Available online at www.sciencedirect.com
ScienceDirect
Bioorganic & Medicinal Chemistry Letters 17 (2007) 2987–2991
Bioorganic & Medicinal Chemistry Letters

Discovery of heterobicyclic templates for novel metabotropic glutamate receptor subtype 5 antagonists

Santosh S. Kulkarni and Amy Hauck Newman*

Medicinal Chemistry Section, National Institute on Drug Abuse, Intramural Research Program, NIH, DHHS, 5500 Nathan Shock Drive, Baltimore, MD 21224, USA

Received 16 March 2007; accepted 21 March 2007
Available online 24 March 2007

Abstract—Investigation of a series of heterobicyclic compounds with essential pharmacophoric features of the metabotropic glutamate receptor 5 (mGluR5) antagonists MPEP and MTEP provided novel structural templates with sub-micromolar affinities at the mGluR5.
Published by Elsevier Ltd.

The metabotropic glutamate receptor 5 (mGluR5) belongs to family C of the G-protein coupled receptors (GPCR) and it mediates the actions of the excitatory neurotransmitter, L-glutamate.[1–3] Recently, preclinical investigation into the role of mGluR5 in anxiety, depression, pain, mental retardation, and drug dependence has suggested that the mGluR5 may be a novel target for therapeutic intervention.[4] In particular, studies using either an mGluR5 antagonist or mGluR5 knockout mice showed reduced locomotor stimulant effects induced by cocaine.[5] Moreover, mGluR5 appears to be involved in the rewarding effects of morphine, nicotine, and ethanol.[6] Thus, development of selective mGluR5 antagonists may provide a novel strategy toward the discovery of medications for various CNS disorders.

The alkyne based non-competitive mGluR5 antagonists MPEP (**1**) and MTEP (**2**) have been used to investigate the role of mGluR5 in CNS disorders.[7] A series of compounds with different structural templates incorporating tetrazoles, phenyl ureas, thiopyrimidines, and arylmethoxy pyridines have been reported recently as mGluR5 antagonists[8] (Fig. 1).

To further explore the SAR at mGluR5 and to seek compounds with novel structural templates, we have designed a series of compounds based on the SAR developed from our diaryl- and heterobiaryl amides.[9] Herein, we describe the discovery of novel heterobicyclic leads and preliminary SAR studies on these compounds.

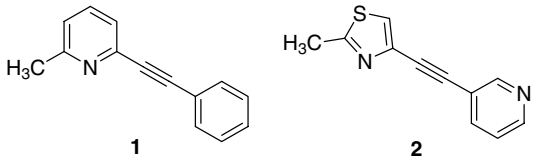


Figure 1. Non-competitive antagonists of mGluR5, MPEP **1** and MTEP **2**.

The allosteric ligand binding site of MPEP-like antagonists at mGluR5 has been predicted to be in the transmembrane region of the receptor.[10] The binding site consists of two hydrophobic regions, wherein the aromatic rings (**a** and **b**) of the compounds interact, with a linker in between, to position these groups in proper orientation. The pyridyl 'N' is essential for activity, and there is a limited tolerance of substitutions on both the aromatic rings. Bearing this in mind, we introduced the pyridyl ring in a bicyclic ring system (heterobicyclic compounds, Fig. 2), whereby the important pharmacophoric groups were kept intact. Thus, a series of quinoline, benzothiazole, and pyridothiazole analogues were synthesized, as depicted in Schemes 1–4, and evaluated for binding at mGluR5.

