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Regioselective Click Chemistry for Construction of Arylpiperazinyl 1,2,3-Triazole Derivative Libraries as Dopamine D_4/D_3 Receptor Ligands

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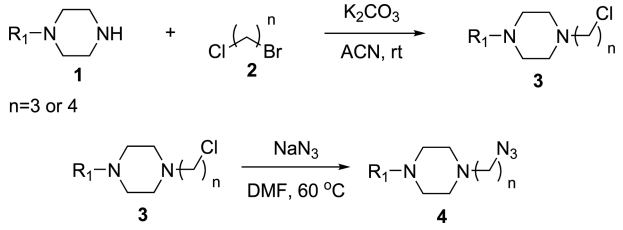
The Huisgen 1,3-dipolar cycloaddition between azides and alkynes stands out as the most direct way of assembling 1,2,3-triazole functionality.[1,2] Since CuAAC was first reported, the click chemistry, copper-catalyzed azide-alkyne cycloaddition (CuAAC), became a synthetic tool for the regioselective formation of 1,4-disubstituted 1,2,3-triazoles under very mild conditions,[3] and a number of applications in medicinal chemistry, organic synthesis, chemical biology, materials science, and polymer chemistry have been reported.[3]

In particular, 1,2,3-triazole structures have been the key bioisostere for medicinal chemistry due to their wide applicability in the drug development fields.[4,5] However, with the exception of our previous report,[6] no report has been issued on application of click chemistry for disubstituted 1,2,3-triazole derivatives as dopamine receptors ligands.

In our previous report, arylpiperazinylpropyl and butyl 1,2,3-triazole derivatives were synthesized from two regioisomeric trialzole alcohols as building blocks through thermal Huisgen reaction without any regioselectivity for dopamine receptor ligands.[6] These arylpiperazinyl alkyl 1,2,3-triazole derivatives showed good binding affinity selective for dopamine D_3/D_4 receptors. In this paper, we describe improved strategy for the regioselective synthesis of derivatives using click chemistry. Since metal catalyzed azide-alkyne cycloaddition could serve as a useful tool for the development of selective ligands for dopamine D_3 receptor[7] or D_4 receptor,[8] 1,4-disubstituted 1,2,3-triazole derivatives were synthesized selectively through CuAAC and 1,5-disubstituted 1,2,3-triazole derivatives were synthesized *via* Ru-catalyzed 1,3-dipolar azide-alkyne cycloaddition.

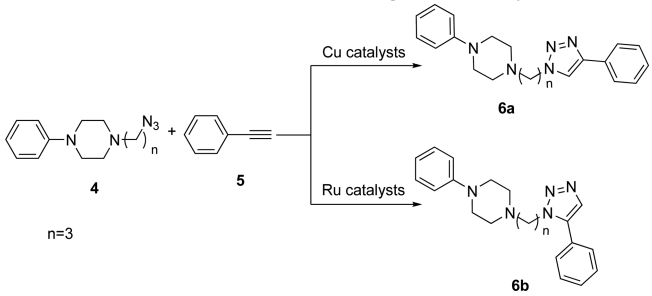
The synthetic strategies of arylpiperazinyl alkyl 1,2,3-triazole derivatives are shown in Schemes 1 and 2. Preparation of the building blocks (**4**) is described in Scheme 1. The arylpiperazines (**3**) was synthesized in 65% yield from 3-chloro-1-bromopropane/4-chloro-1-bromobutane (**2**) and arylpiperazines (**1**) in the presence of K_2CO_3 in acetonitrile at room temperature. The piperazinyl nitrogen reacted selectively with bromide to form chloroalkyl substituted piperazines. Azido-arylpiperazines (**4**) were synthesized from chloroalkyl arylpiperazines (**3**) and NaN_3 in *N,N*-dimethylformamide at 60 °C in 90% yields.

