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Versatile Synthesis of Disubstituted Triazole Library for Dopamine and Serotonin Receptor Ligands†

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In the field of medicinal chemistry an extensive efforts have been made to explore potent and selective ligands for dopamine D_3[1]or D_4[2] receptor for the discovery of antipsychotic drugs.[3] Heterocyclic compounds bearing 1, 2, 3-triazole have long been the focus of synthetic chemistry due to their broad spectrum of applications in biological, pharmaceutical, and material areas.[4,5] The incorporation of 'click' chemistry,[6,7] the Cu(I)-catalyzed Huisgen [2 + 3] dipolar cycloaddition reaction between an organic azide and an alkyne to form 1,4-disubstituted tirazoles with exclusive selectivity, has recently become a laboratorial preference toward the construction of compound libraries,[8] along with applications in organic chemistry,[9,10] drug discovery.[11] Combinatorial chemistry often requires maximization of product distribution to achieve high diversity of the library generation. For the construction of substituted triazole libraries, we wanted to produce both isomeric triazoles at the same time. For this reason, classical [2+3] cycloaddition route to triazoles was chosen and studied for the construction of triazole libraries though the reaction condition is much harsher than the 'click' chemistry. In many instances, controlled microwave heating under sealed vessel conditions has been demonstrated to dramatically reduce reaction times, increase product yields, and enhance product purities by reducing unwanted side reactions compared to conventional synthetic methods.[12,13] Also, spectacular rate-enhancing effect of water as the reaction medium is widely reported for numerous organic reactions.[14] As a part of ongoing search for selective GPCR receptor ligands,[15] we selected triazole library as a good candidate for identifying sub-type selective ligands for GPCRs.

Herein we wish to report a microwave assisted synthesis of triazole library by using water as a solvent or a solvent free synthesis of virtually equal amount of both isomeric triazoles with high yield and high purity (Scheme1, Table 1).

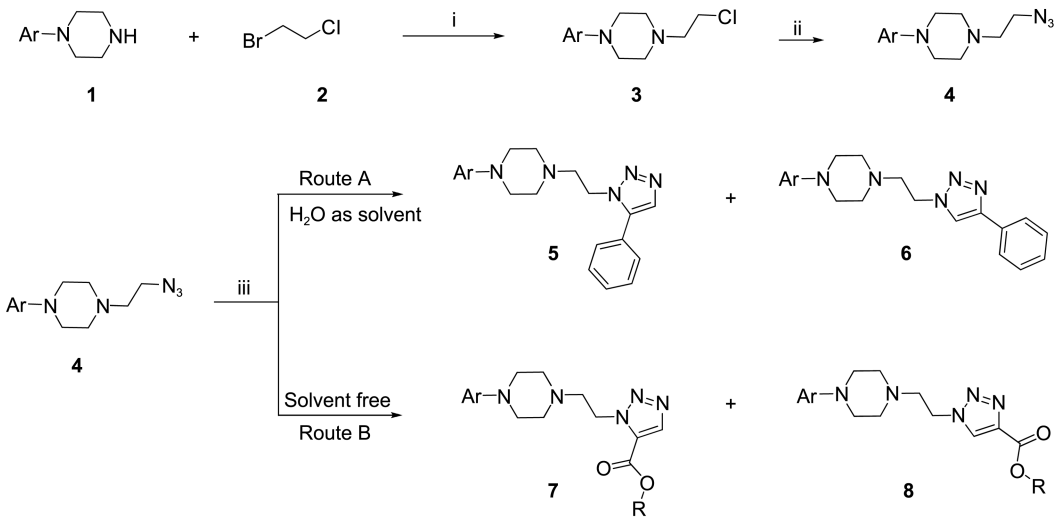
Derivatives **3** were synthesized with 52% yield by carrying out a simple nucleophilic substitution reaction of piperazine derivatives with 1-bromo-2-chloroethane **2** using potassium carbonate as a base in acetone at room temperature. Successive treatment of the products with sodium azide produced the derivatives **4** in 92% yield. Derivatives **4** were then treated with ethynylbenzene, methyl propiolate and ethyl propiolate under a microwave condition to obtain a mixture of 1,4- and 1,5-isomers (scheme1, Table 1) in 90-99% yield (yield of mixture of two isomers) by two different routes. To our delight, both 1,4- and 1,5-isomer were obtained in appreciable amount. With methyl propiolate, both isomers were obtained in similar amount. When methyl ester was replaced by ethyl ester, 1,4-isomer was obtained in larger amount than the 1,5-isomer though the ratio of two isomeric products was less than 2 in most cases. Size of the substituent does not appear to affect the isomeric ratio as phenylacetylene produced equal amount of isomers in most cases. Results from the entries 3, 4, 8, 9 and 11 strongly indicate that electronic environment, though remote, affects the product ratio. Both 1,4- and 1,5-isomers were easily separated and identity of the structures was confirmed by NOE experiment.[16]

For the route A, we used ethynylbenzene and azide derivatives for the synthesis of triazole in water and for route B, methyl propiolate and ethyl propiolate with azide derivatives without any solvent. The reaction condition does not appear to alter the ratio of products. This synthetic strategy of triazole derivatives provides good diversity in the library construction as both 1,4- and 1,5-isomers of triazoles would be produced. Table 1 summarizes the isolated yields and ratio of isomeric products through route A and route B.

