http://dx.doi.org/10.5012/bkcs.2013.34.11.3467

Construction of a Library of Arylpiperazinyl 1,2,3-Triazole Derivatives as Ligands for Dopamine D_3/D_4 Receptor

Ju Myung Kwak, Ji Soo Moon, Jea I Choi, Ravichandran N. Murugan,[§] Woo Kyu Park,[†]
Jae Yang Gong,[‡] Hee Yoon Lee,[§,*] and Hun Yeong Koh[*]

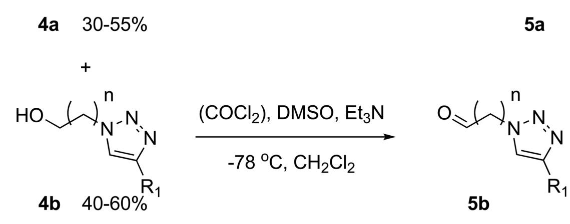
Department of Chemistry, Inha University, Nam-gu, Incheon 402-751, Korea. [*]E-mail: hykoh@inha.ac.kr
[†]Pharmaceutical Screening Research Team, Korea Research Institute of Chemical Technology, Daejeon 305-343, Korea
[‡]College of Pharmacy, Keimyung Univeristy, 1095 dalgubeol-daegu 704-701, Korea
[§]Department of Chemistry, Korea Advanced Institute of Science and Technology, Daejeon 305-701, Korea
[*]E-mail: leehy@kaist.ac.kr

Received August 5, 2013, Accepted August 6, 2013

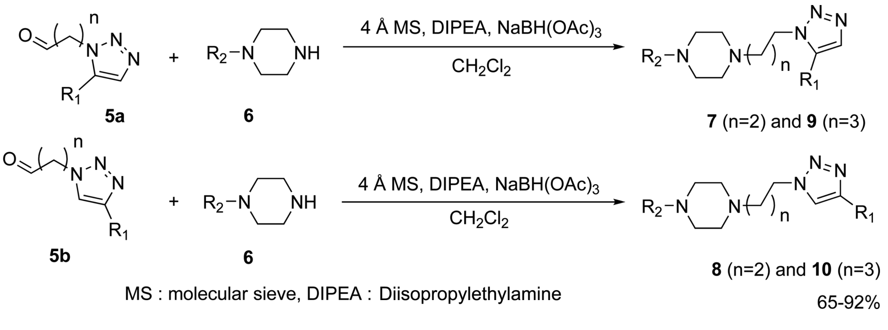
Key Words : Dopamine receptor ligand, 1,2,3-Triazole, Arylpiperazine, Heterocyclization, Microwave reaction.

Most antipsychotic drugs are based on dopamine receptor antagonism. Therefore, to discover new antipsychotic drugs,[1-3] it is important to develop subtype selective ligands for the dopamine receptor. In particular, heterocyclic structures such as 1,2,3-triazoles have been the focus of medicinal chemistry research owing to their appearance as a useful scaffold and wide application in click chemistry.[4,5] Previously synthesized dopamine receptor ligands include arylpiperazinyl ethyl 1,2,3-triazole derivatives.[6] In this study, a new library of 1,2,3-triazole arylpiperazine derivatives, possessing propyl or butyl carbon chains in between arylpiperazine and 1,2,3-triazole moieties, were designed and synthesized in an effort to further understand the structure-activity relationship, and their binding affinities towards dopamine D_3 and D_4 receptors were evaluated.

