Synthesis and Biological Evaluation of Substituted Pyrazole Constrained Piperazine Derivative Library for Dopamine Receptor Antagonist

Kamalkishor P. Landge,[†] Hyun Ju Song,[†] Jung Gook Lee,[†] Sang Eun Chae,[‡] Ae Nim Pae,[‡] Woo Kyu Park,[§] Vasu Sampath,[¶] Hee Yoon Lee,[¶,*] and Hun Yeong Koh[†,*]

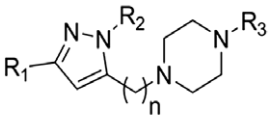
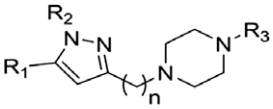
[†]*Department of Chemistry, Inha University, Incheon 22212, Korea. *E-mail: hykoh@inha.ac.kr*
[‡]*Neuro-Medicine Center, Korea Institute of Science and Technology, Seoul, Korea*
[§]*Center for Drug Discovery Technology, Korea Research Institute of Chemical Technology, Korea*
[¶]*Department of Chemistry, Korea Advanced Institute of Science and Technology, Daejeon 34141, Korea. *E-mail: leehy@kaist.ac.kr*
Received October 13, 2016, Accepted October 19, 2016, Published online November 21, 2016

Keywords: Dopamine receptor, Serotonin receptors, Reductive amination, Schizophrenia, G-protein-coupled receptors

The D_2-like dopamine receptors including the subtypes D_2, D_3, and D_4 are members of the large family of G-protein-coupled receptors (GPCRs), also referred to as seven transmembrane receptors. Many central nervous system (CNS)-related diseases like schizophrenia, Parkinson's disease, drug addiction, and erectile dysfunction are associated with D_2-like dopamine receptors.[1] D_3 receptors are localized in the limbic areas of the brain, specifically in the group of neural granule cells located within the ventral striatum in the brains of most animals.[2] The dopamine D_4 receptor is expressed predominantly within the CNS, and despite low abundance relative to the D_2 receptor, localization in the cortex suggests an important functional role. The role of D_4 receptor antagonists in CNS disorders such as schizophrenia has been extensively investigated and it has also been shown that the D_4 receptor could be associated with ADHD, depression, substance abuse, and cognitive disorders.[3] In connection with search for selective ligands for various GPCRs, we have recently reported[4] the design and synthesis of arylpiperazine derivative with isoxazole ring libraries as dopamine receptor antagonist and serotonine receptor antagonist. In further continuation of our research, we developed and synthesized different compounds with piperazine derivative, pyrazole ring with phenyl, *t*-butyl, and benzene derivatives, with isopropyl, propyl as a side chain.

In the synthetic part, diketone **3** was synthesized by opening γ-butyrolactone or δ-valerolactone ring with activated ketone **1** in the presence of sodium methoxide as base in benzene for 12–15 h at room temperature in 57–77% yield. Diketone **3** was easily cyclized with phenyl hydrazine in methanol solvent for 5–12 h at room temperature to produce a mixture of two isomeric pyrazoles **4** and **5** in 30–84% yield. By applying Dess–Martin reagent (when, $n = 3$) and PCC with SiO_2 (when, $n = 2$) for oxidation of alcohols of the mixture of **4** and **5** afforded pyrazolyl aldehydes **6** and **7**, respectively, in dichloromethane at room temperature for 3–5 h in 60–94% yields and two isomeric aldehydes were separated by column chromatography. Following the combinatorial chemistry protocol developed for solution phase combinatorial library formation,[5] reductive amination of the prepared pyrazolyl aldehydes **6** and **7** with a variety of commercially available arylpiperazine derivatives (Table 1) by using $NaBH(OAc)_3$[6] produced HCl salts of the products **8** and **9** derivatives after acid treatment of the reaction products in good yields with high purities (Scheme 1, Table 1). Identities and purities of products were confirmed by ^1H NMR, MS spectroscopies, and HPLC. In the present study, we synthesized a small focused library of more than 200 pyrazolylpiperazine compounds with different side chain and were evaluated *in vitro* for dopamine and serotonin receptors.[7] Table 2 shows the binding affinities for dopamine and serotonin receptors of derivatives from reaction Scheme 1, while Table 3 shows binding affinities only for dopamine D_4 receptor of some selected compounds. By studying the biological data, *syn*-isomeric compounds with 3,4-dimethylphenylpiperazine, 2-OMe-phenylpiperazine, 4-F-phenylpiperazine, and 4-Cl-phenyl piperazine with pyrazole derivatives (**8-4**, **8-4′**, **8-5**, **8-5′**, **8-6**, **8-6′**, **8-7**, **8-7′**) attached to isopropyl and propyl as the side chain showing binding affinities 29.5, 6.5, 33.8, 39.8, 30.4, 9.7, 24.8, and 6.4 nM, respectively, as selective dopamine D_4 receptor antagonists. The *anti*-isomeric compounds with 2,3-dimethylphenylpiperazine, 3,4-dimethylphenylpiperazine, 2-OMe-phenylpiperazine, 4-F-phenylpiperazine, and 4-Cl-phenylpiperazine (**9-3′**, **9-4′**, **9-5′**, **9-6′**,**9-7′**, **9-4**, **9-7**) with pyrazole derivatives with isopropyl and propyl as the side chain also show good binding affinities 49, 11.5, 31.0, 42, 16.2, 17.7, and 19.8 nM. Aside from these