Regioselective synthesis of 1,2,3-triazole derivatives was performed through cycloaddition reaction between alkynes and azides in the presence of Cu or Ru catalysts. Various Cu and Ru based catalysts were tested for the regioselective construction of 1,2,3-triazole derivatives as shown in the Table 1.



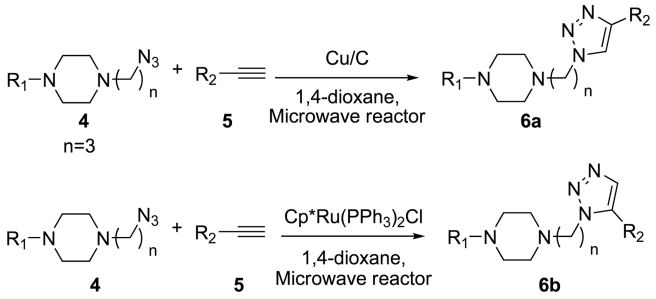
Scheme 1. Synthesis of arylpiperazinyl alkyl azides.

Table 1. Reaction conditions used for regioselective syntheses



Entry[a]	Catalyst	Solvent	Time	Yield[b]	Ratio[12] (*anti:syn*) **6a** : **6b**
1[c]	Cu/C	Dioxane	10 min	68	100:0
2[c]	$CuSO_4$	Dioxane	20 min	55	100:0
3[c]	$Cu(NO_3)_2$	Dioxane	10 min	60	100:0
4[c]	Cu (powder)	Dioxane	10 min	67	100:0
5[c]	Cu/C	H_2O	10 min	14	100:0
6[c]	Cu/C	ACN	10 min	68	100:0
7[d]	$Cp^*Ru(PPh_3)_2Cl$	Dioxane	30 min	61	3.8:96.2
8[d]	$Cp^*Ru(PPh_3)_2Cl$	ACN	30 min	56	4.2:95.8

[a]all reactions were performed in a microwave reactor at 150W, 90 °C. [b]Isolated yield of major product. [c]using 2 mol % of catalyst, 1,4-disubstituted product was synthesized. [d]1,5-disubstituted product was synthesized



Scheme 2. Regioselective preparation of 1,4- or 1,5-disubstituted 1,2,3-triazole derivatives.

Regioselective formation of 1,4-disubstituted 1,2,3-triazole derivatives were tested by using Cu/C,[7] $CuSO_4$, $Cu(NO_3)_2$ or Cu(powder) (Table 1. Entries 1-4). All the catalysts showed good selectivity with exclusive formation of 1,4-disubstituted compounds. The reaction conditions with Cu/C catalyst showed highest yields (Table 1. Entry 1). Reactions in dioxane and acetonitrile produced better yields than water. (Table 1. Entries 1, 5 and 6). Synthesis of 1,5-disubstituted 1,2,3-triazole derivatives was investigated using Ru catalysts (Table 1. Entry 7 and 8). Pentamethyl cyclopentadienyl ruthenium bistriphenylphosphine chloride [Cp*Ru(PPh_3)$_2$Cl] catalyst produced good results for the 1,5-disubstituted 1,2,3-triazole formation reaction in acetonitrile or dioxane.

Based on the results in the Table 1, a library of 1,4-disubstituted and 1,5-disubstituted arylpiperazinyl 1,2,3-triazole derivatives were constructed using the Cu/C or [Cp*Ru(PPh_3)$_2$Cl] catalysts in 1,4-dioxane at 90 °C for 10 min using a microwave reactor (Scheme 2). Products were characterized by ^{1}H NMR and LC-MS.

Constructed library of 1,4-disubstituted and 1,5-disubstituted 1,2,3-triazole derivatives is shown in the Table 2.