The synthesis of 1,2,3-triazole arylpiperazine derivatives is shown in Schemes 1 and 2. The preparation of building block (**5**) is described in Scheme 2. Azido compound (**2**) was synthesized in 90% yield from 3-chloropropanol/4-chlorobutanol using NaN_3 in *N*,*N*-dimethylformamide at 50 °C for 15 h. The cycloaddition reaction of **2** with a phenyl alkyne **3** using a microwave reactor at 150 °C in H_2O or solvent-free conditions for 1 h gave a mixture of 1,2,3-triazole derivatives (**4a** and **4b**).[7-9] Each regioisomer was obtained in 30-60% isolated yield after purification through flash column chromatography. 1,2,3-triazole alcohol **4a**/**4b** was oxidized at −78 °C for 1 h under Swern oxidation conditions[10] and yielded the corresponding 1,2,3-triazole aldehyde **5a**/**5b** in over 80% yield. Finally, a focused library of arylpiperazinyl 1,2,3-triazole compounds (**7**, **8**, **9**, and **10**) was constructed via a simple reductive amination reaction between building block (**5a**/**5b**) and **6** using $NaBH(OAc)_3$ (Scheme 1, Table 1, Figure 1). The products were charac-



Scheme 2. Synthesis of Building Block **5**.



MS : molecular sieve, DIPEA : Diisopropylethylamine

Scheme 1. Synthesis of arylpiperazine 1,2,3-triazole derivatives.

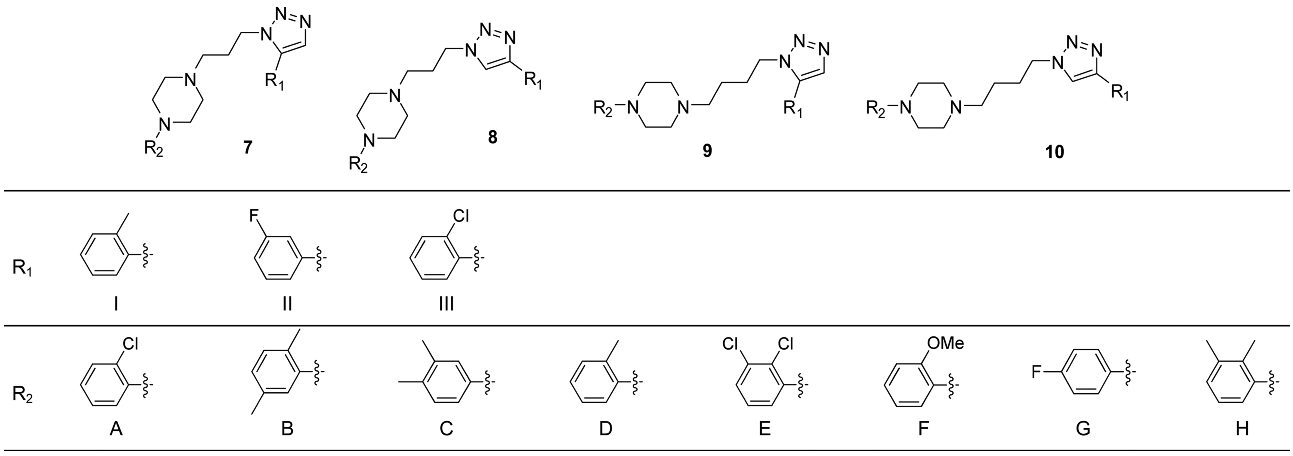


Figure 1. Library of arylpiperazinyl 1,2,3-triazole derivatives.

terized by ^{1}H NMR and LC-MS.

The synthesized arylpiperazinyl 1,2,3-triazole library members were tested for their binding affinities towards the dopamine D_3 and D_4 receptors.[11,12]