A library of 54 molecules as HCl salts was tested *in vitro* for dopamine and serotonin receptor binding (Table 2),[17,18] even though the size of the linker between piperazine ring and triazole was not considered optimal for dopamine or serotonin binding. Among these 54 molecules some molecules showed relatively good binding affinity and selectivity for sub-type dopamine and serotonin receptors.

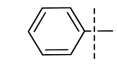
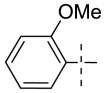
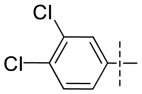
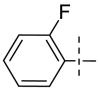
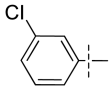
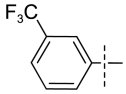
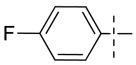
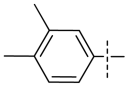
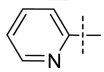
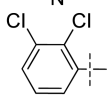
1,5-Isomers with 2,3-dimethyl, *o*-methoxy, 3,4-dichloro, *o*-fluoro and 3,4-dimethyl attached to phenyl piperazine ring (**5b**, **5c**, **5d**, **5e** and **5i**) show good binding affinities for dopamine D_4 receptor. These compounds also show good binding affinities to 5-HT_{1A} and 5-HT_{2A}.

†This paper is dedicated to Professor Eun Lee on the occasion of his honourable retirement.



Scheme 1. Reagents and reaction conditions: i. K_2CO_3, Acetone, rt, 15 hrs. 52%, ii. NaN_3, DMF, 50 °C, 10 hrs. 92%, iii. Route A: ethynylbenzene, MW. 150 °C, 150 W, 2 h, Route B: Methyl propiolate/Ethyl propiolate, MW., 100 °C,100 W, 1 h.

Table 1.

Entry	Ar	Route A				R	Route B			
		5	Yield	**6**	Yield		**7**	Yield	**8**	Yield
01		**5a**	45.2	**6a**	53.8	CH_3	**7a**	45.2	**8a**	52.3
						CH_2CH_3	**7a′**	18.4	**8a′**	62.5
02		**5b**	42.7	**6b**	54.8	CH_3	**7b**	45.2	**8b**	50.7
						CH_2CH_3	**7b′**	30.4	**8b′**	54.3
03		**5c**	28.5	**6c**	70.2	CH_3	**7c**	20.5	**8c**	72.3
						CH_2CH_3	**7c′**	14.7	**8c′**	80.5
04		**5d**	21.4	**6d**	75.8	CH_3	**7d**	23.7	**8d**	68.2
						CH_2CH_3	**7d′**	9.1	**8d′**	65.6
05		**5e**	45.7	**6e**	52.1	CH_3	**7e**	36.8	**8e**	51.4
						CH_2CH_3	**7e′**	19.4	**8e′**	79.9
06		**5f**	43.3	**6f**	52.8	CH_3	**7f**	40.5	**8f**	52.8
						CH_2CH_3	**7f′**	7.3	**8f′**	41.5
07		**5g**	40.3	**6g**	52.3	CH_3	**7g**	38.2	**8g**	54.2
						CH_2CH_3	**7g′**	14	**8g′**	61.5
08		**5h**	40.7	**6h**	53.8	CH_3	-[a]	-	-[a]	-
						CH_2CH_3	-[a]	-	-[a]	-
09		**5i**	20.4	**6i**	76.4	CH_3	-[a]		-[a]	
						CH_2CH_3	-[a]		-[a]	
10		**5j**	30.75	**6j**	68.3	CH_3	**7j**	33	**8j**	53.3
						CH_2CH_3	-[a]	-	-[a]	
11		-[a]		-[a]		CH_3	-[a]	-	-[a]	
						CH_2CH_3	**7k′**	19.8	**8k′**	73

[a]not synthesized

While the 1,5-isomers show selective binding activity to dopamine D_4 and serotonins, the 1,4-isomers do not show any binding activities to dopamine or serotonin receptors. When the phenyl substituent of the triazole ring was replaced by electron withdrawing ester group, the 1,5-isomers **7i** and **7d** show good binding affinity only to 5-