The 7-substituted quinolines were obtained as shown in Scheme 1. The 7-chloro-2-methyl quinoline **4** was

Keywords: Metabotropic glutamate receptor 5; Non-competitive antagonist; Suzuki–Miyaura coupling.
* Corresponding author. Tel.: +1 410 550 6568x114; fax: +1 410 550 6855; e-mail: anewman@intra.nida.nih.gov

0960-894X/$ - see front matter Published by Elsevier Ltd.
doi:10.1016/j.bmcl.2007.03.066

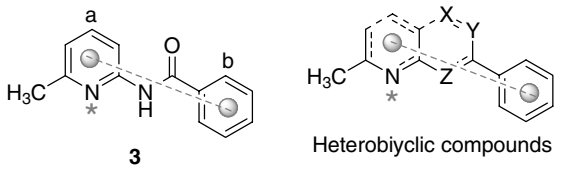
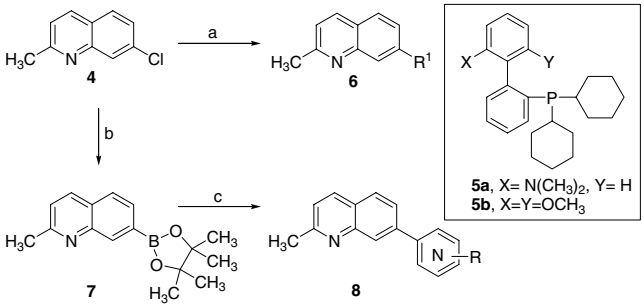
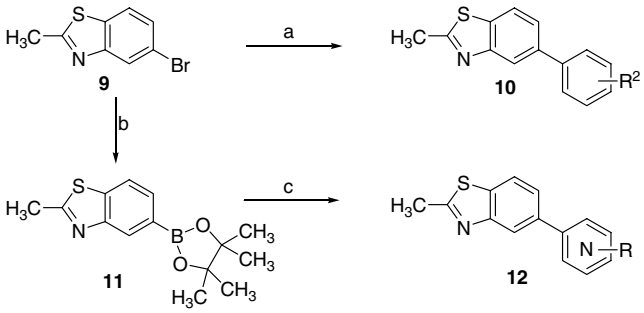


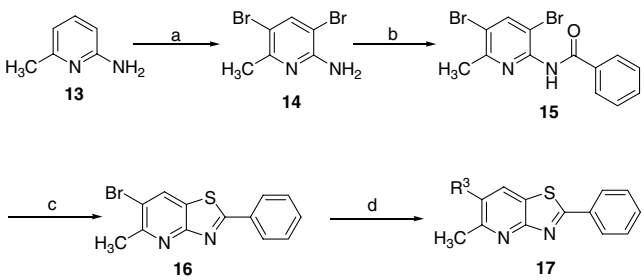
Figure 2. Design of heterobicyclic mGluR5 antagonsits.



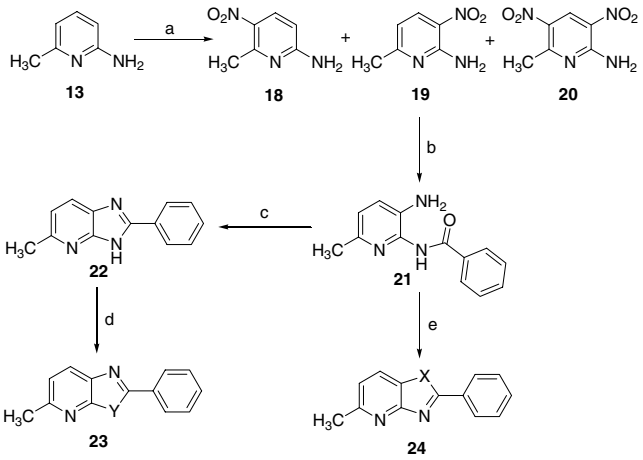
Scheme 1. Synthesis of compounds **6**–**8**. Reagents and conditions: (a) aryl boronic acid, $Pd(OAc)_2$, **5a**–**b**, K_3PO_4, toluene, ethanol, 100 °C, overnight, 55–95%; (b) bis(pinacolato)diboron, KOAc, **5b**, $Pd(OAc)_2$, 100 °C, 60 h, 95%; (c) Ar-Br, $PdCl_2(dppf)$, 2 M Na_2CO_3, dioxane, 100 °C, 40–88%; Ar-Cl, $Pd(OAc)_2$, **5b**, K_3PO_4, dioxane, H_2O, 100 °C, overnight, 43–86%.