Among the 60 molecules in the constructed library, few molecules showed highly potent binding affinities (less than 10 nM) towards either the dopamine D_3 or the D_4 receptors (Table 1). For example, the propyl-tethered compounds (entries 3, 9, 13, and 28) and some butyl-tethered compounds (entries 31 and 33) showed stronger binding affinities for the dopamine D_4 receptor. The propyl-tethered compound–entry 28–(where, R_1 is III, R_2 is C, and regioisomer is **8**) exhibited the best binding affinity for the dopamine D_4 receptor (4.5 nM). The butyl-tethered compound (entry 42) showed strong binding affinities for both the D_3 and D_4 receptors. The butyl-tethered compounds (entries 47, 50, and 52) showed strong binding affinities towards the D_3 receptor. The butyl-tethered compound–entry 47–(where, R_1 is II, R_2 is E, and regioisomer is **10**) exhibited the best binding affinity for the dopamine D_3 receptor (4.9 nM). Next, we assessed the selectivity with which the ligands bound to either receptor. The propyl-tethered compound–entry 3–(where, R_1 is I, R_2 is C, and regioisomer is 7) showed the highest selectivity of binding, with a binding affinity of 5.2 nM for the D_4 receptor compared to a binding affinity of 4609 nM for the D_3 receptor. The propyl-tethered compounds–entries 13 and 28–(where R_1s are II and III, respectively, R_2 is C, and regioisomers are **7** and **8**, respectively) also displayed high selectivity (6.5 and 4.5 nM, respectively) for the dopamine D_4 receptor over the D_3 receptor (5557 and 2618 nM). In contrast, the butyl-tethered compounds–entries 47, 50, and 52–(where, R_1s are II, II, and III, respectively, R_2 is E, H, and E, respectively, and regioisomers are **10**, **10**, and **9**, respectively) exhibited better selectivity towards the dopamine D_3 receptor with binding affinities of 4.9, 9.9, and 7.1 nM, respectively compared to the binding affinities of 455.8, 695.1, and 482.2 nM for the dopamine D_4 receptor. Interestingly, the butyl-tethered compound–entry 42–(where, R_1 is II, R_2 is E, and regioisomer is **9**) showed potent activity towards both the dopamine D_3 and D_4 receptors (5.7 and 5.4 nM). In general, all propyl-tethered (entries 1-30) and most butyl-tethered compounds showed better binding affinity for

Table 1. *In vitro* Binding affinities of arylpiperazinyl 1,2,3-triazole derivatives for Dopamine receptor D_3/D_4

Entry	R_1	R_2	Regio isomer	IC_{50} (nM)	
				D_4	D_3
1	I	A	7	85	183
2		B		230	2435
3		C		5.2	4609
4		D		31.5	644
5		E		12.8	111
6		A	8	23.1	152
7		B		98	855
8		C		43.0	1309
9		D		8	879
10		E		91	135
11	II	A	7	70	552
12		B		177	2500
13		C		6.5	5557
14		D		71	887
15		E		20.2	95
16		A	8	197	770
17		B		571	1481
18		C		93	3411
19		D		147	941
20		E		96	139
21	III	A	7	21.9	135
22		B		103	694
23		C		48.9	1120
24		D		51	1299
25		E		61	89
26		A	8	198	545
27		B		291	1825
28		C		4.5	2618
29		D		52	2988
30		E		16.2	73

Table 1. Continued

Entry	R_1	R_2	Regio isomer	IC_{50} (nM)	
				D_4	D_3
31	I	A	**9**	5.7	90.7
32		E		22.8	56.4
33		F		4.7	472.9
34		G		38.6	2786.0
35		H		25.0	203.6
36		A	**10**	286.6	114.7
37		E		144.5	15.2
38		F		193.7	299.3
39		G		134.5	2077.0
40		H		272.0	110.3
41	II	A	**9**	33.4	49.8
42		E		5.7	5.4
43		F		18.6	54.9
44		G		10.6	1800.0
45		H		15.7	69.6
46		A	**10**	846.3	42.7
47		E		455.8	4.9
48		F		165.4	72.0
49		G		178.3	756.4
50		H		695.1	9.9
51	III	A	**9**	454.0	63.1
52		E		482.2	7.1
53		F		163.9	99.2
54		G		32.2	478.4
55		H		377.6	43.5
56		A	**10**	10.9	37.9
57		E		25.0	19.0
58		F		17.4	309.4
59		G		48.9	958.3
60		H		39.1	163.7
Olanzapine				98.4	175

the dopamine D_4 receptor compared to the dopamine D_3 receptor. However, few butyl-tethered compounds (entries 36, 37, 40, 46, 47, 48, 50, 51, 52, 53, and 55) exhibited better binding affinities towards the dopamine D_3 receptor compared to the dopamine D_4 receptor.