In the synthesis of arylpiperazinyl 1,2,3-triazole derivatives (**6**), Aryl piperazine moieties (where, R_1 is A, B, C, D, E, F, G, H, I, J or K) and aryl 1,2,3-triazole moieties (where, R_2 is A or L) were linked through propyl or butyl chains. A library of 1,4-disubstituted 1,2,3-triazole derivatives using Cu/C catalyst and 1,5-disubstituted 1,2,3-triazole derivatives using Cp*Ru(PPh_3)$_2$Cl catalyst were constructed in good yields.

The binding affinities of synthesized 1,2,3-triazole derivatives for dopamine D_3 and D_4 receptors were tested.[9,10] Most compounds showed varying binding affinities for dopamine D_3 and D_4 . Entries 10 and 29 (Table 3) showed excellent binding affinities for dopamine D_4 and entries 24 with dopamine D_3. Propyl linked 1,2,3-triazole derivatives produced better results for dopamine D_4 than D_3 but butyl linked compounds produced better results for dopamine D_3 than D_4. It is quite intriguing that the slight change of the tether length changed the selectivity between D_3 and D_4. When two aryl parts are connected with propyl tether, compounds showed D_4 selectivity regardless of the position of the R_2 group. This trend indicates that the spacer between two aryl groups plays an important role in distinguishing two receptors. Between 1,4-substitution and 1,5-substitution, 1,5-substitution provided better D_4 selectivity with propyl tether. Sub-

Table 2. The library construction of 1,4 or 1,5 disubstituted 1,2,3 triazolederivatives[a]

Entries	R_1	R_2	catalyst	n	Yield[b]
1	A	A	Cu/C	3	76
2	B				58
3	C				85
4	D				82
5	E				75
6	A		[Cp*Ru(PPh_3)$_2$Cl]		89
7	B				88
8	C				87
9	D				89
10	E				79
11	F	L	Cu/C		84
12	G				88
13	H				65
14	I				82
15	J				80
16	F		[Cp*Ru(PPh_3)$_2$Cl]		75
17	G				70
18	H				89
19	I				79
20	J				83
21	B	A	Cu/C	4	74
22	C				81
23	F				79
24	J				75
25	K				74
26	B		[Cp*Ru(PPh_3)$_2$Cl]		69
27	C				83
28	F				84
29	J				82
30	K				76
31	B	L	Cu/C		78
32	C				79
33	F				71
34	J				76
35	K				65
36	B		[Cp*Ru(PPh_3)$_2$Cl]		69
37	C				82
38	F				74
39	J				73
40	K				71

[a]all reactions were performed in a microwave reactor at 150W, 90 °C using 2 mol % of catalyst. [b]Isolated yield of the major product

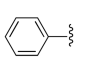
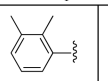
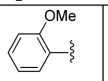
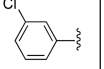
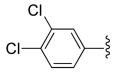
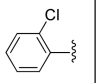
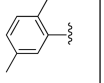
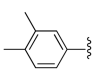
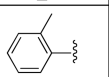
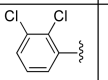
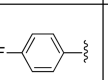
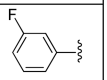
R_1 and R_2			
 A	 B	 C	 D
 E	 F	 G	 H
 I	 J	 K	 L

Table 3. *In vitro* binding affinities of selected compounds for Dopamine receptor D_3/D_4[11]

Entries[a]	R_1	R_2	Binding affinities (nM)[b]	
			D_4	D_3
1	A	A	539	1637
2	B		135	367
3	C		90	1000
4	D		298	1201
5	E		68	1797
6	A		294	2259
7	B		32	247
8	C		36	1551
9	D		60	956
10	E		5.9	2102
21	B		929	71.6
22	C		207	54.3
23	F		190	44.7
24	J		383	10.7
25	K		112	139
26	B		83.4	85.3
27	C		18.3	85.6
28	F		47.7	27.3
29	J		10.6	18.4
30	K		45.1	1391

[a]Entry numbers were same as those of compounds in the Table 2.

stitution around the phenyl ring of the arylpiperazine also showed a dramatic improvement of D_4 selectivity as *ortho*-, and 3,4-disubstituted ligands provided the enhanced selectivity (entries 3, 5, 8 and 10). On the other hand, butyl tether seemed to provide only the slight selectivity for D_3. Contrary to the propyl tether, butyl tether provided better selectivity with 1,4-substitution than 1,5-substitution. It is clear that 2,3-disubstituted compounds (entries 21 and 24) provides good selectivity for D_3.