Scheme 2. Synthesis of compounds **10**–**12**. Reagents and conditions: (a) aryl boronic acid, $Pd(PPh_3)_4$, 2 M aq Na_2CO_3, toluene, ethanol, reflux 5 h, 65–70%; (b) bis(pinacolato)diboron, KOAc, $PdCl_2(dppf)$, DMF, 105 °C, 3 h, 95%; (c) Ar-Br, $PdCl_2(dppf)$, 2 M Na_2CO_3, dioxane, 100 °C, 65%; Ar-Cl, $Pd(OAc)_2$, **5b**, K_3PO_4, dioxane, H_2O, 100 °C, overnight, 40%.



Scheme 3. Synthesis of compounds **15**–**17**. Reagents and conditions: (a) NBS, DMF, rt, 1 h, 95%; (b) benzoyl chloride, pyridine, reflux, 80%; (c) Lawesson's reagent, HMPA, 140 °C, 1 h, ~95%; (d) i—Anhydrous NaOAc, 10% Pd/C, methanol, 60 psi, 45 h; or ii—sodium methoxide, Cu(I)Br, DMF, 120 °C, 30 min; or iii—aryl boronic acid, $Pd(PPh_3)_4$, 2 M aq Na_2CO_3, toluene, ethanol, reflux, 5 h, 50–90%.



Scheme 4. Synthesis of compounds **22**–**24**. Reagents and conditions: (a) Concd HNO_3, Concd H_2SO_4; (b) i—benzoyl chloride, toluene, dioxane, reflux, 24 h, 35%; ii—10% Pd/C, methanol, H_2, 60 psi, rt, ~98%; (c) NaOAc, gl. HOAc, 90%; (d) NaH, aryl/alkyl halides, DMF, ~40%; (e) i—benzaldehyde, 4A molecular sieves, methanol; ii—$NaBH_3CN$, rt, 1 h; iii—NaOAc, gl. HOAc, overall 86%.

treated with various substituted aryl boronic acids under Suzuki–Miyaura conditions using the biphenyl phosphine ligands **5a**–**b** to give a set of substituted quinolines **6**.[11] In further exploration of the SAR, boronic ester **7** was synthesized using the biphenyl phosphine catalyst and coupled with either heteroaryl bromides or chlorides.

Similarly, benzothiazole compounds (**10**–**12**) were synthesized (Scheme 2) by Suzuki coupling on compound **9**. Additionally the boronic ester (**11**) was synthesized under standard Miyaura borylation conditions and then subjected to Suzuki coupling with various heteroaryl bromides or chlorides.[12]

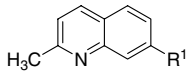
In addition, the pyridothiazole and imidazopyridine compounds were synthesized as shown in Schemes 3 and 4. wherein, 6-methyl 2-amino pyridine **13** was brominated with excess *N*-bromo succinimide (NBS). The benzamide (**15**) was then prepared with relative ease, which underwent cyclization in the presence of Lawesson's reagent to afford bromopyridothiazole **16**.[13] The compound **16** was then treated with various reagents to give a small set of substituted pyridothiazoles (**17**).

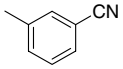
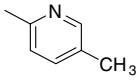
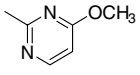
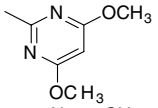
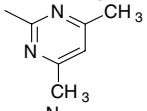
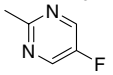
The imidazopyridines were obtained by nitrating the 6-methyl-2-amino pyridine **13** to obtain a mixture of regioisomeric nitropyridines (**18**–**20**), which were purified with extreme care by steam distillation.[14] The 3-nitro compound **19** was treated with benzoyl chloride to obtain the benzamide, which was cyclized into imidazopyridine **22**, after reduction of the nitro group.[15] The substituted imidazopyridines were synthesized by treating compound **22** with various alkyl or arylalkyl bromides in the presence of NaH. Compound **24** was obtained by treating the benzamide **21** with benzaldehyde under reductive amination conditions, followed by cyclization.[16]

