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Bioorganic & Medicinal Chemistry Letters
Bioorganic & Medicinal Chemistry Letters 17 (2007) 4873–4877

Synthesis and binding affinity of new pyrazole and isoxazole derivatives as potential atypical antipsychotics☆

María Barceló,[a] Enrique Raviña,[a] Christian F. Masaguer,[a,*] Eduardo Domínguez,[b] Filipe Miguel Areias,[b] José Brea[b] and María I. Loza[b]

[a]*Departamento de Química Orgánica, Laboratorio de Química Farmacéutica, Universidad de Santiago de Compostela, E-15782 Santiago de Compostela, Spain*
[b]*Departamento de Farmacología, Facultad de Farmacia, Universidad de Santiago de Compostela, E-15782 Santiago de Compostela, Spain*

Received 22 May 2007; revised 11 June 2007; accepted 12 June 2007
Available online 14 June 2007

Abstract—We describe the synthesis and binding affinities on D_2, 5-HT_{2A} and 5-HT_{2C} receptors of 6-aminomethyl-6,7-dihydro-1*H*-indazol-4(5*H*)-ones and 6-aminomethyl-6,7-dihydro-3-methyl-benzo[*d*]isoxazol-4(5*H*)-ones, as conformationally constrained butyrophenone analogues. One of the new compounds showed good in vitro binding features, and a Meltzer's ratio characteristic of an atypical antipsychotic profile.

Schizophrenia is a complex disorder affecting ca. 1% of the population.[1] The use of classical (typical) neuroleptics such as haloperidol (Fig. 1) for the treatment of this disease is associated with severe mechanism-related side effects, including induction of acute extrapyramidal symptoms (EPS).[2] Also, these compounds are ineffective against the negative symptoms of schizophrenia. The clinical efficacy of classical antipsychotics in the treatment of schizophrenia and other psychotic disorders is directly related to their ability to block dopamine D_2 receptors in the brain.[3] However, it has been reported that the blockage of the dopamine receptor in the striatum is closely associated with extrapyramidal side effects.[4]

The introduction of clozapine (Fig. 1) for treatment-resistant schizophrenia gave rise to a new group of atypical or nonclassical antipsychotics that have no EPS at the doses frequently used in therapy, and are effective also against the negative symptoms.[5] Clozapine exhibits potent affinities at multiple receptors,[6] its action at 5-HT receptors is now thought to mediate its beneficial effects on cognition, negative symptoms and the low incidence of EPS,[7] but it also displays affinity for dopamine receptors, related to its efficacy on positive symptoms, as well as α-adrenergic, muscarinic and histaminergic (H_1) receptors. Meltzer et al.[8] related the special clinical profile of clozapine and other atypical antipsychotics with an empirical ratio, the so-called Meltzer Index, between D_2 and 5-HT_{2A} receptors.[9] They proposed that this ratio

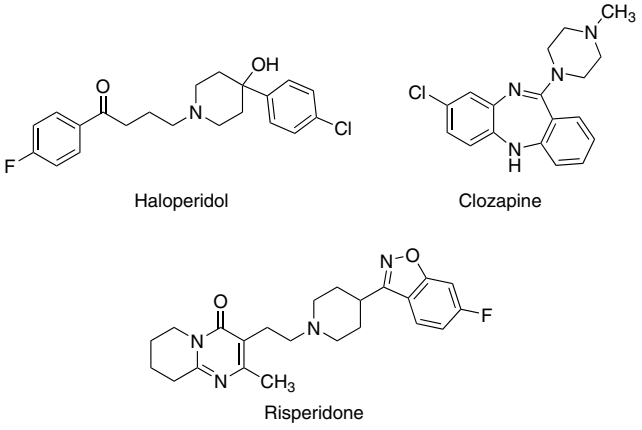

Figure 1. Structures of some antipsychotics.

Keywords: Pyrazole; Isoxazole; Butyrophenones; Antipsychotics; Dopamine; Serotonin.

☆ This is the 36th paper in the series 'Synthesis and CNS Activity of Conformationally Restricted Butyrophenones'; for preceding paper, see Ref. 21.