In summary, improved methods for regioselective synthesis of 1,2,3-triazole derivatives in high yields within short reaction time were developed. In general, each regioselective 1,2,3-triazole libraries were constructed using selective Cu/C catalyst or $Cp^*Ru(PPh_3)_2Cl$ catalyst *via* click chemistry. Thus constructed library of compounds provided important information on the selectivity between D_3 and D_4 receptors for the future design of a drug candidate with a better selectivity or dual activity.

Experimental

General Procedure; Synthesis of 4-Phenyl-piperazinyl 3-Chloro Propane (3). A solution of 1-bromo-3-chloropropane ((**1**) where $n = 3$, 1.46 g, 9.24 mmol) and phenylpiperazine (1 g, 6.16 mmol) containing K_2CO_3 (1.3 g, 9.24 mmol) in acetonitrile (30 mL) under a nitrogen atmosphere was stirred well at 25 °C for 10 h. The progress of the reaction was monitored by TLC. The reaction mixture was filtered and the solvent was evaporated. The product obtained was washed with water and the aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were dried over Na_2SO_4 and filtered. The product was obtained after evaporating the solvent using a rotary evaporator as a slightly brown colored liquid and was purified by column chromatography (EA:*n*-Hex = 1:2) to produce **3** (0.96 g, 4.00 mmol) in 65% yield.

^{1}H NMR (200 MHz, $CDCl_3$) δ 7.26 (m, 2H), 6.93 (d, 2H), 6.83 (t, 1H), 3.62 (t, 2H), 3.20 (t, 4H), 2.61 (t, 4H), 2.52 (t, 2H), 2.00 (t, 2H).

General Procedure; Synthesis of 4-Phenyl-piperazinyl 3-Azidopropane (4). A solution of 4-phenyl-piperazinyl 3-chloro propane (**3**) (where, $n = 3$ and 0.7 g, 2.93 mmol) and NaN_3 (0.38 g, 5.86 mmol) in DMF (30 mL) was stirred well in a nitrogen atmosphere at 60 °C for 5 h. The progress of the reaction was monitored by TLC. The reaction mixture was then filtered and the solvent was evaporated off. The product obtained was washed with water and extracted with ethyl acetate (3 × 50 mL). The collected organic layer was dried over Na_2SO_4 and filtered. The product was isolated after evaporating the solvent using a rotary evaporator and purified by column chromatography (EA:*n*-Hex = 1:2). The final yield was 90%.

^{1}H NMR (200 MHz, $CDCl_3$) δ 7.26 (m, 2H), 6.94 (t, 2H), 6.83 (t, 1H), 3.37 (t, 2H), 3.20 (d, 4H), 2.61 (t, 4H), 2.48 (t, 2H), 1.81 (m, 2H).

General Procedure for the Synthesis of 1-Phenyl-4-(3-4-phenyl-1*H*-1,2,3-triazole-1-yl)propyl)piperazine (6a). A solution of 4-phenyl-piperazinyl 3-azidopropane (**4**) (0.10 g, 0.41 mmol) and phenylacetylene (62 mg, 0.61 mmol) containing Cu/C (100 mg, 2 mol %) in 2 mL of 1,4-dioxane was placed in a microwave reactor (150W/90 °C/10 min). The progress of the reaction was monitored by TLC. After reaction completion, water was added and the organic layer was separated. The organic layer was then dried over $MgSO_4$ and filtered to remove $MgSO_4$. Finally, the product was purified by flash column chromatography (EA:isopropyl alcohol = 9:1). The final yield of the product was 68%.

