



(86) Date de dépôt PCT/PCT Filing Date: 2005/01/24

(87) Date publication PCT/PCT Publication Date: 2005/09/01

(85) Entrée phase nationale/National Entry: 2006/08/01

(86) N° demande PCT/PCT Application No.: IB 2005/000172

(87) N° publication PCT/PCT Publication No.: 2005/080361

(30) Priorité/Priority: 2004/02/02 (US60/541,151)

(51) Cl.Int./Int.Cl. *C07D 295/096* (2006.01),
A61P 11/06 (2006.01), *A61K 31/4025* (2006.01),
A61P 37/00 (2006.01), *C07D 209/44* (2006.01),
C07D 213/30 (2006.01), *C07D 215/227* (2006.01),
C07D 217/22 (2006.01), *C07D 231/30* (2006.01),
C07D 237/14 (2006.01), *C07D 237/32* (2006.01),
C07D 239/26 (2006.01), *C07D 239/34* (2006.01),
C07D 241/08 (2006.01), *C07D 403/04* (2006.01)

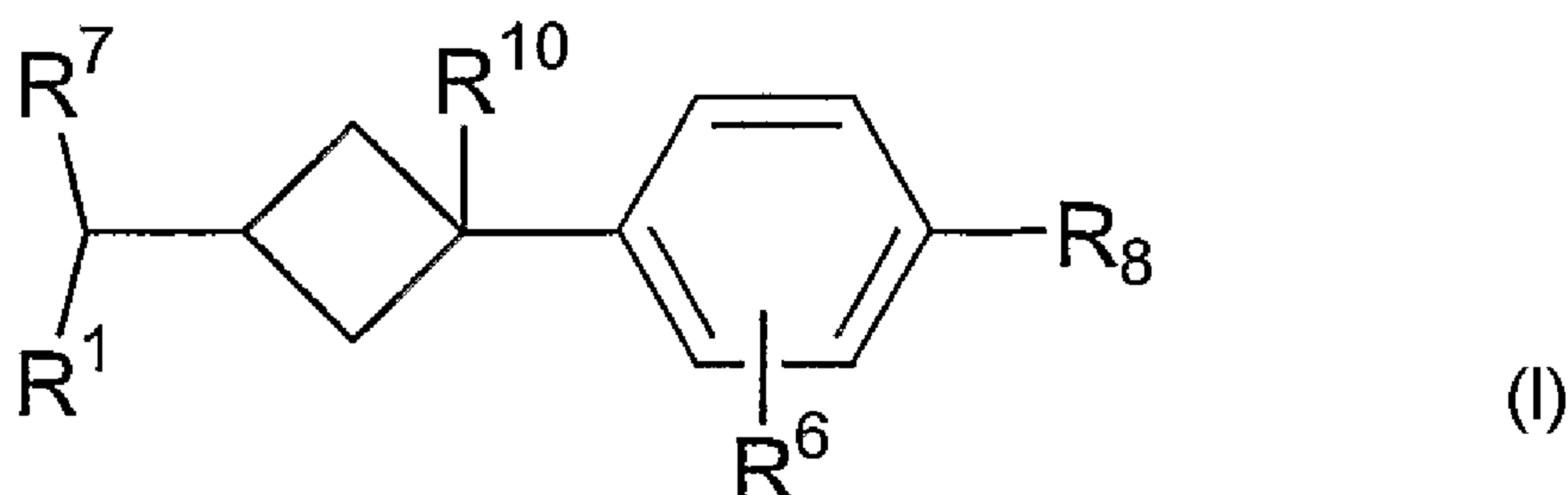
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(54) Titre : MODULATEURS DU RECEPTEUR DE L'HISTAMINE-3

(54) Title: HISTAMINE-3 RECEPTOR MODULATORS



(57) **Abrégé/Abstract:**

This invention is directed to a compound of the formula (I) as defined herein, or a pharmaceutically acceptable salt thereof; a pharmaceutical composition containing a compound of formula (I), a method of treatment of a disorder or condition that may be treated by modulating histamine H3 receptors, the method comprising administering to a mammal in need of such treatment a compound of formula (I) as described above, and a method of treatment of a disorder or condition selected from the group consisting of depression, mood disorders, schizophrenia, anxiety disorders, Alzheimer's disease, attention-deficit hyperactivity disorder (ADHD), psychotic disorders, sleep disorders, obesity, dizziness, epilepsy, motion sickness, respiratory diseases, allergy, allergy-induced airway responses, allergic rhinitis, nasal congestion, allergic congestion, congestion, hypotension, cardiovascular disease, diseases of the GI tract, hyper and hypo motility and acidic secretion of the gastro-intestinal tract, the method comprising administering to a mammal in need of such treatment a compound of formula (I) as described above.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
1 September 2005 (01.09.2005)

PCT

(10) International Publication Number
WO 2005/080361 A1

(51) International Patent Classification⁷: **C07D 295/096**,
231/30, 239/34, 237/14, 239/26, 237/32, 209/44, 241/08,
217/22, 215/227, 403/04, 213/30, A61K 31/4025, A61P
37/00, 11/06

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(21) International Application Number:
PCT/IB2005/000172

(22) International Filing Date: 24 January 2005 (24.01.2005)

(25) Filing Language: English

(26) Publication Language: English

(81) Designated States (*unless otherwise indicated, for every
kind of national protection available*): AE, AG, AL, AM,
AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN,
CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI,
GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE,
KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD,
MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG,
PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM,
TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM,
ZW.

(30) Priority Data:
60/541,151 2 February 2004 (02.02.2004) US

(84) Designated States (*unless otherwise indicated, for every
kind of regional protection available*): ARIPO (BW, GH,
GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM,
ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI,
FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO,
SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN,
GQ, GW, ML, MR, NE, SN, TD, TG).

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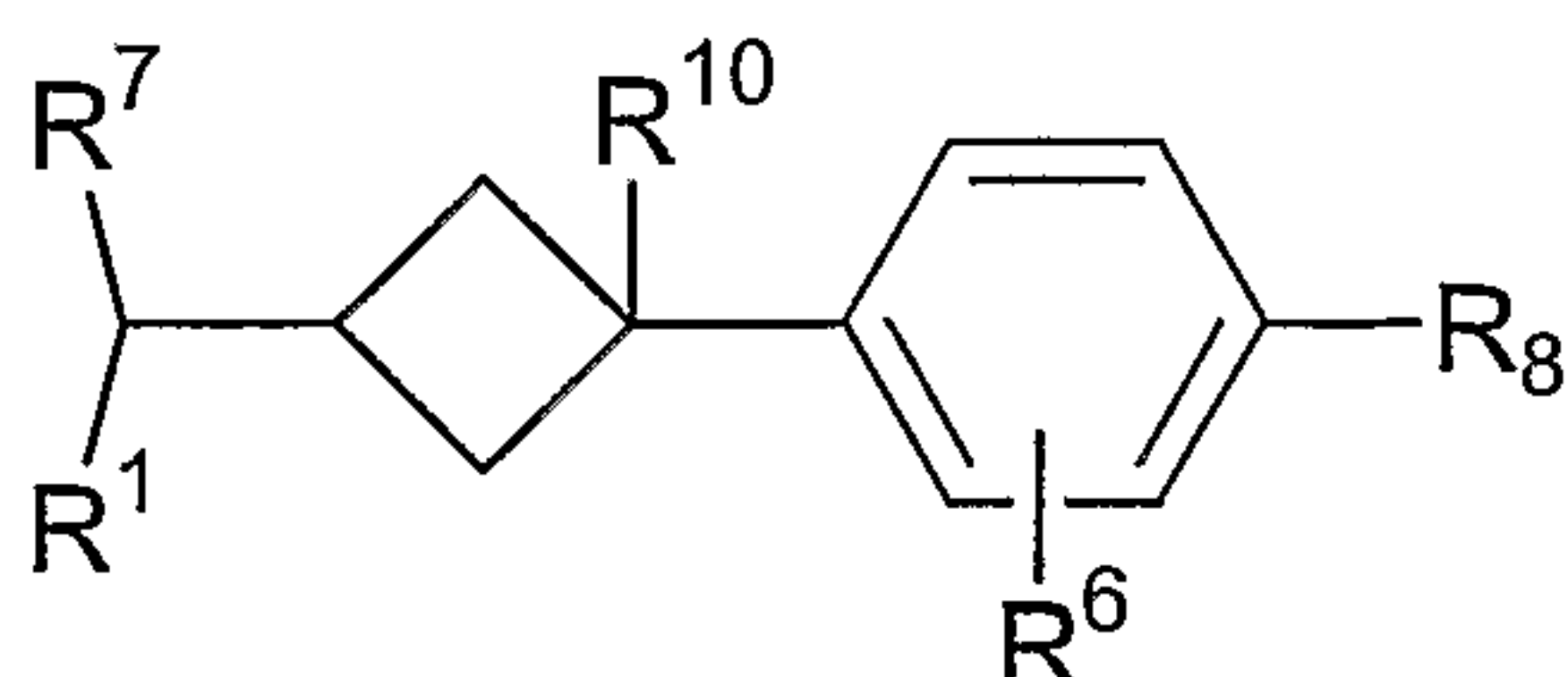
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Published:

— *with international search report*

*For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.*

(54) Title: HISTAMINE-3 RECEPTOR MODULATORS



(I)

(57) **Abstract:** This invention is directed to a compound of the
formula (I) as defined herein, or a pharmaceutically acceptable
salt thereof; a pharmaceutical composition containing a com-
pound of formula (I), a method of treatment of a disorder or
condition that may be treated by modulating histamine H₃ re-
ceptors, the method comprising administering to a mammal in
need of such treatment a compound of formula (I) as described
above, and a method of treatment of a disorder or condition

selected from the group consisting of depression, mood disorders, schizophrenia, anxiety disorders, Alzheimer's disease, atten-
tion-deficit hyperactivity disorder (ADHD), psychotic disorders, sleep disorders, obesity, dizziness, epilepsy, motion sickness, res-
piratory diseases, allergy, allergy-induced airway responses, allergic rhinitis, nasal congestion, allergic congestion, congestion, hy-
potension, cardiovascular disease, diseases of the GI tract, hyper and hypo motility and acidic secretion of the gastro-intestinal tract,
the method comprising administering to a mammal in need of such treatment a compound of formula (I) as described above.



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HISTAMINE-3 RECEPTOR MODULATORS

Background of the Invention

This invention is directed to compounds of formula I described herein, to pharmaceutical composition comprising such compounds, and to methods of treatment of disorders or conditions that may be treated by modulating histamine H3 receptors using such compounds.

Histamine is a well-known mediator in hypersensitive reactions, such as allergies, hay fever, and asthma, which are commonly treated with antagonists of histamine or "antihistamines." It has also been established that histamine receptors exist in at least two distinct types, referred to as H receptor, or HR, and H2 receptor, or H2R.

A third histamine receptor, the H3 receptor, is believed to play a role in neurotransmission in the central nervous system, where the H3 receptor is thought to be disposed presynaptically on histaminergic nerve endings (Nature, 302, S32- 837 (1983)). The existence of the H3 receptor has been confirmed by the development of selective H3 receptor agonists and antagonists (Nature, 327, 117-123 (1987)) and has subsequently been shown to regulate the release of their neurotransmitters in both the central nervous system and peripheral organs, particularly the lungs, cardiovascular system and gastrointestinal tract.

A number of diseases or conditions may be treated with histamine H3 receptor ligands wherein the H3 ligand may be an antagonist, inverse agonist, agonist or partial agonist, see: (Imamura et al., Circ.Res., (1996) 78, 475-481); (Imamura et. al., Circ.Res., (1996) 78, 863-869); (Lin et al., Brain Res. (1990) 523, 325-330); (Monti et al., Neuropsychopharmacology (1996) 15, 31 35); (Sakai, et al., Life Sci. (1991) 48, 2397-2404); (Mazurkiewicz- Kwilecki and Nsonwah, Can. J. Physiol. Pharmacol. (1989) 67, 75-78); (Panula, P. et al., Neuroscience (1998) 44, 465-481); (Wada et al., Trends in Neuroscience (1991) 14,415); (Monti et al., Eur. J. Pharmacol. (1991) 205, 283); (Mazurkiewicz-Kwilecki and Nsonwah, Can. J. Physiol. Pharmacol. (1989) 67, 75-78); (Haas et al., Behav. Brain Res. (1995) 66, 41-44); (De Almeida and Izquierdo, Arch. Int. Pharmacodyn. (1986) 283, 193-198); (Kamei et al., Psychopharmacology (1990) 102, 312-318); (Kamei and Sakata, Jpn. J. Pharmacol. (199 1) 57, 437-482); (Schwartz et al., Psychopharmacology; The fourth Generation of Progress, Bloom and Kupfer (eds.), Raven Press, New York, (1995) 3 97); (Shaywitz et al., Psychopharmacology (1984) 82, 73-77); (Dumery and Blozovski, Exp. Brain Res. (1987) 67, 61-69); (Tedford et al., J. Pharmacol. Exp. Ther. (1995) 275, 598-604); (Tedford et al., Soc. Neurosci. Abstr. (1996) 22, 22); (Yokoyama et al., Eur. J. Pharmacol. (1993) 234,129); (Yokoyama and Iinuma, CNS Drugs (1996) 5, 321); (Onodera et al., Prog. Neurobiol. (1994) 42, 685); (Leurs and Timmerman, Prog. Drug Res. (1992) 39,127); (The Histamine H3 Receptor, Leurs and Timmerman (eds), Elsevier Science, Amsterdam, The Netherlands (1998); (Leurs et al., Trends in Pharm. Sci. (1998) 19, 177-183); (Phillips et al. ,

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Annual Reports in Medicinal Chemistry (1998) 33, 31-40); (Matsubara et al. , Eur. J. Pharmacol. (1992) 224, 145); (Rouleau et al., J. Pharmacol. Exp. Ther. (1997) 281, 1085); (Adam Szelag, "Role of histamine H3-receptors in the proliferation of neoplastic cells in vitro", Med. Sci. Monit., 4(5): 747- 755, (1998)); (Fitzsimons, C., H. Duran, F. Labombarda, B. Molinari and E. Rivera, "Histamine receptors signalling in epidermal tumor cell lines with H-ras gene alterations", Inflammation Res., 47 (Suppl. 1): S50-S51, (1998)); (R. Leurs, R.C. Vollinga and H. Timmerman, "The medicinal chemistry and therapeutic potentials of ligand of the histamine H3 receptor", Progress in Drug Research 45: 170-165, (1995)); (R. Levi and N.C.E. Smith, "Histamine H3-receptors: A new frontier in myocardial ischemia", J. Pharm. Exp. Ther., 292: 825-830, (2000)); (Hatta, E., K Yasuda and R. Levi, "Activation of histamine H3 receptors inhibits carrier-mediated norepinephrine release in a human model of protracted myocardial ischemia", J. Pharm. Exp. Ther., 283: 494-500, (1997); (H. Yokoyama and K. Iinuma, "Histamine and Seizures: Implications for the treatment of epilepsy", CNS Drugs, 5(5): 321-330, (1995)); (K. Hukukami, H. Yokoyama, K. Onodera, K. Iinuma and T. Watanabe, AQ-0 145, "A newly developed histamine H3 antagonist, decreased seizure susceptibility of electrically induced convulsions in mice", Meth. Find. Exp. Clin. Pharmacol., 17(C): 70-73, (1995); (Delaunois A., Gustin P., Garbarg M., and Ansay M., "Modulation of acetylcholine, capsaicin and substance P effects by histamine H3 receptors in isolated perfused rabbit lungs", European Journal of Pharmacology 277(2-3):243-50, (1995)); and (Dimitriadou, et al., "Functional relationship between mast cells and C- sensitive nerve fibres evidenced by histamine H3-receptor modulation in rat lung and spleen", Clinical Science 87(2):151-63, (1994). Such diseases or conditions include cardiovascular disorders such as acute myocardial infarction; memory processes, dementia and cognition disorders such as Alzheimer's disease and attention-deficit hyperactivity disorder; neurological disorders such as Parkinson's disease, schizophrenia, depression, epilepsy, and seizures or convulsions; cancer such as cutaneous carcinoma," medullary thyroid carcinoma and melanoma; respiratory disorders such as asthma; sleep disorders such as narcolepsy; vestibular dysfunction such as Meniere's disease; gastrointestinal disorders, inflammation, migraine, motion sickness, obesity, pain, and septic shock.

H3 receptor antagonists have also been previously described in, for example, WO 03/050099, WO 02/0769252, and WO 02/12224. The histamine H3 receptor, or H3R, regulates the release of histamine and other neurotransmitters, including serotonin and acetylcholine. H3R is relatively neuron specific and inhibits the release of certain monoamines such as histamine. Selective antagonism of H3R raises brain histamine levels and inhibits such activities as food consumption while minimizing non-specific peripheral consequences. Antagonists of the receptor increase synthesis and release of cerebral histamine and other monoamines. By this mechanism, they induce a prolonged wakefulness,

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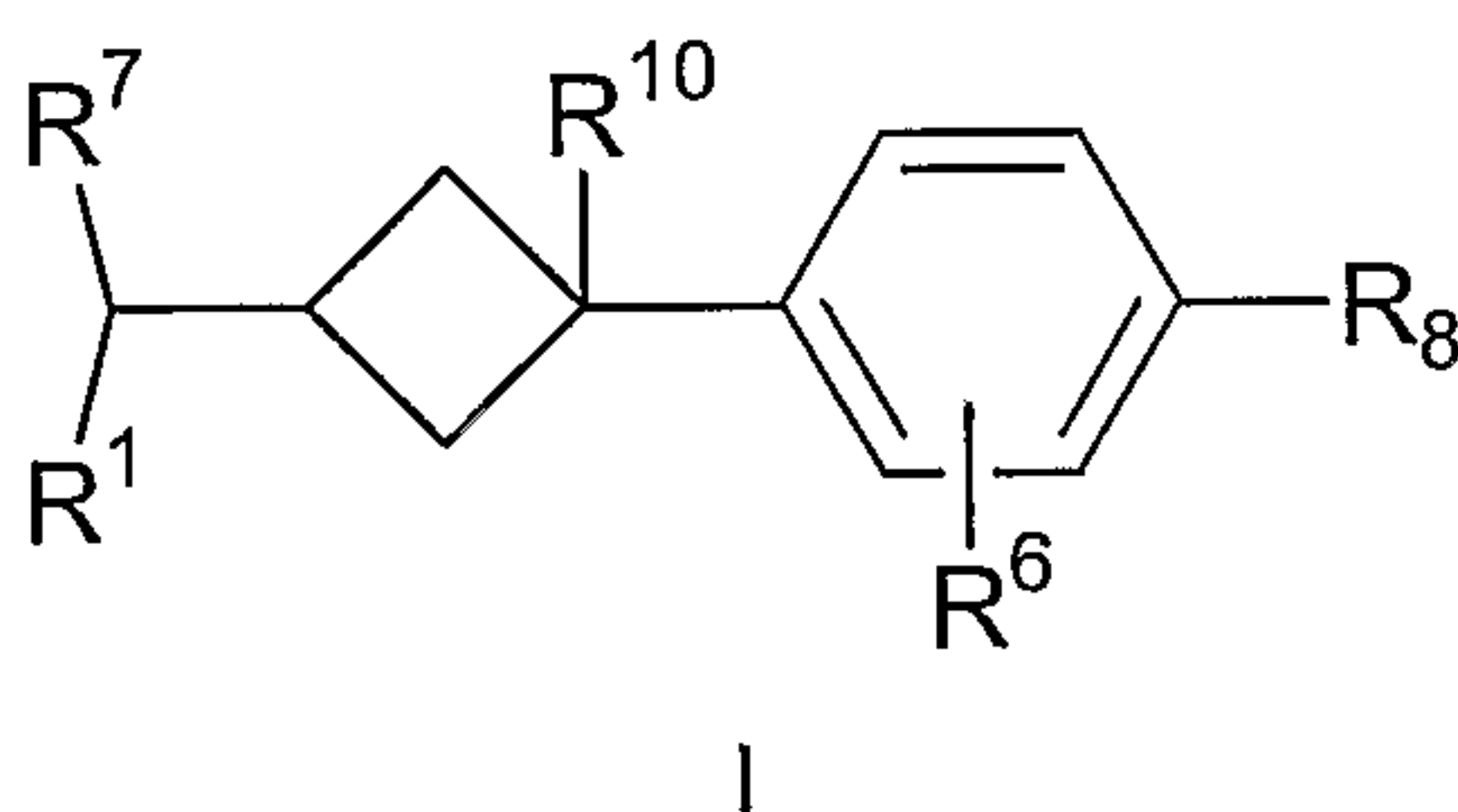
improved cognitive function, reduction in food intake and normalization of vestibular reflexes. Accordingly, the receptor is an important target for new therapeutics in Alzheimer disease, mood and attention adjustments, including attention deficit hyperactive disorder (ADHD), cognitive deficiencies, obesity, dizziness, schizophrenia, epilepsy, sleeping disorders, narcolepsy and motion sickness, and various forms of anxiety.

The majority of histamine H3 receptor antagonists to date resemble histamine in possessing an imidazole ring which may be substituted, as described, for example, in WO96/38142. Non-imidazole neuroactive compounds such as beta histamines (Arrang, Eur. J. Pharm. 1985, 111:72-84) demonstrated some histamine H3 receptor activity but with poor potency. EP 978512 and EP 0982300A2 disclose non-imidazole alkylamines as histamine H3 receptor antagonists. WO 00/06254 describes non-imidazole alkylamines as histamine-3 receptor ligands. Other receptor antagonists have been described in WO02/32893 and WO02/06233.

This invention is directed to histamine H3 receptor modulators, including antagonists and inverse agonists, useful for treating the conditions listed in the preceding paragraphs. The compounds of this invention are highly selective for the histamine H3 receptor vs. other histamine receptors, and possess remarkable drug disposition properties (pharmacokinetics). In particular, the compounds of this invention selectively distinguish H3R from the other receptor subtypes H1R, H2R. In view of the art's interest in histamine H3 receptor agonists, inverse agonists and antagonists, novel compounds which interact with the histamine H3 receptor would be a highly desirable contribution to the art. The present invention provides such a contribution to the art being based on the finding that a novel class of cyclobutyl aryl diamines has a high and specific affinity to the histamine H3 receptor.

Summary of the Invention

This invention is directed to a compound of the formula I



or a pharmaceutically acceptable salt thereof, wherein:

- R¹ is selected from the group consisting of N₃, OR⁴, and NR²R³;
- R² and R³ are each independently selected from the group consisting of hydrogen;
- C₁-C₈ alkyl optionally substituted with 1 to 4 halogens;
- C₁-C₄ alkyl group optionally substituted with a substituent selected from the group consisting of OH, one to four C₁-C₄ alkyl, C₃-C₇ cycloalkyl, C₁-C₄ dialkylamino, C₆-C₁₄ aryl

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optionally substituted with a halogen and optionally substituted with C₆-C₁₀ aryloxy optionally substituted with one to two halogens, and 5-10-membered heteroaryl optionally substituted with a C₆-C₁₀ aryl group and optionally substituted with one to three C₁-C₄ alkyl groups;

C₃-C₇ cycloalkyl;

5 C₆-C₁₄ aryl;

3-8-membered heterocycloalkyl optionally substituted with one or more C₁-C₄ alkyl-carbonyl group;

C₆-C₁₀ arylsulfonyl optionally substituted with one or more C₁-C₂ alkyl;

5-10-membered heteroaryl; and

10 C₆-C₁₄ aryl-C₀-C₄ alkylene-O-C₀-C₄ alkyl, wherein each C₀-C₄ alkyl and each C₀-C₄ alkylene is optionally substituted with one to four C₁-C₄ alkyl;

wherein R³ can be further selected from the group consisting of

C₆-C₁₄ arylcarbonyl-C₆-C₁₄ aryl; C₆-C₁₄ arylcarbonyl-3-8-membered heterocycloalkyl; C₃-C₈ cycloalkylcarbonyl-C₆-C₁₄ aryl; C₃-C₈ cycloalkylcarbonyl-3-8-membered heterocycloalkyl; 3-8-membered heterocycloalkylcarbonyl-C₆-C₁₄ aryl; and 3-8-membered heterocycloalkylcarbonyl-3-8-membered heterocycloalkyl;

or R³ and R² together with the nitrogen of the NR²R³ group form a first 5-, 6-, or 7-membered aliphatic ring, wherein one of the carbons in the first 5-, 6-, or 7-membered aliphatic ring is optionally replaced by O, S, NR^{2'}, or CO, and the first 5-, 6-, or 7-membered aliphatic ring is optionally fused to a C₆-C₁₀ arylene and is optionally substituted at a ring carbon with a substituent selected from the group consisting of

5-10-membered heteroaryl optionally substituted with one or more halogens and optionally substituted with one or more C₁-C₂ alkyl,

25 C₁-C₄ alkoxy optionally substituted with one or more C₁-C₂ alkoxy and optionally substituted with one or more C₁-C₄ dialkylaminocarbonyl, and

one or two C₁-C₄ alkyl optionally and independently substituted with one or more C₁-C₂ alkoxy;

wherein R^{2'} is

hydrogen;

30 C₁-C₈ alkyl optionally substituted with 1 to 4 halogens;

5-10-membered heteroaryl optionally substituted with a substituent selected from the group consisting of halogen, C₁-C₄ alkyl, C₁-C₂ alkoxy, C₆-C₁₀ aryl, C₁-C₄ alkylaminocarbonyl, and cyano;

35 C₁-C₄ alkyl group optionally substituted with a substituent selected from the group consisting of C₁-C₂ alkoxycarbonyl, 5-10-membered heteroaryl optionally substituted with one or more C₁-C₂ alkyl, one to four C₁-C₄ alkyl, C₃-C₇ cycloalkyl, and C₆-C₁₄ aryl;

C₆-C₁₀ aryl optionally substituted with one or two C₁-C₂ alkyl;

C₁-C₄ alkylcarbonyl;
 or C₆-C₁₄ aryl-C₀-C₄ alkylene-O-C₀-C₄ alkyl, wherein each C₀-C₄ alkyl and each C₀-C₄ alkylene is optionally substituted with one to four C₁-C₄ alkyl;

R⁴ is

5

hydrogen;

C₁-C₈ alkyl optionally substituted with 1 to 4 halogens;

C₁-C₄ alkyl optionally substituted with a substituent selected from the group consisting of

10

C₃-C₇ cycloalkyl,

5-10-membered heteroaryl, and

C₆-C₁₄ aryl optionally substituted with a substituent selected from the group consisting of one, two or three halogens, cyano, one or two C₁-C₂ alkoxy, C₁-C₂ di- or tri-fluoroalkyl, C₁-C₄ alkyl optionally substituted with C₆-C₁₀ arylsulfonyl, nitro, and 5-10-membered heteroaryl;

5-10-membered heteroaryl optionally fused to a C₆-C₁₀ arylene group that is optionally substituted with one or more halogens or one or more C₁-C₂ alkoxy, wherein the 5-10-membered heteroaryl is optionally substituted with a substituent selected from the group consisting of:

C₆-C₁₀ aryl optionally substituted with one or more halogens, one or more C₁-C₂ alkoxy, or one or more C₁-C₂ alkyl;

20

C₆-C₁₀ arylcarbonyl optionally substituted with one or more halogens;

one or more halogens;

one to three C₁-C₄ alkyl groups optionally substituted with one or more C₆-C₁₀ aryl optionally and independently substituted with one or more halogens or one or more C₁-C₂ alkoxy;

25

C₁-C₂ di- or tri-fluoroalkyl;

1 to 2 C₁-C₂ alkoxy groups;

3-8-membered heterocycloalkyl;

5-10-membered heteroaryl-amino;

C₁-C₂ alkylaminocarbonyl-C₁-C₂-alkylamino;

30

C₆-C₁₀ arylaminocarbonyl;

C₆-C₁₀ arylaminocarbonyl-C₁-C₂-alkylamino optionally substituted with one or more halogens at the C₆-C₁₀ aryl moiety of C₆-C₁₀ arylaminocarbonyl;

5-10-membered heteroaryl optionally substituted with one or more C₆-C₁₀ aryl or one or more C₁-C₂ alkyl;

35

C₆-C₁₀ aryloxy optionally substituted with one or more C₁-C₂ alkoxy or one or more halogens; and

C₁-C₄ dialkylamino;

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C₆-C₁₄ aryl optionally substituted with one or more halogens and optionally substituted with one or more C₆-C₁₀ aryloxy optionally and independently substituted with one to two halogens;

5 C₆-C₁₄ aryl-C₀-C₄ alkylene-O-C₀-C₄ alkyl, wherein each C₀-C₄ alkyl and each C₀-C₄ alkylene is optionally substituted with one to four C₁-C₄ alkyl;

or

C₆-C₁₀ arylsulfonyl optionally substituted with C₁-C₂ alkyl;

R⁶ is hydrogen, C₁-C₄ alkyl or halogen;

10 R⁷ is hydrogen, SO₂C₁-C₁₀ alkyl, C₁-C₈ alkyl optionally substituted with 1 to 4 halogens, C₃-C₇ cycloalkyl-C₀-C₄ alkyl, C₆-C₁₄ aryl-C₀-C₄ alkyl, 5-10-membered heteroaryl-C₀-C₄ alkyl, or C₆-C₁₄ aryl-C₀-C₄ alkylene-O-C₀-C₄ alkyl, wherein each C₀-C₄ alkyl and each C₀-C₄ alkylene is optionally substituted with one to four C₁-C₄ alkyl;

R¹⁰ is OH, halogen or hydrogen;

15 R⁸ is CN, -CHR⁷NR^{2''}R^{3''} or C(=NR¹²)-NR¹³R^{13'}, wherein R¹³ and R^{13'} are each independently hydrogen or C₁-C₆ alkyl and R¹² is hydrogen, C₁-C₆ alkyl OH, O-C₁-C₆ alkyl, NH₂, NHC₁-C₆ alkyl, or N(C₁-C₆ alkyl)₂,

or wherein C(=NR¹²)-NR¹³R^{13'} represents a five-membered heteroaryl group, wherein R¹² is O, NH, or NC₁-C₆ alkyl, R¹³ and R^{13'} taken together represent N or CR^{13''} double bonded to the nitrogen of the NR¹³R^{13'} group, and R^{13''} is hydrogen or C₁-C₆ alkyl;

20 or when R⁸ is *ortho* to R⁶, R⁶ and R⁸ together with the carbons of the aromatic ring to which R⁶ and R⁸ are attached may form a 5-membered carbocyclic ring;

25 R^{2''} is hydrogen, C₁-C₈ alkyl optionally substituted with 1 to 4 halogens, C₃-C₇ cycloalkyl-C₀-C₄ alkyl, C₆-C₁₄ aryl-C₀-C₄ alkyl, 5-10-membered heteroaryl-C₀-C₄ alkyl, or C₆-C₁₄ aryl-C₀-C₄ alkylene-O-C₀-C₄ alkyl, wherein each C₀-C₄ alkyl and each C₀-C₄ alkylene is optionally substituted with one to four C₁-C₄ alkyl;

30 R^{3''} is hydrogen, C₁-C₈ alkyl optionally substituted with 1 to 4 halogens, C₆-C₁₄ aryl, C₆-C₁₄ arylcarbonyl-C₆-C₁₄ aryl, C₆-C₁₄ arylcarbonyl-3-8-membered heterocycloalkyl, C₃-C₈ cycloalkylcarbonyl-C₆-C₁₄ aryl, C₃-C₈ cycloalkylcarbonyl-3-8-membered heterocycloalkyl, 3-8-membered heterocycloalkyl, 3-8-membered heterocycloalkylcarbonyl-C₆-C₁₄ aryl, or 3-8-membered heterocycloalkylcarbonyl-3-8-membered heterocycloalkyl;

or R^{3''} and R^{2''} together with the nitrogen of the CHR⁷NR^{2''}R^{3''} group form a second 5-, 6- or 7-membered aliphatic ring, wherein one of the carbons in the second 5-, 6-, or 7-membered aliphatic ring is optionally replaced by O, S, NR¹¹, or C=O and the second 5-, 6-, or 7-membered aliphatic ring is optionally substituted with one or two C₁-C₄ alkyl or optionally substituted with OH, wherein R¹¹ is hydrogen, C₁-C₈ alkyl optionally substituted with 1 to 4 halogens, C₃-C₇ cycloalkyl-C₀-C₄ alkyl, C₆-C₁₄ aryl-C₀-C₄ alkyl, 5-10-membered heteroaryl-C₀-

C₄ alkyl, or C₆-C₁₄ aryl-C₀-C₄ alkylene-O-C₀-C₄ alkyl, wherein each C₀-C₄ alkyl and each C₀-C₄ alkylene is optionally substituted with one to four C₁-C₄ alkyl; and

R⁷ is hydrogen, C₁-C₈ alkyl optionally substituted with 1 to 4 halogens, C₃-C₇ cycloalkyl-C₀-C₄ alkyl, C₆-C₁₄ aryl-C₀-C₄ alkyl, 5-10-membered heteroaryl-C₀-C₄ alkyl, C₆-C₁₄ aryl-C₀-C₄ alkylene-O-C₀-C₄ alkyl, wherein each C₀-C₄ alkyl and each C₀-C₄ alkylene is optionally substituted with one to four C₁-C₄ alkyl, or SO₂C₁-C₁₀ alkyl.

This invention is also directed to:

a pharmaceutical composition for treating, for example, a disorder or condition that may be treated by modulating histamine H₃ receptors, the composition comprising a compound of formula I as described above, and optionally a pharmaceutically acceptable carrier;

a method of treatment of a disorder or condition that may be treated by modulating histamine H₃ receptors, the method comprising administering to a mammal in need of such treatment a compound of formula I as described above; and

a pharmaceutical composition for treating, for example, a disorder or condition selected from the group consisting of depression, mood disorders, schizophrenia, anxiety disorders, Alzheimer's disease, attention-deficit hyperactivity disorder (ADHD), psychotic disorders, sleep disorders, obesity, dizziness, epilepsy, motion sickness, respiratory diseases, allergy, allergy-induced airway responses, allergic rhinitis, nasal congestion, allergic congestion, hypotension, cardiovascular disease, diseases of the GI tract, hyper and hypo motility and acidic secretion of the gastro-intestinal tract, the composition comprising a compound of formula I as described above, and optionally a pharmaceutically acceptable carrier.

This invention is also directed to a method of treatment of a disorder or condition selected from the group consisting of the disorders or conditions listed herein, the method comprising administering to a mammal in need of such treatment a compound of formula I as described above.

The invention is also directed to a composition comprising a compound of formula I, a histamine H₁ antagonist, and optionally a pharmaceutically acceptable carrier.

The invention is also directed to a method of treatment of a condition selected from the group consisting of allergic rhinitis, nasal congestion, and allergic congestion in a mammal, the method comprising administering a compound of formula I and a histamine H₁ antagonist to a mammal in need of such treatment.

The invention is also directed to a composition comprising a compound of formula I, a neurotransmitter re-uptake blocker and optionally a pharmaceutically acceptable carrier.

The invention is also directed to a method of treatment of a condition selected from the group consisting of depression, mood disorders and schizophrenia in a mammal, the

method comprising administering a compound of formula I and a neurotransmitter re-uptake blocker to a mammal in need of such treatment.

The pharmaceutical composition and method of this invention may also be used for preventing a relapse in a disorder or condition described in the previous paragraphs.

- 5 Preventing such relapse is accomplished by administering to a mammal in need of such prevention a compound of formula I as described above and is contemplated as a method of treatment.

Detailed Description of the Invention

- 10 The compound of the present invention may have optical centers and therefore may occur in different enantiomeric configurations. Formula I, as depicted above, includes all enantiomers, diastereomers, and other stereoisomers of the compounds depicted in structural formula I, as well as racemic and other mixtures thereof. Individual isomers can be obtained by known methods, such as optical resolution, optically selective reaction, or chromatographic separation in the preparation of the final product or its intermediate.

- 15 Isotopically-labeled compounds of formula I, including compounds of formula I isotopically-labeled to be detectable by PET or SPECT, are also within the scope of the invention.

Cis and trans isomers of the inventive compound of formula I are also within the scope of the invention.

- 20 When a first group or substituent is substituted by two or more groups or substituents, the invention includes without limitation embodiments in which a combination of such groups or substituents is present. For example, a 5-10-membered heteroaryl optionally substituted with a substituent selected from the group consisting of "halogen, C₁-C₄ alkyl, C₁-C₂ alkoxy, C₆-C₁₀ aryl, C₁-C₄ alkylaminocarbonyl, and cyano" is a 5-10-membered heteroaryl which may
25 be substituted with any of the substituents within the quotation marks or with a combination of the substituents within the quotation marks.

When a first group or substituent is substituted by two or more groups or substituents, it is understood that the number of such substituents may not exceed the number of positions in the first group or substituent that are available for substitution.

- 30 The term "alkyl" refers to straight or branched chains of carbon atoms. Exemplary alkyl groups are C₁-C₆ saturated alkyl groups, which include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, isopentyl, hexyl, and the like, including all regioisomeric forms thereof, and straight and branched chain forms thereof. The term "alkyl" is also used to denote straight or branched chains of carbon atoms having one or more carbon-carbon double
35 bonds, such as vinyl, allyl, butenyl, and the like, as well as straight or branched chains of carbon atoms having one or more carbon-carbon triple bonds, such as ethynyl, propargyl, butynyl, and the like. The term "aryl" denotes a cyclic, aromatic hydrocarbon. Examples of

aryl groups include phenyl, naphthyl, anthracenyl, phenanthrenyl, and the like. The terms "alkoxy" and "aryloxy" denote "O-alkyl" and "O-aryl", respectively. The term "cycloalkyl" denotes a cyclic group of carbon atoms, where the ring formed by the carbon atoms may be saturated or may comprise one or more carbon-carbon double bonds in the ring. Examples of cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and the like, as well as cyclopentenyl, cyclopentadienyl, cyclohexenyl, cyclohexadienyl, cyclobutadienyl, and the like. As used herein, the term "cycloalkyl" is also intended to denote a cyclic group comprising at least two fused rings, such as adamantanyl, decahydronaphthalinyl, norbornanyl, where the cyclic group may also have one or more carbon-carbon double bonds in one or both rings, such as in bicyclo[4.3.0]nona-3,6(1)-dienyl, dicyclopentadienyl, 1,2,3,4-tetrahydronaphthalinyl (tetralinyl), indenyl, and the like. The term "halogen" represents chloro, fluoro, bromo, and iodo. The term "heteroaryl" denotes a monocyclic or bicyclic aromatic group wherein one or more carbon atoms are replaced with heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur. If the heteroaryl group contains more than one heteroatom, the heteroatoms may be the same or different. Preferred heteroaryl groups are five- and six-membered rings that contain from one to three heteroatoms independently selected from oxygen, nitrogen, and sulfur. Examples of preferred five- and six-membered heteroaryl groups include benzo[b]thienyl, chromenyl, furyl, imidazolyl, indazolyl, indoliziny, indolyl, isobenzofuranyl, isoindolyl, isoquinolyl, isothiazolyl, isoxazolyl, naphthyridinyl, oxadiazolyl, oxazinyl, oxazolyl, phthalazinyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridyl, pyrimidyl, pyrrolyl, quinoliziny, quinolyl, quinoxalinyl, thiazolyl, thienyl, triazinyl, triazolyl, and xanthenyl.

The term "heterocycloalkyl" denotes a cycloalkyl system, wherein "cycloalkyl" is defined above, in which one or more of the ring carbon atoms are replaced with a heteroatom selected from the group consisting of nitrogen, oxygen, and sulfur. Examples of such heterocycloalkyl groups include azabicycloheptanyl, azetidiny, benzazepiny, 1,3-dihydroisoindolyl, indoliny, tetrahydrofuryl, tetrahydroquinoliny, tetrahydroisoquinoliny, morpholiny, piperazinyl, piperidyl, pyrrolidinyl, and, tetrahydro-2H-1,4-thiazinyl.

A cyclic group may be bonded to another group in more than one way. If no particular bonding arrangement is specified, then all possible arrangements are intended. For example, the term "pyridyl" includes 2-, 3-, or 4-pyridyl, and the term "thienyl" includes 2- or 3-thienyl.

The term "C₀-C₄" includes the embodiment where there are no carbons in a chain. Thus, for example, the groups "C₃-C₇ cycloalkyl-C₀-C₄ alkyl," "C₆-C₁₄ aryl-C₀-C₄ alkyl," "5-10-membered heteroaryl-C₀-C₄ alkyl," and "C₆-C₁₄ aryl-C₀-C₄ alkylene-O-C₀-C₄ alkyl" include C₃-C₇ cycloalkyl, C₆-C₁₄ aryl, 5-10-membered heteroaryl, and C₆-C₁₄ aryl- O-C₀-C₄ alkyl, respectively.

The term "C₁-C₄ dialkylamino" refers to a dialkylamino group in which each alkyl group is independently a C₁-C₄ alkyl group.

"Modulating histamine H₃ receptors," as used herein, refers to acting as a histamine H₃ receptor modulator. Examples of histamine H₃ receptor modulators include histamine H₃ receptor antagonists and histamine H₃ receptor inverse agonists. Similarly, "modulating histamine H₃ receptors," includes acting as a histamine H₃ receptor antagonist and includes acting as a histamine H₃ receptor inverse agonist.

A "unit dosage form" as used herein is any form that contains a unit dose of the compound of formula I. A unit dosage form may be, for example, in the form of a tablet or a capsule. The unit dosage form may also be in liquid form, such as a solution or suspension.

The histamine H₃ receptor modulators of the invention are useful for treating, in particular, ADHD, obesity, anxiety disorders and respiratory diseases. Respiratory diseases that may be treated by the present invention include adult respiratory distress syndrome, acute respiratory distress syndrome, bronchitis, chronic bronchitis, chronic obstructive pulmonary disease, cystic fibrosis, asthma, emphysema, rhinitis and chronic sinusitis.

Anxiety disorders include, for example, generalized anxiety disorder, panic disorder, PTSD, and social anxiety disorder. Mood adjustment disorders include, for example, depressed mood, mixed anxiety and depressed mood, disturbance of conduct, and mixed disturbance of conduct and depressed mood. Attention adjustment disorders include, for example, in addition to ADHD, attention-deficit disorders or other cognitive disorders due to general medical conditions. Psychotic disorders include, for example, schizoaffective disorders and schizophrenia; sleep disorders include, for example, narcolepsy and enuresis.

Examples of the disorders or conditions which may be treated by the compound, composition and method of this invention are also as follows: depression, including, for example, depression in cancer patients, depression in Parkinson's patients, Postmyocardial Infarction depression, depression in patients with human immunodeficiency virus (HIV), Subsyndromal Symptomatic depression, depression in infertile women, pediatric depression, major depression, single episode depression, recurrent depression, child abuse induced depression, post partum depression, DSM-IV major depression, treatment-refractory major depression, severe depression, psychotic depression, post-stroke depression, neuropathic pain, manic depressive illness, including manic depressive illness with mixed episodes and manic depressive illness with depressive episodes, seasonal affective disorder, bipolar depression BP I, bipolar depression BP II, or major depression with dysthymia; dysthymia; phobias, including, for example, agoraphobia, social phobia or simple phobias; eating disorders, including, for example, anorexia nervosa or bulimia nervosa; chemical dependencies, including, for example, addictions to alcohol, cocaine, amphetamine and other psychostimulants, morphine, heroin and other opioid agonists, phenobarbital and other

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barbiturates, nicotine, diazepam, benzodiazepines and other psychoactive substances; Parkinson's diseases, including, for example, dementia in Parkinson's disease, neuroleptic-induced parkinsonism or tardive dyskinesias; headache, including, for example, headache associated with vascular disorders; withdrawal syndrome; age-associated learning and mental disorders; apathy; bipolar disorder; chronic fatigue syndrome; chronic or acute stress; conduct disorder; cyclothymic disorder; somatoform disorders such as somatization disorder, conversion disorder, pain disorder, hypochondriasis, body dysmorphic disorder, undifferentiated disorder, and somatoform NOS; incontinence; inhalation disorders; intoxication disorders; mania; oppositional defiant disorder; peripheral neuropathy; post-traumatic stress disorder; late luteal phase dysphoric disorder; specific developmental disorders; SSRI "poop out" syndrome, or a patient's failure to maintain a satisfactory response to SSRI therapy after an initial period of satisfactory response; and tic disorders including Tourette's disease.