* Corresponding author. Tel.: +34 981 594 628; fax: +34 981 594 912; e-mail: qojcfm@usc.es

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doi:10.1016/j.bmcl.2007.06.045

may be used to discriminate atypical antipsychotics (ratio >1.12) from classical antipsychotics (<1.09). Experimental and clinical studies seem to confirm the major role of the 5-HT_{2A} receptor for the atypical profile of the antipsychotics.[10] Additionally, many of the atypical antipsychotic agents block not only 5-HT_{2A}, but also other serotonin receptors, particularly 5-HT_{2C}.[11] It has also been suggested that 5-HT_{2C} receptor blockade is responsible for reducing EPS.[12] These findings have made the 5-HT_{2C} receptor a potential target in the treatment of psychotic illnesses.[13]

Four decades after its introduction into the clinic, clozapine remains the prototype of atypical antipsychotic drugs, and no currently available agents appear to have the spectrum of efficacy of this drug. However, treatment with clozapine is associated with an increased risk of agranulocytosis,[14] which strongly limits its therapeutic use. Hence, the discovery of a more-effective, side-effects free therapy for the treatment of schizophrenia remains a challenging research goal.

Over the last few years, we have been working on the modulation of the butyrophenone system, with the aim of combining the antagonism at the 5-HT_2 family and the D_2 receptors in a single molecule.[15] We have reported the synthesis, pharmacology and molecular modelling of the 'aminobutyrophenones' (substructure marked bold) called QF0408B, QF0409B, QF1003B and QF1004B (Fig. 2), which show high affinity for the 5-HT_{2A} receptor subtype, with pK_i values of 8.06, 8.37, 7.29 and 7.97, respectively.[16] As part of our ongoing work on the development of strategies for the preparation of new atypical antipsychotics, we explored the possibility of synthesizing analogues of the above-mentioned aminobutyrophenones, in which the furan or pyrrole ring of these compounds was replaced by pyrazole and isoxazole, to form a tetrahydro-indazolone or -benzisoxazolone system, respectively, considering that the substitution of –CH= by –N= in aromatic rings has been one of the most-successful applications of classical isosterism.[17] In this paper, we report the synthesis of two new series of conformationally constrained aminobutyrophenones, and the evaluation of their affinity on several dopamine and serotonin receptors.

For the synthesis of the indazolones **15** and **16**, and benzisoxazolones **17** we have used 5-(methoxymethyl)cyclohexane-1,3-dione **1** (Scheme 1) as a starting material, which was prepared from the commercial 3,5-dimethoxy- (or 3,4,5-trimethoxy-) benzoic acid in a four-step procedure, as previously described by our research laboratory.[18]

