

Regioselective Click Chemistry for Construction of Arylpiperazinyl 1,2,3-Triazole Derivative Libraries as Dopamine D₄/D₃ Receptor Ligands

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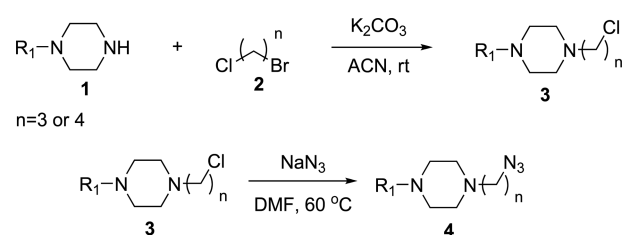
The Huisgen 1,3-dipolar cycloaddition between azides and alkynes stands out as the most direct way of assembling 1,2,3-triazole functionality.^{1,2} Since CuAAC was first reported, the click chemistry, copper-catalyzed azide-alkyne cycloaddition (CuAAC), became a synthetic tool for the regioselective 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 triazole 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 D₃/D₄ 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 D₃ receptor⁷ or D₄ 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 K₂CO₃ in acetonitrile at room temperature. The piperazinyl nitrogen reacted selectively with bromide to form chloroalkyl substituted piperazines. Azido-aryl piperazines (**4**) were synthesized from chloroalkyl arylpiperazines (**3**) and NaN₃ in *N,N*-dimethylformamide at 60 °C in 90% yields.

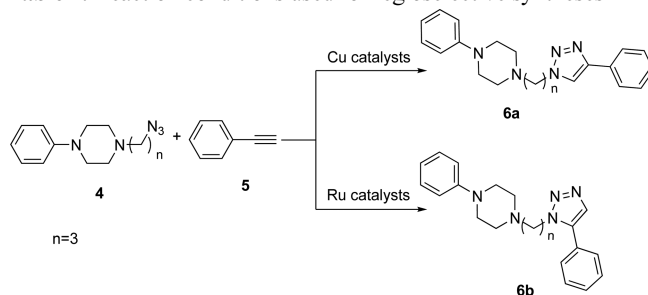
Regioselective synthesis of 1,2,3-triazole derivatives was



Scheme 1. Synthesis of arylpiperazinyl alkyl azides.

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.

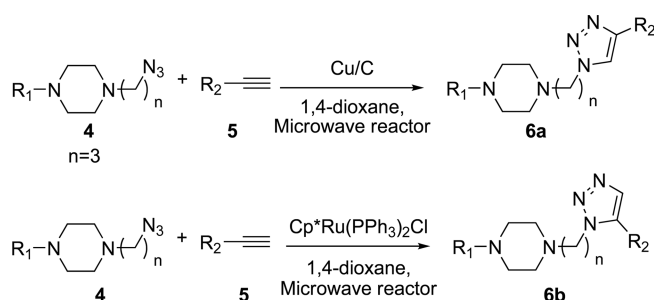
Table 1. Reaction conditions used for regioselective syntheses



Entry ^a	Catalyst	Solvent	Time	Yield ^b	Ratio ¹² (<i>anti</i> : <i>syn</i>) 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 ₂ O	10 min	14	100:0
6 ^c	Cu/C	ACN	10 min	68	100:0
7 ^d	Cp*Ru(PPh ₃) ₂ Cl	Dioxane	30 min	61	3.8:96.2
8 ^d	Cp*Ru(PPh ₃) ₂ Cl	ACN	30 min	56	4.2:95.8

^aall reactions were performed in a microwave reactor at 150W, 90 °C.

^bIsolated yield of major product. ^cusing 2 mol % of catalyst, 1,4-disubstituted product was synthesized. ^d1,5-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 CuSO₄, Cu(NO₃)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 bistrisphenylphosphine chloride [Cp*Ru(PPh₃)₂Cl] 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(PPh₃)₂Cl] catalysts in 1,4-dioxane at 90 °C for 10 min using a microwave reactor (Scheme 2). Products were characterized by ¹H 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, R₁ is A, B, C, D, E, F, G, H, I, J or K) and aryl 1,2,3-triazole moieties (where, R₂ 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(PPh₃)₂Cl catalyst were constructed in good yields.

The binding affinities of synthesized 1,2,3-triazole derivatives for dopamine D₃ and D₄ receptors were tested.^{9,10} Most compounds showed varying binding affinities for dopamine D₃ and D₄. Entries 10 and 29 (Table 3) showed excellent binding affinities for dopamine D₄ and entries 24 with dopamine D₃. Propyl linked 1,2,3-triazole derivatives produced better results for dopamine D₄ than D₃ but butyl linked compounds produced better results for dopamine D₃ than D₄. It is quite intriguing that the slight change of the tether length changed the selectivity between D₃ and D₄. When two aryl parts are connected with propyl tether, compounds showed D₄ selectivity regardless of the position of the R₂ 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 D₄ selectivity with propyl tether. Sub-

Table 2. The library construction of 1,4 or 1,5 disubstituted 1,2,3 triazole derivatives^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

^aall reactions were performed in a microwave reactor at 150W, 90 °C using 2 mol % of catalyst. ^bIsolated yield of the major product

R ₁ and R ₂			

Table 3. *In vitro* binding affinities of selected compounds for Dopamine receptor D₃/D₄¹¹

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

^aEntry 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 D₄ 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 D₃. 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 D₃.

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(PPh₃)₂Cl catalyst *via* click chemistry. Thus constructed library of compounds provided important information on the selectivity between D₃ and D₄ 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 K₂CO₃ (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 Na₂SO₄ 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.

¹H NMR (200 MHz, CDCl₃) 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 NaN₃ (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 Na₂SO₄ 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%.

¹H NMR (200 MHz, CDCl₃) 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 MgSO₄ and filtered to remove MgSO₄. Finally, the product was purified by flash column chromatography (EA:isopropyl alcohol = 9:1). The final yield of the product was 68%.

¹H NMR (Entry 1) (400 MHz, CDCl₃) 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 C₂₁H₂₅N₅ [M + H]⁺ 347.2110, found 348.3.

Other arylpiperazinyl 1,2,3-triazole derivatives were synthesized similarly and characterized by ¹H 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(PPh₃)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%.

^1H 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 $\text{C}_{21}\text{H}_{25}\text{N}_5$ $[\text{M} + \text{H}]^+$ 347.2110, found 348.3.

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

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- Compounds were evaluated *in vitro* for dopamine D_3 and D_4 receptors binding affinity by measuring their ability to displace radio ligand ($[\text{^3H}]$ Methylspiperone for D_3 , $[\text{^3H}]$ 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.
- These binding affinities were not described in our previous report.
- The ratio for each *syn* and *anti* isomer in Table 1 was identified by HPLC under the following condition.
*Solvent; $\text{H}_2\text{O}:\text{MeOH} = 30:70$
*Column; Hypersil GOLD (4.6×250 mm, $5 \mu\text{m}$)