As used herein, "mammal" is any member of the class mammalia. As an example, the mammal, in need of the treatment or prevention may be a human. As another example, the mammal in need of the treatment or prevention may be a mammal other than a human.

A compound of formula I which is basic in nature is capable of forming a wide variety of different salts with various inorganic and organic acids. The acid addition salts are readily prepared by treating the base compounds with a substantially equivalent amount of the chosen mineral or organic acid in an aqueous solvent medium or in a suitable organic solvent such as methanol or ethanol. Upon careful evaporation of the solvent, the desired solid salt is obtained.

The acids which are used to prepare the pharmaceutically acceptable acid salts of the active compound used in formulating the pharmaceutical composition of this invention that are basic in nature are those which form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions. Non-limiting examples of the salts include the acetate, benzoate, .beta.-hydroxybutyrate, bisulfate, bisulfite, bromide, butyne-1,4-dioate, carpoate, chloride, chlorobenzoate, citrate, dihydrogenphosphate, dinitrobenzoate, fumarate, glycollate, heptanoate, hexyne-1,6-dioate, hydroxybenzoate, iodide, lactate, maleate, malonate, mandelate, metaphosphate, methanesulfonate, methoxybenzoate, methylbenzoate, monohydrogenphosphate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, oxalate, phenylbutyrate, phenylproionate, phosphate, phthalate, phylacetate, propanesulfonate, propiolate, propionate, pyrophosphate, pyrosulfate, sebacate, suberate, succinate, sulfate, sulfite, sulfonate, tartrate, xylenesulfonate, acid phosphate, acid citrate, bitartrate, succinate, gluconate, saccharate, nitrate, methanesulfonate and pamoate [i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)] salts.

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In a preferred embodiment of the composition of the invention comprising a compound of formula I, a histamine H₁ antagonist, and optionally a pharmaceutically acceptable carrier, the combined amounts of the compound of formula I and of the histamine H₁ antagonist are effective in the treatment of the condition selected from the group consisting of allergic rhinitis, nasal congestion, and allergic congestion. In exemplary embodiments of the composition, histamine H₁ antagonists include loratidine (ClaritinTM), desloratidine (ClarinexTM), fexofenadin (AllegraTM) and cetirizine (ZyrtecTM).

In a preferred embodiment of the composition of the invention comprising a compound of formula I, a neurotransmitter re-uptake blocker and optionally a pharmaceutically acceptable carrier, the combined amounts of the compound of formula I and of the neurotransmitter re-uptake blocker are effective in the treatment of the condition selected from the group consisting of depression, mood disorders and schizophrenia. Exemplary neurotransmitter re-uptake blockers include selective serotonin re-uptake inhibitors (SSRIs) or non-selective serotonin, dopamine, or norepinephrine reuptake inhibitors, including fluoxetine (ProzacTM); sertraline (ZoloftTM), described in U.S. Pat. No. 4,536,518 assigned to Pfizer Inc., incorporated by reference herein; paroxetine (PaxilTM); and ziprasidone (GeodonTM), described in U.S. Pat. Nos. 4,831,031, 4,883,795, and 6,245,766, incorporated by reference herein.

Exemplary embodiments of the present invention include the compound of formula I in which

- (A) R¹⁰ is hydrogen, F or OH;
- (B) R⁶ is hydrogen;
- (C) R⁷ is hydrogen or C₁-C₆ alkyl, such as methyl;
- (D) R⁸ is CHR^{7'}NR^{2''}R^{3''} preferably wherein R^{7'} is hydrogen and R^{3''} and R^{2''} together with the nitrogen of the CHR^{7'}NR^{2''}R^{3''} group form a second 5-, 6- or 7-membered aliphatic ring, wherein one of the carbons in the second 5-, 6-, or 7-membered aliphatic ring is optionally replaced by O, S, NR¹¹, or C=O and the second 5-, 6-, or 7-membered aliphatic ring is optionally substituted with one or two C₁-C₄ alkyl or optionally substituted with OH, wherein R¹¹ is hydrogen, C₁-C₈ alkyl optionally substituted with 1 to 4 halogens, C₃-C₇ cycloalkyl-C₀-C₄ alkyl, C₆-C₁₄ aryl-C₀-C₄ alkyl, 5-10-membered heteroaryl-C₀-C₄ alkyl, or C₆-C₁₄ aryl-C₀-C₄ alkylene-O-C₀-C₄ alkyl, wherein each C₀-C₄ alkyl and each C₀-C₄ alkylene is optionally substituted with one to four C₁-C₄ alkyl; and most preferably wherein R^{7'} is hydrogen and R^{3''} and R^{2''} together with the nitrogen of the CHR^{7'}NR^{2''}R^{3''} group form a pyrrolidinyl, morpholinyl, 3-hydroxypyrrolidinyl, or piperidinyl group;
- or wherein R^{7'} is hydrogen and R^{3''} and R^{2''} are each the same or a different C₁-C₄ alkyl group, such as a methyl group for each of R^{3''} and R^{2''}; or
- or wherein R^{7'} is hydrogen or C₁-C₆ alkyl, such as methyl;

and/or

(E) R^1 is selected from the group consisting of

a) NR^2R^3 , wherein R^2 and R^3 are each independently selected from the group consisting of

5 C_1 - C_4 alkyl optionally substituted with a substituent selected from the group consisting of OH, C_3 - C_7 cycloalkyl, C_1 - C_4 dialkylamino, C_6 - C_{14} aryl optionally substituted with one or more halogens and optionally substituted with C_6 - C_{10} aryloxy optionally substituted with one to two halogens, and 5-10-membered heteroaryl optionally substituted with a C_6 - C_{10} aryl group and optionally substituted with one to three C_1 - C_4 alkyl groups;

10 C_3 - C_7 cycloalkyl;

3-8-membered heterocycloalkyl optionally substituted with one or more C_1 - C_4 alkylcarbonyl groups;

and

C_6 - C_{10} arylsulfonyl optionally substituted with one or more C_1 - C_2 alkyl;

15 or R^3 and R^2 together with the nitrogen of the NR^2R^3 group form a first 5, 6, or 7-membered aliphatic ring, wherein one of the carbons in the first 5, 6, or 7-membered aliphatic ring is optionally replaced by O, S, $NR^{2'}$, or CO, and the first 5, 6, or 7-membered aliphatic ring is optionally fused to a C_6 - C_{10} arylene and is optionally substituted at a ring carbon with a substituent selected from the group consisting of

20 5-10-membered heteroaryl optionally substituted with one or more halogens and optionally substituted with one or more C_1 - C_2 alkyl,

C_1 - C_4 alkoxy optionally substituted with one or more C_1 - C_2 alkoxy and optionally substituted with one or more C_1 - C_4 dialkylaminocarbonyl, and

one or two C_1 - C_4 alkyl optionally and independently substituted with one or more C_1 - C_2 alkoxy;

25 wherein $R^{2'}$ is

5-10-membered heteroaryl optionally substituted with a substituent selected from the group consisting of halogen, C_1 - C_4 alkyl, C_1 - C_2 alkoxy, C_6 - C_{10} aryl, C_1 - C_4 alkylaminocarbonyl, and cyano;

30 C_1 - C_4 alkyl optionally substituted with a substituent selected from the group consisting of C_1 - C_2 alkoxy carbonyl and 5-10-membered heteroaryl optionally substituted with one or more C_1 - C_2 alkyl;

C_6 - C_{10} aryl optionally substituted with one or two C_1 - C_2 alkyl;

or C_1 - C_4 alkylcarbonyl;

35 preferably wherein R^2 and R^3 are each independently C_1 - C_4 alkyl, or R^3 and R^2 together with the nitrogen of the NR^2R^3 group form a first 5, 6, or 7-membered aliphatic ring,

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wherein one of the carbons in the first 5, 6, or 7-membered aliphatic ring is optionally replaced by O, S, NR^{2'}, or CO

wherein R^{2'} is C₁-C₄ alkyl; more preferably wherein R³ and R² together with the nitrogen of the NR²R³ group form a pyrrolidinyl, morpholinyl, 3-hydroxypyrrolidinyl, or piperidinyl group;

b) OR⁴, wherein R⁴ is

C₁-C₄ alkyl optionally substituted with C₆-C₁₄ aryl optionally substituted with a substituent selected from the group consisting of

one, two or three halogens, cyano, one or two C₁-C₂ alkoxy, C₁-C₂ di- or tri-fluoroalkyl, and C₁-C₄ alkyl optionally substituted with C₆-C₁₀ arylsulfonyl, nitro, or 5-10-membered heteroaryl;

5-10-membered heteroaryl optionally fused to a C₆-C₁₀ arylene group that is optionally substituted with one or more halogens or one or more C₁-C₂ alkoxy, wherein the 5-10-membered heteroaryl is optionally substituted with a substituent selected from the group consisting of:

C₆-C₁₀ aryl optionally substituted with one or more halogens, one or more C₁-C₂ alkoxy, or one or more C₁-C₂ alkyl;

C₆-C₁₀ arylcarbonyl optionally substituted with one or more halogens;

one or more halogens;

one to three C₁-C₄ alkyl groups optionally substituted with one or more C₆-C₁₀ aryl optionally substituted with one or more halogens or one or more alkoxy;

C₁-C₂ di- or tri-fluoroalkyl;

one or two C₁-C₂ alkoxy groups;

3-8-membered heterocycloalkyl;

5-10-membered heteroaryl-amino;

C₁-C₂ alkylaminocarbonyl-C₁-C₂-alkylamino;

C₆-C₁₀ arylaminocarbonyl;

C₆-C₁₀ arylaminocarbonyl-C₁-C₂-alkylamino optionally substituted with one or more halogens at the C₆-C₁₀ aryl moiety of C₆-C₁₀ arylaminocarbonyl;

5-10-membered heteroaryl optionally substituted with one or more C₆-C₁₀ aryl or one or more C₁-C₂ alkyl;

C₆-C₁₀ aryloxy optionally substituted with one or more C₁-C₂ alkoxy or one or more halogens; and

C₁-C₄ dialkylamino;

or

C₆-C₁₀ arylsulfonyl optionally substituted with C₁-C₂ alkyl;

preferably wherein R¹ is OR⁴, wherein R⁴ is C₁-C₄ alkyl

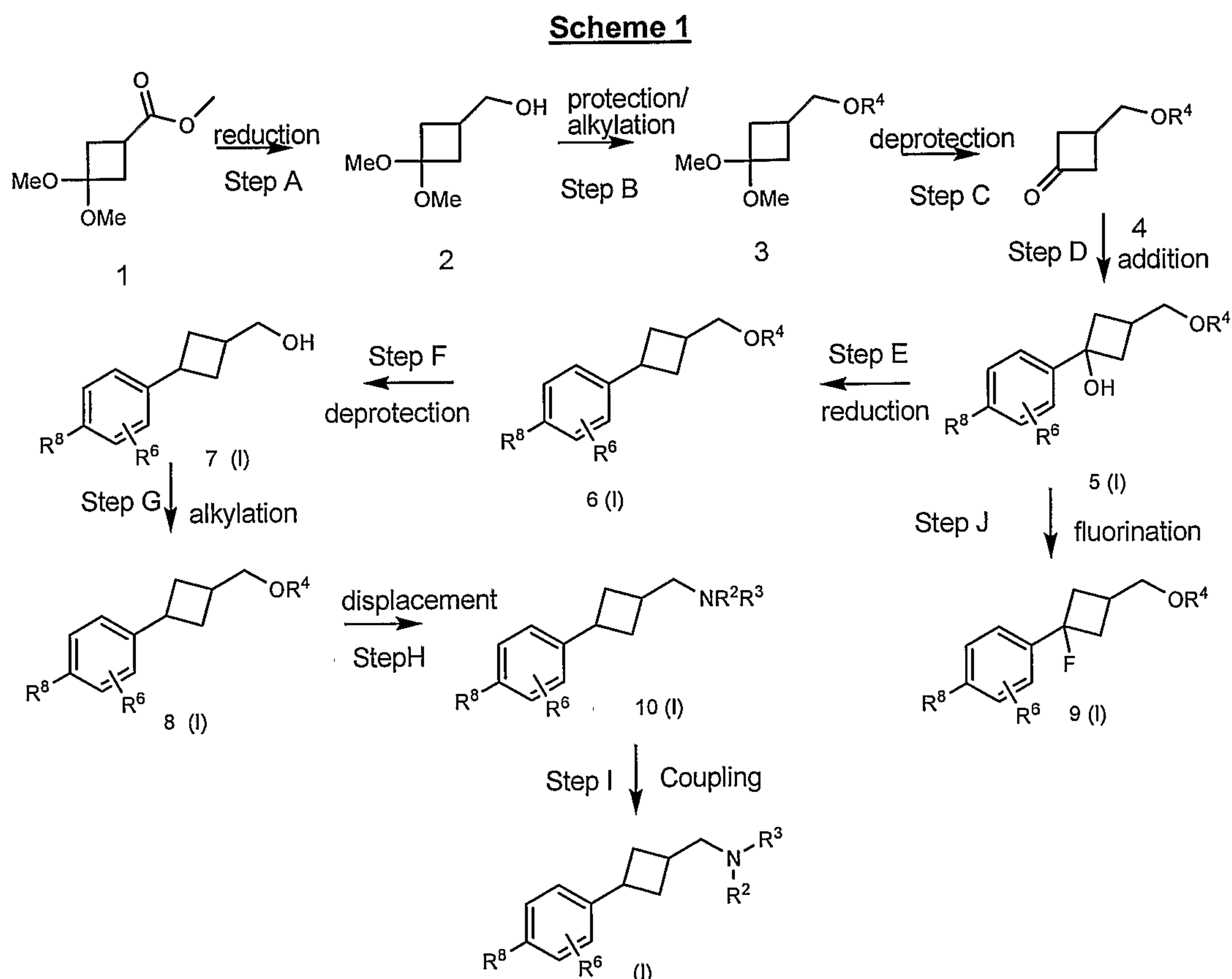
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and

c) N₃.

Exemplary embodiments of the present invention also include any combination of the foregoing embodiments (A)-(E).

5 Exemplary compounds of formula (I) according to the invention may be prepared by Scheme 1:



In Scheme 1, compounds of the formula (I) are prepared as follows.

10 Step A:

The compounds of the general formula (I) are synthesized from 3,3-dimethoxycyclobutanecarboxylic acid methyl ester, (1) (J. Org. Chem. 1988, 53, 3841 and J. Org. Chem. 1996, 61, 2174). The ester (1) is reduced with an appropriate reduction reagent such as e.g. lithium aluminum hydride, or sodium borohydride and aluminum trichloride in diglyme.

15 The reaction is normally effected in an aprotic solvent, such as tetrahydrofuran, or diethyl ether at a reaction temperature below from about 0 C to the reflux temperature of the solvent employed, yielding the alcohol (2).

Step B:

20 The protecting group of alcohol (2) may be chosen from the protective groups known in the art and described in the literature (e.g. T.W Greene; P. G. Wuts, Protective Groups in

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Organic Synthesis, 3rd edition, John Wiley&Sons Inc. New York, 1999). For example protection/alkylation of alcohol (2) can be accomplished by reaction of (2) in a reaction inert solvent such as tetrahydrofuran, with a base, i.e. sodium hydride, potassium t-butoxide and with alkyl halide for example benzyl bromide, or sulfonyl chloride, for example p-toluenesulfonyl chloride to give an ether or tosylate, respectively (3).

Step C:

The ketal protection group of (3) is removed by methods known in the art (e.g. T.W Greene; P. G. Wuts, Protective Groups in Organic Synthesis, 3rd edition, John Wiley&Sons Inc. New York, 1999). The preferred method of ketal removal is by reaction of (3) in acetone, with an acid, such as hydrogen chloride, p-toluenesulfonic acid monohydrate, or pyridinium p-toluenesulfonate, at a temperature between about room temperature and about the reflux temperature of the solvent employed to give ketone (4).

Step D:

The ketone (4) is reacted with an aryl bromide in the presence of an organometallic reagent, such as an organolithium, organomagnesium halide, organocerium, organotitanium, organozinc, organocopper, or organoaluminum reagent to form alcohol (5). An organomagnesium halide (Grignard reagent) or organolithium reagent is preferred. The reaction is typically effected in a reaction-inert-solvent, such as tetrahydrofuran, at a temperature between about -78° C and about room temperature to yield (5) a compound of formula (I).

Step E:

Reduction of the benzyl alcohol (5) is accomplished by reaction of (5) with an acid, preferable with trifluoroacetic acid, either neat or in a reaction-inert-solvent, such as methylene chloride or 1,2-dichloroethane and in the presence of a reducing reagent such as a silane, preferable triethylsilane, triisopropylsilane, or triphenylsilane at a reaction temperature from about room temperature to the reflux temperature of the solvent employed, where about 65° C is the preferred reaction temperature, yields (6) a compound of formula (I).

Step F:

When R⁴ of (6) is a protection group this group is removed by methods known in the art (e.g. T.W Greene; P. G. Wuts, Protective Groups in Organic Synthesis, 3rd edition, John Wiley&Sons Inc. New York, 1999). For example, when the protection group is a benzyl ether, the preferred method of removal is by reaction of (6) under standard hydrogenation conditions, preferable using palladium black in the presence of hydrogen, at a pressure of around 45 psi in ethyl alcohol or ethyl acetate yields (7) a compound of formula (I). In the case where the protection group is a tosylate, the preferred method of removal is by reaction of (6) in a protic solvent, preferable methanol with magnesium metal at room temperature to give (7) a compound of formula (I).

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Step G:

The compound of the type (7) is treated with a base, i.e. sodium hydride, potassium t-butoxide, triethyl amine in a reaction-inert-solvent where preferred solvent is tetrahydrofuran and with an alkyl halide, heteroaryl halide, acid chloride, or sulfonyl chloride, such as, for
5 example, benzyl bromide, 2-bromopyridine, acetyl chloride, or p-toluensulfonyl chloride, to yield a compound of the type (8), which is compound of formula (I).

Step H:

Reaction of a compound of the type (8), where $-OR^4$ is equal to a leaving group, such as a tosyl group, with an amide or an amine in a reaction-inert-solvent, where preferred
10 solvent is dimethyl acetamide yields (10), a compound of formula (I).

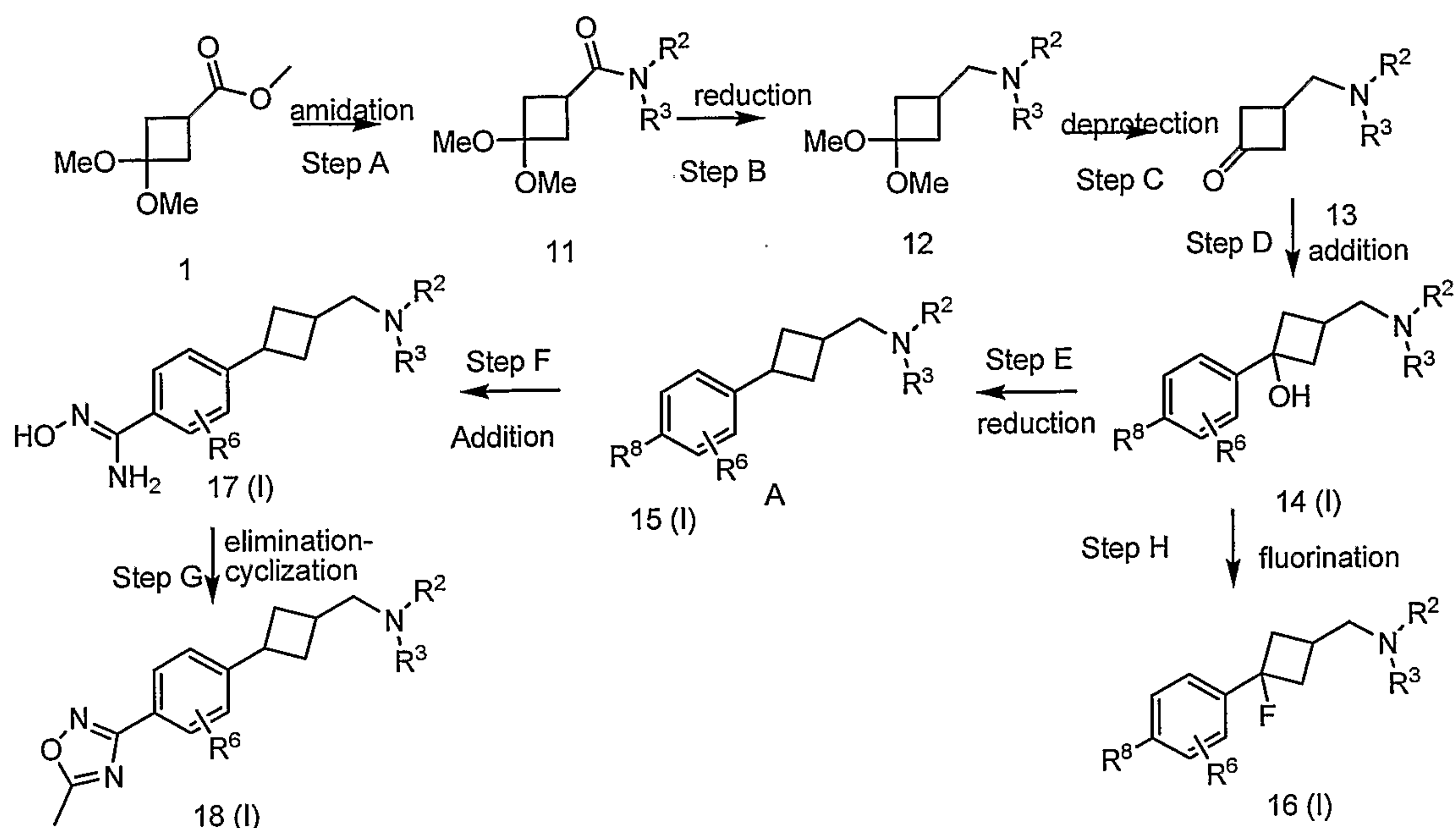
Step I:

The compound of the type (10) where R^2 and/or R^3 is H is reacted in the presence of a trialkyl base, such as triethylamine or diisopropylethylamine, sodium hydride, with a carbonyl donor, such as an alkyl chloroformate, an acid chloride, an acid anhydride, a sulfonyl
15 chloride, isocyanate, or an activated carboxylic derivative prepared from a carboxylic acid and an activating reagent such as a polymer-supported coupling agent, or, alternatively, dicyclohexylcarbodiimide, 1,1-carbonyldiimidazole, tripropylphosphonic anhydride, an alkyl chloroformate, bis-(2-oxo-3-oxazolidinyl)phosphinic chloride, or benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate, in a reaction-inert-solvent, such as
20 methylene chloride, ethyl acetate, pyridine, tetrahydrofuran or diethyl ether to give a compound of the formula (I).

Step: J

The compound of the type (5) is reacted with N-fluorobenzenesulfonimide in a reaction-inert-solvent, where preferred solvent is toluene at a reaction temperature from room
25 temperature to the reflux temperature of the solvent employed, where 110° C is an exemplary reaction temperature, to give (9), a compound of formula (I).

Exemplary compounds of formula (I) according to the invention may also be prepared by Scheme 2:

Scheme 2

In Scheme 2, compounds of the formula (I) are prepared as follows.

Step A:

- 5 The compounds of the general formula (I) are synthesized from 3,3-dimethoxy-cyclobutanecarboxylic acid methyl ester, (1) (J. Org. Chem. 1988, 53, 3841 and J. Org. Chem. 1996, 61, 2174). The ester (1) is reacted with an amine, primary or secondary in the presence of magnesium bromide in a reaction-inert-solvent, where preferred solvent is acetonitrile, at a reaction temperature of about room temperature to the reflux temperature of the solvent employed, where the preferred temperature of the oil bath is 90° C to yield amide (11).

Step B:

- 15 The amide (11) is reduced with an appropriate reduction reagent such as e.g. lithium aluminum hydride, or borane in tetrahydrofuran. The reaction is normally effected in an aprotic solvent, such as tetrahydrofuran, or diethyl ether at a reaction temperature from about 0° C to the reflux temperature of the solvent employed, yielding the amine (12).

Step C:

- 20 The ketal protection group of (12) is removed by methods known in the art (e.g. T.W. Greene; P. G. Wuts, Protective Groups in Organic Synthesis, 3rd edition, John Wiley&Sons Inc. New York, 1999). The preferred method of ketal removal is by reaction of (12) in acetone, with an acid, such as hydrogen chloride, p-toluenesulfonic acid monohydrate, or pyridinium p-toluenesulfonate, at a temperature between about room temperature and about the reflux temperature of the solvent employed to give ketone (13).

Step D:

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The ketone (13) is reacted with an aryl bromide in the presence of an organometallic reagent, such as an organolithium, organomagnesium halide, organocerium, organotitanium, organozinc, organocopper, or organoaluminum reagent to form alcohol (14). An organomagnesium halide (Grignard reagent) or organolithium reagent is preferred. The
5 reaction is typically effected in a reaction-inert-solvent, such as tetrahydrofuran, at a temperature between about -78°C and about room temperature to yield (14), a compound of formula (I).

Step E:

Reduction of the benzyl alcohol (14) is accomplished by reaction of (14) with an acid,
10 preferably with trifluoroacetic acid, either neat or in a reaction-inert-solvent, such as methylene chloride or 1,2-dichloroethane and in the presence of a reducing reagent such as a silane, preferable triethylsilane, triisopropylsilane, or triphenylsilane at a reaction temperature from about room temperature to the reflux temperature of the solvent employed, where about 65°C is the preferred reaction temperature, yields (15) a compound of formula
15 (I). Alternatively, removal of the hydroxyl group of (14) is accomplished in a two step procedure: First, alcohol (14) is treated with an acid, where methane sulfonic acid is preferred in a reaction inert solvent, where 1,2-dichloroethane is preferred at a reaction temperature about 65°C . The resulting crude material is reduced using well-established
20 conditions. Reaction of the crude olefin in 1,2-dichloroethane in the presence of palladium on carbon and in the presence of hydrogen, 45 psi, yields (15), a compound of the formula (I).

Step F:

Reaction of a compound of the type (15), where $\text{R}^8 = \text{CN}$ in a polar protic solvent, where lower alcohol solvents are preferred, i.e. methyl alcohol, in the presence of a base, preferably sodium bicarbonate, with hydroxylamine hydrochloride salt at a reaction
25 temperature of about 70°C gives (17), a compound of the formula (I).

Step G:

Reaction of (17) with acetic anhydride in a reaction inert solvent, such as 1,2-dichloroethane at the reflux temperature of the solvent employed, yields (18), a compound of formula (I).

30 Step H:

The compound of the type (14) is reacted with N-fluorobenzenesulfonimide in a reaction-inert-solvent, where preferred solvent is toluene at a reaction temperature from room temperature to the reflux temperature of the solvent employed, where 110°C is preferred, gives (16), a compound of formula (I).

35 Exemplary compounds of formula I in accordance with the present invention are the following:

3-Benzylloxymethyl-1-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutanol,

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- 1-[4-(3-Benzoyloxymethyl-cyclobutyl)-benzyl]-pyrrolidine,
 1-[4-(3-Benzoyloxymethyl-cyclobutyl)-benzyl]-pyrrolidine,
 [3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutyl]-methanol,
 Toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester,
 5 3-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxymethyl]-benzonitrile,
 2-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxymethyl]-benzonitrile,
 4-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxymethyl]-benzonitrile,
 1-{4-[3-(3-Methoxy-benzoyloxymethyl)-cyclobutyl]-benzyl}-pyrrolidine,
 1-{4-[3-(3-Fluoro-benzoyloxymethyl)-cyclobutyl]-benzyl}-pyrrolidine,
 10 1-{4-[3-(4-Trifluoromethoxy-benzoyloxymethyl)-cyclobutyl]-benzyl}-pyrrolidine,
 1-(4-{3-[(3-Chloro-2-fluoro-phenyl)methoxymethyl]-cyclobutyl}-benzyl)-pyrrolidine,
 1-{4-[3-(3-Methoxy-benzoyloxymethyl)-cyclobutyl]-benzyl}-pyrrolidine,
 1-(4-{3-[(3,4-Dichloro-phenyl)methoxymethyl]-cyclobutyl}-benzyl)-pyrrolidine,
 1-(4-{3-[(3,5-Difluoro-phenyl)methoxymethyl]-cyclobutyl}-benzyl)-pyrrolidine,
 15 1-{4-[3-(3-Methyl-benzoyloxymethyl)-cyclobutyl]-benzyl}-pyrrolidine,
 1-{4-[3-(3-Fluoro-benzoyloxymethyl)-cyclobutyl]-benzyl}-pyrrolidine,
 1-{4-[3-(4-Fluoro-benzoyloxymethyl)-cyclobutyl]-benzyl}-pyrrolidine,
 1-{4-[3-(4-Trifluoromethyl-benzoyloxymethyl)-cyclobutyl]-benzyl}-pyrrolidine,
 1-(4-{3-[(2,4-Difluoro-phenyl)methoxymethyl]-cyclobutyl}-benzyl)-pyrrolidine,
 20 1-(4-{3-[(3,4-Difluoro-phenyl)methoxymethyl]-cyclobutyl}-benzyl)-pyrrolidine,
 1-{4-[3-(3-Trifluoromethyl-benzoyloxymethyl)-cyclobutyl]-benzyl}-pyrrolidine,
 1-{4-[3-(4-tert-Butyl-benzoyloxymethyl)-cyclobutyl]-benzyl}-pyrrolidine,
 1-{4-[3-(2-Fluoro-benzoyloxymethyl)-cyclobutyl]-benzyl}-pyrrolidine,
 1-{4-[3-(3-Difluoromethoxy-benzoyloxymethyl)-cyclobutyl]-benzyl}-pyrrolidine,
 25 1-{4-[3-(2-Benzenesulfonylmethyl-benzoyloxymethyl)-cyclobutyl]-benzyl}-pyrrolidine,
 1-{4-[3-(1-Phenyl-ethoxymethyl)-cyclobutyl]-benzyl}-pyrrolidine,
 1-{4-[3-(4-Methyl-benzoyloxymethyl)-cyclobutyl]-benzyl}-pyrrolidine,
 1-{4-[3-(3-Nitro-benzoyloxymethyl)-cyclobutyl]-benzyl}-pyrrolidine,
 1-(4-{3-[(2-Methoxy-5-nitro-phenyl)methoxymethyl]-cyclobutyl}-benzyl)-pyrrolidine,
 30 1-{4-[3-(3-Trifluoromethoxy-benzoyloxymethyl)-cyclobutyl]-benzyl}-pyrrolidine,
 1-(4-{3-[(3,5-Dimethoxy-phenyl)methoxymethyl]-cyclobutyl}-benzyl)-pyrrolidine,
 2-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxymethyl]-pyridine,
 1-(4-{3-[(2,3,4-Trifluoro-phenyl)methoxymethyl]-cyclobutyl}-benzyl)-pyrrolidine,
 1-{4-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxymethyl]-phenyl}-1H-
 35 pyrazole,
 1-(4-{3-[(3,5-Dimethyl-phenyl)methoxymethyl]-cyclobutyl}-benzyl)-pyrrolidine,
 2-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyrimidine,

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- 8-Methoxy-2-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-quinoline,
 7-Fluoro-4-methyl-2-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-quinoline,
 4,6-Dimethyl-2-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyrimidine,
 2-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyrazine,
 5 2,5-Dimethyl-3-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyrazine,
 2-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyridine,
 2-Methyl-6-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyridine,
 3-Methoxy-6-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyridazine,
 1-{4-[3-(2-Bromo-benzyloxymethyl)-cyclobutyl]-benzyl}-pyrrolidine,
 10 2,4-Dimethoxy-6-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyrimidine,
 cis-Toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester,
 trans-Toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl
 ester,
 trans-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutyl]-methanol,
 15 cis-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutyl]-methanol,
 cis-4,6-Dimethyl-2-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyrimidine,
 cis-2-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyrimidine,
 cis-5-Ethyl-2-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyrimidine,
 cis-3-Methyl-6-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyridazine,
 20 trans-4,6-Dimethyl-2-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-
 pyrimidine,
 trans-2-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyrimidine,
 trans-5-Ethyl-2-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyrimidine,
 trans-3-Methyl-6-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyridazine,
 25 cis-5-Methyl-4-piperidin-3-yl-2-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-
 pyrimidine,
 cis-Pyridin-4-yl-{6-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyridazin-3-
 yl}-amine,
 cis-2-{[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]oxy}-4-trifluoromethyl-
 30 pyrimidine,
 cis-5-Phenyl-2-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyrimidine,
 cis-(4-Chloro-phenyl)-{6-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-
 pyridazin-3-yl}-methanone,
 cis-1,3-Dimethyl-1-{6-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-
 35 pyridazin-3-yl}-urea,
 cis-4-Pyrrolidin-3-yl-2-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-
 pyrimidine,

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- cis-4-Methyl-6-pyrrolidin-3-yl-2-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyrimidine,
- cis-4-(3-Chloro-phenyl)-2-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-quinazoline,
- 5 cis- 3-(3-Chloro-phenyl)-1-methyl-1-{6-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyridazin-3-yl}-urea,
- cis-5-(4-Methoxy-phenoxy)-2-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyrimidine,
- cis-4-Pyridin-2-yl-2-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-quinazoline,
- 10 cis-5-(3-Chloro-phenoxy)-2-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyrimidine,
- cis-4-Phenyl-6-piperidin-4-yl-2-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyrimidine,
- 15 cis-3-(3-Methyl-5-phenyl-pyrazol-1-yl)-6-{[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]oxy}-pyridazine,
- 5-Fluoro-4-piperidin-4-yl-2-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyrimidine,
- cis- 3-Piperazin-1-yl-6-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyridazine,
- 20 cis- 4-Phenyl-2-{[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]oxy}-6-trifluoromethyl-pyrimidine,
- cis-4-Methyl-6-piperidin-4-yl-2-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyrimidine,
- 25 cis-1-Methyl-4-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-phthalazine,
- cis-2-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-4-o-tolyl-pyrimidine,
- cis-5-(5-Iodo-2-methoxy-benzyl)-3-{[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutyl]methoxy}-pyridazine,
- cis-5-Methyl-4-piperidin-4-yl-2-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyrimidine,
- 30 cis-4-(2-Methyl-2H-pyrazol-3-yl)-2-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-quinazoline,
- cis-6-Methyl-2-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyrimidine-4-carboxylic acid phenylamide,
- 35 cis-4-Phenyl-2-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyrimidine,
- cis- 3-(2-Methoxy-benzyl)-6-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyridazine,

- cis-Dimethyl-{6-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyridazin-3-yl}-amine,
- cis-4-Methyl-6-phenyl-2-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyrimidine,
- 5 cis-5-Methyl-4-pyrrolidin-3-yl-2-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyrimidine,
- cis-3-(3,5-Dimethyl-pyrazol-1-yl)-6-{[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]oxy}-pyridazine,
- cis-3-(2,5-Dimethyl-pyrrol-1-yl)-6-{[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]oxy}-pyridazine,
- 10 cis-5-(3-Chloro-phenyl)-2-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyrimidine,
- cis-5-(4-Methoxy-phenyl)-2-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyrimidine,
- 15 cis-4-Phenyl-6-pyridin-2-yl-2-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyrimidine,
- cis-4-Phenyl-6-piperidin-3-yl-2-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyrimidine,
- 2-{4-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-piperazin-1-yl}-pyrimidine,
- 20 Dimethyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amine,
- 1-{4-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-piperazin-1-yl}-ethanone,
- 4-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-morpholine,
- 5-Fluoro-2-{4-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-piperazin-1-yl}-pyrimidine,
- 25 cis-4-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-morpholine,
- cis-1-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-piperazine,
- cis-5-Fluoro-2-{4-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-piperazin-1-yl}-pyrimidine,
- cis-1-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-pyrrolidine,
- 30 cis-1-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-piperidine,
- cis-2-{1-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-pyrrolidin-2-yl}-pyridine,
- cis-(2R,6S)-2,6-Dimethyl-4-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-morpholine,
- trans-1-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-pyrrolidine,
- 35 trans-1-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-piperidine,
- trans-2-{1-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-pyrrolidin-2-yl}-pyridine,

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trans-4-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-morpholine,
 trans-1-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-piperazinyl para-
 toluenesulfonate,
 trans-5-Fluoro-2-{4-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-piperazin-1-
 5 yl}-pyrimidine,
 trans-2-{Ethyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amino}-ethanol,
 trans-3,5-Dimethyl-1-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-piperidine,
 trans-Cyclohexyl-methyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amine,
 trans-Benzyl-methyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amine,
 10 trans-2-Methyl-1-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-piperidine,
 trans-3-Methyl-1-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-piperidine,
 trans-4-Methyl-1-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-piperidine,
 trans-2-Methyl-1-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-pyrrolidine,
 trans-2,6-Dimethyl-1-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-piperidine,
 15 trans-Methyl-pyridin-3-ylmethyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-
 amine,
 trans-(2R,5R)-2,5-Dimethyl-1-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-
 pyrrolidine,
 trans-Cyclopropylmethyl-propyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-
 20 amine,
 trans-2-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-2,3-dihydro-1H-
 isoindole,
 trans-(2R,6S)-2,6-Dimethyl-4-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-
 morpholine,
 25 trans-4-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-piperazin-2-one,
 trans-(S)-2-Methoxymethyl-1-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-
 pyrrolidine,
 trans-(3,5-Bis-trifluoromethyl-benzyl)-{[3-(4-pyrrolidin-1-ylmethyl-phenyl)-
 cyclobutyl]methyl}-amine,
 30 trans-(5-Methyl-pyrazin-2-ylmethyl)-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-
 cyclobutylmethyl]-amine,
 trans-(2-Methyl-pyridin-3-ylmethyl)-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-
 cyclobutylmethyl]-amine,
 trans-Pyridin-2-ylmethyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amine,
 35 trans-trans-2-{4-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-piperazin-1-yl}-
 isonicotinonitrile,

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- trans-Methyl-pyridin-2-ylmethyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amine,
- trans-(3-Chloro-5-trifluoromethyl-pyridin-2-ylmethyl)-{[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutyl]methyl}-amine,
- 5 trans-3-Ethyl-5-((R)-1-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-pyrrolidin-2-yl)-[1,2,4]oxadiazole,
- trans-(6-Methyl-pyridin-2-ylmethyl)-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amine,
- trans-(2-Chloro-6-fluoro-benzyl)-propyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amine,
- 10 trans-[3-(3,5-Dimethyl-pyrazol-1-yl)-benzyl]-methyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amine,
- trans-1-(5-Chloro-2-methoxy-benzyl)-4-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-piperazine,
- 15 trans-(3S,4aS,8aS)-2-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-decahydro-isoquinoline-3-carboxylic acid tert-butylamide,
- trans-(1-Benzyl-piperidin-4-ylmethyl)-methyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amine,
- trans-(S)-1-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-pyrrolidine-2-carboxylic acid amide,
- 20 trans-(8-Methoxy-quinolin-5-ylmethyl)-methyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amine,
- trans-4-(4-Chloro-phenoxy)-1-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-piperidine,
- 25 trans-4-(2-Methoxy-phenoxy)-1-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-piperidine,
- trans-4-(3-Chloro-phenoxy)-1-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-piperidine,
- trans-Methyl-(4-phenoxy-benzyl)-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amine,
- 30 trans-[1-(2-Methoxy-ethyl)-piperidin-4-ylmethyl]-methyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amine,
- trans-1-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-4-p-tolyloxy-piperidine,
- trans-2-{Benzyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amino}-ethanol,
- 35 trans-[2-(3,4-Dimethoxy-phenyl)-ethyl]-methyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amine,
- trans-Methyl-prop-2-ynyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amine,

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- trans-4-Pyrrolidin-1-yl-1-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-
piperidine,
trans-Isopropyl-(2-methoxy-ethyl)-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-
cyclobutylmethyl]-amine,
5 trans-1-Benzyl-4-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-piperazine,
trans-1-Ethyl-4-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-piperazine,
trans-2-{Isopropyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amino}-
ethanol,
trans-(2-Methoxy-ethyl)-propyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-
10 amine,
trans-Methyl-((R)-1-phenyl-ethyl)-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-
cyclobutylmethyl]-amine,
trans-(4S,4aS)-4-Phenyl-1-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-
decahydro-quinolin-4-ol,
15 trans-1-{4-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-piperazin-1-yl}-
ethanone,
trans-1-Methyl-4-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-[1,4]diazepane,
trans-2-{4-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-piperazin-1-yl}-
nicotinonitrile,
20 trans-Ethyl-(2-methoxy-ethyl)-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-
amine,
trans-Methyl-(3-methyl-pyridin-2-ylmethyl)-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-
cyclobutylmethyl]-amine,
trans-Diethyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amine,
25 trans-Benzyl-isopropyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amine,
trans-(S)-2-Pyrrolidin-1-ylmethyl-1-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-
cyclobutylmethyl]-pyrrolidine,
trans-((S)-1-Benzyl-pyrrolidin-3-yl)-ethyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-
cyclobutylmethyl]-amine,
30 trans-tert-Butyl-(2-methoxy-ethyl)-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-
cyclobutylmethyl]-amine,
trans-4-(2-Chloro-phenoxy)-1-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-
piperidine,
trans-N-Ethyl-N',N'-dimethyl-N-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-
35 ethane-1,2-diamine,
trans-Dicyclopropylmethyl-methyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-
cyclobutylmethyl]-amine,

- trans-Butyl-methyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amine,
trans-N,N,N'-Trimethyl-N'-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-
ethane-1,2-diamine,
trans-1-(1-Methyl-1H-imidazol-2-ylmethyl)-4-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-
5 cyclobutylmethyl]-piperazine,
trans-2,5-Dimethyl-1-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-2,5-
dihydro-1H-pyrrole,
trans-((S)-1-Benzyl-pyrrolidin-3-yl)-methyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-
cyclobutylmethyl]-amine,
10 trans-(4-Fluoro-benzyl)-methyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-
amine,
trans-1-Phenyl-8-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-1,3,8-triaza-
spiro[4.5]decan-4-one,
trans-2-{Methyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amino}-ethanol,
15 trans-3-Benzyl-7-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-5,6,7,8-
tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine,
trans-3-{Benzyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amino}-propan-
1-ol,
trans-Isobutyl-methyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amine,
20 trans-Ethyl-isopropyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amine,
trans-Dimethyl-[(R)-1-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-pyrrolidin-
3-yl]-amine,
trans-Isopropyl-methyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amine,
trans-Methyl-(5-propyl-1H-pyrazol-3-ylmethyl)-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-
25 cyclobutylmethyl]-amine,
trans-(1R,2S)-2-{Methyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amino}-
1-phenyl-propan-1-ol,
trans-2-{1-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-piperidin-4-yl}-
benzooxazole,
30 trans-3-Propyl-7-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-5,6,7,8-
tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine,
trans-Benzyl-((R)-1-phenyl-ethyl)-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-
cyclobutylmethyl]-amine,
trans-tert-Butyl-ethyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amine,
35 trans-1-Methyl-4-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-piperazine,
trans-Isopropyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-(1,3,5-trimethyl-
1H-pyrazol-4-ylmethyl)-amine,