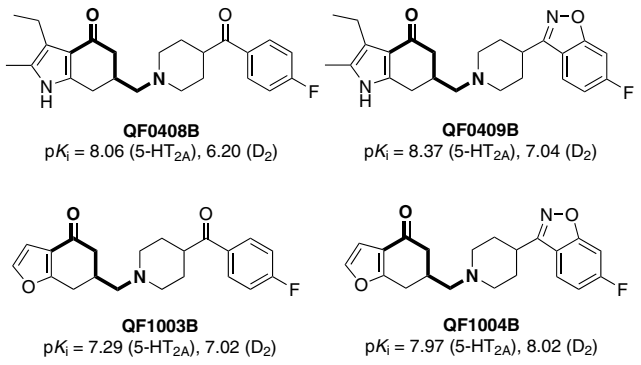


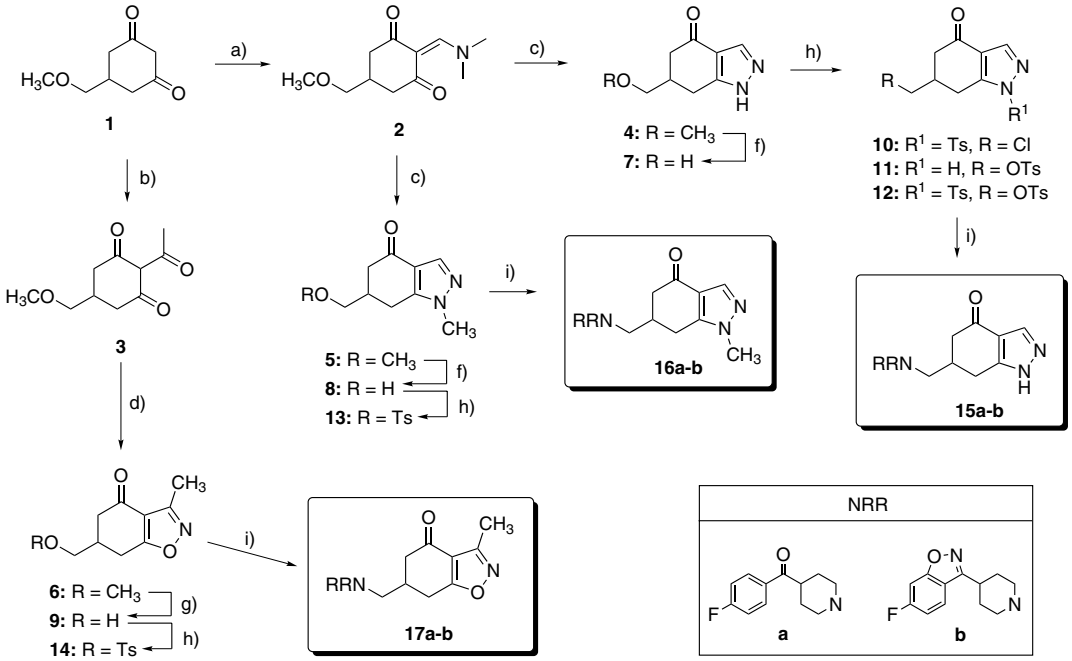
Figure 2. Structures of some heterocyclic aminobutyrophenones.

The synthon **1** was condensed with *N*,*N*-dimethylformamide dimethylacetal (DMFDMA) to give amino ketone **2** in 95% yield. On the other hand, **1** was converted into 2-acetyl derivative **3** by treatment with acetic anhydride and triethylamine in the presence of 4-(dimethylamino)-pyridine (DMAP) in 69% yield. By a Michael addition–elimination/cyclodehydration process, using hydrazine dihydrochloride and NaOH at reflux, **2** was transformed into pyrazole **4** in 70% yield, and methylhydrazine at reflux afforded **5** as a single regioisomer, also in 70% yield. In the same way, condensation of **3** with hydroxylamine hydrochloride in the presence of KOH yielded **6** in 71%. Methyl ethers of **4** and **5** were cleaved with BBr_3 in CH_2Cl_2 at −40 °C → rt, affording the corresponding alcohols **7** and **8** in 81% and 40% yield, respectively. Forcing these conditions (2 mol equiv BBr_3, higher temperatures, or longer reaction times) or using other reagents, such as trimethylsilane iodide, gave complex mixtures of products.

Similarly, methylether cleavage of benzisoxazolone **6** with BBr_3 led to alcohol **9** in a modest 30% yield. The addition of 15-crown-5 to BBr_3 allowed us to improve the yield up to 56%.

Tosylation of **7** was complicated due to the reaction between the unprotected nitrogen of the pyrazole ring and the tosyl chloride: first attempts for tosylation of the hydroxyl group led to a mixture of chloride **10**, monotosylate **11** and ditosylate **12**. Then, we decided to increase the number of equivalents of tosyl chloride to force the formation of ditosyl derivative **12**, to further deprotect the pyrazole ring; under these conditions, ditosylate **12** was obtained in 50% yield as the only product. Tosylation of alcohols **8** and **9** under standard conditions furnished the corresponding sulfonates **13** and **14** in 71% and 61% yield, respectively. Tosylates **12**–**14** were converted into the required amines **15**–**17** by nucleophilic displacement of the tosyl group by the corresponding substituted piperidines ***a*** or ***b*** (Scheme 1). Yields and conditions of the synthesized piperidine derivatives are collected in Table 1.[19] Nucleophilic substitution reaction of ditosylate **12** by piperazines proceeded with simultaneous attack at the electron-deficient sulfur atom of the *N*-tosylpyrazole, which resulted in deprotection of the pyrazole ring, affording the desired amines **15a** and **15b** in a single step. Deprotection of *N*-tosylpyrazoles with hydrazine has been reported,[20] but this is, to our knowledge, the first example of this cleavage with a secondary amine.