The compounds were evaluated for biological activity in a rat brain membrane preparation using [^{3}H]MPEP as the radioligand to measure binding affinity at mGluR5. Data for all novel compounds described herein were obtained through the NIMH PDSP program using methods cited[17] in Tables 1–3 and compared with reference compound **1** and a diarylamide analogue **3a**.[9a]

Substitution of a phenyl ring at the 7 position of quinoline (compound **6a**) showed 50% radioligand displacement at a concentration of 10 μM at mGluR5; a substantial decrease in affinity as compared to MPEP. Moreover, substitution with the bioisosteric thiophene

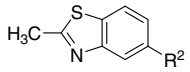
Table 1. Structures and mGluR5 binding affinities of substituted quinolines

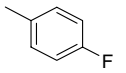
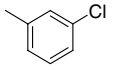
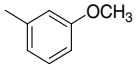
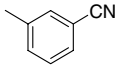
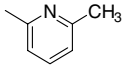
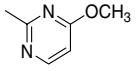


Compound	R^1	mGluR5 binding affinity $K_i \pm$ SEM (μM)
6a		50%
6b		<1%[a]
6c		0.11 ± 0.02
8a		28%[a]
8b		>60
8c		>20
8d		9%[a]
8e		1.55 ± 0.17
8f		5.43 ± 0.83
8g		2.09 ± 0.40
8h		>1%[a]
1	MPEP	0.02 ± 0.001
3a[c]	—	0.33 ± 0.02[b]

[a] Percent inhibition at 10 μM.
[b] IC_{50} (μM) using methods described in Ref. 9a.
[c] 3-cyano-*N*-(6-methylpyridin-2-yl)benzamide from Ref. 9a.

Table 2. Representative structures and mGluR5 binding affinities of substituted benzothiazoles



Compound	R^2	mGluR5 binding affinity $K_i \pm$ SEM (μM)
10a		NA[a]
10b		NA[a]
10c		43.39 ± 3.29[b]
10d		43.05 ± 2.47[b]
10e		2.10 ± 0.58
12a		17%[c]
12b		29%[c]
12c		39%[c]

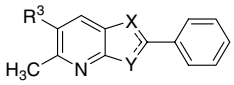
[a] Not active at 100 μM.
[b] IC_{50} (μM) using methods described in Ref. 9a.
[c] Percent inhibition at 10 μM.

(**6b**) completely eliminated activity. Substitution on the 7-phenyl ring however improved activity for some analogues, for example, **6c** with a 3-CN group showed a $K_i = 110$ nM in the mGluR5 binding assay. A similar improvement in affinity was observed in the diarylamide series, wherein the 3-CN compound (**3a**) showed improved activity over the unsubstituted lead compound.[9a] In a related series of compounds, substitution with pyridine and pyrimidine rings as a part of aryl ring '**b**' improved the mGluR5 affinity.[9b] Thus, a small set of substituted pyridines/pyrimidines (**8a**–**h**) at the 7-position of the quinoline ring were prepared. Nevertheless, none of these compounds showed any improvement in mGluR5 activity, thereby illustrating a limited tolerance of substitution with inconsistent SAR across different templates.

Substitution on the appended phenyl ring (compounds **10b**–**e**) provided benzothiazoles with moderate affinity (Table 2). The 3-CN compound **10e** showed the highest affinity for mGluR5 in this set. Substitution with either pyridyl or pyrimidinyl rings (**12a**–**c**) did not improve mGluR5 binding affinity, as observed previously in the quinoline series.