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- trans-4-{Benzyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amino}-butan-1-ol,
- trans-(1R,2R)-2-{Methyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amino}-1-phenyl-propan-1-ol,
- 5 trans-Benzyl-ethyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amine,
- trans-6-{4-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-piperazin-1-yl}-nicotinonitrile,
- trans-Methyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-(2-trifluoromethyl-benzyl)-amine,
- 10 trans-3-(3-Methoxy-phenyl)-6-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-5,6,7,8-tetrahydro-4H-1,2,3a,6-tetraaza-azulene,
- trans-Methyl-phenethyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amine,
- trans-3-{Pyridin-2-ylmethyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amino}-propan-1-ol,
- 15 trans-Bis-pyridin-2-ylmethyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amine,
- trans-Bis-(3-chloro-benzyl)-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amine,
- trans-Cyclopropyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-(1,3,5-trimethyl-1H-pyrazol-4-ylmethyl)-amine,
- 20 trans-Methyl-pyridin-4-ylmethyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amine,
- trans-3-(3,4-Difluoro-phenyl)-6-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-5,6,7,8-tetrahydro-4H-1,2,3a,6-tetraaza-azulene,
- 25 3-Pyrrolidin-1-ylmethyl-1-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutanol,
- 1-(4-Piperidin-1-ylmethyl-phenyl)-3-pyrrolidin-1-ylmethyl-cyclobutanol,
- 1-(4-Benzylloxymethyl-phenyl)-3-pyrrolidin-1-ylmethyl-cyclobutanol,
- 4-(1-Hydroxy-3-pyrrolidin-1-ylmethyl-cyclobutyl)-benzonitrile,
- 1-(4-Morpholin-4-ylmethyl-phenyl)-3-piperidin-1-ylmethyl-cyclobutanol,
- 30 3-Morpholin-4-ylmethyl-1-(4-morpholin-4-ylmethyl-phenyl)-cyclobutanol,
- 1-(4-Dimethylaminomethyl-phenyl)-3-pyrrolidin-1-ylmethyl-cyclobutanol,
- 3-(4-Pyrimidin-2-yl-piperazin-1-ylmethyl)-1-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutanol,
- 1-[4-(3-Pyrrolidin-1-ylmethyl-cyclobutyl)-benzyl]-pyrroline,
- 35 4-[4-(3-Piperidin-1-ylmethyl-cyclobutyl)-benzyl]-morpholine,
- 1-[4-(3-Pyrrolidin-1-ylmethyl-cyclobutyl)-benzyl]-piperidine,
- Dimethyl-[4-(3-pyrrolidin-1-ylmethyl-cyclobutyl)-benzyl]-amine,

- 4-(3-Pyrrolidin-1-ylmethyl-cyclobutyl)-benzonitrile,
 4-(3-Pyrrolidin-1-ylmethyl-cyclobutyl)-N-hydroxy-benzamidine,
 5-Methyl-3-[4-(3-pyrrolidin-1-ylmethyl-cyclobutyl)-phenyl]-[1,2,4]oxadiazole,
 4-(3-Pyrrolidin-1-ylmethyl-cyclobutyl)-benzylamine,
 5 1-(3-p-Tolyl-cyclobutylmethyl)-pyrrolidine,
 trans-1-[4-(3-Benzylloxymethyl-cyclobutyl)-benzyl]-pyrrolidine, and
 trans-1-[4-(3-Azidomethyl-cyclobutyl)-benzyl]-pyrrolidine.
- Preferred examples of compounds according to the present invention include:
- trans-2-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyrimidine;
 10 trans-5-Ethyl-2-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyrimidine;
 trans-3-Methyl-6-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyridazine;
 cis-5-Methyl-4-piperidin-3-yl-2-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-
 pyrimidine;
 cis-Pyridin-4-yl-{6-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyridazin-3-
 15 yl}-amine;
 cis-2-{[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]oxy}-4-trifluoromethyl-
 pyrimidine;
 cis-5-Phenyl-2-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyrimidine;
 cis-(4-Chloro-phenyl)-{6-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-
 20 pyridazin-3-yl}-methanone;
 cis-1, 3-Dimethyl-1-{6-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-
 pyridazin-3-yl}-urea;
 cis-4-Pyrrolidin-3-yl-2- [3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-
 pyrimidine;
 25 cis-4-Methyl-6-pyrrolidin-3-yl-2-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-
 pyrimidine;
 cis-4- (3-Chloro-phenyl)-2-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-
 quinazoline;
 cis- 3-(3-Chloro-phenyl)-1-methyl-1- {6-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-
 30 cyclobutylmethoxy]-pyridazin-3-yl}-urea;
 cis-5- (4-Methoxy-phenoxy)-2-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-
 pyrimidine;
 cis-4-Pyridin-2-yl-2- [3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-
 quinazoline;
 35 cis-5- (3-Chloro-phenoxy)-2-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-
 pyrimidine;

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- cis-4-Phenyl-6-piperidin-4-yl-2-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyrimidine;
- cis-3- (3-Methyl-5-phenyl-pyrazol-1-yl)-6-[[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]oxy]-pyridazine;
- 5 5-Fluoro-4-piperidin-4-yl-2- [3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyrimidine;
- cis- 3-Piperazin-1-yl-6-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyridazine;
- cis- 4-Phenyl-2-[[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]oxy]-6-trifluoromethyl-pyrimidine;
- 10 cis-4-Methyl-6-piperidin-4-yl-2-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyrimidine;
- cis-1-Methyl-4- [3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-phthalazine;
- cis-2- [3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-4-o-tolyl-pyrimidine;
- 15 cis-5- (5-Iodo-2-methoxy-benzyl)-3-[[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutyl]methoxy]-pyridazine;
- cis-5-Methyl-4-piperidin-4-yl-2- [3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyrimidine;
- cis-4- (2-Methyl-2H-pyrazol-3-yl)-2-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-quinazoline;
- 20 cis-6-Methyl-2[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyrimidine-4-carboxylic acid phenylamide;
- cis-4-Phenyl-2- [3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyrimidine;
- cis- 3-(2-Methoxy-benzyl)-6-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyridazine;
- 25 cis-Dimethyl- {6-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyridazin-3-yl}-amine;
- cis-4-Methyl-6-phenyl-2- [3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyrimidine;
- 30 cis-5-Methyl-4-pyrrolidin-3-yl-2- [3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyrimidine;
- cis-3-(3,5-Dimethyl-pyrazol-1-yl)-6-[[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]oxy]-pyridazine;
- cis-3-(2,5-Dimethyl-pyrrol-1-yl)-6-[[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]oxy]-pyridazine;
- 35 cis-5- (3-Chloro-phenyl)-2-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyrimidine;

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cis-5- (4-Methoxy-phenyl)-2-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyrimidine;

cis-4-Phenyl-6-pyridin-2-yl-2- [3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyrimidine;

5 cis-4-Phenyl-6-piperidin-3-yl-2- [3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyrimidine;

2-{4-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-piperazin-1-yl}-pyrimidine;

Dimethyl- [3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amine;

1-{4-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-piperazin-1-yl}- ethanone;

10 4-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-morpholine;

5-Fluoro-2- {4-[3- (4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-piperazin-1-yl}-pyrimidine;

cis-4- [3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-morpholine;

trans-4-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-thiomorpholine;

15 trans-6-{4-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-piperazin-1-yl}-nicotinonitrile;

trans-1-Methanesulfonyl-4-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-piperazine;

20 trans-1-Ethanesulfonyl-4-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-piperazine;

trans-1-(Propane-2-sulfonyl)-4-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-piperazine;

trans-2-Methyl-1-{4-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-piperazin-1-yl}-propan-1-one;

25 trans-(1S,4S)-2-Methanesulfonyl-5-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-2,5-diaza-bicyclo[2.2.1]heptane;

cis-1-{4-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-piperazin-1-yl}-ethanone; and

cis-4-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-thiomorpholine.

30 In the examples below the following terms are intended to have the following, general meaning:

DIPEA: diisopropylethylamine

DMF: dimethylformamide

MgSO₄: magnesium sulfate

35 DMA: dimethyl acetamide

LRMS: low resolution mass spectrometry

°C: degrees Celsius

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- calcd; calculated
 d; day(s); doublet (spectral)
 DCE: 1,2-dichlorethane
 EtOAc: ethyl acetate
 5 g: grams
 hr; hours
 Hz: hertz
 J: coupling constant (in NMR)
 L: liter(s)
 10 LAH: lithium aluminum hydride
 MHz: megahertz
 Min: minute(s)
 m/z mass to charge ratio (in mass spectrometry)
 obsd: observed
 15 PPTs: pyridinium p-toluenesulfonate:
 TsO: p-toluenesulfonate
 Rf: retention factor (in chromatography)
 Rt: retention time (in chromatography)
 rt: room temperature
 20 s: singlet (NMR), second(s)
 t: triplet
 TFA: trifluoroacetic acid
 TFAA: trifluoroacetic anhydride
 THF: tetrahydrofuran
 25 TLC: thin layer chromatography
 Ts: tosyl, p-toluenesulfonyl
 TsOH: p-toluenesulfonic acid

Solvents were purchased and used without purification. Yields were calculated for material judged homogenous by thin layer chromatography and NMR. Thin layer
 30 chromatography was performed on Merck Kieselgel 60 F 254 plates eluting with the solvents indicated, visualized by a 254 nm UV lamp, and stained with either an aqueous KMnO_4 solution or an ethanolic solution of 12-molybdophosphoric acid. Flash column chromatography was performed with using either pre-packed Biotage[□] or ISCO[□] columns using the size indicated. Nuclear magnetic resonance (NMR) spectra were acquired on a
 35 Unity 400 or 500 at 400 MHz or 500 MHz for ^1H , respectively, and 100 MHz or 125 MHz for ^{13}C NMR, respectively. Chemical shifts for proton ^1H NMR spectra are reported in parts per million relative to the singlet of CDCl_3 at 7.24 ppm. Chemical shifts for ^{13}C NMR spectra are

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reported in parts per million downfield relative to the center line of the triplet of CDCl₃ at 77.0 ppm. Mass spectra analyses were performed on a APCI Gilson 215, micromass ZMD (50% Acetonitrile / 50% water) spectrometer.

HPLC was performed according to the following methods:

5 Method A: Preparative conditions (Waters 600 & Waters 2767 Sample Manager);
Column: Waters Symmetry C₁₈, 5µm, 30 x 150 mm steel column, part # WAT248000, serial #
M12921A01; solvent A – 0.1% Trifluoroacetic acid/water; solvent B – Acetonitrile; volume of
injection: 850 µL; time 0.0, 100% solvent A, 0% solvent B, flow 20; time 2.0, 100% solvent A,
0% solvent B, flow 20; time 12.0, 0% solvent A, 100% solvent B, flow 20; time 15.0, 0%
10 solvent A, 100% solvent B, flow 20; time 15.1, 100% solvent A, 0% solvent B, flow 20; time
20.0, 100% solvent A, 0% solvent B, flow 20.

Mass spectral (micromassZO) conditions; Capillary(kV): 3.0; Cone (V): 20; Extractor
(V): 3.0; RF Lens (V): 0.5; Source temp. (°C): 120; Desolvation temp. (°C): 360; Desolvation
gas flow (L/hr): 450; Cone gas flow (L/hr): 150; LM Resolution: 15; HM Resolution: 15; Ion
15 Energy: 0.2; Multiplier: 550.

Splitter; Acurate by LC Packings, 1/10,000; Upchurch needle valve setting: 14; Make
up pump (Waters 515) Flow (ml/min.): 1.

PDA (Waters 996) Settings; Start/End wavelength (nm): 200/600; Resolution: 1.2;
Sample Rate: 1; Channels: TIC, 254 nm and 220 nm.

20 Method B: Preparative conditions (Waters 600 & Waters 2767 Sample Manager);
Column: Waters Xterra PrepMS C₁₈ column, 5µm, 30 x 150 mm steel column, part #
186001120, serial # T22881T 09; solvent A – 0.1% Trifluoroacetic acid/water; solvent B –
Acetonitrile; volume of injection: 1050 µL; time 0.0, 100% solvent A, 0% solvent B, flow 20;
time 2.0, 100% solvent A, 0% solvent B, flow 20; time 12.0, 0% solvent A, 100% solvent B,
25 flow 20; time 14.0, 0% solvent A, 100% solvent B, flow 20; time 14.1, 100% solvent A, 0%
solvent B, flow 20; time 19.1, 100% solvent A, 0% solvent B, flow 20.

Mass spectral (micromassZO) conditions; Capillary(kV): 3.0; Cone (V): 20; Extractor
(V): 3.0; RF Lens (V): 0.5; Source temp. (°C): 120; Desolvation temp. (°C): 360; Desolvation
gas flow (L/hr): 450; Cone gas flow (L/hr): 150; LM Resolution: 15; HM Resolution: 15; Ion
30 Energy: 0.2; Multiplier: 550.

Splitter; Acurate by LC Packings, 1/10,000; Upchurch needle valve setting: 14; Make
up pump (Waters 515) Flow (ml/min.): 1.

PDA (Waters 996) Settings; Start/End wavelength (nm): 200/600; Resolution: 1.2;
Sample Rate: 1; Channels: TIC, 254 nm and 220 nm.

35 Method C: Preparative conditions (Waters 600 & Waters 2767 Sample Manager);
Column: Waters Symmetry C₁₈, 5µm, 30 x 150 mm steel column, part # WAT248000, serial #
M12921A01; solvent A – 0.1% Trifluoroacetic acid/water; solvent B – Acetonitrile; volume of

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injection: 850 μ L; time 0.0, 90% solvent A, 10% solvent B, flow 20; time 10.0, 0% solvent A, 100% solvent B, flow 20; time 12.0, 0% solvent A, 100% solvent B, flow 20.

Mass spectral (micromassZO) conditions; Capillary(kV): 3.0; Cone (V): 20; Extractor (V): 3.0; RF Lens (V): 0.5; Source temp. ($^{\circ}$ C): 120; Desolvation temp. ($^{\circ}$ C): 360; Desolvation
5 gas flow (L/hr): 450; Cone gas flow (L/hr): 150; LM Resolution: 15; HM Resolution: 15; Ion Energy: 0.2; Multiplier: 550.

Splitter; Acurate by LC Packings, 1/10,000; Upchurch needle valve setting: 14; Make up pump (Waters 515) Flow (ml/min.): 1.

PDA (Waters 996) Settings; Start/End wavelength (nm): 200/600; Resolution: 1.2;
10 Sample Rate: 1; Channels: TIC, 254 nm and 220 nm.

The following intermediates may be prepared by the procedures shown:

Intermediate 1 - General procedure A: -

Step A:

(3,3-Dimethoxy-cyclobutyl)-methanol. To a stirring solution of 3,3-dimethoxy-
15 cyclobutanecarboxylic acid methyl ester, (J. Org. Chem. 1988, 53, 3841 and J. Org. Chem. 1996, 61, 2174) (15.0 g, 86.1 mmol) in 40 mL of tetrahydrofuran at 0 $^{\circ}$ C (ice/water bath) was added dropwise a solution of lithium aluminum hydride (103.3 mL, 1M tetrahydrofuran). After the addition was complete the reaction was warmed to room temperature and stirred 12
20 hours. The reaction was worked-up using the method of Feiser and Feiser, and then filtered through a plug of Celite and concentrated under reduced pressure to yield (3,3-dimethoxy-cyclobutyl)-methanol (12.4 g, 99% crude yield) as a colorless oil. This material was used without further purification

500 MHz ^{1} H NMR (CDCl₃) δ 3.64 (d, J = 5.7Hz, 2H), 3.15 (s, 3H), 3.13 (s, 3H), 2.32-
2.23 (m, 3H), 1.94 (bs, 1H), 1.92-1.84 (m, 2H); 125 MHz ^{13} C NMR (CDCl₃) δ 101.0, 66.9,
25 48.7, 48.4, 34.3, 27.0; C7 H14 O3, 146.185, MS Low res (M-OCH₃) = 115.1;

Intermediate 2 - General procedure A:

Step B:

[(3,3-Dimethoxy-cyclobutyl)methoxymethyl]-benzene. To a stirring solution of crude
(3,3-dimethoxy-cyclobutyl)-methanol (11.9 g, 81.5 mmol) in 100 mL of tetrahydrofuran at
30 room temperature was added a solution of potassium t-butoxide (163 mL, 1M tetrahydrofuran). The reaction was allowed to stir for 30 minutes and then benzyl bromide (10.2 mL, 85.6 mmol) was added. After 30 minutes TLC analysis indicated complete consumption of starting material. The reaction was quenched with water and diluted with methylene chloride. The organic layer was separated, dried over magnesium sulfate, filtered,
35 and concentrated under reduced pressure. Purification of this material was accomplished by flash column chromatography using a Biotage Column 75 medium, eluting with a gradient of hexanes through 5% EtOAc/hexanes. The product containing fractions were collected and

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concentrated under reduced pressure to give the title compound (13.2 g, 69% yield), as a colorless oil.

R_f = 0.75 (40% EtOAc / Hexanes); 500 MHz ¹H NMR (CDCl₃) δ 7.36-7.25 (m, 5H), 4.52 (s, 2H), 3.48 (d, J = 7.0Hz, 2H), 3.16 (s, 3H), 3.12 (s, 3H), 2.44-2.26 (m, 3H), 1.90-1.84 (m, 2H); 100 MHz ¹³C NMR (CDCl₃) δ 138.8, 128.6, 127.9, 127.8, 101.1, 74.7, 73.2, 48.6, 48.4, 34.9, 24.9; C₁₄ H₂₀ O₃, 236.309, MS Low res (M-OCH₃) = 205.3.

Intermediate 3 - General procedure A:

Step C

3-Benzyloxymethyl-cyclobutanone. To a stirring solution of [(3,3-dimethoxy-cyclobutyl)methoxymethyl]-benzene (13.0 g, 55.1 mmol) in 200 mL of a mixture of acetone:water (3:1) was added p-toluenesulfonic acid mono hydrate (2.1 g, 11.0 mmol). The reaction mixture was heated to 65 C for 45 minutes. Both TLC and GS/MS analysis indicated complete consumption of starting material. The reaction was cooled to room temperature and then the acetone was removed under reduced pressure. The resulting mixture was diluted with ethyl acetate and washed with an aqueous solution 5% NaOH. The layers were separated and the organic layer was dried over magnesium sulfate, filtered through a fritted funnel and then concentrated under reduced pressure. Purification of this material was accomplished by flash chromatography using a Biotage Column 75 small, eluting with a 10% EtOAc/hexanes. The product containing fractions were collected and concentrated under reduced pressure to yield the title compound (6.0 g, 58 % yield) as a colorless oil.

R_f = 0.35 (30% EtOAc / Hexanes); 500 MHz ¹H NMR (CDCl₃) δ 7.39-7.27 (m, 5H), 4.56 (s, 2H), 3.59 (d, J = 6.3Hz, 2H), 3.18-3.08 (m, 2H), 2.92-2.84 (m, 2H), 2.75-2.64 (m, 1H); 100 MHz ¹³C NMR (CDCl₃) δ 207.6, 138.3, 128.7, 127.9, 127.8, 73.4, 73.1, 50.2, 23.9; C₁₂ H₁₄ O₂, 190.241, GC/MS 190, Retention time = 2.46min (Stationary phase: HP-1, fused silica, description: 12m x 0.202mm x0.33um. temperature limits: -60 C to 325 C, ramp rate = 30 C/ min, solvent delay = 0.4min)

The following compounds may be prepared by the procedures below:

Example 1 - General procedure A:

Step D:

3-Benzyloxymethyl-1-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutanol. To a stirring solution of 1-(4-bromo-benzyl)-pyrrolidine (1.9 g, 7.9 mmol) in 13 mL of tetrahydrofuran at -78 C (iPrOH/dry ice) was added slowly down the side of the flask a solution of n-butyl lithium (3.2 mL, 7.9 mmol, 2.5 M in THF). After 30 minutes a precooled -78 C (iPrOH/CO₂ ice) solution of 3-benzyloxymethyl-cyclobutanone (1.0 g, 5.3 mmol, in 1 mL of THF) was added via cannula down the side of the flask (wash 1 mL). The resulting solution was stirred at -78 C for 30 minutes, then quenched with a saturated solution of aqueous NH₄OH and diluted with EtOAc. The layers were separated and the organic layer was dried over magnesium sulfate, filtered

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through a fritted funnel and then concentrated under reduced pressure. Purification of this material was accomplished by flash column chromatography using a Biotage column, eluting with a gradient of 2% MeOH/CH₂Cl₂ w/ 0.1% NH₄OH through 30% MeOH/CH₂Cl₂ w/ 0.1% NH₄OH. The product containing fractions were collected and concentrated under reduced pressure to yield the title compound (1.3 g, 71% yield) as a colorless oil and a 3:1 mixture of cis:trans isomers.

R_f = 0.45 (15%MeOH/CH₂Cl₂ w/ 0.1% NH₄OH); ¹H NMR; cis:trans isomers, diagnostic peaks 400 MHz ¹H NMR (CDCl₃) δ 7.36 - 7.25 (m), 7.22 - 7.06 (m), 6.57 - 6.54 (m), 4.59 (s), 4.50 (s), 3.64 - 3.58 (m), 3.53 (s), 2.56 - 2.50 (m), 2.42 - 2.21 (m), 1.82 - 1.77 (m); LRMS m/z Calcd for C₂₃ H₂₉ N O₂, 351.487; obsd LRMS (M+1) 352.4;

Example 2 - General procedure A:

Step E

1-[4-(3-Benzyloxymethyl-cyclobutyl)-benzyl]-pyrrolidine. To a stirring solution of 3-benzyloxymethyl-1-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutanol (1.0 g, 2.8 mmol) in 10 mL of 1,2-dichloroethane was added triethyl silane (4.5 mL, 28.5 mmol) followed by the addition of trifluoroacetic acid (4.4 mL, 57.0 mmol). The reaction was then heated to 75 °C (oil bath). After 1 hour the reaction was cooled to room temperature and then concentrated under reduced pressure. The crude material was taken up in EtOAc and washed with an aqueous solution of 1M NaOH. The layer were separated and the organic layer was dried over magnesium sulfate, filtered through a fritted funnel and concentrated under reduced pressure. Purification of this material was accomplished by flash column chromatography using a 45 g ISCO column, eluting with a gradient of 2% MeOH/CH₂Cl₂ w/ 0.1% NH₄OH, through 10% MeOH/CH₂Cl₂ w/ 0.1% NH₄OH. The product containing fractions were collected and concentrated to give the title compound (yield not determined due to presence of TFA) as a colorless oil and a 1:1 mixture of cis:trans isomers. Further purification of this material is not required.

Scale-up: To a stirring solution of 3-benzyloxymethyl-1-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutanol (21.6g, 61.5 mmol) in neat triethyl silane (49 mL, 307 mmol) was added trifluoroacetic acid (47 mL, 615 mmol). The reaction was then heated to 75 °C (oil bath). After 30 minutes the reaction was cooled to room temperature and then concentrated under reduced pressure and used without further purification.

R_f = 0.3 (10%MeOH/CH₂Cl₂ w/ 0.1%NH₄OH); cis:trans isomers, diagnostic peaks 400 MHz ¹H NMR (CDCl₃) δ 7.36-7.29 (m), 7.27-7.16 (m), 4.57 (s), 4.48 (s), 4.08 (s), 3.60 (d, J = 7.5 Hz), 3.42 (d, J = 5.8Hz), 2.61-2.53 (m), 2.48-2.41 (m), 2.24-2.19 (m); cis:trans isomers, diagnostic peaks 100 MHz ¹³C NMR (CDCl₃) δ 148, 138.8, 130.4, 128.6, 127.4, 74.3, 73.3, 58.2, 52.9, 36.6, 33.1, 31.5, 30.9, 23.1; LRMS m/z Calcd for C₂₃ H₂₉ N O, 335.488; obsd LRMS (M+1), 336.4.

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Example 3 - General procedure A:

Step F:

[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutyl]-methanol. To a stirring solution of crude 1-[4-(3-benzyloxymethyl-cyclobutyl)-benzyl]-pyrrolidine TFA salt prepared above (61.5 mmol) in 250 mL of ethyl alcohol was added palladium black (4.0 g, 20% by wt). The Parr bottle was then pressurized with H₂ to 45 psi. After complete consumption of starting material as evident by LRMS the reaction vessel was evacuated (removal of H₂ gas), then the reaction was filtered through a plug of Celite, and concentrated under reduced pressure. The residual was diluted with CH₂Cl₂ and washed with a saturated solution of NaHCO₃. The aqueous layer was back extracted with 3:1 CHCl₃:iPrOH. The organic layers were dried over magnesium sulfate, filtered through a fritted funnel and concentrated under reduced pressure. Purification of this material was accomplished by flash chromatography, using a Biotage column 75 large, eluting with a gradient of 2% MeOH/CH₂Cl₂ w/ 0.2% NH₄OH, through 20% MeOH/CH₂Cl₂ w/ 0.2% NH₄OH. The product containing fractions were collected and concentrated, ¹³C NMR revealed the presence of TFA. The product was free based by reaction with aqueous K₂CO₃, and extracted with 3:1 CHCl₃:iPrOH to yield the title compound (11.9 g, 79% yield) as a colorless oil and a mixture of cis:trans isomers.

R_f = 0.33 (10% MeOH/CH₂Cl₂ w/ 0.1% NH₄OH); ¹H NMR; cis:trans isomers, diagnostic peaks 400 MHz ¹H NMR (CDCl₃) δ 7.3 (m), 3.65 - 3.64 (m), 3.46 - 3.45 (m), 2.60 - 2.58 (m), 1.81 - 1.80 (m); cis:trans isomers, diagnostic peaks 100 MHz ¹³C NMR (CDCl₃) δ 145.7, 145.2, 135.2, 129.5, 126.6, 67.3, 66.7, 60.3, 54.1, 36.6, 35.9, 33.5, 33.1, 31.2, 23.4; ; LRMS m/z Calcd for C₁₆ H₂₃ N O 245.364; obsd LRMS (M+1) 246.3.

Example 4 - General procedure A:

Step G:

Toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester. To a stirring solution of [3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutyl]-methanol (0.56 g, 2.3 mmol) prepared above in 5 mL of dichloromethane was added triethyl amine (1.6 mL, 2.7 mmol) followed by 4-(dimethyl amino)pyridine (2.8 mg, 0.23 mmol) and p-toluene sulfonyl chloride (0.52g, 2.7mmol). After 1 hr the reaction was quenched with a saturated aqueous solution of NaHCO₃. The reaction was diluted and extracted with dichloromethane. The organic layers were dried over magnesium sulfate, filtered through a fritted funnel, and concentrated under reduced pressure. Purification of this material was accomplished by flash column chromatography, using a 40g ISCO column, eluting with a gradient of 4%, 6%, and 10% MeOH/CH₂Cl₂. The product containing fractions were collected and concentrate under reduced pressure to give the title compound (0.82 g, 93% yield) as a colorless oil and a mixture of cis:trans isomers.

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R_f = 0.29 (10%MeOH/CH₂Cl₂ w/ 0.1% NH₄OH); ¹H NMR; cis:trans isomers, diagnostic peaks 400 MHz ¹H NMR (CDCl₃) δ 7.83 - 7.77 (m), 7.37 - 7.32 (m), 7.27 - 7.23 (m), 7.13 - 7.06 (m), 4.18 (s), 3.99 (s), 3.59 (bs), 3.53 - 3.49 (m), 2.64 - 2.55 (m), 2.52 (bs), 2.45 (d, J = 3.7 Hz), 2.29 - 2.12 (m), 1.86 - 1.72 (m); cis:trans isomers, diagnostic peaks 100 MHz ¹³C NMR (CDCl₃) δ 144.9, 133.4, 130.1, 129.2, 129.1, 128.1, 74.2, 73.8, 60.5, 54.4, 36.1, 35.9, 32.4, 30.9, 23.6, 21.9; LRMS m/z Calcd for C₂₃ H₂₉ N O₃ S 399.56; obsd LRMS (M+1) 400.3.

Example 5 - General procedure A:

Step G:

10 3-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxymethyl]-benzonitrile. To a stirring solution of [3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutyl]-methanol (50.0 mg, 0.20 mmol) prepared above (Step F) in 3 mL of tetrahydrofuran was added a solution of KotBu (0.42 mL, 0.41 mmol, 1M THF). After 30 minutes 3-(bromomethyl)-benzonitrile (42.0 mg, 0.21 mmol), in 1 mL of THF was added and then the reaction was heated to 40 °C (oil bath).
15 After 3 hours the reaction was quenched with water and diluted with EtOAc. The layers were separated and the organic layer was dried over MgSO₄, filtered through a fitted funnel and concentrated under reduced pressure. This material was purified by flash chromatography using a 4 g ISCO column, eluting with a gradient of 2%, 4%, 8% MeOH/CH₂Cl₂ w/ 0.1 % NH₄OH. The product containing fractions were collected and concentrated to give the title
20 compound (29.0 mg, 39% yield) as a colorless oil and a mixture of cis:trans isomers.

R_f = 0.63 (10% MeOH/CH₂Cl₂ w/ 0.1% NH₄OH); ¹H NMR; cis:trans isomers, diagnostic peaks 400 MHz ¹H NMR (CDCl₃) δ 7.66 - 7.55 (m), 7.48 - 7.42 (m), 7.29 - 7.25 (m), 7.20 - 7.14 (m), 4.58 (s), 4.53 (s), 3.66 (d J = 7.0 Hz), 3.62 (s), 2.62 - 2.47 (m), 2.32 - 2.20 (m), 1.94 - 1.86 (m), 1.81 - 1.78 (m); cis:trans isomers, diagnostic peaks 100 MHz ¹³C NMR (CDCl₃) δ 140.5, 131.9, 131.8, 131.4, 131.3, 131.1, 129.4, 126.5, 119.1, 112.7, 75.6, 74.9, 72.1, 71.9, 60.5, 54.3, 36.7, 36.2, 33.2, 31.6, 23.6; LRMS m/z Calcd for C₂₄ H₂₈ N₂ O 360.498 obsd LRMS (M+1) 361.4.

Example 6

2-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxymethyl]-benzonitrile.

30 Preparation as described for Example 5, General Procedure A, Step G.

R_f = 0.54 (10% MeOH/CH₂Cl₂ w/ 0.1% NH₄OH); cis:trans isomers, diagnostic peaks 400 MHz ¹H NMR (CDCl₃) δ 7.67 - 7.58 (m), 7.41 - 7.36 (m), 7.28 - 7.14 (m), 4.75 (s), 4.70 (s), 3.74 (d, J = 7.0 Hz), 3.60 (s), 2.66 - 2.61 (m), 2.52 - 2.45 (m), 2.32 - 2.25 (m), 1.97 - 1.89 (m), 1.80 - 1.77 (m); cis:trans isomers, diagnostic peaks 100 MHz ¹³C NMR (CDCl₃)
35 δ 142.6, 133.1, 132.9, 129.2, 128.2, 126.5, 126.4, 111.7, 75.8, 75.3, 70.9, 70.7 60.6, 54.3, 36.7, 36.3, 31.6, 30.8, 23.6; LRMS m/z Calcd for C₂₄ H₂₈ N₂ O 360.498: obsd LRMS (M+1) 361.4.

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Example 7

4-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxymethyl]-benzonitrile.

Preparation as described for Example 5, General Procedure A, Step G.

Rf = 0.29 (10% MeOH/CH₂Cl₂ w/ 0.1% NH₄OH); cis:trans isomers, diagnostic peaks

5 400 MHz ¹H NMR (CDCl₃) δ 7.66 - 7.62 (m), 7.48 - 7.42 (m), 7.28 - 7.24 (m), 7.19 - 7.13 (m), 4.61 (s), 4.56 (s), 3.47 (d, J = 6.2 Hz), 3.66 (d, J = 7.5 Hz), 3.61 (s, 2H), 2.64 - 2.44 (m), 2.33 - 2.17 (m), 1.95 - 1.87 (m), 1.81 - 1.78 (m); cis:trans isomers, diagnostic peaks 100 MHz ¹³C NMR (CDCl₃) δ 144.5, 132.4, 129.2, 127.9, 127.8, 126.5, 75.6, 75.0, 72.2, 60.5, 54.3, 36.7, 33.2, 30.9, 23.6; LRMS m/z Calcd for C₂₄ H₂₈ N₂ O 360.498; obsd LRMS (M+1) 361.4.

10 Example 8

1-{4-[3-(3-Methoxy-benzyloxymethyl)-cyclobutyl]-benzyl}-pyrrolidine. Preparation as described for Example 5, General Procedure A, Step G.

Rf = 0.40 10%MeOH/CH₂Cl₂ w/ 0.1% NH₄OH); cis:trans isomers, diagnostic peaks

15 400 MHz ¹H NMR (CDCl₃) δ 7.35 - 7.16 (m), 6.95 - 6.80 (m), 4.55 (s), 4.49 (s), 3.81 (d, J = 5.4 Hz), 3.75 (bs), 2.70 - 2.55 (m), 2.50 - 2.44 (m), 2.31 - 2.19 (m), 1.90 - 1.84 (m); cis:trans isomers, diagnostic peaks 100 MHz ¹³C NMR (CDCl₃) δ 140.5, 129.6, 126.8, 120.1, LRMS m/z Calcd for C₂₄ H₃₁ N O₂ 365.514; obsd LRMS (M+1) 366.4.

Example 9

1-{4-[3-(3-Fluoro-benzyloxymethyl)-cyclobutyl]-benzyl}-pyrrolidine. Preparation as described for Example 5, General Procedure A, Step G.

Rf = 0.29 (10%MeOH/CH₂Cl₂ w/ 0.1% NH₄OH); cis:trans isomers, diagnostic peaks

25 400 MHz ¹H NMR (CDCl₃) δ 7.32 - 7.24 (m), 7.19 - 7.08 (m), 6.97 - 6.95 (m), 4.55 (s), 4.50 (s), 3.63 (d, J = 7.5 Hz), 3.59 (s), 2.60 - 2.59 (m), 2.51 - 2.44 (m), 2.31 - 2.21 (m), 1.91 - 1.88 (m), 1.79 - 1.76 (m); cis:trans isomers, diagnostic peaks 100 MHz ¹³C NMR (CDCl₃) δ 130.1, 129.0, 126.5, 123.1, 114.6, 114.4, 75.3, 72.5, 60.6, 54.4, 36.7, 36.2, 33.3, 31.7, 23.6, LRMS m/z Calcd for C₂₃ H₂₈ F N O 353.478; obsd LRMS (M+1) 354.4.

Example 10 - General procedure A

Step G

Alternative high through-put procedure:

30 Benzyl bromides (0.132 mmol, 1.05 equiv) were pre-weighed into 2-dram vials. A stock solution of [3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutyl]-methanol and KOtBu was made. Using the following amounts times the number of reactions run, (30.7 mg, 0.125 mmol, 1 equiv) dissolved in 0.75 ml of dry THF and a solution of KOtBu (1 N in THF, 0.25 ml, 0.25 mmol, 2 equiv) was added. This mixture was shaken at room temperature for ~15 minutes (yellow cloudy solution). After ~15 minutes 1 ml of this stock solution was added to each bromide starting material. The resulting reactions were heated and shaken at 45 °C for 20 hours. After 20 hours the reactions were quenched with 0.5 ml of MeOH and loaded by

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hand onto Silicycle SCX SPE cartridge and then rinsed with CH₂Cl₂. The vials were changed and eluted with 5 ml of MeOH then switched to a tared vials and eluted with 7.5 ml of 1 N TEA in MeOH. Stripped off solvent, weighed. Purification was accomplished using the HPLC reported method. The product containing fractions were compressed into tared vials.

5 1-{4-[3-(4-Trifluoromethoxy-benzyloxymethyl)-cyclobutyl]-benzyl}-pyrrolidine.

Rt = 4.48 min HPLC method A; LRMS m/z Calcd for C₂₄ H₂₈ F₃ N O₂ 419.491
obsd LRMS (M+1) 420.13.

Example 11

1-(4-{3-[(3-Chloro-2-fluoro-phenyl)methoxymethyl]-cyclobutyl}-benzyl)-pyrrolidine.

10 Preparation as described for Example 10, General Procedure A, Step G.

Rt = 4.72 min HPLC method A; LRMS m/z Calcd for C₂₃ H₂₇ Cl F N O 387.929;
obsd LRMS (M+1) 388.13.

Example 12

15 1-{4-[3-(3-Methoxy-benzyloxymethyl)-cyclobutyl]-benzyl}-pyrrolidine. Preparation as
described for Example 10, General Procedure A, Step G.

Rt = 4.63 min HPLC method A; LRMS m/z Calcd for C₂₄ H₃₁ N O₂ 365.52; obsd
LRMS (M+1) 366.16.

Example 13

1-(4-{3-[(3,4-Dichloro-phenyl)methoxymethyl]-cyclobutyl}-benzyl)-pyrrolidine.

20 Preparation as described for Example 10, General Procedure A, Step G.

Rt = 4.85 min HPLC method A; LRMS m/z Calcd for C₂₃ H₂₇ Cl₂ N O 403.00; obsd
LRMS (M+1) 404.08.

Example 14

1-(4-{3-[(3,5-Difluoro-phenyl) methoxymethyl]-cyclobutyl}-benzyl)-pyrrolidine.

25 Preparation as described for Example 10, General Procedure A, Step G.

Rt = 4.7 min HPLC method A; LRMS m/z Calcd for C₂₃ H₂₇ F₂ N O 371.475; obsd
LRMS (M+1) 372.15.

Example 15

30 1-{4-[3-(3-Methyl-benzyloxymethyl)-cyclobutyl]-benzyl}-pyrrolidine. Preparation as
described for Example 10, General Procedure A, Step G.

Rt = 9.19 min HPLC method C; LRMS m/z Calcd for C₂₄ H₃₁ N O 349.521; obsd
LRMS (M+1) 350.4.

Example 16

35 1-{4-[3-(3-Fluoro-benzyloxymethyl)-cyclobutyl]-benzyl}-pyrrolidine. Preparation as
described for Example 10, General Procedure A, Step G.

Rt = 9.63 min HPLC method C; LRMS m/z Calcd for C₂₃ H₂₈ F N O 353.484; obsd
LRMS (M+1) 354.4.

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Example 17

1-{4-[3-(4-Fluoro-benzyloxymethyl)-cyclobutyl]-benzyl}-pyrrolidine. Preparation as described for Example 10, General Procedure A, Step G.

Rt = 8.91 min HPLC method C; LRMS m/z Calcd for C₂₃ H₂₈ F N O 353.484; obsd

5 LRMS (M+1) 354.4.

Example 18

1-{4-[3-(4-Trifluoromethyl-benzyloxymethyl)-cyclobutyl]-benzyl}-pyrrolidine.

Preparation as described for Example 10, General Procedure A, Step G.

Rt = 9.50 min HPLC method C; LRMS m/z Calcd for C₂₄ H₂₈ F₃ N O 403.492; obsd

10 LRMS (M+1) 404.4.

Example 19

1-(4-{3-[(2,4-Difluoro-phenyl)methoxymethyl]-cyclobutyl}-benzyl)-pyrrolidine.

Preparation as described for Example 10, General Procedure A, Step G.

Rt = 9.03 min HPLC method C; LRMS m/z Calcd for C₂₃ H₂₇ F₂ N O 371.475; obsd

15 LRMS (M+1) 372.4.

Example 20

1-(4-{3-[(3,4-Difluoro-phenyl)methoxymethyl]-cyclobutyl}-benzyl)-pyrrolidine.

Preparation as described for Example 10, General Procedure A, Step G.

Rt = 9.06 min HPLC method C; LRMS m/z Calcd for C₂₃ H₂₇ F₂ N O 371.475 obsd

20 LRMS (M+1) 372.4.

Example 21

1-{4-[3-(3-Trifluoromethyl-benzyloxymethyl)-cyclobutyl]-benzyl}-pyrrolidine.

Preparation as described for Example 10, General Procedure A, Step G.

Rt = 9.45 min HPLC method C; LRMS m/z Calcd for C₂₄ H₂₈ F₃ N O 403.492; obsd

25 LRMS (M+1) 404.4.

Example 22

1-{4-[3-(4-tert-Butyl-benzyloxymethyl)-cyclobutyl]-benzyl}-pyrrolidine. Preparation as described for Example 10, General Procedure A, Step G.

Rt = 10.15 min HPLC method C; LRMS m/z Calcd for C₂₇ H₃₇ N O 391.602; obsd

30 LRMS (M+1) 392.5.

Example 23

1-{4-[3-(2-Fluoro-benzyloxymethyl)-cyclobutyl]-benzyl}-pyrrolidine. Preparation as described for Example 10, General Procedure A, Step G.

Rt = 8.89 min HPLC method C; LRMS m/z Calcd for C₂₃ H₂₈ F N O 353.484; obsd

35 LRMS (M+1) 354.4.

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Example 24

1-{4-[3-(3-Difluoromethoxy-benzyloxymethyl)-cyclobutyl]-benzyl}-pyrrolidine.

Preparation as described for Example 10, General Procedure A, Step G.

Rt = 9.09 min HPLC method C; LRMS m/z Calcd for C₂₄ H₂₉ F₂ N O₂ 401.501;

5 obsd LRMS (M+1) 402.4.

Example 25

1-{4-[3-(2-Benzenesulfonylmethyl-benzyloxymethyl)-cyclobutyl]-benzyl}-pyrrolidine.

Preparation as described for Example 10, General Procedure A, Step G.

Rt = 8.95 min HPLC method C; LRMS m/z Calcd for C₃₀ H₃₅ N O₃ S 489.682; obsd

10 LRMS (M+1) 490.5.

Example 26

1-{4-[3-(1-Phenyl-ethoxymethyl)-cyclobutyl]-benzyl}-pyrrolidine. Preparation as

described for Example 10, General Procedure A, Step G.

Rt = 9.09 min HPLC method C;

15 Example 27

1-{4-[3-(4-Methyl-benzyloxymethyl)-cyclobutyl]-benzyl}-pyrrolidine. Preparation as

described for Example 10, General Procedure A, Step G.

Rt = 9.19 min HPLC method C; LRMS m/z Calcd for C₂₄ H₃₁ N O 349.521; obsd

LRMS (M+1) 350.4.

20 Example 28

1-{4-[3-(3-Nitro-benzyloxymethyl)-cyclobutyl]-benzyl}-pyrrolidine. Preparation as

described for Example 10, General Procedure A, Step G.

Rt = 8.83 min HPLC method C;

Example 29

25 1-(4-{3-[(2-Methoxy-5-nitro-phenyl)methoxymethyl]-cyclobutyl}-benzyl)-pyrrolidine.

Preparation as described for Example 10, General Procedure A, Step G.

Rt = 8.89 min HPLC method C; LRMS m/z Calcd for C₂₄ H₃₀ N₂ O₄ 410.518; obsd

LRMS (M+1) 411.4.

Example 30

30 1-{4-[3-(3-Trifluoromethoxy-benzyloxymethyl)-cyclobutyl]-benzyl}-pyrrolidine.

Preparation as described for Example 10, General Procedure A, Step G.

Rt = 9.09 min HPLC method C; LRMS m/z Calcd for C₂₄ H₂₈ F₃ N O₂ 419.491; obsd

LRMS (M+1) 420.4.

Example 31

35 1-(4-{3-[(3,5-Dimethoxy-phenyl)methoxymethyl]-cyclobutyl}-benzyl)-pyrrolidine.

Preparation as described for Example 10, General Procedure A, Step G.

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Rt = 8.95 min HPLC method C; LRMS m/z Calcd for C₂₅ H₃₃ N O₃ 395.547; obsd LRMS (M+1) 396.4.

Example 32

2-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxymethyl]-pyridine. Preparation as described for Example 10, General Procedure A, Step G.

Rt = 9.09 min HPLC method C; LRMS m/z Calcd for C₂₂ H₂₈ N₂ O 336.481; obsd LRMS (M+1) 337.4.

Example 33

1-(4-{3-[(2,3,4-Trifluoro-phenyl)methoxymethyl]-cyclobutyl}-benzyl)-pyrrolidine Preparation as described for Example 10, General Procedure A, Step G.

Rt = 9.19 min HPLC method C; LRMS m/z Calcd for C₂₃ H₂₆ F₃ N O 389.465; obsd LRMS (M+1) 390.4.

Example 34

1-{4-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxymethyl]-phenyl}-1-H-pyrazole Preparation as described for Example 10, General Procedure A, Step G.

Rt = 8.83 min HPLC method C; LRMS m/z Calcd for C₂₆ H₃₁ N₃ O 401.556; obsd LRMS (M+1) 402.4.

Example 35

1-(4-{3-[(3,5-Dimethyl-phenyl)methoxymethyl]-cyclobutyl}-benzyl)-pyrrolidine. Preparation as described for Example 10, General Procedure A, Step

Rt = 9.56 min HPLC method C; LRMS m/z Calcd for C₂₅ H₃₃ N O 363.548 obsd LRMS (M+1) 364.4.

