

US00RE46117E

(19) **United States**
 (12) **Reissued Patent**
 Sonesson et al.

(10) **Patent Number:** **US RE46,117 E**
 (45) **Date of Reissued Patent:** **Aug. 23, 2016**

(54) **MODULATORS OF DOPAMINE
 NEUROTRANSMISSION**

(71) Applicant: **Teva Pharmaceuticals International
 GmbH, Jona (CH)**

(72) Inventors: **Clas Sonesson, Billdal (SE); Bengt
 Andersson, Göteborg (SE); Susanna
 Waters, Göteborg (SE); Nicholas
 Waters, Göteborg (SE); Joakim
 Tedroff, Danderyd (SE)**

(73) Assignee: **TEVA PHARMACEUTICALS
 INTERNATIONAL GMBH, Jona (CH)**

(21) Appl. No.: **14/693,783**

(22) Filed: **Apr. 22, 2015**

Related U.S. Patent Documents

Reissue of:

(64) Patent No.: **6,903,120**
 Issued: **Jun. 7, 2005**
 Appl. No.: **10/168,173**
 PCT Filed: **Dec. 22, 2000**
 PCT No.: **PCT/SE00/02674**
 § 371 (c)(1),
 (2) Date: **Nov. 21, 2002**
 PCT Pub. No.: **WO01/46145**
 PCT Pub. Date: **Jun. 28, 2001**

(30) **Foreign Application Priority Data**

Dec. 22, 1999 (SE) 9904724

(51) **Int. Cl.**

C07D 211/22 (2006.01)
C07D 405/00 (2006.01)
C07D 211/20 (2006.01)
C07D 211/32 (2006.01)
C07D 405/06 (2006.01)
C07D 211/34 (2006.01)
C07D 211/18 (2006.01)
C07D 295/155 (2006.01)
C07D 211/24 (2006.01)
C07D 211/70 (2006.01)
C07D 211/00 (2006.01)
C07D 295/073 (2006.01)
C07D 295/096 (2006.01)
C07D 295/112 (2006.01)

(52) **U.S. Cl.**

CPC **C07D 295/073** (2013.01); **C07D 211/18**
 (2013.01); **C07D 211/20** (2013.01); **C07D**
211/22 (2013.01); **C07D 211/24** (2013.01);
C07D 211/32 (2013.01); **C07D 211/34**
 (2013.01); **C07D 211/70** (2013.01); **C07D**
295/096 (2013.01); **C07D 295/112** (2013.01);
C07D 295/155 (2013.01); **C07D 405/06**
 (2013.01)

(58) **Field of Classification Search**

CPC **C07D 211/18**
 USPC **514/331**
 See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

3,326,916 A 6/1967 Creighton
 3,458,521 A 7/1969 Jack et al.

(Continued)

FOREIGN PATENT DOCUMENTS

BG 64315 12/1998
 EP 0 060 179 A1 2/1982

(Continued)

OTHER PUBLICATIONS

Substances in GB 1464525 (De 2502119).

Altomare et al., "Quantitative Structure-Metabolism Relationship Analyses of MAO-Mediated Toxication of 1-Methyl-4-phenyl-1, 2,3,6-tetrahydropyridine and Analogues" Chem. Res. Toxicol. 1992, 5, 366-375.

Amos D. Korczyn: "Parkinson's Disease", Tel Aviv University, Rama Aviv, Israel; Chapter 126; 1995 <http://www.acnp.org/94/GN401000142/Default.htm>.

Berberian, et al., "Comparison of Schistosomicidal Activity of Xanthenones and 4-Methyl-3-chloroanilines and Their Hydroxymethyl Analogs in Swiss Mice and Syrian Hamsters Infected with Schistosoma mansoni", Jpurnal of Medicinal Chemistry, Jul. 1969, pp. 607-610, vol. 12, No. 4, American Chemical Society, Washington, DC.

Bergel et al., 1944, pp. 261 to 264. Beilstein Registry No. 183878 and 206256; Beilstein Institute for Organic Chemistry, Germany.

Beugelmans, et al., "Synthèse d'heterocycles à 5 et 6 chaînons par une stratégie combinant des réactions SNAr et SRN1", Bull Soc Chim Fr., 1995, pp. 306-313, vol. 132, Elsevier, Paris, FR.

(Continued)

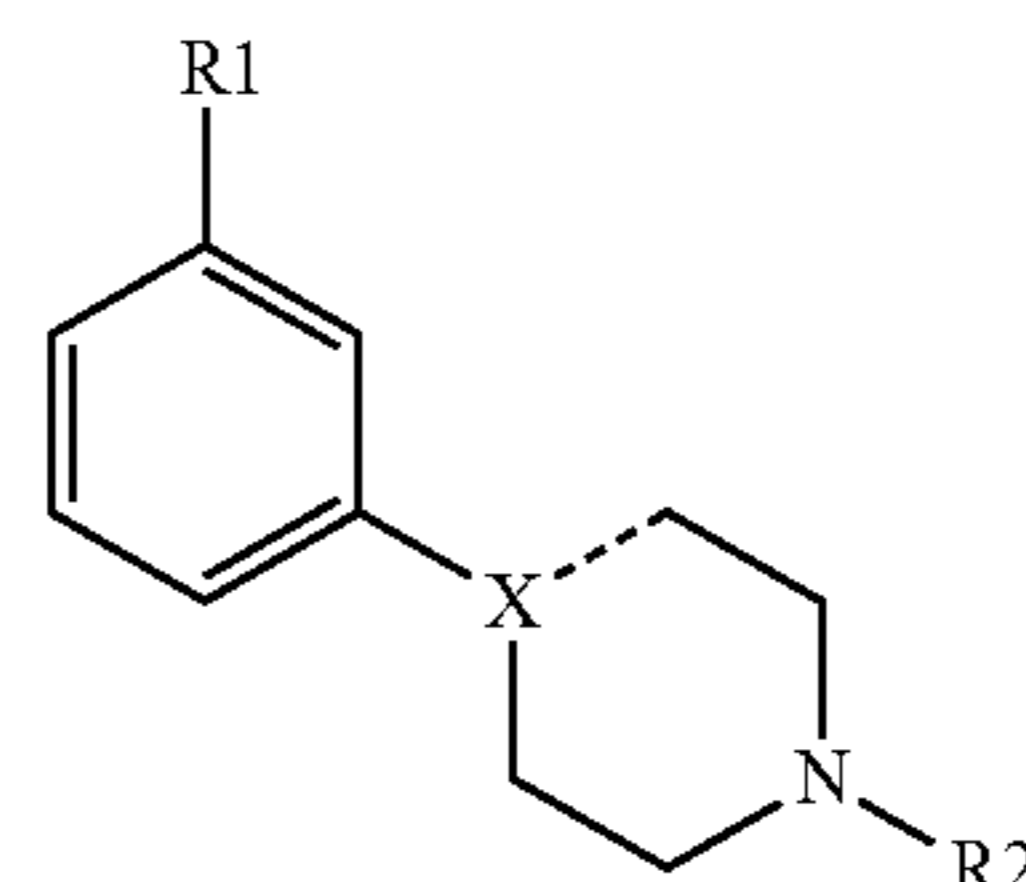
Primary Examiner — Shri Ponnaluri

(74) *Attorney, Agent, or Firm* — John P. White; Gary J. Gershik; Cooper & Dunham LLP

(57) **ABSTRACT**

New 3-substituted 4-(phenyl-N-alkyl)-piperazine and 4-(phenyl-N-alkyl)-piperidine compounds of Formula (1), wherein X N, CH, or C, however X may only be C when the compound comprises a double bond at the dotted line; R₁ is OSO₂CF₃, OSO₂CH₃, SOR₃, SO₂R₃, COR₃, NO₂, or CONHR₃ and when X is CH or C R₁ may also be CF₃, CN, F, Cl, Br, or I; R₂ is a C₁-C₄ alkyl, an allyl, CH₂SCH₃, CH₂CH₂OCH₃, CH₂CH₂CH₂F, CH₂CF₃, 3,3,3-trifluoropropyl, 4,4,4-trifluorobutyl, or —(CH₂)—R₄; R₃ is a C₁-C₃ alkyl CF₃, or N(R₂)₂; R₄ is a C₃-C₆ cycloalkyl, 2-tetrahydrofuran or 3-tetrahydrofuran, as well as pharmaceutically acceptable salts thereof are disclosed. Also pharmaceutical compositions comprising the above compounds and methods wherein the above compounds are used for treatment of disorders in the central nervous system are disclosed

(1)



39 Claims, No Drawings

(56)

References Cited

U.S. PATENT DOCUMENTS

3,539,573	A	11/1970	Schmutz et al.
4,048,314	A	9/1977	Kubela et al.
4,202,898	A	5/1980	Depoortere
4,267,328	A	5/1981	Najer et al.
4,333,942	A	6/1982	Eistetter et al.
4,415,736	A	11/1983	Ciganek et al.
4,485,109	A	11/1984	Ciganek et al.
4,504,660	A	3/1985	Klaubert et al.
4,699,910	A	10/1987	Banholzer et al.
5,462,947	A	10/1995	Andersson et al.
5,502,050	A	3/1996	Gross
6,057,371	A	5/2000	Glennon
6,121,259	A	9/2000	Yelle et al.
6,159,979	A	12/2000	Gaster et al.
6,175,015	B1	1/2001	Yuan et al.
6,653,325	B2	11/2003	Svensson
6,670,378	B2	12/2003	Svensson et al.
6,924,374	B2	8/2005	Sonesson et al.
7,417,043	B2	8/2008	Sonesson et al.
RE41,315	E	5/2010	Sonesson et al.
7,763,639	B2	7/2010	Sonesson et al.
7,923,459	B2	4/2011	Gauthier et al.
9,006,445	B2	4/2015	Sonesson et al.
9,012,476	B2	4/2015	Zimmermann et al.
9,139,525	B2	9/2015	Wikström
2003/0004169	A1	1/2003	Sonesson et al.
2003/0109532	A1	6/2003	Sonesson et al.
2007/0149542	A1	6/2007	Sonesson et al.
2007/0238878	A1	10/2007	Desmond et al.
2010/0105736	A1	4/2010	Wikström
2010/0197712	A1	8/2010	Carlsson et al.
2011/0206782	A1	8/2011	Zhang et al.
2013/0150406	A1	6/2013	Zimmermann et al.
2013/0197031	A1	8/2013	Sonesson
2013/0267552	A1	10/2013	Waters et al.
2014/0088140	A1	3/2014	Hayden
2014/0088145	A1	3/2014	Hayden
2014/0315951	A1	10/2014	Sonesson et al.
2014/0378508	A1	12/2014	Merav Bassan et al.
2015/0202302	A1	7/2015	Licht et al.
2015/0209346	A1	7/2015	Hayden
2015/0216850	A1	8/2015	Hayden
2015/0374677	A1	12/2015	Schmidt et al.

FOREIGN PATENT DOCUMENTS

EP	0060179	A1	9/1982
EP	0094159	A1	11/1983
EP	0 369 887		5/1990
EP	0369887	A2	5/1990
EP	0 533 267	A1	9/1992
EP	0533266	A1	3/1993
EP	0533267	A1	3/1993
EP	0533268	A1	3/1993
EP	0661266	A1	7/1995
EP	0675118	A2	10/1995
EP	0867183	A1	9/1998
EP	1295873		3/2003
EP	1419773	A2	5/2004
EP	2030619	A1	3/2009
FR	1459013		11/1966
GB	850662		10/1960
GB	1060160		3/1967
GB	1464525		2/1977
GB	1 560 271		2/1980
GB	2 027 703		2/1980
GB	1539/77		2/1980
GB	1560271	*	2/1980
GB	2027703		2/1980
GB	2078746		1/1982
GB	2083476	A	3/1982
JP	55-22690		7/1979
JP	6-509069		10/1994
JP	5-503517		9/1998

NL	6510107	*	2/1966
RU	2140920		12/1995
WO	WO 89/05799		6/1989
WO	WO89/05799	A1	6/1989
WO	WO 91/09594		7/1991
WO	92/18475	A2	10/1992
WO	WO 93/00313		1/1993
WO	WO 93/04684		3/1993
WO	WO 95/11880		5/1995
WO	WO 95/17385		6/1995
WO	WO 95/33729		12/1995
WO	WO 97/03986		2/1997
WO	WO 97/23216		7/1997
WO	WO 98/11068		3/1998
WO	WO 98/56787		12/1998
WO	WO 99/03470		1/1999
WO	WO 00/03713		1/2000
WO	WO 00/03714		1/2000
WO	WO 00/78728		12/2000
WO	WO00/78728	A1	12/2000
WO	WO 01/81343		11/2001
WO	WO 01/96301		12/2001
WO	WO 02/05819		1/2002
WO	WO 02/13807		2/2002
WO	WO 02/36071		5/2002
WO	WO 02/36123		5/2002
WO	WO 02/56745		7/2002
WO	WO 02/059108		8/2002
WO	WO 2004/099150	A2	11/2004
WO	WO 2005/019215	A1	3/2005
WO	WO 2005/121092	A1	12/2005
WO	WO 2006/034441		3/2006
WO	WO 2007/076875		7/2007
WO	WO 2008/075070		6/2008
WO	WO 2008/148840		12/2008
WO	WO 2008/148849		12/2008
WO	WO 2008/148851		12/2008
WO	WO 2008/148868		12/2008
WO	WO 2011/107583	A1	9/2011
WO	WO 2011/145669		11/2011
WO	WO 2012/028635		3/2012
WO	WO 2012/039660		3/2012
WO	WO 2012/146936		11/2012
WO	WO 2013/038259	A1	3/2013
WO	WO 2014/134127		9/2014
WO	WO 2014/165827		10/2014

OTHER PUBLICATIONS

"Biologic Test Methods", Burger's Medicinal Chemistry, Fourth Edition, Part III, Edited by Manfred E. Wolff, pp. 872-873, John Wiley & Sons, NY, USA.

Bloom et al. (Editors), "Psychopharmacology—The Fourth Generatic of Progress", Chapter 149, Pharmacotherapy of Alcoholism, pp. 1745-1752, Chapter 25, pp. 283, 292, Chapter 120, pp. 1417, 1420, chapter 123, pp. 1447, 1452, 1455-1457, chapter 142, pp. 1653, 1661, chapter 141, pp. 1643, 1649, 1650, chapter 54, pp. 743.

Bray, George A.; "Obesity, Fat Intake, and Chronic Disease"; Pennington Biomedical Research Center, Louisiana State University, Baton Rouge, Louisiana; Chapter 137; 1995 <http://www.acnp.org/g4/GN401000154/Default.htm>.

Bunney et al., "Schizophrenia and Glutamate"; Department of Pharmacology, University of Goteborg, Goteborg, Sweden; Chapter 101, 1995 <http://www.acnp.org/g4/GN401000116/Default.htm>.

Calligaro et al. "The synthesis and biological activity of some known and putative metabolites of the atypical antipsychotic agent olanzapine," Bioorganic and Medicinal Chemistry Letters, vol. 7, No. 1, Jan. 7, 1997, pp. 25-30(6).

Dorwald "Side Reaction in Organic Synthesis" p. ix (2005).

Egawa, et al., "A New Synthesis of 7H-Pyrido[1,2,3-de][1,4]benzoxazine Derivatives Including an Antibacterial Agent, Ofloxacin1", Chemical & Pharmaceutical Bulletin, Oct. 1986, pp. 4098-4102, vol. 34, No. 10, Pharmaceutical Society of Japan, Tokyo, JP.

Elslager, et al., "Folate Antagonists. 3. 2,4-Diamino-6-(heterocyclic)quinazolines, a Novel Class of Antimetabolites with

(56)

References Cited

OTHER PUBLICATIONS

Potent Antimalarial and Antibacterial Activity", *Journal of Medicinal Chemistry*, 1972, pp. 827-836, vol. 15, No. 8, American Chemical Society, Washington, DC.

Feldman et al. (Editors) "Principles of Neuropsychopharmacology", Chapter 17—Mind Altering Drugs, (1997), pp. 731, 762, 763, Sinauer Associates, Inc., Publishers, Sunderland, Massachusetts, USA.

Geyer et al., "Animal Models of Psychiatric Disorders" Department of Neuropharmacology, The Scripps Research Institute, La Jolla, California; Chapter 68, 1995.1.

Gressner et al. "Synthesis and Dihydropteridine Reductase Inhibitory Effects of Potential Metabolites of the Neurotoxin 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine" *J. Med. Chem.* 1985, 28, 311-317.

Halmi, Katherine A. "Basic Biological Overview of Eating Disorders"; Cornell Medical Center—Westchester Division, White Plains, New York; Chapter 138; 1995 <http://www.acnp.org/g4/GB401000155/Default.htm>.

Henry, "A Facile Synthesis of Piperazines from Primary Amines (1)", *Journal of Heterocyclic Chemistry*, 1966, pp. 503-511, vol. 3, No. 4, Heterocorporation, USA.

Katritzky et al. (1971) Abstract "Conformational Analysis of Saturated Heterocycles" CA75:48309 (1971).

Koob, George F. "Animal Models of Drug Addiction"; Department of Neuropharmacology, The Scripps Research Institute, Lo Jolla, California; Chapter 66, pp. 759, 745-746, 760, 744 and 1725, 1995 <http://www.acnp.org/g4/GN401000072/Default.htm>.

Manoury, et al., "Synthesis and Analgesic Activities of Some (4-Substituted phenyl-1-piperazinyl)alkyl 2-Aminobenzoates and 2-Aminocotinates", *Journal of Medicinal Chemistry*, 1979, pp. 554-559, vol. 22, No. 5, American Chemical Society, Washington, DC.

Meal, Michel Le, "Mesocorticolimbic Dopaminergic Neurons Functional and Regulatory Roles"; Universite de Bordeaux, Bordeaux, France; Chapter 25, pp. 283 and 292, 1995, <http://www.acnp.org/g4/GN401000025/Default.htm>.

Moore et al., "Dopaminergic Neuronal Systems in the Hypothalamus"; Department of Pharmacology and Toxicology, Michigan State University, East Lansing, Michigan; Chapter 22; 1995. <http://www.acnp.org/g4/GN401000022/CH.html>.

Price et al., "Pharmacological Challenges in Anxiety Disorders"; University of Florida College of Medicine, Gainesville, Florida; Chapter 111; 1995 <http://www.acnp.org/g4/GN401000126/Default.htm>.

Rajsner et al., "4,4-Bis(4-Fluorophenyl)Butylamines and Their Cyclic Analogues; an Efficient synthesis of the Neuroleptic Penfluridol," *Collection of Czechoslovak Chemical Communications*, 1978, 43(7), pp. 1760-1777.

Rosenfeld et al., "Gas chromatographic method for analysis of butyrophenones based on the Hofmann degradation reaction" STN Accession No. 1977:60610, Abstract of *Journal of Chromatography* (1976), 129.

Roth et al., "Biochemical Pharmacology of Midbrain Dopamine Neurons"; Chapter 21; Yale University of Medicine; New Haven, CT; 1995. <http://www.acnp.org/g4/GN401000021/Default.htm>.

Sanner "Selective dopamine D4 receptor antagonists" *Exp. Opino Ther. Patents* vol. 8(4) p. 383-393 (1998).

Seeman, Philip, "Dopamine Receptors Clinical Correlates"; Department of Pharmacology and Psychiatry, University of Toronto, Toronto, Ontario, Canada; Chapter 26, pp. 295-301, 1995. <http://www.acnp.org/g4/GN401000027/Default.htm>.

Weber et al., "1,3-Di(2-[5-3H]tolyl)guanidine: A selective ligand that labels σ -type receptors for psychotomimetic opiates and antipsychotic drugs" *Proc. Natl. Acad. Sci. USA* vol. 83, pp. 8784-8788, Nov. 1986 *Neurobiology*.

Yasou Oshiro et al., "Novel Antipsychotic Agents with Dopamine Autoreceptor Agonist Properties: Synthesis and Pharmacology of 7-[4-(4-Phenyl-1-piperazinyl)butoxy]-3,4-dihydro-2(1H)-quinolinone Derivatives" *J. Med. Chem.* 1995, 41, 658-667.

U.S. Appl. No. 10/168,297, Sonesson et al.

DN 65:38471 Feb. 1966 (also cited as NL 6510107, published Feb. 1966).

Joseph Coyle et al. *Alzheimer's Disease: A Disorder of Cortical Cholinergic Innervation Science* vol. 219 Mar. 11, 1983: 1184-1190.

Grunblatt et al (PubMed Abstract 10335493) *J Neural Transm Suppl.* 1999; 55:57-70. "Potent neuroprotective and antioxidant activity of apomorphine in MPTP and 6-hydroxydopamine induced neurotoxicity."

Grunblatt et al (PubMed Abstract 10863545) *Ann N Y Acad Sci.* 2000;899:262-73. "Neuroprotective strategies in Parkinson's disease using the models of 6-hydroxydopamine and MPTP."

Chemical Abstract CA 132:35590. "Synthesis of piperidine analogs of 1-(3-chlorophenyl)piperazine, a well known serotonin ligand." Radl et al., *Journal of Heterocyclic Chemistry* (1999), 36(4), pp. 1017-1022.

Chemical Abstract CA 116:250000. "Quantitative structure-metabolism relationship analyses of MAO-mediated toxication of 1-methyl-4-phenyl-1,2,3,5-tetrahydropyridine and analogs." Altomare et al., *Chemical Research in Toxicology* (1992), 5(3), pp. 366-375.