^{1}H NMR (Entry 1) (400 MHz, $CDCl_3$) δ 7.86 (d, 2H), 7.78 (s, 1H), 7.43 (t, 2H), 7.35 (t, 2H), 6.92 (d, 2H), 6.86 (t, 2H), 4.51 (t, 2H), 3.20 (t, 4H), 2.61 (t, 4H), 2.45 (t, 2H), 2.18 (m, 2H). ESI-MS *m/z* calcd for $C_{21}H_{25}N_5$ $[M + H]^+$ 347.2110, found 348.3.

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

General Procedure for the Synthesis of 1-Phenyl-4-(3-5-phenyl-1*H*-1,2,3-triazole-1-yl)propyl)piperazine (6b). A solution of 4-phenyl-piperazinyl 3-azidopropane (**4**) (100 mg, 0.4 mmol) and phenylacetylene (62 mg, 0.61 mmol) containing $Cp^*Ru(PPh_3)_2Cl$ (6.4 mg, 0.008 mmol, 2 mol %) in 2 mL of 1,4-dioxane was reacted in a microwave reactor (150W/90 °C/10 min). The progress of the reaction was monitored by TLC. After reaction completion, water was

added, the organic layer was separated, dried over $MgSO_4$ and then filtered to remove $MgSO_4$. Finally, the product was purified by flash column chromatography (EA:isopropyl alcohol = 9:1). The final yield of the product was 76%.

^{1}H NMR (Entry 7) (400 MHz, $CDCl_3$) δ 7.71 (s, 1H), 7.49–7.46 (m, 4H), 7.28–7.25 (m, 3H), 6.92–6.86 (m, 3H), 4.48 (t, 2H), 3.10 (m, 4H), 2.47 (d, 4H), 2.36 (t, 2H), 2.10 (m, 2H). ESI-MS *m/z* calcd for $C_{21}H_{25}N_5$ $[M + H]^+$ 347.2110, found 348.3.

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

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References

1. Huisgen, R.; Szeimies, G.; Mobius, L. *Chem. Ber.* **1967**, *100*, 2494.
2. Huisgen, R. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, NY, 1984; Vol. 1, p 1.
3. Leoneti, V. A.; Campo, V. L.; Gomes, A. S.; Field, R. A.; Carvalho, I. *Tetrahedron* **2010**, *66*, 9475.
4. Kolb, H. C.; Sharpless, K. B. *Drug Discovery Today* **2003**, *8*, 1128.
5. Trom, G. C.; Pirali, T.; Billington, R. A.; Canonico, P. L.; Sorba, G.; Genazzani, A. A. *Med. Res. Rev.* **2008**, *28*, 278.
6. Kwak, J. M.; Moon, J. S.; Murugan, R. N.; Park, W. K.; Gong, J. Y.; Lee, H. Y.; Koh, H. Y. *Bull. Korean Chem. Soc.* **2013**, *34*, 3467.
7. Lipshutz, B. H.; Taft, B. R. *Angew. Chem. Int. Ed.* **2006**, *45*, 8235.
8. Zhang, L.; Chen, X.; Xue, P.; Sun, H. H. Y.; Williams, I. D.; Sharpless, K. B.; Fokin, V. V.; Jia, G. *J. Am. Chem. Soc.* **2005**, *127*, 15998.
9. (a) Pazos, A.; Hoyer, D.; Palacios, J. M. *Eur. J. Pharmacol.* **1985**, *106*, 539. (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.
10. Compounds were evaluated *in vitro* for dopamine D_3 and 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 D_4 stably expressed in CHO or Sf9 cells, respectively.
11. These binding affinities were not described in our previous report.
12. The ratio for each *syn* and *anti* isomer in Table 1 was identified by HPLC under the following condition.
    *Solvent; H_2O:MeOH = 30:70
    *Column; Hypersil GOLD (4.6 × 250 mm, 5 μm)