Example 36 - General procedure A:

Step G:

25 2-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyrimidine To a stirring solution of [3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutyl]-methanol (38.0 mg, 0.16 mmol) prepared above (Step F) in 1.5 mL of THF was added 2-chloropyrimidine (21.3 mg, 0.19 mmol) followed by a solution of *KOtBu* (310 μ L, 0.31 mmol, 1 M THF). The reaction immediately turned to a dark pink/milky solution. When mass spectral analysis indicated complete consumption of starting alcohol (15 minutes) the reaction was quenched with an aqueous solution of NH_4Cl . The reaction was diluted with a 3:1 mixture of chloroform/isopropyl alcohol. The layers were separated and the organic layer was dried over MgSO_4 , filtered through a fritted glass filter, and concentrated under reduced pressure to yield the title compound as a mixture of *cis:trans* isomers. Conversion to the HCl salt was accomplished by dissolving the free base in EtOAc, and then adding 1 eq of a solution of HCl (1 M THF). The colorless solid was collected and dried under reduced pressure to yield 45 mg of a colorless solid, and as a mixture of isomers.

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R_f = 0.25 (25% MeOH/CH₂Cl₂w/0.2%NH₄OH); cis:trans isomers, diagnostic peaks
 400 MHz ¹H NMR (CDCl₃) δ 8.46 (d, J = 5.0Hz), 8.44 (d, J = 5.0Hz), 7.43-7.39 (m), 7.21-7.14
 (m), 6.90-6.86 (m), 4.46 (d, J = 7.5Hz), 4.28 (d, J' = 6.2Hz), 3.95 (s), 3.67-3.58 (m), 3.42-3.35
 (m), 2.80-2.71 (m), 2.52-2.46 (m), 2.34-2.25 (m), 1.99-1.91 (m); cis:trans isomers, diagnostic
 5 peaks 100 MHz ¹³C NMR (CDCl₃) δ 165.6, 159.5, 147.1, 130.3, 127.1, 115.2, 71.5, 70.1,
 58.9, 53.3, 36.5, 32.8, 31.3, 30.1, 23.4; LRMS m/z Calcd for C₂₀ H₂₅ N₃ O 323.438; obsd
 LRMS (M+1) 324.4.

Example 37

8-Methoxy-2-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-quinoline.

10 Preparation as described for Example 36, General Procedure A, Step G using the appropriate
 starting materials.

R_f = 0.30 (10% MeOH/ CH₂Cl₂ w/0.2% NH₄OH); cis:trans isomers, diagnostic peaks
 500 MHz ¹H NMR (CDCl₃) δ 7.92-7.88 (m), 7.52-7.42 (m), 7.27-7.19 (m), 7.0-6.95 (m), 6.90-
 6.87 (m), 4.62 (d, J = 7.1Hz, major isomer), 4.44 (d, J = 5.8Hz, minor isomer), 4.03 (s), 3.70-
 15 3.62 (m, major isomer), 3.43-3.34 (m, minor isomer), 3.04 (bs), 2.80-2.70 (m, major isomer),
 2.52-2.44 (m, minor isomer), 2.37-2.24 (m), 2.02-1.92 (m); cis:trans isomers, diagnostic peaks
 125 MHz ¹³C NMR (CDCl₃) δ 162.1, 154.1, 147.7, 139.1, 130.5, 127.4, 124.1, 119.8, 113.7,
 109.2, 69.3, 56.5, 53.1, 36.6, 32.9, 31.5, 30.4, 23.3; LRMS m/z Calcd for C₂₆ H₃₀ N₂ O₂
 402.535; obsd LRMS (M+1) 403.4.

20 Example 38

7-Fluoro-4-methyl-2-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-quinoline.

Preparation as described for Example 36, General Procedure A, Step G using the appropriate
 starting materials.

R_f = 0.25 (10% MeOH/ CH₂Cl₂ w/0.2% NH₄OH); cis:trans isomers, diagnostic peaks
 25 400 MHz ¹H NMR (CDCl₃) δ 7.79-7.74 (m), 7.50-7.40 (m), 7.30-7.20 (m), 7.10-7.05 (m), 4.54
 (d, J = 7.4Hz, major isomer), 4.36 (d, J = 5.8Hz, minor isomer), 4.04 (s), 3.72-3.62 (m, major
 isomer), 3.45-3.35 (m, minor isomer), 2.80-2.82 (m), 2.70-2.67 (m), 2.51 (s), 2.53-2.45 (m),
 2.35-2.26 (m), 2.04-1.95 (m); cis:trans isomers, diagnostic peaks 100 MHz ¹³C NMR (CDCl₃)
 δ 130.5, 130.4, 127.3, 127.2, 125.8, 125.7, 113.4, 113.2, 112.6, 112.1, 111.9, 69.5, 69.2,
 30 58.6, 53.2, 36.6, 32.9, 31.4, 30.3, 23.3, 19.0; LRMS m/z Calcd for C₂₆ H₂₉ F N₂ O 404.526;
 obsd LRMS (M+1) 405.4.

Example 39

4,6-Dimethyl-2-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyrimidine.

35 Preparation as described for Example 36, General Procedure A, Step G using the appropriate
 starting materials.

R_f = 0.20 (10% MeOH/ CH₂Cl₂ w/0.2% NH₄OH); cis:trans isomers, diagnostic peaks
 400 MHz ¹H NMR (CDCl₃) δ 7.43-7.34 (m), 7.23-7.11 (m), 6.61 (s, major isomer), 6.59 (s,

minor isomer), 4.44 (d, J = 7.0Hz, major isomer), 4.25 (d, J = 6.6Hz, minor isomer), 3.90 (s), 3.66-3.57 (m, major isomer), 3.43-3.34 (m, minor isomer), 2.88 (bs), 2.77-2.69 (m), 2.52-2.46 (m), 2.35 (s), 2.33 (s), 1.97-1.88 (m); cis:trans isomers, diagnostic peaks 100 MHz ¹³C NMR (CDCl₃) δ 169.3, 165.4, 130.1, 127.1, 114.1, 71.3, 70.6, 59.1, 53.4, 36.3, 31.4, 30.7, 30.3, 24.1, 23.4; LRMS m/z Calcd for C₂₂ H₂₉ N₃ O 351.491; obsd LRMS (M+1) 352.4.

Example 40

2-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyrazine. Preparation as described for Example 36, General Procedure A, Step G using the appropriate starting materials.

R_f = 0.25 (10% MeOH/ CH₂Cl₂ w/0.2% NH₄OH); cis:trans isomers, diagnostic peaks 500 MHz ¹H NMR (CDCl₃) δ 8.16 (d, J = 1.7Hz, major isomer), 8.14 (d, J = 1.3Hz, minor isomer), 8.04-7.97 (m), 7.52-7.40 (m), 7.20-7.15 (m), 4.39 (d, J = 7.1Hz, major isomer), 4.21 (d, J = 6.2Hz, minor isomer), 4.04 (s, major isomer), 4.03 (s, minor isomer), 3.64-3.56 (m, major isomer), 3.42-3.32 (m, minor isomer), 3.04 (bs), 2.76-2.64 (m), 2.45 (dddd, J = 2.9, 2.9, 2.9, 2.9Hz), 2.31-2.21 (m), 2.02-1.94 (m), 1.92 (dddd, J = 2.5, 2.5, 2.5, 2.5Hz); cis:trans isomers, diagnostic peaks 100 MHz ¹³C NMR (CDCl₃) δ 160.6, 160.5, 147.3, 146.9, 140.7, 136.6, 136.1, 130.5, 127.2, 70.1, 69.7, 58.5, 53.2, 36.5, 36.1, 32.7, 31.2, 30.1, 23.3; LRMS m/z Calcd for C₂₀ H₂₅ N₃ O 323.438; obsd LRMS (M+1) 324.3.

Example 41

2,5-Dimethyl-3-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyrazine. Preparation as described for Example 36, General Procedure A, Step G using the appropriate starting materials.

R_f = 0.28 (10% MeOH/ CH₂Cl₂ w/0.2% NH₄OH); cis:trans isomers, diagnostic peaks 500 MHz ¹H NMR (CDCl₃) δ 7.78 (s, major isomer), 7.76 (s, minor isomer), 7.44-7.35 (m), 7.22-7.15 (m), 4.40 (d, J = 7.1Hz, major isomer), 4.22 (d, J = 5.8Hz, minor isomer), 3.90 (s, major isomer), 3.88 (s, minor isomer), 3.68-3.59 (m, major isomer), 3.43-3.34 (m, minor isomer), 2.92-2.84 (bm), 2.76-2.65 (m), 2.45 (dddd, J = 2.5, 2.5, 2.5, 2.5Hz), 2.38-2.26 (m), 1.98 (dddd, J = 2.5, 2.5, 2.5, 2.5Hz), 1.95-1.87 (m); cis:trans isomers, diagnostic peaks 100 MHz ¹³C NMR (CDCl₃) δ 158.1, 157.9, 147.7, 146.8, 141.1, 134.4, 130.2, 127.1, 69.3, 59.1, 53.5, 36.6, 36.2, 32.8, 31.4, 30.2, 23.4, 20.9, 19.0; LRMS m/z Calcd for C₂₂ H₂₉ N₃ O 351.491; obsd LRMS (M+1) 352.3.

Example 42

2-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyridine. Preparation as described for Example 36, General Procedure A, Step G using the appropriate starting materials.

R_f = 0.25 (10% MeOH/ CH₂Cl₂ w/0.2% NH₄OH); cis:trans isomers, diagnostic peaks 500 MHz ¹H NMR (CDCl₃) δ 8.11 (dd, J = 1.3, 1.3Hz), 8.08 (dd, J = 1.7, 1.7Hz), 7.54-

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7.48(m), 7.44-7.38 (m), 6.84-6.77 (m), 6.73-6.67 (m), 4.40 (d, J = 6.5Hz, major isomer), 4.21 (d, J = 6.2Hz, minor isomer), 3.91 (s), 3.68-3.58 (m, major isomer), 3.44-3.25 (m, minor isomer), 2.89 (bm), 2.77-2.65 (m), 2.47 (dddd, J = 2.5, 2.5, 2.5, 2.5Hz), 2.32-2.24 (m), 1.96 (dddd, J = 2.9, 2.9, 2.9, 2.9Hz), 1.98-1.87 (m); cis:trans isomers, diagnostic peaks 100 MHz
 5 ¹³C NMR (CDCl₃) δ 164.3, 147.0, 138.7, 130.1, 127.1, 116.8, 111.3, 69.4, 59.1, 53.5, 36.6, 32.9, 31.4, 30.7, 23.4; LRMS m/z Calcd for C₂₁ H₂₆ N₂ O 322.449; obsd LRMS (M+1) 323.3.

Example 43

2-Methyl-6-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyridine.

10 Preparation as described for Example 36, General Procedure A, Step G using the appropriate starting materials.

R_f = 0.25 (10% MeOH/ CH₂Cl₂ w/0.2% NH₄OH); cis:trans isomers, diagnostic peaks 500 MHz ¹H NMR (CDCl₃) δ 7.47-7.38 (m), 7.25-7.18 (m), 6.69-6.64 (m), 6.52-6.47 (m), 4.38 (d, J = 7.5Hz, major isomer), 4.20 (d, J = 6.2Hz, minor isomer), 3.98 (s), 3.69-3.59 (m, major isomer), 3.44-3.34 (m, minor isomer), 3.00 (bs), 2.77-2.66 (m), 2.48 (dddd, J = 2.5, 2.5, 2.5, 2.5Hz), 2.41 (s, major isomer), 2.39 (s, minor isomer), 2.34-2.26 (m), 2.02-1.92 (m); cis:trans isomers, diagnostic peaks 100 MHz ¹³C NMR (CDCl₃) δ 163.8, 156.5, 147.4, 139.0, 130.4, 127.2, 115.9, 107.3, 69.2, 58.8, 53.3, 36.6, 33.0, 31.4, 30.4, 23.4; LRMS m/z Calcd for C₂₂ H₂₈ N₂ O 336.476; obsd LRMS (M+1) 337.4.

20 Example 44

3-Methoxy-6-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyridazine.

Preparation as described for Example 36, General Procedure A, Step G using the appropriate starting materials.

R_f = 0.25 (10% MeOH/ CH₂Cl₂ w/0.2% NH₄OH); cis:trans isomers, diagnostic peaks 25 500 MHz ¹H NMR (CDCl₃) δ 7.45-7.38 (m), 7.22-7.15 (m), 6.92-6.86 (m), 4.52 (d, J = 8.0Hz, major isomer), 4.33 (d, J = 5.8Hz, minor isomer), 3.99 (s, major isomer), 3.97 (s, minor isomer), 3.93 (s), 3.67-3.54 (m, major isomer), 3.44-3.33 (m, minor isomer), 2.82 (bm), 2.80-2.70 (m), 2.47 (dddd, J = 2.5, 2.5, 2.5, 2.5Hz), 2.33-2.23 (m), 1.99-1.88 (m); cis:trans isomers, diagnostic peaks 100 MHz ¹³C NMR (CDCl₃) δ 162.1, 146.9, 131.0, 130.3, 129.0, 127.1, 30 121.7, 70.6, 59.1, 54.7, 53.7, 53.4, 36.5, 36.1, 32.7, 31.3, 30.5, 30.1, 28.5, 23.4; LRMS m/z Calcd for C₂₁ H₂₇ N₃ O₂ 353.463; obsd LRMS (M+1) 354.4.

Example 45

1-{4-[3-(2-Bromo-benzyloxymethyl)-cyclobutyl]-benzyl}-pyrrolidine. Preparation as described for Example 10, General Procedure A, Step G.

35 R_t = 4.75 min HPLC method A; LRMS m/z Calcd for C₂₃ H₂₈ Br N O 414.39; obsd LRMS (M+2) 416.04.

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Example 46

2,4-Dimethoxy-6-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyrimidine.

Preparation as described for Example 36, General Procedure A, Step G using the appropriate starting materials.

5 R_f = 0.3 (10% MeOH/CH₂Cl₂ w/0.2% NH₄OH); cis:trans isomers, diagnostic peaks
400 MHz ¹H NMR (CDCl₃) δ 7.49-7.43 (m), 7.25-7.18 (m), 4.02 (bs), 3.68-3.56 (m, major
isomer), 3.44-3.34 (m, minor isomer), 3.07 (bs), 2.33-2.22 (m), 2.05-1.98 (m); cis:trans
isomers, diagnostic peaks 100 MHz ¹³C NMR (CDCl₃) δ 173.0, 147.5, 130.6, 127.3, 70.1,
58.6, 53.1, 36.5, 31.4, 31.2, 28.9, 23.3; LRMS m/z Calcd for C₂₂ H₂₉ N₃ O₃ 383.489; obsd
10 LRMS (M+1) 384.4

Example 47 and Example 48

Separation of the cis:trans isomers of Example 4 (General procedure A, Step G) was
accomplished by preparative HPLC using a 10 cm x 25 cm Chiralpak AD column, eluting with
85/15 heptane/EtOH at a flow rate of 275 mL/min. Sample information: load/injection 1.8
15 grams, solubility: 1.8 g/ 10 mL (4:1 MeOH/CH₂Cl₂).

Example 47

cis-Toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester.

Analytical Rt= 8.5 min, UV max 250 (Chiralpak AD, 4.6x250 mm, 85/15
heptane/ethanol with 0.25% DEA, 1 mL/min); R_f=0.35 (10% MeOH/ CH₂Cl₂ w/0.2%
20 NH₄OH); 400 MHz ¹H NMR (CDCl₃) δ 7.77 (d, J= 8.3Hz, 2H), 7.31 (d, J = 9.9Hz, 2H), 7.22
(d, J = 7.9Hz, 2H), 7.06 (d, J = 7.9Hz, 2H), 3.98 (d, J = 6.2Hz, 2H), 3.56 (s, 2H), 3.39-3.30 (m,
1H), 2.61-2.52 (m, 1H), 2.50-2.44 (m, 4H), 2.41 (s, 3H), 2.40-2.35 (m, 2H), 1.86-1.77 (m, 2H),
1.76-1.69 (m, 4H); 100 MHz ¹³C NMR (CDCl₃) δ 145.0, 143.7, 137.4, 133.4, 130.1, 129.1,
128.1, 126.4, 74.2, 60.6, 54.4, 35.9, 32.5, 30.3, 23.7, 21.9; LRMS m/z Calcd for C₂₃ H₂₉ N
25 O₃ S 399.552; obsd LRMS (M+1) 400.3.

Example 48

trans-Toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester.

Analytical Rt = 12.9 min, UV max 250 ((Chiralpak AD, 4.6x250 mm, 85/15
30 heptane/ethanol with 0.25% DEA, 1 mL/min)); R_f = 0.35 (10% MeOH/ CH₂Cl₂ w/0.2%
NH₄OH); 400 MHz ¹H NMR (CDCl₃) δ 7.82 (d, J= 8.1Hz, 2H), 7.35 (d, J = 7.8Hz, 2H), 7.25
(d, J = 8.2Hz, 2H), 7.12 (d, J = 8.2Hz, 2H), 4.18 (d, J = 7.4Hz, 2H), 3.57 (s, 2H), 3.56-3.47 (m,
1H), 2.66-2.56 (m, 1H), 2.51-2.46 (m, 4H), 2.44 (s, 3H), 2.30-2.10 (m, 2H), 2.20-2.12 (m, 2H),
1.80-1.70 (m, 4H); 100 MHz ¹³C NMR (CDCl₃) δ 145.0, 144.1, 137.4, 133.4, 130.1, 129.1,
35 128.1, 126.4, 73.9, 60.6, 54.4, 36.1, 32.1, 30.9, 23.7, 14.4; LRMS m/z Calcd for C₂₃ H₂₉ N
O₃ S; 399.552 obsd LRMS (M+1) 400.3.

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Example 49 - General Procedure A:

Step F

trans-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutyl]-methanol. To a stirring solution of : trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester
5 (example 48) (

0.5 g, 1.2 mmol) in methyl alcohol (12.5 mL) was added magnesium turning. After 16 hours the reaction turned from a colorless solutions to a milky white solution. The reaction was quenched by the addition of 1 mL of an aqueous solution of 15 % NaOH and water. The solids were filtered off through a plug of celite and the aqueous layer was extracted with 3:1
10 CH₃Cl:isopropyl alcohol. The combined organic layer were dried over MgSO₄, filtered through a fritted funnel and concentrated under reduced pressure to yield the title compound (242 mg, 79 % yield) as a colorless oil. This material was processed without further purification.

R_f = 0.26 (10% MeOH/CH₂Cl₂ w/ 0.1% NH₄OH; mono HCl salt 500 MHz ¹H NMR (CD₃OD) δ 7.45 (d, 8.3 Hz, 2H), 7.37 (d, J = 8.3 Hz, 2H), 4.34 (s, 2H), 3.71 (d, J = 7.0 Hz, 2H), 3.62 (dddd, J= 8.3, 8.3, 8.3, 8.3 Hz, 1H), 3.48-3.44 (m, 2H), 3.21-3.14 (m, 2H), 2.47(app
15 sep. J = 7.0 Hz, 1H), 2.26-2.22 (m, 4H), 2.19-2.15 (m, 2H), 2.05-1.94 (m, 2H); 100 MHz ¹³C NMR (CDCl₃) δ 145.5, 135.9, 129.4, 126.5, 66.5, 60.5, 54.2, 36.6, 33.2, 31.3, 23.5; LRMS m/z Calcd for C₁₆ H₂₃ N O, 245.364; obsd LRMS (M+1) 246.4.

Example 50

cis-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutyl]-methanol. Preparation as
20 described for Example 49, General Procedure A, Step F using Example 47 as the starting materials.

R_f = 0.26 (10%MeOH/CH₂Cl₂ w/ 0.1% NH₄OH); 400 MHz ¹H NMR (CDCl₃) δ 7.60 (d, J = 7.9 Hz, 1H), 7.31 (d, J = 7.9 Hz, 2H), 7.16 (d, J = 7.9 Hz, 2H), 3.78 (s, 2H), 3.60 (d, J =
25 5.8 Hz, 2H), 3.40 (dddd, J = 8.3, 8.3, 8.3, 8.3 Hz, 1H), 2.76 (bs), 2.55 -2.43 (m), 1.90 - 1.81 (m); LRMS m/z Calcd for C₁₆ H₂₃ N O 245.364; obsd LRMS (M+1) 246.4.

Example 51

cis 4,6-Dimethyl-2-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyrimidin. Preparation as described for Example 36, General Procedure A, Step G using the appropriate
30 starting materials, and the alcohol Example 50 (cis-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutyl]-methanol).

R_f = 0.21(10%MeOH/CH₂Cl₂ w/ 0.1%NH₄OH); 500 MHz ¹H NMR (CDCl₃) δ 7.27 (d, J = 7.9 Hz, 2H), 7.16 (d, J = 7.9 Hz, 2H), 6.63 (s, 1H), 4.30 (d, J = 6.6 Hz, 2H), 3.65 (s, 2H), 3.47 - 3.37 (m, 1H), 2.82 - 2.72 (m, 1H), 2.62 - 2.49 (m, 6H), 2.37 (s, 6H), 2.02-1.97 (m, 2H),
35 1.83 - 1.78 (m, 4H); 100 MHz ¹³C NMR (CDCl₃) δ 169.3, 165.3, 145.0, 129.3, 126.6, 114.0, 71.6, 60.2, 54.1, 36.4, 33.2, 30.7, 24.0, 23.5; LRMS m/z Calcd for C₂₂ H₂₉ N₃ O 351.491; obsd LRMS (M+1) 352.4.

Example 52

cis-2-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyrimidine. Preparation as described for Example 36, General Procedure A, Step G using the appropriate starting materials, and the alcohol Example 50 (cis-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutyl]-methanol).

R_f = 0.39 (10%MeOH/CH₂Cl₂ w/ 0.1% NH₄OH); 500 MHz ¹H NMR (CDCl₃) δ 8.48 (d, J = 4.9 Hz, 2H), 7.25 (d, J = 8.3 Hz, 2H), 7.15 (d, J = 7.9 Hz, 2H), 6.90 (t, 1H), 4.33 (d, J = 6.2 Hz, 2H), 3.60 (s, 2H), 3.48 - 3.38 (m, 1H), 2.85 - 2.72 (m, 1H), 2.60 - 2.47 (m, 6H), 2.05 - 1.95 (m, 2H), 1.81 - 1.72 (m, 4H); 100 MHz ¹³C NMR (CDCl₃) δ 165.6, 159.4, 144.6, 136.4, 129.2, 126.5, 115.1, 71.8, 60.5, 54.2, 36.4, 33.1, 30.5, 23.6; LRMS m/z Calcd for C₂₀ H₂₅ N₃ O 323.438; obsd LRMS (M+1) 324.3.

Example 53

cis-5-Ethyl-2-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyrimidine. Preparation as described for Example 36, General Procedure A, Step G using the appropriate starting materials, and the alcohol Example 50 (cis-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutyl]-methanol).

R_f = 0.24 (10%MeOH/CH₂Cl₂ w/ 0.1% NH₄OH); 500 MHz ¹H NMR (CDCl₃) δ 8.32 (s, 2H), 7.26 (d, J = 8.3Hz, 2H), 7.16 (d, J = 7.9Hz, 2H), 4.30 (d, J = 6.2Hz, 2H), 3.63 (s, 2H), 3.48-3.37 (m, 1H), 2.84-2.72 (m, 1H), 2.60-2.48 (m, 8H), 2.04-1.94 (m, 2H), 1.84-1.74 (m, 4H), 1.22 (t, 3H); 100 MHz ¹³C NMR (CDCl₃) δ 169.4, 129.4, 126.7, 114.0, 70.7, 60.2, 54.1, 36.6, 31.5, 30.3, 24.1, 23.6; LRMS m/z Calcd for C₂₂ H₂₉ N₃ O 351.491; obsd LRMS (M+1) 352.3.

Example 54

cis-3-Methyl-6-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyridazine. Preparation as described for Example 36, General Procedure A, Step G using the appropriate starting materials, and the alcohol Example 50 (cis-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutyl]-methanol).

R_f = 0.46 (10%MeOH/CH₂Cl₂ w/ 0.1% NH₄OH); 500 MHz ¹H NMR (CDCl₃) δ 7.32 (d, J = 8.3 Hz, 2H), 7.21-7.15 (m, 3H), 6.86 (d, J = 9.1 Hz, 1H), 4.43 (d, J = 6.2 Hz, 2H), 3.75 (s, 2H), 3.48-3.36 (m, 1H), 2.84 - 2.68 (m, 5H), 2.57 (s, 3H), 2.55 - 2.46 (m, 2H), 2.06 - 1.95 (m, 2H), 1.90 - 1.82 (m, 4H); 100 MHz ¹³C NMR (CDCl₃) δ 164.0, 155.3, 145.5, 130.1, 129.6, 129.0, 126.8, 117.7, 70.9, 59.8, 53.9, 36.2, 32.9, 30.6, 23.5, 21.7; LRMS m/z Calcd for C₂₁ H₂₇ N₃ O 337.464; obsd LRMS (M+1) 338.4.

Example 55

trans-4,6-Dimethyl-2-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyrimidine.. Preparation as described for Example 36, General Procedure A, Step G using the

appropriate starting materials, and the alcohol Example 49 (trans-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutyl]-methanol).

R_f = 0.28 (10%MeOH/CH₂Cl₂ w/ 0.2% NH₄OH); 500 MHz ¹H NMR (CDCl₃) δ 7.29 (d, J = 8.3 Hz, 2H), 7.21 (d, J = 7.9 Hz, 2H), 6.66 (s, 1H), 4.49 (d, J = 7.5 Hz, 2H), 3.72 - 3.60 (m, 3H), 2.86-2.72 (m, 1H), 2.64-2.52 (m, 4H), 2.41(s, 6H), 2.38 - 2.33 (m, 4H), 1.85 - 1.78 (m, 4H); 100 MHz ¹³C NMR (CDCl₃) δ 169.4, 129.4, 126.7, 114.0, 70.7, 60.2, 54.1, 36.6, 31.5, 30.3, 24.1, 23.6; LRMS m/z Calcd for C₂₂ H₂₉ N₃ O 351.491; obsd LRMS (M+1) 352.4.

Example 56

trans-2-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyrimidine.

Preparation as described for Example 36, General Procedure A, Step G using the appropriate starting materials, and the alcohol Example 49 (trans-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutyl]-methanol).

R_f = 0.32 (10%MeOH/CH₂Cl₂ w/ 0.2% NH₄OH); 500 MHz ¹H NMR (CDCl₃) δ 8.51 (d, J = 4.6 Hz, 2H), 7.30 (d, J = 8.3 Hz, 2H), 7.20 (d, J = 8.3 Hz, 2H), 6.93 (dd, J = 2.1, 2.1Hz, 1H), 4.51 (d, J = 7.5 Hz, 2H), 3.72 - 3.60 (m, 3H), 2.87-2.76 (m, 1H), 2.64-2.56 (m, 4H), 2.38-2.30 (m, 4H), 1.86 - 1.76 (m, 4H); 100 MHz ¹³C NMR (CDCl₃) δ 165.7, 159.5, 159.4, 145.4, 129.4, 126.7, 115.1, 71.2, 60.2, 54.1, 36.4, 30.1, 23.6; LRMS m/z Calcd for C₂₀ H₂₅ N₃ O 323.438; obsd LRMS (M+1) 324.4.

Example 57

trans-5-Ethyl-2-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyrimidine.

Preparation as described for Example 36, General Procedure A, Step G using the appropriate starting materials, and the alcohol Example 49 (trans-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutyl]-methanol).

R_f = 0.35 (10%MeOH/CH₂Cl₂ w/ 0.2% NH₄OH; 500 MHz ¹H NMR (CDCl₃) δ 8.34 (s, 2H), 7.29 (d, J = 8.3 Hz, 2H), 7.19 (d, J = 8.3 Hz, 2H), 4.48 (d, J = 7.5 Hz, 2H), 3.70 - 3.62 (m, 3H), 2.86 - 2.74 (m, 1H), 2.66 - 2.54 (m, 6H), 2.36 - 2.32 (m, 4H), 1.86 - 1.78 (m, 4H), 1.23 (t, 3H); 100 MHz ¹³C NMR (CDCl₃) δ 164.4, 158.7, 145.6, 129.9, 129.4, 126.6, 71.03, 60.2, 54.1, 36.5, 31.5, 30.2, 23.5, 22.9, 15.5; LRMS m/z Calcd for C₂₂ H₂₉ N₃ O 351.491; obsd LRMS (M+1) 352.4.

Example 58

trans-3-Methyl-6-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyridazine.

Preparation as described for Example 36, General Procedure A, Step G using the appropriate starting materials, and the alcohol Example 49 (trans-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutyl]-methanol).

R_f = 0.35 (10%MeOH/CH₂Cl₂ w/ 0.2% NH₄OH; 500 MHz ¹H NMR (CDCl₃) δ 7.24 (d, 7.9 Hz, 2H), 7.20-7.15 (m, 3H), 6.85 (d, J = 9.1Hz, 1H), 4.61 (d, J = 7.5 Hz, 2H), 3.70-3.58

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(m, 1H), 3.57 (s, 2H), 2.83 - 2.72 (m, 1H), 2.57 (s, 3H), 2.53-2.44 (m, 4H), 2.38-2.44 (m, 4H), 1.79 - 1.71 (m, 4H); 100 MHz ¹³C NMR (CDCl₃) δ 164.1, 155.3, 144.9, 136.7, 130.1, 129.2, 126.5, 117.7, 70.7, 60.5, 54.3, 36.6, 31.5, 30.1, 23.6, 21.7; LRMS m/z Calcd for C₂₁H₂₇N₃O 337.461; obsd LRMS (M+1) 338.2;

5 Example 59 - General Procedure A:

 Step G

 cis-5-Methyl-4-piperidin-3-yl-2-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyrimidine

 Alternative high through-put procedure is described.

10 The appropriate starting heteroaryl chlorides (0.15 mmol, 3 equiv) were pre-weighed into 2-dram vials. A stock solution of alcohol (Example 50, cis-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutyl]-methanol) (0.5 mL, 12.3 mg, 0.05 mmol, 1 equiv) was added to the starting heteroaryl chlorides. To this solution was added a THF solution of K₂CO₃ (0.15 mL, 0.15 mmol, 1 N in THF, 3 equiv). The reaction was allowed to shake at room temperature overnight. The reactions were then quenched by the addition of 0.5 ml of MeOH and loaded onto Silicycle SCX SPE cartridge. The cartridge was rinsed with CH₂Cl₂. Changed vials and eluted with 5 ml of MeOH. Switched to tared vials and eluted with 7.5 ml of 1 N TEA in MeOH. The solvent was removed under reduced pressure.. Starting heteroaryl-chlorides containing protecting groups were deprotected by adding 0.5 ml of 1:1 CH₂Cl₂/TFA and shaking at room temp for ~1 hour. Prepared TFA salts of remaining samples. Purification was accomplished using the HPLC reported method. The product containing fractions were compressed into tared vials to yield the title compound.

 Rt = 6.83 min HPLC method B; LRMS m/z Calcd for C₂₆H₃₆N₄O 420.597; obsd LRMS (M+1) 421.59;

25 Example 60

 cis-Pyridin-4-yl-{6-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyridazin-3-yl}-amine. Preparation as described for Example 59, General Procedure A, Step G.

 Example 61

30 cis-2-{[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]oxy}-4-trifluoromethyl-pyrimidine. Preparation as described for Example 59, General Procedure A, Step G.

 Rt = 8.69 min HPLC method B; ; LRMS m/z Calcd for C₂₁H₂₄F₃N₃O 391.435; obsd LRMS (M+1). 392.4;

 Example 62

 cis-5-Phenyl-2-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyrimidine.

35 Preparation as described for Example 59, General Procedure A, Step G.

 Rt = 4.15 min HPLC method B; LRMS m/z Calcd for C₂₆H₂₉N₃O 399.535; obsd LRMS (M+1). 400.25.

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Example 63

cis-(4-Chloro-phenyl)-{6-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyridazin-3-yl}-methanone. Preparation as described for Example 59, General Procedure A, Step G.

5 Rt = 9.49 min HPLC method B; LRMS m/z Calcd for C₂₇ H₂₈ LRMS m/z Calcd for C₂₇ H₂₈ N₃ O₂ 461.99; obsd LRMS (M+1). 462.5;

Example 64

cis-1, 3-Dimethyl-1-{6-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyridazin-3-yl}-urea. Preparation as described for Example 59, General Procedure A, Step G.

10 Example 65

cis-4-Pyrrolidin-3-yl-2-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyrimidine. Preparation as described for Example 59, General Procedure A, Step G.

Rt = 3.68 min HPLC method B; LRMS m/z Calcd for C₂₄ H₃₂ N₄ O 392.544; obsd LRMS (M+1) 393.29.

15 Example 66

cis-4-Methyl-6-pyrrolidin-3-yl-2-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyrimidine. Preparation as described for Example 59, General Procedure A, Step G.

Rt = 3.73 min HPLC method B; LRMS m/z Calcd for C₂₅ H₃₄ N₄ O 406.571; obsd LRMS (M+1) 407.34.

20 Example 67

cis-4-(3-Chloro-phenyl)-2-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-quinazoline. Preparation as described for Example 59, General Procedure A, Step G.

Rt = 4.44 min HPLC method B; LRMS m/z Calcd for C₃₀ H₃₀ Cl N₃ O 483.00; obsd LRMS (M+1) 484.22.

25 Example 68

cis-3-(3-Chloro-phenyl)-1-methyl-1-{6-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyridazin-3-yl}-urea. Preparation as described for Example 59, General Procedure A, Step G.

30 Rt = 4.13 min HPLC method B; LRMS m/z Calcd for C₂₈ H₃₂ LRMS m/z Calcd for C₂₈ H₃₂ N₅ O₂ 505.00; obsd LRMS (M+1) 506.23.

Example 69

cis-5-(4-Methoxy-phenoxy)-2-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyrimidine. Preparation as described for Example 59, General Procedure A, Step G.

35 Rt = 4.17 min HPLC method B; LRMS m/z Calcd for C₂₇ H₃₁ N₃ O₃ 445.56; obsd LRMS (M+1) 446.26.

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Example 70

cis-4-Pyridin-2-yl-2-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-quinazoline. Preparation as described for Example 59, General Procedure A, Step G.

Rt = 4.10 min HPLC method B; LRMS m/z Calcd for C₂₉ H₃₀ N₄ O 450.583; obsd
5 LRMS (M+1) 451.26.

Example 71

cis-5- (3-Chloro-phenoxy)-2-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyrimidine. Preparation as described for Example 59, General Procedure A, Step G.

Rt = 4.28 min HPLC method B; LRMS m/z Calcd for C₂₆ H₂₈ Cl N₃ O₂ 449.979;
10 obsd LRMS (M+1) 450.23.

Example 72

cis-4-Phenyl-6-piperidin-4-yl-2-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyrimidine. Preparation as described for Example 59, General Procedure A, Step G.

Rt = 3.89 min HPLC method B; LRMS m/z Calcd for C₃₁ H₃₈ N₄ O 482.668; obsd
15 LRMS (M+1) 483.33.

Example 73

cis-3- (3-Methyl-5-phenyl-pyrazol-1-yl)-6-[[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]oxy]-pyridazine. Preparation as described for Example 59, General Procedure A, Step G.

Rt = 4.19 min HPLC method B; LRMS m/z Calcd for C₃₀ H₃₃ N₅ O 479.625; obsd
20 LRMS (M+1) 480.29.

Example 74

5-Fluoro-4-piperidin-4-yl-2-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyrimidine. Preparation as described for Example 59, General Procedure A, Step G.

Rt = 3.74 min HPLC method B; LRMS m/z Calcd for C₂₅ H₃₃ F N₄ O 424.561; obsd
25 LRMS (M+1) 425.31.

Example 75

cis- 3-Piperazin-1-yl-6-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyridazine. Preparation as described for Example 59, General Procedure A, Step G.

Rt = 3.65 min HPLC method B; LRMS m/z Calcd for C₂₄ H₃₃ N₅ O 407.559; obsd
30 LRMS (M+1) 408.32.

Example 76

cis- 4-Phenyl-2-[[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]oxy]-6-trifluoromethyl-pyrimidine. Preparation as described for Example 59, General Procedure A,
35 Step G.

Rt= 4.41 min HPLC method B; LRMS m/z Calcd for C₂₇ H₂₈ F₃ N₃ O 467.532; obsd
LRMS (M+1). 468.24

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Example 77

cis-4-Methyl-6-piperidin-4-yl-2-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyrimidine. Preparation as described for Example 59, General Procedure A, Step G.

Rt = 3.72 min HPLC method B; LRMS m/z Calcd for C₂₆ H₃₆ N₄ O 420.597; obsd

5 LRMS (M+1) 421.33.

Example 78

cis-1-Methyl-4-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-phthalazine.

Preparation as described for Example 59, General Procedure A, Step G.

Rt = 3.73 min HPLC method B; LRMS m/z Calcd for C₂₅ H₂₉ N₃ O 387.524; obsd

10 LRMS (M+1) 388.26.

Example 79

cis-2-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-4-o-tolyl-pyrimidine.

Preparation as described for Example 59, General Procedure A, Step G.

Rt = 4.17 min HPLC method B; LRMS m/z Calcd for C₂₇ H₃₁ N₃ O 413.562; obsd

15 LRMS (M+1) 414.31.

Example 80

cis-5-(5-Iodo-2-methoxy-benzyl)-3-[[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutyl]methoxy]-pyridazine. Preparation as described for Example 59, General Procedure A, Step G.

20 Rt = 4.13 min HPLC method B; LRMS m/z Calcd for C₂₈ H₃₂ I N₃ O₂ 569.48; obsd
LRMS (M+1) 570.21.

Example 81

cis-5-Methyl-4-piperidin-4-yl-2-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyrimidine. Preparation as described for Example 59, General Procedure A, Step G.

25 Rt = 3.73 min HPLC method B; LRMS m/z Calcd for C₂₆ H₃₆ N₄ O 420.597; obsd
LRMS (M+1) 421.35.

Example 82

cis-4-(2-Methyl-2H-pyrazol-3-yl)-2-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-quinazoline. Preparation as described for Example 59, General Procedure A, Step G.

30 Rt = 4.08 min HPLC method B; LRMS m/z Calcd for C₂₈ H₃₁ N₅ O 453.587; obsd
LRMS (M+1) 454.30.

Example 83

cis-6-Methyl-2[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyrimidine-4-carboxylic acid phenylamide. Preparation as described for Example 59, General Procedure A, Step G.

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Rt = 4.18 min HPLC method B; LRMS m/z Calcd for C₂₈ H₃₂ N₄ O₂ 456.587; obsd LRMS (M+1) 457.27.

Example 84

cis-4-Phenyl-2- [3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyrimidine.

5 Preparation as described for Example 59, General Procedure A, Step G.

Rt = 4.13 min HPLC method B; LRMS m/z Calcd for C₂₆ H₂₉ N₃ O 399.535; obsd LRMS (M+1) 400.29.

Example 85

10 cis- 3-(2-Methoxy-benzyl)-6-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyridazine. Preparation as described for Example 59, General Procedure A, Step G.

Rt = 3.93 min HPLC method B; LRMS m/z Calcd for C₂₈ H₃₃ N₃ O₂ 443.588; obsd LRMS (M+1) 444.29.

Example 86

15 cis-Dimethyl- {6-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyridazin-3-yl}-amine. Preparation as described for Example 59, General Procedure A, Step G.

Rt = 3.67 min HPLC method B; LRMS m/z Calcd for C₂₂ H₃₀ N₄ O 366.506; obsd LRMS (M+1) 367.27.

Example 87

20 cis-4-Methyl-6-phenyl-2- [3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyrimidine. Preparation as described for Example 59, General Procedure A, Step G.

Rt = 4.15 min HPLC method B; LRMS m/z Calcd for C₂₇ H₃₁ N₃ O 413.562; obsd LRMS (M+1) 414.30.

Example 88

25 cis-5-Methyl-4-pyrrolidin-3-yl-2- [3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyrimidine. Preparation as described for Example 59, General Procedure A, Step G.

Rt = 3.72 min HPLC method B; LRMS m/z Calcd for C₂₅ H₃₄ N₄ O 406.571; obsd LRMS (M+1) 407.32.

Example 89

30 cis-3-(3,5-Dimethyl-pyrazol-1-yl)-6-[[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]oxy]-pyridazine. Preparation as described for Example 59, General Procedure A, Step G.

Rt = 4.06 min HPLC method B; LRMS m/z Calcd for C₂₅ H₃₁ N₅ O 417.554; obsd LRMS (M+1) 418.29.

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Example 90

cis-3-(2,5-Dimethyl-pyrrol-1-yl)-6-[[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]oxy]-pyridazine. Preparation as described for Example 59, General Procedure A, Step G.

5 Rt = 4.13 min HPLC method B; LRMS m/z Calcd for C₂₆ H₃₂ N₄ O 416.566; obsd LRMS (M+1) 417.28.

Example 91

cis-5- (3-Chloro-phenyl)-2-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyrimidine. Preparation as described for Example 59, General Procedure A, Step G.

10 Rt = 4.24 min HPLC method B; LRMS m/z Calcd for C₂₆ H₂₈ Cl N₃ O 433.98; obsd LRMS (M+1) 434.23.

Example 92

cis-5- (4-Methoxy-phenyl)-2-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyrimidine. Preparation as described for Example 59, General Procedure A, Step G.

15 Rt = 4.14 min HPLC method B; LRMS m/z Calcd for C₂₇ H₃₁ N₃ O₂ 429.561; obsd LRMS (M+1) 430.29.

Example 93

cis-4-Phenyl-6-pyridin-2-yl-2- [3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyrimidine. Preparation as described for Example 59, General Procedure A, Step G.

20 Rt = 4.26 min HPLC method B; LRMS m/z Calcd for C₃₁ H₃₂ N₄ O 476.621; obsd LRMS (M+1) 477.29.

Example 94

cis-4-Phenyl-6-piperidin-3-yl-2- [3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyrimidine. Preparation as described for Example 59, General Procedure A, Step G.

25 Rt = 3.89 min HPLC method B; LRMS m/z Calcd for C₃₁ H₃₈ N₄ O 482.668; obsd LRMS (M+1) 483.33.

Example 95 - General procedure A:

Step H:

30 2-{4-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-piperazin-1-yl}-pyrimidine.
To a stirring solution of toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester (159.9 mg, 0.40 mmol) prepared above (Example 4, General Procedure A, Step G) in 2 mL of THF was added 1-(2-pyrimidyl)piperazine (136.2 mg, 0.8 mmol) followed by a solution of KOtBu (136 μ L, 0.8 mmol, 1M THF). The reaction was heated to 70 °C (oil bath). After 1 hour DMF (1 mL) was added along with K₂CO₃ (2 eq).
35 The reaction was then heated to 100 °C. After 3 hours the reaction was cooled to rt and concentrated under reduced pressure. The resulting mixture was diluted with CH₂Cl₂,

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quenched with a saturated aqueous solution of NaHCO_3 . The two layers were separated and the aqueous layer was back extracted with 3:1 chloroform: isopropyl alcohol. The combined organic layers were dried over MgSO_4 , filtered through a fritted funnel and concentrated under reduced pressure. Purification of this material was accomplished by flash column chromatography using a 10 g ISCO column, eluting with a gradient of 5%, 10%, 20% MeOH/ CH_2Cl_2 w/ 0.1 % NH_4OH . The product containing fractions were collected and concentrated under reduced pressure to give the title compound (70.0 mg, 44%) as a colorless oil, and a mixture of cis:trans isomers. The bis-HCl salt was generated by dissolving the title compound in EtOAc and then a solution of HCl (2 eq, 1M HCl, THF) was added. The colorless solid was collected and dried under reduced pressure.

R_f = 0.44 (20% MeOH/ CH_2Cl_2 w/ 0.1% NH_4OH ; diagnostic peaks, cis: trans isomers ^1H NMR (CDCl_3) δ 8.28 (d, J = 5.0 Hz), 6.45 (dd, J = 5.0, 5.0 Hz), 3.60-3.51 (m), 3.35-3.40 (m); diagnostic peaks ; cis:trans isomers ^{13}C NMR 125 MHz (CDCl_3) δ 157.9, 129.3, 109.9, 65.6, 43.8, 23.5; LRMS m/z Calcd for $\text{C}_{24}\text{H}_{33}\text{N}_5$ 391.56; obsd LRMS ($M+1$) 392.5.

Example 96

Dimethyl- [3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amine. Preparation as described for Example 95, General Procedure A, Step H.