Carlsson et al., "Interactions Between Glutamatergic and Monoaminergic Systems within the Basal Ganglia—Implications for Schizophrenia and Parkinson's Disease", *TINS*, (1990), pp. 272-276, vol. 13, No. 7, Elsevier Science Publishers Ltd., United Kingdom.

Bloom et al. (Editors), "Psychopharmacology—The Fourth Generation of Progress", Chapter 21, pp. 227, 237, Chapter 22, pp. 245, 254, Chapter 25, pp. 283, 292, Chapter 26, pp. 295-301, Chapter 66, pp. 759-760, 1725, 744-746, Chapter 68, pp. 787, 793-795, Chapter 80, pp. 921-925, 927-928, Chapter 101, pp. 1205, 1207-1209, Chapter 111, pp. 1311, 1317, 1318, 1320, Chapter 126, pp. 1479-1482, Chapter 137, pp. 1591, 1600, Chapter 138, pp. 1609-1610, 1612, (1995), Raven Press, New York, New York, USA.

Gesner et al., *J Med Chem.* Mar. 1985;28(3):311-7. Synthesis and dihydropteridine reductase inhibitory effects of potential metabolites of the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine.

Klaubert, et al., "N-(Aminophenyl)oxamic Acids and Esters a Potent, Orally Active Antiallergy Agent", *J. Med. Chem.*, 1981, p. 742-748, vol. 24, American Chemical Society, Washington, DC.

Morita, et al., "Practical Application of the Palladium-catalyzed Amination in Phenylpiperazine Synthesis: An Efficient Synthesis of a Metabolite of the Antipsychotic Agent Aripiprazole", *Tetrahedron*, May 7, 1998, pp. 4811-4818, vol. 54, No. 19, Pergamon, Elsevier Science Ltd., Oxford, England & NY, US.

Nacci et al. "Antiblastic Substances, LII. Tylophorine Analogs. 1. Synthesis and Cytostotic and Cytotoxic Activity of 3-(3,4-dimethoxyphenyl)piperidine", *Farmaco, Edizione Scientifica*, vol. 328, No. 5, 1973, pp. 399-419.

Oshiro, Yasou et al., "Novel Antipsychotic Agents with Dopamine Autoreceptor Agonist Properties: Synthesis and Pharmacology of 7-[4-(4-Phenyl-1-piperazinyl)butoxy]-3,4-dihydro-2(1H)-quinolinone Derivatives", *J. Med. Chem.*, 1998, pp. 658-667, vol. 41, American Chemical Society, Washington, DC.

Self, et al., "cine and tele Substitutions in the Reaction of 2,3-Dinitroaniline with Secondary Amines", *J.C.S. Chem. Comm.*, 1980, pp. 281-282, Royal Society of Chemistry, UK.

Smaill, et al., "Mono- and difunctional nitrogen mustard analogues of the DNA minor groove binder pibenzimol. Synthesis, cytotoxicity and interaction with DNA", *Anti-Cancer Drug Design*, 1998, pp. 221-242, vol. 13, Oxford University Press.

Takai, et al., "Reaction of Spiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-one Derivatives and Related Compounds with Phosphorus Oxychloride", *Chemical & Pharmaceutical Bulletin.*, May 1986, pp. 1901-1906, vol. 34, No. 5, Pharmaceutical Society of Japan, Tokyo, JP.

Zhang, et al., "Studies on antimalarials. III. Synthesis and antimalarial effects of some derivatives of 2,4-diamino-6-substituted piperazinylquinazolines", *Acta Pharmaceutica Sinica*, Jun. 1981, pp. 415-424, vol. 16, No. 6, Shanghai Inst. Pharm. Ind. Res., Shanghai, Peop. Rep. of China.

International Preliminary Examination Report including an International Search of the International Preliminary Examining Authority, completed Mar. 21, 2002, in connection with PCT International Application No. PCT/SE00/02674, filed Dec. 22, 2000.

(56)

References Cited

OTHER PUBLICATIONS

- European Search Report for European Patent Application No. 03027034.2 (European Publication No. 1419773 A3).
- Jul. 26, 2005 Office Action in connection with U.S. Appl. No. 11/016,967.
- Aug. 23, 2005 Response to Jul. 26, 2005 Office Action in connection with U.S. Appl. No. 11/016,967.
- Dec. 7, 2005 Office Action in connection with U.S. Appl. No. 11/016,967.
- Apr. 7, 2006 Response to Dec. 7, 2005 Office Action in connection with U.S. Appl. No. 11/016,967.
- Jun. 28, 2006 Office Action in connection with U.S. Appl. No. 11/016,967.
- Sep. 27, 2006 Response to Jun. 28, 2006 Office Action in connection with U.S. Appl. No. 11/016,967.
- Aug. 9, 2007 Office Action in connection with U.S. Appl. No. 11/016,967.
- Jan. 9, 2008 Response to Aug. 9, 2007 Office Action in connection with U.S. Appl. No. 11/016,967.
- Office Action issued Apr. 28, 2003 in connection with European Patent Application No. 00 989162.3-2101.
- Nov. 6, 2003 response to Office Action issued Apr. 28, 2003 in connection with European Patent Application No. 00 989162.3-2101.
- Citation of Prior Art under 37 C.F.R. §1.501, including Jul. 12, 2006 Korean Official Action issued in Korean Application No. 2005-7024520.
- Office Action issued Oct. 18, 2004 in connection with European Patent Application No. 00 989162.3-2101.
- Oct. 23, 2007 Office Action issued in connection with Canadian Patent No. 2,394,602.
- Apr. 23, 2008 Response to Oct. 23, 2007 Office Action issued in connection with Canadian Patent No. 2,394,602.
- English language translation of Apr. 8, 2009 Office Action issued in connection with Bulgarian Patent Application No. 106841.
- Jun. 25, 2009 Response to Apr. 8, 2009 Office Action issued in connection with Bulgarian Patent Application No. 106841.
- English language translation of First Office Action issued in connection with Brazilian Patent Application No. PI0016611-1, received Apr. 16, 2010.
- Jun. 18, 2010 Response to First Office Action issued in connection with Brazilian Patent Application No. PI0016611-1.
- Nov. 5, 2010 Official Action issued by the Mexican Patent Office in connection with Mexican Patent Application No. PA/A/2005011920.
- Jan. 11, 2011 Response to Nov. 5, 2010 Official Action issued by the Mexican Patent Office in connection with Mexican Patent Application No. PA/A/2005011920.
- Feb. 3, 2009 Office Action issued by the Russian Patent Office in connection with Russian Patent Application No. 2005117612.
- Response to Feb. 3, 2009 Office Action issued by the Russian Patent Office in connection with Russian Patent Application No. 2005117612.
- Aug. 31, 2009 Office Action issued in connection with Bulgarian Patent Application No. 110211 (including English language translation).
- Sep. 30, 2008 Office Action issued in connection with Croatian Patent Application No. P 2005 0784A (including English language translation).
- Dec. 2, 2008 Response to Sep. 30, 2008 Office Action issued in connection with Croatian Patent Application No. P 2005 0784A.
- Jun. 2, 2009 Search Report issued by the European Patent Office in connection with European Patent Application No. 03027033.4.
- Jan. 13, 2010 Official Action issued by the European Patent Office in connection with European Patent Application No. 03027033.4.
- May 7, 2010 Response to Jan. 13, 2010 Official Action issued by the European Patent Office in connection with European Patent Application No. 03027033.4.
- Office Action in connection with Japanese Patent Application No. 2001-547056 with response initially due May 24, 2011 (including English language translation).
- Oct. 19, 2011 Office Action in connection with Japanese Patent Application No. 2001-547056 (including English language translation).
- Feb. 21, 2012 Response to Oct. 19, 2011 Office Action in connection with Japanese Patent Application No. 2001-547056.
- Apr. 12, 2013 Office Action in connection with Japanese Patent Application No. 2011-116406 (including English language translation).
- Aug. 9, 2013 Response to Apr. 12, 2013 Office Action in connection with Japanese Patent Application No. 2011-116406.
- Aug. 26, 2013 Office Action in connection with Japanese Patent Application No. 2011-116406 (including English language translation).
- Nov. 27, 2013 Response to Aug. 26, 2013 Office Action in connection with Japanese Patent Application No. 2011-116406.
- Dec. 13, 2013 Office Action in connection with Japanese Patent Application No. 2011-116406 (including English language translation).
- Mar. 12, 2015 Response to Dec. 13, 2013 Office Action in connection with Japanese Patent Application No. 2011-116406.
- Birgitta Johansson, Arvid Carlsson, Maria L. Carlsson, Magdalen Karlsson, Marie K.L. Nilsson, Elisabeth Nordquist-Brandt and Lars Rönnbäck, Placebo-controlled cross-over study of the monoaminergic stabiliser (-)-OSU6162 in mental fatigue following stroke or traumatic brain injury, *Acta Neuropsychiatrica* / vol. 24 / Issue 05 / Oct. 2012, pp. 266-274 (abstract).
- Dyhring T, Nielsen EØ, Sonesson C, Pettersson F, Karlsson J, Svensson P, Christophersen P, Waters N., The dopaminergic stabilizers pridopidine (ACR16) and (-)-OSU6162 display dopamine D(2) receptor antagonism and fast receptor dissociation properties. *Eur J Pharmacol.* Feb. 25, 2010;628(1-3):19-26 (abstract).
- Sahlholm K, Århem P, Fuxe K, Marcellino D., The dopamine stabilizers ACR16 and (-)-OSU6162 display nanomolar affinities at the σ -1 receptor. *Mol Psychiatry.* Jan. 2013;18(1):12-4.
- Rung, Johan P., et al. The dopaminergic stabilizers (-)-OSU6162 and ACR16 reverse (+)-MK-801-induced social withdrawal in rats. *Prog Neuropsychopharmacol Biol Psychiatry.* Jun. 2005; 29(5):833-9.
- Tedroff J, Ekesbo A, Sonesson C, Waters N, Carlsson A., Long-lasting improvement following (-)-OSU6162 in a patient with Huntington's disease. *Neurology.* Oct. 22, 1999;53(7):1605-6.
- Sonesson et al., "Substituted (S)-Phenylpiperidines and Rigid Congeners as Preferential Dopamine Autoreceptor Antagonists: Synthesis and Structure-Activity Relationships"; *Journal of Medicinal Chemistry*, 1994 American Chemical Society; pp. 2735-2752.
- U.S. Appl. No. 14/975,248, Unpublished, Raeann Wu et al.
- U.S. Appl. No. 15/052,368, Unpublished, Michal Geva et al.
- Rung et al. "Effects of the dopamine stabilizers (S)-(-)-OSU6162 and ACR16 on prolactin secretion in drug-naive and monoamine depleted rats." *Naunyn Schmiedebergs Arch Pharmacol.* Jul. 2011; 384(1):39-45 (abstract).
- Ponten et al. "In vivo pharmacology of the dopaminergic stabilizer pridopidine" *Eur J Pharmacol*, Oct. 10, 2010;644(1-3):88-95.
- Willner, Paul "Dopaminergic Mechanisms in Depression and Mania"; Department of Psychology, University College of Swansea, Wales, United Kingdom; Chapter 80; 1995 <http://www.acnp.org/g4/GB401000093/Default.htm>.
- U.S. Appl. No. 10/168,297, filed Nov. 20, 2002.*
- Joseph T. Coyle et al, *Science* vol. 219, 1184-1190(1983).*
- Grunblatt et al(PubMed Abstract 10335493).*
- Grunblatt et al(PubMed Abstract 10863545).*
- Chemical Abstract CA 132:35590. "Synthesis of piperidine analogs of 1-(3-chlorophenyl)piperazine, a well known serotonin ligand." Radl et al., *Journal of Heterocyclic Chemistry* (1999), 36(4), pp. 1017-1022.
- Chemical Abstract CA 116:250000. "Quantitative structure-metabolism relationship analysis of MAO-mediated toxication of 1-methyl-4-phenyl-1,2,3,5-tetrahydropyridine and analogs." Cosimo et al., *Chemical Research in Toxicology* (1992), 5(3), pp. 366-375.
- Feldman et al. (Editors), "*Principles of Neuropsychopharmacology*", Chapter 17—Mind Altering Drugs, (1997), pp. 731, 762, 763, Sinauer Associates, Inc., Publishers, Sunderland, Massachusetts, USA.

* cited by examiner

MODULATORS OF DOPAMINE NEUROTRANSMISSION

Matter enclosed in heavy brackets [] appears in the original patent but forms no part of this reissue specification; matter printed in italics indicates the additions made by reissue; a claim printed with strikethrough indicates that the claim was canceled, disclaimed, or held invalid by a prior post-patent action or proceeding.

This application is a *reissue application of U.S. Pat. No. 6,903,120, issued Jun. 7, 2005 from U.S. Ser. No. 10/168,173, filed Nov. 21, 2002, which was a §371 national stage of PCT International Application No. PCT/SE00/02674, filed Dec. 22, 2000, which claims priority of Swedish Patent Application No. 9904724-3, filed Dec. 22, 1999.*

FIELD OF THE INVENTION

The present invention relates to new modulators of dopamine neurotransmission, and more specifically to new substituted 4-(phenyl N-alkyl)-piperazines and 4-(phenyl N-alkyl)-piperidines, and use thereof.

BACKGROUND OF THE INVENTION

Dopamine is a neurotransmitter in the brain. Since this discovery, made in the 1950s, the function of dopamine in the brain has been intensely explored. To date, it is well established that dopamine is essential in several aspects of brain function including motor, cognitive, sensory, emotional and autonomous (e.g. regulation of appetite, body temperature, sleep) functions. Thus, modulation of dopaminergic function may be beneficial in the treatment of a wide range of disorders affecting brain functions. In fact, both neurologic and psychiatric disorders are treated with medications based on interactions with dopamine systems and dopamine receptors in the brain.

Drugs that act, directly or indirectly, at central dopamine receptors are commonly used in the treatment of neurologic and psychiatric disorders, e.g. Parkinson's disease and schizophrenia. Currently available dopaminergic pharmaceuticals have severe side effects, such as extrapyramidal side effects and tardive dyskinesia in dopaminergic antagonists used as antipsychotic agents, and dyskinesias and psychoses in dopaminergic agonists used as anti-Parkinson's agents. Therapeutic effects are unsatisfactory in many respects. To improve efficacy and reduce side effects of dopaminergic pharmaceuticals, novel dopamine receptor ligands with selectivity at specific dopamine receptor sub-types or regional selectivity are sought for. In this context, also partial dopamine receptor agonists, i.e. dopamine receptor ligands with some but not full intrinsic activity at dopamine receptors, are being developed to achieve an optimal degree of stimulation at dopamine receptors, avoiding excessive dopamine receptor blockade or excessive stimulation.

Compounds belonging to the class of substituted 4-(phenyl-N-alkyl)-piperazine and substituted 4-(phenyl-N-alkyl)-piperidines have been previously reported. Among these compounds, some are inactive in the CNS, some display serotonergic or mixed serotonergic/dopaminergic pharmacological profiles while some are full or partial dopamine receptor agonists or antagonists with high affinity for dopamine receptors.

A number of 4-phenylpiperazines and 4-phenylpiperidine derivatives are known and described, for example Costall et al. *European J. Pharm.* 31, 94, (1975), Mewshaw et al. *Bioorg. Med. Chem. Lett.*, 8, 295, (1998). The reported compounds are substituted 4-phenylpiperazine's, most of them being 2-, 3- or 4-OH phenyl substituted and displaying DA autoreceptor agonist properties.

Fuller R. W. et al, *J. Pharmacol. Exp. Therapeut.* 218, 636, (1981) disclose substituted piperazines (e.g. 1-(m-trifluoromethylphenyl)piperazine) which reportedly act as serotonin agonists and inhibit serotonin uptake. Fuller R. W. et al, *Res. Commun. Chem. Pathol. Pharmacol.* 17, 551, (1977) disclose the comparative effects on the 3,4-dihydroxyphenylacetic acid and *Res. Commun. Chem. Pathol. Pharmacol.* 29, 201, (1980) disclose the comparative effects on the 5-hydroxyindole acetic acid concentration in rat brain by 1-(p-chlorophenol)-piperazine.

Boissier J. et al *Chem Abstr.* 61:10691c, disclose disubstituted piperazines. The compounds are reportedly adrenolytics, antihypertensives, potentiators of barbiturates, and depressants of the central nervous system.

A number of different substituted piperazines have been published as ligands at 5-HT_{1A} receptors, for example Glennon R. A. et al *J. Med. Chem.*, 31, 1968, (1988), van Steen B. J., *J. Med. Chem.*, 36, 2751, (1993), Mokrosz, J. et al, *Arch. Pharm. (Weinheim)* 328, 143-148 (1995), and Dukat M.-L., *J. Med. Chem.*, 39, 4017, (1996). Glennon R. A. discloses, in international patent applications WO 93/00313 and WO 91/09594 various amines, among them substituted piperazines, as sigma receptor ligands. Clinical studies investigating the properties of sigma receptor ligands in schizophrenic patients have not generated evidence of antipsychotic activity, or activity in any other CNS disorder. Two of the most extensively studied selective sigma receptor antagonists, BW234U (rimcazole) and BMY14802, have both failed in clinical studies in schizophrenic patients (Borison et al, 1991, *Psychopharmacol Bull* 27(2): 103-106; Gewirtz et al, 1994, *Neuropsychopharmacology* 10:37-40).

Further, WO 93/04684 and GB 2027703 also describe specific substituted piperazines useful in the treatment of CNS disorders.

SUMMARY OF THE INVENTION

The object of the present invention is to provide new pharmaceutically active compounds, especially useful in treatment of disorders in the central nervous system, which do not have the disadvantages of the above described substances.

In the work leading to the present invention, it was found that it is desired to provide substances with specific pharmacological properties, namely substances that have modulating effects on dopamine neurotransmission. These properties have not been described earlier, and they are not possible to obtain with the earlier known compounds. The compounds according to the present invention have a very surprising and interesting dualistic dopaminergic action profile with antagonist-like effects on brain neurochemistry and mild agonist-like effects on normal behavior, but they induce inhibition of behavior in states of hyperactivity.

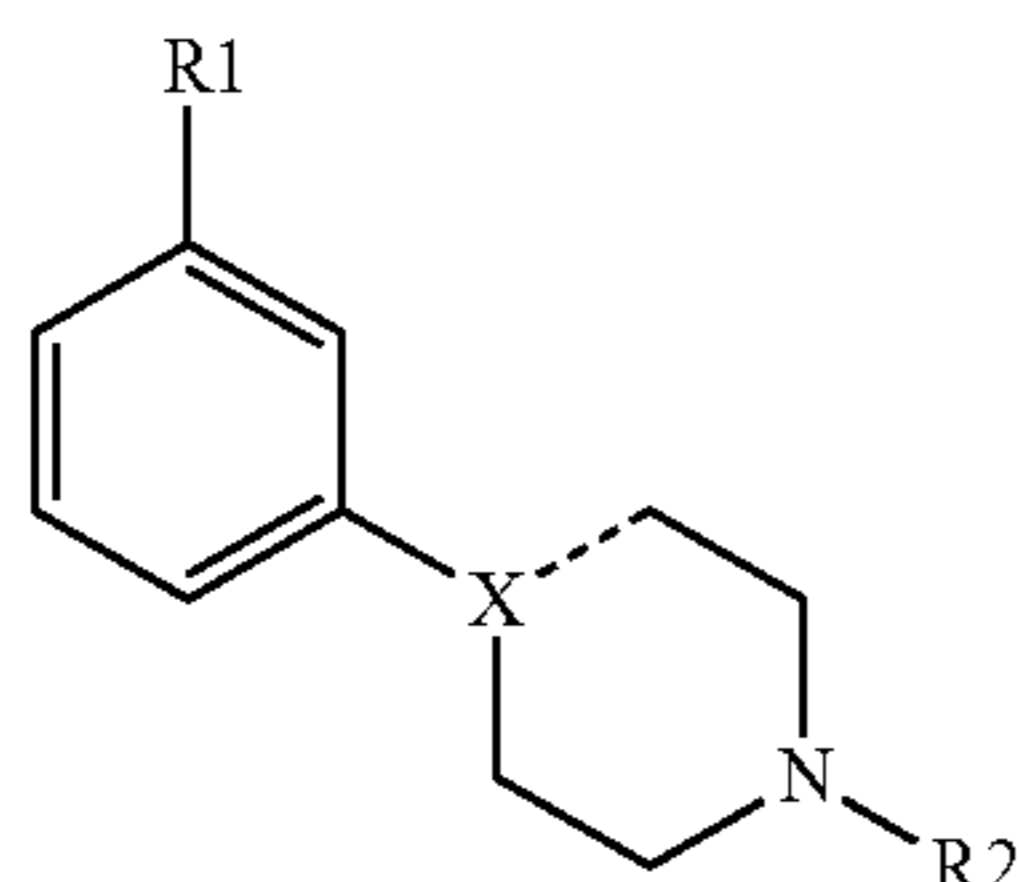
The present invention thus relates to new 3-substituted 4-(phenyl-N-alkyl) piperazines and 3-substituted 4-(phenyl-N-alkyl) piperidines in the form of free base or pharmaceutically acceptable salts thereof, pharmaceutical compositions containing said compounds and use of said compounds in therapy.