The affinity of the compounds **15**–**17** for cloned human D_2, 5-HT_{2A} and 5-HT_{2C} receptors was evaluated in in vitro binding assays using the radioligands [^{3}H]spiperone, [^{3}H]ketanserin and [^{3}H]mesulergine, respectively, according to our previously described procedures.[21] K_i values (expressed as pK_i) were calculated according to



Scheme 1. Reagents and conditions: (a) DMFDMA, THF, 80 °C, 3 h, 95%; (b) Ac_2O, Et_3N, DMAP, $CHCl_3$, rt, 24 h, 69%; (c) $NH_2NH_2{\cdot}2HCl$, NaOH, MeOH, 80 °C, 4 h, 70%; (d) NH_2NHCH_3, MeOH, 80 °C, 2.5 h, 70%; (e) $NH_2OH{\cdot}HCl$, KOH, MeOH, C_6H_6, rt, 48 h, 71%; (f) BBr_3, CH_2Cl_2, −40 °C → rt, 24 h, 40–81%; (g) BBr_3, 15-crown-5, CH_2Cl_2, −30 °C, 4 h, 56%; (h) TsCl, Py, rt, 24 h, 50–71%; (i) HNRR, solvent, reflux (see Table 1).

Table 1. Conditions and yields of synthesized compounds **15**–**17**

Compound	Solvent	Time (h)	Yield[a] (%)	Microanalysis	Mp (°C)
15a	CH_3CN	24	24	$C_{20}H_{22}FN_3O_2{\cdot}2HCl{\cdot}0.5H_2O$	220–223
15b	CH_3CN	72	44	$C_{20}H_{21}FN_4O_2{\cdot}2HCl{\cdot}2.9H_2O$	204–207
16a	CH_3CN	96	27	$C_{21}H_{24}FN_3O_2$	169–170
16b	C_6H_6	19	47	$C_{21}H_{23}FN_4O_2{\cdot}HCl$	220–221
17a	CH_3CN	31	50	$C_{21}H_{23}FN_2O_3{\cdot}0.1H_2O$	129–130
17b	CH_3CN	24	50	$C_{21}H_{22}FN_3O_3{\cdot}HCl{\cdot}0.35H_2O$	212–215

[a] Yields after purification by column chromatography.

Table 2. Binding affinities for compounds **15a**,**b**–**17a**,**b** (see Scheme 1) and reference antipsychotics

Compound	pK_i[a]			pK_i ratio
	5-HT_{2A}	5-HT_{2C}	D_2	5-HT_{2A}/D_2
15a (QF4104B)	7.37 ± 0.22	<5	6.40 ± 0.15	1.15
15b (QF4108B)	8.67 ± 0.19	6.91 ± 0.16	6.95 ± 0.06	1.25
16a (QF4124B)	7.52 ± 0.16	6.96 ± 0.18	<5	—
16b (QF4128B)	7.76 ± 0.44	6.15 ± 0.30	<5	—
17a (QF4214B)	7.39 ± 0.12	<5	<5	—
17b (QF4218B)	7.76 ± 0.32	6.13 ± 0.27	6.92 ± 0.30	1.12
QF0409B[b]	8.37 ± 0.80	6.42 ± 0.02	7.04 ± 0.07	1.19
QF1004B[b]	7.97 ± 0.03	6.47 ± 0.26	8.02 ± 0.11	0.99
Haloperidol	6.78 ± 0.25	5.14 ± 0.18	9.22 ± 0.12	0.73
Clozapine	8.04 ± 0.31	7.98 ± 0.11	6.65 ± 0.17	1.21
Risperidone	9.30 ± 0.25	8.13 ± 0.16	8.21[c]	1.13

[a] Values are means of two separate experiments.
[b] Data from Ref. 16.
[c] Value taken from Ref. 23.

the Cheng–Prusoff equation,[22] and the in vitro receptor binding data are summarized in Table 2.