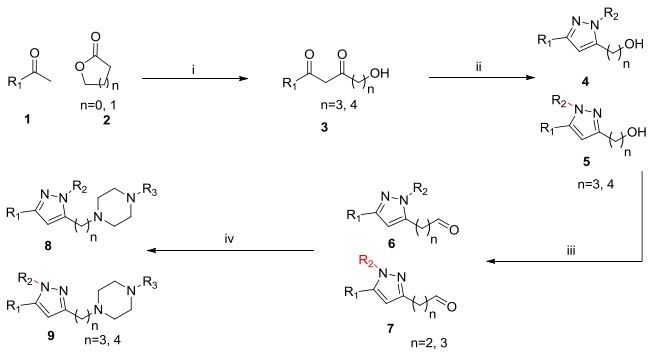
Table 1. A pyrazole library with three points of diversity

Sr.No	R_1	R_2	R_3	*n*	 **8**	 **9**
01	i-pr[a]/pr[b]	Ph	Ph	**4**	**8-1[a](70)[c]/8-1′[b](75)**	**9-1[a](71)[c]/9-1′[b](71)**
02			2-F-Ph		**8-2(71)/8-2′(80)**	**9-2(65)/9-2′(71)**
03			2,3-diMe-Ph		**8-3(65)/8-3′(81)**	**9-3(68)/9-3′(71)**
04			3,4-diMe-Ph		**8-4(68)/8-4′(80)**	**9-4(70)/9-4′(71)**
05			2-MeO-Ph		**8-5(68)/8-5′(75)**	**9-5(64)/9-5′(71)**
06			4-F-Ph		**8-6(68)/8-6′(73)**	**9-6(64)/9-6′(71)**
07			4-Cl-Ph		**8-7(65)/8-7′(63)**	**9-7(70)/9-7′(71)**
08			3-CF_3-Ph		**8-8(65)/8-8′(68)**	**9-8(68)/9-8′(71)**
09			2-Pyrimidine		**8-9(64)/8-9′(76)**	**9-9(60)/9-9′(71)**
10			2-Pyridine		**8-10(70)/8-10′(78)**	**9-10(73)/9-10′(71)**
11			$(4\text{-F-Ph})_2CH$		**8-11(72)/8-11′(64)**	**9-11(70)/9-11′(71)**
12	Ph	Ph	4-MeO-Ph	**3**	**8-12(93)**	—[d]
13	4-Me-Ph	*t*-Bu	Ph	**3**	**8-13(90)**	—
14			2-F-Ph		**8-14(76)**	—
15			3,4-diMe-Ph		**8-15(84)**	—
16	4-MeO-Ph	*t*-Bu	4-MeO-Ph	**3**	**8-16(73)**	—
17			2-F-Ph		**8-17(91)**	—
18			4-Cl-Ph		**8-18(55)**	—
19			3,4-diMe-Ph		**8-19(80)**	**3**
20	4-MeO-Ph	Ph	2-F-Ph	**3**	**8-20(53)**	—
21			4-Cl-Ph		**8-21(82)**	—
22			2,3-diMe-Ph		**8-22(93)**	—
23	4-Cl-Ph	*t*-Bu	Ph	**3**	**8-23(89)**	—
24			3,4-diMe-Ph		**8-24(87)**	—
25	4-F-Ph	*t*-Bu	4-Cl-Ph	**3**	**8-25(80)**	—
26			2,3-diMe-Ph		**8-26(75)**	—
27			4-MeO-Ph		**8-27(58)**	—
28			3,4-diCl-Ph		**8-28(85)**	—
29	2-thiophene	*t*-Bu	3,4-diCl-Ph	**3**	**8-29(94)**	—
30	Propyl	*t*-Bu	2,4-diMe-Ph	**3**	**8-30(98)**	**9-30(84)**
31			2,3-diMe-Ph		**8-31(92)**	**9-31(81)**
32			3,4-diMe-Ph		**8-32(98)**	**9-32(69)**
33	Propyl	Ph	3,4-diMe-Ph	**3**	**8-33(85)**	**9-33(92)**