Further investigation into other related heterocyclic ring systems that could be modified was undertaken. In this

Table 3. Representative structures and mGluR5 binding affinities of pyridothiazole or imidazopyridine compounds



Compound	R^3	X	Y	mGluR5 binding affinity $K_i \pm$ SEM (μM)
16	Br	S	N	1%[a]
17a	H	S	N	16%[a]
17b	OCH_3	S	N	<1%[a]
17c	Ph	S	N	33.48 ± 2.24[b]
17d	4′F–Ph	S	N	3%[a]
17e	3′Cl–Ph	S	N	1%[a]
17f	3′CN–Ph	S	N	13%[a]
17g	2-Thioph-	S	N	>10
22	H	N	NH	>10
23a	H	N	NCH_2Ph	>10
23b	H	N	NCH_2-c-C_3H_5	<1%[a]
23c	H	N	NCH_3	<1%[a]
24	H	NCH_2Ph	N	>10

[a] Percent inhibition at 10 μM.
[b] IC_{50} (μM) using methods described in Ref. 9a.

pursuit, compounds with a pyridothiazole or imidazopyridine scaffold were synthesized. However, none of this series (**16**–**24**) gave improved mGluR5 activity. In the pyridothiazole series, substitution with additional aromatic rings (**17c**–**g**) to potentially improve the activity by gaining additional hydrophobic interactions did not yield any tractable SAR. Similarly exploration of binding sites in the linker region (**23a**–**c** and **24**) on the imidazopyridine template showed no improvement in activity.

Thus, modifications to seek novel structural templates yielded some substituted quinolines and benzothiazoles with moderate mGluR5 binding affinities. However, there was a limited tolerance of substitution with little discernable SAR in these series of compounds. Similarly, no SAR could be obtained from a large set of compounds recently reported by Zhao et al. as positive allosteric modulators at mGluR5.[18] The discovery of only a few active compounds from exhaustive efforts in structural modifications depicts the inherent difficulty in optimizing the activity at this receptor. In the present study, as observed previously, substitution with a cyano group at the 3′ position of the appended phenyl ring provided some improvements in mGluR5 activity. A superimposition of these templates on the MPEP **1** and compound **3a** analogues shows good overlap of the pharmacophoric features (see Fig. 3). Although there are few minor differences in the overlap, it is difficult to account for the dramatic changes in activity across different templates.

In summary, we identified two structural templates with moderate mGluR5 antagonist activity. Most structural modification did not yield compounds with any improvement in mGluR5 affinity. In the functional assay measuring the hydrolysis of phosphoinositide at mGluR5 in CHO cells, compound **6c** showed antagonist activity ($IC_{50} = 0.26 \pm 0.05$ μM)[19] hence this template may provide a new lead for further SAR investigation.

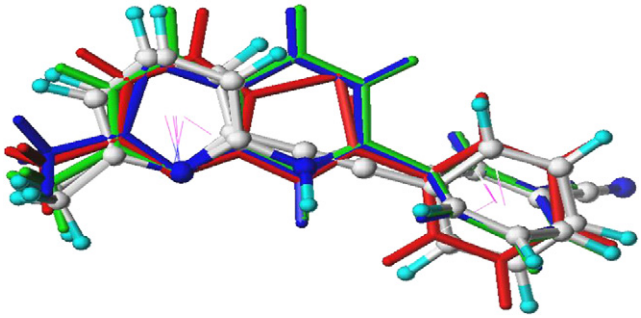


Figure 3. Superimposition of MPEP **1**, compounds **3**, **6a** (green), **10a** (blue), and **17a** (red).

Acknowledgments

SSK was supported by a NIH-visiting fellowship. We thank Dr. Mu-Fa Zou for critically reading this manuscript. We acknowledge Ms. Barbara Nightingale for technical assistance, Dr. Bryan Roth, Director of the National Institute on Mental Health-Psychoactive Drug Screening Program (PDSP), for his support and Ms. Estela Lopez for help with the PDSP database. This work was supported by the NIDA-IRP, NIH.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2007.03.066.