All compounds displayed higher affinity for the serotonin 5-HT_{2A} receptor [pK_i values ranging between 7.37 (**15a**) and 8.67 (**15b**)] than for the serotonin 5-HT_{2C} or dopamine D_2 receptors. Also, those compounds bearing a 6-fluorobenzisoxazolylpiperidine moiety (amine ***b***) showed higher affinities for the 5-HT_{2A} receptor than those with a 4-fluorobenzoylpiperidine fragment

(amine ***a***). Compounds **15a**, **15b** and **17b** expressed a modest affinity for the dopamine D_2 receptors compared to haloperidol or risperidone, but similar to that of clozapine. Compounds **16a**, **16b** and **17a** are not considered as potential antipsychotics because of their low affinity to D_2 receptors, although **17a** could have an interesting profile as selective 5-HT_{2A} compound ($pK_i = 7.39$, $K_i = 40.7$ nM). At the 5-HT_{2C} receptor, compounds **15b**, **16a**, **16b** and **17b** showed pK_i values ranging between 6.13 and 6.96, whereas compounds **15a** and **17a** were inactive. The highest affinity compound was **15b** (**QF4108B**), with high affinity at the 5-HT_{2A} receptors ($pK_i = 8.67$, $K_i = 2.1$ nM), and moderate affinity for 5-HT_{2C} and D_2 receptors (both pK_is' values around 6.9). This behaviour could be attributed to the presence of an NH group in compound **15b** (and not in compounds **16** or **17**), which could establish an additional interaction with an acceptor group in the D_2 receptor binding site. On the basis of the 5-HT_{2A}/D_2 antagonism hypothesis, it is also worth mentioning the indazolone **15b** as a potential atypical antipsychotic, with a Meltzer's ratio of 1.25, higher than 1.12, the value from which Meltzer predicts an atypical profile for antipsychotics.[8]

In comparison with its benzisoxazolylpiperidine analogues **QF0409B** and **QF1004B** (Fig. 2), aminobutyrophenone compound **15b** exhibits similar affinities for the 5-HT_{2A}, 5-HT_{2C} and D_2 receptors to those of indolone derivative **QF0409B**, but a lower affinity for the D_2 receptors compared to **QF1004B** (one order of magnitude), which causes a more favourable 5-HT_{2A}/D_2 pK_i ratio in **15b**. Again, a favourable interaction between N–H (in the pyrrole or the pyrazole ring) and the receptors could be the cause of the similar binding profile of **15b** and **QF0409B**.

For antipsychotics, like the great majority of drugs aimed at CNS targets, the blood–brain barrier (BBB) must be crossed for a therapeutic effect to be exerted. The most important molecular descriptors used to predict BBB penetration are polar surface area (PSA), log *P* and the molecular volume. Therefore, we calculated PSA, C log *P* and molecular volume values for compound **15b** using different software programs and compared them to the values obtained for reference antipsychotics (see Table 3).

For good brain permeation, the PSA—a measure of a molecule's hydrogen-bonding capacity—of the compound should be below a certain limit. Two differing limits have been proposed: van de Waterbeemd et al.[24] suggest a limit of 90 Å^2, whereas Kelder et al.[25] have a lower limit of 60–70 Å^2. The value of polar surface area (75.2 Å^2) indicates that compound **15b** could penetrate the BBB. Lipophilicity (C log *P*) correlates positively with BBB penetration, and the mean value for C log *P* for the marketed CNS drugs is 2.5,[26] which is in good agreement with the range found by Hansch et al.[27] The C log *P* value of indazolone **15b** was calculated as 2.49, which also indicates that this compound has potential to penetrate the BBB. With regard to molecular volume, for compound **15b** there are no significant differences with those of haloperidol, risperidone or clozapine.

Table 3. Calculated polar surface areas (PSA), C log *P* values and volumes for compound **15b** and reference antipsychotics

Compound	PSA[a] (Å^2)	C log *P*[b]	Volume[a] (Å^3)	log *BB*[c]
15b	75.02	2.49	323.968	−0.22
Haloperidol	40.54	4.63	336.979	0.31
Risperidone	64.17	3.37	374.488	−0.13
Clozapine	35.16	3.21	292.303	0.21

[a] Molinspiration cheminformatics (www.molinspiration.com).
[b] OSIRIS Property Explorer, Actelion Pharmaceuticals Ltd (http://www.organic-chemistry.org/prog/peo/index.html).
[c] Predicted from ChemSilico (https://secure.chemsilico.com/).