[a] Derivatives with isopropyl.
[b] Derivatives with propyl.
[c] Yield in percentage.
[d] Second isomer does not formed.

selective derivatives, only compounds with phenyl piperazine and 3-CF_3 phenyl piperazine attached to pyrazole derivatives show useful binding affinities as 42.3 and 5.2 nM, respectively.

In some part, we evaluated some compounds only for dopamine receptor D_4 (Table 3) which showed IC_{50} value in between 100 and 200 nM and near to a reference compound Haloperidol. From Tables 1 and 3, we can conclude that compounds with different side chain (Ph-H, 4-Me-Ph, 4-OMe-Ph, 4-Cl-Ph, 4-F-Ph, thiophene, and propyl) with substituted pyrazole by phenyl and isopropyl group (8–12 ~ 8–33, 9–30 ~ 9–33) which are attached to different piperazine compounds are better compounds for dopamine receptor D_4. In addition to the D_4 activity, most of the compounds are useful for serotonin receptor with good affinity for $5HT_1$a.



Scheme 1. Reagents and reaction conditions: (i) NaOMe, Benzene, rt, 12–15 h, 57–77%; (ii) $PhNHNH_2$, CH_3OH, rt, 5–12 h, 30–84%; (iii) (a) Dess–Martin periodinane, CH_2Cl_2, rt, 3 h, 60–67%. (When, n = 3) (b) PCC, SiO_2, rt, 5 h, 55–94% (When, n = 2); (iv) R_3, DIPEA, $NaBH(OAc)_3$, CH_2Cl_2, 4ÅMS, 12 h, rt, 44–94%.

Experimental

General Procedure for the Synthesis of Derivatives 8 and 9: To a solution of syn or anti 4-(3-isopropyl-1-phenyl-1H-pyrazol-5-yl)butanol (when, R_1 = i-pr and R_2 = Ph) (60 mg, 0.234 mmol), 1-phenylpiperazine (when, R_3 = Ph) (31.6 mg, 0.234 mmol) and DIPEA (0.061 ml, 0.351 mmol) in dichloromethane (5 mL) at rt, 4 Å molecular sieve was added and stirred for 30 min. After the mixture being stirred for 30 min, $NaBH(OAc)_3$ (149 mg, 0.702 mmol) was added and the mixture was stirred for 12 h. Saturated $NaHCO_3$ solution was added and the mixture was extracted with ethyl acetate (5 mL × 5). The organic layers were dried over anhydrous $MgSO_4$ and concentrated. The residue was purified by flash column

Table 2. Binding affinity of dopamine and serotonin receptor

Compound	Binding affinity (IC_{50}, nM)							
	D_4	D_3	D_2	5-HT_{1A}	5-HT_{2A}	5-HT_{2C}	5-HT_6	5-HT_7
8-1	118	219	582	62	218	5318	>10000	21
8-2	102	185	224	41	176	2711	>10000	23
8-3	75	200	359	47	53	273	4536	111
8-4	29.5	1070	1029	129	24	239	2624	62
8-5	33.8	498	132	7.0	1219	3479	7419	7.7
8-6	30.4	1799	1893	93	68	3671	1984	58
8-7	24.8	894	2791	416	58	3256	3261	99
8-8	414	823	587	63	247	579	3635	24
8-10	206	2021	4122	36	989	10000	>10000	42
9-2	133	220	941	49	260	3885	6550	143
9-3	71	150	3107	9.8	29	296	1611	6.9
9-4	17.7	396	298	38	70	274	1021	156
9-5	55	103	20	4.9	2167	3377	>10000	26
9-7	19.8	787	1249	191	107	2088	1330	271
9-8	141	156	399	12	333	443	991	40
9-10	460	942	2725	42	2023	>10000	10000	146
9-11	1024	151	822	2276	38	258	2233	1861
8-1′	42.3	695	530	69	366	7003	10000	48
8-2′	135	228	146	32	549	2717	>10000	72
8-3′	106	106	192	8.6	46	301	2317	13
8-4′	6.5	392	576	20	24	230	1191	118
8-5′	39.8	414	119	4.5	1165	2508	6029	8.0
8-6′	9.7	1467	-	35	69	1612	4840	67
8-7′	6.4	4216	662	235	48	3806	3388	128
8-8′	5.2	1812	529	236	89	2357	3054	150
8-10′	153	1146	1435	48	310	9637	>10000	54
8-11′	337	108	180	1727	29	811	751	689
9-1′	84	392	875	18	209	1554	5161	75
9-2′	155	476	444	21	615	3787	5387	175
9-3′	49	97	609	21	104	370	943	56
9-4′	11.5	578	800	85	91	529	759	230
9-5′	31.0	142	87	3.9	2167	2941	5377	20
9-6′	42	834	3133	24	47	2050	1268	124
9-7′	16.2	498	2055	61	48	1630	1357	281
9-9′	302	1768	1344	27	>10000	>10000	>10000	1204
9-10′	132	626	1084	4.1	2375	4112	9239	152

