:10, twice a week.

10

Chemicals

The radioligand [³H] LSD 60-240 Ci/mmol, obtained from Amersham Pharmacia Biotech, (Buckinghamshire, England) was in ethanol and stored at -20°C. The compounds were dissolved in 100% DMSO and diluted with binding buffer.

15

Disposable

Compounds were diluted in Costar 96 well V-bottom polypropylene plates (Corning Inc. Costar, NY, USA). Samples were incubated in Packard Optiplate (Packard Instruments B.V., Groningen, The Netherlands). The total amount of added radioligand was measured in Packard 24-well Barex plates (Packard Instruments B.V., Groningen, The Netherlands) in the presence of MicroscintTM 20 scintillation fluid (Packard Bioscience, Meriden, CT, USA).

20

Buffer

The binding buffer consisted of 20 mM HEPES, 150 mM NaCl, 10 mM MgCl₂, and 1 mM, EDTA, pH 7.4.

25

Methods

Membrane preparation

Cells were grown to approximately 90% confluence on 24.5 x 24.5 mm culture dishes. The medium was aspirated, and after rinsing with ice-cold PBS, the cells were scraped off using 25 mL Tris buffer (50 mM Tris-HCl, 1 mM EDTA, 1 mM EGTA, pH 7.4) and a window scraper. The cells were then broken with a Polytron homogeniser, and remaining particulate matter was removed by low-speed centrifugation, 1000x g for 5 min.

30

Finally, the membranes were collected by high-speed centrifugation (20 000x g), suspended in binding buffer, and frozen in aliquots at -70°C.

Radioligand binding

5 Frozen cell membranes were thawed, immediately rehomogenized with a Polytron homogenizer, and coupled to SPA wheat germ agglutinin beads (Amersham Life Sciences, Cardiff, England) for 30 min under continuous shaking of the tubes. After coupling, the beads were centrifuged for 10 minutes at 1000 g, and subsequently suspended in 20 mL of binding buffer per 96-well plate. The binding reaction was then initiated by adding
10 radioligand and test compounds to the bead-membrane suspension. Following incubation at room temperature, the assay plates were subjected to scintillation counting.

The original SPA method was followed except for that membranes were prepared from HEK293 cells expressing the human 5-HT₆ receptor instead of from HeLa cells (Dinh DM, Zaworski PG, Gill GS, Schlachter SK, Lawson CF, Smith MW. Validation of
15 human 5-HT₆ receptors expressed in HeLa cell membranes: saturation binding studies, pharmacological profiles of standard CNS agents and SPA development. (The Upjohn Company Technical Report 7295-95-064 1995;27 December). The specific binding of [³H]-LSD was saturable, while the non-specific binding increased linearly with the concentration of added radioligand. [³H]-LSD bound with high affinity to 5-HT₆
20 receptors. The K_d value was estimated to 2.6± 0.2 nM based on four separate experiments.

The total binding at 3 nM of [³H]-LSD, the radioligand concentration used in the competition experiments, was typically 6000 dpm, and the specific binding more than 70%. 5-HT caused a concentration dependent inhibition of [³H]-LSD binding with an overall average K_i value of 236 nM when tested against two different membrane preparations.
25 The inter assay variability over three experiments showed a CV of 10% with an average K_i values of 173 nM (SD 30) and a Hill coefficient of 0.94 (SD 0.09). The intra assay variation was 3% (n=4). All unlabelled ligands displaced the specific binding of [³H]-LSD in a concentration-dependent manner, albeit at different potencies. The rank order of affinity for the 5-HT₆ receptor of reference compounds was methiothepin (K_i 2 nM)
30 >mianserin (190 nM) ≈ 5-HT (236 nM) >methysergide (482 nM) > mesulergine (1970 nM).

Protein determination

Protein concentrations were determined with BioRad Protein Assay (Bradford MM. A rapid and sensitive method for the quantitation of microgram quantities of protein utilizing the principle of protein-dye binding. Anal. Biochem. 1976;72:248-54). Bovine
 5 serum albumin was used as standard.

Scintillation counting

The radioactivity was determined in a Packard TopCount™ scintillation counter (Packard Instruments, Meriden, CT, USA) at a counting efficiency of approximately 20 %.
 10 The counting efficiency was determined in separate sets of experiments.

Saturation experiments

At least 6 concentrations in duplicates of radioligand (0.1-20 nM of [³H]-LSD) were used in saturation experiments. The specific binding was calculated as the difference
 15 between total binding and non-specific binding, which was determined as the binding of radioligand in the presence of 5 μM lisuride. B_{max} and the dissociation constant, K_d, were determined from the non-linear regression analysis using equation 1. L_u is the unbound concentration of radioligand, and is y is the amount bound.

$$y = \frac{B_{\max} \cdot Lu}{Lu + Kd} \quad (\text{equation 1})$$

20

Competition experiments

Total- and non-specific binding of radioligand was defined in eight replicates of each. Samples containing test compound were run in duplicate at 11 concentrations. Incubations were carried out at room temperature for 3 hours. The IC₅₀ value, i.e. the
 25 concentration of test compound that inhibited 50% of the specific binding of radioligand, was determined with non linear regression analysis and the K_i value was calculated using equation 2 [Cheng Y.C. Biochem. Pharmacol. 22, 3099-3108, 1973].

$$Ki = \frac{IC_{50}}{1 + \frac{L}{Kd}} \quad (\text{equation 2})$$

L = concentration of radioligand

30 K_d = Affinity of radioligand

(b) *5-HT₆ Intrinsic Activity Assay*

Antagonists to the 5-HT₆ receptor were characterized by measuring inhibition of 5-HT induced increase in cAMP in HEK 293 cells expressing the human 5-HT₆ receptor (see Boess et al. (1997) *Neuropharmacology* 36: 713-720). Briefly, HEK293/5-HT₆ cells were
5 seeded in polylysine coated 96-well plates at a density of 25,000 / well and grown in DMEM (Dulbecco's Modified Eagle Medium) (without phenol-red) containing 5% dialyzed Foetal Bovine Serum for 48 h at 37°C in a 5% CO₂ incubator. The medium was then aspirated and replaced by 0.1 mL assay medium (Hanks Balance Salt Solution containing 20 mM HEPES, 1.5 mM isobutylmethylxanthine and 1 mg/mL bovine serum
10 albumin). After addition of test substances, 50 µl dissolved in assay medium, the cells were incubated for 10 min at 37°C in a 5% CO₂ incubator. The medium was again aspirated and the cAMP content was determined using a radioactive cAMP kit (Amersham Pharmacia Biotech, BIOTRAK RPA559). The potency of antagonists was quantified by determining the concentration that caused 50% inhibition of 5-HT (at [5-HT]= 8 times EC₅₀) evoked
15 increase in cAMP, using the formula $fKi = IC_{50} / (1 + [5HT] / EC_{50})$.

The compounds in accordance with the invention have a selective affinity to 5-HT₆ receptors with K_i and IC_{50,corr} values between 0.5 nM and 5 µM or display a % inhibition of [³H]-LSD ≥ 20 % at 50 nM and are antagonists, agonists or partial agonists at 5-HT₆. The compounds show good selectivity over 5-HT_{1a}, 5-HT_{1b}, 5-HT_{2a}, 5-HT_{2b}, 5-HT_{2c}.

20

(c) *In vivo assay of reduction of food intake*

For a review on serotonin and food intake, see Blundell, J.E. and Halford, J.C.G. (1998) *Serotonin and Appetite Regulation. Implications for the Pharmacological Treatment of Obesity*. *CNS Drugs* 9:473-495.

25 Obese (ob/ob) mouse is selected as the primary animal model for screening as this mutant mouse consumes high amounts of food resulting in a high signal to noise ratio. To further substantiate and compare efficacy data, the effect of the compounds on food consumption is also studied in wild type (C57BL/6J) mice. The amount of food consumed during 15 hours of infusion of compounds is recorded.

30 Male mice (obese C57BL/6JBom-Lep^{ob} and lean wild-type C57BL/6JBom; Bomholtsgaard, Denmark) 8-9 weeks with an average body weight of 50 g (obese) and 25 g (lean) are used in all the studies. The animals are housed singly in cages at 23±1°C, 40-

60 % humidity and have free access to water and standard laboratory chow. The 12/12-h light/dark cycle is set to lights off at 5 p.m. The animals are conditioned for at least one week before start of study.

The test compounds are dissolved in solvents suitable for each specific compound such as cyclodextrin, cyclodextrin/methane sulphonic acid, polyethylene glycol/methane sulphonic acid, saline. Fresh solutions are made for each study. Doses of 30, 50 and 100 mg kg⁻¹ day⁻¹ are used. The purity of the test compounds is of analytical grade.

The animals are weighed at the start of the study and randomized based on body weight. Alzet osmotic minipumps (Model 2001D; infusion rate 8 µl/h) are used and loaded essentially as recommended by the Alzet technical information manual (Alza Scientific Products, 1997; Theeuwes, F. and Yam, S.I. Ann. Biomed. Eng. 4(4). 343-353, 1976). Continuous subcutaneous infusion with 24 hours duration is used. The minipumps are either filled with different concentrations of test compounds dissolved in vehicle or with only vehicle solution and maintained in vehicle pre-warmed to 37°C (approx. 1h). The minipumps are implanted subcutaneously in the neck/back region under short acting anesthesia (metofane/enflurane). This surgical procedure lasts approximately 5 min.

The weight of the food pellets are measured at 5 p.m. and at 8 p. m. for two days before (baseline) and one day after the implantation of the osmotic minipumps. The weighing is performed with a computer assisted Mettler Toledo PR 5002 balance. Occasional spillage is corrected for. At the end of the study the animals are killed by neck dislocation and trunk blood sampled for later analysis of plasma drug concentrations.

The plasma sample proteins are precipitated with methanol, centrifuged and the supernatant is transferred to HPLC vials and injected into the liquid chromatography /mass spectrometric system. The mass spectrometer is set for electrospray positive ion mode and Multiple Reaction Monitoring. A linear regression analysis of the standards forced through the origin is used to calculate the concentrations of the unknown samples.

Food consumption for 15 hours is measured for the three consecutive days and the percentage of basal level values is derived for each animal from the day before and after treatment. The values are expressed as mean ± SD and ± SEM from eight animals per dose group. Statistical evaluation is performed by Kruskal-Wallis one-way ANOVA using the percent basal values. If statistical significance is reached at the level of p<0.05, Mann-Whitney U-test for statistical comparison between control and treatment groups is performed.

The compounds according to the invention show an effect (i.e., reduction of food intake) in the range of 5-200 mg/kg/d.

Table 4. Functional in vitro data at the h-5-HT receptor (fKi). Data are expressed as fKi, =IC₅₀/(1+[5HT]/EC₅₀). The potency of antagonists was quantified by determining the concentration that caused 50% inhibition of 5-HT (at [5-HT]= 8 times EC₅₀) evoked increase in cAMP, using the formula fKi =IC₅₀/(1+[5HT]/EC₅₀).

Table 4.

EXAMPLE	fKi (nM)
1	87
12	87
28	66
32	54
33	20

Table 5. Competitive binding in vitro data at the h-5-HT receptor (Ki). The IC₅₀ value, i.e. the concentration of test compound that inhibited 50% of the specific binding of radioligand ([³H]-LSD), was determined with non linear regression analysis and the K_i

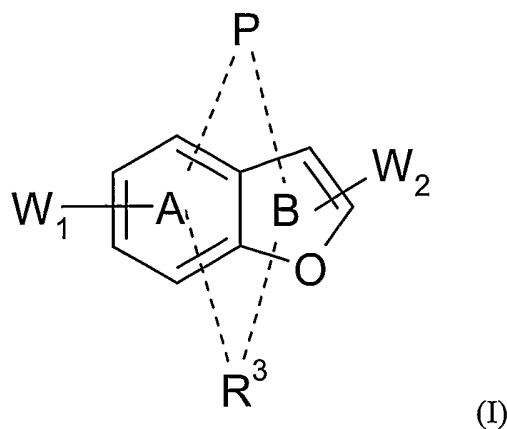
value was calculated using the equation $K_i = \frac{IC_{50}}{1 + \frac{L}{K_d}}$

Table 5.