References and notes

1. Conn, P. J.; Pin, J. P. *Annu. Rev. Pharmacol. Toxicol.* **1997**, *37*, 205.
2. Spooren, W. P. J. M.; Gasparini, F.; Salt, T. E.; Kuhn, R. *TIPS* **2001**, *22*, 331.

3. Swanson, C. J.; Bures, M.; Johnson, M. P.; Linden, A. M.; Monn, J. A.; Schoepp, D. D. *Nature Rev. Drug Discov.* **2005**, *4*, 131.
4. (a) Brodkin, J.; Busse, C.; Sukoff, S. J.; Varney, M. A. *Pharmacol. Biochem. Behav.* **2002**, *23*, 207; (b) Tatarczynska, E.; Klodzinska, A.; Chojnacka-Wojcik, E.; Palucha, A.; Gasparini, F.; Kuhn, R.; Pilc, A. *Br. J. Pharmacol.* **2001**, *132*, 1423; (c) Dolan, S.; Kelly, J. G.; Monteiro, A. M.; Nolan, A. M. *Pain* **2003**, *106*, 501; (d) Yan, Q. J.; Rammal, M.; Tranfaglia, M.; Bauchwitz, R. P. *Neuropharmacology* **2005**, *49*, 1053; (e) Li, X.; Need, A. B.; Baez, M.; Witkin, J. M. *J. Pharmacol. Exp. Ther.* **2006**, *319*, 254; (f) Bear, M. F. *Genes Brain Behav.* **2005**, *4*, 393.
5. Chiamulera, C.; Eping-Jordon, M. P.; Zocchi, A.; Marcon, C.; Cottiny, C.; Tacconi, S.; Corsi, M.; Orzi, F.; Conquet, F. *Nature Neurosci.* **2001**, *4*, 873.
6. (a) Popik, P.; Wrobel, M. *Neuropharmacology* **2002**, *43*, 1210; (b) Paterson, N. E.; Semenova, S.; Gasparini, F.; Markou, A. *Psychopharmacology (Berl.)* **2003**, *167*, 257; (c) Backstrom, P.; Bachteler, D.; Koch, S.; Hyytia, P.; Spanagel, R. *Neuropsychopharmacology* **2004**, *29*, 921.
7. (a) Gasparini, F.; Floersheim, P.; Flor, P. J.; Heinrich, M.; Inderbitzin, W.; Ott, D.; Pagano, A.; Stierlin, C.; Stoehr, N.; Vranesic, I.; Kuhn, R. *Farmaco* **2001**, *56*, 95; (b) Cosford, N. D.; Tehrani, L.; Roppe, J.; Schweiger, E.; Smith, N. D.; Anderson, J.; Bristow, L.; Brodkin, J.; Jiang, X.; McDonald, I.; Rao, S.; Washburn, M.; Varney, M. A. *J. Med. Chem.* **2003**, *46*, 204.
8. (a) Roppe, J.; Smith, N. D.; Huang, D.; Tehrani, L.; Wang, B.; Anderson, J.; Brodkin, J.; Chung, J.; Jiang, X.; King, C.; Munoz, B.; Varney, M. A.; Prasit, P.; Cosford, N. D. *J. Med. Chem.* **2004**, *47*, 4645; (b) Wallberg, A.; Nilsson, K.; Osterlund, K.; Peterson, A.; Elg, S.; Raboisson, P.; Baur, U.; Hammerland, L. G.; Mattsson, J. P. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1142; (c) Hammerland, L. G.; Johansson, M.; Malmstrom, J.; Mattsson, J. P.; Minidis, A. B. E.; Nilsson, K.; Peterson, A.; Wensbo, D.; Wallberg, A.; Osterlund, K. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2467; (d) Buttelmann, B.; Peters, J. U.; Ceccarelli, S.; Kolczewski, S.; Vieira, E.; Prinssen, E. P.; Spooren, W.; Schuler, F.; Huwyler, J.; Porter, R. H. P.; Jaeschke, G. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1892.
9. (a) Kulkarni, S. S.; Nightangle, B.; Dersch, C. M.; Rothman, R. B.; Newman, A. H. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3371; (b) Kulkarni, S. S.; Newman, A. H. *Bioorg. Med. Chem. Lett.*, **2007**, *17*, 2074.