In summary, synthetic methods for obtaining arylpiperazinyl 1,2,3-triazole derivatives in high yields within a short reaction time using a microwave reactor were developed. In general, the propyl-tethered derivatives were selective and exhibited potent binding affinities for the dopamine D_4 receptor, whereas the butyl-tethered derivatives exhibited potent binding affinities for the dopamine D_3 receptor. The constructed library is expected to be a good guide for the development of selective ligands for D_3 and D_4 receptors.

Experimental

General Procedure for the Synthesis of 3-Azido Propanol 2. A solution of alcohol (**1**) (where, n = 3 and 5 g, 36.0 mmol) and NaN_3 (4.67 g, 71.9 mmol) in DMF (50 mL) under a nitrogen atmosphere was stirred well at 50 °C for 15 h. The progress of reaction was monitored by TLC. The reaction mixture was filtered after 15 h and the solvent was evaporated. The product obtained was washed with water and extracted with ethyl acetate (3 × 50 m). The collected organic layer was dried over $NaSO_4$ and filtered. The product was isolated after evaporating the solvent using a rotary evaporator as a slightly brown colored liquid with 90% yield.

^1H NMR (200 MHz, $CDCl_3$) δ 3.76 (t, 2H, *J* = 5.8 Hz), 3.45 (t, 2H, *J* = 6.2 Hz), 1.87-1.78 (m, 2H).

General Procedure for the Synthesis of 3-(5-*o*-tolyl-1*H*-1,2,3-triazole-1-yl)-propan-1-ol (4a) and 3-(4-*o*-tolyl-1*H*-1,2,3-triazole-1-yl)-propan-1-ol (4b). A solution of azido alcohol 2 (where, n = 3, 500 mg, 4.9 mmol) and 2-ethynyl toluene (573.8 mg, 5.0 mmol) was reacted using a microwave reactor at 150 W, 150 °C for 1 h. The progress of reaction was monitored by TLC. After the completion of reaction, the reaction mixture was washed with water and the product was extracted with ethyl acetate (3 × 25 mL). The crude product thus obtained was purified by column chromatography (EA:*n*-Hex = 4:6) to give a liquid containing **4a** and **4b** in 40% and 50% yields, respectively.

^1H NMR of compound **4a** (200 MHz, $CDCl_3$) δ 7.70 (s, 1H), 7.49-7.38(m, 4H), 4.35 (t, 2H, *J* = 7.0 Hz), 3.65 (t, 2H, 6.0 Hz), 2.19 (s, 3H), 2.09-1.95 (m, 3H).

^1H NMR of **4b** (200 MHz, $CDCl_3$) δ 7.78-7.73 (m, 1H), 7.69 (s, 1H), 7.38-7.18 (m, 3H), 4.59 (t, 2H, *J* = 7.0 Hz), 3.70 (t, 2H, *J* = 6.0 Hz), 2.46 (s, 3H), 2.25-2.12 (m, 2H), 2.00 (br s, 1H).

Other aryl alcohol 1,2,3-triazole derivatives were synthesized similarly and characterized by ^1H NMR.

General Procedure for Synthesis of 3-(5-*o*-tolyl-1*H*-1,2,3-triazole-1-yl)-propan-1-al (5a). A solution of oxalyl chloride (0.26 mL, 2.9 mmol) in 4 mL of methylene chloride was stirred at -78 °C and then DMSO (0.4 mL, 5.8 mmol) in 2 mL of methylene chloride was added over 10 min. Next, a solution of 3-(5-*o*-tolyl-1*H*-1,2,3-triazole-1-yl)-propan-1-ol (**4a**) in 2 mL of methylene chloride was added to the reaction mixture over 30 min using a dropping funnel. Next, Et_3N (1.3 mL, 9.7 mmol) was added to the reaction mixture and stirred for 5 min. The temperature of the reaction mixture was then raised to room temperature, and then stirred for 1 h. The progress of reaction was monitored by TLC (EA:*n*-Hex = 1:2). Water (10 mL) was added to the reaction mixture and the organic layer was separated and dried over $MgSO_4$. The reaction mixture filtrated to remove $MgSO_4$ and then the solvent was removed. The product was purified over column chromatography (EA:*n*-Hex = 1:4) to give a liquid with 53% yield.