Example	Ki (nM)
92	5.56
36	20
67	13
84	7.5
85	7
86	7
87	5.3
89	14
91	56
54	17.4

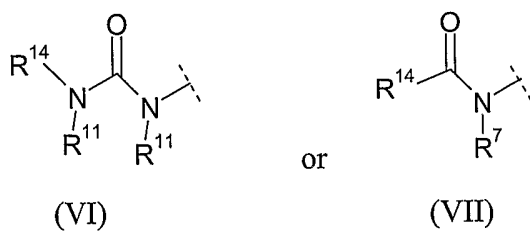
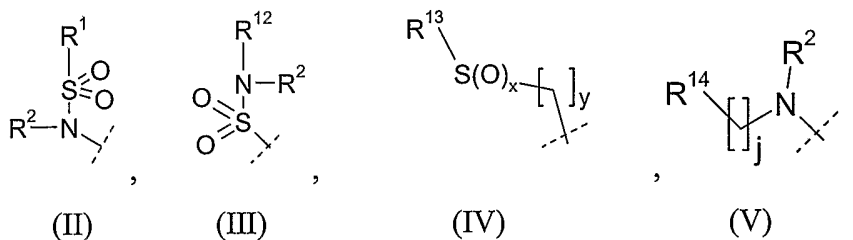
Claims

1. A compound of the Formula (I):



5 wherein:

P is selected from a substituent of Formula (II)-(VII):



10 wherein:

x, y and j are each independently selected from 0, 1, and 2 ;

wherein the dashed bonds denote that P and R³, respectively, may be attached to either the A or B ring at any carbon atom that allows the substitution, provided that P and R³ are not both simultaneously attached to ring B;

15

R¹ is selected from:

(a) C₁₋₆-alkyl,

- (b) C₁₋₆-alkoxy-C₁₋₆-alkyl,
(c) C₃₋₆-alkenyl,
(d) hydroxy-C₁₋₆-alkyl,
(e) halo-C₁₋₆-alkyl,
5 (f) aryl,
(g) arylcarbonylmethyl,
(h) aryl-C₃₋₆-alkenyl,
(i) aryl-C₁₋₆-alkyl,
(j) C₃₋₇-cycloalkyl,
10 (k) heteroaryl,
(l) 4-piperidinyl,
(m) N-substituted 4-piperidinyl, wherein the substituents are selected from C₁₋₆-alkyl and aryl-C₁₋₆-alkyl,
(o) heteroaryl-C₁₋₆-alkyl,
15 wherein any heteroaryl or aryl residue, alone or as part of another group may be substituted, independently, in one or more positions with a substituent selected from:
(a) hydrogen,
(b) halogen,
(c) C₁₋₆-alkyl,
20 (d) hydroxy,
(e) C₁₋₆-alkoxy,
(f) C₂₋₆-alkenyl,
(g) C₂₋₃-alkynyl,
(h) phenyl,
25 (i) phenoxy,
(j) benzyloxy,
(k) benzoyl,
(l) benzyl,
(m) -OCF₃,
30 (n) -CN,
(o) hydroxy-C₁₋₆-alkyl,
(p) C₁₋₆-alkoxy-C₁₋₆-alkyl,
(q) halo-C₁₋₆-alkyl,
(r) -NR⁹R⁹,

- (s) $-\text{NO}_2$,
- (t) $-\text{CONR}^9\text{R}^9$,
- (u) $-\text{NR}^7\text{COR}^{10}$,
- (v) $-\text{C}(=\text{O})\text{R}^{10}$,
- 5 (x) C_{1-6} -alkoxycarbonyl,
- (y) C_{1-6} -alkylthio,
- (z) $-\text{SCF}_3$,
- (aa) $-\text{CHF}=\text{CH}_2$,
- (ab) methylsulfonyl, or
- 10 (ac) $-\text{COOH}$

with the proviso that when the substituent on the said aryl or heteroaryl residue is selected from phenyl, phenoxy, benzyloxy, benzoyl and benzyl, the phenyl ring thereof may be optionally substituted by one or more of halogen, C_{1-4} -alkyl, C_{1-4} -alkylthio, C_{1-4} -alkoxy, cyano, or trifluoromethyl;

15

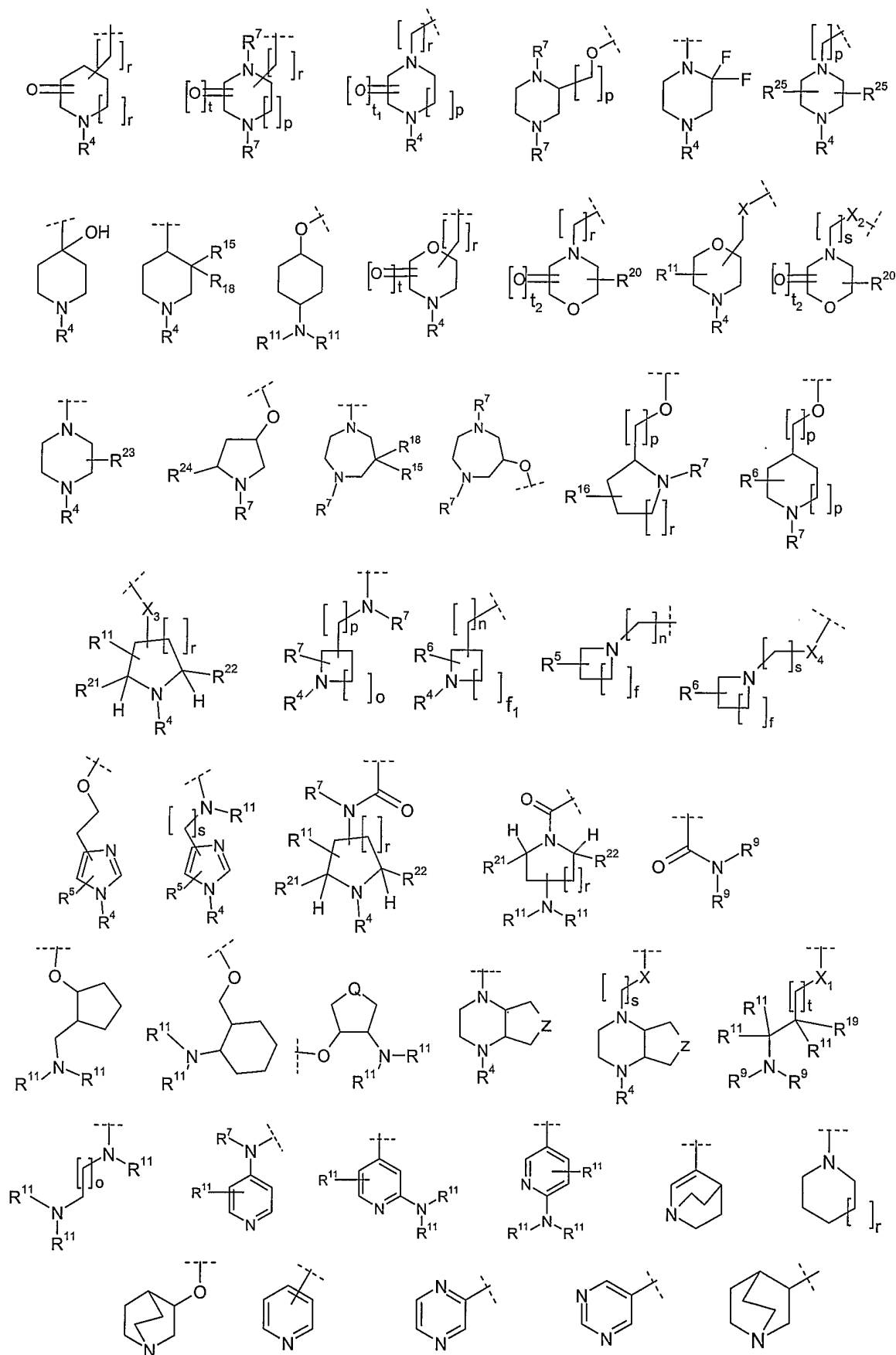
R^2 is selected from:

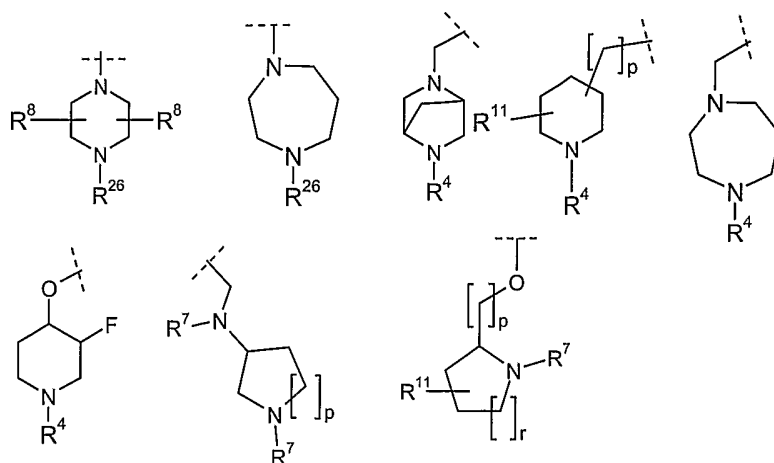
- (a) hydrogen,
- (b) C_{1-6} -alkyl,
- (c) C_{1-6} -alkoxy- C_{2-6} alkyl,
- 20 (d) hydroxy- C_{2-6} -alkyl,
- (e) $-(\text{CH}_2)_m-\text{CH}_2-\text{F}$, wherein m is 2-4,
- (f) 3,3,3-trifluoropropyl, or
- (g) C_{1-4} -alkylsulfonyl, provided that P is selected from a substituent of formula (V);

25 W_1 and W_2 are each independently selected from:

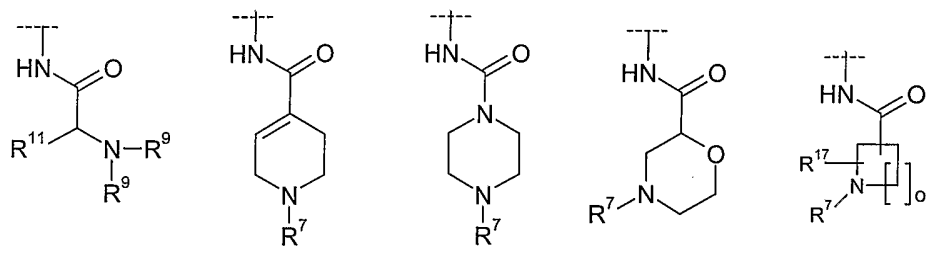
- (a) hydrogen,
- (b) halogen,
- (c) C_{1-6} -alkyl,
- (d) hydroxy,
- 30 (e) C_{1-6} -alkoxy,
- (f) C_{1-6} -alkylthio,
- (g) C_{2-6} -alkenyl,
- (h) phenyl,

- (i) phenoxy,
 (j) benzyloxy,
 (k) benzoyl,
 (l) benzyl,
 5 (m) -OCF₃,
 (n) -CN,
 (o) hydroxy-C₁₋₆-alkyl,
 (p) C₁₋₆-alkoxy-C₁₋₆-alkyl,
 (q) halo-C₁₋₆-alkyl,
 10 (r) -CONR⁹R⁹,
 (s) -C(=O)R¹⁰,
 (t) C₁₋₆-alkoxycarbonyl,
 (u) -SCF₃, or
 (v) -CHF=CH₂,
- 15 with the proviso that when W₁ and W₂ are selected from phenyl, phenoxy, benzoyl, benzyloxy and benzyl, the phenyl ring thereof may be optionally substituted by one or more of halogen, C₁₋₄-alkyl, C₁₋₄-alkoxy, cyano, or trifluoromethyl, and with the further proviso that, when W₁ and W₂ are not selected from methoxy, methyl and halogen, at least one of W₁ and W₂ is selected from hydrogen;
- 20 R³ is H when P is a substituent of Formula (II) wherein R¹ is N-substituted 4-piperidinyl, or R³ is a group selected from:

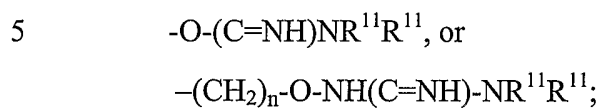




R^3 may also be a group selected from:



and further from a group selected from



wherein:

- $n = 0, 1, 2$ or 3
 r is each independently $0, 1$ or 2 ,
 10 $o = 1, 2$, or 3 ,
 p is each independently 1 or 2 ,
 $s = 2$ or 3 ,
 $t = 0$ or 1 ,
 $t_1 = 1$ or 2 ,
 15 $t_2 = 0$ or 1 ,
 $f = 1, 2, 3$ or 4 , and
 $f_1 = 1, 2$ or 4 ;

with the proviso that when t_1 and p simultaneously are 1 , r is not 0 ;

- 20 X is selected from O, NR^7 and S ;
 X_1 is selected from NR^7 and S ;

X_2 is selected from O, NR^7 and S, provided that X_2 is selected from NR^7 and S when $t_2 = 0$;

X_3 is selected from NR^7 and S, provided that X_3 is selected from S when $r = 1$;

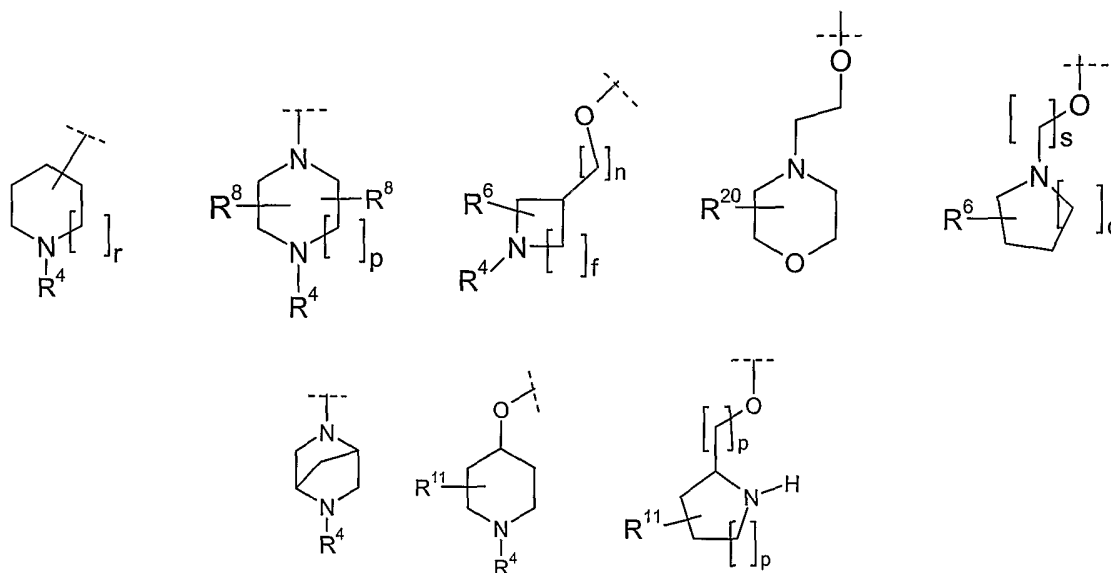
X_4 is selected from O, NR^7 and S, provided that X_4 is selected from S and NR^7 when f is selected from 2, 3, and 4;

Q is selected from CH_2 , SO_2 and oxygen, provided that when Q is SO_2 or oxygen, p is 1;

Z is selected from SO_2 and oxygen;

when P is a group selected from a substituent of Formula (V) – (VII), R^3 is additionally

selected from the following groups:



wherein:

$n = 0, 1, 2$ or 3

$r = 0, 1$ or 2 ,

$o = 1, 2$, or 3 ,

$p = 1$ or 2 ,

$s = 2$ or 3 , and

$f = 1, 2, 3$ or 4 ;

wherein R^4 is a group selected from:

(a) hydrogen,

(b) C_{1-6} -alkyl,

(c) 2-cyanoethyl,

- (d) hydroxy-C₂₋₆-alkyl,
- (e) C₃₋₆-alkenyl,
- (f) C₃₋₆-alkynyl,
- (g) C₃₋₇-cycloalkyl,
- 5 (h) C₃₋₇-cycloalkyl-C₁₋₄-alkyl,
- (i) C₁₋₆-alkoxy-C₂₋₆-alkyl
- (j) -C(=NH)-N-R¹¹R¹¹,
- (k) -C(=O)-N-R¹¹R¹¹,
- (l) -CH₂-CO-N-R¹¹R¹¹, or
- 10 (m) 3,3,3-trifluoropropyl;