10. (a) Pagano, A.; Ruegg, D.; Litschig, S.; Stoehr, N.; Stierlin, C.; Heinrich, M.; Floersheim, P.; Prezeau, L.; Carroll, F.; Pin, J. P.; Cambria, A.; Vranesic, I.; Flor, P. J.; Gasparini, F.; Kuhn, R. *J. Biol. Chem.* **2000**, *275*, 33750; (b) Malherbe, P.; Kratochwil, N.; Zenner, M. T.; Piussi, J.; Diener, C.; Kratzeisen, C.; Fischer, C.; Porter, R. H. *Mol. Pharmacol.* **2003**, *64*, 823.
11. (a) Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685; (b) Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550.
12. Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem.* **1995**, *60*, 7508.
13. Hutchinson, I.; Chua, M. S.; Browne, H. L.; Trapani, V.; Bradshaw, T. D.; Westwell, A. D.; Stevens, M. F. G. *J. Med. Chem.* **2001**, *44*, 1446.
14. Parker, E. D.; Shive, W. *J. Am. Chem. Soc.* **1947**, *69*, 63.
15. Molina, P.; Alajarin, M.; Vidal, A. *Tetrahedron* **1989**, *45*, 4263.
16. All compounds were purified by flash chromatography and characterized by spectroscopic and microanalytical techniques. The final products were crystallized as the HBr salts for biological evaluation. The spectral data supported the assigned structures, for example, *2-methyl-7-(pyrimidin-2-yl)quinoline*, **8c**, mp 276–278 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.78 (s, 3H), 7.22–7.24 (t, J = 4.8 Hz, 1H), 7.31–7.33 (d, J = 8.8 Hz, 1H), 7.87–7.89 (d, J = 8.4 Hz, 1H), 8.07–8.09 (d, J = 8.4 Hz, 1H), 8.53–8.56 (dd, J = 2, 8.4 Hz, 1H), 8.86–8.87 (d, J = 4.8 Hz, 2H), 9.18 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 25.66, 119.60, 123.09, 125.12, 127.96, 128.11, 129.33, 136.08, 138.87, 148.24, 157.60, 159.79, 164.70; IR (Neat, cm^{-1}) 3401.1, 1606.4, 1566.4, 1554.6, 1420.2, 1406.9; GC-MS (EI) *m/z* 221 (M^+); Anal. ($C_{14}H_{11}N_3 \cdot HBr \cdot H_2O$) C, H, N. The experimental and spectral data for all other compounds are reported in the Supporting information.
17. Binding affinities were determined by the National Institute on Mental Health-Psychoactive Drug Screening Program as described in http://pdsp.med.unc.edu/indexR.html.
18. Zhao, Z.; Wisnoski, D. D.; O'Brien, J. A.; Lemaire, W.; Williams, D. L.; Jacobson, M. A.; Wittman, M.; Ha, S. N.; Schaffhauser, H.; Sur, C.; Pettibone, D. J.; Duggan, M. E.; Conn, P. J.; Hartman, G. D.; Lindsley, C. W. *Bioorg. Med. Chem. Lett.* **2006**, *17*, 1386.
19. Functional assay data were provided by the National Institute on Mental Health-Psychoactive Drug Screening Program (PDSP) using methods described in Shi, Q.; Savage, J. E.; Hufeisen, S. J.; Rauser, L.; Grajkowska, E.; Ernsberger, P.; Wroblewski, J. T.; Nadeau, J. H.; Roth, B. L. *J. Pharmacol. Exp. Ther.* **2003**, *305*, 131.