^1H NMR of (**5a**) δ 9.78 (s, 1H), 7.67 (s, 1H), 7.45-7.22 (m, 4H), 4.42 (t, 2H, *J* = 7.0 Hz), 3.18 (t, 2H, *J* = 7.0 Hz), 2.19 (s, 3H).

Other aryl aldehyde 1,2,3-triazole derivatives were synthesized similarly and characterized by ^1H NMR.

General Procedure for Synthesis of 1-(2-Chlorophen-

yl)-4-(3-5-phenyl-1*H*-1,2,3-triazole-1-yl)propyl)piperazine (7a). A solution of 3-(5-*o*-tolyl-1*H*-1,2,3-triazole-1-yl)-propan-1-al (**5a**) (50 mg, 0.22 mmol) and 1-(2-chlorophenyl)-piperazine (67.9 mg, 0.3 mmol) in 5 mL of methylene chloride was stirred at room temperature for 10 min. Molecular sieve (0.6 g, 4 Å) and DIPEA (0.12 mL, 0.7 mmol) were added slowly. After 30 min, $NaBH(OAc)_3$ (146.2 mg, 0.7 mmol) was added and stirred for 12 h. The progress of reaction was monitored by TLC. After completion of the reaction, water was added and the organic layer was separated. The organic layer was dried over $MgSO_4$ and then filtered to remove $MgSO_4$. Finally, the product was purified by flash column chromatography (EA:*n*-Hex = 4:1) to give the product in 87% yield.

^{1}H NMR (Entry 1) (400 MHz, MeOH-d_4) δ 7.77 (s, 1H), 7.47-7.33 (m, 4H), 7.29-7.22 (m, 3H), 7.09-7.03 (m, 2H), 4.37 (t, 2H, J = 6.4 Hz), 3.63-3.57 (m, 4H), 3.39 (d, 2H, J = 6.4 Hz), 3.36 (br s, 2H), 3.10-3.06 (m, 2H), 2.58 (br s, 2H), 2.16 (s, 3H). ESI-MS *m/z* calcd for $C_{22}H_{26}ClN_5$ $[M + H]^+$ 396.1955, found 396.1618.

Other arylpiperazinyl 1,2,3-triazole derivatives were synthesized similarly and characterized ^{1}H NMR.