R⁵ is selected from:

- (a) hydrogen,
- (b) C₁₋₄-alkyl,
- 15 (c) hydroxy-C₁₋₄-alkyl,
- (d) C₁₋₄-alkoxymethyl,
- (e) halo-C₁₋₄-alkyl,
- (f) -NR¹¹R¹¹,
- (g) -CO-NR¹¹R¹¹,
- 20 (h) hydroxy, provided that the said hydroxy group is not attached to a carbon atom adjacent to a ring nitrogen atom, or
- (i) fluorine, provided that the said fluorine atom is not attached to a carbon atom adjacent to a ring nitrogen atom;

25 R⁶ is selected from:

- (a) hydrogen,
- (b) C₁₋₄-alkyl,
- (c) hydroxy-C₁₋₄-alkyl,
- (d) C₁₋₄-alkoxy-C₁₋₄-alkyl,
- 30 (e) hydroxy, provided that the said hydroxy group is not attached to a carbon atom adjacent to a heterocyclic ring nitrogen atom, and further provided that the said heterocyclic ring is not substituted with oxo,
- (f) fluorine, provided that the said fluorine atom is not attached to a carbon atom adjacent to a ring nitrogen atom, or

(g) halo-C₁₋₄-alkyl;

R⁷ is each independently selected from:

- 5 (a) hydrogen, provided that R⁷ is not hydrogen when present simultaneously with r and said r is 1 or 2,
(b) C₁₋₄-alkyl,
(c) hydroxy-C₂₋₄-alkyl, or
(d) methoxy-C₂₋₄-alkyl;

10 R⁸ is each independently selected from:

- (a) hydrogen, or
(b) C₁₋₄-alkyl, and
when both R⁸ simultaneously are selected from C₁₋₄-alkyl, said C₁₋₄-alkyls may be attached to the same or different carbon atoms, or when two groups are present at
15 the same carbon atom they may together form a cyclopropane ring;

R⁹ is each independently selected from:

- (a) hydrogen,
(b) C₁₋₆-alkyl
20 (c) C₃₋₇-cycloalkyl, or

wherein the two R⁹ groups together with the nitrogen to which they are attached form a heterocyclic ring; and provided that when the two R⁹ groups form a piperazine ring, the nitrogen of the said piperazine ring that allows the substitution is optionally substituted with C₁₋₄-alkyl, and further provided that when the two R⁹ groups form a piperidine ring,
25 any ring carbon atom in the said piperidine ring may be optionally substituted with methyl;

R¹⁰ is selected from:

- (a) C₁₋₆-alkyl,
(c) aryl, or
30 (d) heteroaryl,

wherein heteroaryl or aryl may be substituted in one or more positions with substituents selected from halogen, C₁₋₄-alkyl, C₁₋₄-alkoxy, cyano, trifluoromethyl;

R¹¹ is each independently selected from:

- (a) hydrogen,
- (b) methyl, or
- (c) ethyl, provided that R^{11} is present in a group R^4 or R^{26} selected from $-\text{CH}_2\text{-CO-N-R}^{11}\text{R}^{11}$;

5

R^{12} is selected from:

- (a) hydrogen,
- (b) C_{1-6} -alkyl,
- (c) aryl,
- 10 (d) aryl- C_{1-6} -alkyl,
- (e) C_{3-7} -cycloalkyl,
- (f) C_{3-7} -cycloalkyl- C_{1-4} -alkyl,
- (g) heteroaryl, or
- (h) heteroaryl- C_{1-6} -alkyl,

15 wherein any heteroaryl or aryl residue, alone or as part of another group, is optionally substituted, independently, in one or more positions with substituents selected from:

- (a) hydrogen,
- (b) halogen,
- (c) C_{1-6} -alkyl,
- 20 (d) hydroxy,
- (e) C_{1-6} -alkoxy,
- (f) C_{2-6} -alkenyl,
- (g) C_{2-6} -alkynyl,
- (h) phenyl,
- 25 (i) phenoxy,
- (j) benzyloxy,
- (k) benzoyl,
- (l) benzyl,
- (m) $-\text{OCF}_3$,
- 30 (n) $-\text{CN}$,
- (o) hydroxy- C_{1-6} -alkyl,
- (p) C_{1-6} -alkoxy- C_{1-6} -alkyl,
- (q) halo- C_{1-6} -alkyl,
- (r) $-\text{NR}^9\text{R}^9$,

- (s) $-\text{NO}_2$,
(t) $-\text{CONR}^9\text{R}^9$,
(u) $-\text{NR}^7\text{COR}^{10}$,
(v) $-\text{C}(=\text{O})\text{R}^{10}$,
5 (x) C_{1-6} -alkoxycarbonyl,
(y) C_{1-6} -alkylthio,
(z) $-\text{SCF}_3$,
(aa) $-\text{CHF}=\text{CH}_2$,
(ab) methylsulfonyl, or
10 (ac) $-\text{COOH}$

with the proviso that when the substituent on the said aryl or heteroaryl residue is selected from phenyl, phenoxy, benzyloxy, benzoyl, and benzyl, the phenyl ring thereof may be optionally substituted by one or more of halogen, C_{1-4} -alkyl, C_{1-4} -alkoxy, cyano, or trifluoromethyl;

15

R^{13} is selected from:

- (a) C_{1-6} -alkyl,
(b) C_{3-6} -cycloalkyl,
(c) aryl,
20 (d) heteroaryl,
(e) aryl- C_{1-2} -alkyl, or
(f) heteroaryl- C_{1-2} -alkyl,

wherein any heteroaryl or aryl residue may be substituted in one or more positions with substituents selected from halogen, C_{1-4} -alkyl, C_{1-4} -alkoxy, cyano, trifluoromethyl, and
25 acetyl;

R^{14} is selected from:

- (a) aryl,
(b) heteroaryl,
30 (c) aryl- C_{1-3} -alkyl, or
(d) heteroaryl- C_{1-3} -alkyl;

wherein any heteroaryl or aryl residue may be substituted in one or more positions with substituents selected from halogen, C_{1-4} -alkyl, C_{1-4} -alkoxy, cyano, and trifluoromethyl;

R¹⁵ is selected from:

- (a) fluorine, or
- (b) hydroxy;

5

R¹⁶ is selected from:

- (a) hydrogen, provided that $r = 0$,
- (b) amino,
- (c) dimethylamino,
- (d) F, or
- (e) OH;

10

R¹⁷ is selected from:

- (a) hydrogen,
- (b) C₁₋₄-alkyl,
- (c) hydroxy, provided that the said hydroxy group is not attached to a carbon atom adjacent to a ring nitrogen atom;

15

R¹⁸ is selected from:

- (a) hydrogen, or
- (b) fluorine;

20

R¹⁹ is selected from:

- (a) hydrogen,
- (b) methyl,
- (c) trifluoromethyl, or
- (d) C₁₋₂-alkoxymethyl;

25

and provided that at least one of R¹⁹ and R¹¹, when present simultaneously, is selected from a non-hydrogen substituent, and further provided that when R¹⁹ is selected from trifluoromethyl or C₁₋₂-alkoxymethyl, each R¹¹ is selected from hydrogen;

30

R²⁰ is selected from:

- (a) hydrogen,
- (b) C₁₋₄-alkyl,

- (c) hydroxy-C₁₋₄-alkyl,
- (d) C₁₋₄-alkoxy-C₁₋₄-alkyl, or
- (e) fluoromethyl;

with the proviso that when t_2 is 1, R^{20} is H;

5

R^{21} and R^{22} are each independently selected from:

- (a) hydrogen, or
- (b) methyl,

provided that, when present at the same time as R^{11} , at least two of R^{11} , R^{21} and R^{22} are
10 selected from hydrogen;

R^{23} is selected from:

- (a) hydroxy-C₁₋₄-alkyl,
- (b) C₁₋₄-alkoxymethyl,
- 15 (c) halo-C₁₋₄-alkyl, or
- (d) $-\text{CO}-\text{NR}^{11}\text{R}^{11}$, provided that R^4 is not selected from
 $-\text{C}(=\text{NH})-\text{N}-\text{R}^{11}\text{R}^{11}$, $-\text{C}(=\text{O})-\text{N}-\text{R}^{11}\text{R}^{11}$, and $-\text{CH}_2-\text{CO}-\text{N}-\text{R}^{11}\text{R}^{11}$;

R^{24} is selected from:

- 20 (a) hydroxymethyl,
- (b) methoxymethyl, or
- (c) fluoromethyl;

R^{25} is each independently selected from

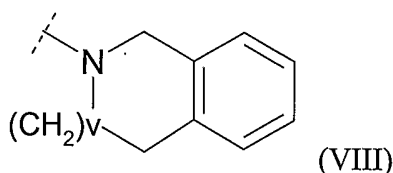
- 25 (a) hydrogen,
- (b) C₁₋₄-alkyl,
- (c) hydroxy-C₁₋₄-alkyl,
- (d) C₁₋₄-alkoxy-C₁₋₄-alkyl, or
- (e) fluoromethyl,

30 with the proviso that when both R^{25} simultaneously are selected from C₁₋₄-alkyls, wherein said C₁₋₄-alkyls may be attached to the same or different carbon atoms and with the further proviso that when one R^{25} is selected from hydroxy-C₁₋₄-alkyl, C₁₋₄-alkoxy-C₁₋₄-alkyl, and fluoromethyl, the other R^{25} represents hydrogen; and

R²⁶ is selected from

- (a) 2-cyanoethyl,
- (b) C₃₋₆-alkenyl,
- (c) C₃₋₆-alkynyl,
- 5 (d) C₃₋₇-cycloalkyl,
- (e) C₃₋₇-cycloalkyl-C₁₋₄-alkyl,
- (f) -CH₂-CO-NR¹¹R¹¹, or
- (g) 3,3,3-trifluoropropyl;

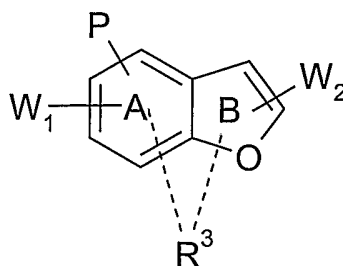
- 10 with the proviso that R² and R¹² in Formula (III) are not simultaneously selected from hydrogen; and with the further proviso that the said R² and R¹² together may form a heterocyclic ring selected from piperidine, pyrrolidine, morpholine, piperazine thiomorpholine, and provided that when R² and R¹² together form a piperazine ring, the distal piperazine nitrogen is optionally substituted by C₁₋₄ alkyl or aryl, and wherein said
- 15 aryl may be substituted in one or more positions with substituents selected from halogen, C₁₋₄-alkyl, C₁₋₄-alkoxy, cyano, trifluoromethyl; or R² and R¹² together form a heteroaromatic ring of Formula (VIII):



- 20 wherein v is 0, 1 or 2; and further provided that when R¹⁵ is selected from hydroxy, R¹⁸ is selected from hydrogen; and pharmaceutically acceptable salts, hydrates, solvates, geometrical isomers, tautomers, optical isomers, and prodrug forms thereof.

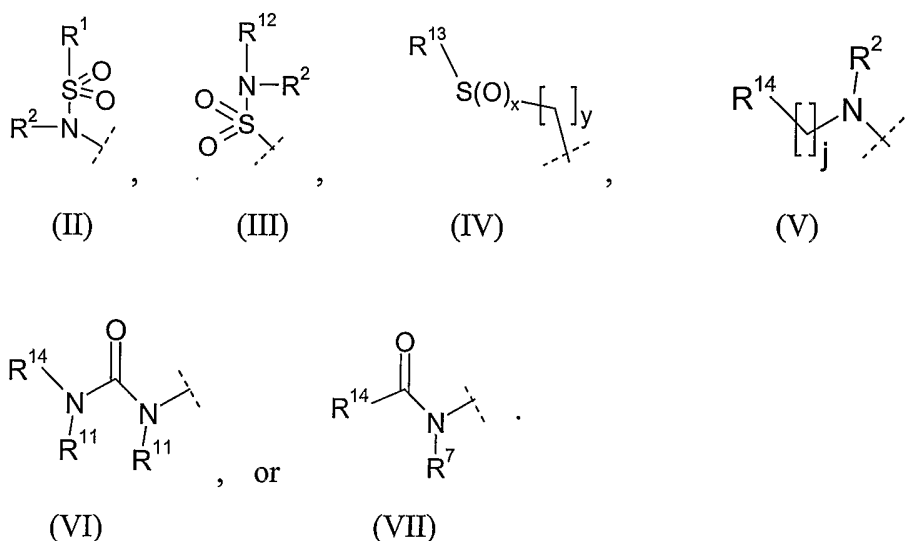
25

2. The compound according to claim 1 of the general formula (1b)



wherein:

P is selected from a substituent of Formula (II)-(VII):



5

wherein:

x, y and j are each independently selected from 0, 1, and 2 ;

wherein the dashed bonds denote that R³ may be attached to either the A or B ring at any carbon atom that allows the substitution;

10

R¹ is selected from:

- (a) C₁₋₆-alkyl,
- (b) C₁₋₆-alkoxy-C₂₋₆-alkyl,
- (c) C₃₋₆-alkenyl,
- 15 (d) hydroxy-C₂₋₆-alkyl,
- (e) halo-C₁₋₆-alkyl,
- (f) aryl,
- (g) arylcarbonylmethyl,
- (h) aryl-C₃₋₆-alkenyl,
- 20 (i) aryl-C₁₋₆-alkyl,
- (j) C₃₋₇-cycloalkyl,
- (k) heteroaryl,
- (o) heteroaryl-C₁₋₆-alkyl,

wherein any heteroaryl or aryl residue, alone or as part of another group may be optionally substituted, independently, in one or more positions with a substituent selected from:

- (b) halogen,
- (c) C₁₋₆-alkyl,
- 5 (d) hydroxy,
- (e) C₁₋₆-alkoxy,
- (f) C₂₋₆-alkenyl,
- (g) C₂₋₃-alkynyl,
- (h) phenyl,
- 10 (i) phenoxy,
- (j) benzyloxy,
- (k) benzoyl,
- (l) benzyl,
- (m) -OCF₃,
- 15 (n) -CN,
- (o) hydroxy-C₁₋₆-alkyl,
- (p) C₁₋₆-alkoxy-C₁₋₆-alkyl,
- (q) halo-C₁₋₆-alkyl,
- (r) -NR⁹R⁹,
- 20 (s) -NO₂,
- (t) -CONR⁹R⁹,
- (u) -NR⁷COR¹⁰,
- (v) -C(=O)R¹⁰,
- (x) C₁₋₆-alkoxycarbonyl,
- 25 (y) C₁₋₆-alkylthio,
- (z) -SCF₃,
- (aa) -CHF=CH₂,
- (ab) methylsulfonyl, or
- (ac) -COOH,

30 with the proviso that when the substituent on the said aryl or heteroaryl residue is selected from phenyl, phenoxy, benzyloxy, benzoyl and benzyl, the phenyl ring thereof may be optionally substituted by one or more of halogen, C₁₋₄-alkyl, C₁₋₄-alkylthio, C₁₋₄-alkoxy, cyano, or trifluoromethyl;

R² is selected from:

- (a) hydrogen,
- (b) C₁₋₆-alkyl,
- 5 (c) C₁₋₆-alkoxy-C₂₋₆ alkyl,
- (d) hydroxy-C₂₋₆ -alkyl,
- (e) -(CH₂)_m-CH₂-F, wherein m is 2-4, or
- (g) C₁₋₄-alkylsulfonyl, provided that P is selected from a substituent of formula (V);

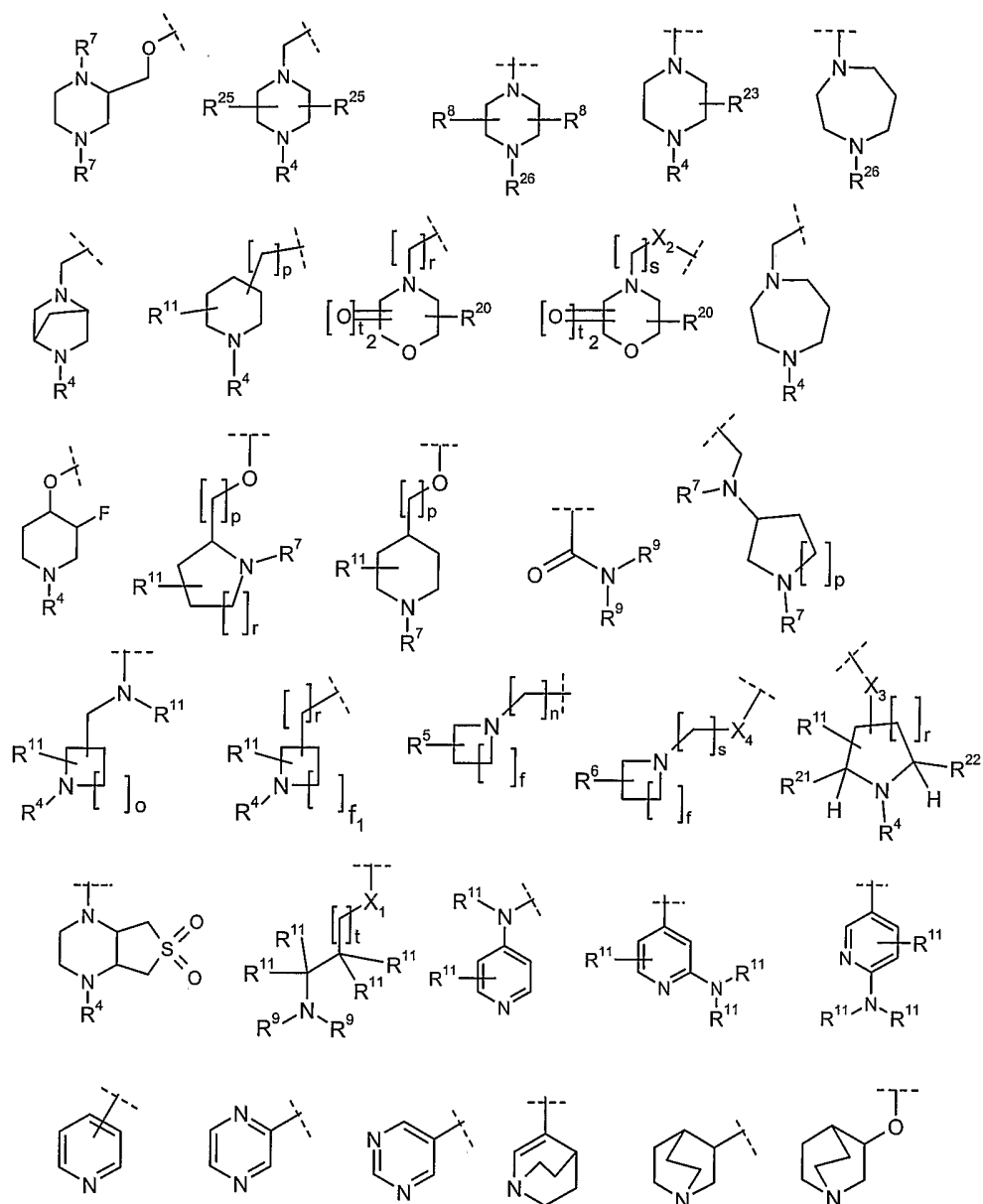
10 W₁ and W₂ are each independently selected from:

- (a) hydrogen,
- (b) halogen,
- (c) C₁₋₆-alkyl,
- (d) hydroxy,
- 15 (e) C₁₋₆-alkoxy,
- (f) C₁₋₆-alkylthio,
- (g) C₂₋₆-alkenyl,
- (m) -OCF₃,
- (n) -CN,
- 20 (o) hydroxy-C₁₋₆-alkyl,
- (p) C₁₋₆-alkoxy-C₁₋₆-alkyl,
- (q) halo-C₁₋₆-alkyl,
- (r) -CONR⁹R⁹,
- (s) -C(=O)R¹⁰,
- 25 (t) C₁₋₆-alkoxycarbonyl,
- (u) -SCF₃, or
- (v) -CHF=CH₂,

with the proviso that when W₁ and W₂ are not selected from hydroxy, methoxy, methyl and halogen, at least one of W₁ and W₂ is selected from hydrogen;

30

R³ is a group selected from:



wherein

$n = 0, 1, 2$ or 3 ,

$r = 0, 1$ or 2 ,

5 $o = 1, 2$ or 3 ,

$p = 1$ or 2 ,

$s = 2$ or 3 ,

$t = 0$ or 1 ,

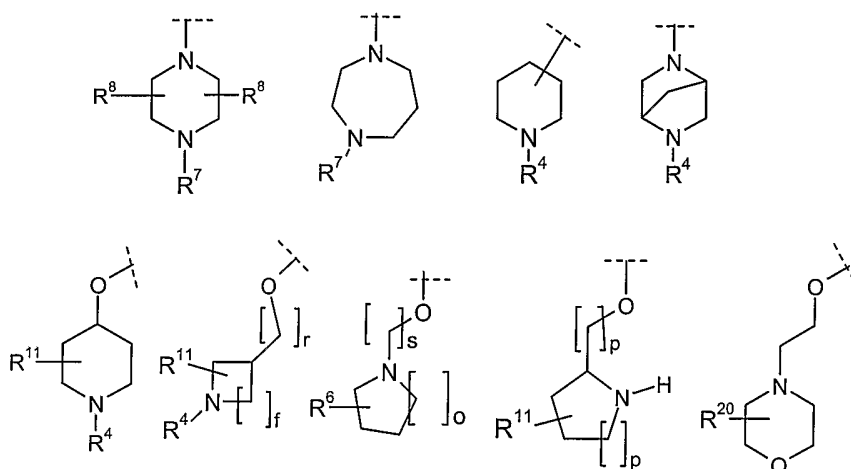
$t_2 = 0$ or 1 ,

10 $f = 1, 2, 3$ or 4 , and

$f_1 = 1, 2$ or 4 ;

- X_1 is selected from NR^7 and S;
 X_2 is selected from O, NR^7 and S, provided that when $t_2 = 0$ and $s = 2$ then X_2 is selected from NR^7 and S;
 X_3 is selected from NR^7 and S, provided that X_3 is selected from S when $r = 1$;
 5 X_4 is selected from O, NR^7 and S, provided that X_4 is selected from S and NR^7 when f is selected from 2 and 3, and R^6 simultaneously is selected from hydrogen and C_{1-4} alkyl;

when P is a group selected from a substituent of Formula (V) – (VII), R^3 is additionally selected from the following groups:



10

wherein:

- $r = 0, 1$ or 2 ,
 $o = 1, 2$ or 3 ,
 p is each independently 1 or 2 ,
 15 $s = 2$ or 3 , and
 $f = 1, 2, 3$ or 4 ;

R^4 is selected from:

- (a) hydrogen,
 20 (b) C_{1-6} -alkyl,
 (c) 2-cyanoethyl,
 (d) hydroxy- C_{2-6} -alkyl,
 (e) C_{3-6} -alkenyl,
 (f) C_{3-6} -alkynyl,
 25 (g) C_{3-7} -cycloalkyl,

- (h) C₃₋₇-cycloalkyl-C₁₋₄-alkyl,
- (i) C₁₋₆-alkoxy-C₂₋₆-alkyl
- (l) -CH₂-CO-N-R¹¹R¹¹, or
- (m) 3,3,3-trifluoropropyl;

5

R⁵ is selected from:

- (a) hydrogen,
- (b) C₁₋₄-alkyl,
- (c) hydroxy-C₁₋₄-alkyl,
- 10 (d) C₁₋₄-alkoxymethyl,
- (e) halo-C₁₋₄-alkyl,
- (f) -NR¹¹R¹¹,
- (h) hydroxy, provided that the said hydroxy group is not attached to a carbon atom adjacent to a ring nitrogen atom, or
- 15 (i) fluorine, provided that the said fluorine atom is not attached to a carbon atom adjacent to a ring nitrogen atom;

R⁶ is selected from:

- (a) hydrogen,
- 20 (b) C₁₋₄-alkyl,
- (c) hydroxy-C₁₋₄-alkyl,
- (d) C₁₋₄-alkoxy-C₁₋₄-alkyl,
- (e) hydroxy, provided that the said hydroxy group is not attached to a carbon atom adjacent to a heterocyclic ring nitrogen atom,
- 25 (f) fluorine, provided that the said fluorine atom is not attached to a carbon atom adjacent to a ring nitrogen atom, or
- (g) halo-C₁₋₄-alkyl;

R⁷ is each independently selected from:

- 30 (a) hydrogen, provided that R⁷ is not hydrogen when present simultaneously with r and said r is 1 or 2,
- (b) C₁₋₄-alkyl,
- (c) hydroxy-C₂₋₄-alkyl, or
- (d) methoxy-C₂₋₄-alkyl;

R⁸ is each independently selected from:

- (a) hydrogen, or
- (b) C₁₋₄-alkyl, with the proviso that when both R⁸ simultaneously are selected from C₁₋₄-alkyl, said C₁₋₄-alkyl may be attached to the same or different carbon atoms, or when two groups are present at the same carbon atom they may together form a cyclopropane ring;

R⁹ is each independently selected from:

- (a) hydrogen,
- (b) C₁₋₆-alkyl
- (c) C₃₋₇-cycloalkyl, or

the two R⁹ groups together with the nitrogen to which they are attached form a heterocyclic ring; and provided that when the two R⁹ groups form a piperazine ring, the nitrogen of the said piperazine ring that allows the substitution may be optionally substituted with C₁₋₄-alkyl; and further provided that when the two R⁹ groups form a piperidine ring, any ring carbon atom in the said piperidine ring may be optionally substituted with methyl;

R¹⁰ is selected from:

- (a) C₁₋₆-alkyl,
- (c) aryl, or
- (d) heteroaryl,

wherein heteroaryl or aryl may be optionally substituted in one or more positions with substituents selected from halogen, C₁₋₄-alkyl, C₁₋₄-alkoxy, cyano, trifluoromethyl;

R¹¹ is each independently selected from:

- (a) hydrogen,
- (b) methyl, or
- (c) ethyl, provided that R¹¹ is present in a group R⁴ or R²⁶ selected from -CH₂-CO-N-R¹¹R¹¹;

R¹² is selected from:

- (a) hydrogen,

- (b) C₁₋₆-alkyl,
- (c) aryl,
- (d) aryl-C₁₋₆-alkyl,
- (e) C₃₋₇-cycloalkyl,
- 5 (f) C₃₋₇-cycloalkyl-C₁₋₄-alkyl,
- (g) heteroaryl, or
- (h) heteroaryl-C₁₋₆-alkyl,

wherein any heteroaryl or aryl residue, alone or as part of another group, may be optionally substituted, independently, in one or more positions with substituents selected from:

- 10 (b) halogen,
- (c) C₁₋₆-alkyl,
- (d) hydroxy,
- (e) C₁₋₆-alkoxy,
- (f) C₂₋₆-alkenyl,
- 15 (g) C₂₋₃-alkynyl,
- (h) phenyl,
- (i) phenoxy,
- (j) benzyloxy,
- (k) benzoyl,
- 20 (l) benzyl,
- (m) -OCF₃,
- (n) -CN,
- (o) hydroxy-C₁₋₆-alkyl,
- (p) C₁₋₆-alkoxy-C₁₋₆-alkyl,
- 25 (q) halo-C₁₋₆-alkyl,
- (r) -NR⁹R⁹,
- (s) -NO₂,
- (t) -CONR⁹R⁹,
- (u) -NR⁷COR¹⁰,
- 30 (v) -C(=O)R¹⁰,
- (x) C₁₋₆-alkoxycarbonyl,
- (y) C₁₋₆-alkylthio,
- (z) -SCF₃,

(aa) $-\text{CHF}=\text{CH}_2$,

(ab) methylsulfonyl, or

(ac) $-\text{COOH}$,

5 with the proviso that when the substituent on the said aryl or heteroaryl residue is selected from phenyl, phenoxy, benzyloxy, benzoyl, and benzyl, the phenyl ring thereof may be optionally substituted by one or more of halogen, C_{1-4} -alkyl, C_{1-4} -alkoxy, cyano, or trifluoromethyl;