3

One subject of the invention is to provide new compounds for therapeutic use, and more precisely compounds for modulation of dopaminergic systems in the mammalian brain, including human brain.

Another subject of the invention is to provide compounds with therapeutic effects after oral-administration.

More precisely, the present invention relates to 3-substituted 4-(phenyl N-alkyl)-piperazine and 4-(phenyl-N-alkyl)-piperidine compounds of Formula 1:



and pharmaceutically acceptable salts thereof, wherein:

X is selected from the group consisting of N, CH, and C, however X may only be C when the compound comprises a double bond at the dotted line;

R₁ is selected from the group consisting of OSO₂CF₃, OSO₂CH₃, SOR₃, SO₂R₃, COR₃, NO₂, and CONHR₃, wherein R₃ is as defined below, and when X is CH or C R₁ may also be selected from the group consisting of CF₃, CN, F, Cl, Br, and I;

R₂ is selected from the group consisting of C₁-C₄ alkyls, allyls, CH₂SCH₃, CH₂CH₂OCH₃, CH₂CH₂CH₂F, CH₂CF₃, 3,3,3-trifluoropropyl, 4,4,4-trifluorobutyl, and -(CH₂)-R₄, wherein R₄ is as defined below;

R₃ is selected from the group consisting of C₁-C₃ alkyls, CF₃, and N(R₂)₂, wherein R₂ is as defined above;

R₄ is selected from the group consisting of C₃-C₆ cycloalkyls, 2-tetrahydrofuran and 3-tetrahydrofuran.

The compounds according to the present invention possess dopamine-modulating properties and are useful in treating numerous central nervous system disorders including both psychiatric and neurological symptoms.

Diseases in which compounds with modulating effects on dopaminergic systems may be beneficial are in disorders related to ageing, for preventing bradykinesia and depression and for the improvement of mental functions. They may also be used to improve cognitive functions and related emotional disturbances in neurodegenerative and developmental disorders as well as after brain damage.

The compounds according to the invention can be used to improve all symptoms of psychosis, including schizophrenia and schizophreniform disorders as well as drug induced psychotic disorders. The compounds according to the invention may also be used in behavioral disorders usually first diagnosed in infancy, childhood, or adolescence as well as in impulse control disorders. Also, speech disorders such as stuttering may improve. They may also be used for treating substance abuse disorders as well as disorders characterized by misuse of food.

Mood and anxiety disorders, personality disorders, and conversion hysteria may also be treated with the compounds according to the invention.

Neurological indications include the treatment of Huntington's disease and other movement disorders as well as movement disorders induced by drugs. Restless legs and related disorders as well as narcolepsy may also be treated with

4

compounds included according to the invention. They may also improve mental and motor function in Parkinson's disease, and in related parkinsonian syndromes. They may also be used to ameliorate tremor of different origins. They may be used in the treatment of headaches and used to improve brain function following vascular or traumatic brain injury. Moreover, they may be used to relieve pain in conditions characterized by increased muscle tone.

The compounds according to the present invention have unexpectedly been found to act specifically on dopaminergic systems in the brain. They have effects on biochemical indices in the brain with the characteristic features of selective dopamine antagonists, e.g. producing increases in concentrations of dopamine metabolites.

Yet, dopamine receptor antagonists characteristically suppress behavioral activity and induce catalepsy, while the compounds of this invention show no, or only limited, inhibitory effects on spontaneous locomotion. In contrast they may induce a slight behavioral activation with concomitant increases in small-scale movements, e.g. stops in the center of the behavior recording arena, similar to that induced by dopaminergic agonists. The behavioral activation is limited, not reaching the profound increases in activity induced by direct or indirect dopaminergic agonists. On the other hand, the preferred substances reduce the increase in activity induced by direct or indirect dopaminergic agonists, i.e. d-amphetamine and congeners.

Thus, the compounds of this invention surprisingly show an interesting dualistic dopaminergic action profile with antagonist like effects on brain neurochemistry and mild agonist like effects on normal behavior, but inhibition of behavior in states of hyperactivity. The action profile suggests modulatory effects on dopaminergic functions, clearly different from known compounds belonging to these chemical classes or effects anticipated of typical dopamine receptor antagonists or agonists from these or other chemical classes.

Given the involvement of dopamine in a large variety of CNS functions and the clinical shortcomings of presently available pharmaceuticals acting on dopamine systems, the novel class of dopaminergic modulators presented in this invention may prove superior to presently known dopaminergic compounds in the treatment of several disorders related to dysfunctions of the CNS, in terms of efficacy as well as side effects.

Some compounds according to the invention have been found to have surprisingly good pharmacokinetic properties including high oral bioavailability. They are thus suitable for the preparation of orally administered pharmaceuticals. There is no guidance in the prior art how to obtain compounds with this effect on dopamine systems in the brain.

DETAILED DESCRIPTION OF THE INVENTION

Pharmacology

Evidence is available that neurotransmission in the CNS is disturbed in psychiatric and neurologic diseases. In many instances, for example in schizophrenia or Parkinson's disease, pharmacotherapies based on antagonism or agonism at dopamine receptors are useful, but not optimal. In recent years much efforts have been put on finding novel and selective ligands for dopamine receptor subtypes (D₁, D₂, D₃, D₄, D₅) with the aim to improve efficacy and reduce side effects.

The present invention offers another principle for novel therapeutics based on interactions with dopamine systems. The compounds according to the invention have effects on brain neurochemistry similar to antagonists at dopamine D₂ receptors. In contrast to currently used dopamine receptor

5

antagonists the compounds according to the invention show no or limited inhibitory effects on spontaneous locomotion. They may induce behavioral activation with concomitant increases in small-scale movements, e.g. stops in the center of the behavior recording arena, similar to that induced by dopaminergic agonists. The behavioral activation is limited, not reaching the profound increases in activity induced by direct or indirect dopamine receptor agonists. Surprisingly, the preferred substances can actually reduce the increase in activity induced by direct or indirect dopaminergic agonists, i.e. d-amphetamine and congeners.

The preferred structures are substituted in the meta position on the aromatic ring. An example of such a compound is methanesulfonic acid 3-(1-propyl-piperidin-4-yl)-phenyl ester, which is shown in Example 14 below. In rat, this compound increases 3,4-dihydroxyphenylacetic acid in the striatum from 1265±74 (controls) to 3208±236 ng/g tissue at 50 µmol/kg s.c. in combination with a slight increase in behavioral activity; 1485±328 cm/30 min (controls) to 2126±240 cm/30 min at 50 µmol/kg s.c., n=4. Another preferred example of a compound according to the invention is 4-(3-methanesulfonyl-phenyl)-1-propyl-piperidine, further illustrated in Example 6. In rat, this compound increases 3,4-dihydroxy-phenylacetic acid in the striatum from 914±19 (controls) to 1703±19 ng/g tissue at 50 µmol/kg s.c. This increase in dopamine turnover is followed by a trend towards an increase in motor activity from 2030±299 cm/60 min to 2879±398 cm/60 min p=0.14. In animals habituated to the motilitymeter box the compound described in Example 6, 4-(3-methanesulfonyl-phenyl)-1-propyl-piperidine, increases behavioral activity from 476±279 cm/60 min (controls) to 1243±72 cm/60 min, p<0.05, n=4, and 4-dihydroxyphenylacetic acid in the striatum from 975±23 (controls) to 2074±144 ng/g tissue at 50 µmol/kg s.c., p<0.05, n=4.

In addition, the compound described in Example 6, 4-(3-methanesulfonyl-phenyl)-1-propyl-piperidine, has the preferred ability to reduce behavioral activation induced by both d-amphetamine (1.5 mg/kg s.c.) and dizolcipine (Mk-801, 0, 7 mg/kg i.p.). d-Amphetamine hyperactivity is reduced from 10694±2165 cm/60 min to 1839±344 cm/60min, p<0.05 n=4, at 50 µmol/kg s.c. of the compound described in Example 6 and behavioral activation induced by dizolcipine (Mk-801) is reduced from 32580±4303 cm/60 min to 18197±1389 cm/60 min p<0.05, at 50 µmol/kg sc. Surprisingly, the compound described in Example 6 has an oral availability (F) of 85% in rat.

Unlike the somewhat similar compounds described in WO91/09594, the compound of Example 6, 4-(3-methanesulfonyl-phenyl)-1-propyl-piperidine, lacks affinity at the sigma receptor, <50% inhibition of [³H]-DTG binding (according to a method for measurement of sigma binding described by Shirayama Y. et al., 1993, Eur. J. Pharmacol. 237, p 117) at 10 µmol/L to rat brain membranes.

In order to demonstrate the surprising effects of the compounds according to the invention, some of the compounds have been compared to similar compounds according to prior art. The compounds-used for comparison with the compounds according to the invention in the comparative examples are thus not compounds according to the invention since they do not exhibit the desired properties.

COMPARATIVE EXAMPLE 1

4-(4-methanesulphonyl-phenyl)-1-propyl piperidine illustrates that substitution in the para position yields inactive compounds. 4-(4-methanesulphonyl-phenyl)-1-propyl piperidine has no effect on 3,4-dihydroxyphenyl-acetic acid in

6

the striatum as demonstrated in the neurochemical experiment; 988±70 (controls) ng/g tissue and 928±51 ng/g tissue at 50 µmol/kg s.c. 4-(4-methanesulphonyl-phenyl)-1-propyl piperidine does not have the properties desired according to the invention.

COMPARATIVE EXAMPLE 2

To further illustrate the importance of the substitution on the aromatic ring for the desired properties, 4-phenyl-1-propyl-piperidine is demonstrated to lack activity in the behavioral assay in the non-pre-treated rat, 3661±494 cm/60 min, controls, to 2553±471 cm/60 min, p>0.05, n=4, at 33 µmol/kg and lacks effects on 3,4-dihydroxyphenyl-acetic acid in the striatum as demonstrated in the neurochemical experiment; 1027±31 (controls) ng/g tissue and 1190±70 ng/g tissue at 33 µmol/kg s.c., p>0.05., 4-phenyl-1-propyl-piperidine] also lacks the desired inhibition of behavioral activity in the d-amphetamine stimulated (17295±4738 cm/60 min, d-amphetamine, to 13764±2919 cm/60 min, n=4, p>>0.05 at 33 µmol/kg.

COMPARATIVE EXAMPLE 3

Further, 1-phenyl-4-propyl-piperazine, described as sigma receptor binding compound in WO91/09594, is found to reduce behavioral activity in the non-pre-treated animal, from 3370±227, controls, to 1923±204 cm/60 min, n=4, p<0.05 at 33 µmol/kg s.c., thus lacking the properties sought for.

COMPARATIVE EXAMPLE 4

Substitution in the ortho position as exemplified by 1-(2-methoxy-phenyl)-4-propyl piperazine yields a compound which increases 3,4-dihydroxyphenylacetic acid in the striatum from 1028±9 (controls) ng/g tissue to 3836±65 ng/g tissue at 50 µmol/kg s.c., p<0.05, n=4. This is followed by the behavioral inhibition not sought for in the present invention; 1651±300 cm/60 min (controls) to 67±34 cm/60 min, at 50 µmol/kg s.c., p<0.05, n=4.

COMPARATIVE EXAMPLE 5

The properties of the substituent in the meta position are important. 1-propyl-4-(3-trifluoro-methyl-phenyl) piperazine increases 3,4-dihydroxyphenyl-acetic acid in the striatum from 1066±46 (controls) ng/g tissue to 3358±162 ng/g tissue at 50 µmol/kg s.c., p<0.05, n=4, however, followed by behavioral inhibition from 1244±341 cm/60 min (controls) to 271±137 at 50 µmol/kg s.c., p<0.05, n=4, thus, lacking the properties sought for in the present invention.

COMPARATIVE EXAMPLE 6

Further, the compound of 3-(4-Propyl-piperazine-1-yl)-benzotrile increases 3,4-dihydroxyphenyl-acetic acid in the striatum from 1432±57 (controls) ng/g tissue to 4498±243 ng/g tissue at 100 µmol/kg s.c., p<0.05, n=4, and reduces 5-hydroxy-indole acetic acid from 630±16 (controls) ng/g tissue to 484±26 ng/g tissue at 100 µmol/kg s.c., p<0.05, n=4. These effects are followed by behavioral inhibition from 3959±688 cm/60 min (controls) to 634±266 at 100 µmol/kg s.c., p<0.05, n=4, thus, lacking the properties sought for in the present invention. 3-(4-Propyl-piperazine-1-yl)-benzotrile has the following properties: m.p. 159° C. (fumarate) MS m/z (relative intensity, 70 eV) 229 (M+, 28), 200 (bp), 157 (27), 129 (22), 70 (25).

COMPARATIVE EXAMPLE 7

Another example of the importance of the substituent is preparation 14 which has no effect on 3,4-dihydroxyphenylacetic acid in the striatum; 1121 ± 36 (controls) ng/g tissue to 1169 ± 42 ng/g tissue at $50 \mu\text{mol/kg}$ s.c.

COMPARATIVE EXAMPLE 8

The physicochemical properties of the substituent on the basic nitrogen is also important for the desired profile. It is not possible to use any substituent, which is exemplified by 1-phenethyl-4-(3-trifluoromethyl-phenyl)-piperazine described as a sigma receptor ligand in WO 91/09594 and WO 93/00313 which has some effects on 3,4-dihydroxyphenylacetic acid in the striatum; 852 ± 33 (controls) to 1406 ± 77 ng/g tissue at $50 \mu\text{mol/kg}$ s.c., $p < 0.05$, $n=4$, but also reduces both 5-hydroxyindoleacetic acid in the striatum from 358 ± 20 (controls) to 289 ± 16 ng/g tissue at $50 \mu\text{mol/kg}$ s.c., $p < 0.05$, $n=4$, and serotonin (5-HT) from 379 ± 10 (controls) to 282 ± 6 ng/g tissue at $50 \mu\text{mol/kg}$ s.c., $p < 0.05$, $n=4$, which is an undesired property according to this invention but in accordance with the reported IC_{50} of $20,3 \text{ nM}$ at the 5-HT_{1A} receptor (WO 93/00313).

COMPARATIVE EXAMPLE 9

In addition, 1-benzyl-4-(3-methanesulfonyl-phenyl)-piperidine and 3-(1-benzyl-piperidin-4-yl)-phenol, compounds with benzylic substitution on the basic nitrogen, both has the undesired property to interact with serotonin systems in the brain. 1-Benzyl-4-(3-methanesulfonyl-phenyl)-piperidine increases 5-hydroxyindoleacetic acid in the striatum from 428 ± 20 (controls) to 487 ± 7 ng/g tissue at $50 \mu\text{mol/kg}$ s.c., $p < 0.05$, $n=4$, and reduces serotonin (5-HT) from 442 ± 15 (controls) to 345 ± 18 ng/g tissue at $50 \mu\text{mol/kg}$ s.c., $p < 0.05$, $n=4$, and induces the serotonin behavioral syndrome (serotonin behavioral syndrome is e.g. described by Tricklebank et al., 1985, Eur. J. Pharmacol, 106, pp 271-282). 3-(1-Benzyl-piperidin-4-yl)-phenol has the undesired ability to increase 5-hydroxyindoleacetic acid in the striatum from 404 ± 10 (controls) to 492 ± 26 ng/g tissue at $50 \mu\text{mol/kg}$ s.c., $p < 0.05$, $n=4$, and reduces serotonin in the limbic region (5-HT) from 734 ± 8 (controls) to 677 ± 20 ng/g tissue at $50 \mu\text{mol/kg}$ s.c., $p < 0.05$, $n=4$.

COMPARATIVE EXAMPLE 10

Substitution on the basic nitrogen according to 2-[4-(3-methanesulfonyl-phenyl)-piperazin-1-yl]-ethanol] (described in GB 2027703) renders compounds which are inactive in the behavioral activity test; 3238 ± 1089 cm/60 min (controls) to 3782 ± 962 cm/60 min at $33 \mu\text{mol/kg}$ s.c., $n=4$, $p > 0.05$, as well as in the neurochemical test; effects on 3,4-dihydroxyphenylacetic acid in the striatum; 1158 ± 126 (controls) to 1239 ± 162 ng/g tissue at $33 \mu\text{mol/kg}$ s.c., $n=4$, $p > 0.05$.

The compounds according to the invention are especially suitable for treatment of disorders in the central nervous system, and particularly for treatment of dopamine mediated disorders. They may, e.g. used to ameliorate symptoms of mood disorders, in obesity as an anorectic agent and in other eating disorders, to improve cognitive functions and related emotional disturbances, to improve cognitive and motor dysfunctions associated with developmental disorders, to improve all symptoms of schizophrenia and schizophreniform disorders as well as other psychoses, to improve ongoing

ing symptoms as well as to prevent the occurrence of new psychotic episodes, to regulate pathological disorders due to intake of food, coffee, tea, tobacco, alcohol, addictive drugs etc.

The compounds according to the invention can thus be used to treat symptoms in e.g.:

schizophrenia and other psychotic disorders, such as catatonic, disorganized, paranoid, residual or differentiated schizophrenia; schizophreniform disorder; schizoaffective disorder; delusional disorder; brief psychotic disorder; shared psychotic disorder; psychotic disorder due to a general medical condition with delusions and/or hallucinations;

mood disorders, such as depressive disorders, e.g., dysthymic disorder or major depressive disorder; bipolar disorders, e.g., bipolar I disorder, bipolar II disorder, and cyclothymic disorder; mood disorder due to a general medical condition with depressive, and/or manic features; and substance-induced mood disorder;

anxiety disorders, such as acute stress disorder, agoraphobia without history of panic disorder, anxiety disorder due to general medical condition, generalized anxiety disorder, obsessive-compulsive disorder, panic disorder with agoraphobia, panic disorder without agoraphobia, posttraumatic stress disorder, specific phobia, social phobia, and substance-induced anxiety disorder;

eating disorders, such as anorexia nervosa, bulimia nervosa, and obesity;

sleep disorders, such as dyssomnias, e.g., breathing-related sleep disorder, circadian rhythm sleep disorder, hypersomnia, insomnia, narcolepsy, and "jet lag";

impulse-control disorders not elsewhere classified, such as intermittent explosive disorder, kleptomania, pathological gambling, pyromania, and trichotillomania;

personality disorders, such as paranoid, schizoid or schizotypal disorder; antisocial, borderline, histrionic, and narcissistic disorder; and avoidant, dependent, obsessive-compulsive disorder;

medication-induced movement disorders, such as neuroleptic induced parkinsonism, neuroleptic malignant syndrome, neuroleptic induced acute and tardive dyskinesia, neuroleptic induced akathisia, neuroleptic induced tardive dyskinesia, medication induced tremor, and medication induced dyskinesias;

substance-related disorders, such as abuse, dependence, anxiety disorder, intoxication, intoxication delirium, psychotic disorder, psychotic disorder with delusions, mood disorder, persisting amnesic disorder, persisting dementia, persisting perception disorder, sexual dysfunction, sleep disorder, withdrawal, and withdrawal delirium due to use or misuse of alcohol, amphetamine (or amphetamine-like substances), caffeine, cannabis, cocaine, hallucinogens, inhalants, nicotine, opioids, phencyclidine (or phencyclidine-like substances), sedative substances, hypnotic substances, and/or anxiolytic substances;

disorders usually first diagnosed in infancy, childhood, or adolescence, such as mental retardation; learning disorders; motor skills disorders, e.g. developmental coordination disorder; communication disorders, e.g. expressive language disorder, phonological disorder, receptive-expressive language disorder and stuttering; pervasive developmental disorders, e.g. Asperger's disorder, autistic disorder, childhood disintegrative disorder, and Rett's disorder; attention-deficit and disruptive behavior disorders, e.g. attention-deficit/hyperactivity disorder, conduct disorder, and oppositional defiant dis-

9

order; feeding and eating disorders of infancy or early childhood, e.g. feeding disorder of infancy or early childhood, pica, rumination disorder; tic disorders, e.g. chronic motor or vocal tic disorder, and Tourette's disorder; other disorders of infancy, childhood, or adolescence, e.g. selective mutism, and stereotypic movement disorder;

delirium, dementia, amnesic and other cognitive disorders, such as Alzheimer's, Creutzfeldt-Jakob disease, dead trauma, Huntington's disease, HIV disease, Pick's disease, and diffuse Lewy body dementia;

conversion hysteria;

conditions connected to normal aging, such as disturbances in motor functions and mental functions;

Parkinson's Disease and related disorders, such as multiple system atrophies, e.g. striatonigral degeneration, olivopontocerebellar atrophy, and shydramer syndrome; progressive supranuclear palsy; corticobasal degeneration; and vascular parkinsonism;

tremors, such as essential, orthostatic, rest, cerebellar, and secondary tremor

headaches, such as migraine, cluster headache, tension type headache, and paroxysmal headache;

movement disorders, such as dyskinesias, e.g. in general medicine condition, secondary to trauma or vascular insult, hemiballism, athetosis, Sydenham's chorea, and paroxysmal; dystonias; Ekbom's syndrome (restless legs); Wilson's Disease; Hallerworden-Spatz disease;

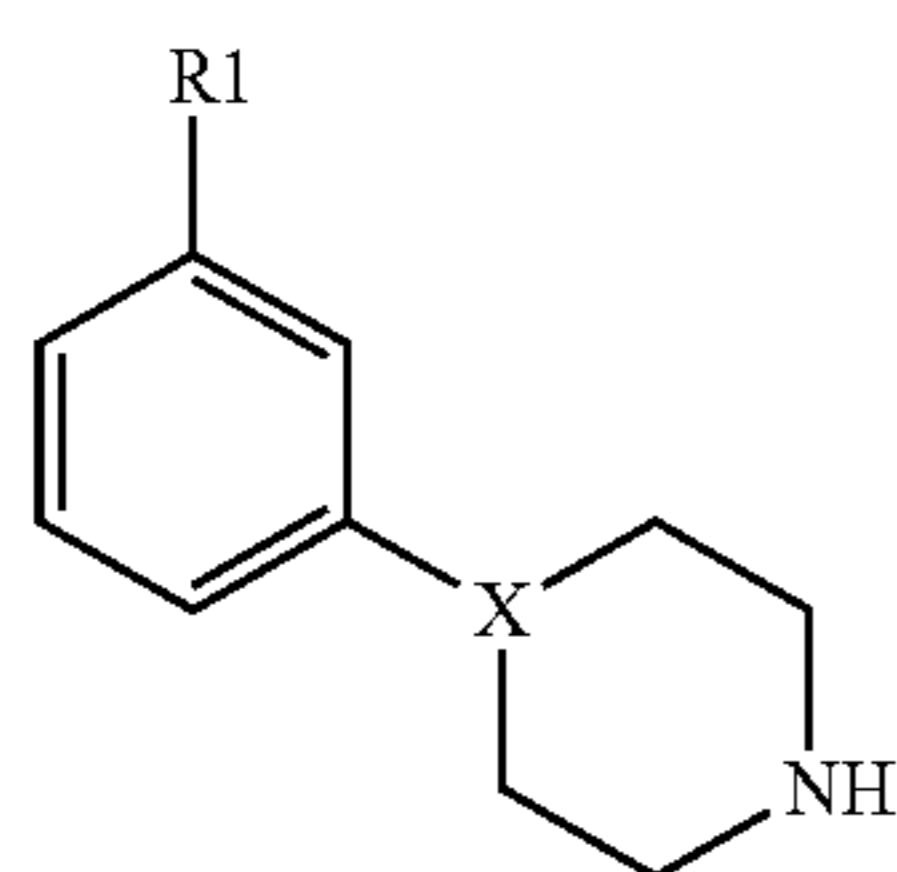
rehabilitation medicine, e.g. to improve rehabilitation after vascular or traumatic brain injury;

pain in conditions characterized by increased muscular tone, such as fibromyalgia, myofascial syndrome, dystonia, and parkinsonism; as well as

conditions related to the above that fall within the larger categories but does not meet the criteria of any specific disorder within those categories.