Table 3. Binding affinity of dopamine receptor D_4

Sr. no.	Compound	IC_{50}, nM	Sr. no.	Compound	IC_{50}, nM
01	**8-12**	179	14	**8-25**	120
02	**8-13**	146	15	**8-26**	153
03	**8-14**	142	16	**8-27**	110
04	**8-15**	159	17	**8-28**	179
05	**8-16**	148	18	**8-29**	107
06	**8-17**	117	19	**8-30**	16
07	**8-18**	118	20	**8-31**	62
08	**8-19**	103	21	**8-32**	59
09	**8-20**	151	22	**8-33**	199
10	**8-21**	114	23	**9-30**	123
11	**8-22**	165	24	**9-31**	130
12	**8-23**	174	25	**9-32**	122
13	**8-24**	106	26	**9-33**	8
Haloperidol		160			

chromatography (EtOAc: Hexane = 3:1) to give the compound **8-1** in 70% and **9-1** in 71%.

^{1}H NMR of compound **8-1**: ^{1}H NMR (400 MHz, MeOH-d_4) δ 7.73–7.64 (m, 5H), 7.33–7.29 (m, 2H), 7.10–7.07 (m, 2H), 7.00–6.96 (m, 1H), 6.74 (s, 1H), 3.90–3.60 (m, 4H), 3.31–3.26 (m, 7H), 3.00–2.90 (m, 2H), 2.02–1.85 (m, 4H), 1.26 (d, 6H, J = 7.2 Hz).

^{1}H NMR of compound **9-1**: ^{1}H NMR (400 MHz, MeOH-d_4) δ 7.71–7.65 (m, 5H), 7.31–7.27 (m, 2H), 7.04 (d, 2H, J = 8 Hz), 6.95 (t, 1H, J = 7.5 Hz), 6.74 (s, 1H), 3.81 (d, 2H, J = 11.6 Hz), 3.64(d, 2H, J = 10 Hz), 3.23–3.14 (m, 7H), 2.77 (t, 2H, J = 7.5 Hz), 1.85–1.77 (m, 4H), 1.40 (d, 6H, J = 6.8 Hz).

^{1}H NMR of compound **8-1′**: ^{1}H NMR (400 MHz, MeOH-d_4) δ 7.61–7.47 (m, 5H), 7.31–7.27 (m, 2H), 7.03–7.11 (m, 2H), 6.96–6.92 (m, 1H), 6.36 (s, 1H), 3.88–3.30 (m, 4H), 3.30–3.23 (m, 4H), 3.20–3.03 (m, 2H), 2.80 (t, 2H, J = 7.2 Hz), 2.62 (t, 2H, J = 7.6 Hz), 1.95–1.80 (m, 4H), 1.64–1.58 (m, 2H), 0.91 (t, 3H, J = 7.4 Hz).

^{1}H NMR of compound **9-1′**: ^{1}H NMR (400 MHz, MeOH-d_4) δ 7.65–7.57 (m, 5H), 7.30–7.26 (m, 2H), 7.03–7.00 (m, 2H), 6.95 (m, 1H), 6.55 (s, 1H), 3.80 (d, 2H, J = 11.6 Hz), 3.62 (d, 2H, J = 10.8 Hz), 3.20–3.14 (m, 6H), 2.80–2.72 (m, 4H), 1.83–1.73 (m, 6H), 1.03 (t, 3H, J = 7.4 Hz).