Several computational methods have been employed for the prediction of BBB-penetrating and nonpenetrating compounds with overall accuracies from 75% to 97%.[28] QSAR models for brain permeation are based on the log of the blood–brain barrier coefficient (log *BB*). To assess whether our compounds are likely to permeate BBB, we calculated the log *BB* value for compound **15b** using a software program based on topological descriptors[29] and compared it to the values obtained for the selection of antipsychotics (see Table 3). Experimental values of log *BB* published cover the range from about −2.00 to +1.04. Within this range, compounds with log *BB* > 0.30 cross the BBB readily, while compounds with a log *BB* < −1.00 are poorly distributed to the brain.[30] For compound **15b**, the log *BB* = −0.22, not too far from that of risperidone (log *BB* = −0.13), seems to indicate a medium BBB penetration.

In summary, new conformationally constrained butyrophenone analogues in the pyrazole and isoxazole series have been synthesized, and their binding affinities were determined. From these data compound **15b** has emerged, which showed the higher affinities for D_2, 5-HT_{2A} and 5-HT_{2C} receptors between the new compounds, and a Meltzer's ratio characteristic of an atypical antipsychotic profile. Moreover, different molecular descriptors and a prediction program suggested that this compound has the potential to penetrate the blood–brain barrier.

Acknowledgment

This work was supported by Spanish *Ministerio de Educación y Ciencia* (Grants SAF2005-08025-C01 and SAF2005-08025-C03) and *Xunta de Galicia* (Grants PGIDIT06PXIC203104PN and PGIDIT06 PXIC 203051PN). A Ph.D. fellowship (FPU) has been granted to M. Barceló by the *Ministerio de Educación y Ciencia*.

References and notes

1. Reynolds, G. P. *Trends Pharmacol. Sci.* **1992**, *13*, 116.
2. Altar, C. A.; Martin, A. R.; Thurkauf, A., 6th ed. In *Burger's Medicinal Chemistry and Drug Discovery*;