Synthesis

The synthesis of the present compounds is carried out by methods that are conventional for the synthesis of related known compounds. The syntheses of compounds in Formula 1, in general, comprise the reaction of an intermediate that supplies the alkyl group with an intermediate piperidine or piperazine that supplies the amine group of Formula 2:

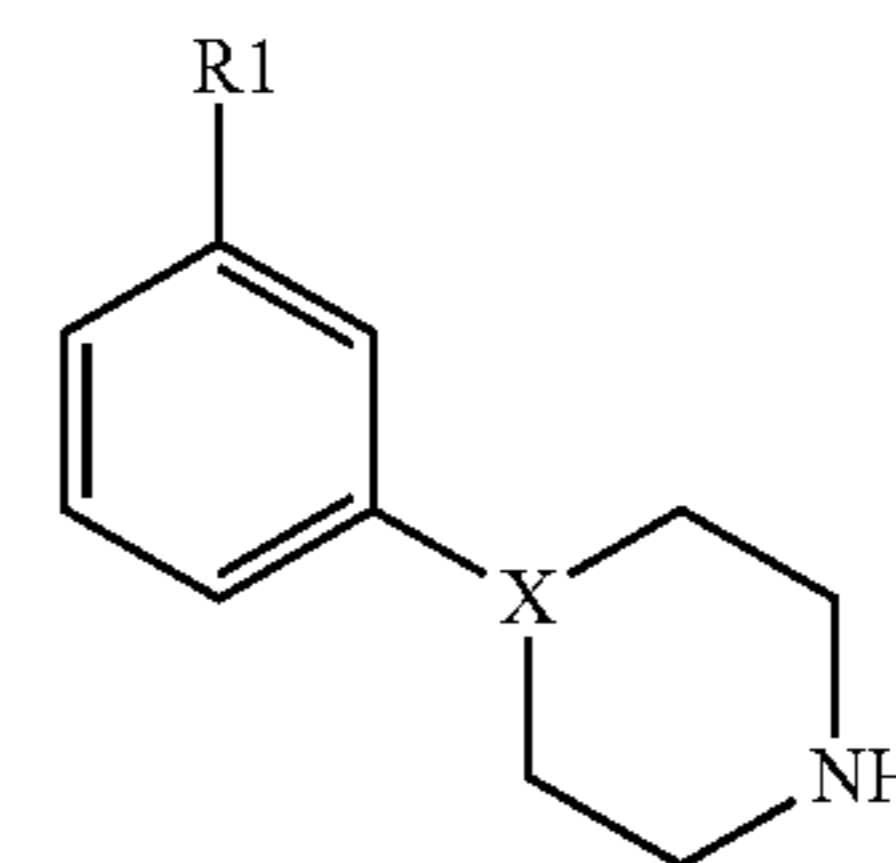


A convenient method of synthesis of the present compounds is by use of an alkyl iodide (e.g. 1-propyl-iodide). Alternatively, other leaving groups besides iodide may be used on the alkyl group, of course, such as sulfonates, particularly methanesulfonate or toluenesulfonate, bromo and the like. The alkyl intermediate is reacted with the appropriate amine in the presence of any convenient acid scavenger. The usual bases such as alkali metal or alkaline earth metal carbonates, bicarbonates and hydroxides are useful acid scavengers, as are some organic bases such as trialkylamines and

10

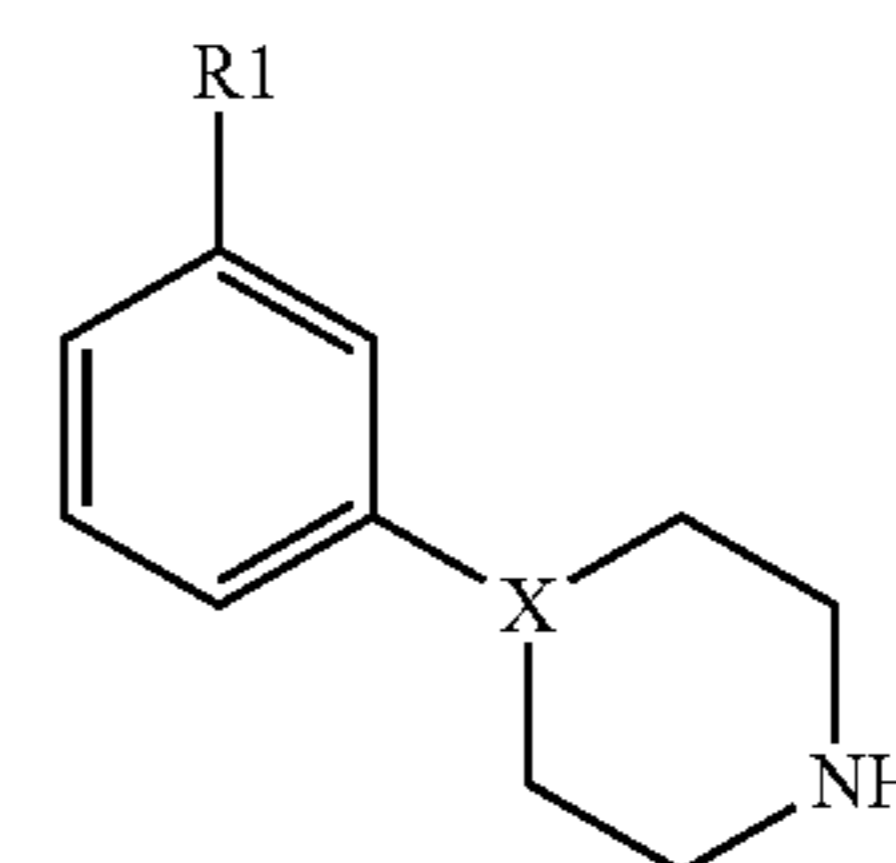
trialkanolamines. The reaction medium for such reactions may be any convenient organic solvent which is inert to the basic conditions; acetonitrile, esters such as ethylacetate and the like and halogenated alkane solvents are useful. Usually the reactions will be carried out at elevated temperatures such as from ambient temperature to the reflux temperature of the reaction mixture, particularly from 50° C. to about 100° C.

Another convenient method of synthesis of the present compounds involves reductive amination with an amine of Formula 2:

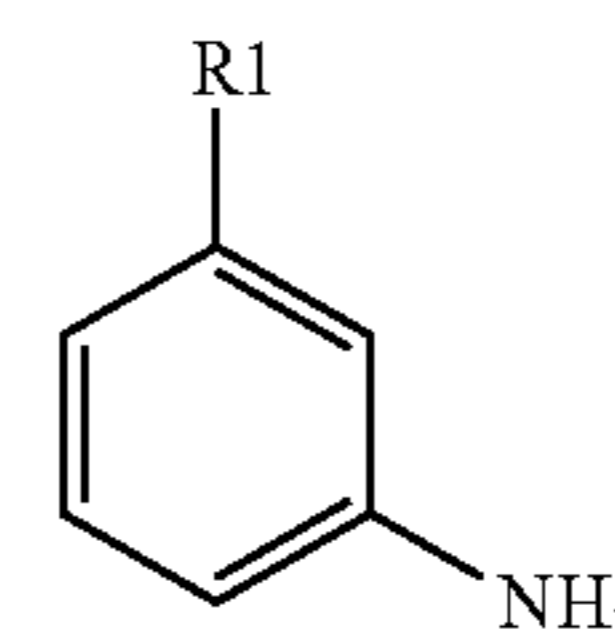


with an aldehyde or ketone, either in the presence of a reducing agent such as sodium cyanoborohydride or sodium triacetoxyborohydride or followed by reduction, e.g. using catalytic hydrogenation, to give a corresponding compound of Formula 1.

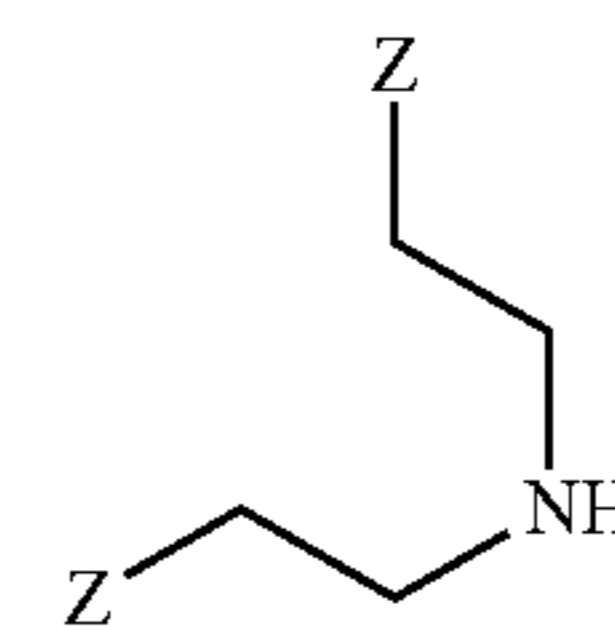
Compounds of Formula 3



wherein X=N is accomplished by reacting compounds of Formula 4:



with compounds of Formula 5:

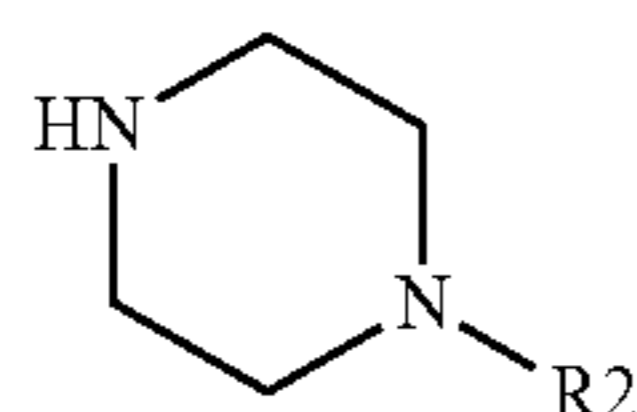


where Z is a leaving group like iodide. Other leaving groups besides iodide may be used on the alkyl group, of course, such as sulfonates, particularly methanesulfonate or toluene-

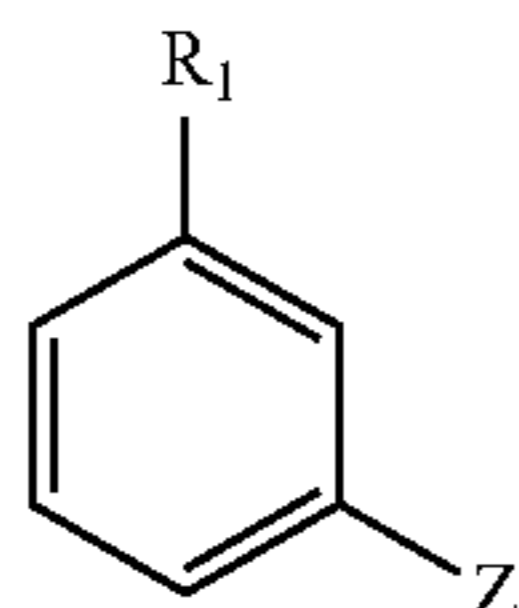
11

sulfonate, bromo and the like. The alkyl intermediate is reacted with the appropriate amine in the presence of any convenient acid scavenger. The usual bases such as alkali metal or alkaline earth metal carbonates, bicarbonates and hydroxides are useful acid scavengers, as are some organic bases such as trialkylamines and trialkanolamines. The reaction is performed in a suitable solvent such as n-butanol by heating at about 50-150° C.

Compounds of the Formula 1 wherein X=N is also accomplished by reacting compounds of Formula 6:



with an aryl substituted with a leaving group of Formula 7:



where Z is halide e.g. chloro, bromo, iodo, or sulfonate e.g. —OSO₂CF₃, or —OSO₂F, in the presence of a base and a zerovalent transition metal catalyst such as Pd or Ni, according to known method (Tetrahedron Letters, vol 37, 1996, 4463-4466, J. Org. Chem., vol. 61, 1996, 1133-1135).

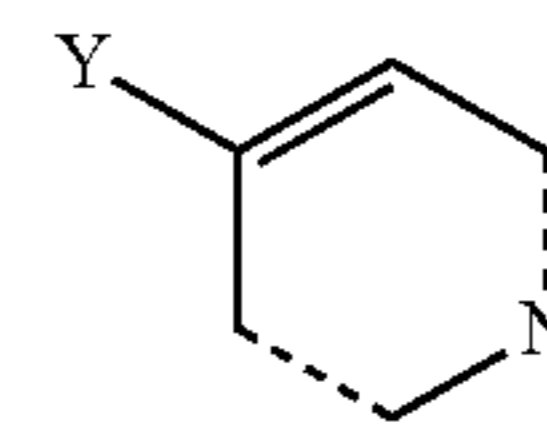
The catalyst, preferably Pd will have the ability to form ligand complex and undergo oxidative addition. Typical Pd catalysts will be Pd₂(dba)₃ (wherein dba refers to di-benzylidene acetone), Pd(PPh₃)₄, Pd(OAc)₂, or PdCl₂[P(o-tol)₃]₂ and typical phosphine ligands will be BINAP, P(o-tol)₃, dppf, or the like. The usual bases such as alkali metal or alkaline earth metal carbonates, bicarbonates and alkoxides are useful acid scavengers, as are some organic bases such as trialkylamines and trialkanolamines. The reaction medium for such reactions may be any convenient organic solvents, which are inert to the basic conditions; acetonitrile, toluene, dioxane, NMP (N-methyl-2-pyrrolidone), DME (dimethoxyethane), DMF (N,N-dimethylformamide), DMSO (dimethylsulfoxide) and THF (tetrahydrofuran) solvents are useful. Usually the reactions will be carried out at elevated temperatures such as from ambient temperature to the reflux temperature of the reaction mixture, particularly from 50° C. to about 120° C.

Compounds of the Formula 1 wherein X=N is also accomplished by reacting compounds of Formula 6 with an aryl substituted with a leaving group (e.g. F or Cl) via nucleophilic aromatic displacement reactions in the presence of a base as explained above.

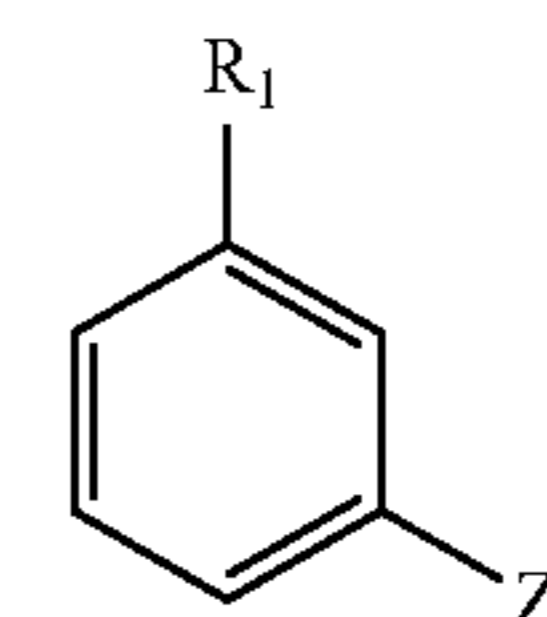
Compounds of the Formula 1 wherein X=CH is also accomplished by transition metal catalyzed cross-coupling reaction, known as, for example, Suzuki and Stille reactions, to those skilled in the art.

The reaction may be carried out between compounds of Formula 8:

12



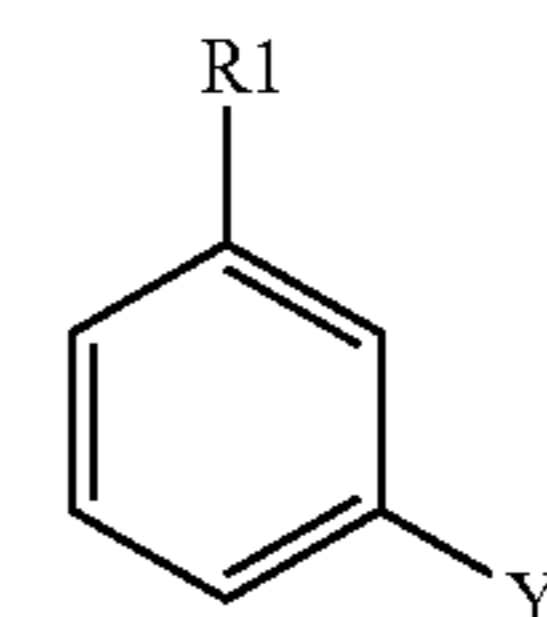
wherein Y is, for example, a dialkylborane, dialkenylborane or boronic acid (e.g. BEt₂, B(OH)₂ (dotted lines can be double bonds)) or a trialkyltin (e.g. SnMe₃, SnBu₃), and an aryl substituted with a leaving group of Formula 7:



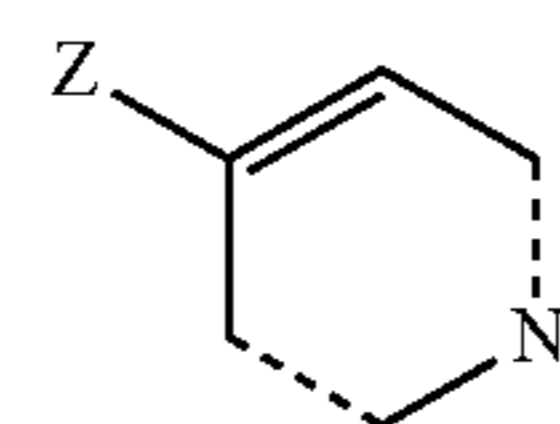
(for definition of Z, see above) in the presence of a base and a zerovalent transition metal catalyst such as Pd or Ni, according to known methods (Chem. Pharm. Bull., vol 33, 1985, 4755-4763, J. Am. Chem. Soc., vol. 109, 1987, 5478-5486., Tetrahedron Lett., vol. 33, 1992, 2199-2202). In addition, Y can also be a zinc- or magnesium-halide group (e.g. ZnCl₂, ZnBr₂, ZnI₂, MgBr₂, MgI₂) according to known methods (Tetrahedron Lett., vol. 33, 1992, 5373-5374, Tetrahedron Lett., vol. 37, 1996, 5491-5494).

The catalyst, preferably Pd will have the ability to form ligand complex and undergo oxidative addition. The definition of ligands, bases and solvents, is mentioned above.