R^{13} is selected from:

10 (a) C_{1-6} -alkyl,

(b) C_{3-6} -cycloalkyl,

(c) aryl,

(d) heteroaryl,

(e) aryl- C_{1-2} -alkyl, or

15 (f) heteroaryl- C_{1-2} -alkyl,

wherein any heteroaryl or aryl residue may be optionally substituted in one or more positions with substituents selected from halogen, C_{1-4} -alkyl, C_{1-4} -alkoxy, cyano, trifluoromethyl, and acetyl;

20 R^{14} is selected from:

(a) aryl,

(b) heteroaryl,

(c) aryl- C_{1-3} -alkyl, or

(d) heteroaryl- C_{1-3} -alkyl,

25 wherein any heteroaryl or aryl residue may be substituted in one or more positions with substituents selected from halogen, C_{1-4} -alkyl, C_{1-4} -alkoxy, cyano, and trifluoromethyl;

R^{20} is each independently selected from:

(a) hydrogen, or

30 (b) methyl;

with the proviso that when $t_2 = 1$, then R^{20} is hydrogen;

R^{21} and R^{22} are each independently selected from:

(a) hydrogen, or

(b) methyl,

provided that, when present simultaneously with R^{11} , at least two of R^{11} , R^{21} and R^{22} are selected from hydrogen;

5

R^{23} is selected from:

(a) hydroxy- C_{1-4} -alkyl,

(b) C_{1-4} -alkoxymethyl, or

(c) halo- C_{1-4} -alkyl;

10

R^{25} is each independently selected from

(a) hydrogen,

(b) C_{1-4} -alkyl,

(c) hydroxy- C_{1-4} -alkyl,

15

(d) C_{1-4} -alkoxy- C_{1-4} -alkyl, or

(e) fluoromethyl,

with the proviso that when both R^{25} simultaneously are selected from C_{1-4} -alkyl, said C_{1-4} -alkyl may be attached to the same or different carbon atoms, and with the further proviso that when one R^{25} is selected from hydroxy- C_{1-4} -alkyl, C_{1-4} -alkoxy- C_{1-4} -alkyl, and
20 fluoromethyl, the other R^{25} represents hydrogen;

R^{26} is selected from:

(a) 2-cyanoethyl,

(b) C_{3-6} -alkenyl,

25

(c) C_{3-6} -alkynyl,

(d) C_{3-7} -cycloalkyl,

(e) C_{3-7} -cycloalkyl- C_{1-4} -alkyl,

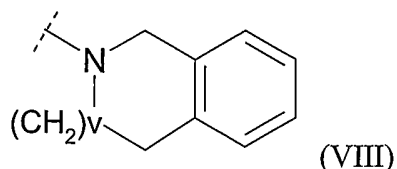
(f) $-CH_2-CO-NR^{11}R^{11}$, or

(g) 3,3,3-trifluoropropyl; and

30

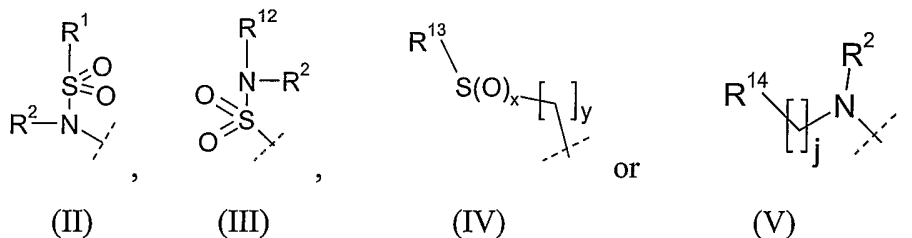
with the proviso that R^2 and R^{12} in Formula (III) are not simultaneously selected from hydrogen; and with the further proviso that the said R^2 and R^{12} together may form a heterocyclic ring selected from piperidine, pyrrolidine, morpholine, piperazine thiomorpholine, and provided that when R^2 and R^{12} together form a piperazine ring, the

distal piperazine nitrogen may be optionally substituted by C₁₋₄ alkyl or aryl, and wherein said aryl may be optionally substituted in one or more positions with substituents selected from halogen, C₁₋₄-alkyl, C₁₋₄-alkoxy, cyano, trifluoromethyl; or R² and R¹² together form a heteroaromatic ring of Formula (VIII):



wherein v is 0 or 1.

3. The compound according to claim 1 or 2, wherein P is selected from a substituent of Formula (II)-(V)



wherein x is 2, y is 0 and j is 1;

R¹ is selected from

(f) aryl,

(i) aryl-C₁₋₃-alkyl,

(k) heteroaryl,

(o) heteroaryl-C₁₋₃-alkyl,

wherein any heteroaryl or aryl residue, alone or as part of another group may be optionally substituted, independently, in one or more positions with a substituent selected from:

(b) halogen,

(c) C₁₋₄-alkyl,

(d) hydroxy,

(e) C₁₋₄-alkoxy,

(m) -OCF₃,

(n) -CN,

(o) hydroxy-C₁₋₄-alkyl,

(p) C₁₋₂-alkoxy-C₁₋₂-alkyl,

- 5 (q) halo-C₁₋₃-alkyl,
 (r) -NR⁹R⁹,
 (t) -CONR⁹R⁹,
 (u) -NR⁷COR¹⁰,
 (v) -C(=O)R¹⁰,
 (x) C₁₋₃-alkoxycarbonyl,
 (y) C₁₋₃-alkylthio, or
 (ab) methylsulfonyl,

10 R² is selected from:

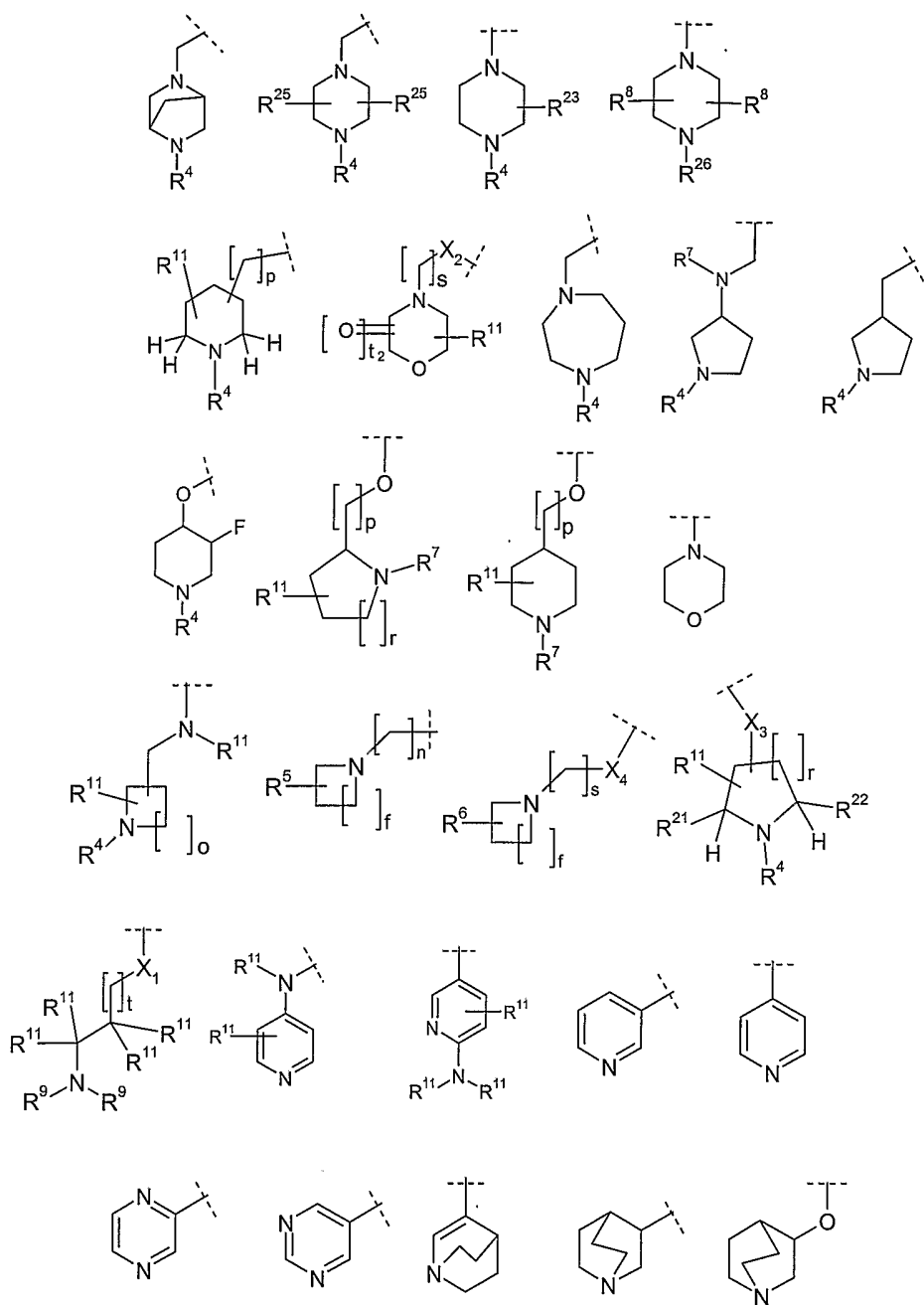
- (a) hydrogen,
 (b) C₁₋₄-alkyl,

W₁ and W₂ are each independently selected from:

- 15 (a) hydrogen,
 (b) halogen,
 (c) C₁₋₄-alkyl,
 (d) hydroxy,
 (e) C₁₋₄-alkoxy,
 20 (f) C₁₋₄-alkylthio,
 (m) -OCF₃,
 (n) -CN,
 (o) hydroxy-C₁₋₂-alkyl,
 (p) C₁₋₂-alkoxy-C₁₋₂-alkyl,
 25 (q) -CF₃,
 (r) -CONR⁹R⁹,
 (s) acetyl,
 (t) C₁₋₄-alkoxycarbonyl, or

with the proviso that when W₁ and W₂ are not selected from methoxy, methyl and halogen,
 30 at least one of W₁ and W₂ is selected from hydrogen;

R³ is a group selected from:



wherein:

5 $n = 0, 1, 2$ or 3

r is $0, 1$ or 2 ,

$o = 1, 2$, or 3 ,

p is 1 or 2 ,

$s = 2$ or 3 ,

10 $t = 0$ or 1 ,

$t_2 = 0$ or 1, and

$f = 1, 2, 3$ or 4;

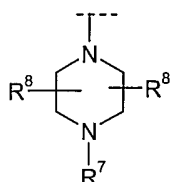
X_1 is selected from NR^7 and S;

- 5 X_2 is selected from O, NR^7 and S, provided that X_2 is selected from NR^7 and S when $t = 0$ and $s = 2$;

X_3 is selected from NR^7 and S, provided that X_3 is selected from S when $r = 1$;

X_4 is selected from O, NR^7 and S, provided that X_4 is selected from S and NR^7 when f is selected from 2 and 3, and R^6 simultaneously is selected from hydrogen and C_{1-4} alkyl; or;

- 10 when P is a group selected from formula (V) wherein $j = 1$, R^3 is additionally selected from the following group;



R^4 is selected from:

- 15 (a) hydrogen,
 (b) C_{1-4} -alkyl,
 (d) hydroxy- C_{2-4} -alkyl,
 (g) C_{3-6} -cycloalkyl,
 (h) C_{3-6} -cycloalkyl- C_{1-4} -alkyl,
 20 (i) C_{1-4} -alkoxy- C_{2-4} -alkyl
 (m) 3,3,3-trifluoropropyl;

R^5 is selected from:

- (a) hydrogen,
 25 (b) C_{1-4} -alkyl,
 (c) hydroxy- C_{1-4} -alkyl,
 (d) C_{1-4} -alkoxymethyl,
 (e) halo- C_{1-4} -alkyl,
 (f) $-NR^{11}R^{11}$,
 30 (g) hydroxy, provided that the said hydroxy group is not attached to a carbon atom adjacent to a ring nitrogen atom, or

(h) fluorine, provided that the said fluorine atom is not attached to a carbon atom adjacent to a ring nitrogen atom;

R⁶ is selected from:

- 5 (a) hydrogen,
 (b) C₁₋₄-alkyl,
 (c) hydroxy-C₁₋₄-alkyl,
 (d) C₁₋₄-alkoxy-C₁₋₄-alkyl,
 (e) hydroxy, provided that the said hydroxy group is not attached to a carbon atom
10 adjacent to a heterocyclic ring nitrogen atom,
 (f) fluorine, provided that the said fluorine atom is not attached to a carbon atom
 adjacent to a ring nitrogen atom, or
 (g) halo-C₁₋₄-alkyl;

15 R⁷ is each independently selected from:

- (a) hydrogen, provided that R⁷ is not hydrogen when present simultaneously with r
 and said r is 1 or 2,
 (b) C₁₋₄-alkyl,
 (c) hydroxy-C₂₋₄-alkyl, or
20 (d) methoxy-C₂₋₄-alkyl;

R⁸ is each independently selected from:

- (a) hydrogen, or
 (b) C₁₋₄-alkyl, with the proviso that when both R⁸ simultaneously are selected from
25 C₁₋₄-alkyl, said C₁₋₄-alkyl may be attached to the same or different carbon atoms,
 or when two groups are present at the same carbon atom they may together form a
 cyclopropane ring;

R⁹ is each independently selected from:

- 30 (a) hydrogen,
 (b) C₁₋₆-alkyl, or

the two R⁹ groups together with the nitrogen to which they are attached form a heterocyclic ring; and provided that when the two R⁹ groups form a piperazine ring, the

nitrogen of the said piperazine ring that allows the substitution is optionally substituted with C₁₋₄-alkyl;

R¹⁰ is selected from:

- 5 (a) C₁₋₆-alkyl,
 (c) aryl, or
 (d) heteroaryl,

wherein heteroaryl or aryl may be substituted in one or more positions with substituents selected from halogen, C₁₋₄-alkyl, C₁₋₄-alkoxy, cyano, trifluoromethyl;

10

R¹¹ is each independently selected from:

- (a) hydrogen, or
 (b) methyl,
 (c) ethyl, provided that R¹¹ is present in a group R²⁶ selected from -CH₂-CO-
15 NR¹¹R¹¹;

R¹² is selected from:

- (a) hydrogen,
 (c) aryl,
20 (d) aryl-C₁₋₃-alkyl,
 (g) heteroaryl, or
 (h) heteroaryl-C₁₋₃-alkyl,

wherein any heteroaryl or aryl residue, alone or as part of another group, may be optionally substituted, independently, in one or more positions with substituents selected
25 from

- (b) halogen,
 (c) C₁₋₄-alkyl,
 (d) hydroxy,
 (e) C₁₋₄-alkoxy,
30 (m) -OCF₃,
 (n) -CN,
 (o) hydroxy-C₁₋₃-alkyl,
 (p) C₁₋₃-alkoxy-C₁₋₃-alkyl,
 (q) halo-C₁₋₄-alkyl,

- (r) $-NR^9R^9$,
 (t) $-CONR^9R^9$,
 (u) $-NR^7COR^{10}$,
 (v) $-C(=O)R^{10}$,
 5 (x) C_{1-3} -alkylthio, or
 (ab) methylsulfonyl;

R^{13} is selected from:

- (c) aryl,
 10 (d) heteroaryl,
 (e) aryl- C_{1-2} -alkyl, or
 (f) heteroaryl- C_{1-2} -alkyl,

wherein any heteroaryl or aryl residue may be optionally substituted in one or more positions with substituents selected from halogen, C_{1-4} -alkyl, C_{1-4} -alkoxy, cyano,
 15 trifluoromethyl and acetyl;

R^{14} is selected from:

- (a) aryl,
 (b) heteroaryl,
 20 (c) aryl- C_{1-3} -alkyl, or
 (d) heteroaryl- C_{1-3} -alkyl;

wherein any heteroaryl or aryl residue may be optionally substituted in one or more positions with substituents selected from halogen, C_{1-4} -alkyl, C_{1-4} -alkoxy, cyano, and trifluoromethyl;

25

R^{21} and R^{22} are each independently selected from:

- (a) hydrogen, or
 (b) methyl,
 30 provided that, when present simultaneous with R^{11} , at least two of R^{11} , R^{21} and R^{22} are selected from hydrogen;

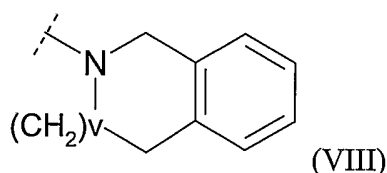
R^{23} is selected from:

- (a) hydroxy- C_{1-4} -alkyl,

- (b) C₁₋₄-alkoxymethyl, or
- (c) halo-C₁₋₄-alkyl;

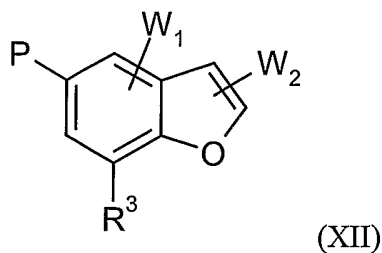
R²⁵ is selected from:

- 5 (a) hydrogen,
- (b) C₁₋₄-alkyl,
- (c) hydroxy-C₁₋₄-alkyl,
- (d) C₁₋₄-alkoxy-C₁₋₄-alkyl, or
- (e) fluoromethyl;
- 10 with the proviso that when both R²⁵ simultaneously are selected from C₁₋₄-alkyl, said C₁₋₄-alkyl may be attached to the same or different carbon atoms, and with the further proviso that when one R²⁵ is selected from hydroxy-C₁₋₄-alkyl, C₁₋₄-alkoxy-C₁₋₄-alkyl, and fluoromethyl; the other R²⁵ represents hydrogen;
- 15 R²⁶ is selected from:
 - (e) C₃₋₇-cycloalkyl-C₁₋₄-alkyl,
 - (f) -CH₂-CO-NR¹¹R¹¹, or
 - (g) 3,3,3-trifluoropropyl;
- 20 with the proviso that R² and R¹² in Formula (III) are not simultaneously selected from hydrogen; and with the further proviso that the said R² and R¹² together may form a heterocyclic ring selected from piperidine, pyrrolidine, morpholine, piperazine, thiomorpholine, and provided that when R² and R¹² together form a piperazine ring, the distal piperazine nitrogen may be optionally substituted by C₁₋₄ alkyl or aryl, and wherein
- 25 said aryl may be substituted in one or more positions with substituents selected from halogen, C₁₋₄-alkyl, C₁₋₄-alkoxy, cyano, trifluoromethyl; or R² and R¹² together form a heteroaromatic ring of Formula (VIII):



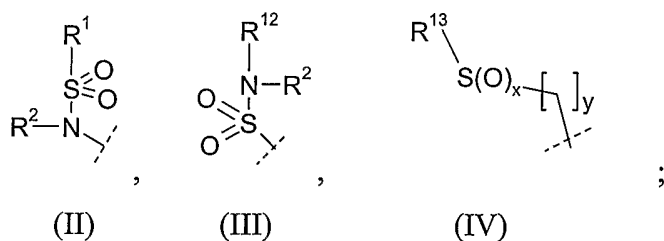
wherein v is 0 or 1.

4. The compound according to any one of claims 1 to 3, which has the general Formula (XII):



5

5. The compound according to claim 4, wherein
P is selected from a substituent of Formula (II) –(IV)



x is 2 and y is 0;

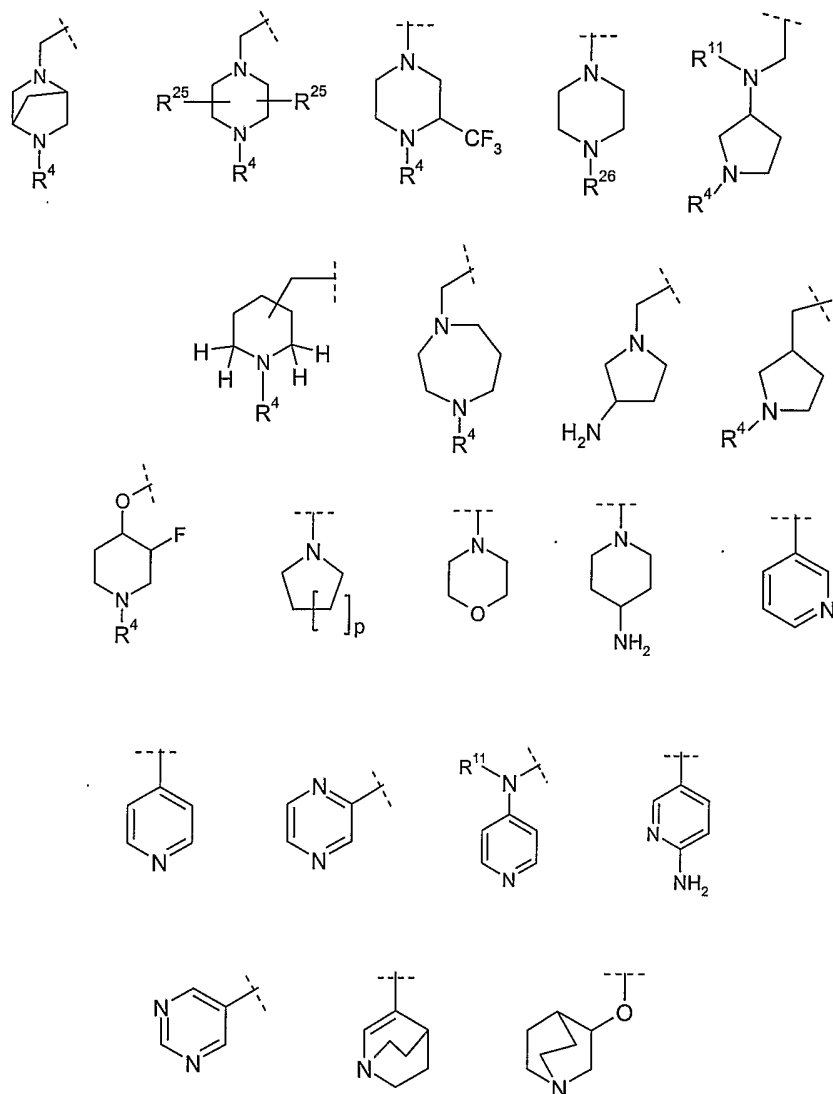
10

R¹ is selected from aryl and heteroaryl, wherein any heteroaryl or aryl residue may be optionally substituted, independently, in one or more positions with a substituent selected from halogen, C₁₋₄-alkyl C₁₋₄-alkoxy and trifluoromethyl;

15 R² is selected from hydrogen;

W₁ and W₂ are hydrogen;

R³ is a group selected from



wherein

$p = 1 \text{ or } 2$;

5 R^4 is selected from:

- (a) hydrogen, or
- (b) C_{1-4} -alkyl;

R^{11} is each independently selected from:

- 10 (a) hydrogen, or
- (b) methyl,
- (c) ethyl, provided that R^{11} is present in a group R^{26} selected from $-CH_2-CO-NR^{11}R^{11}$;

R^{12} and R^{13} are each independently selected from aryl and heteroaryl, wherein any heteroaryl or aryl residue may be optionally substituted, independently, in one or more positions with a substituent selected from halogen, C_{1-4} -alkyl, C_{1-4} -alkoxy, and CF_3 ;

5

R^{25} is selected from:

- (a) hydrogen, or
- (b) C_{1-4} -alkyl;

10

R^{26} is selected from:

- (e) C_{3-7} -cycloalkyl- C_{1-4} -alkyl,
- (f) $-CH_2-CO-NR^{11}R^{11}$, or
- (g) 3,3,3-trifluoropropyl.

15

6. The compound according to claim 5, wherein

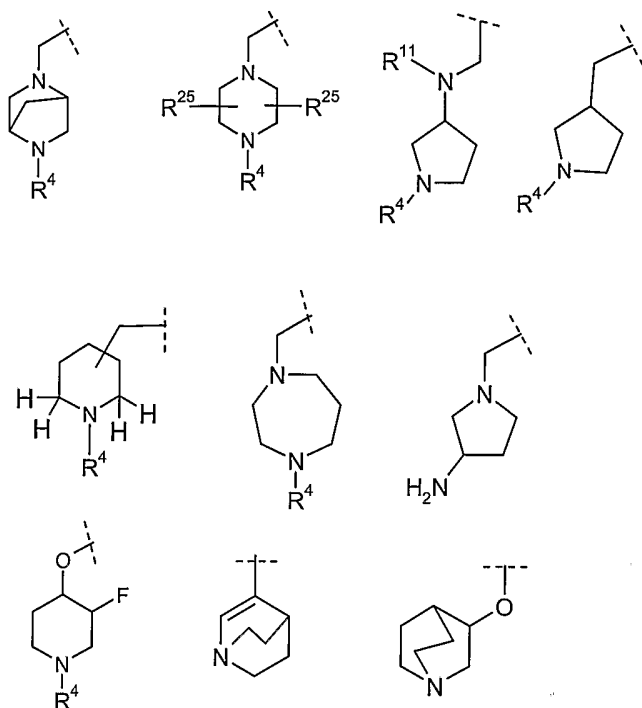
R^1 , R^{12} and R^{13} are each independently selected from phenyl or substituted phenyl selected from 2-methoxy-5-methylphenyl, 2-methylphenyl, 4-methylphenyl, 4-fluorophenyl, 3,4-dimethoxyphenyl, 2-chlorophenyl, 2-trifluoromethylphenyl, 2,6-dichlorophenyl, 3-chloro-4-methylphenyl, 3-methylphenyl, 3,6-dichloro-2-methylphenyl, and 2-chloro-5-fluorophenyl; or heteroaryl or substituted heteroaryl selected from 2-thienyl, 5-chloro-2-thienyl, 5-chloro-and 1,3-dimethyl-1H-pyrazol-4-yl; and

20

R^2 is selected from hydrogen;

25

7. The compound according to any one of claims 5 to 6, wherein R^3 is a group selected from:



; wherein

R^4 is each independently selected from:

- (a) hydrogen, or
- (b) methyl,

5

R^{11} is each independently selected from:

- (a) hydrogen, or
- (b) methyl;

10 R^{25} is each independently selected from:

- (a) hydrogen, or
- (b) methyl.

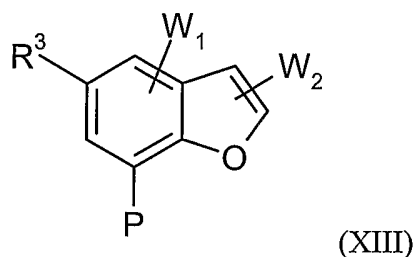
8. The compound according to claim 5, wherein R^4 is selected from:

- 15 (a) hydrogen,
- (b) methyl, or
- (c) ethyl.

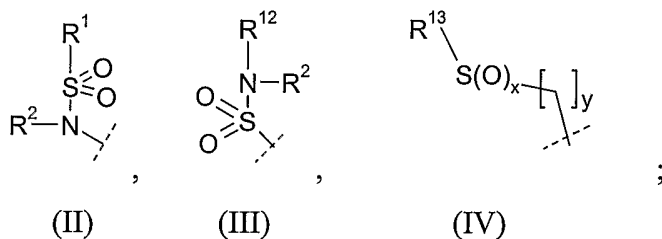
9. The compound according to any one of claims 5 to 8, wherein R^4 or R^{11} is selected from

20 hydrogen.