R_f = 0.43 (20%MeOH/ CH_2Cl_2 w/ 0.1% NH_4OH); LRMS m/z Calcd for $\text{C}_{18}\text{H}_{28}\text{N}_2$ 272.433; obsd LRMS ($M+1$) 273.4.

Example 97

1-{4-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-piperazin-1-yl}- ethanone
Preparation as described for Example 95, General Procedure A, Step H.

R_f = 0.11 (20%MeOH/ CH_2Cl_2 w/ 0.1% NH_4OH); LRMS m/z Calcd for $\text{C}_{22}\text{H}_{33}\text{N}_3\text{O}$ 355.523;obsd LRMS ($M+1$) 356.4.

Example 98

4-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-morpholine. Preparation as described for Example 95, General Procedure A, Step H.

R_f = 0.25 (15%MeOH/ CH_2Cl_2 w/ 0.1% NH_4OH); LRMS m/z Calcd for $\text{C}_{20}\text{H}_{30}\text{N}_2\text{O}$ 314.47; obsd LRMS ($M+1$) 315.4.

Example 99

5-Fluoro-2- {4-[3- (4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-piperazin-1-yl}-pyrimidine. Preparation as described for Example 95, General Procedure A, Step H.

R_f = 0.11 (10% MeOH/ CH_2Cl_2 w/ 0.1% NH_4OH ; 3:1 (cis: trans) ^1H NMR (CDCl_3) δ diagnostic peaks 8.17 (s), 3.60-3.51 (m), 3.42-3.35 (m); 3:1 (cis: trans) ^{13}C NMR (CDCl_3) δ diagnostic peaks 159.1, 153.0, 150.5, 145.4, 126.6, 64.6, 23.6; LRMS m/z Calcd for $\text{C}_{24}\text{H}_{32}\text{F N}_5$ 409.55; obsd LRMS ($M+1$) 410.4;

Example 100 - General Procedure A:

Step H

cis-4- [3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-morpholine. To a stirring
 cis-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester (example
 5 47) (0.41 g, 1.0 mmol) in DMA (5 mL) was added an amine for example morpholine (0.18 g, 2
 mmo). The reaction was then heated to 100 °C (oil bath). After 4 hr the reaction was cooled
 to rt and concentrated under reduced pressure. Purification of this material was
 accomplished by flash column chromatography, using a 45 g ISCO column, eluting with a
 gradient of 5%, 10%, 20%, 60% MeOH/CH₂Cl₂ with 0.1 % NH₄OH. The product containing
 10 fractions were collected and concentrated to yield the title compound (214 mg) as the TsOH
 salt. This material was free based by stirring in solid K₂CO₃ and MeOH for 2 hours. After 2 hr
 the methanolic solution was concentrated, diluted with CH₂Cl₂, filtered, and concentrated
 under reduced pressure to give the free base. The HCl salt was made by taken the freebase
 up in EtOAc and then adding a solution of HCl (2 eq, 1 M HCl, THF) to give a colorless solid.

15 R_f = 0.48 (10% MeOH/CH₂Cl₂ w/0.1% NH₄OH); 400 MHz 1H NMR (CDCl₃) δ 7.23
 (d, J = 7.9 Hz, 2H), 7.11 (d, J = 7.9 Hz, 2H), 3.70-3.65 (m, 4H), 3.56 (s, 2H), 3.41-3.34 (m,
 1H), 2.53-2.36 (m, 13H), 1.81-1.74 (m, 6H); 100 MHz 13C NMR (CDCl₃) δ 144.4, 137.0
 129.0, 126.3, 67.2, 65.9, 60.7, 54.4, 54.1, 36.7, 35.9, 29.8, 23.6; LRMS m/z Calcd for C₂₀
 H₃₀ N₂ O 314.47; obsd LRMS (M+1) 315.3.

20 Example 101

cis-1- [3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-piperazine. Preparation
 as described for Example 100, General Procedure A, Step H.

R_f = 0.14 (20 % MeOH/CH₂Cl₂ w/ 0.1 % NH₄OH; 400 MHz 1H NMR (CDCl₃) δ 7.21
 (d, J = 8.3 Hz, 2H), 7.08 (d, J = 8.9 Hz, 2H), 4.57 (bs, 1H) 3.56 (s, 2H), 3.39-3.29 (m, 1H),
 25 2.94-2.92 (m 4H), 2.49-2.40 (m, 13H), 1.79-1.70 (m, 6H); LRMS m/z Calcd for C₂₀ H₃₁ N₃,
 313.486; obsd LRMS (M+1) 314.3.

Example 102

cis-5-Fluoro-2- {4-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-piperazin-1-yl}-
 pyrimidine. Preparation as described for Example 100, General Procedure A, Step H.

30 R_f = 0.27 (10% MeOH/CH₂Cl₂); 400 MHz 1H NMR (CDCl₃) s 8.17 (s, 2H), 7.24 (d,
 J = 7.9 Hz, 2H), 7.12 (d, J = 7.9 Hz, 2H), 3.77-3.74 (m, 4H), 3.59 (s, 2H), 3.42-3.33 (m, 1H),
 2.54-2.46 (m, 13 H), 1.81-1.75 (m, 6H); 100 MHz 13C NMR (CDCl₃) δ 159.1, 153.0, 150.5,
 145.4, 145.2, 144.6, 136.7, 129.1, 126.4, 65.6, 60.6, 54.3, 53.3, 44.5, 35.9, 30.0, 23.6; LRMS
 m/z Calcd for C₂₄ H₃₂ F N₅ 409.55; obsd LRMS (M+1) 410.4.

35 Example 103

cis-1- [3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-pyrrolidine. Preparation
 as described for Example 100, General Procedure A, Step H.

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Rf = 0.2 (15% MeOH/CH₂Cl₂ w/0.1% NH₄OH); 400 MHz ¹H NMR (CDCl₃) δ 7.22 (d, J = 7.9 Hz, 2H), 7.11 (d, J = 7.9 Hz, 2H), 3.56 (s, 2H), 3.39-3.30 (m, 1H), 2.52-2.48 (bm, 13H), 1.81-1.71 (bm, 10H); 100 MHz ¹³C NMR (CDCl₃) δ 144.7, 136.8, 129.0, 126.4, 63.2, 60.6, 54.7, 54.3, 36.5, 35.7, 31.5, 23.6; LRMS m/z Calcd for C₂₀ H₃₀ N₂ 298.471; obsd LRMS (M+1) 299.4.

Example 104

cis-1- [3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-piperidine. Preparation as described for Example 100, General Procedure A, Step H.

Rf = 0.28 (15% MeOH/CH₂Cl₂ w/0.1% NH₄OH); 400 MHz ¹H NMR (CDCl₃) δ 7.22 (d, J = 7.9 Hz, 2H), 7.10 (d, J = 7.9 Hz, 2H), 3.56 (s, 2H), 3.38-3.29 (m, 1H), 2.53-2.30 (m, 13H), 1.80-1.71 (m, 6H), 1.59-1.54 (m, 4H), 1.42-1.40 (m, 2H); 100 MHz ¹³C NMR (CDCl₃) δ 144.7, 136.8, 129.0, 126.4, 66.3, 60.6, 54.9, 54.3, 36.7, 36.2, 30.2, 26.0, 24.5, 23.6; LRMS m/z Calcd for C₂₁ H₃₂ N₂ 312.498; obsd LRMS (M+1) 313.4.

Example 105

cis-2- {1-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-pyrrolidin-2-yl}-pyridine. Preparation as described for Example 100, General Procedure A, Step H.

Rf = 0.25 (15% MeOH/CH₂Cl₂ w/0.1% NH₄OH); LRMS m/z Calcd for C₂₅ H₃₃ N₃ 375.557; obsd LRMS (M+1) 376.4.

Example 106

cis- (2R,6S)-2,6-Dimethyl-4-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-morpholine. Preparation as described for Example 100, General Procedure A, Step H.

Rf = 0.29 (10% MeOH/CH₂Cl₂ w/ 0.1% NH₄OH); 400 MHz ¹H NMR (CDCl₃) δ 7.25 (d, J = 7.9 Hz, 2H), 7.11 (d, J = 7.9 Hz, 2H), 3.70-3.62 (m, 2H), 3.57 (s, 2H), 3.34 (dddd, J = 7.9, 7.9, 7.9, 7.9 Hz, 1H), 2.70-2.66 (m, 2H), 2.53-2.48 (m, 7H), 2.39-2.35 (m, 2H), 1.80-1.67 (m, 8H), 1.13 (d, J = 6.2 Hz, 6H); 100 MHz ¹³C NMR (CDCl₃) δ 144.6, 136.7, 129.1, 126.4, 71.8, 65.5, 60.6, 59.9, 54.3, 36.7, 35.9, 29.8, 23.6, 19.5; LRMS m/z Calcd for C₂₂ H₃₄ N₂ O 342.524; obsd LRMS (M+1) 343.4:

Example 107

trans-1- [3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-pyrrolidine. To a stirring solution of Example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester) (200 mg, 0.5 mmol) in DMA (1.5 mL) was added the appropriate amine, for example pyrrolidine (84 uL, 1.0 mmol). The reaction was then heated to 110°C (oil bath). After 12 hr the reaction was cooled to rt and concentrated under reduced pressure. This material was free based by stirring in solid K₂CO₃ and MeOH for 2 hours. After 2 hr of stirring silica gel was added to the vessel (dry pack) and the methanolic slurry was concentrated. Purification of this material was accomplished by flash column chromatography using a 12 g ISCO column, eluting with a gradient of 5%-10% MeOH/CH₂Cl₂ with 0.2 %

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NH₄OH. The product containing fractions were collected and concentrated to give the title compound as a colorless oil. The HCl salt was made by taken the freebase up in EtOAc and then adding a solution of HCl (2 eq, 1 M HCl, THF) to give a colorless solid.

R_f = 0.2 (15% MeOH/CH₂Cl₂ w/ 0.1% NH₄OH); 500 MHz ¹H NMR (CDCl₃) δ 7.25 (d, J = 7.9 Hz, 2H), 7.18 (d, J = 7.9 Hz, 2H), 3.57 (s, 2H), 3.52 (dddd, J = 7.9, 7.9, 7.9, 7.9 Hz, 1), 2.66 (d, J = 7.5 Hz, 2H), 2.56-2.47 (m, 9H), 2.33-2.25 (m, 2H), 2.21-2.14 (m, 2H), 1.80-1.72 (m, 8H); 100 MHz ¹³C NMR (CDCl₃) δ 145.3, 136.8, 129.1, 126.5, 62.5, 60.6, 54.8, 54.4, 36.5, 33.5, 30.9, 23.6; LRMS m/z Calcd for C₂₀ H₃₀ N₂ 298.471; obsd LRMS (M+1) 299.4.

10 Example 108

trans-1- [3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-piperidine. Preparation as described for Example 107, using the appropriate amine and the tosylate Example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester).

R_f = 0.25 (15% MeOH/CH₂Cl₂ w/ 0.1% NH₄OH); 500 MHz ¹H NMR (CDCl₃) δ 7.25 (d, J = 7.9 Hz, 2H), 7.19 (d, J = 7.9 Hz, 2H), 3.57 (s, 2H), 3.52 (dddd, J = 7.9, 7.9, 7.9, 7.9 Hz, 1H), 2.61-2.13 (m, 15H), 1.80-1.72 (m, 4H), 1.59-1.55 (m, 4H), 1.44-1.41 (m, 2H); 100 MHz ¹³C NMR (CDCl₃) δ 145.3, 136.9, 129.1, 126.5, 65.7, 60.7, 55.1, 54.4, 36.5, 34.0, 29.5, 26.1, 24.6, 23.6; LRMS m/z Calcd for C₂₁ H₃₂ N₂ 312.498; obsd LRMS (M+1) 313.3.

Example 109

20 trans-2- {1-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-pyrrolidin-2-yl}-pyridine. Preparation as described for Example 107, using the appropriate amine and the tosylate Example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester).

R_f = 0.3 (15% MeOH/CH₂Cl₂ w/ 0.1% NH₄OH); 100 MHz ¹³C NMR (CDCl₃) δ 164.9, 149.1, 145.3, 136.8, 129.0, 126.4, 122.0, 121.6, 121.3, 71.6, 60.9, 60.6, 54.6, 54.4, 36.3, 34.0, 33.5, 32.9, 30.7, 23.6, 23.4; LRMS m/z Calcd for C₂₅ H₃₃ N₃ 375.557; obsd LRMS (M+1) 376.4.

Example 110

30 trans-4- [3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-morpholine. Preparation as described for Example 107, using the appropriate amine and the tosylate Example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester).

R_f 0.25 (15%MeOH/CH₂Cl₂ w/ 0.1% NH₄OH); 400 MHz ¹H NMR (CDCl₃) δ 7.25 (d, J = 7.9Hz, 2H), 7.17 (d, J = 7.1Hz, 2H), 3.71-3.66 (m, 4H), 3.57 (bs, 2H), 3.57-3.49 (m, 1H), 2.58-2.38 (m, 11H), 2.30-2.21 (m, 2H), 2.20-2.12 (m, 2H), 1.81-1.69 (bm, 4H); 100 MHz ¹³C NMR (CDCl₃) δ 145.1, 136.9, 129.1, 126.4, 67.2, 64.9, 60.6, 54.4, 54.1, 36.5, 33.5, 28.9, 23.6; LRMS m/z Calcd for C₂₀ H₃₀ N₂ O 314.47; obsd LRMS (M+1) 315.2

Example 111

trans-1- [3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-piperazine-TsOH.

Preparation as described for Example 107, using the appropriate amine and the tosylate
 5 Example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl
 ester).

Rf = 0.15 (20% MeOH/CH₂Cl₂ w/ 0.1% NH₄OH); 400 MHz ¹H NMR (CDCl₃) δ 7.70
 (d, J = 7.9 Hz, 2H), 7.26 (d, J = 8.2 Hz, 2H), 7.12-7.09 (m, 4H), 4.60 (bs, 1H), 3.78 (s, 2H),
 3.43 (dddd, J = 7.9, 7.9, 7.9, 7.9 Hz, 1H), 3.13-3.06 (m, 4H), 2.88-2.68 (m, 4H), 2.56-2.35 (m,
 7H) 2.26 (s, 3H), 2.15-2.00 (m, 4H), 1.84-1.78 (m, 4H); mono TsOH salt 100 MHz ¹³C NMR
 10 δ 146.1, 142.0, 140.6, 133.2, 129.8, 129.2, 126.8, 126.1, 63.7, 59.5, 53.9, 50.4, 44.1, 36.3,
 33.0, 28.5, 23.3, 21.5; LRMS m/z Calcd for C₂₀ H₃₁ N₃ 313.486; obsd LRMS (M+1) 314.4.

Example 112

trans-5-Fluoro-2- {4-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-piperazin-1-
 yl}-pyrimidine. Preparation as described for Example 107, using the appropriate amine and
 15 the tosylate Example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-
 cyclobutylmethyl ester).

Rf = 0.35 (10% MeOH/CH₂Cl₂ w/ 0.1% NH₄OH); 500 MHz ¹H NMR (CDCl₃) δ 8.17
 (s, 2H), 7.26 (d, J = 8.3 Hz, 2H), 7.19 (d, J = 7.9 Hz, 2H), 3.76 (dd, J = 5.0, 5.0 Hz, 4H), 3.58
 (s, 2H), 3.58-3.51 (m, 1H), 2.61-2.56 (m, 3H), 2.48-2.43 (m, 8H), 2.32-2.15 (m, 4H), 1.78-1.72
 20 (m, 4H); 100 MHz ¹³C NMR (CDCl₃) δ 159.1, (153.0, 150.5), 145.4, 145.2, 136.8, 129.1,
 126.5, 64.6, 60.6, 54.4, 53.4, 44.5, 36.5, 33.6, 29.1, 23.6; LRMS m/z Calcd for C₂₄ H₃₂ F N₅
 409.55; obsd LRMS (M+1) 410.4.

Example 113

trans-2- {Ethyl- [3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amino}-ethanol.

25 Preparation as described for Example 107, using the appropriate amine and the tosylate
 Example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl
 ester).

Rf = 0.12 (10% MeOH/CH₂Cl₂ w/ 0.1% NH₄OH); 500 MHz ¹H NMR (CDCl₃) δ 7.27
 (d, J = 7.9 Hz, 2H), 7.18 (d, J = 8.3 Hz, 2H), 3.58 (s, 2H), 3.58 -3.50 (m, 1H), 3.54 (t, J = 5.4
 30 Hz, 2H), 3.10 (bs, 1H), 2.65-2.48 (m, 11H), 2.29-2.22 (m, 2H), 2.15-2.09 (m, 2H), 1.79-1.73
 (m, 4H), 1.03 (t, J = 7.0 Hz, 3H); 100 MHz ¹³C NMR (CDCl₃) δ 145.1, 136.8, 129.1, 126.5,
 60.6, 59.1, 58.5, 55.1, 54.4, 47.8, 36.5, 32.8, 29.3, 23.6, 11.9; LRMS m/z Calcd for C₂₀ H₃₂
 N₂ O 316.486; obsd LRMS (M+1) 317.4.

Example 114

35 trans-3, 5-Dimethyl-1- [3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-piperidine.

Preparation as described for Example 107, using the appropriate amine and the tosylate

Example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester).

Rf = 0.15 (10% MeOH/CH₂Cl₂ w/ 0.1% NH₄OH); LRMS m/z Calcd for C₂₃ H₃₆ N₂ 340.551; obsd LRMS (M+1) 341.5.

5 Example 115

trans-Cyclohexyl-methyl- [3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amine. Preparation as described for Example 107, using the appropriate amine and the tosylate Example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester).

10 Rf = 0.15 (10% MeOH/CH₂Cl₂ w/ 0.1% NH₄OH); 100 MHz ¹³C NMR (CDCl₃) δ 145.4, 136.9, 129.1, 126.5, 63.4, 60.7, 59.1, 54.4, 38.8, 36.6, 33.3, 29.9, 28.8, 26.7, 26.4, 23.6; LRMS m/z Calcd for C₂₃ H₃₆ N₂ 340.551; obsd LRMS (M+1) 341.5.

Example 116

trans-Benzyl-methyl- [3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amine. Preparation as described for Example 107, using the appropriate amine and the tosylate Example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester).

15 Rf = 0.5 (10% MeOH/CH₂Cl₂ w/ 0.1% NH₄OH); 100 MHz ¹³C NMR (CDCl₃) δ 145.2, 139.6, 136.7, 129.3, 129.2, 128.4, 127.1, 126.5, 63.2, 62.9, 60.6, 54.4, 42.8, 36.5, 33.2, 29.5, 23.6; LRMS m/z Calcd for C₂₄ H₃₂ N₂ 348.531; obsd LRMS (M+1) 349.4.

Example 117

trans-2-Methyl-1- [3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-piperidine. Preparation as described for Example 107, using the appropriate amine and the tosylate Example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester).

25 Rf = 0.15 (10% MeOH/CH₂Cl₂ w/ 0.1% NH₄OH); LRMS m/z Calcd for C₂₂ H₃₄ N₂ 326.525; obsd LRMS (M+1) 327.5.

Example 118

trans-3-Methyl-1- [3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-piperidine. Preparation as described for Example 107, using the appropriate amine and the tosylate Example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester).

30 Rf = 0.15 (10% MeOH/CH₂Cl₂ w/ 0.1% NH₄OH); 100 MHz ¹³C NMR (CDCl₃) δ 145.3, 136.8, 129.1, 126.5, 65.4, 62.6, 60.7, 54.4, 36.4, 33.9, 33.3, 31.3, 29.5, 25.8, 23.6, 20.1; LRMS m/z Calcd for C₂₂ H₃₄ N₂ 326.525; obsd LRMS (M+1) 327.5.

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Example 119

trans-4-Methyl-1- [3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-piperidine.

Preparation as described for Example 107, using the appropriate amine and the tosylate
Example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl
5 ester).

Rf = 0.15 (10% MeOH/CH₂Cl₂ w/ 0.1% NH₄OH); 100 MHz ¹³C NMR (CDCl₃)
δ 145.3, 136.8, 129.1, 126.5, 65.3, 60.7, 54.3, 36.5, 34.5, 34.0, 31.0, 29.6, 23.6, 22.2; LRMS
m/z Calcd for C₂₂ H₃₄ N₂ 326.525; obsd LRMS (M+1) 327.5.

Example 120

10 trans-2-Methyl-1- [3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-pyrrolidine.

Preparation as described for Example 107, using the appropriate amine and the tosylate
Example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl
ester).

Rf = 0.14 (10% MeOH/CH₂Cl₂ w/ 0.1% NH₄OH); 100 MHz ¹³C NMR (CDCl₃)
15 δ 145.4, 136.8, 129.1, 126.5, 60.7, 54.8, 54.4, 36.5, 33.9, 33.5, 32.2, 30.8, 23.6, 22.0, 19.5;
LRMS m/z Calcd for C₂₁ H₃₂ N₂ 312.498; obsd LRMS (M+1) 313.5.

Example 121

trans-2, 6-Dimethyl-1- [3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-piperidine.

Preparation as described for Example 107, using the appropriate amine and the tosylate
20 Example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl
ester).

Rf = 0.15 (10% MeOH/CH₂Cl₂ w/ 0.1% NH₄OH); LRMS m/z Calcd for C₂₃ H₃₆ N₂
340.551; obsd LRMS (M+1) 341.5.

Example 122

25 trans-Methyl-pyridin-3-ylmethyl- [3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-
amine. Preparation as described for Example 107, using the appropriate amine and the
tosylate Example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-
cyclobutylmethyl ester).

Rf = 0.2 (10% MeOH/CH₂Cl₂ w/ 0.1% NH₄OH); LRMS m/z Calcd for C₂₃ H₃₁ N₃
30 349.519; obsd LRMS (M+1) 350.4.

Example 123

trans- (2R, 5R)-2,5-Dimethyl-1-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-
pyrrolidine. Preparation as described for Example 107, using the appropriate amine and the
tosylate Example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-
35 cyclobutylmethyl ester).

Rf = 0.25 (15 % MeOH/CH₂Cl₂ w/ 0.1% NH₄OH); LRMS m/z Calcd for C₂₂ H₃₄ N₂
326.525; obsd LRMS (M+1) 327.5.

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Example 124

trans-Cyclopropylmethyl-propyl- 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-
amine. Preparation as described for Example 107, using the appropriate amine and the
tosylate Example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-
5 cyclobutylmethyl ester).

Rf = 0.15 (10% MeOH/CH₂Cl₂ w/ 0.1% NH₄OH); 400 MHz ¹H NMR (CDCl₃) δ 7.26
(d, J = 7.9 Hz, 2H), 7.18 (d, 7.9 Hz, 2H), 3.59 (s, 2H), 3.51 (dddd, J = 7.9, 7.9, 7.9, 7.9 Hz,
1H), 2.70 (d, J = 7.5 Hz, 2H), 2.58-2.46 (m, 7H), 2.29 (d, J = 6.2 Hz, 2H), 2.28-2.13 (m, 4H),
1.80-1.76 (m, 4H), 1.52-1.43 (m, 2H), 0.89-0.83 (m, 4H), 0.51-0.46 (m, 2H), 0.11-0.07 (m,
10 2H); 100 MHz ¹³C NMR (CDCl₃) δ 145.5, 136.8, 129.1, 126.5, 60.7, 59.9, 59.5, 56.6, 54.4,
36.5, 33.4, 29.5, 23.6, 20.1, 12.2, 8.8, 4.1; LRMS m/z Calcd for C₂₃ H₃₆ N₂ 340.551; obsd
LRMS (M+1) 341.5.

Example 125

trans-2- [3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-2,3-dihydro-1H-
15 isoindole. Preparation as described for Example 107, using the appropriate amine and the
tosylate Example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-
cyclobutylmethyl ester).

Rf = 0.35 (10% MeOH/CH₂Cl₂ w/ 0.1% NH₄OH); 500 MHz ¹H NMR (CDCl₃) δ 7.31-
7.17 (m, 8H), 3.96 (s, 4H), 3.66-3.58 (m, 1H), 3.61 (s, 2H), 2.95 (d, J = 7.5 Hz, 2H), 2.66-2.58
20 (m, 1H), 2.56-2.48 (m, 4H), 2.38-2.24 (m, 4H), 1.84-1.76 (m, 4H); 100 MHz ¹³C NMR
(CDCl₃) δ 145.3, 140.4, 136.9, 129.1, 126.9, 126.5, 122.5, 61.9, 60.7, 59.6, 54.4, 36.6, 33.2,
30.8, 23.7; LRMS m/z Calcd for C₂₄ H₃₀ N₂ 346.515; obsd LRMS (M+1) 347.5.

Example 126

trans- (2R,6S)-2,6-Dimethyl-4-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-
25 morpholine. Preparation as described for Example 107, using the appropriate amine and the
tosylate Example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-
cyclobutylmethyl ester).

Rf = 0.35 (10% MeOH/CH₂Cl₂ w/ 0.1% NH₄OH); 500 MHz ¹H NMR (CDCl₃) δ 7.26
(d, J = 8.3 Hz, 2H), 7.17 (d, J = 8.3 Hz, 2H), 3.70-3.64 (m, 2H), 3.57 (s, 2H), 3.53 (dddd, J =
30 7.9, 7.9, 7.9, 7.9 Hz, 1H), 2.70-2.67 (m, 2H), 2.59-2.47 (m, 7H), 2.30-2.12 (m, 4H), 1.79-1.68
(m, 6H), 1.13 (d, J = 6.2 Hz, 6H); 100 MHz ¹³C NMR (CDCl₃) δ 145.2, 136.8, 129.1, 126.5,
71.8, 64.6, 60.6, 60.0, 54.3, 36.4, 33.5, 28.9, 23.6, 19.4; LRMS m/z Calcd for C₂₂ H₃₄ N₂ O
342.524; obsd LRMS (M+1) 343.5.

Example 127

trans-4- [3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-piperazin-2-one.
Preparation as described for Example 107, using the appropriate amine and the tosylate

Example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester).

R_f = 0.15 (10% MeOH/CH₂Cl₂ w/ 0.1% NH₄OH); 100 MHz ¹³C NMR (CDCl₃) δ 170.3, 144.9, 136.9, 129.1, 126.4, 63.2, 60.6, 57.2, 54.3, 49.9, 49.5, 43.0, 42.5, 41.4, 36.5, 33.1, 28.8, 23.6; LRMS m/z Calcd for C₂₀ H₂₉ N₃ O 327.469; obsd LRMS (M+1) 328.5.

Example 128

trans- (S)-2-Methoxymethyl-1-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-pyrrolidine. Preparation as described for Example 107, using the appropriate amine and the tosylate Example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester).

R_f = 0.15 (10% MeOH/CH₂Cl₂ w/ 0.1% NH₄OH); 500 MHz ¹H NMR (CDCl₃) δ 7.25 (d, J = 8.3 Hz, 2H), 7.19 (d, J = 8.3 Hz, 2H), 3.58 (s, 2H), 3.51 (dddd, J = 7.9, 7.9, 7.9, 7.9 Hz, 1H), 3.42 (dd, J = 9.5, 5.0 Hz, 1H), 3.36 (s, 3H), 3.27 (dd, J = 9.1, 6.6 Hz, 1H), 3.12-3.02 (m, 2H), 2.61-2.44 (m, 7H), 2.30-2.09 (m, 6H), 1.93-1.84 (m, 1H), 1.80-1.58 (m, 6H); 100 MHz ¹³C NMR (CDCl₃) δ 145.4, 136.8, 129.1, 126.5, 63.9, 61.9, 60.7, 59.4, 55.32, 54.4, 36.5, 33.6, 33.3, 30.9, 28.6, 23.6, 23.3; LRMS m/z Calcd for C₂₂ H₃₄ N₂ O 342.524; obsd LRMS (M+1) 343.3.

Example 129

trans- (3,5-Bis-trifluoromethyl-benzyl)-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutyl]methyl-amine. Preparation as described for Example 107, using the appropriate amine and the tosylate Example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester).

R_f = 0.72 (20% MeOH/CH₂Cl₂ w/ 0.1% NH₄OH); 500 MHz ¹H NMR (CDCl₃) δ 7.84 (bs, 2H), 7.77 (bs, 1H), 7.27 (d, J = 8.3 Hz, 2H), 7.18 (d, J = 7.9 Hz, 2H), 3.96 (s, 2H), 3.60 (s, 2H), 3.59-3.52 (m, 1H), 2.84 (d, J = 7.5 Hz, 2H), 2.55-2.43 (m, 5H), 2.34-2.26 (m, 2H), 2.19-2.11 (m, 2H), 1.83-1.74 (m, 4H); LRMS m/z Calcd for C₂₅ H₂₈ F₆ N₂ 470.498; obsd LRMS (M+1) 471.4.

Example 130

trans-(5-Methyl-pyrazin-2-ylmethyl)-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amine. Preparation as described for Example 107, using the appropriate amine and the tosylate Example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester).

R_f = 0.58 (20% MeOH/CH₂Cl₂ w/ 0.1% NH₄OH); 500 MHz ¹H NMR (CDCl₃) δ 8.48 (d, J = 1.2 Hz, 1H), 8.39 (d, 0.8 Hz, 1H), 7.24 (d, J = 8.3 Hz, 2H), 7.16 (d, J = 7.9 Hz, 2H), 3.93 (s, 2H), 3.57 (s, 2H), 3.60-3.50 (m, 1H), 2.84 (d, J = 7.5 Hz, 2H), 2.54 (s, 3H), 2.52-2.45 (m, 5H), 2.33-2.24 (m, 2H), 2.28-2.20 (m, 2H), 1.80-1.72 (m, 2H); LRMS m/z Calcd for C₂₂ H₃₀ N₄ 350.507; obsd LRMS (M+1) 351.5;

Example 131

trans-(2-Methyl-pyridin-3-ylmethyl)-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amine. Preparation as described for Example 107, using the appropriate amine and the tosylate Example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester).

R_f = 0.13 (20% MeOH/CH₂Cl₂ w/ 0.1% NH₄OH); 500 MHz ¹H NMR (CDCl₃) δ 8.39 (dd, J = 1.7, 1.7Hz, 1H), 7.63 (dd, J = 1.7, 1.7Hz, 1H), 7.26 (d, J = 7.9Hz, 2H), 7.18 (d, J = 7.9Hz, 2H), 7.15-7.08 (m, 1H), 3.81 (s, 2H), 3.60 (s, 2H), 3.62-3.52 (m, 1H), 2.86 (d, J = 7.5Hz, 2H), 2.58 (s, 3H), 2.56-2.44 (m, 5H), 2.36-2.25 (m, 2H), 2.19-2.11 (m, 2H), 1.82-1.74 (m, 4H); LRMS m/z Calcd for C₂₃ H₃₁ N₃ 349.519; obsd LRMS (M+1) 350.5;

Example 132

trans-Pyridin-2-ylmethyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amine. Preparation as described for Example 107, using the appropriate amine and the tosylate Example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester).

R_f = 0.28 (20% MeOH/CH₂Cl₂ w/ 0.1% NH₄OH); 500 MHz ¹H NMR (CDCl₃) δ 8.56 (dd J = 0.8, 0.8Hz, 1H), 7.65 (ddd, J = 2.1, 2.1, 2.1Hz, 1H), 7.32 (d, J = 7.5Hz, 1H), 7.26 (d, J = 7.9Hz, 2H), 7.17 (d, J = 7.9Hz, 2H), 7.20-7.12 (m, 1H), 3.94 (s, 2H), 3.58 (s, 2H), 3.52-3.50 (m, 1H), 2.86 (d, J = 7.5Hz, 2H), 2.51-2.42 (m, 5H), 2.32-2.24 (m, 2H), 2.20-2.10 (m, 2H), 1.88 (bs, 1H), 1.80-1.72 (m, 4H); LRMS m/z Calcd for C₂₂ H₂₉ N₃ 335.492; obsd LRMS (M+1) 336.4;

Example 133

trans-2-[4-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-piperazin-1-yl]-isonicotinonitrile. Preparation as described for Example 107, using the appropriate amine and the tosylate Example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester).

R_f = 0.97 (20% MeOH/CH₂Cl₂ w/ 0.1% NH₄OH); 500 MHz ¹H NMR (CDCl₃) δ 8.26 (d, J = 5.8Hz, 1H), 7.28 (d, J = 8.3Hz, 2H), 7.20 (d, J = 7.9Hz, 2H), 6.79 (s, 1H), 6.73 (d, J = 6.2Hz, 1H), 3.62 (s, 2H), 3.60-3.50 (m, 6H), 2.60 (s, 3H), 2.60-2.45 (m, 7H), 2.34-2.15 (m, 4H), 1.85-1.72 (m, 4H); LRMS m/z Calcd for C₂₆ H₃₃ N₅ 415.582; obsd LRMS (M+1) 416.5;

Example 134

trans-Methyl-pyridin-2-ylmethyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amine. Preparation as described for Example 107, using the appropriate amine and the tosylate Example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester).

R_f = 0.15 (10% MeOH/CH₂Cl₂ w/ 0.1% NH₄OH); 500 MHz ¹H NMR (CDCl₃) δ 8.55-8.52 (m, 1H), 7.67-7.62 (m, 1H), 7.45 (d, J = 7.9Hz, 1H), 7.25 (d, J = 7.9Hz, 2H), 7.17 (d, J =

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7.9Hz, 2H), 7.17-7.12 (m, 1H), 3.66 (s, 2H), 3.60 (s, 2H), 3.48 (dddd, J = 8.7, 8.7, 8.7, 8.7Hz, 1H), 2.65-2.46 (m, 7H), 2.26 (s, 3H), 2.25-2.08 (m, 4H), 1.82-1.70 (m, 4H); LRMS m/z Calcd for C₂₃ H₃₁ N₃ 349.519; obsd LRMS (M+1) 350.4;

Example 135

- 5 trans-(3-Chloro-5-trifluoromethyl-pyridin-2-ylmethyl)-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amine. Preparation as described for Example 107, using the appropriate amine and the tosylate Example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester).

- 10 R_f = 0.34 (10% MeOH/CH₂Cl₂ w/ 0.1% NH₄OH); 500 MHz ¹H NMR (CDCl₃) δ 8.75 (d, J = 0.8Hz, 1H), 7.89 (d, J = 1.7Hz, 1H), 7.28 (d, J = 7.9Hz, 2H), 7.19 (d, J = 8.3Hz, 2H), 4.13 (s, 2H), 3.63 (s, 2H), 3.53-3.51 (m, 1H), 2.90 (d, J = 7.5Hz, 2H), 2.60-2.48 (m, 5H), 2.36-2.25 (m, 2H), 2.22-2.15 (m, 2H), 1.85-1.75 (m, 4H); LRMS m/z Calcd for C₂₃ H₂₇ LRMS m/z Calcd for Cl F₃ N₃ 437.934; obsd LRMS (M+1) 438.3;

Example 136

- 15 trans-3-Ethyl-5-[(R)-1-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-pyrrolidin-2-yl]-[1,2,4]oxadiazole. Preparation as described for Example 107, using the appropriate amine and the tosylate Example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester).

- 20 R_f = 0.55 (10% MeOH/CH₂Cl₂ w/ 0.1% NH₄OH); 500 MHz ¹H NMR (CDCl₃) δ 7.26 (d, J = 7.9Hz, 2H), 7.15 (d, J = 7.9Hz, 2H), 3.88 (dd, J = 5.8, 5.8Hz, 1H), 3.60 (s, 2H), 3.53-3.43 (m, 1H), 3.25-3.18 (m, 1H), 2.83-2.77 (m, 2H), 2.75-2.62 (m, 1H), 2.53-2.40 (m, 6H), 2.35-2.00 (m, 8H), 1.95-1.85 (m, 1H), 1.84-1.75 (m, 4H), 1.33 (t, 3H); LRMS m/z Calcd for C₂₄ H₃₄ N₄ O 394.56; obsd LRMS (M+1) 395.5.

Example 137

- 25 trans-(6-Methyl-pyridin-2-ylmethyl)-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amine. Preparation as described for Example 107, using the appropriate amine and the tosylate Example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester).

- 30 R_f = 0.27 (10% MeOH/CH₂Cl₂ w/ 0.1% NH₄OH); 500 MHz ¹H NMR (CDCl₃) δ 7.50 (dd, J = 7.5, 7.5Hz, 1H), 7.25 (d, J = 7.9Hz, 2H), 7.17 (d, J = 7.9Hz, 2H), 7.12 (d, J = 7.9Hz, 1H), 7.00 (d, J = 7.5Hz, 1H), 3.89 (s, 2H), 3.58 (s, 2H), 3.60-3.50 (m, 1H), 2.86 (d, J = 7.5Hz, 2H), 2.53 (s, 3H), 2.52-2.45 (m, 5H), 2.32-2.23 (m, 2H), 2.20-2.10 (m, 2H), 1.87 (bs, 1H), 1.80-1.73 (m, 4H); LRMS m/z Calcd for C₂₃ H₃₁ N₃ 349.519; obsd LRMS (M+1) 350.2.

Example 138 (General Procedure A)

- 35 Step H (Alternative high speed synthetic procedure).

trans-(2-Chloro-6-fluoro-benzyl)-propyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amine. To preweighed amines (0.2 mmol, 2 equiv) in a 2-dram vial was

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added a solution of tosylate of example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester) (39.9 mg, 0.1 mmol, 1 equiv) dissolved in 0.4 ml of DMA and then a solution of TEA (0.014 ml, 0.1 mmol, 1 equiv, in 0.1 mL of DMA) was added. The reaction was then heated to 100 °C while being shaken. After heating over night the reactions were concentrated by blowing a stream of nitrogen over vials. The resulting gums were then dissolved in 1 mL of MeOH and K₂CO₃ (15.2 mg, 0.11 mmol) was added. The resulting slurries were shaken for 30 minutes and then the solvent was removed under reduced pressure. The residual was slurried in CH₂Cl₂, filtered through an empty SPE cartridge, washed with 2.5 mL of CH₂Cl₂, and then loaded onto a SCX SPE cartridge. The cartridge was washed with 1.5 mL of CH₂Cl₂ (discarded), 5 mL of MeOH (discarded) and then the cartridge was washed with 1 N TEA in MeOH into a tared vial. The solvent was removed under reduced pressure and then TFA salts were prepared by dissolving samples in 0.25 mL of CH₂Cl₂ and adding 0.015 mL TFA/0.5 mL CH₂Cl₂. The solutions were shaken at room temperature for 15 minutes and then the solvent was removed by blowing a stream of nitrogen over the samples. Purification of the resulting samples was accomplished using the indicated method, the product containing fraction were collected and then concentrating under reduced pressure to yield the title compound as the TFA salt.

Rt = 4.18 min HPLC method B; LRMS m/z Calcd for C₂₆ H₃₄ LRMS m/z Calcd for Cl F N₂ 428.00; obsd LRMS (M+1) 429.25.

Example 139

trans-[3-(3,5-Dimethyl-pyrazol-1-yl)-benzyl]-methyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amine. Preparation as described for Example 138, using the appropriate amine and the tosylate of example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester).

Rt = 4.15 min HPLC method B; LRMS m/z Calcd for C₂₉ H₃₈ N₄ 442.647; obsd LRMS (M+1) 443.32.

Example 140

trans-1-(5-Chloro-2-methoxy-benzyl)-4-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-piperazine. Preparation as described for Example 138, using the appropriate amine and the tosylate of example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester).

Rt = 4.10 min HPLC method B; TFA salt 125 MHz ¹³C NMR (CD₃OD) δ 161.6 (q, J (C-F) = 35.3Hz, TFA), 157.3, 147.4, 131.7, 130.7, 130.4, 128.7, 127.2, 125.5, 120.8, 116.8 (q, J (C-F) = 291.6Hz, TFA), 112.6, 61.3, 57.7, 55.3, 54.3, 53.5, 50.1, 49.0, 35.7, 32.2, 26.7, 22.5; LRMS m/z Calcd for C₂₈ H₃₈ LRMS m/z Calcd for Cl N₃ O 467.00; obsd LRMS (M+1) 468.26.

Example 141

trans- (3S,4aS,8aS)-2-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-decahydro-isoquinoline-3-carboxylic acid tert-butylamide. Preparation as described for Example 138, using the appropriate amine and the tosylate of example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester).

Rt = 4.25 min HPLC method B; LRMS m/z Calcd for C₃₀ H₄₇ N₃ O 465.721; obsd LRMS (M+1) 466.40.

Example 142

trans- (1-Benzyl-piperidin-4-ylmethyl)-methyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amine. Preparation as described for Example 138, using the appropriate amine and the tosylate of example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester).

Rt = 3.98 min HPLC method B; TFA salt 100 MHz ¹³C NMR (CD₃OD) δ 161.6 (q, J (C-F) = 35.3Hz, TFA), 147.3, 131.2, 130.5, 130.1, 129.2, 129.0, 128.7, 127.2, 116.8 (q, J (C-F) = 291.6Hz, TFA), 61.4, 60.6, 57.7, 53.5, 51.4, 40.1, 35.6, 32.4, 29.4, 27.1, 26.8, 22.6; LRMS m/z Calcd for C₃₀ H₄₃ N₃ 445.691; obsd LRMS (M+1) 446.35.

Example 143

trans- (S)-1-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-pyrrolidine-2-carboxylic acid amide. Preparation as described for Example 138, using the appropriate amine and the tosylate of example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester).

Rt = 3.80 min HPLC method B; TFA salt 125 MHz ¹³C NMR (CD₃OD) δ 169.8, 161.6 (q, J (C-F) = 35.3Hz, TFA), 147.3, 130.4, 128.7, 127.2, 116.8 (q, J (C-F) = 291.6Hz, TFA), 67.5, 59.9, 57.7, 55.2, 53.5, 35.6, 31.8, 29.5, 28.0, 22.8, 22.6; LRMS m/z Calcd for C₂₁ H₃₁ N₃ O 341.496; obsd LRMS (M+1) 342.27.

Example 144

trans- (8-Methoxy-quinolin-5-ylmethyl)-methyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amine. Preparation as described for Example 138, using the appropriate amine and the tosylate of example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester).

Rt = 3.90 min HPLC method B; LRMS m/z Calcd for C₂₈ H₃₅ N₃ O 429.604; obsd LRMS (M+1) 430.27.

Example 145

trans-4- (4-Chloro-phenoxy)-1-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-piperidine. Preparation as described for Example 138, using the appropriate amine and the tosylate of example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester).

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Rt = 4.28 min HPLC method B; LRMS m/z Calcd for C₂₇ H₃₅ LRMS m/z Calcd for C₂₇ H₃₅ Cl N₂ O 438.00; obsd LRMS (M+1) 439.24.

Example 146

trans-4- (2-Methoxy-phenoxy)-1-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-piperidine. Preparation as described for Example 138, using the appropriate amine and the tosylate of example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester).

Rt = 4.18 min HPLC method B; LRMS m/z Calcd for C₂₈ H₃₈ N₂ O₂ 434.62; obsd LRMS (M+1) 435.30.

10 Example 147

trans-4- (3-Chloro-phenoxy)-1-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-piperidine. Preparation as described for Example 138, using the appropriate amine and the tosylate of example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester).

15 Rt = 4.32 min HPLC method B; LRMS m/z Calcd for C₂₇ H₃₅ Cl N₂ O 438.00; obsd LRMS (M+1) 439.26.

Example 148

trans-Methyl- (4-phenoxy-benzyl)-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amine. Preparation as described for Example 138, using the appropriate amine and the tosylate of example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester).

Rt = 4.32 min HPLC method B; LRMS m/z Calcd for C₃₀ H₃₆ N₂ O 440.627; obsd LRMS (M+1) 441.29.

Example 149

25 trans- [1-(2-Methoxy-ethyl)-piperidin-4-ylmethyl]-methyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amine. Preparation as described for Example 138, using the appropriate amine and the tosylate of example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester).

30 Rt = 3.83 min HPLC method B; TFA salt 100 MHz ¹³C NMR (CD₃OD) δ 161.6 (q, J (C-F) = 35.3Hz, TFA), 147.3, 130.5, 128.7, 127.3, 116.8 (q, J (C-F) = 291.6Hz, TFA), 65.6, 61.4, 60.6, 57.7, 56.6, 53.5, 52.2, 40.1, 35.6, 32.3, 29.3, 27.1, 26.8, 22.5; LRMS m/z Calcd for C₂₆ H₄₃ N₃ O 413.646; obsd LRMS (M+1) 414.33.