Alternatively, the transition metal catalyzed cross-coupling reaction can be performed with the opposite substitution pattern:



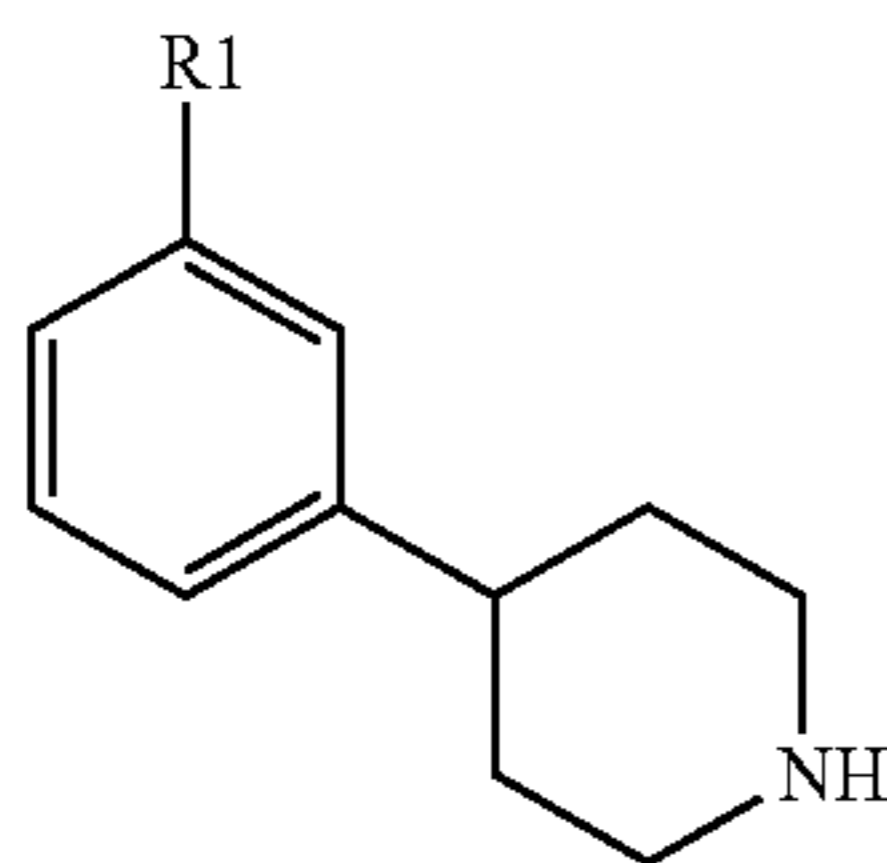
with an heteroaryl/alkenyl substituted with a leaving group of Formula 10:



in the presence of a base and a zerovalent transition metal catalyst such as Pd or Ni, according known methods discussed in the previous paragraph.

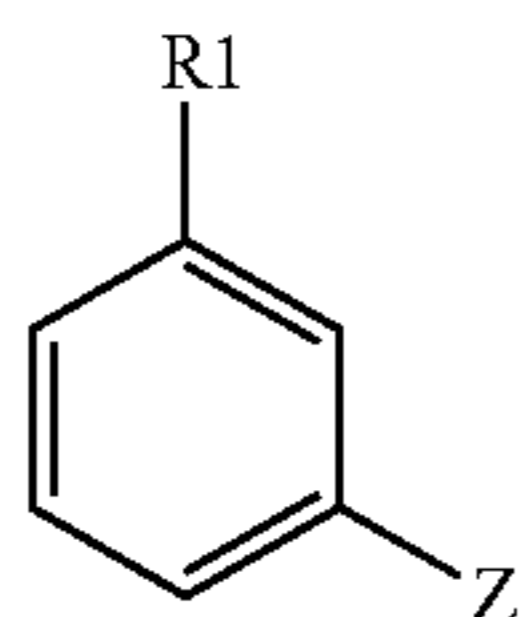
13

Compounds of Formula 11:

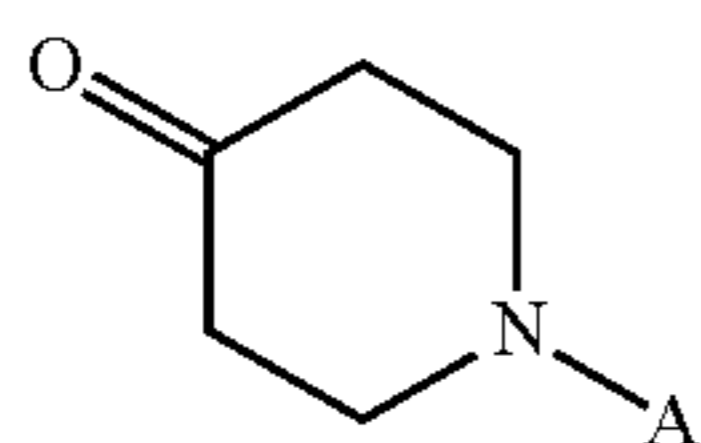


can be prepared by catalytic hydrogenation of the tetrahydropyridine or pyridine from the previous paragraph, using standard methods known in the art, generally with palladium on carbon, PtO₂, or Raney nickel as the catalyst. The reaction is performed in an inert solvent, such as ethanol or ethyl acetate, either with or without a protic acid, such as acetic acid or HCl. When the pyridine ring is quaternized with an alkyl group the ring can be partly reduced by NaBH₄ or NaCNBH₄, yielding the tetrahydropyridine analog which can further be reduced with catalytic hydrogenation.

Another convenient method of syntheses of compounds of the Formula 1, wherein X=CH is also accomplished by treating arylhalides of Formula 7:



wherein Z is Cl, Br, or I, with alkyllithium reagents, for example, butyllithium, sec-butyllithium or tert-butyllithium, preferably butyllithium or Mg (grignard reaction) in an inert solvent. Suitable solvents include, for example ether or tetrahydrofuran, preferably tetrahydrofuran. Reaction temperatures range from about -110° C. to about 60° C. The intermediate lithium anions or magnesium anions thus formed may then be further reacted with a suitable electrophile of

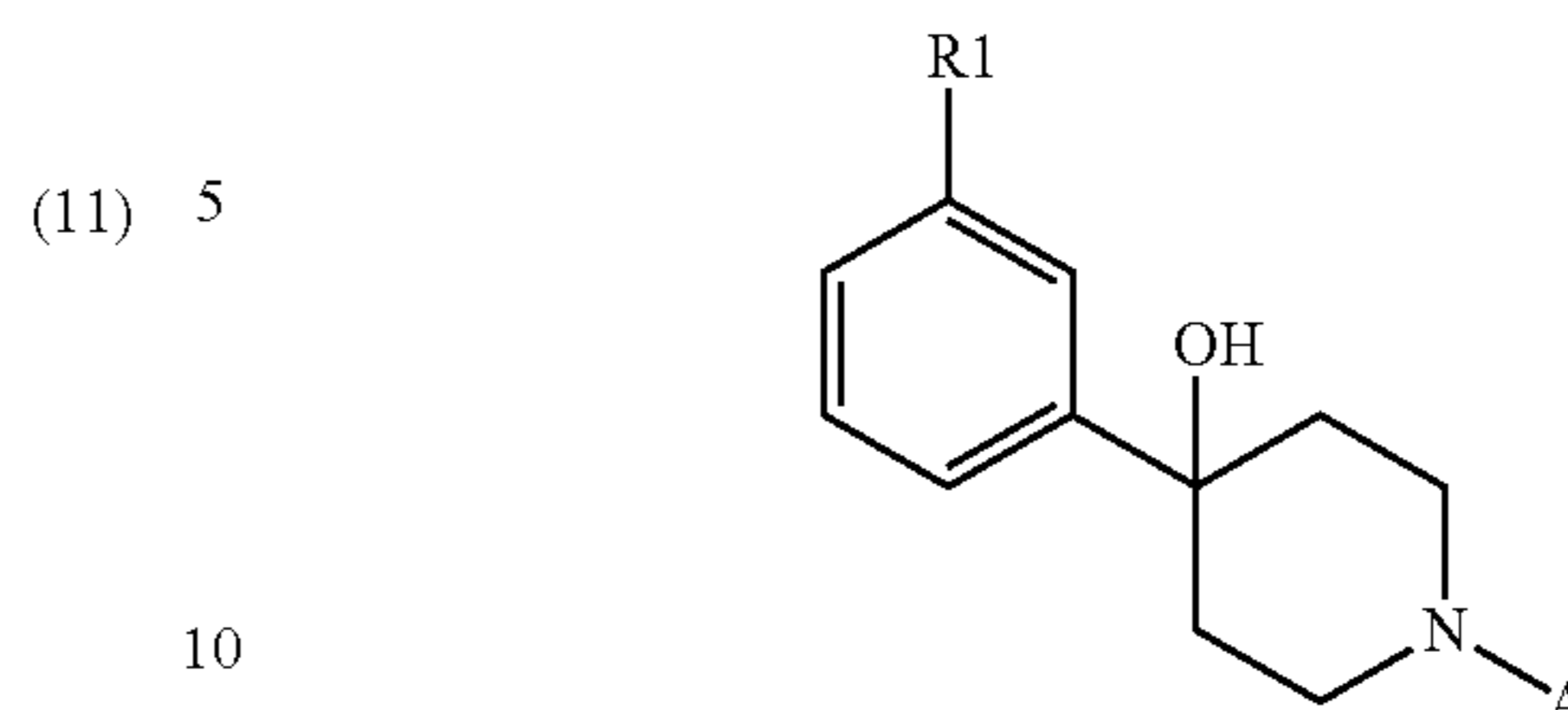


wherein A is defined as a protecting group like t-Boc (tert-butoxycarbonyl), Fmoc (fluorenylmethoxycarbonyl), Cbz (benzyloxycarbonyl) or an alkyl group like benzyl.

14

The intermediates of Formula 13:

(13)



which are formed require that the hydroxy group be removed so as to result in compounds of Formula 1 (X=CH).

This step may be accomplished by one of several standard methods known in the art. For example, a thiocarbonyl derivative (for example a xanthate) may be prepared and removed by a free radical process, of which are known to those skilled in the art. Alternatively, the hydroxyl group may be removed by reduction with a hydride source such as triethylsilane under acidic conditions, using such as, for example, trifluoroacetic acid or boron trifluoride. The reduction reaction can be performed neat or in a solvent, such as methylene chloride. A further alternative would be to first convert the hydroxyl group to a suitable leaving group, such as tosylate or chloride, using standard methods. The leaving group is then removed with a nucleophilic hydride, such as, for example, lithium aluminium hydride. This last reaction is performed typically in an inert solvent, such as, ether or tetrahydrofuran.

Another alternative method for removing the hydroxyl group is to first dehydrate the alcohol to an olefin with a reagent such as Burgess salt (*J. Org. Chem.*, vol 38, 1973, 26) followed by catalytic hydrogenation of the double bond under standard conditions with a catalyst such as palladium on carbon. The alcohol may also be dehydrated to the olefin by treatment with acid such as p-toluenesulfonic acid or trifluoroacetic acid.

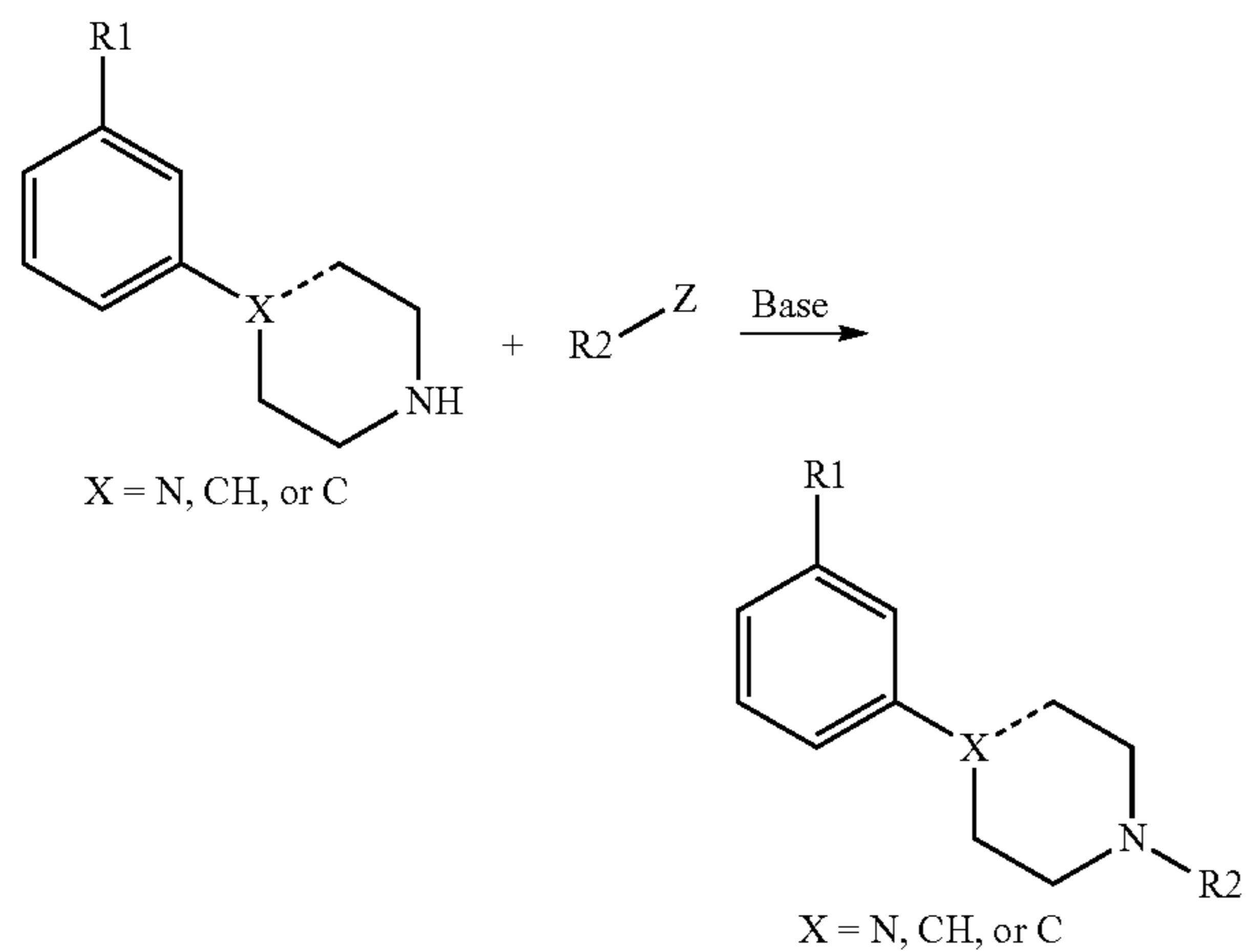
The protecting group, A, is removed under standard conditions known by those skilled in the art. For example, t-Boc cleavages are conveniently carried out with trifluoroacetic acid either neat or in combination with methylene chloride. F-moc is conveniently cleaved off with simple bases such as, ammonia, piperidine, or morpholine, usually in polar solvents such as DMF and acetonitrile. When A is Cbz or benzyl, these are conveniently cleaved off under catalytic hydrogenation conditions. The benzyl group can also be cleaved off under N-dealkylation conditions such as treatment with α -chloroethyl chloroformate (*J. Org. Chem.*, vol 49, 1984, 2081-2082).

It is further possible to convert a radical R₁ in a compound of the Formula 1 into another radical R₁, e.g. by oxidizing methylsulfide to methylsulfone (for example by m-chloroperoxybenzoic acid), substitution of a triflate or halide group with a cyano group (for example palladium catalyzed cyanation), substitution of triflate or halide group with a ketone (for example palladium catalyzed Heck reaction with butyl vinyl ether), substitution of a triflate or halide group with a carboxamide (for example, palladium catalyzed carbonylation), or cleaving an ether by, for example, converting a methoxy group into the corresponding hydroxyl derivative, which can further be converted into the corresponding mesylate or triflate. The terms mesylate and triflate refers to OSO₂CH₃, CH₃SO₃ or OSO₂CF₃, CF₃SO₃, respectively.

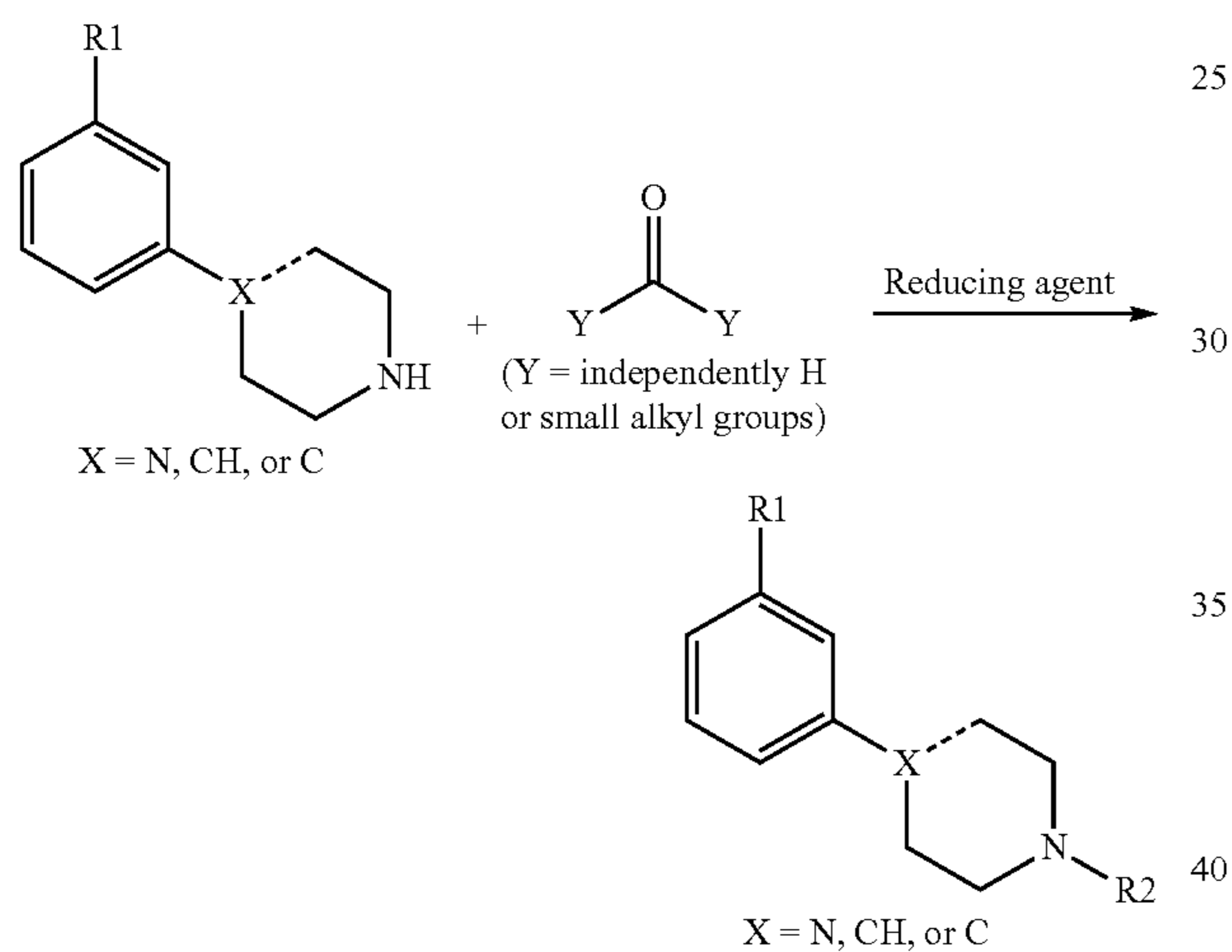
In summary, the general process for preparing the present compounds has six main variations, which may briefly be described as follows:

15

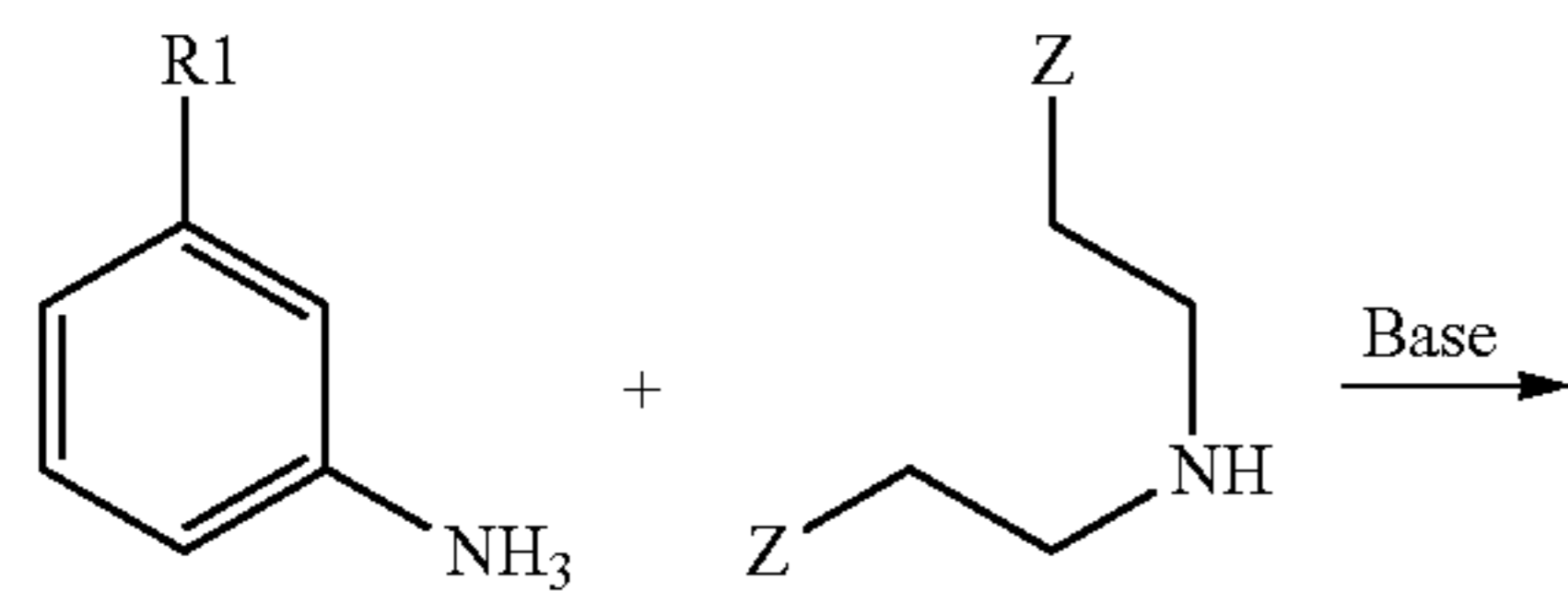
according to Scheme 1:



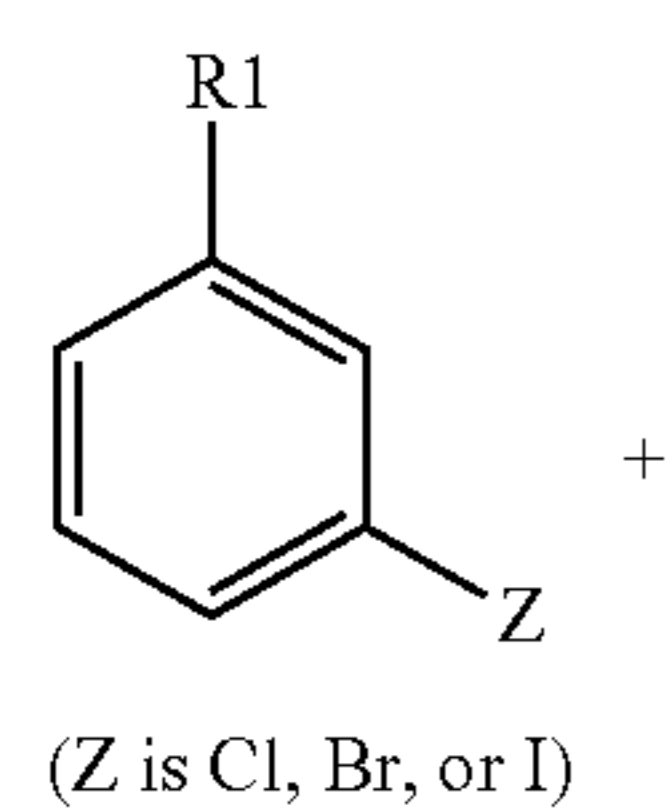
or according to Scheme 2:



or according to Scheme 3:



or according to Scheme 6:

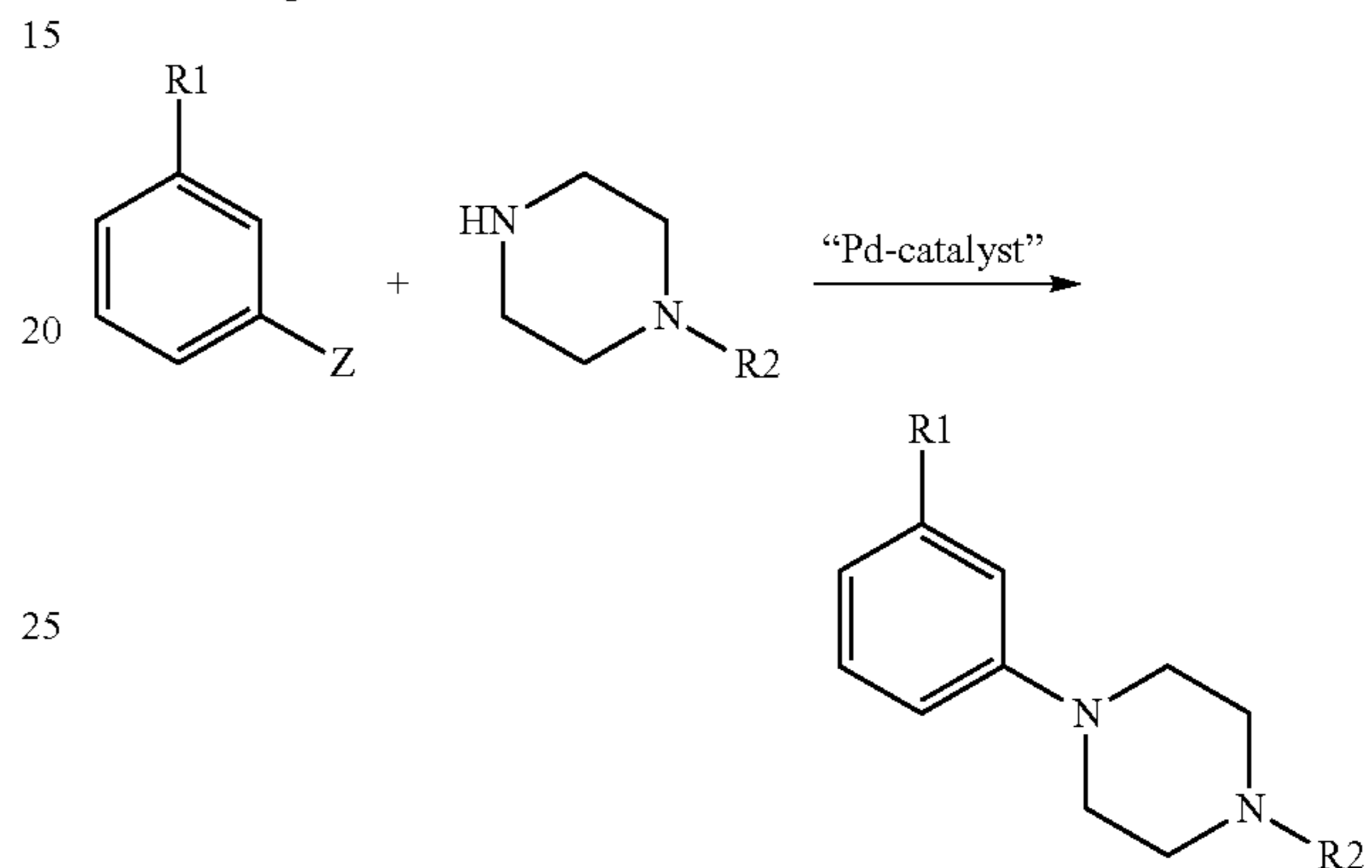


16

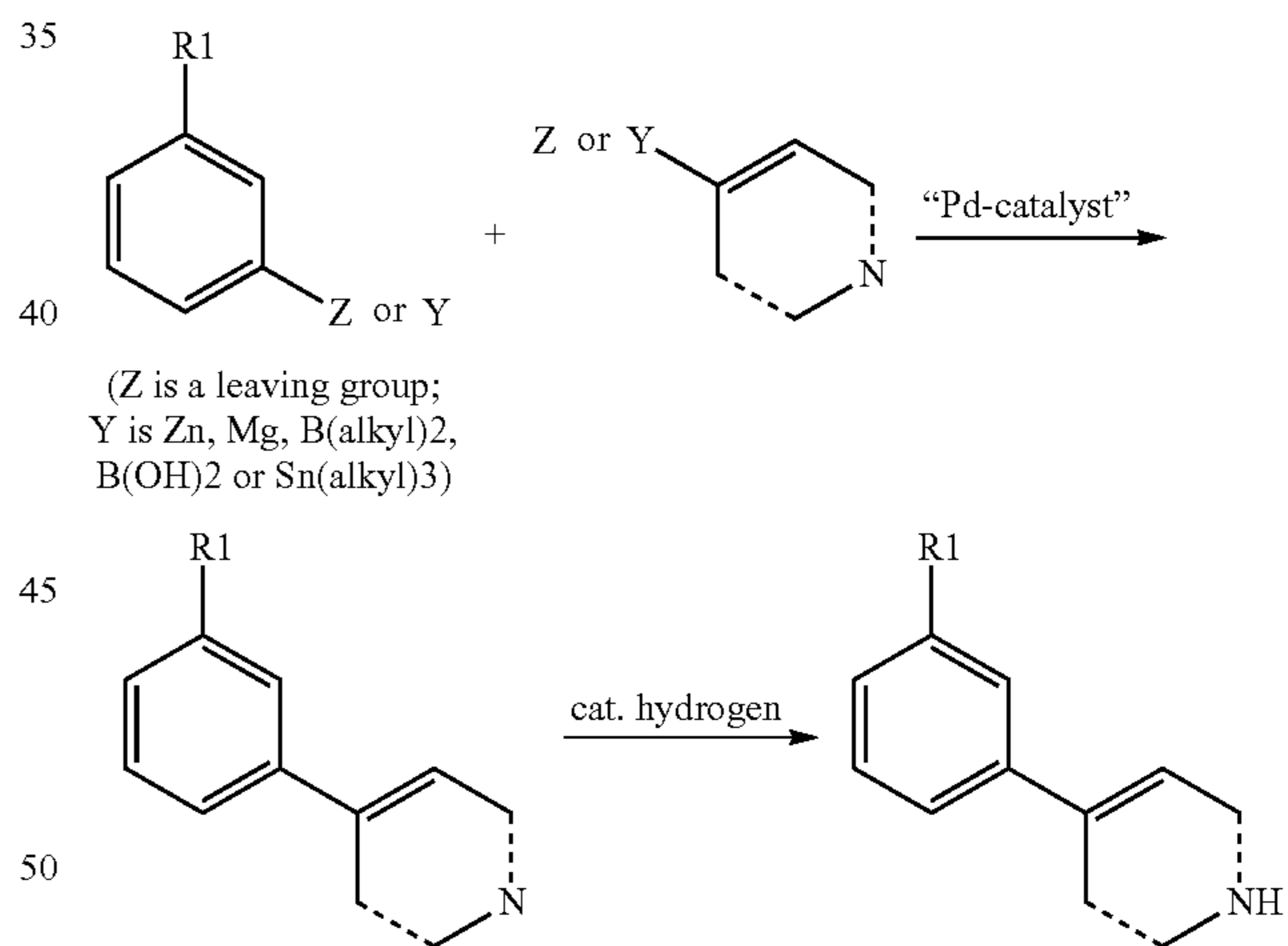
-continued



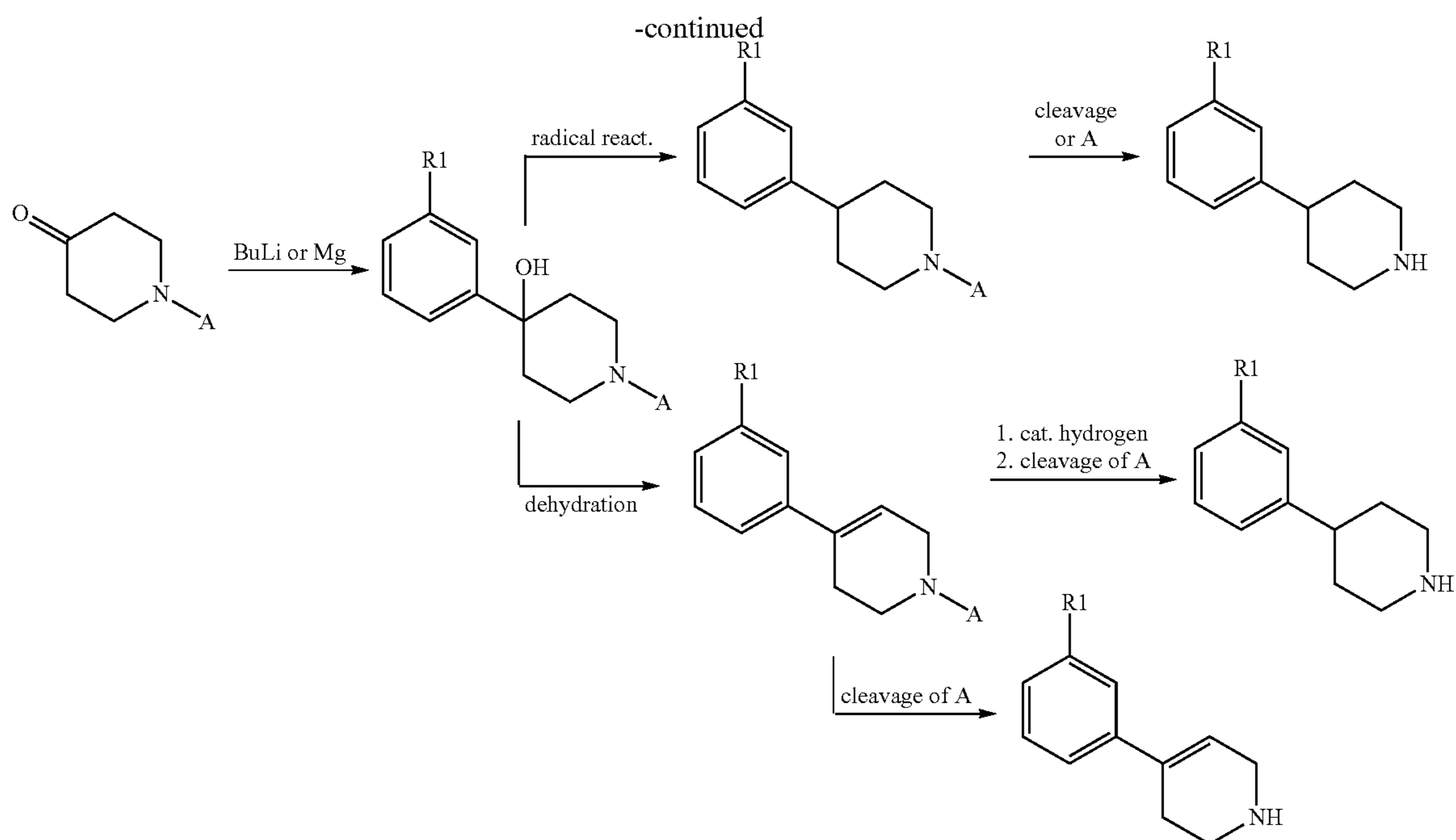
or according to Scheme 4:



or according to Scheme 5:



17



18

As used herein the term C₁-C₄ alkyl refers to an alkyl containing 1-4 carbon atoms in any isomeric form. The various carbon moieties are defined as follows: Alkyl refers to an aliphatic hydrocarbon radical and includes branched or unbranched forms such as methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl. The term cycloalkyl refers to a radical of a saturated cyclic hydrocarbon such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl.

The term "patient" used herein refers to an individual in need of the treatment according to the invention.

The term "treatment" used herein relates to both treatment in order to cure or alleviate a disease or a condition, and to treatment in order to prevent the development of a disease or a condition. The treatment may either be performed in an acute or in a chronic way.

Both organic and inorganic acids can be employed to form non-toxic pharmaceutically acceptable acid addition salts of the compounds according to the invention. Illustrative acids are sulfuric, nitric, phosphoric, hydrochloric, citric, acetic, lactic, tartaric, palmoic, ethane disulfonic, sulfamic, succinic, cyclohexylsulfamic, fumaric, maleic, and benzoic acid. These salts are readily prepared by methods known in the art.

The pharmaceutical composition containing a compound according to the invention may also comprise substances used to facilitate the production of the pharmaceutical preparation or the administration of the preparations. Such substances are well known to people skilled in the art and may for example be pharmaceutically acceptable adjuvants, carriers and preservatives.

In clinical practice the compounds used according to the present invention will normally be administered orally, rectally, or by injection, in the form of pharmaceutical preparations comprising the active ingredient either as a free base or as a pharmaceutically acceptable non-toxic, acid addition salt, such as the hydrochloride, lactate, acetate, sulfamate salt, in association with a pharmaceutically acceptable carrier. The carrier may be a solid, semisolid or liquid preparation. Usually the active substance will constitute between 0.1 and 99% by weight of the preparation, more specifically between 0.5

and 20% by a weight for preparations intended for injection and between 0.2 and 50% by weight for preparations suitable for oral administration.

To produce pharmaceutical preparations containing the compound according to the invention in the form of dosage units for oral application, the selected compound may be mixed with a solid excipient, e.g. lactose, saccharose, sorbitol, mannitol, starches such as potato starch, corn starch or amylopectin, cellulose derivatives, a binder such as gelatine or polyvinyl-pyrrolidone, and a lubricant such as magnesium stearate, calcium stearate, polyethylene glycol, waxes, paraffin, and the like, and then compressed into tablets. If coated tablets are required, the cores, prepared as described above, may be coated with a concentrated sugar solution which may contain e.g. gum arabic, gelatine, talcum, titanium dioxide, and the like. Alternatively, the tablet can be coated with a polymer known to the man skilled in the art, dissolved in a readily volatile organic solvent or mixture of organic solvents. Dyestuffs may be added to these coatings in order to readily distinguish between tablets containing different active substances or different amounts of the active compound.

For the preparation of soft gelatine capsules, the active substance may be admixed with e.g. a vegetable oil or polyethylene glycol. Hard gelatine capsules may contain granules of the active substance using either the mentioned excipients for tablets e.g. lactose, saccharose, sorbitol, mannitol, starches (e.g. potato starch, corn starch or amylopectin), cellulose derivatives or gelatine. Also liquids or semisolids of the drug can be filled into hard gelatine capsules.

Dosage units for rectal application can be solutions or suspensions or can be prepared in the form of suppositories comprising the active substance in a mixture with a neutral fatty base, or gelatine rectal capsules comprising the active substance in admixture with vegetable oil or paraffin oil. Liquid preparations for oral application may be in the form of syrups or suspensions, for example solutions containing from about 0.2% to about 20% by weight of the active substance herein described, the balance being sugar and mixture of ethanol, water, glycerol and propylene glycol. Optionally

19

such liquid preparations may contain coloring agents, flavoring agents, saccharine and carboxymethylcellulose as a thickening agent or other excipients known to the man in the art.

Solutions for parenteral applications by injection can be prepared in an aqueous solution of a water-soluble pharmaceutically acceptable salt of the active substance, preferably in a concentration of from 0.5% to about 10% by weight. These solutions may also contain stabilizing agents and/or buffering agents and may conveniently be provided in various dosage unit ampoules. The use and administration to a patient to be treated in the clinic would be readily apparent to an ordinary skill in the art.

In therapeutical treatment an effective amount or a therapeutic amount of the compounds according to the invention are from about 0.01 to about 500 mg/kg body weight daily, preferably 0.1-10 mg/kg body weight daily. The compounds may be administered in any suitable way, such as orally or parenterally. The daily dose will preferably be administered in individual dosages 1 to 4 times daily.

It is known for those skilled in the art that replacing a hydrogen in a non-substituted position in the aromatic ring with a fluorine atom may block the possibility for enzymatic hydroxylation which render the compound low oral bioavailability. This type of exchange (H to F) seldom changes the pharmacological profile. Thus, it may be important, in some cases to introduce a fluorine atom in any non-substituted positions in the aromatic ring of compounds of Formula 1 to improve the oral bioavailability.

The invention is further illustrated in the examples below, which in no way are intended to limit the scope of the invention.

EXAMPLE 1

1-(3-Methanesulfonyl-phenyl)-4-propyl-piperazine

A suspension of 1-(3-methanesulfonyl-phenyl)-piperazine (350 mg) and ground K_2CO_3 (403 mg) was stirred in CH_3CN (25 mL) at room temperature. 1-Iodopropane (712 μL) was added. The mixture was refluxed overnight. The reaction mixture was filtered and the volatiles were evaporated in vacuum. The oily residue was chromatographed on a silica column with $MeOH:CH_2Cl_2$ (1:30 (v/v)) as eluent. Collection of the fractions containing pure product and evaporation of the solvent afforded pure 1-(3-methanesulfonyl-phenyl)-4-propyl-piperazine (220 mg). The amine was converted into the HCl salt and recrystallized from ethanol/diethylether: m.p. 233° C. MS m/z (relative intensity, 70 eV) 282 (M^+ , 30), 254 (15), 253 (bp), 210 (17), 70 (21).

The following compounds according to Examples 2-11 were prepared in a manner similar to the one described in Example 1.

EXAMPLE 2

1-Propyl-4-(3-Trifluoromethanesulfonyl-phenyl)-piperazine

MS m/z (relative intensity, 70 eV) 336 (M^+ , 16), 307 (bp), 77 (18), 70 (38), 56 (23).

20

EXAMPLE 3

1-[3-(4-Propyl-piperazin-1-yl)-phenyl]-ethanone

Beginning with 1-(3-Piperazin-1-yl-phenyl)-ethanone and n-Pr-I: m.p. 119° C. (oxalate), MS m/z (rel. intensity, 70 eV) 246 (M^+ , 10), 217 (33), 132 (18), 70 (bp), 56 (41); Rf 0.23 (EtOAc).

EXAMPLE 4

1-Propyl-4-(3-trifluoromethyl-phenyl)-piperidine

Beginning with 4-(3-Trifluoromethyl-phenyl)-piperidine and n-Pr-I: m.p. 195° C. (HCl), MS m/z (rel. intensity, 70 eV) 271 (M^+ , 4), 243 (16), 242 (bp), 159 (13), 70 (49).