10. The compound according to any one of claims 1 to 3, which has the general Formula (XIII):



- 5 11. The compound according to claim 10, wherein
P is selected from a substituent of Formula (II) –(IV)

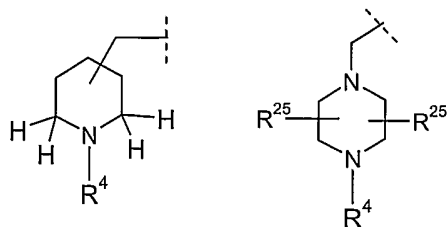


x is 2 and y is 0;

- R¹ is selected from aryl and heteroaryl, wherein any heteroaryl or aryl residue may be
10 optionally substituted, independently, in one or more positions with a substituent selected
from halogen, C₁₋₄-alkyl, trifluoromethoxy, and C₁₋₄-alkoxy;

R² is selected from hydrogen;

- 15 W₁ and W₂ are hydrogen;



R³ is a group selected from

wherein

R⁴ is each independently selected from:

- 20 (a) hydrogen, or
(b) C₁₋₄-alkyl;

R²⁵ is each independently selected from:

(a) hydrogen, or

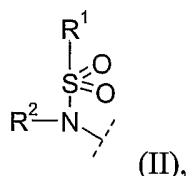
(b) C₁₋₄-alkyl, with the proviso that when both R²⁵ represent C₁₋₄-alkyl, said C₁₋₄-

5 alkyl may be attached to the same or different carbon atoms;

R¹² and R¹³ are each independently selected from aryl and heteroaryl, wherein any heteroaryl or aryl residue may be optionally substituted, independently, in one or more positions with a substituent selected from halogen, C₁₋₄-alkyl, trifluoromethyl, and C₁₋₄-
10 alkoxy.

12. The compound according to claim 11, wherein

P is selected from a substituent of Formula (II)

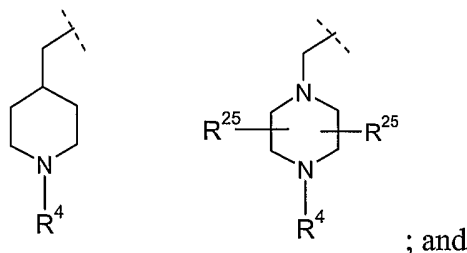


R¹ is selected from 2-methoxy-5-methylphenyl;

15 R² is selected from hydrogen;

W₁ and W₂ are hydrogen;

R³ is a group selected from:



R⁴ is each independently selected from

20 a) hydrogen, or

b) methyl;

R²⁶ is each independently selected from

a) hydrogen, or

25 b) methyl.

13. The compound according to any one of claims 1 to 12, which is selected from
- N-(7-{Methyl[3-(methylamino)propyl]amino}-1-benzofuran-5-yl)benzenesulfonamide hydrochloride,
- N-(7-Piperidin-1-yl-1-benzofuran-5-yl)benzenesulfonamide,
- 5 4-Fluoro-N-(7-piperidin-1-yl-1-benzofuran-5-yl)benzenesulfonamide,
- 3,4-Dimethoxy-N-(7-piperidin-1-yl-1-benzofuran-5-yl)benzenesulfonamide hydrochloride,
- 3,4-Dimethoxy-N-(7-pyrrolidin-1-yl-1-benzofuran-5-yl)benzenesulfonamide,
- N-(7-Pyrrolidin-1-yl-1-benzofuran-5-yl)benzenesulfonamide,
- 10 4-Fluoro-N-(7-pyrrolidin-1-yl-1-benzofuran-5-yl)benzenesulfonamide hydrochloride,
- 4-Fluoro-N-(7-morpholin-4-yl-1-benzofuran-5-yl)benzenesulfonamide hydrochloride,
- N-(7-Morpholin-4-yl-1-benzofuran-5-yl)benzenesulfonamide hydrochloride,
- 15 3,4-Dimethoxy-N-(7-morpholin-4-yl-1-benzofuran-5-yl)benzenesulfonamide,
- 2-Methoxy-5-methyl-N-(7-pyridin-4-yl-1-benzofuran-5-yl)benzenesulfonamide,
- N-(7-Pyridin-3-yl-1-benzofuran-5-yl)benzenesulfonamide trifluoroacetate,
- 2-Methoxy-5-methyl-N-(7-pyridin-3-yl-1-benzofuran-5-yl)benzenesulfonamide trifluoroacetate,
- 20 N-(7-Pyrazin-2-yl-1-benzofuran-5-yl)benzenesulfonamide trifluoroacetate,
- N-(7-Pyrimidine-5-yl-1-benzofuran-5-yl)benzenesulfonamide hydrochloride, and,
- N-[7-(1-Aza-bicyclo[2.2.2]oct-2-en-3-yl)-benzofuran-5-yl]-2-methoxy-5-methyl-benzenesulfonamide hydrochloride,
- 2-[4-(5-{[(2-Chlorophenyl)sulfonyl]amino}-1-benzofuran-7-yl)piperazin-1-yl]-
- 25 N,N-diethylacetamide hydrochloride,
- N,N-diethyl-2-[4-(5-{[(2-methoxy-5-methylphenyl)sulfonyl]amino}-1-benzofuran-7-yl)piperazin-1-yl]acetamide hydrochloride,
- N-[7-(1-Azabicyclo[2.2.2.]oct-3-yloxy)-1-benzofuran-5-yl]benzenesulfonamide hydrochloride,
- 30 N-[7-(1-Azabicyclo[2.2.2.]oct-3-yloxy)-1-benzofuran-5-yl]-2-chlorobenzenesulfonamide hydrochloride,
- N-[7-(1-Azabicyclo[2.2.2.]oct-3-yloxy)-1-benzofuran-5-yl]-2-methoxy-5-benzenesulfonamide hydrochloride,

- N-{7-[(2-Morpholin-4-ylethyl)amino]-1-benzofuran-5-yl}benzenesulfonamide hydrochloride,
- 2-Methoxy-5-methyl-N-{7-[(2-morpholin-4-ylethyl)amino]-1-benzofuran-5-yl}benzenesulfonamide hydrochloride,
- 5 N-{7-[(2-Morpholin-4-ylethyl)amino]-1-benzofuran-5-yl}-2-(trifluoromethyl)benzenesulfonamide hydrochloride,
- 2,6-Dichloro-N-{7-[(2-morpholin-4-ylethyl)amino]-1-benzofuran-5-yl}benzenesulfonamide hydrochloride,
- N-(7-{[2(Dimethylamino)ethyl]amino}-1-benzofuran-5-yl)-2-methoxy-5-
- 10 benzenesulfonamide hydrochloride,
- 2-Chloro-N(7-{[2-(dimethylamino)]-1-benzofuran-5-yl})benzenesulfonamide hydrochloride,
- N-[7-(Pyridin-4-ylamino)-1-benzofuran-5-yl]benzenesulfonamide hydrochloride,
- 2-Chloro-N-[7-(pyridin-4-ylamino)-1-benzofuran-5-yl]benzenesulfonamide
- 15 hydrochloride,
- 2-Methoxy-5-methyl-N-[7-(pyridin-4-ylamino)-1-benzofuran-5-yl]benzenesulfonamide hydrochloride,
- 2-Methoxy-5-methyl-N-[7-(piperazin-1-ylcarbonyl)-1-benzofuran-5-yl]benzenesulfonamide hydrochloride,
- 20 2-Methoxy-5-methyl-N-[7-(piperazin-1-ylmethyl)-1-benzofuran-5-yl]benzenesulfonamide hydrochloride,
- N-{7-[(3-Aminopyrrolidin-1-yl)methyl]-1-benzofuran-5-yl}-2-methoxy-5-methylbenzenesulfonamide hydrochloride,
- N-[7(6,6-Dioxidohexahydrothieno[3,4-b]pyrazin-1(2H)-yl)-1-benzofuran-5-yl]-2-
- 25 methoxy-5-methylbenzenesulfonamide hydrochloride,
- N-[7(6,6-Dioxidohexahydrothieno[3,4-b]pyrazin-1(2H)-yl)-1-benzofuran-5-yl]benzenesulfonamide hydrochloride,
- N-{7-[(2-Pyrrolidin-1-ylethyl)amino]-1-benzofuran-5-yl}benzenesulfonamide hydrochloride,
- 30 2-Methoxy-5-methyl-N-{7-[(2-pyrrolidin-1-ylethyl)amino]-1-benzofuran-5-yl}benzenesulfonamide hydrochloride,
- N-{7-[(2-Pyrrolidin-1-ylethyl)amino]-1-benzofuran-5-yl}-2-(trifluoromethyl)benzenesulfonamide hydrochloride,

3-Chloro-4-methyl-N-{7-[(2-pyrrolidin-1-ylethyl)amino]-1-benzofuran-5-yl}benzenesulfonamide hydrochloride,

2-Methoxy-5-methyl-N-{7-[(3-morpholin-4-ylpropyl)amino]-1-benzofuran-5-yl}benzenesulfonamide hydrochloride,

5 N-{7-[(3-Morpholin-4-ylpropyl)amino]-1-benzofuran-5-yl}-2-(trifluoromethyl)benzenesulfonamide hydrochloride,

3-Chloro-4-methyl-N-{7-[(3-morpholin-4-ylpropyl)amino]-1-benzofuran-5-yl}benzenesulfonamide hydrochloride,

10 N-[7-({[(2R)-1-Ethylpyrrolidin-2-yl]methyl}amino)-1-benzofuran-5-yl]benzenesulfonamide hydrochloride,

N-[7-({[(2R)-1-Ethylpyrrolidin-2-yl]methyl}amino)-1-benzofuran-5-yl]-2-methoxy-5-methylbenzenesulfonamide hydrochloride,

N-[7-({[(2R)-1-Ethylpyrrolidin-2-yl]methyl}amino)-1-benzofuran-5-yl]-2-(trifluoromethyl)benzenesulfonamide hydrochloride,

15 N-[7-({[(2R)-1-Ethylpyrrolidin-2-yl]methyl}amino)-1-benzofuran-5-yl]-3-methylbenzenesulfonamide hydrochloride,

N-[7-({[(2R)-1-Ethylpyrrolidin-2-yl]methyl}amino)-1-benzofuran-5-yl]thiophene-2-sulfonamide hydrochloride,

20 5-Chloro-N-[7-({[(2R)-1-ethylpyrrolidin-2-yl]methyl}amino)-1-benzofuran-5-yl]thiophene-2-sulfonamide hydrochloride,

5-Chloro-N-[7-({[(2R)-1-ethylpyrrolidin-2-yl]methyl}amino)-1-benzofuran-5-yl]-1,3-dimethyl-1H-pyrazole-4-sulfonamide hydrochloride,

N-(7-{[3-(2-Methylpiperidin-1-yl)propyl]amino}-1-benzofuran-5-yl)benzenesulfonamide hydrochloride,

25 2-Methoxy-5-methyl-N-(7-{[3-(2-methylpiperidin-1-yl)propyl]amino}-1-benzofuran-5-yl)benzenesulfonamide hydrochloride,

N-(7-{[3-(2-Methylpiperidin-1-yl)propyl]amino}-1-benzofuran-5-yl)-2-(trifluoromethyl)benzenesulfonamide hydrochloride,

30 5-Chloro-1,3-dimethyl-N-(7-{[3-(2-methylpiperidin-1-yl)propyl]amino}-1-benzofuran-5-yl)-1H-pyrazole-4-sulfonamide hydrochloride,

N-[7-(6-Aminopyridin-3-yl)-1-benzofuran-5-yl]-2-methoxy-5-methylbenzenesulfonamide,

N-{7-[4-(Cyclopropylmethyl)piperazin-1-yl]-1-benzofuran-5-yl}-2-methoxy-5-methylbenzenesulfonamide hydrochloride,

- 2-Methoxy-5-methyl-N-{7-[4-(3,3,3-trifluoropropyl)piperazin-1-yl]-1-benzofuran-5-yl}benzenesulfonamide hydrochloride,
- 2-Methoxy-5-methyl-N-{7-[3-(trifluoromethyl)piperazin-1-yl]-1-benzofuran-5-yl}benzenesulfonamide hydrochloride,
- 5 N-[7-(Aminopiperidin-1-yl)-1-benzofuran-5-yl]-2-(trifluoromethyl)benzenesulfonamide hydrochloride,
- N-[7-(Aminopiperidin-1-yl)-1-benzofuran-5-yl]-benzenesulfonamide hydrochloride,
- N-[7-(Aminopiperidin-1-yl)-1-benzofuran-5-yl]-2-chlorobenzenesulfonamide
- 10 hydrochloride,
- N-[7-(Aminopiperidin-1-yl)-1-benzofuran-5-yl]-2-methoxy-5-methylbenzenesulfonamide hydrochloride,
- N-(7-{[cis-3-Fluoropiperidin-4-yl]oxy}-1-benzofuran-5-yl)-2-methoxy-5-methylbenzenesulfonamide hydrochloride,
- 15 N-(7-{trans-3-Fluoropiperidin-4-yl]oxy}-1-benzofuran-5-yl)-2-methoxy-5-methylbenzenesulfonamide hydrochloride ,
- N-(7-{[cis-3-Fluoropiperidin-4-yl]oxy}-1-benzofuran-5-yl)-2-(trifluoromethyl)benzenesulfonamide hydrochloride,
- N-(7-{[trans-3-Fluoropiperidin-4-yl]oxy}-1-benzofuran-5-yl)-2-
- 20 (trifluoromethyl)benzenesulfonamide hydrochloride,
- 2-Chloro-N-(7-{[trans-3-fluoropiperidin-4-yl]oxy}-1-benzofuran-5-yl)benzenesulfonamide hydrochloride,
- N-(7-{[trans-3-Fluoropiperidin-4-yl]oxy}-1-benzofuran-5-yl)-3-methylbenzenesulfonamide hydrochloride,
- 25 3,6-Dichloro-N-(7-{[trans-3-fluoropiperidin-4-yl]oxy}-1-benzofuran-5-yl)-2-methylbenzenesulfonamide hydrochloride,
- 2-Chloro-5-fluoro-N-(7-{[trans-3-fluoropiperidin-4-yl]oxy}-1-benzofuran-5-yl)benzenesulfonamide hydrochloride,
- N-(2-Methoxy-5-methylphenyl)-7-[(3-methylpiperazin-1-yl)methyl]-1-benzofuran-
- 30 5-sulfonamide hydrochloride,
- N-(2-Methylphenyl)-7-(piperazin-1-ylmethyl)-1-benzofuran-5-sulfonamide, trifluoroacetate,
- 7-[(3,5-Dimethylpiperazin-1-yl)methyl]-N-(2-methylphenyl)-1-benzofuran-5-sulfonamide, trifluoroacetate,