Abraham, D. J., Ed.; John Wiley: New Jersey, 2003; Vol. 6, p 599.
3. (a) Seeman, P.; Chou-Wong, M.; Tadesco, J.; Wong, K. *Nature* **1976**, *261*, 717; (b) Peroutka, S. J.; Snyder, S. H. *Am. J. Psychiatry* **1980**, *173*, 1518; (c) Hartman, D. S.; Civelli, O. *Prog. Drug Res.* **1997**, *48*, 173.
4. (a) Sanberg, P. R. *Nature* **1980**, *284*, 472; (b) Nowak, K.; Welsch-Kunze, S.; Kuschinsky, K. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1988**, *337*, 385.
5. (a) Fitton, A.; Heel, R. C. *Drugs* **1990**, *40*, 722; (b) Schwarz, J. T.; Brotman, A. W. *Drugs* **1992**, *44*, 981; (c) Rosenheck, R.; Cramer, J.; Xu, W.; Thomas, J.; Henderson, W.; Frisman, L.; Fye, C.; Charney, D. *N. Engl. J. Med* **1997**, *337*, 809.
6. Roth, B. L.; Sheffler, D. J.; Kroeze, W. J. *Nat. Rev. Drug Disc.* **2004**, *3*, 353.
7. (a) Meltzer, H. Y.; Li, Z.; Kaneda, Y.; Ichikawa, J. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **2003**, *27*, 1159; (b) Roth, B. L.; Hanizavareh, S. M.; Blum, A. E. *Psychopharmacology* **2004**, *174*, 17.
8. (a) Meltzer, H. Y.; Matsubara, S.; Lee, J. C. *Psychopharmacol. Bull.* **1989**, *25*, 390; (b) Roth, B. L.; Tandra, S.; Burgess, L. H.; Sibley, D. R.; Meltzer, H. Y. *Psychopharmacology* **1995**, *120*, 365; (c) Roth, B. L.; Meltzer, H. Y.; Khan, N. *Adv. Pharmacol.* **1998**, *42*, 482.
9. Lowe, J. A., III *Curr. Med. Chem.* **1994**, *1*, 50.
10. (a) Van Oekelen, D.; Luyten, W. H. M. L.; Leysen, J. E. *Life Sci.* **2003**, *72*, 2429; (b) Sipes, T. E.; Geyer, M. A. *Brain Res.* **1997**, *761*, 97; (c) Okuyama, S.; Chaki, S.; Kawashima, N.; Suzuki, Y.; Ogawa, S.; Kumagai, T.; Nakazato, A.; Nagamine, M.; Yamaguchi, K.; Tomisawa, K. *Br. J. Pharmacol.* **1997**, *121*, 515.
11. Di Matteo, V.; Cacchio, M.; Di Giulio, C.; Di Giovanni, G.; Esposito, E. *Pharmacol. Biochem. Behav.* **2002**, *71*, 607.
12. Reavill, C.; Kettle, A.; Holland, V.; Riley, G.; Blackburn, T. P. *Br. J. Pharmacol.* **1999**, *126*, 572.
13. Wood, M. D.; Heidbreder, C.; Reavill, C.; Ashby, C. R., Jr.; Middlemiss, D. N. *Drug Dev. Res.* **2001**, *54*, 88.
14. Lieberman, J. A.; Hohn, C. A.; Mikane, J.; Rai, K.; Pisciotta, A. V.; Salz, B. L.; Howard, A. *J. Clin. Psychiatry* **1988**, *49*, 271.
15. (a) Cortizo, L.; Santana, L.; Raviña, E.; Orallo, F.; Fontenla, J. A.; Castro, E.; de Ceballos, M. *J. Med. Chem.* **1991**, *34*, 2242; (b) Fontenla, J. A.; Osuna, J. A.; Rosa, E.; Castro, E.; Loza, I.; G-Ferreiro, T.; Calleja, J. M.; Sanz, F.; Rodriguez, J.; Fueyo, J.; Raviña, E.; Masaguer, C. F.; Vidal, A.; de Ceballos, M. *J. Med. Chem.* **1994**, *37*, 2564; (c) Raviña, E.; Masaguer, C. F. *Curr. Med. Chem. CNS Agents* **2001**, *1*, 43.
16. (a) Masaguer, C. F.; Raviña, E.; Loza, I.; Fontenla, J. A. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 913; (b) Brea, J.; Rodrigo, J.; Carrieri, A.; Sanz, F.; Cadavid, M. I.; Enguix, M. J.; Villazón, M.; Mengod, G.; Caro, Y.; Masaguer, C. F.; Raviña, E.; Centeno, N. B.; Carotti, A.; Loza, M. I. *J. Med. Chem.* **2002**, *45*, 54.
17. (a) Wermuth, C. G. In *The Practice of Medicinal Chemistry*; Wermuth, C. G., Ed., 2nd ed.; Academic Press: Amsterdam, 2003; p 193; (b) Patani, G. A.; LaVoie, E. J. *Chem. Rev.* **1996**, *96*, 3147; (c) Kier, L. B.; Hall, L. H. *Chem. Biodiv.* **2004**, *1*, 138.