EXAMPLE 5

1-Butyl-4-(3-trifluoromethyl-phenyl)-piperidine

Beginning with 4-(3-Trifluoromethyl-phenyl)-piperidine and n-Bu-Br: m.p. 222° C. (HCl), MS m/z (rel. intensity, 70 eV) 285 (M^+ , 3), 243 (12), 242 (bp), 70 (51), 56 (17).

EXAMPLE 6

4-(3-Methanesulfonyl-phenyl)-1-propyl-piperidine

m.p. 200° C. (HCl) MS m/z (relative intensity, 70 eV) 281 (M^+ , 5), 252 (bp), 129 (20), 115 (20), 70 (25).

EXAMPLE 7

4-(3-Methanesulfonyl-phenyl)-1-propyl-1,2,3,6-tetrahydro-pyridine

Beginning with 4-(3-methanesulfonyl-phenyl)-1,2,3,6-tetrahydro-pyridine and iodopropane: MS m/z (relative intensity, 70 eV) 279 (M^+ , 26), 250 (bp), 171 (6), 128 (12), 115 (8).

EXAMPLE 8

4-(3-Methanesulfonyl-phenyl)-1-ethyl-piperidine

Beginning with 4-(3-methanesulfonyl-phenyl)-piperidine and iodoethane: m.p. 158° C. (HCl). MS m/z (rel. intensity, 70 eV) 267 (M^+ , 20), 252 (bp), 130 (10), 115 (12), 84 (20);

EXAMPLE 9

1-Isopropyl-4-(3-methanesulfonyl-phenyl)-piperidine

Beginning with 4-(3-methanesulfonyl-phenyl)-piperidine and i-propylbromide: m.p. 220° C. (HCl); MS m/z (rel. intensity, 70 eV) 281 (M^+ , 4), 266 (bp), 187 (5), 129 (5), 115 (5)

EXAMPLE 10

4-(3-Methanesulfonyl-phenyl)-1-butyl-piperidine

Beginning with 4-(3-methanesulfonyl-phenyl)-piperidine and n-BuCl. MS m/z (rel. intensity, 70 eV) 295 (M^+ , 3), 252 (bp), 130 (5), 115 (3), 70 (8).

21

EXAMPLE 11

1-Isobutyl-4-(3-methanesulfonyl-phenyl)-piperidine

Beginning with 4-(3-methanesulfonyl-phenyl)-piperidine and *i*-butylbromide; m.p. 212° C. (HCl); MS m/z (rel. intensity, 70 eV) 295 (M+, 1), 252 (80), 129 (40), 115 (50), 70 (bp).

EXAMPLE 12

3-(1-Propyl-piperidin-4-yl)-benzotrile

A solution of 3-(1-propyl-piperidin-4-yl)-benzamide (350 mg) and POCl₃ (326 μL) in dry DMF (6 ml) was heated at 80° C. for 3 h under an argon atmosphere. Evaporation of the solvent yielded a dark, oily residue, which was dissolved in water. The solution was basified and extracted with CH₂Cl₂. The combined organic phases were dried (MgSO₄), filtered and evaporated. The oily residue was chromatographed on a silica column with MeOH:CH₂Cl₂ (1:19 (v/v)) as eluent. Collection of the fractions containing pure product and evaporation of the solvent afforded pure 3-(1-Propyl-piperidin-4-yl)-benzotrile (127 mg). The amine was converted into the fumarate salt and recrystallized from ethanol/diethylether: m.p. 122° C.; MS m/z (relative intensity, 70 eV) 228 (M+, 2), 199 (42), 129 (26), 70 (bp) 56 (53).

EXAMPLE 13

1-sec-Butyl-4-(3-methanesulfonyl-phenyl)-piperidine

4-(3-methanesulfonyl-phenyl)-piperidine hydrochloride (20 mg), glacial acetic acid (4.4 mg) and 2-butanone (5.1 mg) were mixed in 1,2-dichloroethane (5 mL). Sodium triacetoxymethylborohydride (23.5 mg) was added to the solution and the reaction mixture was stirred at room temperature under a nitrogen atmosphere for 5 h (G.L.C. analysis indicated a complete reaction). The reaction was quenched with saturated aqueous NaHCO₃ and the product was extracted with CH₂Cl₂. The combined organic phases were dried (MgSO₄), filtered, and the solvent was evaporated to afford 1-sec-butyl-4-(3-methanesulfonyl-phenyl)-piperidine as an oily residue. The product was chromatographed on a silica column with CH₂Cl₂:MeOH (9:1 (v/v)) as eluent. Collection of the fractions containing pure product and evaporation of the solvent afforded pure amine (15 mg, 71%); MS m/z (relative intensity, 70 eV) 295 (M+, 1), 280 (7), 266 (bp), 187 (4), 129 (4).

EXAMPLE 14

Methanesulfonic acid
3-(1-propyl-piperidin-4-yl)-phenyl ester

A solution of 3-(1-propyl-piperidin-4-yl)-phenol (340 mg) and triethylamine (187 mg) in 20 ml of CH₂Cl₂ was cooled to 0° C. Then methanesulfonyl chloride (194 mg) dissolved in 10 ml of CH₂Cl₂ was added dropwise. The reaction mixture was allowed to reach room temperature and then stirred for 2.5 h at 25° C. The reaction was finally quenched with water. The organic layer was separated and washed with 10% HCl and then 10% Na₂CO₃.

After drying (MgSO₄) the solvent was removed under reduced pressure. The residue was chromatographed on a silica column using MeOH:CH₂Cl₂ (1:9 (v/v)) as eluent. The fractions containing pure methanesulfonic acid 3-(1-propyl-piperidin-4-yl)-phenyl ester were collected, and the solvent

22

was removed in vacuum, affording 206 mg of the title compound. (MS m/z (rel. intensity, 70 eV) 297 (M+, 3), 268 (bp), 189 (24), 131 (13), 79 (16);

The following compounds in Examples 15-19 were prepared in a manner similar to the one described in Example 14.

EXAMPLE 15

Methanesulfonic acid
3-(1-ethyl-piperidin-4-yl)-phenyl ester

Beginning with 3-(1-ethyl-piperidin-4-yl)-phenol and methanesulfonyl chloride. MS m/z (rel. intensity, 70 eV) 283 (M+, 6), 268 (bp), 189 (54), 131 (20), 79 (70);

EXAMPLE 16

Methanesulfonic acid
3-(1-butyl-piperidin-4-yl)-phenyl ester

Beginning with 3-(1-butyl-piperidin-4-yl)-phenol and methanesulfonyl chloride. MS m/z (rel. intensity, 70 eV) 311 (M+, 3), 268 (bp), 189 (20), 131 (18), 79 (12);

EXAMPLE 17

Methanesulfonic acid
3-(4-propyl-piperazin-1-yl)-phenyl ester

Beginning with 3-(4-propyl-piperazin-1-yl)-phenol and methanesulfonyl chloride: m.p. 143-144° C. (fumarate); MS m/z (rel. intensity, 70 eV) 298 (M+, 35), 269 (95), 121 (25), 84 (30), 70 (bp);

EXAMPLE 18

Trifluoro-methanesulfonic acid
3-(1-propyl-piperidin-4-yl)-phenyl ester

Beginning with 3-(1-propyl-piperidin-4-yl)-phenol and triflic anhydride MS m/z (rel. intensity, 70 eV) 351 (M+, 4), 322 (65), 189 (30), 131 (20), 69 (bp).

EXAMPLE 19

Trifluoro-methanesulfonic acid
3-(1-ethyl-piperidin-4-yl)-phenyl ester

Beginning with 3-(1-ethyl-piperidin-4-yl)-phenol and triflic anhydride: MS m/z (rel. intensity, 70 eV) 337 (M+, 4), 322 (65), 189 (30), 131 (20), 69 (bp).

EXAMPLE 20

1-[3-(1-Propyl-piperidin-4-yl)-phenyl]-ethanone

To a stirred solution of trifluoro-methanesulfonic acid 3-(1-propyl-piperidin-4-yl)-phenyl ester (300 mg) in DMF (4 ml) under argon atm at r.t. was subsequently added NEt₃ (356 μL), butyl vinyl ether (823 μL), 1,3-bis (diphenylphosphino) propane (50 mg), and Pd(OAc)₂ (19 mg). The reaction mixture was then heated to 80° C. and after 2 h the reaction was stopped. 5% Hydrochloric acid solution (6 ml) was added and the combined mixture stirred for 45 min. Then CH₂Cl₂ was added and the phases were separated. The aqueous layer was then extracted with CH₂Cl₂. The combined organic phases were dried (MgSO₄), filtered and evaporated to dryness. The

23

crude product was purified by flash chromatography (MeOH:CH₂Cl₂ (1:9 (v/v))). Collection of the fractions containing pure product and evaporation of the solvent afforded pure 1-[3-(1-Propyl-piperidin-4-yl)-phenyl]-ethanone (35 mg). MS m/z (rel. intensity, 70 eV) 245 (M+, 4), 216 (bp), 100 (19), 70 (36), 57 (13).

EXAMPLE 21

1-Propyl-4-(3-trifluoromethylsulfonylphenyl)-1,2,3,6-tetrahydropyridine

4-(3-Trifluoromethylsulfonylphenyl)-Pyridine (0.3 g) was dissolved in 1-iodo-propane (2 ml) and heated to 100° C. for 2 h. Then the volatiles were evaporated and the residue redissolved in abs EtOH (20 ml) and NaBH₄ (340 mg) was added portions wise at -20° C. The mixture was then allowed to reach r.t. and stirred over night. To the mixture was added 10% Na₂CO₃ solution (20 ml). The aqueous layer was extracted with CH₂Cl₂ and the combined organic phases were dried (MgSO₄), filtered and evaporated to dryness. The crude product was purified by flash chromatography (MeOH:CH₂Cl₂ (1:9 (v/v))) Collection of the fractions containing pure product and evaporation of the solvent afforded pure 1-propyl-4-(3-trifluoromethyl-sulfonylphenyl)-1,2,3,6-tetrahydropyridine (150 mg). MS m/z (rel. intensity, 70 eV) 333 (M+, 21), 305 (16), 304 (bp), 171 (14), 128 (14). Rf 0.55 (MeOH)

EXAMPLE 22

1-Propyl-4(3-trifluoromethylsulfonylphenyl)-piperidine

Beginning with 1-propyl-4-(3-trifluoromethyl-sulfonylphenyl)-1,2,3,6-tetrahydropyridine, 1-Propyl-4(3-trifluoromethylsulfonylphenyl)-piperidine was recovered by the procedure described in Preparation 9. MS m/z (relative intensity, 70 eV) 335 (M+, 3), 307 (17), 306 (bp), 173 (26), 70 (10).

EXAMPLE 23

1-Allyl-4-(3-methanesulfonyl-phenyl)-piperidine

Beginning with 4-(3-methanesulfonyl-phenyl)-piperidine and allylbromide, the titled compound was recovered by the procedure described in Example 1. MS m/z (relative intensity, 70 eV) 279 (M+, 74), 96 (bp), 82 (98), 68 (74), 55 (93). Rf=0.42 (MeOH), 0.08 (EtOAc).

EXAMPLE 24

4-(3-Methanesulfonyl-phenyl)-1-(tetrahydro-furan-2-ylmethyl)-piperidine

Beginning with 4-(3-methanesulfonyl-phenyl)-piperidine and tetrahydrofurfuryl chloride, the titled compound was recovered by the procedure described in Example 1. MS m/z (relative intensity, 70 eV) 323 (M+, 1), 252 (bp), 129 (9), 115 (6), 70 (17). Rf=0.3 (MeOH), 0.03 (EtOAc).

Syntheses of intermediates used in the above Examples are described in the preparations below.

PREPARATION 1

4-Hydroxy-4-(3-methylsulfonyl-phenyl)-piperidin-1-carboxylic acid tert-butyl ester

1-Bromo-3-methylsulfonyl-benzene (5.0 g, 24.6 mmol) was dissolved in dry THF (40 ml) and cooled to -78° C. under

24

a stream of Argon (g). n-BuLi (12.8 ml, 2.5 M in hexane, 31.9 mmol) was added dropwise via syringe and the reaction mixture was stirred for an additional 30 min at -78° C., then the temperature was increased to 0° C. for 5 min and then decreased to -78° C. 1-tert-Butoxycarbonyl-4-piperidone (5.4 g, 27.06 mmol) dissolved in dry THF (30 ml) was added via syringe. The reaction mixture was allowed to reach room temperature and then stirred for 1 hour, and finally quenched with saturated ammonium chloride solution (30 ml). The mixture was extracted several times with EtOAc and the combined organic phases were dried (MgSO₄), filtered and evaporated to dryness. The oily residue was chromatographed on a silica column using CH₂Cl₂:MeOH (19:1 (v/v)) as eluent, yielded 4-hydroxy-4-(3-methylsulfonyl-phenyl)-piperidin-1-carboxylic acid tert-butyl ester (6 g, 76%). MS m/z (relative intensity, 70 eV) 323.1 (M+, 6), 223.0 (11), 178.0 (7), 152 (3), 57.0 (bp), 56 (30).

PREPARATION 2

1-Benzyl-4-(3-methoxy-phenyl)-piperidin-4-ol

Beginning with 3-bromoanisole (5 g) and 1-benzyl-4-piperidone (5.5 g), 4.58 g of 1-benzyl-4-(3-methoxy-phenyl)-piperidin-4-ol was recovered by the procedure described in Preparation 1. MS m/z (relative intensity, 70 eV) 297 (M+, 8), 279 (13), 206 (28), 146 (17), 91 (bp).

PREPARATION 3

1-Benzyl-4-(3-trifluoromethyl-phenyl)-piperidin-4-ol

Beginning with 3-trifluoromethyl-iodobenzene (3 g) and 1-benzyl-4-piperidone (2.1 g), 1.75 g of the title compound was recovered by the procedure described in preparation 1. MS m/z (rel. intensity, 70 eV) 335 (M+, 29), 244 (22), 146 (19), 91 (bp), 56 (19).

PREPARATION 4

4-(3-Methylsulfonyl-phenyl)-1,2,3,6-tetrahydro-pyridine

4-Hydroxy-4-(3-methylsulfonyl-phenyl)-piperidin-1-carboxylic acid tert-butyl ester (3.97 g) was dissolved in CH₂Cl₂ (500 ml) and trifluoroacetic acid (80 ml) was added in one portion. The mixture was refluxed for one hour and then washed with two portions of 10%-Na₂CO₃, dried (MgSO₄), filtered and evaporated to dryness. Yield 2.07 g. MS m/z (relative intensity, 70 eV) 205 (M+, 73), 158 (44), 129 (95), 128 (80), 82 (bp).

PREPARATION 5

1-Benzyl-4-(3-methoxy-phenyl)-1,2,3,6-tetrahydro-pyridine

Beginning with 1-Benzyl-4-(3-methoxy-phenyl)-piperidin-4-ol (4.5 g) and trifluoroacetic acid (80 ml), 3.5 g of 1-benzyl-4-(3-methoxy-phenyl)-1,2,3,6-tetrahydro-pyridine was recovered by the procedure described in Preparation 4. MS m/z, (relative intensity, 70 eV) 279 (M+, 35), 145 (13), 115 (15), 91 (bp) 65 (22).

25

PREPARATION 6

1-Benzyl-4-(3-trifluoromethyl-phenyl)-1,2,3,6-tetrahydro-pyridine

Beginning with 1-Benzyl-4-(3-trifluoromethyl-phenyl)-piperidin-4-ol (1.74 g), 1.44 g of the title compound was recovered by the procedure described in preparation 4 (neat CF_3COOH). MS m/z (rel. intensity, 70 eV) 317 (M+, 71), 226 (13), 172 (15), 91 (bp), 65 (17).

PREPARATION 7

4-(3-Methylsulfanyl-phenyl)-3,6-dihydro-2H-pyridine-1-carboxylic acid methyl ester

4-(3-Methylsulfanyl-phenyl)-1,2,3,6-tetrahydro-pyridine (2 g) and NET_3 (1 g) were dissolved in CH_2Cl_2 (75 ml) and cooled to 0°C . Methyl chloroformate (0.96 g) dissolved in CH_2Cl_2 (20 ml) was added dropwise and the reaction mixture was then allowed to reach room temperature. After an additional two hours at room temperature the reaction mixture was washed with 10% Na_2CO_3 solution, dried (MgSO_4), filtered and concentrated by evaporation. The oily residue was chromatographed on a silica column using CH_2Cl_2 :
MeOH (19:1 (v/v)) as eluent, 4-(3-methylsulfanyl-phenyl)-3,6-dihydro-2H-pyridine-1-carboxylic acid methyl ester (1.4 g). MS m/z (relative intensity, 70 eV) 263 (M+45), 248 (89), 129 (83), 128 (bp), 59 (96).

PREPARATION 8

4-(3-Methanesulfonyl-phenyl)-3,6-dihydro-2H-pyridine-1-carboxylic acid methyl ester

4-(3-Methylsulfanyl-phenyl)-3,6-dihydro-2H-pyridine-1-carboxylic acid methyl ester (1.4 g) was dissolved in CH_2Cl_2 (150 ml) and cooled to 0°C . m-Chloroperoxybenzoic acid (2.48 g) was added portions wise and the mixture was stirred at room temperature for three hours. The resulting clear solution was washed with 10%- Na_2CO_3 solution, dried (MgSO_4), filtered and concentrated by evaporation and yielding an oily residue (1.3 g). MS m/z (relative intensity, 70 eV) 295 (M+, 19), 280 (56), 129 (70), 128 (89), 59 (bp).

PREPARATION 9

4-(3-Methanesulfonyl-phenyl)-piperidin-1-carboxylic acid methyl ester

4-(3-Methanesulfonyl-phenyl)-3,6-dihydro-2H-pyridine-1-carboxylic acid methyl ester (2.0 g) was dissolved in methanol (40 ml). Concentrated hydrochloric acid (2 ml) and Pd/C (500 mg) were added. The resulting mixture was hydrogenated under a hydrogen gas pressure (50 psi) for 8 h and then filtered through a pad of celite. The solvent was evaporated in vacuum and the residue was purified by flash chromatography (CH_2Cl_2 : MeOH, 3:1 (v/v)). Yield 0.92 g MS m/z (relative intensity, 70 eV) 297 (M+, 54), 282 (62), 238 (bp), 115 (92), 56 (93).

PREPARATION 10

4-(3-Methoxy-phenyl)-piperidine

Beginning with 1-Benzyl-4-(3-methoxy-phenyl)-1,2,3,6-tetrahydro-pyridine (5.1 g) and 900 mg Pd/C, 1.7 g of 4-(3-

26

Methoxy-phenyl)-piperidine was recovered by the procedure described in Preparation 9. The oily residue was purified by flash chromatography (SiO_2 , CH_2Cl_2 :MeOH, 3:1 (v/v) with 1% NET_3) to give the pure title compound. MS m/z (relative intensity, 70 eV) 191 (M+, 75), 160 (60), 83 (55), 57 (80), 56 (bp)

PREPARATION 11

4-(3-Trifluoromethyl-phenyl)-piperidine

Beginning with 1-Benzyl-4-(3-trifluoromethyl-phenyl)-1,2,3,6-tetrahydro-pyridine (1.44 g), 1 g of the title compound as HCl salt was recovered by the procedure described in preparation 9. m.p. 202°C . (HCl); MS m/z (rel. intensity, 70 eV) 229 (M+, 44), 228 (33), 83 (12), 57 (54), 56 (bp).

PREPARATION 12

4-(3-Methanesulfonyl-phenyl)-piperidine

4-(3-Methanesulfonyl-phenyl)-piperidin-1-carboxylic acid methyl ester (0.92 g) dissolved in ethanol (15 ml) and 8 M HCl (40 ml) was refluxed for 12 hours. The mixture was then evaporated in vacuum to dryness. Yield 0.85 g MS m/z (relative intensity, 70 eV) 239 (M+, 59), 238 (50), 69 (20), 57 (79), 56 (bp).

PREPARATION 13

3-Piperidin-4-yl-phenol

4-(3-Methoxy-phenyl)-piperidine (1.7 g) was dissolved in 48-% HBr (60 ml) and stirred at 120°C . under an Argon-atmosphere for 3 h. The excess of HBr was then evaporated and absolute ethanol added and evaporated. This procedure was repeated several times to yield dry crystals of 3-piperidin-4-yl-phenol×HBr (2.3 g). MS m/z (relative intensity, 70 eV) 177 (M+, bp), 176 (23), 91 (14), 57 (44), 56 (60).

PREPARATION 14

3-(1-Propyl-piperidin-4-yl)-phenol×HBr

Beginning with 3-piperidin-4-yl-phenol×HBr (300 mg) and n-propyl iodide (200 mg), 340 mg of 3-(1-propyl-piperidin-4-yl)-phenol was recovered by the procedure described in Example 1. The HBr salt was prepared to provide the title compound. MS m/z (rel. intensity, 70 eV) 219 (M+, 21), 190 (bp), 119 (22), 91 (30), 70 (63); m.p. $181-184^\circ\text{C}$. (HBr).

PREPARATION 15

3-(1-Ethyl-piperidin-4-yl)-phenol

Beginning with 3-piperidin-4-yl-phenol×HBr (200 mg) and Ethyl iodide (121 mg), 120 mg of 3-(1-ethyl-piperidin-4-yl)-phenol was recovered by the procedure described in Example 1. MS m/z (rel. intensity, 70 eV) 205 (M+, 12), 190 (bp), 119 (36), 91 (22), 70 (87).