References

1. Sokoloff, P.; Giros, B.; Martres, M.-P.; Bouthenet, M.-L.; Schwartz, J.-C. *Nature* **1990**, *347*, 146-151.
2. Van Tol, H. M.; Bunzow, J. R.; Guan, H. C.; Sunahara, R. K.; Seeman, P.; Niznik, H. B.; Civelli, O. *Nature* **1991**, *30*, 610.
3. (a) Enguehard-Gueiffier, C.; Hübner, H.; El Hakmaoui, A.; Allouchi, H.; Gmeiner, P.; Argiolas, A.; Melis, M. R.; Gueiffier, A. *J. Med. Chem.* **2006**, *49*, 3938-3947. (b) Löber, S.; Hübner, H.; Gmeiner, P. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2955-2959. (c) Mohr, P.; Decker, M.; Enzensperger, C.; Lehmann, J. *J. Med. Chem.* **2006**, *49*, 2110-2116. (d) Leopoldo, M.; Lacivita, E.; Colabufo, N. A.; Beradi, F.; Perrone, R. *J. Pharm. Pharmacol.* **2006**, *58*, 209-218. (e) Chen, J.; Ding, K.; Levant, B.; Wang, S. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 443-446. (f) Lentz, C.; Boeckler, F.; Hübner, H.; Gmeiner, P. *Bioorg. Med. Chem.* **2005**, *13*, 4434-4442.
4. For reviewing: (a) Wamhoff, H. *In Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon: Oxford, UK, 1984; Vol. 5, pp 669-732. (b) Katritzky, A. R.; Zhang, Y.; Singh, S. K. *Heterocycles* **2003**, *60*, 1225-1239. (c) Abu-Orabi, S. T.; Atfah, M. A.; Jibril, I.; Mari'i, F. M.; Ali, A. A.-S. *J. Heterocycl. Chem.* **1989**, *26*, 1461-1468. (d) Krivopalov, V. P.; Shkurko, O. P. *Russ. Chem. Rev.* **2005**, *74*, 339-379.
5. Chen, X.; Wang, W. *Annu. Rep. Med. Chem.* **2003**, *38*, 333-346.
6. Kamalkishor, P. L.; Seo, Y. W.; Kwak, J. M.; Park, W. K.; Gong, J. Y.; Lee, H. Y.; Koh, H. Y. *Bull. Korean Chem. Soc.* **2011**, *32*, 3101.
7. (a) *Microwaves in Organic Synthesis*, 2nd ed.; Loupy, A., Ed.; Wiley-VCH: Weinheim, Germany, 2006. (b) Kappe, C. O.; Stadler, A. *Microwaves in Organic and Medicinal Chemistry*; Wiley-VCH: Weinheim, Germany, 2005.
8. (a) Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250-6284, and references cited therein. (b) Roberts, B. A.; Strauss, C. R. *Acc. Chem. Res.* **2005**, *38*, 653-661. (c) Kappe, C. O.; Dallinger, D. *Nature Rev. Drug Discov.* **2006**, *5*, 51-63. (d) Collins, J. M.; Leadbeater, N. E. *Org. Biomol. Chem.* **2007**, *5*, 1141-1150. (e) Dallinger, D.; Kappe, C. *O. Chem. Rev.* **2007**, *107*, 2563-2591. (f) Appukkuttan, P.; Van der Eycken, E. *Eur. J. Org. Chem.* **2008**, 1133-1155.
9. (a) Li, C. *J. Chem. Rev.* **1993**, *93*, 2023. (b) *Organic Synthesis in Water*; Grieco, P. A., Ed.; Blackie: London, 1998. (c) Breslow, R. *In Water as Solvent for Chemical Reactions*; Anastas, P. T., Williamson, T. C., Eds.; Oxford University Press: Oxford, 1998. (d) Kumar, *A. Chem. Rev.* **2001**, *101*, 1. (e) Lindstörm, U. M.; Andersson, F. *Angew. Chem., Int. Ed.* **2006**, *45*, 548. (f) Li, C. J.; Chen, L. *Chem. Soc. Rev.* **2006**, *35*, 68. (g) Pirrung, M. C. *Chem.-Eur. J.* **2006**, *12*, 1213. (h) Herrerías, C. I.; Yao, X.; Li, Z.; Li, C.-J. *Chem. Rev.* **2007**, *107*, 2546.
10. Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651.
11. (a) Pazos, A.; Hoyer, D.; Palacios, J. M. *Eur. J. Pharmacol.* **1985**, *106*, 539-546. (b) Park, W. K.; Jeong, D.; Cho, H.; Lee, S. J.; Cha, M. Y.; Pae, A. N.; Choi, K. I.; Koh, H. Y.; Kong, J. Y. *Pharmacol. Biochem. Behav.* **2005**, *82*, 361-372.
12. Compounds were evaluated *in vitro* for dopamine D_3, D_4 receptors binding affinity by measuring their ability to displace radio ligand ([^{3}H]Methylspiperone for D_3, [^{3}H]YM-09151-2 for D_4) from the cloned human dopamine receptors D_3 and D4.2 which were stably expressed in CHO or Sf9 cells, respectively.