18. Pita, B.; Masaguer, C. F.; Raviña, E. *Tetrahedron Lett.* **2000**, *41*, 9835.
19. Data for selected compounds: Compound **15a**: IR: 1667. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.98 (s, 1H); 7.97 (dd, J = 8.9, 5.4 Hz, 2H); 7.14 (t, J = 17.2, 8.6 Hz, 2H); 3.20–3.11 (m, 2H); 2.99–2.85 (m, 2H); 2.68–2.54 (m, 3H); 2.46–2.04 (m, 5H); 1.87–1.78 (m, 4H). MS (EI): *m*/*z* 355 (M^+).
Compound **15b**: IR: 1665, 1616. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.00 (s, 1H); 7.68 (dd, J = 8.7, 5.1 Hz, 1H); 7.23 (dd, J = 8.5, 2.1 Hz, 1H); 7.06 (dt, J = 8.8, 2.0 Hz, 1H); 3.18–2.94 (m, 5H); 2.73–2.11 (m, 7H); 2.09–2.02 (m, 4H). MS (EI): *m*/*z* 368 (M^+).
Compound **16a**: IR: 1666. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.97 (dd, J = 8.8, 5.4 Hz, 2H); 7.84 (s, 1H); 7.14 (t, J = 8.6 Hz, 2H); 3.83 (s, 3H); 3.22–3.10 (m, 2H); 3.06–2.97 (m, 2H); 2.89–2.86 (m, 1H); 2.63–2.35 (m, 4H); 2.28–2.04 (m, 1H); 1.89–1.80 (m, 2H). MS (CI): *m*/*z* 370 (100).
Compound **16b**: IR: 1662, 1613. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.85 (s, 1H); 7.67 (dd, J = 8.7, 5.1 Hz, 1H); 7.25–7.22 (m, 1H); 7.06 (dt, J = 8.8, 2.1 Hz, 1H); 3.84 (s, 3H); 3.09–2.93 (m, 5H); 2.65–2.40 (m, 3H); 2.30–2.22 (m, 4H); 2.18–2.06 (m, 4H). MS (EI): *m*/*z* 382 (M^+).
Compound **17a**: IR: 1682. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.96 (dd, J = 8.8, 5.5 Hz, 2H); 7.14 (t, J = 8.5 Hz, 2H); 3.25–3.15 (m, 2H); 2.96–2.85 (m, 2H); 2.76–2.61 (m, 3H); 2.46 (s, 3H); 2.40 (d, J = 6.6 Hz, 1H); 2.33–2.06 (m, 4H); 1.85–1.83 (m, 4H). MS (EI): *m*/*z* 370 (M^+).
Compound **17b**: IR: 1683, 1610. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.67 (dd, J = 8.7, 5.1 Hz, 1H); 7.23 (dd, J = 8.5, 2.1 Hz, 1H); 7.05 (dt, J = 8.8, 2.1 Hz, 1H); 3.20 (dd, J = 17.3, 4.6 Hz, 1H); 3.08–2.92 (m, 3H); 2.77–2.61 (m, 3H); 2.45 (s, 3H); 2.45–2.42 (m, 1H); 2.34–2.13 (m, 4H); 2.09–2.00 (m, 4H). MS (EI): *m*/*z* 383 (M^+).
20. Tominaga, Y.; Shigemitsu, Y.; Sasaki, K. *J. Heterocycl. Chem.* **2002**, *39*, 571.
21. Brea, J.; Castro, M.; Loza, M. I.; Masaguer, C. F.; Raviña, E.; Dezi, C.; Pastor, M.; Sanz, F.; Cabrero-Castel, A.; Galán-Rodríguez, B.; Fernández-Espejo, E.; Maldonado, R.; Robledo, P. *Neuropharmacology* **2006**, *51*, 251.
22. Cheng, Y.-C.; Prusoff, W. H. *Biochem. Pharmacol.* **1973**, *22*, 3099.
23. Schotte, A.; Janssen, P. F.; Gommeren, W.; Luyten, W. H.; Van Gompel, P.; Lesage, A. S.; De Loore, K.; Leysen, J. E. *Psychopharmacology* **1996**, *124*, 57.
24. van de Waterbeemd, H.; Camenisch, G.; Folkers, G.; Chretien, J. R.; Raevsky, O. A. *J. Drug Target.* **1998**, *6*, 151–165.
25. Kelder, J.; Grootenhuis, P. D. J.; Bayada, D. M.; Delbressine, L. P. C.; Ploemen, J.-P. *Pharm. Res.* **1999**, *16*, 1514.
26. Leeson, P. D.; Davis, A. M. *J. Med. Chem.* **2004**, *47*, 6338.
27. Hansch, C.; Steward, A. R.; Anderson, S. M.; Bentley, D. *J. Med. Chem.* **1967**, *11*, 1.
28. Zhao, Y. H.; Abraham, M. H.; Ibrahim, A.; Fish, P. V.; Cole, S.; Lewis, M. L.; de Groot, M. J.; Reynolds, D. P. *J. Chem. Inf. Model.* **2007**, *47*, 170.
29. http://www.chemsilico.com/CS_prBBB/BBBhome.html.
30. (a) Iyer, M.; Mishra, R.; Han, Y.; Hopfinger, A. J. *Pharm. Res.* **2002**, *19*, 1611; (b) Abraham, M. H.; Takacs-Novak, K.; Mitchell, R. C. *J. Pharm. Sci.* **1997**, *86*, 310.