Example 150

35 trans-1- [3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-4-#p!-tolylloxy-piperidine. Preparation as described for Example 138, using the appropriate amine and the tosylate of example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester).

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Rt = 4.30 min HPLC method B; LRMS m/z Calcd for C₂₈ H₃₈ N₂ O 418.621; obsd LRMS (M+1) 419.31.

Example 151

trans-2- {Benzyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amino}-ethanol.

- 5 Preparation as described for Example 138, using the appropriate amine and the tosylate of example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester).

Rt = 3.70 min HPLC method B; LRMS m/z Calcd for C₂₅ H₃₄ N₂ O 378.557; obsd LRMS (M+1) 379.30.

- 10 Example 152

trans- [2-(3,4-Dimethoxy-phenyl)-ethyl]-methyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amine. Preparation as described for Example 138, using the appropriate amine and the tosylate of example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester).

- 15 Rt = 3.76 min HPLC method B; TFA salt 100 MHz ¹³C NMR (CD₃OD) δ 161.6 (q, J (C-F) = 35.3Hz, TFA), 149.7, 148.6, 147.3, 130.5, 128.9, 128.7, 127.2, 121.1, 116.8 (q, J (C-F) = 291.6Hz, TFA), 112.5, 112.2, 60.7, 57.7, 57.6, 55.3, 53.5, 39.6, 35.7, 32.2, 31.9, 29.7, 26.8, 22.6; LRMS m/z Calcd for C₂₇ H₃₈ N₂ O₂ 422.609; obsd LRMS (M+1) 423.28.

Example 153

- 20 trans-Methyl-prop-2-ynyl- [3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amine. Preparation as described for Example 138, using the appropriate amine and the tosylate of example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester).

- 25 Rt = 3.60 min HPLC method B; TFA salt 125 MHz ¹³C NMR (CD₃OD) δ 161.6 (q, J (C-F) = 35.3Hz, TFA), 147.3, 130.5, 128.8, 127.2, 116.8 (q, J (C-F) = 291.6Hz, TFA), 80.3, 71.7, 59.8, 57.7, 53.5, 45.0, 39.6, 35.6, 31.9, 26.8, 22.6; LRMS m/z Calcd for C₂₀ H₂₈ N₂ 296.455; obsd LRMS (M+1) 297.20.

Example 154

- 30 trans-4-Pyrrolidin-1-yl-1-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-piperidine. Preparation as described for Example 138, using the appropriate amine and the tosylate of example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester).

- 35 Rt = 3.50 min HPLC method B; TFA salt 125 MHz ¹³C NMR (CD₃OD) δ 161.6 (q, J (C-F) = 35.3Hz, TFA), 147.3,, 130.5, 128.7, 127.2, 116.8 (q, J (C-F) = 291.6Hz, TFA), 61.5, 58.9, 57.7, 53.5, 52.0, 50.7, 35.6, 32.3, 26.8, 26.2, 22.7, 22.5; LRMS m/z Calcd for C₂₅ H₃₉ N₃ 381.604; obsd LRMS (M+1) 382.34.

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Example 155

trans-Isopropyl- (2-methoxy-ethyl)-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amine. Preparation as described for Example 138, using the appropriate amine and the tosylate of example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester).

Rt = 3.62 min HPLC method B; LRMS m/z Calcd for C₂₂ H₃₆ N₂ O 344.539; obsd LRMS (M+1) 345.20.

Example 156

trans-1-Benzyl-4- [3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-piperazine. Preparation as described for Example 138, using the appropriate amine and the tosylate of example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester).

Rt = 3.63 min HPLC method B; TFA salt 400 MHz ¹H NMR (CD₃OD) δ 7.52-7.35 (m, 9H), 4.33 (s, 2H), 4.19 (s, 2H), 3.72-3.60 (m, 1H), 3.58-3.11 (m, 14H), 2.91-2.79 (m, 1H), 2.46-2.30 (m, 4H), 2.22-2.10 (m, 2H), 2.05-1.92 (m, 2H); TFA salt 125 MHz ¹³C NMR (CD₃OD) δ 161.6 (q, J (C-F) = 35.3Hz, TFA), 147.4, 131.1, 130.6, 130.4, 129.5, 128.9, 128.7, 127.2, 116.8 (q, J (C-F) = 291.6 Hz, TFA), 61.2, 60.5, 57.7, 53.5, 49.8, 35.7, 32.2, 26.7, 22.5; LRMS m/z Calcd for C₂₇ H₃₇ N₃ 403.61; obsd LRMS (M+1) 404.33.

Example 157

trans-1-Ethyl-4- [3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-piperazine. Preparation as described for Example 138, using the appropriate amine and the tosylate of example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester).

Rt = 3.47 min HPLC method B; LRMS m/z Calcd for C₂₂ H₃₅ N₃ 341.539; obsd LRMS (M+1) 342.28.

Example 158

trans-2- {Isopropyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amino}-ethanol. Preparation as described for Example 138, using the appropriate amine and the tosylate of example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester).

Rt = 3.64 min HPLC method B; LRMS m/z Calcd for C₂₁ H₃₄ N₂ O 330.513; obsd LRMS (M+1) 331.30.

Example 159

trans- (2-Methoxy-ethyl)-propyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amine. Preparation as described for Example 138, using the appropriate amine and the tosylate of example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester).

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Rt = 3.63 min HPLC method B; LRMS m/z Calcd for C₂₂ H₃₆ N₂ O 344.539; obsd LRMS (M+1) 345.26.

Example 160

trans-Methyl- ((R)-1-phenyl-ethyl)-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amine. Preparation as described for Example 138, using the appropriate amine and the tosylate of example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester).

Rt = 3.70 min HPLC method B; LRMS m/z Calcd for C₂₅ H₃₄ N₂ 362.558; obsd LRMS (M+1) 363.30.

10 Example 161

trans- (4S,4aS)-4-Phenyl-1-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-decahydro-quinolin-4-ol. Preparation as described for Example 138, using the appropriate amine and the tosylate of example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester).

15 Rt = 3.80 min HPLC method B; LRMS m/z Calcd for C₃₁ H₄₂ N₂ O 458.686; obsd LRMS (M+1) 459.33.

Example 162

trans-1- {4-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-piperazin-1-yl}-ethanone. Preparation as described for Example 138, using the appropriate amine and the tosylate of example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester).

25 Rt = 3.57 min HPLC method B; TFA salt 125 MHz ¹³C NMR (CD₃OD) δ 170.6, 161.6 (q, J (C-F) = 35.3Hz, TFA), 147.3, 130.5, 128.7, 127.2, 116.8 (q, J (C-F) = 291.6Hz, TFA), 61.4, 57.7, 53.5, 51.5, 43.0, 38.2, 35.6, 32.2, 26.6, 22.6, 19.7; LRMS m/z Calcd for C₂₂ H₃₃ N₃ O 355.523; obsd LRMS (M+1) 356.28.

Example 163

trans-1-Methyl-4- [3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-[1,4]diazepane. Preparation as described for Example 138, using the appropriate amine and the tosylate of example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester).

30 Rt = 3.46 min HPLC method B; TFA salt 125 MHz ¹³C NMR (CD₃OD) δ 161.6 (q, J (C-F) = 35.3Hz, TFA), 147.3, 130.5, 128.7, 127.2, 116.8 (q, J (C-F) = 291.6Hz, TFA), 62.0, 57.7, 55.5, 53.5, 53.3, 50.4, 43.4, 35.6, 32.0, 26.9, 22.5, 20.6; LRMS m/z Calcd for C₂₂ H₃₅ N₃ 341.539; obsd LRMS (M+1) 342.28.

35 Example 164

trans-2- {4-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-piperazin-1-yl}-nicotinonitrile. Preparation as described for Example 138, using the appropriate amine and

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the tosylate of example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester).

Rt = 3.65 min HPLC method B; LRMS m/z Calcd for C₂₆ H₃₃ N₅ 415.582 obsd LRMS (M+1) 416.24.

5 Example 165

trans-Ethyl- (2-methoxy-ethyl)-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amine. Preparation as described for Example 138, using the appropriate amine and the tosylate of example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester).

10 Rt = 3.56 min HPLC method B; LRMS m/z Calcd for C₂₁ H₃₄ N₂ O 330.513; obsd LRMS (M+1) 331.25.

Example 166

trans-Methyl- (3-methyl-pyridin-2-ylmethyl)-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amine. Preparation as described for Example 138, using the appropriate amine and the tosylate of example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester).

20 Rt = 3.64 min HPLC method B; TFA salt 100 MHz ¹³C NMR (CD₃OD) δ 161.6 (q, J (C-F) = 35.3Hz, TFA), 148.4, 147.3, 146.4, 138.0, 132.1, 130.5, 128.7, 127.2, 123.8, 116.8 (q, J (C-F) = 291.6Hz, TFA), 61.4, 57.7, 57.5, 53.5, 41.3, 35.7, 32.0, 27.1, 22.6; LRMS m/z Calcd for C₂₄ H₃₃ N₃ 363.546; obsd LRMS (M+1) 364.27.

Example 167

trans-Diethyl- [3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amine. Preparation as described for Example 138, using the appropriate amine and the tosylate of example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester).

Rt = 3.57 min HPLC method B; LRMS m/z Calcd for C₂₀ H₃₂ N₂ 300.487; obsd LRMS (M+1) 301.23.

Example 168

trans-Benzyl-isopropyl- [3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amine. Preparation as described for Example 138, using the appropriate amine and the tosylate of example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester).

Rt = 3.70 min HPLC method B; LRMS m/z Calcd for C₂₆ H₃₆ N₂ 376.584; obsd LRMS (M+1) 377.30.

35 Example 169

trans-(S)-2-Pyrrolidin-1-ylmethyl-1-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-pyrrolidine. Preparation as described for Example 138, using the

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appropriate amine and the tosylate of example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester).

Rt = 3.48 min HPLC method B; TFA salt 125 MHz ¹³C NMR (CD₃OD) δ 161.6 (q, J (C-F) = 35.3Hz, TFA), 147.3, 130.5, 128.7, 127.2, 116.8 (q, J (C-F) = 291.6Hz, TFA), 64.2, 58.9, 57.8, 57.7, 55.0, 53.5, 35.6, 32.3, 31.7, 28.7, 28.1, 22.8, 22.5, 21.8; LRMS m/z Calcd for C₂₅ H₃₉ N₃ 381.604; obsd LRMS (M+1) 382.30.

Example 170

trans-((S)-1-Benzyl-pyrrolidin-3-yl)-ethyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amine. Preparation as described for Example 138, using the appropriate amine and the tosylate of example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester).

Rt = 3.63 min HPLC method B; LRMS m/z Calcd for C₂₉ H₄₁ N₃ 431.664; obsd LRMS (M+1) 432.30.

Example 171

trans-tert-Butyl-(2-methoxy-ethyl)-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amine. Preparation as described for Example 138, using the appropriate amine and the tosylate of example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester).

Rt = 3.60 min HPLC method B; LRMS m/z Calcd for C₂₃ H₃₈ N₂ O 358.566; obsd LRMS (M+1) 359.30.

Example 172

trans-4-(2-Chloro-phenoxy)-1-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-piperidine. Preparation as described for Example 138, using the appropriate amine and the tosylate of example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester).

Rt = 3.80 min HPLC method B; TFA salt 125 MHz ¹³C NMR (CD₃OD) δ 161.6 (q, J (C-F) = 35.3Hz, TFA), 152.3, 147.4, 130.5, 128.2, 128.1, 127.2, 124.1, 122.8, 122.6, 116.8 (q, J (C-F) = 291.6Hz, TFA), 116.4, 69.8, 68.3, 61.9, 57.7, 53.5, 40.3, 35.7, 32.2, 26.9, 22.6; LRMS m/z Calcd for C₂₇ H₃₅ Cl N₂ O 438.00; obsd LRMS (M+1) 439.20.

Example 173

trans-N-Ethyl-N,N'-dimethyl-N-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-ethane-1,2-diamine. Preparation as described for Example 138, using the appropriate amine and the tosylate of example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester).

Rt = 3.51 min HPLC method B; LRMS m/z Calcd for C₂₂ H₃₇ N₃ 343.555; obsd LRMS (M+1) 344.28.

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Example 174

trans-Dicyclopropylmethyl-methyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amine. Preparation as described for Example 138, using the appropriate amine and the tosylate of example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester).

Rt = 3.68 min HPLC method B; LRMS m/z Calcd for C₂₄ H₃₆ N₂ 352.562; obsd LRMS (M+1) 353.28.

Example 175

trans-Butyl-methyl- [3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amine. Preparation as described for Example 138, using the appropriate amine and the tosylate of example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester).

Rt = 3.62 min HPLC method B; LRMS m/z Calcd for C₂₁ H₃₄ N₂ 314.514; obsd LRMS (M+1) 315.26.

Example 176

trans-N, N,N'-Trimethyl-N'-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-ethane-1, 2-diamine. Preparation as described for Example 138, using the appropriate amine and the tosylate of example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester).

Rt = 3.56 min HPLC method B; TFA salt 125 MHz ¹³C NMR (CD₃OD) δ 161.6 (q, J (C-F) = 35.3Hz, TFA), 147.3, 130.5, 128.7, 127.2, 116.8 (q, J (C-F) = 291.6Hz, TFA), 61.5, 57.7, 53.5, 51.2, 50.4, 42.8, 39.8, 35.6, 32.0, 26.8, 22.5; LRMS m/z Calcd for C₂₁ H₃₅ N₃ 329.528; obsd LRMS (M+1) 330.29.

Example 177

trans-1- (1-Methyl-1H-imidazol-2-ylmethyl)-4-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-piperazine. Preparation as described for Example 138, using the appropriate amine and the tosylate of example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester).

Rt = 3.50 min HPLC method B; TFA salt 125 MHz ¹³C NMR (CD₃OD) δ 161.6 (q, J (C-F) = 35.3Hz, TFA), 147.3, 143.7, 130.5, 128.7, 127.2, 124.5, 118.5 116.8 (q, J (C-F) = 291.6Hz, TFA), 61.3, 57.7, 53.5, 51.8, 50.0, 49.5, 35.6, 33.8, 32.3, 26.6, 22.6; LRMS m/z Calcd for C₂₅ H₃₇ N₅ 407.602; obsd LRMS (M+1) 408.32.

Example 178

trans-2, 5-Dimethyl-1-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-2,5-dihydro-1H-pyrrole. Preparation as described for Example 138, using the appropriate amine and the tosylate of example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester).

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Rt = 3.59 min HPLC method B; LRMS m/z Calcd for C₂₂ H₃₂ N₂ 324.509; obsd LRMS (M+1) 325.26.

Example 179

trans- ((S)-1-Benzyl-pyrrolidin-3-yl)-methyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amine. Preparation as described for Example 138, using the appropriate amine and the tosylate of example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester).

Rt = 3.59 min HPLC method B; TFA salt 125 MHz ¹³C NMR (CD₃OD) δ 161.6 (q, J (C-F) = 35.3Hz, TFA), 147.3, 130.5, 130.2, 130.1, 129.2, 128.7, 127.2, 116.8 (q, J (C-F) = 291.6Hz, TFA), 62.8, 59.9, 58.4, 57.7, 53.5, 52.7, 52.2, 37.8, 35.5, 32.0, 26.9, 25.9, 22.5; LRMS m/z Calcd for C₂₈ H₃₉ N₃ 417.637; obsd LRMS (M+1) 418.31.

Example 180

trans- (4-Fluoro-benzyl)-methyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amine. Preparation as described for Example 138, using the appropriate amine and the tosylate of example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester).

Rt = 3.67 min HPLC method B; LRMS m/z Calcd for C₂₄ H₃₁ F N₂ 366.521; obsd LRMS (M+1) 367.23.

Example 181

trans-1-Phenyl-8-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-1,3,8-triaza-spiro[4.5]decan-4-one. Preparation as described for Example 138, using the appropriate amine and the tosylate of example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester).

Rt = 3.70 min HPLC method B; LRMS m/z Calcd for C₂₉ H₃₈ N₄ O 458.646; obsd LRMS (M+1) 459.26.

Example 182

trans-2- {Methyl- [3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amino}-ethanol. Preparation as described for Example 138, using the appropriate amine and the tosylate of example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester).

Rt = 3.55 min HPLC method B; TFA salt 125 MHz ¹³C NMR (CD₃OD) δ 161.6 (q, J (C-F) = 35.3Hz, TFA), 147.4, 130.5, 128.7, 127.2, 116.8 (q, J (C-F) = 291.6Hz, TFA), 60.7, 57.7, 57.6, 55.1, 53.5, 40.2, 35.7, 32.1, 26.8, 22.6; LRMS m/z Calcd for C₁₉ H₃₀ N₂ O 302.459; obsd LRMS (M+1) 303.23.

Example 183

trans-3-Benzyl-7-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine. Preparation as described for Example 138, using

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the appropriate amine and the tosylate of example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester).

Rt = 3.66 min HPLC method C; LRMS m/z Calcd for C₂₈ H₃₅ N₅ 441.619; obsd LRMS (M+1) 442.25.

5 Example 184

trans-3-{Benzyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amino}-propan-1-ol. Preparation as described for Example 138, using the appropriate amine and the tosylate of example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester).

10 Rt = 3.65 min HPLC method B; LRMS m/z Calcd for C₂₆ H₃₆ N₂ O 392.583; obsd LRMS (M+1) 393.29.

 Example 185

trans-Isobutyl-methyl- [3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amine. Preparation as described for Example 138, using the appropriate amine and the tosylate of example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester).

Rt = 3.61 min HPLC method B; LRMS m/z Calcd for C₂₁ H₃₄ N₂ 314.514; obsd LRMS (M+1) 315.26.

 Example 186

20 trans-Ethyl-isopropyl- [3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amine. Preparation as described for Example 138, using the appropriate amine and the tosylate of example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester).

Rt = 3.56 min HPLC method B; LRMS m/z Calcd for C₂₁ H₃₄ N₂ 314.514; obsd LRMS (M+1) 315.26.

 Example 187

trans-Dimethyl- {(R)-1-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-pyrrolidin-3-yl}-amine. Preparation as described for Example 138, using the appropriate amine and the tosylate of example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester).

30 Rt = 3.47 min HPLC method B; LRMS m/z Calcd for C₂₂ H₃₅ N₃ 341.539; obsd LRMS (M+1) 342.28.

 Example 188

trans-Isopropyl-methyl- [3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amine. Preparation as described for Example 138, using the appropriate amine and the tosylate of example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester).

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Rt = 3.56 min HPLC method B; LRMS m/z Calcd for C₂₀ H₃₂ N₂ 300.487; obsd LRMS (M+1) 301.22.

Example 189

trans-Methyl-(5-propyl-1H-pyrazol-3-ylmethyl)-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amine. Preparation as described for Example 138, using the appropriate amine and the tosylate of example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester).

Rt = 3.65 min HPLC method B; LRMS m/z Calcd for C₂₄ H₃₆ N₄ 380.576; obsd LRMS (M+1) 381.30.

10 Example 190

PF-00580378: trans- (1R,2S)-2-{Methyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amino}-1-phenyl-propan-1-ol. Preparation as described for Example 138, using the appropriate amine and the tosylate of example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester).

15 Rt = 3.70 min HPLC method B; LRMS m/z Calcd for C₂₆ H₃₆ N₂ O 392.583; obsd LRMS (M+1) 393.29.

Example 191

trans-2- {1-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-piperidin-4-yl}-benzooxazole. Preparation as described for Example 138, using the appropriate amine and the tosylate of example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester).

Rt = 3.70 min HPLC method C; LRMS m/z Calcd for C₂₈ H₃₅ N₃ O 429.604; obsd LRMS (M+1) 430.24.

Example 192

25 trans-3-Propyl-7- [3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine. Preparation as described for Example 138, using the appropriate amine and the tosylate of example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester).

30 Rt = 3.57 min HPLC method C; LRMS m/z Calcd for C₂₄ H₃₅ N₅ 393.575; obsd LRMS (M+1) 394.25.

Example 193

trans-Benzyl- ((R)-1-phenyl-ethyl)-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amine. Preparation as described for Example 138, using the appropriate amine and the tosylate of example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester).

35 Rt = 3.82 min HPLC method B; LRMS m/z Calcd for C₃₁ H₃₈ N₂ 438.655; obsd LRMS (M+1) 439.27.

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Example 194

trans-tert-Butyl-ethyl- [3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amine.

Preparation as described for Example 138, using the appropriate amine and the tosylate of
 5 example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl
 ester).

Rt = 3.61 min HPLC method B; LRMS m/z Calcd for C₂₂ H₃₆ N₂ 328.54; obsd LRMS
 (M+1) 329.25.

Example 195

trans-1-Methyl-4- [3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-piperazine.

10 Preparation as described for Example 138, using the appropriate amine and the tosylate of
 example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl
 ester).

Rt = 3.55 min HPLC method B; TFA salt 125 MHz ¹³C NMR (CD₃OD) δ 161.6 (q, J
 (C-F) = 35.3Hz, TFA), 147.6, 130.4, 128.6, 127.2, 116.8 (q, J (C-F) = 291.6Hz, TFA), 61.4,
 15 57.8, 53.5, 51.1, 49.3, 42.4, 35.8, 32.2, 27.0, 22.5 LRMS m/z Calcd for C₂₁ H₃₃ N₃ 327.513;
 obsd LRMS (M+1) 328.29.

Example 196

trans-Isopropyl- [3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-(1,3,5-trimethyl-
 1H-pyrazol-4-ylmethyl)-amine. Preparation as described for Example 138, using the
 20 appropriate amine and the tosylate of example 48 (trans-toluene-4-sulfonic acid 3-(4-
 pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester).

Rt = 3.62 min HPLC method B; LRMS m/z Calcd for C₂₆ H₄₀ N₄ 408.63; obsd LRMS
 (M+1) 409.32.

Example 197

25 trans-4- {Benzyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amino}-butan-1-
 ol. Preparation as described for Example 138, using the appropriate amine and the tosylate
 of example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-
 cyclobutylmethyl ester).

Rt = 3.66 min HPLC method B; LRMS m/z Calcd for C₂₇ H₃₈ N₂ O 406.61; obsd
 30 LRMS (M+1) 407.28.

Example 198

trans- (1R, 2R)-2-{Methyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-
 amino}-1-phenyl-propan-1-ol. Preparation as described for Example 138, using the
 appropriate amine and the tosylate of example 48 (trans-toluene-4-sulfonic acid 3-(4-
 35 pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester).

Rt = 3.69 min HPLC method B; LRMS m/z Calcd for C₂₆ H₃₆ N₂ O 392.583; obsd
 LRMS (M+1) 393.29.

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Example 199

trans-Benzyl-ethyl- [3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amine.

Preparation as described for Example 138, using the appropriate amine and the tosylate of example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester).

Rt = 3.68 min HPLC method B; LRMS m/z Calcd for C₂₅ H₃₄ N₂ 362.558; obsd LRMS (M+1) 363.31.

Example 200

trans-6- {4-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-piperazin-1-yl}-nicotinonitrile. Preparation as described for Example 138, using the appropriate amine and the tosylate of example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester).

Rt = 3.66 min HPLC method B; TFA salt 100 MHz ¹³C NMR (CD₃OD) δ 161.6 (q, J (C-F) = 35.3Hz, TFA), 159.0, 152.4, 147.3, 140.6, 130.5, 128.7, 127.2, 117.8, 116.8 (q, J (C-F) = 291.6Hz, TFA), 106.9, 98.1, 61.4, 57.7, 53.5, 51.4, 41.5, 35.7, 32.2, 26.6, 22.6; LRMS m/z Calcd for C₂₆ H₃₃ N₅ 415.582; obsd LRMS (M+1) 416.25.

Example 201

trans-Methyl- [3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-(2-trifluoromethyl-benzyl)-amine. Preparation as described for Example 138, using the appropriate amine and the tosylate of example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester).

Rt = 3.73 min HPLC method C; LRMS m/z Calcd for C₂₅ H₃₁ F₃ N₂ 416.528; obsd LRMS (M+1) 417.20.

Example 202

trans-3- (3-Methoxy-phenyl)-6-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-5,6,7,8-tetrahydro-4H-1,2,3a,6-tetraaza-azulene. Preparation as described for Example 138, using the appropriate amine and the tosylate of example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester).

Rt = 3.64 min HPLC method C; LRMS m/z Calcd for C₂₉ H₃₇ N₅ O 471.645; obsd LRMS (M+1) 472.28.

Example 203

trans-Methyl-phenethyl- [3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amine. Preparation as described for Example 138, using the appropriate amine and the tosylate of example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester).

Rt = 3.51 min HPLC method B; TFA salt 125 MHz ¹³C NMR (CD₃OD) δ 161.6 (q, J (C-F) = 35.3Hz, TFA), 147.3, 136.3, 130.5, 128.9, 128.7, 128.6, 127.2, 127.1, 116.8 (q, J (C-

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F) = 291.6Hz, TFA), 60.7, 57.7, 57.5, 53.5, 39.6, 35.6, 32.1, 31.9, 30.1, 26.9, 22.6; LRMS m/z Calcd for C₂₅ H₃₄ N₂ 362.558; obsd LRMS (M+1) 363.24.

Example 204

trans-3- {Pyridin-2-ylmethyl- [3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-
5 amino}-propan-1-ol. Preparation as described for Example 138, using the appropriate amine and the tosylate of example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester).

Rt = 3.59 min HPLC method B; TFA salt 125 MHz ¹³C NMR (CD₃OD) δ 161.6 (q, J (C-F) = 35.3Hz, TFA), 150.5, 149.5, 147.3, 138.0, 130.3, 128.7, 127.2, 124.2, 123.7, 116.8 (q, J (C-F) = 291.6Hz, TFA), 59.8, 59.1, 57.7, 57.1, 54.3, 53.5, 35.6, 31.8, 30.8, 26.9, 25.7, 22.6; LRMS m/z Calcd for C₂₅ H₃₅ N₃ O 393.571; obsd LRMS (M+1) 394.25.

Example 205

trans-Bis-pyridin-2-ylmethyl- [3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-
15 amine. Preparation as described for Example 138, using the appropriate amine and the tosylate of example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester).

Rt = 3.60 min HPLC method B; LRMS m/z Calcd for C₂₈ H₃₄ N₄ 426.605; obsd LRMS (M+1) 427.27.

Example 206

20 trans-Bis- (3-chloro-benzyl)-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amine. Preparation as described for Example 138, using the appropriate amine and the tosylate of example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester).

Rt = 3.87 min HPLC method B; LRMS m/z Calcd for C₃₀ H₃₄ Cl₂ N₂ 492.00; obsd
25 LRMS (M+1) 493.16.

Example 207

trans-Cyclopropyl- [3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-(1,3,5-trimethyl-1H-pyrazol-4-ylmethyl)-amine. Preparation as described for Example 138, using the appropriate amine and the tosylate of example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester).

Rt = 3.62 min HPLC method B; LRMS m/z Calcd for C₂₆ H₃₈ N₄ 406.614; obsd LRMS (M+1) 407.29.

Example 208

trans-Methyl-pyridin-4-ylmethyl- [3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-
35 amine. Preparation as described for Example 138, using the appropriate amine and the tosylate of example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester).

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Rt = 3.49 min HPLC method C; LRMS m/z Calcd for C₂₃ H₃₁ N₃ 349.519; obsd LRMS (M+1) 350.25

Example 209

trans-3- (3,4-Difluoro-phenyl)-6-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-5,6,7,8-tetrahydro-4H-1,2,3a,6-tetraaza-azulene. Preparation as described for Example 138, using the appropriate amine and the tosylate of example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester).

Rt = 3.67 min HPLC method C; LRMS m/z Calcd for C₂₈ H₃₃ F₂ N₅ 477.6; obsd LRMS (M+1) 478.23

10 Intermediate 4 - General procedure B

Step A:

(3,3-Dimethoxy-cyclobutyl)-pyrrolidin-1-yl-methanone. To a stirring solution of 3, 3-dimethoxy-cyclobutanecarboxylic acid methyl ester, (J. Org. Chem. 1988, 53, 3841 and J. Org. Chem. 1996, 61, 2174) (1.0 g, 5.7 mmol) in acetonitrile (200 mL) was added pyrrolidine (951 μ L, 11.5 mmol), followed by magnesium bromide (0.53 g, 2.9 mmol). The reaction was then heated to 60 $^{\circ}$ C (oil bath) for 18 hours. After 18 hours a second portion of pyrrolidine (1.9 mL, 23 mmol) and magnesium bromide (0.8 g, 4.3 mmol) were added. The reaction was then heated to 80 $^{\circ}$ C (oil bath) for 48 hours. TLC and MS analysis indicated complete consumption of starting material. The reaction was cooled to room temperature and quenched with a saturated solution of NaHCO₃, and diluted with CH₂Cl₂. The layers were separated and the organic layer was dried over magnesium sulfate, filtered through a fritted funnel and concentrated under reduced pressure. Purification of this material was accomplished by flash column chromatography using a 40M Biotage column, eluting with 70% EtOAc/toluene. The product containing fractions were collected and concentrated under reduced pressure to give the title compound (1.0 g, 86 % yield) as a colorless oil.

Rf = 0.25 (30% Toluene/ EtOAc); 400 MHz ¹H NMR (CDCl₃) δ 3.40 (dd, J = 6.6, 7.1Hz, 2H), 3.30 (dd, J = 6.6, 7.1Hz, 2H), 3.12 (s, 3H), 3.08 (s, 3H), 2.83 (dddd, J = 8.7, 8.7, 8.7, 8.7Hz, 1H), 2.40-2.26 (m, 4H), 1.87 (dddd, J = 7.1, 7.1, 7.1, 7.1Hz, 2H), 1.78 (dddd, J = 6.6, 6.6, 6.6, 6.6Hz, 2H); 125 MHz ¹³C NMR (CDCl₃) δ 172.2, 99.8, 48.9, 48.6, 46.2, 46.1, 34.9, 29.0, 26.3, 24.4; C₁₁ H₁₉ N O₃ 213.275 GC/MS 213, Retention time = 3.42min (Stationary phase: HP-1, fused silica, description: 12m x 0.202mm x0.33 μ m. temperature limits: -60 C to 325 C, ramp rate = 30 C/ min, solvent delay = 0.4min).

Intermediate 5 - General procedure B

Step B:

1-[(3,3-Dimethoxy-cyclobutyl)methyl]-pyrrolidine. To a stirring solution of (3,3-dimethoxy-cyclobutyl)-pyrrolidin-1-yl-methanone (Intermediate 4, General procedure B, Step A) (1.7 g, 8.0 mmol) in THF (50 mL) was added slowly a solution of lithium aluminum hydride

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(12 mL, 12 mmol, 1M THF). After 30 minutes the reaction was quenched by the dropwise addition of H₂O:15% NaOH: H₂O (Fieser and Fieser method). The resulting solids were filtered off using a fritted funnel and celite, and the filter pad was washed with EtOAc. The organic layer was concentrated under reduced pressure to give the title compound (1.6 g, quantitative yield) as a colorless oil. This material was processed without further purification.

400 MHz ¹H NMR (CDCl₃) δ 3.07 (s, 3H), 3.03 (s, 3H), 2.45-2.35 (m, 6H), 2.29-2.22 (m, 2H), 2.17 (dddd, J = 7.1, 7.1, 7.1, 7.1Hz, 1H), 1.72-1.64 (m, 6H); 100 MHz ¹³C NMR (CDCl₃) δ 100.9, 63.0, 54.6, 48.6, 48.3, 36.9, 24.7, 23.5; C₁₁ H₂₁ N O₂ 199.292; GC/MS 199, Retention time = 2.05min (Stationary phase: HP-1, fused silica, description: 12m x 0.202mm x 0.33um. temperature limits: -60 C to 325 C, ramp rate = 30 C/ min, solvent delay = 0.4min).

Intermediate 6 - General procedure B

Step C:

3-Pyrrolidin-1-ylmethyl-cyclobutanone. To a stirring solution of 1-[(3,3-dimethoxycyclobutyl)methyl]-pyrrolidine (intermediate 5, general procedure B, step B) (1.6 g, 8.0 mmol) in 3:1 acetone:H₂O (100 mL) was added p-toluenesulfonic acid mono hydrate (1.5 g, 8.0 mmol). The reaction mixture was heated to 65 C for 1 hour. Both TLC and GS/MS analysis indicated complete consumption of starting material. The reaction was cooled to room temperature and then the acetone was removed under reduced pressure. The resulting mixture was diluted with CH₂Cl₂ and washed with an aqueous solution of NaHCO₃. The aqueous layer was back extracted with 3:1 CHCl₃: iso-propyl alcohol. The combined organic layers were dried over magnesium sulfate, filtered through a fritted funnel and then concentrated under reduced pressure to yield the title compound (0.94 g, 76% yield) as a colorless oil. This material was processed without further purification.

400 MHz ¹H NMR (CDCl₃) δ 3.19-3.10 (m, 2H), 2.85-2.77 (m, 2H), 2.74 (d, 2H), 2.66-2.56 (m, 5H), 1.90-1.77 (m, 4H); 100 MHz ¹³C NMR (CD₃OD) δ 207.9, 61.4, 54.0, 51.2, 29.8, 23.0; C₉ H₁₅ N O 153.223 GC/MS 153, Retention time = 1.60min (Stationary phase: HP-1, fused silica, description: 12m x 0.202mm x 0.33um. temperature limits: -60 C to 325 C, ramp rate = 30 C/ min, solvent delay = 0.4min).

Intermediate 7 (General procedure B)

Step C

3-Piperidin-1-ylmethyl-cyclobutanone. Preparation as described for Intermediate 6 (General procedure B, Steps A-C) using the appropriate starting materials.

R_f = 0.30 (10% MeOH / CH₂Cl₂, 0.1% NH₄OH); 500 MHz ¹H NMR (CDCl₃) δ 3.14-3.04 (m, 2H), 2.76-2.66 (m, 2H), 2.62-2.51 (m, 1H), 2.50-2.44 (m, 2H), 2.43-2.28 (m, 4H), 1.58-1.48 (m, 4H), 1.44-1.34 (m, 2H); 100 MHz ¹³C NMR (CDCl₃) δ 208.4, 65.0, 54.9, 52.2, 26.1, 24.5, 21.9; C₁₀ H₁₇ N O 167.25; GC/MS 167, Retention time = 1.57min (Stationary

phase: HP-1, fused silica, description: 12m x 0.202mm x0.33um. temperature limits: -60 C to 325 C, ramp rate = 30 C/ min, solvent delay = 1.0min)

Example 210 - General procedure B

Step D:

5 3-Pyrrolidin-1-ylmethyl-1-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutanol. To a stirring solution of 1-(4-Bromo-benzyl)-pyrrolidine (Lednicer, Daniel; Lyster, Stanley C.; Duncan, Gordon W. Mammalian antifertility agents. IV. Basic 3,4-dihydronaphthalenes and 1,2,3,4-tetrahydro-1-naphthols. Journal of Medicinal Chemistry (1967), 10(1), 78-84, J. Org. Chem; EN; 46; 17; 1981; 3571-3574) (0.71 g, 2.96 mmol) in THF (13 mL) at -78 °C
10 (isopropanol/CO₂) was added a solution of n-butyl lithium (1.6 mL, 3.93 mmol, 2.5 M hexanes). After 15 minutes a pre-cooled (-78 °C) solution of 3-pyrrolidin-1-ylmethyl-cyclobutanone (Intermediate 6, General procedure B Step C) (0.2 g, 1.3 mmol, in 3 mL THF) was added down the side of the flask. After TLC analysis indicated complete consumption of starting material the reaction was quenched cold by the addition of a saturated solution of
15 NH₄Cl. The reaction was then warmed to room temperature and diluted with CH₂Cl₂. The layers were separated and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were discarded. The aqueous layer was then extracted with 3:1 (CHCl₃: isopropyl alcohol) and the combined organic layers were dried over magnesium sulfate, filtered through a fritted funnel, and concentrated under reduced pressure. The material was
20 purified by trituration using ether:hexanes to yield the title compound (0.24 mg, 58 % yield) as a colorless solid and a mixture of cis:trans isomers.

R_f = 0.22 (20 % MeOH/CH₂Cl₂ w/ 0.1% NH₄OH); cis:trans isomers, diagnostic peaks
400 MHz ¹H NMR (CD₃OD) δ 7.58 (d, J = 7.9 Hz), 3.30-4.10 (m), 2.37-2.25 (m), 2.01-1.91 (m); cis:trans isomers, diagnostic peaks 100 MHz ¹³C NMR (CD₃OD) δ 146.8, 132.7, 130.0,
25 125.7, 60.6, 58.4, 41.9; LRMS m/z Calcd for C₂₀ H₃₀ N₂ O 314.47; obsd LRMS (M+1) 315.2.

Example 211

1-(4-Piperidin-1-ylmethyl-phenyl)-3-pyrrolidin-1-ylmethyl-cyclobutanol. Preparation as described for Example 210 using the appropriate starting materials, 3-pyrrolidin-1-ylmethyl-
30 cyclobutanone (Intermediate 6, General procedure , Step C) and PF-549393-00: 1-(4-Bromo-benzyl)-piperidine (Maier, Roland; Woitun, Eberhard; Mueller, Peter; Hurnaus, Rudolf; Mark, Michael; Eisele, Bernhard; Budzinski, Ralph-Michael. Preparation of N-acylphenylcyclohexylamines as cholesterol biosynthesis inhibitors. Ger. Offen. (1996))

R_f = 0.15 (40% MeOH/CH₂Cl₂ w/ 0.1% NH₄OH; cis: trans, isomers, diagnostic peaks
35 500 MHz ¹H NMR (CDCl₃) δ 7.42 (d, J = 6.2 Hz), 4.10 (bs), 3.42 (s), 2.8-2.33 (m); cis:trans isomers, diagnostic peaks 125 MHz ¹³C NMR (CDCl₃) δ 145.1, 137.3, 129.5, 125.1, 124.8,

73.4, 63.7, 62.8, 62.2, 42.5, 41.6, 26.1, 24.5, 23.7, 23.5; LRMS m/z Calcd for C₂₁ H₃₂ N₂ O 328.497; obsd LRMS (M+1) 329.4.

Example 212

1-(4-Benzyloxymethyl-phenyl)-3-pyrrolidin-1-ylmethyl-cyclobutanol. Preparation as described for Example 210 using the appropriate starting materials, 3-pyrrolidin-1-ylmethyl-cyclobutanone (Intermediate 6, General procedure B, Step C).

R_f = 0.15 (25 % MeOH/CH₂Cl₂ w/ 0.1% NH₄OH); cis:trans isomers, diagnostic peaks, 500 Mz 1H NMR (CDCl₃) δ 7.47 (d, J = 8.3 Hz), 2.65-2.63 (m), 2.50 (d, J = 5.4 Hz), 2.40-2.37 (m); cis:trans isomers, diagnostic peaks 125 MHz 13C NMR (CDCl₃) δ 146.5, 138.5, 137.0, 128.6, 127.9, 125.6, 125.3, 72.6, 72.1, 72.0, 62.8, 54.7, 43.0, 25.6, 23.6; LRMS m/z Calcd for C₂₃ H₂₉ N O₂ 351.487; obsd LRMS (M+1) 352.2.

Example 213

4-(1-Hydroxy-3-pyrrolidin-1-ylmethyl-cyclobutyl)-benzonitrile. Preparation as described for Example 210 using the appropriate starting materials, 3-pyrrolidin-1-ylmethyl-cyclobutanone (Intermediate 6, General procedure B, Step C) and 4-bromo benzonitrile.

R_f = 0.12 (25 % MeOH/CH₂Cl₂ w/ 0.1% NH₄OH); cis:trans isomers, diagnostic peaks, 500 Mz 1H NMR (CDCl₃) δ 7.63-7.69 (bs), 4.76 (bs), 3.42 (s), 2.74-2.68 (m), 2.66-2.61 (m), 2.33-2.26 (m), 1.80-1.74 (m); cis:trans isomers, diagnostic peaks 125 MHz 13C NMR (CDCl₃) δ 152.1, 132.3, 126.0, 119.2, 110.7, 73.5, 61.5, 55.9, 54.6, 50.8, 42.5, 27.0, 23.8, 23.5; LRMS m/z Calcd for C₁₆ H₂₀ N₂ O 256.347 obsd LRMS (M+1) 257.2.

Example 214

1-(4-Morpholin-4-ylmethyl-phenyl)-3-piperidin-1-ylmethyl-cyclobutanol. Preparation as described for Example 210 using the appropriate starting materials, 3-piperidin-1-ylmethyl-cyclobutanone (Intermediate 7) and 4- (4-bromobenzyl) morpholine (Bioorg. Med. Chem. Lett. EN; 12; 20; 2002; 2987-2992).

R_f = 0.22 (10% MeOH/CH₂Cl₂ w/ NH₄OH; mixture, trans: cis isomers, diagnostic peaks 400 MHz 1H NMR (CDCl₃) δ 7.26-7.19 (m), 4.38 (s) and 3.37(s); mixture, cis:trans isomers, diagnostic peaks 100 MHz 13C NMR (CDCl₃) δ 146.7, 145.7, 129.3, 125.4, 124.9, 67.0, 65.8, 55.5, 54.6; LRMS m/z Calcd for C₂₁ H₃₂ N₂ O₂ 344.496; obsd LRMS (M+1) 345.5.

Example 215

3-Morpholin-4-ylmethyl-1-(4-morpholin-4-ylmethyl-phenyl)-cyclobutanol. Preparation as described for Example 210 using the appropriate starting materials, 3-morpholin-4-ylmethyl-cyclobutanone and 4- (4-bromobenzyl) morpholine (Bioorg. Med. Chem. Lett. EN; 12; 20; 2002; 2987-2992).

R_f = 0.24(10%MeOH/CH₂Cl₂ w/ 0.1% NH₄OH); cis:trans isomers, diagnostic peaks, 500 Mz 1H NMR (CDCl₃) δ 7.46 - 7.43 (m), 7.31 - 7.25(m), 3.73 - 3.67 (m), 3.44 (s), 2.48 -

2.37 (m); cistrans isomers, diagnostic peaks, ^{13}C NMR 125 MHz (CDCl_3) δ 145.1, 129.6, 125.3, 73.6, 67.1, 53.7; LRMS m/z Calcd for $\text{C}_{20}\text{H}_{30}\text{N}_2\text{O}_3$ 346.468; obsd LRMS ($M+1$) 347.4.

Example 216

5 1-(4-Dimethylaminomethyl-phenyl)-3-pyrrolidin-1-ylmethyl-cyclobutanol.

Preparation as described for Example 210 using the appropriate starting materials, 3-pyrrolidin-1-ylmethyl-cyclobutanone (Intermediate 6, General procedure B, Step C) and (4-Bromo-benzyl)-dimethyl-amine (J. Amer. Chem. Soc.; EN; 105; 13; 1983; 4136-4142).

R_f = 0.1 (30% MeOH/ CH_2Cl_2 w/ 0.1% NH_4OH); cis:trans isomers, diagnostic peaks
10 400 MHz ^1H NMR (CD_3OD) δ 7.53 major isomer (d, J = 8.3 Hz), 7.31 major isomer (d, J = 8.3 Hz), 2.23 (s), 2.21 (s); LRMS m/z Calcd for $\text{C}_{18}\text{H}_{28}\text{N}_2\text{O}$ 288.432; obsd LRMS ($M+1$) 289.4.

Example 217

3-(4-Pyrimidin-2-yl-piperazin-1-ylmethyl)-1-(4-pyrrolidin-1-ylmethyl-phenyl)-
15 cyclobutanol. Preparation as described for Example 210 using the appropriate starting materials.