PREPARATION 16

3-(1-Butyl-pieridin-4-yl)-phenol

Beginning with 3-piperidin-4-yl-phenol×HBr (200 mg) and n-butyl chloride (73 mg), 118 mg of 3-(1-butyl-piperidin-

27

4-yl)-phenol was recovered by the procedure described in Example 1. MS m/z (rel. intensity, 70 eV) 233 (M+, 6), 190(bp), 119 (42), 91 (26), 70 (45).

PREPARATION 17

1-(3-Methanesulfonyl-phenyl)-piperazine

A mixture of 1-bromo-3-methanesulfonyl-benzene (0.8 g), piperazine (1 g), sodium tert-butoxide (0.5 g) BINAP (42 mg) and [Pd₂(dba)₃] (38 mg) in toluene (7 ml) was heated under argon at 80° C. for 24 h. After cooling to room temperature, the solvent was evaporated to dryness. The crude material was purified by flash chromatography on silica gel using EtOAc. Yield 0.48 g: MS m/z (rel. intensity, 70 eV) 240 (M+, 17), 199 (12), 198 (bp), 119 (9), 56 (7).

PREPARATION 18

1-(3-Trifluoromethanesulfonyl-phenyl)-piperazine

Beginning with 3-bromo-trifluoromethanesulfonyl-benzene and piperazine, the titled cmp was recovered by the procedure described in Preparation 17. MS m/z (rel. intensity, 70 eV) 294 (M+, 22), 252 (bp), 119 (32), 104 (10), 56 (15), (45).

PREPARATION 19

1-(3-Piperazin-1-yl-phenyl)-ethanone

Beginning with 3-bromo-acetophenone and piperazine, the titled cmp was recovered by the procedure described in Preparation 17. MS m/z (rel. intensity, 70 eV) 204 (M+, 5), 162 (35), 77 (30), 57 (35), 56 (bp)

PREPARATION 20

3-(1-Propyl-piperidin-4-yl)-benzoic acid methyl ester

A mixture of trifluoro-methanesulfonic acid 3-(1-propyl-piperidin-4-yl)-phenyl ester (1.2 g), triethyl amine (0.9 g), MeOH (5.4 ml), Pd(OAc)₂ (25 mg) and 1,3-bis(di-phenyl-phosphino)propane (45 mg) in 15 ml DMSO was stirred at room temperature for 15 min. A stream of CO (g) was passed through the solution for 4-5 min., and then the reaction vessel was placed under a slightly positive pressure of CO (g). The temp was increased to 70° C. After 6 h the reaction was allowed to cool to r.t. Water was then added, and the aqueous solution was extracted with five portions of ethyl acetate and the combined organic phases were dried (MgSO₄), and evaporated. The residue was chromatographed on a silica column using MeOH: CH₂Cl₂ (1:9 (v/v)) as eluent. The fractions containing pure titled compound were collected, and the solvent was removed in vacuum, affording 650 mg of the titled compound. (MS m/z (rel. intensity, 70 eV) 261 (M+, 5), 233 (16), 232 (bp), 161 (5), 70 (20)

PREPARATION 21

3-(1-Propyl-piperidin-4-yl)-benzamide

A solution of 3-(1-Propyl-piperidin-4-yl)-benzoic acid methyl ester (0.6 g) and formamide (320 μL) in DMF (9 ml) was heated to 100° C. under a blanket of argon. Sodium methoxide in methanol (30%, 770 μL) was added dropwise and after 1 h, GC analysis revealed the complete absence of

28

starting material and indicated the titled compound as the sole product. After cooling, CH₂Cl₂ was added and the resulting solution was filtered through a pad of celite and evaporated to dryness. The residue was chromatographed on a silica column using MeOH: CH₂Cl₂ (1:3 (v/v)) as eluent. The fractions containing pure titled compound were collected, and the solvent was removed in vacuum, affording 400 mg of the titled compound. m.p. 182° C. (oxalate) (MS m/z (rel. intensity, 70 eV) 246 (M+, 4), 217 (bp), 131 (19), 100 (22), 70 (63).

PREPARATION 22

4-(3-Trifluoromethylsulfonyl-phenyl)-pyridine

1-Bromo-3-trifluoromethylsulfonyl benzene (580 mg) and 4-pyridine-boronic acid (275 mg) was dissolved in toluene (5 ml) and abs EtOH (5 ml). To the mixture was then added Na₂CO₃ (424 mg) and Pd(PPh₃)₄ (119 mg) under an atmosphere of Argon. The resulting mixture was heated to 90° C. for 18 h. Then CH₂Cl₂ was added and the organic phase was washed with water and dried (MgSO₄), filtered and evaporated to dryness. The residue was then used without any further purification. (MS m/z (rel. intensity, 70 eV) 287 (M+, 33), 218 (22), 154 (bp), 127 (56), 69 (27).

The following tests were used for evaluation of the compounds according to the invention.

In Vivo Test: Behavior

For behavioral testing, the animals were placed in separate motility meter boxes 50×50×50 cm equipped with an array of 16×16 photocells (Digiscan activity monitor, RXYZM (16) TAO, Omnitech Electronics, USA), connected to an Omnitech Digiscan analyzer and a Apple Macintosh computer equipped with a digital interface board (NB DIO-24, National Instruments, USA). Behavioral data from each motility meter box, representing the position (center of gravity) of the animal at each time, were recorded at a sampling frequency of 25 Hz and collected using a custom written LABView™ application. The data from each recording session were analyzed with respect to distance traveled and small-scale movements, e.g. stops in the center of the behavioral recording arena, during the recording session. To determine stops in the center, velocity at each time point is calculated as the distance traveled since the preceding sample divided by the time elapsed since the preceding sample. The number of stops is then calculated as the number of times that the velocity changes from a non-zero value to zero. The number of stops in the center of the behavioral recording arena is calculated as the number of stops occurring at a position at least ten centimeters from the edges of the recording arena. For behavioral testing of habituated rats, the animals were placed in the motility meter boxes 30 minutes before the administration of test compound. Each behavioral recording session lasted 6 or 30 minutes, starting immediately after the injection of test compound. Similar behavioral recording procedures was applied for non-habituated rats, habituated rats and drug pre-treated rats. Rats pre-treated with d-amphetamine are given the dose 1,5 mg/kg s.c. 5 min before the behavioral session in the motility meter. Rats pre-treated with dizolcipine (Mk-801) are given the dose 0,7 mg/kg i.p. 90 min before the behavioral session in the motility meter.

In Vivo Test: Neurochemistry

After the behavioral activity sessions the rats were decapitated and their brains rapidly taken out and put on an ice-cold petri-dish. The limbic forebrain, the striatum, the frontal cortex and the remaining hemispherical parts of each rat were dissected and frozen. Each brain part was subsequently analyzed with respect to its content of monoamines and their metabolites. The monoaminergic indices analyzed were dopamine (DA), 3,4-dihydroxy-phenylacetic acid (DOPAC),

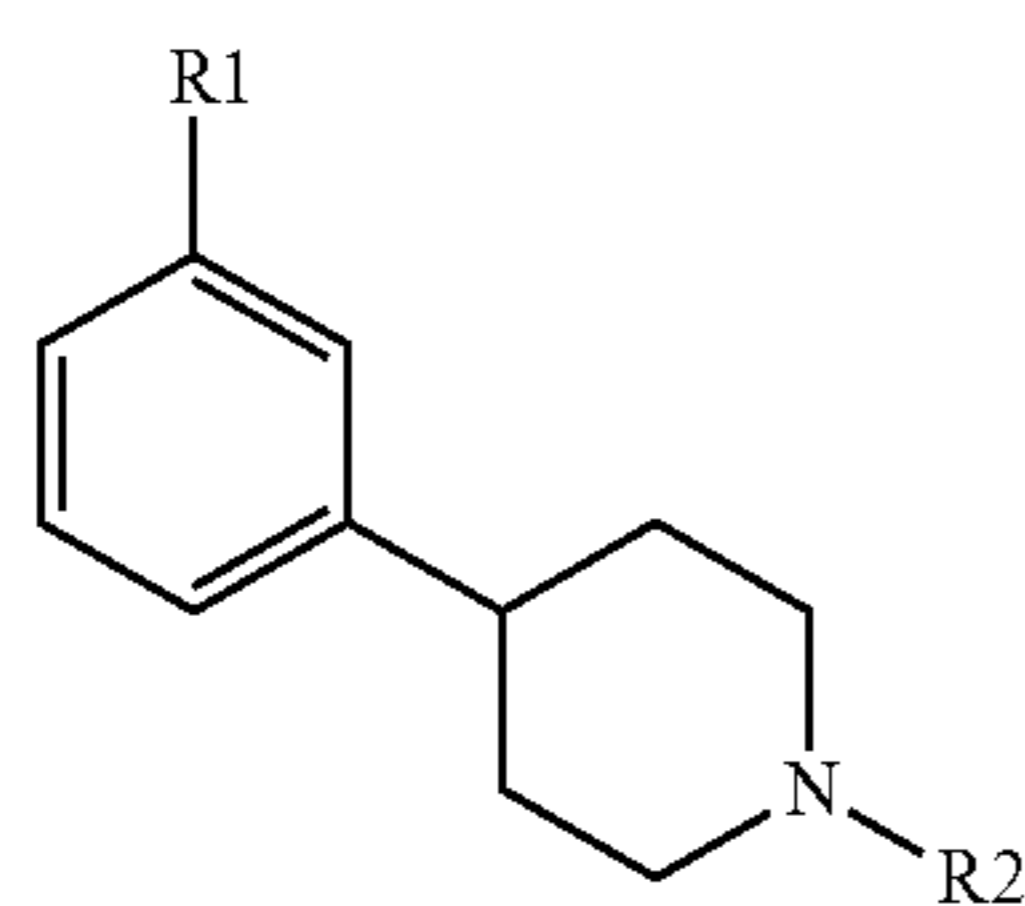
homovanillic acid (HVA), 3-methoxytyramine (3-MT), serotonin (5-HT), 5-hydroxyindole acetic acid (5-HIAA), and noradrenaline (NA). All monoaminergic indices in the dissected tissue were analyzed by means of HPLC with electrochemical detection as described by Svensson K, et al., 1986, Naunyn-Schmiedeberg's Arch Pharmacol 334: 234-245 and references cited therein.

In Vivo Test: Pharmacokinetics in the Rat

To determine oral availability (F) and plasma half life ($t_{1/2}$) of test compounds according to the invention experiments performed in the rat were undertaken. On day one rats were implanted with one catheter in the jugular vein and one catheter in the carotid artery under ketamine anesthesia. On day three test compound is injected either orally or in the jugular vein catheter. Blood samples are collected during 8 hours from the arterial catheter. The blood samples were heparinized and centrifuged. Plasma is collected from the centrifuged samples and frozen. The levels of test compound were subsequently determined in each sample by means of gas chromatography-mass spectrometry (Hewlett-Packard 5972MSD). The plasma samples, taken from the rats of the Sprague-Dawley strain, (0.5 ml) were diluted with water (0.5 ml), and 30 pmol (50 μ l) of ((-)-S-3-(3-Ethylsulfonylphenyl)-N-n-propyl-piperidine as internal standard was added. The pH was adjusted to 11.0 by the addition of 25 μ l saturated Na_2CO_3 . After mixing, the samples were extracted with 4 ml dichloromethane by shaking for 20 min. The organic layer was, after centrifugation, transferred to a smaller tube and evaporated to dryness under a stream of nitrogen and subsequently redissolved in 40 μ l toluene for GC-MS analysis. A standard curve over the range of 1-500 μ mol was prepared by adding appropriate amounts of test compound to blank plasma samples. GC was performed on a HP-Ultra 2 capillary column (12 m \times 0.2 mm ID), and 2 μ l was injected in the splitless mode. The GC temperature was held at 90 $^\circ$ C. for 1 minute following injection, and was then increased by 30 $^\circ$ C./min to the final temperature of 290 $^\circ$ C. Each sample was run in duplicate. The lowest detectable concentration of test compound was generally found to be 1 pmol/ml.

What is claimed is:

[1. A 4-(phenyl-N-alkyl)-piperidine compound of Formula 1:



wherein:

R_1 is selected from the group consisting of OSO_2CF_3 , OSO_2CH_3 , SOR_3 , SO_2R_3 , COCH_3 , and COCH_2CH_3 , wherein R_3 is as defined below;

R_2 is selected from the group consisting of C_2 - C_4 branched or unbranched alkyls, terminal allyl, $\text{CH}_2\text{CH}_2\text{OCH}_3$, $\text{CH}_2\text{CH}_2\text{CH}_2\text{F}$, CH_2CF_3 , 3,3,3-trifluoropropyl, and 4,4,4-trifluorobutyl,

R_3 is selected from the group consisting of C_1 - C_3 alkyls, CF_3 , and $\text{N}(\text{CH}_3)_2$;

or a pharmaceutically acceptable salt thereof, wherein the compound does not have a high binding affinity to sigma receptors.]

[2. A compound according to claim 1, wherein R_1 is selected from the group consisting of OSO_2CF_3 , OSO_2CH_3 , SO_2CH_3 , SO_2CF_3 , COCH_3 , and $\text{SO}_2\text{N}(\text{CH}_3)_2$.]

[3. A compound according to claim 2, wherein R_1 is selected from the group consisting of SO_2CF_3 , SO_2CH_3 , and COCH_3 .]

[4. A compound according to claim 1, wherein R_2 is selected from the group consisting of n-propyl and ethyl.]

5 [5. A compound [according to claim 1, wherein said compound] which is 4-(3-methanesulfonylphenyl)-1-propyl-piperidine or a pharmaceutically acceptable salt thereof.

[6. A pharmaceutical composition comprising [a] the compound according to claim [1] 5 and one or more pharmaceutically acceptable carriers or diluants.

15 [7. The pharmaceutical composition according to claim 6, wherein the pharmaceutical composition is formulated for oral administration.

[8. The pharmaceutical composition according to claim 7, wherein said pharmaceutical composition is formulated as a tablet.

20 [9. The pharmaceutical composition according to claim 7, wherein said pharmaceutical composition is formulated as a capsule.

[10. The pharmaceutical composition according to claim 6, formulated for intravenous (i.v.) administration.

25 [11. A method for treatment of a patient suffering from a condition selected from the group consisting of iatrogenic and non-iatrogenic Parkinsonism, dyskinesias, dystonias, and Tourette's disease, comprising administering a therapeutically active amount of a compound according to claim 1 to said patient.]

30 [12. A method for treatment of a patient suffering from a condition selected from the group consisting of iatrogenic and non-iatrogenic psychoses and hallucinoses, comprising administering a therapeutically active amount of a compound according to claim 1 to said patient.]

35 [13. A method for treatment of a patient suffering from a condition selected from the group consisting of mood and anxiety disorders, comprising administering a therapeutically active amount of a compound according to claim 1 to said patient.]

40 [14. A method for treatment of a patient suffering from a sleep disorder, comprising administering a therapeutically active amount of a compound according to claim 1 to said patient.]

45 [15. A method for treatment of a patient suffering from a condition selected from the group consisting of autism spectrum disorder, ADHD, Huntington's disease and age-related cognitive impairment, comprising administering a therapeutically active amount of a compound according to claim 1 to said patient.]

50 [16. A method for treatment of a patient suffering from a disorder related to abuse of alcohol and substances used as narcotics, comprising administering a therapeutically active amount of a compound according to claim 1 to said patient.]

55 [17. The method according to claim 12, wherein the non-iatrogenic psychoses and hallucinoses are schizophrenia or schizophreniform disorders.]

[18. The method according to claim 13, wherein the mood and anxiety disorder is manodepressive illness, depression or obsessive-compulsive disease.]

[19. A method for treatment of a patient suffering from Parkinson's disease, comprising administering a therapeutically active amount of a compound according to claim 1 to said patient.]

65 [20. A method for treatment of a patient suffering from a condition selected from the group consisting of iatrogenic

31

and non-iatrogenic Parkinsonism, dyskinesias, dystonias, and Tourette's disease comprising administering a therapeutically active amount of a compound according to claim 5 to said patient.

21. A method for treatment of a patient suffering from a condition selected from the group consisting of iatrogenic and non-iatrogenic psychoses and hallucinoses, comprising administering a therapeutically active amount of a compound according to claim 5 to said patient.

22. A method for treatment of a patient suffering from a condition selected from the group consisting of mood and anxiety disorders, comprising administering a therapeutically active amount of a compound according to claim 5 to said patient.

23. A method for treatment of a patient suffering from a sleep disorder, comprising administering a therapeutically active amount of a compound according to claim 5 to said patient.

24. A method for treatment of a patient suffering from a condition selected from the group consisting of autism spectrum disorders, ADHD, Huntington's disease and age-related cognitive impairment, comprising administering a therapeutically active amount of a compound according to claim 5 to said patient.

25. A method for treatment of a patient suffering from a disorder related to abuse of alcohol and substances used as narcotics, comprising administering a therapeutically active amount of a compound according to claim 5 to said patient.

26. The method according to claim 21, wherein the non-iatrogenic psychoses and hallucinoses are schizophrenia or schizophreniform disorders.

27. The method according to claim 22, wherein the mood and anxiety disorder is manodepressive illness, depression or obsessive-compulsive disease.

28. A method for treatment of a patient suffering from Parkinson's disease, comprising administering a therapeutically active amount of a compound according to claim 5 to said patient.

29. A method for treatment of a patient suffering from a condition selected from the group consisting of iatrogenic and non-iatrogenic Parkinsonism, dyskinesias, dystonias, and Tourette's disease, comprising administering a therapeutically active amount of a pharmaceutical composition according to claim 6 to said patient.

30. A method for treatment of a patient suffering from a condition selected from the group consisting of iatrogenic and non-iatrogenic psychoses and hallucinoses, comprising administering a therapeutically active amount of a pharmaceutical composition according to claim 6 to said patient.

31. A method for treatment of a patient suffering from a condition selected from the group consisting of mood and anxiety disorders, comprising administering a therapeutically active amount of a pharmaceutical composition according to claim 6 to said patient.

32. A method for treatment of a patient suffering from a sleep disorder, comprising administering a therapeutically active amount of a pharmaceutical composition according to claim 6 to said patient.

33. A method for treatment of a patient suffering from a condition selected from the group consisting of autism spectrum disorder, ADHD, Huntington's disease and age-related cognitive impairment, comprising administering a therapeutically active amount of a pharmaceutical composition according to claim 6 to said patient.

34. A method for treatment of a patient suffering from a disorder related to abuse of alcohol and substances used as

32

narcotics, comprising administering a therapeutically active amount of a pharmaceutical composition according to claim 6 to said patient.

35. The method according to claim 30, wherein the non-iatrogenic psychoses and hallucinoses are schizophrenia or schizophreniform disorders.

36. The method according to claim 31, wherein the mood and anxiety disorder is manodepressive illness, depression or obsessive-compulsive disease.

37. A method for treatment of a patient suffering from Parkinson's disease, comprising administering a therapeutically active amount of a pharmaceutical composition according to claim 6 to said patient.

38. *The method of claim 24, wherein the condition is Huntington's disease.*

39. *The method of claim 33, wherein the condition is Huntington's disease.*

40. *A method for treatment of a patient suffering from Huntington's disease comprising administering a therapeutically active amount of a pharmaceutical composition according to claim 7 to said patient.*

41. *A method for treatment of a patient suffering from Huntington's disease comprising administering a therapeutically active amount of a pharmaceutical composition according to claim 8 to said patient.*

42. *A method for treatment of a patient suffering from Huntington's disease comprising administering a therapeutically active amount of a pharmaceutical composition according to claim 9 to said patient.*

43. *The compound according to claim 5, wherein the compound is 4-(3-methanesulfonylphenyl)-1-propyl-piperidine hydrochloride.*

44. *The pharmaceutical composition of claim 6, wherein the compound is 4-(3-methanesulfonylphenyl)-1-propyl-piperidine hydrochloride.*

45. *The pharmaceutical composition of claim 7, wherein the compound is 4-(3-methanesulfonylphenyl)-1-propyl-piperidine hydrochloride.*

46. *The pharmaceutical composition of claim 8, wherein the compound is 4-(3-methanesulfonylphenyl)-1-propyl-piperidine hydrochloride.*

47. *The pharmaceutical composition of claim 9, wherein the compound is 4-(3-methanesulfonylphenyl)-1-propyl-piperidine hydrochloride.*

48. *A method for treatment of a patient suffering from Huntington's disease comprising administering a therapeutically active amount of a compound according to claim 43 to said patient.*

49. *A method for treatment of a patient suffering from Huntington's disease comprising administering a therapeutically active amount of a pharmaceutical composition according to claim 44 to said patient.*

50. *A method for treatment of a patient suffering from Huntington's disease comprising administering a therapeutically active amount of a pharmaceutical composition according to claim 45 to said patient.*

51. *A method for treatment of a patient suffering from Huntington's disease comprising administering a therapeutically active amount of a pharmaceutical composition according to claim 46 to said patient.*

52. *A method for treatment of a patient suffering from Huntington's disease comprising administering a therapeutically active amount of a pharmaceutical composition according to claim 47 to said patient.*