Table 2. *In vitro* binding affinity of some selective compounds

Compounds	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
5b	**26**	3975	3018	**43**	**25**	351	5914	7491
6b	2429	2139	>10000	83	262	881	>10000	180
5c	**26**	>10000	1797	**31**	1009	>10000	>10000	1186
6c	694	6943	>10000	145	5960	7124	>10000	398
5d	**41**	>10000	>10000	107	**65**	683	2167	2836
6d	565	>10000	>10000	5210	**95**	>10000	>10000	>10000
5e	**53**	9103	>10000	**67**	1164	>10000	>10000	6454
6e	5981	7539	>10000	946	3852	8440	>10000	3409
5f	222	6595	>10000	**52**	205	1624	7823	772
6f	3552	9418	>10000	201	550	1659	4284	560
5g	243	7123	8954	**55**	141	2238	>10000	989
6g	9351	>10000	>10000	107	773	5315	2001	736
5i	**53**	>10000	>10000	377	**69**	1206	5027	>10000
6i	1944	>10000	>10000	914	146	1636	4564	7719
7j	7008	>10000	>10000	457	**65**	381	6872	1409
8j	>10000	>10000	>10000	661	683	6419	6970	2392
7d	4167	>10000	>10000	2974	**63**	848	3010	>10000
8d	>10000	>10000	>10000	2916	459	1486	>10000	>10000
Clozapine	94.4	531	248	695	9.0	12.5	9.8	74.6
Olanzapine	98.4	175	200	9313	7.4	17.1	11.6	598

HT_{2A} receptor. According to our whole binding data study, we come to conclusion that the 1,5-isomers fit better to the receptors than 1,4-isomers and electronic environment around the trizaole ring plays a big role in the selectivity among receptors.

In summary we developed a diverse synthetic method to produce triazoles with high yield and high purity by using microwave reactor. The structural uniqueness and substitution pattern will be a good guide to the development of selective ligands for many GPCR receptors.

Experimental Section

General Procedure for Synthesis of Chloroethyl Piperazine Derivatives (3). To a solution of compound **1** (when R^1=Ph, 1 g, 6.16 mmol) and K_2CO_3 (1.27 g, 9.24 mmol) in acetone (10 mL), 1-bromo-2-chloroethane **2** (0.61 mL, 7.23 mmol) under nitrogen atmosphere was added dropwise at r.t. and stirred well at rt for 15 hrs. Reaction was monitored on T.L.C. Reaction mixture was filtered after 15 hrs. Filtrate removed solvent using by rotary evaporator. Product was washed with water and extracted with ethyl acetate (50 mL × 3). Product was isolated by column chromatography (E.A.:Hex. = 1:2) as a slight brown colored liquid with 52% yield.

^{1}H NMR derivative **3** when R^1=Ph (200 MHz, $CDCl_3$): δ 7.30-7.22 (m, 2H), 6.94-6.82 (m, 3H), 3.63 (t, 2H), 3.21 (t, 4H), 2.79 (t, 2H), 2.68 (m, 4H).

Other chloroethyl piperazine derivatives were synthesized analogously and identified with the ^{1}H NMR.

General Procedure for Synthesis of Azidoethyl Piperazine Derivatives (4). A solution of compound **3** (when R^1=Ph, 710 mg, 3.16 mmol) and NaN_3 (409.5 mg, 6.29 mmol) in DMF was stirred at 50 °C for 10 hrs. Reaction was monitored on T.L.C. After completion of reaction, reaction mixture was filtered out and DMF was degassed under rotary evaporator at 50 °C. Obtained gelly mass was washed with water and product was extracted with ethyl acetate (25 mL × 3). Product was purified by column chromatography (E.A.:Hex. = 4:6) to give liquid with 92% yield.

^{1}H NMR of derivative **4** when R^1=Ph (200 MHz, $CDCl_3$): δ 7.70-7.22 (m, 2H), 6.95-6.86 (m, 3H), 3.39 (t, 2H), 3.22 (t, 4H), 2.70-2.63 (overlap, m, 6H).

Other azidoethyl piperazine derivatives were synthesized analogously and identified with the ^{1}H NMR.

General Procedure for Synthesis of Triazole-ethyl Piperazine Derivatives (5) and (6).

Route A: A solution of compound **4** (when R^1=Ph, 90 mg, 0.389 mmol) and ethynylbenzene (0.128 mL, 1.15 mmol) in 2 mL of water was stirred in microwave reactor (CEM, Model No.-908005, Serial No.-DU8589) at 150 °C and 150 W for 2 hr. Water was removed from reaction mixture at 50 °C under high vacuum. Obtained jelly mass was purified by column chromatography (THF:$CHCl_3$:Hex = 2:1:2). Syn isomer **5** was separated as a colorless liquid with 40-45% yield and anti isomer **6** was separated as a solid with 45-50% yield.