R_f = 0.3 (20 % MeOH/ CH_2Cl_2 w/ 0.1% NH_4OH); cis: trans isomers, diagnostic peaks,
400 Mz ^1H NMR (CDCl_3) δ 8.13 (d, J = 4.6 Hz), 7.35 (d, J = 7.9 Hz), 7.22-7.14 (m), 6.34 (dd, J = 4.1, 4.1 Hz), 4.16 (bs), 3.67-3.65 (m), 3.47 major isomer (s), 3.45 minor isomer (s), 2.63-2.59 (m), 2.37-2.32 (m) 1.63-1.62 (m); cis:transisomers, diagnostic peaks 100 MHz ^{13}C NMR
20 (CDCl_3) δ 157.9, 145.3, 136.9, 129.3, 124.9, 110.1, 65.0, 54.0, 43.5, 23.3 ; LRMS m/z Calcd for $\text{C}_{24}\text{H}_{33}\text{N}_5\text{O}$ 407.559; obsd LRMS ($M+1$) 408.3.

Example 218 - General Procedure

Step E

1-[4-(3-Pyrrolidin-1-ylmethyl-cyclobutyl)-benzyl]-pyrrolidine. To a stirring solution of
25 3-pyrrolidin-1-ylmethyl-1-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutanol (Example 210, General procedure B, Step D) (0.10 g, 0.32 mmol) in 1,2-dichloroethane (3.2 mL) was added methanesulfonic acid (0.31 g, 3.2 mmol). The reaction was then heated to 65 $^\circ\text{C}$ (oil bath) for 30 minutes. The reaction was then cooled to room temperature and transferred to a Parr bottle. To this crude solution was added 5 mL of MeOH, 10% Pd/C (100 mg), and then the
30 reaction vessel was pressurized to 45 psi with H_2 . After 30 min the reaction was purged with N_2 , filtered through a pad of celite, and concentrated under reduced pressure. Purification of this material was accomplished flash column chromatography using a 15 g ISCO column, pre-packing material on silica, eluting with a gradient of 20%-45% MeOH/ CH_2Cl_2 with 0.1 % NH_4OH . The product containing fractions were collected and concentrated to give the title
35 compound as the (0.97 mg) as the bis-methanesulfonic acid salt.

Alternatively, to a stirring solution of 3-pyrrolidin-1-ylmethyl-1-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutanol (Example 8, General procedure B, Step D) (1.1 g, 3.5 mmol) in TFA (5.4

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mL, 70.1 mmol) was added triethyl silane (5.6 mL, 35.0 mmol). The reaction was then heated to 75 °C (oil bath) for 14 hours. The reaction was then cooled to rt and concentrated under reduced pressure. The residual was taken up in CH₂Cl₂ and washed with NaHCO₃. The aqueous layer was back extracted with 3:1 (CH₃Cl: isopropanol). The combined organic
 5 layers were dried over MgSO₄, filtered through a fritted funnel and concentrated under reduced pressure. Purification of this material was accomplished by flash column chromatography using a 40 M Biotage column, eluting with a gradient of 10%-20% MeOH/CH₂Cl₂ with 0.3% NH₄OH. The product containing fractions were collected and concentrated to give the title compound (324 mg, 18%) as the bis-TFA salt. To this material
 10 in EtOAc was added a solution of HCl (2 eq, 2M THF). The resulting solution was stirred over night, and then filtered through a fritted funnel. The solid was collected and dried under reduced pressure to yield the title compound as the bis-HCl salt and as a mixture of isomers

R_f = 0.3 (30 % MeOH/CH₂Cl₂ w/ 0.1% NH₄OH); cis:trans isomers, TFA salt, diagnostic peaks, 400 Mz 1H NMR (CDCl₃) δ 7.40-7.11 (m), 4.15 (s), 4.14 (s), 3.56-3.36 (m),
 15 3.26 (d, J = 7.8 Hz), 3.08 (d, J = 7.05 Hz); cis:trans isomers, TFA salt, diagnostic peaks 100 MHz 13C NMR (CDCl₃) δ 146.7, 130.6, 128.1, 127.5, 127.3, 60.3, 57.9, 53.8, 52.9, 36.0, 34.7, 32.4; LRMS m/z Calcd for C₂₀ H₃₀ N₂ 298.471, obsd LRMS (M+1) 299.4.

Example 219

4-[4-(3-Piperidin-1-ylmethyl-cyclobutyl)-benzyl]-morpholine. Preparation as described
 20 for Example 218 (General procedure A, Step E) using the appropriate starting material of example 214, 1-(4-morpholin-4-ylmethyl-phenyl)-3-piperidin-1-ylmethyl-cyclobutanol.)

R_f = 0.23 (10% MeOH/CH₂Cl₂ w/ 0.1% NH₄OH); HCl salt, mixture trans: cis isomers, diagnostic peaks 400 MHz 1H NMR (CD₃OD) δ 7.60 (d, J = 8.3 Hz), 7.43 (d, J = 7.9 Hz) one
 set, 7.52 (d, J = 8.3 Hz), 7.37 (d, J = 8.4 Hz), 4.36 (s), 4.35 (s); LRMS m/z Calcd for C₂₁ H₃₂
 25 N₂ O 328.497; obsd LRMS (M+1) 329.5.

Example 220

1-[4-(3-Pyrrolidin-1-ylmethyl-cyclobutyl)-benzyl]-piperidine. Preparation as described
 for Example 218 (General procedure A, Step E) using the appropriate starting material of
 example 211, 1-(4-piperidin-1-ylmethyl-phenyl)-3-pyrrolidin-1-ylmethyl-cyclobutanol

R_f = 0.3 (30 % MeOH/CH₂Cl₂ w/ 0.1% NH₄OH); cis: trans isomers, TFA salt,
 30 diagnostic peaks, 400 Mz 1H NMR (CDCl₃) δ 7.20 major isomer (d, J= 7.9 Hz), 7.13 minor isomer (d, 8.3 Hz), 7.06 major isomer (d, J = 7.9 Hz), 3.78 (s), 3.76 (s), 2.52-2.49 (m), 1.97-1.94 (m), 1.83-1.75 (m); cis:trans isomers, TFA salt, diagnostic peaks, 100 Mz 13C NMR (CDCl₃) δ 145.3, 130.7, 126.8, 61.8, 53.9, 36.1, 23.4; LRMS m/z Calcd for C₂₁ H₃₂ N₂
 35 312.498 obsd LRMS (M+1) 313.4.

Example 221

Dimethyl-[4-(3-pyrrolidin-1-ylmethyl-cyclobutyl)-benzyl]-amine. Preparation as described for Example 218 (General procedure A, Step E) using the appropriate starting material of example 216, 1-(4-dimethylaminomethyl-phenyl)-3-pyrrolidin-1-ylmethyl-cyclobutanol.

R_f = 0.15 (30 % MeOH/CH₂Cl₂ w/ 0.1% NH₄OH); cis: trans isomers, TFA salt, diagnostic peaks, 400 Mz ¹H NMR (CDCl₃) δ 7.20 major isomer (d J = 9.5 Hz), 3.47 minor isomer (s), 3.46 major isomer (s), 3.30-3.28 (m), 2.83-2.80 (m), 2.56-2.53 (m), 2.24 minor isomer (s), 2.23 major isomer (s); LRMS m/z Calcd for C₁₈ H₂₈ N₂ 272.433; obsd LRMS (M+1) 273.4.

Example 222

4-(3-Pyrrolidin-1-ylmethyl-cyclobutyl)-benzonitrile. Preparation as described for Example 218 (General procedure A, Step E) using the appropriate starting material of example 213, 4-(1-Hydroxy-3-pyrrolidin-1-ylmethyl-cyclobutyl)-benzonitrile.

R_f = 0.22 (10 % MeOH/CH₂Cl₂ w/ 0.1% NH₄OH); cis:trans isomers, diagnostic peaks, 500 Mz ¹H NMR (CDCl₃) δ 7.53 (d, J = 6.6 Hz), 7.51 (d, J = 8.3 Hz), 7.29 (d, J = 8.3 Hz), 7.22 (d, J = 8.3 Hz), 3.58 (dddd, J = 7.9, 7.9, 7.9, 7.9 Hz), 3.43-3.36 (m), 2.60-2.48 (m), 2.80-1.76 (m); cis:trans isomers, diagnostic peaks 125 MHz ¹³C NMR (CDCl₃) δ 151.4, 132.5, 132.3, 127.4, 119.4, 109.7, 62.8, 62.0, 54.7, 36.6, 35.2, 33.0, 23.6; LRMS m/z Calcd for C₁₆ H₂₀ N₂ 240.348 obsd LRMS (M+1) 241.3.

Example 223 - General Procedure B:

Step F

4 - (3-Pyrrolidin-1-ylmethyl-cyclobutyl)- N-hydroxy-benzamidine. To a stirring solution of Example 222 (4-(3-Pyrrolidin-1-ylmethyl-cyclobutyl)-benzonitrile) (150 mg, 0.62 mmol) in MeOH (1.5 mL) was added NaHCO₃ (58 mg, 0.62 mmol), followed by hydroxylamine hydrochloride (43.4 mg, 0.62 mmol). The reaction was then heated to 70 °C over night. Both TLC and MS analysis indicated complete consumption of starting material. The reaction was cooled to room temperature and concentrated under reduced pressure. Water was added and a gummy solid formed. The water was removed and the residual was taken up in MeOH and concentrated under reduced pressure to yield the title compound (50 mg, 29% yield). This material was used without further purification.

R_f = 0.22 (15 % MeOH/CH₂Cl₂ w/ 0.1% NH₄OH); cis:trans isomers, diagnostic peaks, 400 Mz ¹H NMR (CD₃OD) δ 7.60-7.52 (m), 7.30-7.15 (m), 3.58-3.41 (m), 2.64 (bs), 1.83 (bs); cis:trans isomers, diagnostic peaks 100 MHz ¹³C NMR (CD₃OD) δ 154.2, 126.3, 62.2, 22.9; LRMS m/z Calcd for C₁₆ H₂₃ N₃ O 273.378; obsd LRMS (M+1) 274.3.

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Example 224 - General Procedure B

Step G

5-Methyl-3- [4-(3-pyrrolidin-1-ylmethyl-cyclobutyl)-phenyl]-[1,2,4] oxadiazole. To a stirring solution of Example 223 (4-(3-Pyrrolidin-1-ylmethyl-cyclobutyl)- N-hydroxy-benzamidine) (89 mg, 0.33 mmol) in 1,2-dichloroethane (1 mL) was added acetic anhydride (200 μ L, 2.1 mmol). The reaction was heated to reflux (oil bath 100 $^{\circ}$ C). After 2.5 hours the reaction was cooled to room temperature, concentrated under reduced pressure and purified. Purification of this material was accomplished by flash column chromatography using a 10 g ISCO column, eluting with a gradient of 2%-5% MeOH/CH₂Cl₂ with 0.2 % NH₄OH. The product containing fractions were collected and concentrated to give the title compound (45 mg, 46% yield) as a mixture of isomers. The HCl salt was made by taking the free base up in EtOAc and adding a solution of HCl (1 eq, 2M in Et₂O), using ether to precipitate a gummy solid, dried under reduced pressure to yield a tan solid.

R_f = 0.3 (10 % MeOH/CH₂Cl₂ w/ 0.1% NH₄OH); cis: trans isomers, diagnostic peaks, 500 Mz ¹H NMR (CDCl₃) δ 3.61-3.57 (m), 3.45-3.39 (m); cis: trans isomers, diagnostic peaks, 125 Mz ¹³C NMR (CDCl₃) δ 176.6, 168.5, 127.6, 127.5, 54.6, 36.6, 35.4, 33.2, 31.0, 23.6; LRMS m/z Calcd for C₁₈ H₂₃ N₃ O 297.4; obsd LRMS (M+1) 298.2.

Example 225

4- (3-Pyrrolidin-1-ylmethyl-cyclobutyl)-benzylamine. To a stirring solution of Example 213 (4-(1-Hydroxy-3-pyrrolidin-1-ylmethyl-cyclobutyl)-benzonitrile) (500 mg, 1.9 mmol) in 20 mL of each MeOH and EtOH was added methanesulfonic acid (1.3 mL, 19.5 mmol), followed by 125 mg of 10% palladium/carbon. The reaction vessel was purged several times with N₂ and then pressurized with 45 psi H₂. After 1 h the reaction mixture was purged with N₂ filtered through a plug of Celite and concentrated under reduced pressure. This mixture was re-dissolved in EtOH (20 mL) then 10% Pd/C (125 mg) was added. As before the reaction vessel was purged several times with N₂, pressurized with 45 psi H₂ and then heated to 50 $^{\circ}$ C . After 2 hours the reaction mixture was purged with N₂, filtered through a plug of Celite, and concentrated under reduced pressure to yield viscous oil. This oil was taken up in MeOH and solid NaOH (780 mg, 19.5 mmol) was added. This mixture was stirred overnight. The solid were then filtered off and the filtrate was concentrated. The HCl salt was made by the first dissolving the residual compound in EtOAc and then a solution of HCl (2N in Et₂O) was added. The solids was collected and dried under reduced pressure. Purification of this material was accomplished by dry pack method flash column chromatography using a 40 g ISCO column, eluting with a gradient of 10%-40% MeOH/CH₂Cl₂ with 0.2% NH₄OH. The product containing fractions were collected and concentrated to give the title compound (350

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mg, 74% yield) as a colorless solid. The HCl salt of the title compound was made treating the title compound in EtOAc with a solution of HCl (2N in Et₂O).

R_f = 0.12 (40 % MeOH/CH₂Cl₂ w/ 0.1% NH₄OH); cis: trans isomers, diagnostic peaks, 400 Mz ¹H NMR (CD₃OD) δ 7.43 (d, J = 8.3 Hz), 7.37 minor isomer (d, J = 7.9 Hz), 7.32 major isomer (d, 8.3 Hz), 4.11(s), major isomer 4.10 (s), 2.08 (bs), 2.01-1.93 (m); cis:trans isomers, diagnostic peaks 100 MHz ¹³C NMR (CD₃OD) δ 145.9, 131.2, 129.2, 127.0, 59.6, 48.6, 43.0, 38.5, 22.8; LRMS m/z Calcd for C₁₆ H₂₄ N₂ 244.38; obsd LRMS (M+1) 245.3.

Example 226

10 1-(3-p-Tolyl-cyclobutylmethyl)-pyrrolidine. To a stirring solution of Example 212, (1-(4-benzyloxymethyl-phenyl)-3-pyrrolidin-1-ylmethyl-cyclobutanol) (200 mg, 0.57 mmol) in EtOH (10 mL) was added methane sulfonic acid (370 uL, 5.7 mmol), followed by 10% Pd/C (200 mg). The reaction vessel was purged with N₂, and then pressurized with 45 psi H₂. After 30 minute the reaction vessel was purged with nitrogen. The reaction was filtered
15 through a plug of Celite and then concentrated under reduced pressure. The residual was dissolved in EtOAc and a solution of HCl (2 N in ether) was added. The solution was decanted and the residual was purified. Purification of this material was accomplished by dry pack flash column chromatography using a 40 g ISCO column, eluting with a gradient of 5%-15% MeOH/CH₂Cl₂ with 0.2% NH₄OH. The product containing fractions were collected and
20 concentrated to give the title compound (100 mg, 77% yield) as a colorless oil. The HCl salt of the title compound was made by dissolving the title compound in ethyl acetate and then adding a solution of HCl (2N in ether), the resulting colorless solid was collected and dried under reduced pressure.

R_f = 0.5 (25 % MeOH/CH₂Cl₂ w/ 0.1% NH₄OH); cis: trans isomers, diagnostic
25 peaks, 400 Mz ¹H NMR (CD₃OD) δ 7.11-7.07 (m), 3.41-3.23 (m), 3.28 (d, J = 7.0 Hz), 2.69 (s), 2.67-2.53 (m), 2.07-2.23 (m); cis:trans isomers, diagnostic peaks 100 MHz ¹³C NMR (CD₃OD) δ 141-8, 135.5, 128.8, 126.2, 60.0, 54.0, 38.5, 38.4, 36.2, 34.5, 28.3, 22.7; LRMS m/z Calcd for C₁₆ H₂₃ N 229.365; obsd LRMS (M+1) 230.2.

Example 227

30 trans-4-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-thiomorpholine.
Preparation as described for Example 138, using the appropriate amine and the tosylate of Example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester). R_f = 0.33 (10% MeOH/CH₂Cl₂ w/ 0.1% NH₄OH); 400 MHz ¹H NMR (CDCl₃) δ 7.24 (d, J = 7.94Hz, 2H), 7.20 (d, J = 7.9Hz, 2H), 3.57 (s, 2H), 3.5 (dddd, J = 8.1, 7.9, 7.9, 8.1Hz,
35 1H), 3.09-3.06 (m, 2H), 2.69-2.61 (m, 4H), 2.58-2.43 (m, 5H), 2.27-2.19 (m, 2H), 2.15-2.08 (m, 2H), 1.79-1.70 (m, 4H); 100 MHz ¹³C NMR (CDCl₃) δ 145.2, 136.7, 129.1, 126.5, 65.2,

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60.6, 55.3, 54.3, 48.1, 36.4, 33.6, 28.1, 23.6; LRMS m/z Calcd for C₂₀ H₃₀ N₂ S 330.5; obsd LRMS APCI (M+1) m/z 331.

Example 228

trans-6-{4-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-piperazin-1-yl}-
5 nicotinonitrile. Preparation as described for Example 138, using the appropriate amine and
the tosylate of Example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-
cyclobutylmethyl ester). R_f = 0.25 (20% MeOH/CH₂Cl₂ w/ 0.4% NH₄OH); 500 MHz ¹H NMR
(CDCl₃) δ 8.36 (s, 1H), 7.54 (dd, J = 2.5, 2.5Hz, 1H), 7.22 (d, J = 8.3Hz, 2H), 7.10 (d, J =
8.3Hz, 2H), 6.54 (dd, J = 0.8Hz, 1H), 3.66-3.62 (m, 4H), 3.54 (s, 2H), 3.41-3.32 (m, 1H), 2.55-
10 2.41 (m, 13H), 1.84-1.70 (m, 6H); 125 MHz ¹³C NMR (CDCl₃) δ 159.5, 152.9, 144.4, 138.9,
137.1, 129.0, 126.3, 118.9, 105.9, 96.3, 65.3, 60.6, 54.3, 53.1, 44.6, 36.7, 35.9, 29.9, 23.6;
LRMS m/z Calcd for C₂₆ H₃₃ N₅ 415.6; obsd LRMS APCI (M+1) m/z 416.

Example 229

trans-1-Methanesulfonyl-4-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-
15 piperazine.

To a stirring solution of the compound of Example 111, (3-(4-Pyrrolidin-1-ylmethyl-
phenyl)-cyclobutylmethyl]-piperazine) (121 mg, 0.38 mmol) in 1,2-dichloroethane (3 mL) was
added diisopropyl ethyl amine (129 uL, 0.77 mmol) followed by dimethyl 4-amino pyridine
(DMAP) (2 mg, 0.02 mmol) followed by methyl sulfonyl chloride (45 uL, 0.77 mmol). The
20 reaction was then heated to 65 C. After 1 hr the reaction was cooled to rt, diluted with EtOAc,
and quenched with 1 N NaOH. The aqueous layer was extracted with EtOAc, the combined
organic layer were dried over MgSO₄, filtered and concentrated under reduced pressure.
Purification of this material was accomplished by generating the di-HCl salt. The bis-HCl salt
was formed by taking the crude di-amine in EtOAc and adding 2 equivalents of HCl (2 M
25 THF). The solid was filtered and washing with EtOAc. The solid was free based with 1N
NaOH, and then extracted with EtOAc, dried, filtered and concentrated to give the title
compound as a tan solid. R_f = 0.55 (30% MeOH/CH₂Cl₂ w/ 0.1% NH₄OH); 500 MHz ¹H
NMR (CDCl₃) δ 7.26 (d, J = 7.9Hz, 2H), 7.17 (d, J = 8.3Hz, 2H), 3.59 (s, 2H), 3.54 (dddd, J =
8.3, 7.9, 7.9, 8.3Hz, 1H), 3.24-3.20 (m, 4H), 2.76 (s, 3H), 2.62-2.48 (m, 11H), 2.32-2.23(m,
30 2H), 2.19-2.11 (m, 2H), 1.81-1.74 (m, 4H); 125 MHz ¹³C NMR (CDCl₃) δ 145.0, 136.7,
128.2, 126.5, 64.0, 60.6, 54.3, 52.8, 46.1, 36.4, 34.3, 33.3, 28.9, 23.6; LRMS m/z Calcd for
C₂₁ H₃₃ N₃ O₂ S 391.6; obsd LRMS APCI (M+1) m/z 392.

Example 230

trans-1-Ethanesulfonyl-4-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-
35 piperazine. Preparation as described for Example 229, using the appropriate ethyl sulfonyl
chloride to yield the compound. R_f = 0.29 (10% MeOH/CH₂Cl₂ w/ 0.2% NH₄OH); 500 MHz
¹H NMR (CDCl₃) δ 7.25 (d, J = 8.3Hz, 2H), 7.16 (d, J = 8.3Hz, 2H), 3.57 (s, 2H), 3.53 (dddd,

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J = 8.3, 7.9, 7.9, 8.3 Hz, 1H), 3.30-3.26 (m, 4H), 2.92 (dd, J = 7.5, 7.1 Hz, 2H), 2.60-2.46 (m, 12H), 2.30-2.21 (m, 2H), 2.18-2.10 (m, 2H), 1.80-1.72 (m, 4H), 1.35 (dd, J = 7.5, 7.5 Hz, 3H); 100 MHz ¹³C NMR (CDCl₃) δ 145.0, 136.8, 128.1, 126.5, 64.1, 60.6, 54.4, 53.2, 46.0, 43.7, 36.4, 33.4, 28.9, 23.6, 8.0; LRMS m/z Calcd for C₂₂ H₃₅ N₃ O₂ S 405.6; obsd LRMS APCI (M+1) m/z 406.

Example 231

trans-1-(Propane-2-sulfonyl)-4-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-piperazine. Preparation as described for Example 229, using the appropriate isopropyl sulfonyl chloride yields the title compound. R_f = 0.32 (10% MeOH/CH₂Cl₂ w/ 0.1% NH₄OH); 400 MHz ¹H NMR (CDCl₃) δ 7.27 (d, J = 7.9 Hz, 2H), 7.18 (d, J = 8.3 Hz, 2H), 3.60 (s, 2H), 3.55 (dddd, J = 8.3, 7.9, 7.9, 8.3 Hz, 1H), 3.39-3.34 (m, 4H), 3.18 (septet, J = 7.1 Hz), 2.62-2.46 (m, 11H), 2.32-2.23 (m, 2H), 2.19-2.12 (m, 2H), 1.82-1.76 (m, 4H), 1.33 (d, J = 6.6 Hz, 6H); 100 MHz ¹³C NMR (CDCl₃) δ 145.2, 136.6, 129.2, 126.5, 64.2, 60.5, 54.5, 53.6, 53.4, 46.5, 36.4, 33.4, 28.9, 23.6, 17.0; LRMS m/z Calcd for C₂₃ H₃₇ N₃ O₂ S 419.6; obsd LRMS APCI (M+1) m/z 420.

Example 232

trans-2-Methyl-1-{4-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-piperazin-1-yl}-propan-1-one. To a stirring solution of Example 111, (3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-piperazine) (100 mg, 0.32 mmol) in 1,2-dichloroethane (4 mL) was added diisopropyl ethylamine (111 uL, 0.64 mmol) followed by the addition of isobutyryl chloride (50 uL, 0.48 mmol). After 15 min the reaction was quenched with 1N NaOH, extracted with dichloromethane. The combined organic layers were dried over MgSO₄, filtered through a fritted funnel and concentrated under reduced pressure. Purification of this material was accomplished by flash column chromatography, using a 12 g ISCO column, eluting with 4% MeOH/CH₂Cl₂ with 0.2% NH₄OH. The product containing fractions were collected and concentrated to give the title compound (118 mg, 97% yield) as colorless oil. R_f = 0.27 (10% MeOH/CH₂Cl₂ w/ 0.2% NH₄OH); 500 MHz ¹H NMR (CDCl₃) δ 7.23 (d, J = 8.3 Hz, 2H), 7.15 (d, J = 8.3 Hz, 2H), 3.61-3.44 (m, 7H), 2.74 (septet, J = 7.1 Hz, 1H), 2.56-2.45 (m, 7H), 2.42-2.34 (m, 4H), 2.28-2.20 (m, 2H), 2.17-2.09 (m, 2H), 1.79-1.70 (m, 4H), 1.08 (d, J = 7.1 Hz, 6H); 125 MHz ¹³C NMR (CDCl₃) δ 175.5, 145.1, 136.7, 129.1, 126.5, 64.3, 60.5, 54.3, 45.6, 41.8, 36.5, 33.4, 30.1, 29.0, 23.6, 19.6; LRMS m/z Calcd for C₂₄ H₃₇ N₃ O 383.6; obsd LRMS APCI (M+1) m/z 384.

Example 233

trans-(1S,4S)-2-Methanesulfonyl-5-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-2,5-diaza-bicyclo[2.2.1]heptane. Preparation as described for Example 138, using the appropriated amine and the tosylate of Example 48 (trans-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester). R_f = 0.24 (10% MeOH/CH₂Cl₂

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w/ 0.2% NH₄OH); 500 MHz ¹H NMR (CDCl₃) δ 7.21 (d, J = 7.9Hz, 2H), 7.13 (d, J = 8.3Hz, 2H), 4.21 (bs, 1H), 3.56-3.45 (m, 5H), 3.15 (dd, J = 2.5Hz, 1H), 2.90 (dd, J = 2.5Hz, 1H), 2.82 (s, 3H), 2.80-2.65 (m, 3H), 2.49-2.42 (m, 4H), 2.39-2.28 (m, 1H), 2.25-2.06 (m, 4H), 1.86 (d, J = 9.0Hz, 1H), 1.77-1.68 (m, 4H), 1.65 (d, J = 9.9Hz, 1H); 125 MHz ¹³C NMR (CDCl₃) δ 145.0, 136.9, 129.1, 126.4, 62.0, 60.6, 59.5, 54.3, 50.9, 38.5, 36.6, 36.4, 32.9, 32.7, 30.8, 23.6; LRMS m/z Calcd for C₂₂ H₃₃ N₃ O₂ S 403.6; obsd LRMS APCI (M+1) m/z 404.

Example 234

cis-1-{4-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-piperazin-1-yl}-ethanone.

10 Preparation as described for Example 100, General Procedure A, Step H, using the appropriated amine and the tosylate of Example 47 (cis-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester). R_f = 0.24 (20% MeOH/CH₂Cl₂ w/ 0.5% NH₄OH); LRMS m/z Calcd for C₂₂ H₃₃ N₃ O 355.5; obsd LRMS APCI (M+1) m/z 356.

Example 235

15 cis-4-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-thiomorpholine.

Preparation as described for Example 100, General Procedure A, Step H, using the appropriated amine and the tosylate of Example 47 (cis-toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester); R_f = 0.25 (20% MeOH/CH₂Cl₂ w/ 0.5% NH₄OH); 400 MHz ¹H NMR (CD₃OD) δ 7.47 (d, J = 7.9Hz, 2H), 7.36 (d, J = 7.9Hz, 2H), 4.34 (s, 2H), 3.75 (d, J = 12.0Hz, 2H), 3.58-3.42 (m, 3H), 3.31-3.10 (m, 8H), 2.92-2.74 (m, 3H), 2.68-2.60 (m, 2H), 2.22-2.11 (m, 2H), 2.05-1.94 (m, 4H); 100 MHz ¹³C NMR (CD₃OD) δ 146.6, 130.4, 128.8, 127.2, 62.3, 57.8, 54.0, 53.6, 36.4, 34.7, 26.4, 24.5, 22.6; LRMS m/z Calcd for C₂₀ H₃₀ N₂ S 330.5; obsd LRMS APCI (M+1) m/z 331.

25 The composition of the present invention may be a composition comprising a compound of formula I and optionally a pharmaceutically acceptable carrier. The composition of the present invention may also be a composition comprising a compound of formula I, a histamine H₁ antagonist and optionally a pharmaceutically acceptable carrier. The composition of the present invention may also be a composition comprising a compound of formula I, a neurotransmitter re-uptake blocker and optionally a pharmaceutically acceptable carrier.

30 The composition of the present invention may be formulated in a conventional manner using one or more pharmaceutically acceptable carriers. The composition may be formulated for oral, buccal, intranasal, parenteral (e.g., intravenous, intramuscular, intraperitoneal, or subcutaneous or through an implant) nasal, vaginal, sublingual, rectal or topical administration or in a form suitable for administration by inhalation or insufflation.

35 For oral administration, the pharmaceutical composition may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically

acceptable excipients such as binding agents such as pregelatinized maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose; fillers such as lactose, microcrystalline cellulose or calcium phosphate; lubricants such as magnesium stearate, talc or silica; disintegrants such as potato starch or sodium starch glycolate; or wetting agents such as sodium lauryl sulphate. The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents such as sorbitol syrup, methyl cellulose or hydrogenated edible fats; emulsifying agents such as lecithin or acacia, non-aqueous vehicles such as almond oil, oily esters or ethyl alcohol; and preservatives such as methyl or propyl p-hydroxybenzoates or sorbic acid.

For buccal administration, the composition may take the form of tablets or lozenges formulated in conventional manner.

The composition of the invention may be formulated for parenteral administration by injection, including using conventional catheterization techniques or infusion. Formulations for injection may be presented in unit dosage form, for example, in ampoules or in multi-dose containers, with an added preservative. The composition may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulating agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient or ingredients in a composition may be in powder form for reconstitution with a suitable vehicle, for example, sterile pyrogen-free water, before use. The term "active ingredient" as used herein refers to a compound of the formula I, a histamine H₁ antagonist, or a neurotransmitter re-uptake blocker.

The composition of the invention may also be formulated in a rectal composition such as suppositories or retention enemas, for example, containing conventional suppository bases such as cocoa butter or other glycerides. A composition for vaginal administration is preferably a suppository that may contain, in addition to the active ingredient or ingredients, excipients such as cocoa butter or a suppository wax. A composition for nasal or sublingual administration is also prepared with standard excipients well known in the art.

For intranasal administration or administration by inhalation, the composition may be conveniently delivered in the form of a solution or suspension from a pump spray container that is squeezed or pumped by the patient or as an aerosol spray presentation from a pressurized container or a nebulizer, with the use of a suitable propellant, for example, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. The pressurized container or nebulizer may

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contain a solution or suspension of the active ingredient or ingredients. Capsules and cartridges, made, for example, from gelatin, for use in an inhaler or insufflator may be formulated containing a powder mix of an active ingredient or ingredients and a suitable powder base such as lactose or starch. The active ingredient or ingredients in the composition may range in size from nanoparticles to microparticles.

5 An exemplary dose of the composition of the invention comprising a compound of formula I for oral, parenteral or buccal administration to the average adult human for the treatment of the conditions referred to herein is about 0.01 to about 1000 mg of the compound of formula I per unit dose which could be administered, for example, 1 to 3 times per day.

10 An exemplary dose of the composition of the invention comprising a compound of formula I and a histamine H₁ antagonist or a neurotransmitter re-uptake blocker for oral, parenteral or buccal administration to the average adult human for the treatment of the conditions referred to herein is about 0.01 to about 500 mg of the compound of formula I and of about 0.01 mg to about 500 mg of the histamine H₁ antagonist or the neurotransmitter re-uptake blocker per unit dose which could be administered, for example, 1 to 3 times per day.

15 Aerosol formulations for treatment of the conditions referred to herein in the average adult human are preferably arranged so that each metered dose or "puff" of aerosol contains about 20 µg to about 1000 µg of the compound of formula I. The overall daily dose with an aerosol will be within the range about 100 µg to about 10 mg. Administration may be several times daily, for example 2, 3, 4 or 8 times, giving for example, 1, 2 or 3 doses each time.

20 Aerosol formulations containing a compound of formula I and a histamine H₁ antagonist or a neurotransmitter re-uptake blocker are preferably arranged so that each metered dose or "puff" of aerosol contains about 100 µg to about 10,000 µg of the compound of formula I and about 100 µg to about 30,000 µg of the histamine H₁ antagonist or the neurotransmitter re-uptake blocker. Administration may be several times daily, for example 1, 3, 4 or 8 times, giving for example, 1, 2 or 3 doses each time. The composition of the invention comprising a compound of formula I and a histamine H₁ antagonist or a neurotransmitter re-uptake blocker may optionally contain a pharmaceutically acceptable carrier and may be administered in both single and multiple dosages as a variety of different dosage forms, such as tablets, capsules, lozenges, troches, hard candies, powders, sprays, aqueous suspension, injectable solutions, elixirs, syrups, and the like. The pharmaceutically acceptable carriers include solid diluents or fillers, sterile aqueous media and various non-toxic organic solvents, etc. Oral pharmaceutical formulations can be suitably sweetened and/or flavored by means of various agents of the type commonly employed for such purposes. In general, the compound of formula I is present in such dosage forms at concentration levels ranging from about 0.1% to about 99.9% by weight of the total composition, i.e., in amounts which are sufficient to provide the desired unit dosage, and the histamine H₁ antagonist or the neurotransmitter re-uptake

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blocker is present in such dosage forms at concentration levels ranging from about 0.1% to about 99.9% by weight of the total composition, i.e., in amounts which are sufficient to provide the desired unit dosage.

5 The compound of formula I and the histamine H₁ antagonist may be administered together or separately. When administered separately, the compound of formula I and the histamine H₁ antagonist may be administered in either order, provided that after administration of the first of the two active ingredients, the second active ingredient is administered within 24 hours or less, preferably 12 hours or less.

10 The compound of formula I and the neurotransmitter re-uptake blocker may be administered together or separately. When administered separately, the compound of formula I and the neurotransmitter re-uptake blocker may be administered in either order, provided that after administration of the first of the two active ingredients, the second active ingredient is administered within 24 hours or less, preferably 12 hours or less.

15 A preferred dose ratio of compound of formula I to the histamine H₁ antagonist or to the neurotransmitter re-uptake blocker for oral, parenteral or buccal administration to the average adult human for the treatment of the conditions referred to herein is from about 0.001 to about 1000, preferably from about 0.01 to about 100.

20 The composition may be homogeneous, wherein by homogeneous it is meant that the active ingredient or ingredients are dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid composition is then subdivided into unit dosage forms of the type described herein containing from about 0.1 to about 1000 mg of the active ingredient or ingredients. Typical unit dosage forms contain from about 1 to about 300 mg, for example about 1, 2, 5, 10, 25, 50 or 100 mg, of the active ingredient or ingredients. The tablets or pills
25 of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the
30 duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The dosage of the active ingredient or ingredients in the composition and methods of this invention may be varied; however, it is necessary that the amount of the active ingredient
35 or ingredients in such a composition be such that a suitable dosage form is obtained. The selected dosage depends upon the desired therapeutic effect, on the route of administration, the particular compounds administered, the duration of the treatment, and other factors. All

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dosage ranges and dosage levels mentioned herein refer to each active ingredient present in the pharmaceutical composition of the present invention, as well as those used in the methods of the present invention. Generally, dosage levels of between about 0.01 and about 100 mg/kg of body weight daily are administered to humans and other mammals. A preferred dosage range in humans is about 0.1 to about 50 mg/kg of body weight daily which can be administered as a single dose or divided into multiple doses. A preferred dosage range in mammals other than humans is about 0.01 to about 10.0 mg/kg of body weight daily which can be administered as a single dose or divided into multiple doses. A more preferred dosage range in mammals other than humans is about 0.1 to about 5.0 mg/kg of body weight daily which can be administered as a single dose or divided into multiple doses.

The pharmaceutical composition comprising the compound of formula I and the histamine H₁ antagonist or the neurotransmitter re-uptake blocker may be administered at dosages of a therapeutically effective amount of the compound of formula I and of the second active ingredient in single or divided doses.

The specific therapeutically effective dose level for any particular patient will depend upon a variety of factors including the disorder being treated and the severity of the disorder; activity of the specific compound employed; the specific composition employed; the age. However, some variation in dosage will necessarily occur depending upon the condition of the subject being treated. The person responsible for administration will, in any event, determine the appropriate dose for the individual subject.

The dosage amounts set forth in this description and in the appended claims may be used, for example, for an average human subject having a weight of about 65 kg to about 70 kg. The skilled practitioner will readily be able to determine any variation in the dosage amount that may be required for a subject whose weight falls outside the about 65 kg to about 70 kg range, based upon the medical history of the subject. The pharmaceutical combinations may be administered on a regimen of up to 6 times per day, preferably 1 to 3 times per day, such as 2 times per day or once daily.

Determination of Biological Activity

The *in vitro* affinity of the compounds in the present invention at the rat or human histamine H₃ receptors can be determined according to the following procedure. Frozen rat frontal brain or frozen human post-mortem frontal brain is homogenized in 20 volumes of cold 50 mM Tris HCl containing 2 mM MgCl₂ (pH to 7.4 at 4 degrees C). The homogenate is then centrifuged at 45,000 G for 10 minutes. The supernatant is decanted and the membrane pellet resuspended by Polytron in cold 50 mM Tris HCl containing 2 mM MgCl₂ (pH to 7.4 at 4 degrees C) and centrifuged again. The final pellet is resuspended in 50 mM Tris HCl containing 2 mM MgCl₂ (pH to 7.4 at 25 degrees C) at a concentration of 12 mg/mL. Dilutions of compounds are made in 10% DMSO / 50 mM Tris buffer (pH 7.4) (at 10 x final

concentration, so that the final DMSO concentration is 1%). Incubations are initiated by the addition of membranes (200 microliters) to 96 well V-bottom polypropylene plates containing 25 microliters of drug dilutions and 25 microliters of radioligand (1 nM final concentration 3H-N-methyl-histamine). After a 1 hour incubation, assay samples are rapidly filtered through

5 Whatman GF/B filters and rinsed with ice-cold 50 mM Tris buffer (pH 7.4) using a Skatron cell harvester. Radioactivity is quantified using a BetaPlate scintillation counter. The percent inhibition of specific binding can then be calculated.

A person of ordinary skill in the art could adapt the above procedure to other assays.