- N-(2-Methylphenyl)-7-[(3-methylpiperazin-1-yl)methyl]-1-benzofuran-5-sulfonamide, trifluoroacetate,
- 7-(1,4-Diazepan-1-ylmethyl)-N-(2-methylphenyl)-1-benzofuran-5-sulfonamide, trifluoroacetate,
- 5 7-[(trans-2,5-Dimethylpiperazin-1-yl)methyl]-N-(2-methylphenyl)-1-benzofuran-5-sulfonamide, trifluoroacetate,
- N-(2-Methylphenyl)-7-[(2R)-2-methylpiperazin-1-ylmethyl]-1-benzofuran-5-sulfonamide, trifluoroacetate,
- N-(2-Methoxy-5-methylphenyl)-7-[(3-methylpiperazin-1-yl)methyl]-1-benzofuran-10 5-sulfonamide, trifluoroacetate,
- 7-(1,4-Diazepan-1-ylmethyl)-N-(2-methoxy-5-methylphenyl)-1-benzofuran-5-sulfonamide, trifluoroacetate,
- N-(2-Methoxy-5-methylphenyl)-7-(piperazin-1-ylmethyl)-1-benzofuran-5-sulfonamide, trifluoroacetate,
- 15 7-[(cis-3,5-Dimethylpiperazin-1-yl)methyl]-N-(2-methoxy-5-methylphenyl)-1-benzofuran-5-sulfonamide, trifluoroacetate,
- 7-[[trans-2,5-Dimethylpiperazin-1-yl]methyl]-N-(2-methoxy-5-methylphenyl)-1-benzofuran-5-sulfonamide, trifluoroacetate,,
- 7-[(1S,4S)-2,5-Diazabicyclo[2.2.1]hept-2-ylmethyl]-N-(2-methoxy-5-methylphenyl)-1-benzofuran-5-sulfonamide, trifluoroacetate,‡
- 20 N-(2-Methoxy-5-methylphenyl)-7-[(2-methylpiperazin-1-yl)methyl]-1-benzofuran-5-sulfonamide, trifluoroacetate,
- 2-Chloro-N-[7-(piperazin-1-ylmethyl)-1-benzofuran-5-yl]benzenesulfonamide dihydrochloride,
- 25 2-Methyl-N-[7-(piperazin-1-ylmethyl)-1-benzofuran-5-yl]benzenesulfonamide, dihydrochloride,
- N-[7-(Piperazin-1-ylmethyl)-1-benzofuran-5-yl]thiophene-2-sulfonamide, dihydrochloride,
- 2-Chloro-N-[7-(1,4-diazepan-1-ylmethyl)-1-benzofuran-5-yl]benzenesulfonamide dihydrochloride,
- 30 N-[7-(1,4-Diazepan-1-ylmethyl)-1-benzofuran-5-yl]-2-methylbenzenesulfonamide, dihydrochloride,
- N-[7-(1,4-Diazepan-1-ylmethyl)-1-benzofuran-5-yl]thiophene-2-sulfonamide dihydrochloride,

- 2-Methoxy-5-methyl-N-{7-[(2-methylpiperazin-1-yl)methyl]-1-benzofuran-5-yl}benzenesulfonamide, dihydrochloride,
- 2-Methyl-N-{7-[(2-methylpiperazin-1-yl)methyl]-1-benzofuran-5-yl}benzenesulfonamide dihydrochloride,
- 5 2,5-Dichloro-N-{7-[(2-methylpiperazin-1-yl)methyl]-1-benzofuran-5-yl}thiophene-3-sulfonamide dihydrochloride,
- 2-Methoxy-5-methyl-N-{7-[(3-methylpiperazin-1-yl)methyl]-1-benzofuran-5-yl}benzenesulfonamide, dihydrochloride,
- N-{7-[(3-Methylpiperazin-1-yl)methyl]-1-benzofuran-5-yl}-2-
- 10 (trifluoromethyl)benzenesulfonamide, dihydrochloride,
- 2-Chloro-N-{7-[(3-methylpiperazin-1-yl)methyl]-1-benzofuran-5-yl}benzenesulfonamide, dihydrochloride,
- N-{7-[(1*S*,4*S*)-2,5-Diazabicyclo[2.2.1]hept-2-ylmethyl]-1-benzofuran-5-yl}-2-methoxy-5-methylbenzenesulfonamide, dihydrochloride,
- 15 N-{7-[(1*S*,4*S*)-2,5-Diazabicyclo[2.2.1]hept-2-ylmethyl]-1-benzofuran-5-yl}-2-(trifluoromethyl)benzenesulfonamide, dihydrochloride,
- N-{7-[(1*S*,4*S*)-2,5-Diazabicyclo[2.2.1]hept-2-ylmethyl]-1-benzofuran-5-yl}-2-methylbenzenesulfonamide, dihydrochloride,
- 2-Methoxy-5-methyl-N-{7-[(trans-2,5-dimethylpiperazin-1-yl)methyl]-1-benzofuran-5-yl}benzenesulfonamide, bistrifluoroacetate,
- 20 2-Methyl-N-{7-[(trans-2,5-dimethylpiperazin-1-yl)methyl]-1-benzofuran-5-yl}benzenesulfonamide, bistrifluoroacetate,
- 2-Chloro-N-{7-[(trans-2,5-dimethylpiperazin-1-yl)methyl]-1-benzofuran-5-yl}benzenesulfonamide, bistrifluoroacetate,
- 25 1-({5-[(2-Methoxy-5-methylphenyl)sulfonyl]-1-benzofuran-7-yl}methyl)piperazine, trifluoroacetate,
- 1-{[5-(Phenylsulfonyl)-1-benzofuran-7-yl]methyl}piperazine, trifluoroacetate,
- 1-({5-[(4-Methylphenyl)sulfonyl]-1-benzofuran-7-yl}methyl)piperazine, trifluoroacetate,
- 30 1-({5-[(2-Methoxy-5-methylphenyl)sulfonyl]-1-benzofuran-7-yl}methyl)-1,4-diazepane, trifluoroacetate,
- 1-{[5-(Phenylsulfonyl)-1-benzofuran-7-yl]methyl}-1,4-diazepane, trifluoroacetate,
- 1-({5-[(4-Methylphenyl)sulfonyl]-1-benzofuran-7-yl}methyl)-1,4-diazepane, trifluoroacetate,

1-({5-[(2-Methoxy-5-methylphenyl)sulfonyl]-1-benzofuran-7-yl}methyl)-2-methylpiperazine, trifluoroacetate,

1-({5-[(2-Methoxy-5-methylphenyl)sulfonyl]-1-benzofuran-7-yl}methyl)-3-methylpiperazine, trifluoroacetate,

5 N-(2-Methylphenyl)-7-[(3R)-pyrrolidin-3-ylamino]methyl}-1-benzofuran-5-sulfonamide, trifluoroacetate,

N-(2-Methylphenyl)-7-(piperidin-4-ylmethyl)-1-benzofuran-5-sulfonamide, trifluoroacetate,

10 N-(2-Methylphenyl)-7-(pyrrolidin-3-ylmethyl)-1-benzofuran-5-sulfonamide, trifluoroacetate,

N-(2-Methylphenyl)-7-(piperidin-3-ylmethyl)-1-benzofuran-5-sulfonamide, trifluoroacetate,

2-Methoxy-5-methyl-N-[7-(piperidin-4-ylmethyl)-1-benzofuran-5-yl]benzenesulfonamide, trifluoroacetate,

15 3-({5-[(4-Methylphenyl)sulfonyl]-1-benzofuran-7-yl}methyl)pyrrolidine, trifluoroacetate,,

2-Methoxy-5-methyl-N-[5-(piperidin-4-ylmethyl)-1-benzofuran-7-yl]benzenesulfonamide, trifluoroacetate,

20 2-Methoxy-5-methyl-N-{5-[(3-methylpiperazin-1-yl)methyl]-1-benzofuran-7-yl}benzenesulfonamide, bis(trifluoroacetate,,

2-Methoxy-5-methyl-N-[5-(piperidin-4-ylmethyl)-1-benzofuran-7-yl]benzenesulfonamide, trifluoroacetate.

14. A compound according to any one of claims 1 to 13 for use in therapy.

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15. A compound according to any one of claims 1 to 13 for use in the treatment or prophylaxis of a 5-HT₆ receptor-related disorder, to achieve reduction of body weight and of body weight gain.

30 16. A compound according to claim 15, wherein the disorder is selected from obesity; type II diabetes; disorders of the central nervous system such as anxiety, depression, panic attacks, memory disorders, cognitive disorders, epilepsy, sleep disorders, migraine, anorexia, bulimia, binge eating disorders, obsessive compulsive disorders, psychoses, Alzheimer's disease, Parkinson's disease, Huntington's chorea, schizophrenia, attention

deficit hyperactive disorder, withdrawal from drug abuse, neurodegenerative diseases characterized by impaired neuronal growth, and pain.

17. A pharmaceutical formulation comprising a compound according to any one of claims
5 1 to 13 as active ingredient, in combination with a pharmaceutically acceptable diluent or carrier.

18. The pharmaceutical formulation according to claim 17 for use in the prophylaxis or
treatment of a 5-HT₆ receptor-related disorder, to achieve reduction of body weight and of
10 body weight gain.

19. The pharmaceutical formulation according to any one of claims 17 or 18, wherein the
disorder is selected from obesity; type II diabetes; disorders of the central nervous system
such as anxiety, depression, panic attacks, memory disorders, cognitive disorders, epilepsy,
15 sleep disorders, migraine, anorexia, bulimia, binge eating disorders, obsessive compulsive
disorders, psychoses, Alzheimer's disease, Parkinson's disease, Huntington's chorea,
schizophrenia, attention deficit hyperactive disorder, withdrawal from drug abuse,
neurodegenerative diseases characterized by impaired neuronal growth, and pain.

20. A method for the prophylaxis or treatment of a 5-HT₆ receptor-related disorder, to
achieve reduction of body weight and of body weight gain, which comprises administering
to a subject in need of such treatment an effective amount of a compound according to any
one of claims 1 to 13.

21. The method according to claim 20, wherein the disorder is selected from obesity; type
25 II diabetes; disorders of the central nervous system such as anxiety, depression, panic
attacks, memory disorders, cognitive disorders, epilepsy, sleep disorders, migraine,
anorexia, bulimia, binge eating disorders, obsessive compulsive disorders, psychoses,
Alzheimer's disease, Parkinson's disease, Huntington's chorea, schizophrenia, attention
30 deficit hyperactive disorder, withdrawal from drug abuse, neurodegenerative diseases
characterized by impaired neuronal growth, and pain.

22. A method for modulating 5-HT₆ receptor activity, which comprises administering to a subject in need of such treatment an effective amount of a compound according to any one of claims 1 to 13.
- 5 23. Use of a compound according to any one of claims 1 to 13 for the manufacture of a medicament for use in the prophylaxis or treatment of a 5-HT₆ receptor-related disorder, to achieve reduction of body weight and of body weight gain.
- 10 24. The use according to claim 21, wherein the disorder is selected from obesity; type II diabetes; disorders of the central nervous system such as anxiety, depression, panic attacks, memory disorders, cognitive disorders, epilepsy, sleep disorders, migraine, anorexia, bulimia, binge eating disorders, obsessive compulsive disorders, psychoses, Alzheimer's disease, Parkinson's disease, Huntington's chorea, schizophrenia, attention deficit hyperactive disorder, withdrawal from drug abuse, neurodegenerative diseases
- 15 characterized by impaired neuronal growth, and pain.
25. A cosmetic composition comprising a compound according to any one of claims 1 to 13 as active ingredient, in combination with a cosmetically acceptable diluent or carrier.
- 20 26. The cosmetic composition according to claim 25 for use in the prophylaxis or treatment of a 5-HT₆ receptor-related disorder, to achieve reduction of body weight and of body weight gain.
- 25 27. The cosmetic composition according to claim 26, wherein the disorder is selected from obesity; type II diabetes; disorders of the central nervous system such as anxiety, depression, panic attacks, memory disorders, cognitive disorders, epilepsy, sleep disorders, migraine, anorexia, bulimia, binge eating disorders, obsessive compulsive disorders, psychoses, Alzheimer's disease, Parkinson's disease, Huntington's chorea, schizophrenia, attention deficit hyperactive disorder, withdrawal from drug abuse, neurodegenerative
- 30 diseases characterized by impaired neuronal growth, and pain.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 2004/001949

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D 307/82, C07D 405/04, A61K 31/343, A61K 31/435, A61K 31/495, A61P 3/04, A61P 25/00

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)

IPC7: C07D, A61K, A61P

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

SE,DK,FI,NO classes as above

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

EPO-INTERNAL, WPI DATA, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02100822 A1 (BIOVITRUM AB), 19 December 2002 (19.12.2002) --	1-27
A	WO 03013510 A1 (SMITHKLINE BEECHAM P.L.C.), 20 February 2003 (20.02.2003) --	1-27
A	WO 9827081 A1 (SMITHKLINE BEECHAM PLC), 25 June 1998 (25.06.1998) --	1-27
P,A	WO 200400828 A1 (BIOVITRUM AB), 31 December 2003 (31.12.2003) --	1-27

☒ 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

"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

1 April 2005

Date of mailing of the international search report

12-04-2005

Name and mailing address of the ISA/

Swedish Patent Office

Box 5055, S-102 42 STOCKHOLM

Facsimile No. +46 8 666 02 86

Authorized officer

Eva Johansson/EÖ

Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 2004/001949**C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 02098857 A1 (F. HOFFMAN-LA ROCHE AG), 12 December 2002 (12.12.2002) --	1-27
A	WO 0132646 A2 (SMITHKLINE BEECHAM P.L.C.), 10 May 2001 (10.05.2001) -- -----	1-27

INTERNATIONAL SEARCH REPORT

International application No.
SE 2004/001949

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.: 20-22
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 20-22 relate to a method of treatment of the human or animal body by surgery or by therapy, as well as diagnostic
.../...
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
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.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
SE 2004/001949

Box II.1

methods /Rule 39.1(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds.

INTERNATIONAL SEARCH REPORT

Information on patent family members

01/03/2005

International application No.

PCT/SE 2004/001949

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INTERNATIONAL SEARCH REPORT

Information on patent family members

01/03/2005

International application No.

PCT/SE 2004/001949

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				TW	591015	B	11/06/2004
				US	6787535	B	07/09/2004
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INTERNATIONAL SEARCH REPORT

Information on patent family members

01/03/2005

International application No.

PCT/SE 2004/001949

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				EP	1228066	A	07/08/2002
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