All the derivatives synthesized analogously and identified by ^{1}H NMR.

Acknowledgment. This work was supported by Inha University Research Grant.

References

1. F. Boeckler, H. Lanig, P. Gmeiner, *J. Med. Chem.* **2005**, *48*, 694.
2. B. Levant, *Pharmacol. Rev.* **1997**, *49*, 231.
3. (a) F. I. Tarazi, R. J. Baldessarini, *Mol. Psychiatry* **1999**, *4*, 529; (b) L. J. Bristow, M. S. Kramer, J. Kulagowski, S. Patel, C. I. Ragan, G. R. Seabrook, *Trends Pharmacol. Sci.* **1997**, *18*, 186; (c) J. T. McCracken, S. L. Smalley, J. J. McGough, L. Crawford, M. Del'Homme, R. M. Cantor, A. Liu, S. F. Nelson, *Mol. Psychiatry* **2000**, *5*, 531; (d) A. Kirley, Z. Hawi, G. Daly, M. Mccarron, C. Mullins, N. Millar, I. Waldman, M. Fitzgerald, M. Gill, *Neuropsychopharmacology* **2002**, *27*, 607; (e) J. M. Swanson, P. Flodman, J. Kennedy, M. A. Spence, R. Moyzis, S. Schuck, M. Murias, J. Moriarity, C. Barr, M. Smith, M. Posner, *Neurosci. Biobehav. Rev.* **2000**, *24*, 21; (f) R. P. Ebstein, R. H. Belmaker, *Mol. Psychiatry* **1997**, *2*, 381; (g) K. Boor, Z. Ronai, Z. Nemoda, P. Gaszner, M. Sasvari-Szekely, A. Guttman, H. Kalasz, *Curr. Med. Chem.* **2002**, *9*, 793; (h) S. B. Powell, M. P. Paulus, D. S. Hartman, T. Godel, M. A. Geyer, *Neuropharmacology* **2003**, *44*, 473.
4. (a) M. Y. Cha, B. C. Choi, K. H. Kang, A. N. Pae, K. I. Choi, Y. S. Cho, H. Y. Koh, H. Y. Lee, D. Jung, J. Y. Kong, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1327; (b) H. S. Youn, E. J. Lee, J. E. Lee, W.-K. Park, D. J. Baek, Y. S. Cho, H. Y. Koh, H. Choo, A. N. Pae, *Bull. Kor. Chem. Soc.* **2009**, *30*, 1873; (c) K. P. Landge, J. S. Oh, A. N. Pae, W. K. Park, J. Y. Gong, H. Y. Koh, S. H. Jung, *Bull. Kor. Chem. Soc.* **2011**, *32*, 2449.
5. K. H. Kang, A. N. Pae, K. I. Choi, Y. S. Cho, B. Y. Chung, J. E. Lee, S. H. Jung, H. Y. Koh, H. Y. Lee, *Tetrahedron Lett.* **2001**, *42*, 1057.
6. A. F. Abdel-Magid, K. G. Carson, B. D. Harris, C. A. Maryanoff, R. D. Shah, *J. Org. Chem.* **1996**, *61*, 3849.
7. (a) A. Pazos, D. Hoyer, J. M. Palacios, *Eur. J. Pharmacol.* **1985**, *106*, 539; (b) W. K. Park, D. Jeong, H. Cho, S. J. Lee, M. Y. Cha, A. N. Pae, K. I. Choi, H. Y. Koh, J. Y. Kong, *Pharmacol. Biochem. Behav.* **2005**, *82*, 361; (c)Compounds were evaluated *in vitro* for dopamine D_2, D_3, D_4 receptors binding affinity by measuring their ability to displace radioligand ([3H]Methylspiperone for D2 and D3, [3H]YM-09151-2 for D4) from the cloned human dopamine receptors D_{2Long}, D_3 and $D_{4.2}$ which were stably expressed in CHO or Sf9 cells, respectively. For serotonin receptors, compounds were biologically evaluated against human recombinant 5-HT_{1A}, 5-HT_{2A}, 5-HT_{2C}, 5-HT_6 and 5-HT_7 receptors stably expressed by CHO-K1 cell lines through [3H]8-OH-DPAT, [3H]Ketanserin, [3H]Mesulergine and [3H]LSD binding assay, respectively).