Table 1. Rat Histamine H3 Receptor Binding

Example #	rH3 K _i (nM)
1	8.34
2	98.79
5	89.23
6	122.11
7	99.25
4	5.65
36	59.6
47	23.16
48	97.99
46	103.55
40	74.34
41	31.98
42	130.98
44	44.35
14	79.44
27	74.23
55	92.64
56	23.47
57	100.5
59	26.24
65	7.28
66	4.75
74	12.48
76	1.89
77	42.47
78	109.73

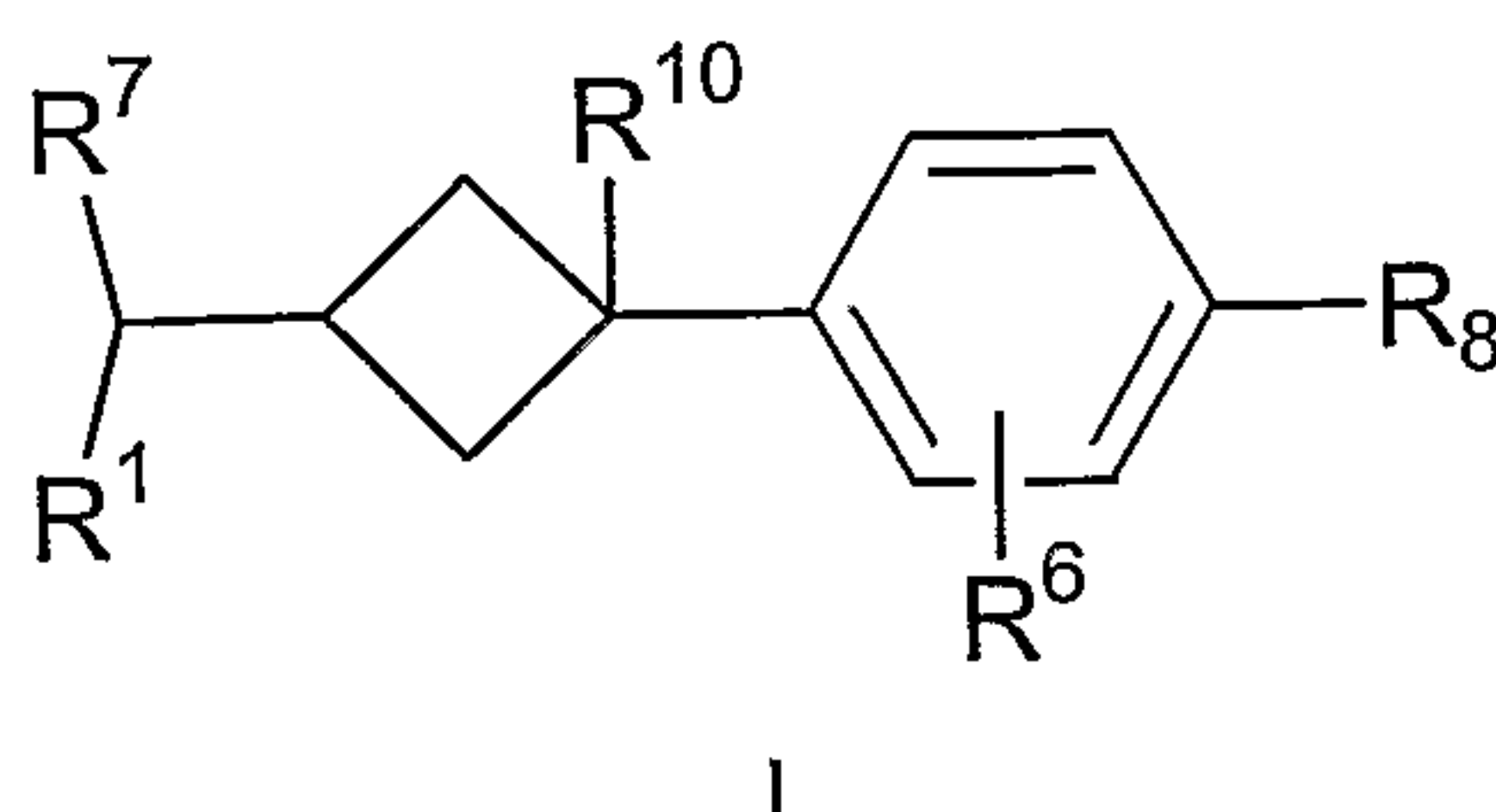
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Example #	rH3 K _i (nM)
81	57.96
83	68.85
88	3.79
90	33.64
92	118.01
100	3.22
101	4.81
102	1.83
103	3.93
104	2.78
105	5.38
106	8.35
107	2.09
108	0.58
109	2.55
110	2.83
112	0.77
113	4.46
114	0.48
115	1.44
116	2.82
117	0.73
118	0.65
119	1.34
120	3.35
121	2.81
122	2.71
123	6.84
124	0.49
125	1.77
126	1.89
127	101.02
128	8.91

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CLAIM:

1. A compound of formula I



- 5 or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from the group consisting of N_3 , OR^4 , and NR^2R^3 ;

R^2 and R^3 are each independently selected from the group consisting of hydrogen;

C_1 - C_8 alkyl optionally substituted with 1 to 4 halogens;

- 10 C_1 - C_4 alkyl group optionally substituted with a substituent selected from the group consisting of OH, one to four C_1 - C_4 alkyl, C_3 - C_7 cycloalkyl, C_1 - C_4 dialkylamino, C_6 - C_{14} aryl optionally substituted with a halogen and optionally substituted with C_6 - C_{10} aryloxy optionally substituted with one to two halogens, and 5-10-membered heteroaryl optionally substituted with a C_6 - C_{10} aryl group and optionally substituted with one to three C_1 - C_4 alkyl groups;

- 15 C_3 - C_7 cycloalkyl;

C_6 - C_{14} aryl;

3-8-membered heterocycloalkyl optionally substituted with one or more C_1 - C_4 alkyl-carbonyl group;

C_6 - C_{10} arylsulfonyl optionally substituted with one or more C_1 - C_2 alkyl;

- 20 5-10-membered heteroaryl; and

C_6 - C_{14} aryl- C_0 - C_4 alkylene-O- C_0 - C_4 alkyl, wherein each C_0 - C_4 alkyl and each C_0 - C_4 alkylene is optionally substituted with one to four C_1 - C_4 alkyl;

wherein R^3 can be further selected from the group consisting of

C_6 - C_{14} arylcarbonyl- C_6 - C_{14} aryl; C_6 - C_{14} arylcarbonyl-3-8-membered heterocycloalkyl;

- 25 C_3 - C_8 cycloalkylcarbonyl- C_6 - C_{14} aryl; C_3 - C_8 cycloalkylcarbonyl-3-8-membered heterocycloalkyl; 3-8-membered heterocycloalkylcarbonyl- C_6 - C_{14} aryl; and 3-8-membered heterocycloalkylcarbonyl-3-8-membered heterocycloalkyl;

- or R^3 and R^2 together with the nitrogen of the NR^2R^3 group form a first 5-, 6-, or 7-membered aliphatic ring, wherein one of the carbons in the first 5-, 6-, or 7-membered aliphatic ring is optionally replaced by O, S, $NR^{2'}$, or CO, and the first 5-, 6-, or 7-membered aliphatic ring is optionally fused to a C_6 - C_{10} arylene and is optionally substituted at a ring carbon with a substituent selected from the group consisting of

5-10-membered heteroaryl optionally substituted with one or more halogens and optionally substituted with one or more C_1 - C_2 alkyl,

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C₁-C₄ alkoxy optionally substituted with one or more C₁-C₂ alkoxy and optionally substituted with one or more C₁-C₄ dialkylaminocarbonyl, and

one or two C₁-C₄ alkyl optionally and independently substituted with one or more C₁-C₂ alkoxy;

5 wherein R^{2'} is

hydrogen;

C₁-C₈ alkyl optionally substituted with 1 to 4 halogens;

5-10-membered heteroaryl optionally substituted with a substituent selected from the group consisting of halogen, C₁-C₄ alkyl, C₁-C₂ alkoxy, C₆-C₁₀ aryl, C₁-C₄ alkylaminocarbonyl, and cyano;

C₁-C₄ alkyl group optionally substituted with a substituent selected from the group consisting of C₁-C₂ alkoxycarbonyl, 5-10-membered heteroaryl optionally substituted with one or more C₁-C₂ alkyl, one to four C₁-C₄ alkyl, C₃-C₇ cycloalkyl, and C₆-C₁₄ aryl;

C₆-C₁₀ aryl optionally substituted with one or two C₁-C₂ alkyl;

15 C₁-C₄ alkylcarbonyl;

or C₆-C₁₄ aryl-C₀-C₄ alkylene-O-C₀-C₄ alkyl, wherein each C₀-C₄ alkyl and each C₀-C₄ alkylene is optionally substituted with one to four C₁-C₄ alkyl;

R⁴ is

hydrogen;

20 C₁-C₈ alkyl optionally substituted with 1 to 4 halogens;

C₁-C₄ alkyl optionally substituted with a substituent selected from the group consisting

of

C₃-C₇ cycloalkyl,

5-10-membered heteroaryl, and

25 C₆-C₁₄ aryl optionally substituted with a substituent selected from the group consisting of one, two or three halogens, cyano, one or two C₁-C₂ alkoxy, C₁-C₂ di- or tri-fluoroalkyl, C₁-C₄ alkyl optionally substituted with C₆-C₁₀ arylsulfonyl, nitro, and 5-10-membered heteroaryl;

5-10-membered heteroaryl optionally fused to a C₆-C₁₀ arylene group that is optionally substituted with one or more halogens or one or more C₁-C₂ alkoxy, wherein the 5-10-membered heteroaryl is optionally substituted with a substituent selected from the group consisting of:

C₆-C₁₀ aryl optionally substituted with one or more halogens, one or more C₁-C₂ alkoxy, or one or more C₁-C₂ alkyl;

C₆-C₁₀ arylcarbonyl optionally substituted with one or more halogens;

35 one or more halogens;

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one to three C₁-C₄ alkyl groups optionally substituted with one or more C₆-C₁₀ aryl optionally and independently substituted with one or more halogens or one or more C₁-C₂ alkoxy;

- 5 C₁-C₂ di- or tri-fluoroalkyl;
- 1 to 2 C₁-C₂ alkoxy groups;
- 3-8-membered heterocycloalkyl;
- 5-10-membered heteroaryl amino;
- C₁-C₂ alkylaminocarbonyl-C₁-C₂-alkyl amino;
- C₆-C₁₀ arylaminocarbonyl;
- 10 C₆-C₁₀ arylaminocarbonyl-C₁-C₂-alkyl amino optionally substituted with one or more halogens at the C₆-C₁₀ aryl moiety of C₆-C₁₀ arylaminocarbonyl;
- 5-10-membered heteroaryl optionally substituted with one or more C₆-C₁₀ aryl or one or more C₁-C₂ alkyl;
- C₆-C₁₀ aryloxy optionally substituted with one or more C₁-C₂ alkoxy or one or more
- 15 halogens; and
- C₁-C₄ dialkyl amino;
- C₆-C₁₄ aryl optionally substituted with one or more halogens and optionally substituted with one or more C₆-C₁₀ aryloxy optionally and independently substituted with one to two halogens;
- 20 C₆-C₁₄ aryl-C₀-C₄ alkylene-O-C₀-C₄ alkyl, wherein each C₀-C₄ alkyl and each C₀-C₄ alkylene is optionally substituted with one to four C₁-C₄ alkyl;
- or
- C₆-C₁₀ arylsulfonyl optionally substituted with C₁-C₂ alkyl;
- R⁶ is hydrogen, C₁-C₄ alkyl or halogen;
- 25 R⁷ is hydrogen, SO₂C₁-C₁₀ alkyl, C₁-C₈ alkyl optionally substituted with 1 to 4 halogens, C₃-C₇ cycloalkyl-C₀-C₄ alkyl, C₆-C₁₄ aryl-C₀-C₄ alkyl, 5-10-membered heteroaryl-C₀-C₄ alkyl, or C₆-C₁₄ aryl-C₀-C₄ alkylene-O-C₀-C₄ alkyl, wherein each C₀-C₄ alkyl and each C₀-C₄ alkylene is optionally substituted with one to four C₁-C₄ alkyl;
- R¹⁰ is OH, halogen or hydrogen;
- 30 R⁸ is CN, -CHR^{7'}NR^{2''}R^{3''} or C(=NR¹²)-NR¹³R^{13'}, wherein R¹³ and R^{13'} are each independently hydrogen or C₁-C₆ alkyl and R¹² is hydrogen, C₁-C₆ alkyl OH, O-C₁-C₆ alkyl, NH₂, NHC₁-C₆ alkyl, or N(C₁-C₆ alkyl)₂,
- or wherein C(=NR¹²)-NR¹³R^{13'} represents a five-membered heteroaryl group, wherein R¹² is O, NH, or NC₁-C₆ alkyl, R¹³ and R^{13'} taken together represent N or CR^{13''} double bonded
- 35 to the nitrogen of the NR¹³R^{13'} group, and R^{13''} is hydrogen or C₁-C₆ alkyl;
- or when R⁸ is *ortho* to R⁶, R⁶ and R⁸ together with the carbons of the aromatic ring to which R⁶ and R⁸ are attached may form a 5-membered carbocyclic ring;

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$R^{2''}$ is hydrogen, C_1 - C_8 alkyl optionally substituted with 1 to 4 halogens, C_3 - C_7 cycloalkyl- C_0 - C_4 alkyl, C_6 - C_{14} aryl- C_0 - C_4 alkyl, 5-10-membered heteroaryl- C_0 - C_4 alkyl, or C_6 - C_{14} aryl- C_0 - C_4 alkylene-O- C_0 - C_4 alkyl, wherein each C_0 - C_4 alkyl and each C_0 - C_4 alkylene is optionally substituted with one to four C_1 - C_4 alkyl;

5 $R^{3''}$ is hydrogen, C_1 - C_8 alkyl optionally substituted with 1 to 4 halogens, C_6 - C_{14} aryl, C_6 - C_{14} arylcarbonyl- C_6 - C_{14} aryl, C_6 - C_{14} arylcarbonyl-3-8-membered heterocycloalkyl, C_3 - C_8 cycloalkylcarbonyl- C_6 - C_{14} aryl, C_3 - C_8 cycloalkylcarbonyl-3-8-membered heterocycloalkyl, 3-8-membered heterocycloalkyl, 3-8-membered heterocycloalkylcarbonyl- C_6 - C_{14} aryl, or 3-8-membered heterocycloalkylcarbonyl-3-8-membered heterocycloalkyl;

10 or $R^{3''}$ and $R^{2''}$ together with the nitrogen of the $CHR^7NR^{2''}R^{3''}$ group form a second 5-, 6- or 7-membered aliphatic ring, wherein one of the carbons in the second 5-, 6-, or 7-membered aliphatic ring is optionally replaced by O, S, NR^{11} , or C=O and the second 5-, 6-, or 7-membered aliphatic ring is optionally substituted with one or two C_1 - C_4 alkyl or optionally substituted with OH, wherein R^{11} is hydrogen, C_1 - C_8 alkyl optionally substituted with 1 to 4
15 halogens, C_3 - C_7 cycloalkyl- C_0 - C_4 alkyl, C_6 - C_{14} aryl- C_0 - C_4 alkyl, 5-10-membered heteroaryl- C_0 - C_4 alkyl, or C_6 - C_{14} aryl- C_0 - C_4 alkylene-O- C_0 - C_4 alkyl, wherein each C_0 - C_4 alkyl and each C_0 - C_4 alkylene is optionally substituted with one to four C_1 - C_4 alkyl; and

R^7 is hydrogen, C_1 - C_8 alkyl optionally substituted with 1 to 4 halogens, C_3 - C_7 cycloalkyl- C_0 - C_4 alkyl, C_6 - C_{14} aryl- C_0 - C_4 alkyl, 5-10-membered heteroaryl- C_0 - C_4 alkyl, C_6 - C_{14}
20 aryl- C_0 - C_4 alkylene-O- C_0 - C_4 alkyl, wherein each C_0 - C_4 alkyl and each C_0 - C_4 alkylene is optionally substituted with one to four C_1 - C_4 alkyl, or SO_2C_1 - C_{10} alkyl.

2. The compound of Claim 1, wherein R^{10} is hydrogen, F or OH.

3. The compound of Claim 1, wherein R^6 is hydrogen.

4. The compound of Claim 1, wherein R^7 is methyl.

25 5. The compound of Claim 1, wherein R^8 is $CHR^7NR^{2''}R^{3''}$ and wherein R^7 is hydrogen and $R^{3''}$ and $R^{2''}$ together with the nitrogen of the $CHR^7NR^{2''}R^{3''}$ group form a second 5-, 6- or 7-membered aliphatic ring, wherein one of the carbons in the second 5-, 6-, or 7-membered aliphatic ring is optionally replaced by O, S, NR^{11} , or CO and the second 5-, 6-, or 7-membered aliphatic ring is optionally substituted with one or two C_1 - C_4 alkyl or optionally
30 substituted with OH, wherein R^{11} is hydrogen, C_1 - C_8 alkyl optionally substituted with 1 to 4 halogens, C_3 - C_7 cycloalkyl- C_0 - C_4 alkyl, C_6 - C_{14} aryl- C_0 - C_4 alkyl, 5-10-membered heteroaryl- C_0 - C_4 alkyl, or C_6 - C_{14} aryl- C_0 - C_4 alkylene-O- C_0 - C_4 alkyl, wherein each C_0 - C_4 alkyl and each C_0 - C_4 alkylene is optionally substituted with one to four C_1 - C_4 alkyl; or R^7 is hydrogen and $R^{3''}$ and $R^{2''}$ together with the nitrogen of the $CHR^7NR^{2''}R^{3''}$ group form a pyrrolidinyl, 3-
35 hydroxypyrrolidinyl, morpholinyl, or piperidinyl group; or R^7 is hydrogen and each of $R^{3''}$ and $R^{2''}$ is methyl.

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6. The compound of claim 1, wherein the compound is selected from the group consisting of:

- 3-Benzyloxymethyl-1-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutanol,
 1-[4-(3-Benzyloxymethyl-cyclobutyl)-benzyl]-pyrrolidine,
 5 1-[4-(3-Benzyloxymethyl-cyclobutyl)-benzyl]-pyrrolidine,
 [3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutyl]-methanol,
 Toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester,
 3-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxymethyl]-benzonitrile,
 2-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxymethyl]-benzonitrile,
 10 4-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxymethyl]-benzonitrile,
 1-{4-[3-(3-Methoxy-benzyloxymethyl)-cyclobutyl]-benzyl}-pyrrolidine,
 1-{4-[3-(3-Fluoro-benzyloxymethyl)-cyclobutyl]-benzyl}-pyrrolidine,
 1-{4-[3-(4-Trifluoromethoxy-benzyloxymethyl)-cyclobutyl]-benzyl}-pyrrolidine,
 1-(4-{3-[(3-Chloro-2-fluoro-phenyl)methoxymethyl]-cyclobutyl}-benzyl)-pyrrolidine,
 15 1-{4-[3-(3-Methoxy-benzyloxymethyl)-cyclobutyl]-benzyl}-pyrrolidine,
 1-(4-{3-[(3,4-Dichloro-phenyl)methoxymethyl]-cyclobutyl}-benzyl)-pyrrolidine,
 1-(4-{3-[(3,5-Difluoro-phenyl)methoxymethyl]-cyclobutyl}-benzyl)-pyrrolidine,
 1-{4-[3-(3-Methyl-benzyloxymethyl)-cyclobutyl]-benzyl}-pyrrolidine,
 1-{4-[3-(3-Fluoro-benzyloxymethyl)-cyclobutyl]-benzyl}-pyrrolidine,
 20 1-{4-[3-(4-Fluoro-benzyloxymethyl)-cyclobutyl]-benzyl}-pyrrolidine,
 1-{4-[3-(4-Trifluoromethyl-benzyloxymethyl)-cyclobutyl]-benzyl}-pyrrolidine,
 1-(4-{3-[(2,4-Difluoro-phenyl)methoxymethyl]-cyclobutyl}-benzyl)-pyrrolidine,
 1-(4-{3-[(3,4-Difluoro-phenyl)methoxymethyl]-cyclobutyl}-benzyl)-pyrrolidine,
 1-{4-[3-(3-Trifluoromethyl-benzyloxymethyl)-cyclobutyl]-benzyl}-pyrrolidine,
 25 1-{4-[3-(4-tert-Butyl-benzyloxymethyl)-cyclobutyl]-benzyl}-pyrrolidine,
 1-{4-[3-(2-Fluoro-benzyloxymethyl)-cyclobutyl]-benzyl}-pyrrolidine,
 1-{4-[3-(3-Difluoromethoxy-benzyloxymethyl)-cyclobutyl]-benzyl}-pyrrolidine,
 1-{4-[3-(2-Benzenesulfonylmethyl-benzyloxymethyl)-cyclobutyl]-benzyl}-pyrrolidine,
 1-{4-[3-(1-Phenyl-ethoxymethyl)-cyclobutyl]-benzyl}-pyrrolidine,
 30 1-{4-[3-(4-Methyl-benzyloxymethyl)-cyclobutyl]-benzyl}-pyrrolidine,
 1-{4-[3-(3-Nitro-benzyloxymethyl)-cyclobutyl]-benzyl}-pyrrolidine,
 1-(4-{3-[(2-Methoxy-5-nitro-phenyl)methoxymethyl]-cyclobutyl}-benzyl)-pyrrolidine,
 1-{4-[3-(3-Trifluoromethoxy-benzyloxymethyl)-cyclobutyl]-benzyl}-pyrrolidine,
 1-(4-{3-[(3,5-Dimethoxy-phenyl)methoxymethyl]-cyclobutyl}-benzyl)-pyrrolidine,
 35 2-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxymethyl]-pyridine,
 1-(4-{3-[(2,3,4-Trifluoro-phenyl)methoxymethyl]-cyclobutyl}-benzyl)-pyrrolidine,

- 1-{4-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxymethyl]-phenyl}-1H-pyrazole,
- 1-(4-{3-[(3,5-Dimethyl-phenyl)methoxymethyl]-cyclobutyl}-benzyl)-pyrrolidine,
- 2-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyrimidine,
- 5 8-Methoxy-2-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-quinoline,
- 7-Fluoro-4-methyl-2-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-quinoline,
- 4,6-Dimethyl-2-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyrimidine,
- 2-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyrazine,
- 2,5-Dimethyl-3-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyrazine,
- 10 2-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyridine,
- 2-Methyl-6-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyridine,
- 3-Methoxy-6-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyridazine,
- 1-{4-[3-(2-Bromo-benzyloxymethyl)-cyclobutyl]-benzyl}-pyrrolidine,
- 2,4-Dimethoxy-6-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyrimidine,
- 15 cis-Toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester,
- trans-Toluene-4-sulfonic acid 3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl ester,
- trans-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutyl]-methanol,
- cis-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutyl]-methanol,
- 20 cis-4,6-Dimethyl-2-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyrimidine,
- cis-2-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyrimidine,
- cis-5-Ethyl-2-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyrimidine,
- cis-3-Methyl-6-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyridazine,
- trans-4,6-Dimethyl-2-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-
- 25 pyrimidine,
- trans-2-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyrimidine,
- trans-5-Ethyl-2-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyrimidine,
- trans-3-Methyl-6-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyridazine,
- cis-5-Methyl-4-piperidin-3-yl-2-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-
- 30 pyrimidine,
- cis-Pyridin-4-yl-{6-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyridazin-3-yl}-amine,
- cis-2-{[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]oxy}-4-trifluoromethyl-pyrimidine,
- 35 cis-5-Phenyl-2-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyrimidine,
- cis-(4-Chloro-phenyl)-{6-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyridazin-3-yl}-methanone,

- cis-1,3-Dimethyl-1-{6-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyridazin-3-yl}-urea,
- cis-4-Pyrrolidin-3-yl-2-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyrimidine,
- 5 cis-4-Methyl-6-pyrrolidin-3-yl-2-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyrimidine,
- cis-4-(3-Chloro-phenyl)-2-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-quinazoline,
- cis- 3-(3-Chloro-phenyl)-1-methyl-1-{6-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyridazin-3-yl}-urea,
- 10 cis-5-(4-Methoxy-phenoxy)-2-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyrimidine,
- cis-4-Pyridin-2-yl-2-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-quinazoline,
- 15 cis-5-(3-Chloro-phenoxy)-2-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyrimidine,
- cis-4-Phenyl-6-piperidin-4-yl-2-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyrimidine,
- cis-3-(3-Methyl-5-phenyl-pyrazol-1-yl)-6-{[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]oxy}-pyridazine,
- 20 5-Fluoro-4-piperidin-4-yl-2-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyrimidine,
- cis- 3-Piperazin-1-yl-6-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyridazine,
- 25 cis- 4-Phenyl-2-{[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]oxy}-6-trifluoromethyl-pyrimidine,
- cis-4-Methyl-6-piperidin-4-yl-2-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyrimidine,
- cis-1-Methyl-4-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-phthalazine,
- 30 cis-2-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-4-o-tolyl-pyrimidine,
- cis-5-(5-Iodo-2-methoxy-benzyl)-3-{[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutyl]methoxy}-pyridazine,
- cis-5-Methyl-4-piperidin-4-yl-2-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyrimidine,
- 35 cis-4-(2-Methyl-2H-pyrazol-3-yl)-2-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-quinazoline,

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- cis-6-Methyl-2-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyrimidine-4-carboxylic acid phenylamide,
- cis-4-Phenyl-2-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyrimidine,
- cis- 3-(2-Methoxy-benzyl)-6-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-
- 5 pyridazine,
- cis-Dimethyl-{6-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyridazin-3-yl}-amine,
- cis-4-Methyl-6-phenyl-2-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyrimidine,
- 10 cis-5-Methyl-4-pyrrolidin-3-yl-2-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyrimidine,
- cis-3-(3,5-Dimethyl-pyrazol-1-yl)-6-{[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]oxy}-pyridazine,
- cis-3-(2,5-Dimethyl-pyrrol-1-yl)-6-{[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]oxy}-pyridazine,
- 15 cis-5-(3-Chloro-phenyl)-2-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyrimidine,
- cis-5-(4-Methoxy-phenyl)-2-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyrimidine,
- 20 cis-4-Phenyl-6-pyridin-2-yl-2-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyrimidine,
- cis-4-Phenyl-6-piperidin-3-yl-2-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethoxy]-pyrimidine,
- 2-{4-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-piperazin-1-yl}-pyrimidine,
- 25 Dimethyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amine,
- 1-{4-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-piperazin-1-yl}-ethanone,
- 4-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-morpholine,
- 5-Fluoro-2-{4-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-piperazin-1-yl}-pyrimidine,
- 30 cis-4-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-morpholine,
- cis-1-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-piperazine,
- cis-5-Fluoro-2-{4-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-piperazin-1-yl}-pyrimidine,
- cis-1-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-pyrrolidine,
- 35 cis-1-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-piperidine,
- cis-2-{1-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-pyrrolidin-2-yl}-pyridine,

- cis-(2R,6S)-2,6-Dimethyl-4-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-morpholine,
- trans-1-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-pyrrolidine,
- trans-1-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-piperidine,
- 5 trans-2-{1-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-pyrrolidin-2-yl}-pyridine,
- trans-4-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-morpholine,
- trans-1-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-piperazineyl paratoluenesulfonate,
- 10 trans-5-Fluoro-2-{4-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-piperazin-1-yl}-pyrimidine,
- trans-2-{Ethyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amino}-ethanol,
- trans-3,5-Dimethyl-1-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-piperidine,
- trans-Cyclohexyl-methyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amine,
- 15 trans-Benzyl-methyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amine,
- trans-2-Methyl-1-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-piperidine,
- trans-3-Methyl-1-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-piperidine,
- trans-4-Methyl-1-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-piperidine,
- trans-2-Methyl-1-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-pyrrolidine,
- 20 trans-2,6-Dimethyl-1-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-piperidine,
- trans-Methyl-pyridin-3-ylmethyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amine,
- trans-(2R,5R)-2,5-Dimethyl-1-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-pyrrolidine,
- 25 trans-Cyclopropylmethyl-propyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amine,
- trans-2-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-2,3-dihydro-1H-isoindole,
- trans-(2R,6S)-2,6-Dimethyl-4-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-morpholine,
- 30 trans-4-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-piperazin-2-one,
- trans-(S)-2-Methoxymethyl-1-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-pyrrolidine,
- trans-(3,5-Bis-trifluoromethyl-benzyl)-{[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutyl]methyl}-amine,
- 35 trans-(5-Methyl-pyrazin-2-ylmethyl)-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amine,

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- trans-(2-Methyl-pyridin-3-ylmethyl)-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-
cyclobutylmethyl]-amine,
- trans-Pyridin-2-ylmethyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amine,
- trans-trans-2-{4-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-piperazin-1-yl}-
- 5 isonicotinonitrile,
- trans-Methyl-pyridin-2-ylmethyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-
amine,
- trans-(3-Chloro-5-trifluoromethyl-pyridin-2-ylmethyl)-{[3-(4-pyrrolidin-1-ylmethyl-
phenyl)-cyclobutyl]methyl}-amine,
- 10 trans-3-Ethyl-5-[(R)-1-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-pyrrolidin-
2-yl]-[1,2,4]oxadiazole,
- trans-(6-Methyl-pyridin-2-ylmethyl)-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-
cyclobutylmethyl]-amine,
- trans-(2-Chloro-6-fluoro-benzyl)-propyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-
- 15 cyclobutylmethyl]-amine,
- trans-[3-(3,5-Dimethyl-pyrazol-1-yl)-benzyl]-methyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-
cyclobutylmethyl]-amine,
- trans-1-(5-Chloro-2-methoxy-benzyl)-4-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-
cyclobutylmethyl]-piperazine,
- 20 trans-(3S,4aS,8aS)-2-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-
decahydro-isoquinoline-3-carboxylic acid tert-butylamide,
- trans-(1-Benzyl-piperidin-4-ylmethyl)-methyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-
cyclobutylmethyl]-amine,
- trans-(S)-1-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-pyrrolidine-2-
- 25 carboxylic acid amide,
- trans-(8-Methoxy-quinolin-5-ylmethyl)-methyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-
cyclobutylmethyl]-amine,
- trans-4-(4-Chloro-phenoxy)-1-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-
piperidine,
- 30 trans-4-(2-Methoxy-phenoxy)-1-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-
piperidine,
- trans-4-(3-Chloro-phenoxy)-1-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-
piperidine,
- trans-Methyl-(4-phenoxy-benzyl)-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-
- 35 cyclobutylmethyl]-amine,
- trans-[1-(2-Methoxy-ethyl)-piperidin-4-ylmethyl]-methyl-[3-(4-pyrrolidin-1-ylmethyl-
phenyl)-cyclobutylmethyl]-amine,

- trans-1-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-4-p-tolyloxy-piperidine,
 trans-2-{Benzyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amino}-ethanol,
 trans-[2-(3,4-Dimethoxy-phenyl)-ethyl]-methyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-
 cyclobutylmethyl]-amine,
 5 trans-Methyl-prop-2-ynyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amine,
 trans-4-Pyrrolidin-1-yl-1-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-
 piperidine,
 trans-Isopropyl-(2-methoxy-ethyl)-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-
 cyclobutylmethyl]-amine,
 10 trans-1-Benzyl-4-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-piperazine,
 trans-1-Ethyl-4-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-piperazine,
 trans-2-{Isopropyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amino}-
 ethanol,
 trans-(2-Methoxy-ethyl)-propyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-
 15 amine,
 trans-Methyl-((R)-1-phenyl-ethyl)-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-
 cyclobutylmethyl]-amine,
 trans-(4S,4aS)-4-Phenyl-1-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-
 decahydro-quinolin-4-ol,
 20 trans-1-{4-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-piperazin-1-yl}-
 ethanone,
 trans-1-Methyl-4-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-[1,4]diazepane,
 trans-2-{4-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-piperazin-1-yl}-
 nicotinonitrile,
 25 trans-Ethyl-(2-methoxy-ethyl)-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-
 amine,
 trans-Methyl-(3-methyl-pyridin-2-ylmethyl)-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-
 cyclobutylmethyl]-amine,
 trans-Diethyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amine,
 30 trans-Benzyl-isopropyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amine,
 trans-(S)-2-Pyrrolidin-1-ylmethyl-1-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-
 cyclobutylmethyl]-pyrrolidine,
 trans-((S)-1-Benzyl-pyrrolidin-3-yl)-ethyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-
 cyclobutylmethyl]-amine,
 35 trans-tert-Butyl-(2-methoxy-ethyl)-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-
 cyclobutylmethyl]-amine,

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- trans-4-(2-Chloro-phenoxy)-1-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-piperidine,
- trans-N-Ethyl-N',N'-dimethyl-N-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-ethane-1,2-diamine,
- 5 trans-Dicyclopropylmethyl-methyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amine,
- trans-Butyl-methyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amine,
- trans-N,N,N'-Trimethyl-N'-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-ethane-1,2-diamine,
- 10 trans-1-(1-Methyl-1H-imidazol-2-ylmethyl)-4-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-piperazine,
- trans-2,5-Dimethyl-1-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-2,5-dihydro-1H-pyrrole,
- trans-((S)-1-Benzyl-pyrrolidin-3-yl)-methyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amine,
- 15 trans-(4-Fluoro-benzyl)-methyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amine,
- trans-1-Phenyl-8-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-1,3,8-triazaspiro[4.5]decan-4-one,
- 20 trans-2-{Methyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amino}-ethanol,
- trans-3-Benzyl-7-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine,
- trans-3-{Benzyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amino}-propan-1-ol,
- 25 trans-Isobutyl-methyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amine,
- trans-Ethyl-isopropyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amine,
- trans-Dimethyl-((R)-1-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-pyrrolidin-3-yl)-amine,
- trans-Isopropyl-methyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amine,
- 30 trans-Methyl-(5-propyl-1H-pyrazol-3-ylmethyl)-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amine,
- trans-(1R,2S)-2-{Methyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amino}-1-phenyl-propan-1-ol,
- trans-2-{1-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-piperidin-4-yl}-benzooxazole,
- 35 trans-3-Propyl-7-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine,

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- trans-Benzyl-((R)-1-phenyl-ethyl)-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amine,
- trans-tert-Butyl-ethyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amine,
- trans-1-Methyl-4-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-piperazine,
- 5 trans-Isopropyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-(1,3,5-trimethyl-1H-pyrazol-4-ylmethyl)-amine,
- trans-4-{Benzyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amino}-butan-1-ol,
- trans-(1R,2R)-2-{Methyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amino}-1-phenyl-propan-1-ol,
- 10 trans-Benzyl-ethyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amine,
- trans-6-{4-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-piperazin-1-yl}-nicotinonitrile,
- trans-Methyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-(2-trifluoromethyl-15 benzyl)-amine,
- trans-3-(3-Methoxy-phenyl)-6-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-5,6,7,8-tetrahydro-4H-1,2,3a,6-tetraaza-azulene,
- trans-Methyl-phenethyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amine,
- trans-3-{Pyridin-2-ylmethyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-20 amino}-propan-1-ol,
- trans-Bis-pyridin-2-ylmethyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amine,
- trans-Bis-(3-chloro-benzyl)-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amine,
- 25 trans-Cyclopropyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-(1,3,5-trimethyl-1H-pyrazol-4-ylmethyl)-amine,
- trans-Methyl-pyridin-4-ylmethyl-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-amine,
- trans-3-(3,4-Difluoro-phenyl)-6-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-30 5,6,7,8-tetrahydro-4H-1,2,3a,6-tetraaza-azulene,
- 3-Pyrrolidin-1-ylmethyl-1-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutanol,
- 1-(4-Piperidin-1-ylmethyl-phenyl)-3-pyrrolidin-1-ylmethyl-cyclobutanol,
- 1-(4-Benzylloxymethyl-phenyl)-3-pyrrolidin-1-ylmethyl-cyclobutanol,
- 4-(1-Hydroxy-3-pyrrolidin-1-ylmethyl-cyclobutyl)-benzonitrile,
- 35 1-(4-Morpholin-4-ylmethyl-phenyl)-3-piperidin-1-ylmethyl-cyclobutanol,
- 3-Morpholin-4-ylmethyl-1-(4-morpholin-4-ylmethyl-phenyl)-cyclobutanol,
- 1-(4-Dimethylaminomethyl-phenyl)-3-pyrrolidin-1-ylmethyl-cyclobutanol,

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3-(4-Pyrimidin-2-yl-piperazin-1-ylmethyl)-1-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutanol,

1-[4-(3-Pyrrolidin-1-ylmethyl-cyclobutyl)-benzyl]-pyrroline,
 4-[4-(3-Piperidin-1-ylmethyl-cyclobutyl)-benzyl]-morpholine,
 5 1-[4-(3-Pyrrolidin-1-ylmethyl-cyclobutyl)-benzyl]-piperidine,
 Dimethyl-[4-(3-pyrrolidin-1-ylmethyl-cyclobutyl)-benzyl]-amine,
 4-(3-Pyrrolidin-1-ylmethyl-cyclobutyl)-benzonitrile,
 4-(3-Pyrrolidin-1-ylmethyl-cyclobutyl)-N-hydroxy-benzamidine,
 5-Methyl-3-[4-(3-pyrrolidin-1-ylmethyl-cyclobutyl)-phenyl]-[1,2,4]oxadiazole,
 10 4-(3-Pyrrolidin-1-ylmethyl-cyclobutyl)-benzylamine,
 1-(3-p-Tolyl-cyclobutylmethyl)-pyrrolidine,
 trans-1-[4-(3-Benzyloxymethyl-cyclobutyl)-benzyl]-pyrrolidine, and
 trans-1-[4-(3-Azidomethyl-cyclobutyl)-benzyl]-pyrrolidine.

7. The compound of claim 1, wherein the compound is selected from the group
 15 consisting of:

trans-4-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-thiomorpholine;
 trans-6-{4-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-piperazin-1-yl}-
 nicotinonitrile;
 trans-1-Methanesulfonyl-4-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-
 20 piperazine;
 trans-1-Ethanesulfonyl-4-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-
 piperazine;
 trans-1-(Propane-2-sulfonyl)-4-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-
 piperazine;
 25 trans-2-Methyl-1-{4-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-piperazin-1-
 yl}-propan-1-one;
 trans-(1S,4S)-2-Methanesulfonyl-5-[3-(4-pyrrolidin-1-ylmethyl-phenyl)-
 cyclobutylmethyl]-2,5-diaza-bicyclo[2.2.1]heptane;
 cis-1-{4-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-piperazin-1-yl}-
 30 ethanone; and
 cis-4-[3-(4-Pyrrolidin-1-ylmethyl-phenyl)-cyclobutylmethyl]-thiomorpholine.

8. A pharmaceutical composition comprising a compound of formula I as described in claim 1, and optionally a pharmaceutically acceptable carrier.

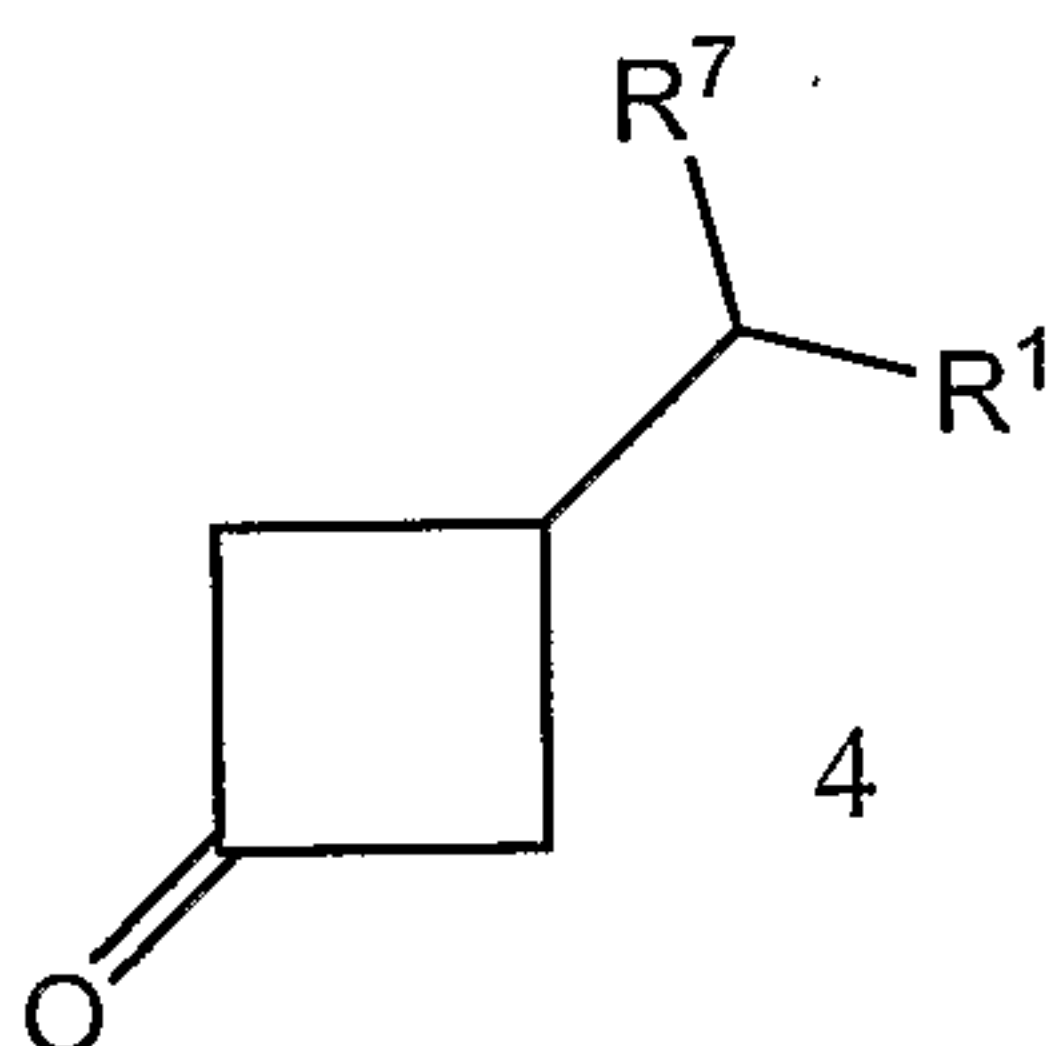
9. A method of treatment of a disorder or condition that may be treated by
 35 modulating histamine H3 receptors, the method comprising administering to a mammal in need of such treatment a compound of formula I as described in Claim 1.

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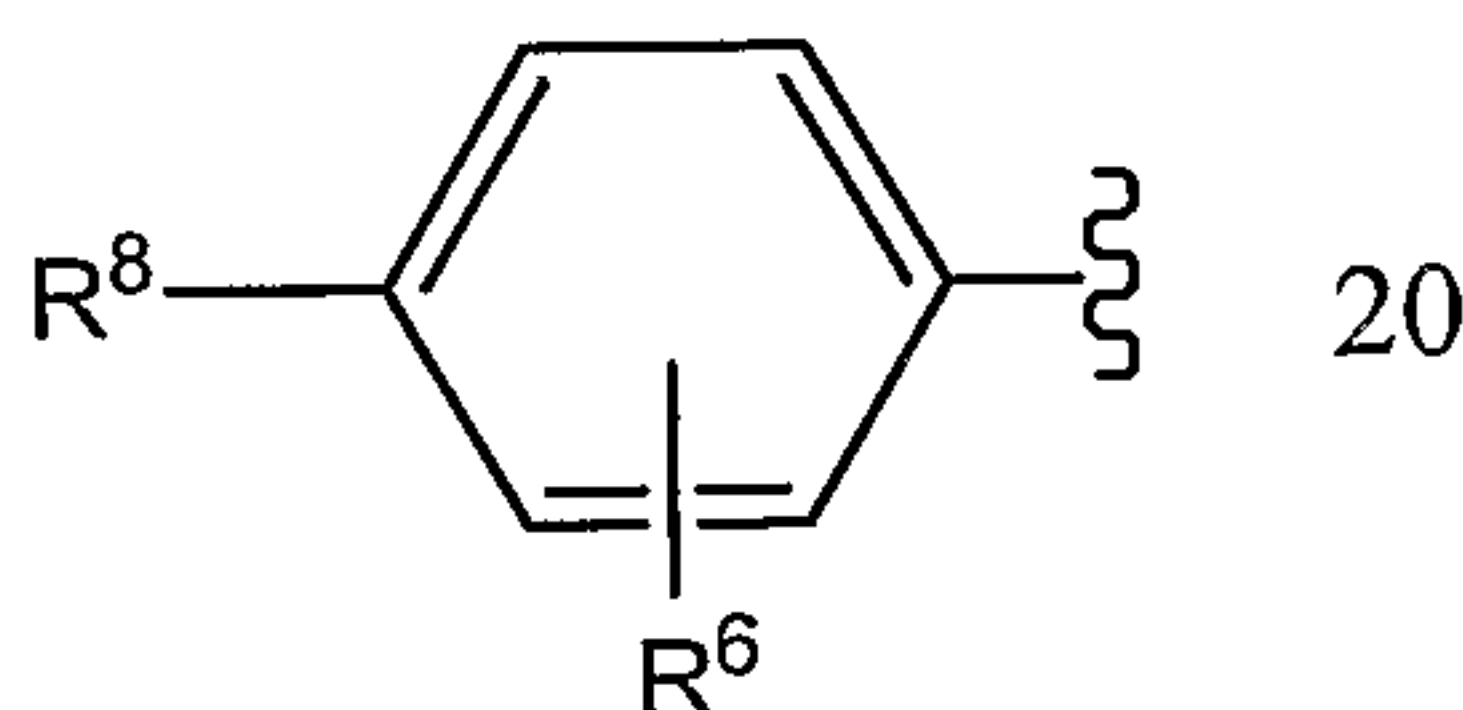
10. A method of treatment of a disorder or condition selected from the group consisting of depression, mood disorders, schizophrenia, anxiety disorders, Alzheimer's disease, attention-deficit hyperactivity disorder (ADHD), psychotic disorders, sleep disorders, obesity, dizziness, epilepsy, motion sickness, respiratory diseases, allergy, allergy-induced
 5 airway responses, allergic rhinitis, nasal congestion, allergic congestion, congestion, hypotension, cardiovascular disease, diseases of the GI tract, hyper and hypo motility and acidic secretion of the gastro-intestinal tract, the method comprising administering to a mammal in need of such treatment a compound of formula I as described in Claim 1.

11. A composition comprising a compound of formula I as defined in claim 1, a
 10 neurotransmitter re-uptake blocker selected from the group consisting of serotonin re-uptake inhibitors, dopamine reuptake inhibitors, and norepinephrine reuptake inhibitors, and optionally a pharmaceutically acceptable carrier.

12. A process for the preparation of a compound according to formula I in claim 1, wherein R^{10} is OH, and wherein the process comprises the step of reacting a compound of
 15 the formula 4

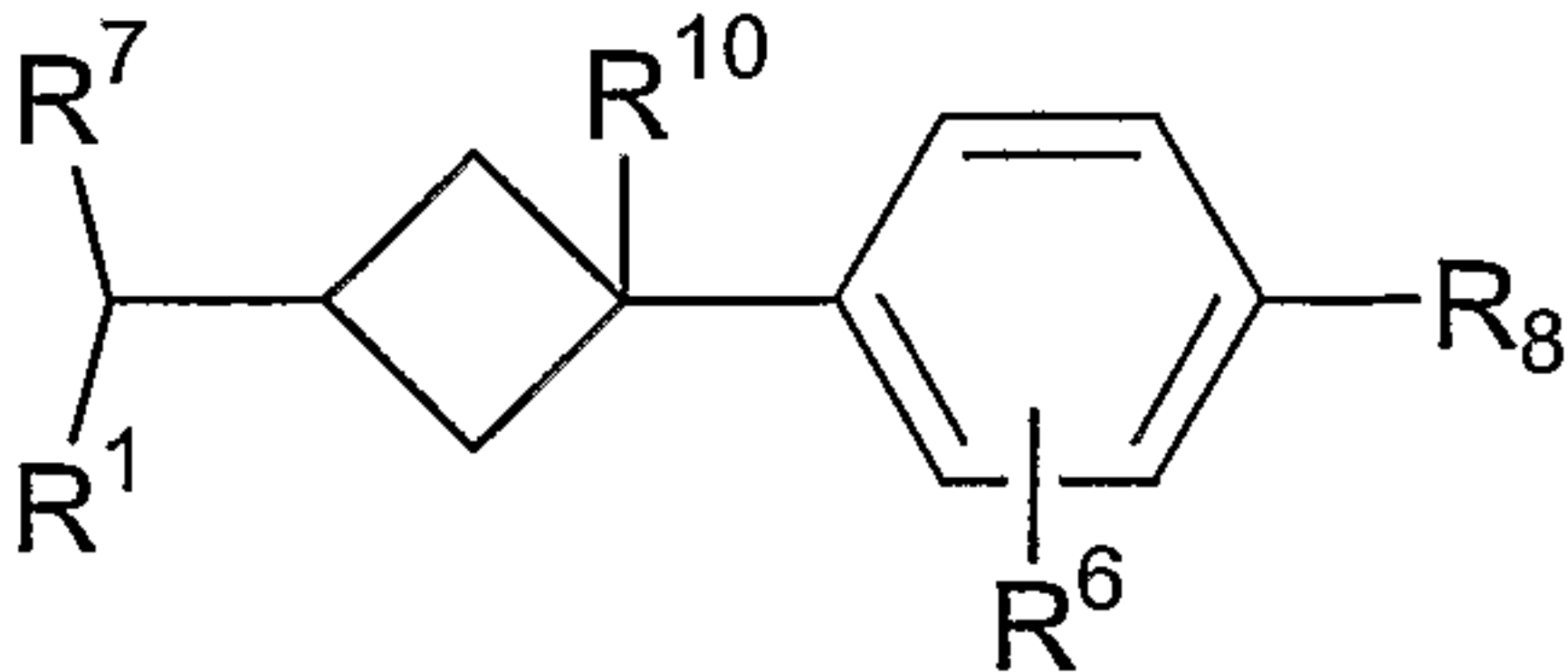


wherein R^1 is OR^4 or NR^2R^3 , with an aryl halide, wherein the aryl group of the aryl halide has
 of the formula 20



20 in the presence of an organometallic reagent.

13. A composition comprising a compound of formula I as defined in claim 1, a histamine H_1 antagonist, and optionally a pharmaceutically acceptable carrier.



(I)