After carrying out a column chromatography, product was dissolved in 2 mL of diethyl ether and treated with 1 M HCl solution in diethyl ether. All HCl salts were prepared by the same method.

Other triazole ethyl piperazine derivatives were synthesized analogously and identified with the ^{1}H NMR.

^{1}H NMR Compound **5a** (400 MHz, MeOH-d_4): δ 7.77(s, 1H), 7.75-7.753 (m, 5H), 7.20-7.18 (m, 2H),6.91-6.88 (m, 2H), 6.87 (m, 1H), 4.61 (t, 2H, J = 6.4 Hz), 2.30 (t, 4H, J = 5.2 Hz), 2.83 (t, 2H, J = 6.4 Hz), 2.49 (t, 4H, J = 5.2 Hz).

^{1}H NMR Compound **6a** (400 MHz, $CDCl_3$): δ 7.94 (s, 1H), 7.83 (d, 2H , J = 6.3 Hz), 7.41 (t, 2H), 7.33 (t, 1H), 7.29-7.26 (m, 2H), 6.93 (d, 2H), 6.87 (t, 1H), 4.55 (t, 2H), 3.21 (t, 4H), 2.93 (t, 2H), 2.69 (t, 4H).

General Procedure for Synthesis of Triazole Carboxylate Derivatives (7a) and (8a).

Route B: A solution of compound **4** (when R^1=Ph, 92 mg, 0.397 mmol) and methyl propiolate (0.106 mL, 1.19 mmol) or ethyl propiolate (0.120 mL, 1.19 mmol) was stirred in microwave reactor (CEM, Model No.-908005, Serial No.-DU8589) at 100 ºC and 100 W for 1 hr. Reaction mixture was purified by column chromatography (THF:$CHCl_3$:Hex = 2:1:2). Syn isomer **7** was separated as a colorless liquid with 40-45% yield and anti isomer **8** was separated as a solid with 45-50% yield.

Compound **7a′** and **8a′** (when R^1=Ph and R^2=CH_2CH_3) were prepared by using the same procedure.

Other triazole carboxylate derivatives were synthesized analogously and identified with ^{1}H NMR.

^{1}H NMR Compound **7a** (400 MHz, MeOH-d_4): δ 8.18 (s, 1H), 7.24-7.19 (m, 2H), 6.96-6.93 (m, 2H), 6.82 (t, 1H, J = 6.4 Hz), 4.95 (t, 2H, J = 6.4 Hz), 3.93 (s, 3H), 3.10 (t, 4H), 2.92 (t, 2H, J = 6.8 Hz), 2.69 (t, 4H, J = 5.2 Hz).

^{1}H NMR Compound **8a** (400 MHz, $CDCl_3$): δ 8.26 (s, 1H), 7.28-7.24 (m, 3H), 6.93-6.85 (m, 2H), 4.55 (t, 2H, J = 5.6 Hz), 3.95 (s, 3H), 3.19-3.17 (m, 4H), 2.90-2.88 (m, 2H), 2.67-2.65 (m, 4H).

^{1}H NMR Compound **7a′** (400 MHz, MeOH-d_4): δ 8.18 (s, 1H), 7.24-7.20 (m, 2H), 6.95-6.93 (m, 2H), 6.85-6.80 (m, 1H), 4.9 (t, 2H, J = 6.8 Hz),4.41 (q, 2H, J = 4.2 Hz), 3.10 (t, 4H), 2.91 (t, 2H, J = 6.4 Hz), 2.68 (t, 4H), 1.39 (t, 3H, J = 7.2 Hz).

^{1}H NMR Compound **8a′** (400 MHz, MeOH-d_4): δ 8.58 (s, 1H), 7.24-7.20 (m, 2H), 6.96-6.94 (m, 2H), 6.85-6.80 (m, 1H), 4.64 (t, 2H, J = 6.4 Hz), 4.39 (q, 2H, J = 6.8 Hz), 3.13 (t, 4H), 2.92 (t, 2H, J = 6.4 Hz), 2.69 (t, 4H), 1.37 (t, 3H, J = 8 Hz).

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16. In the 1,5- isomers, after irradiation of triazole proton there is no enhancement of ethyl proton. On the other hand, after irradiation of triazole proton in the 1,4-isomers, there is clear enhancement of ethyl proton which comes near 4.6 ppm and 2.81 ppm.
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18. Compounds were evaluated *in vitro* for dopamine D_2, D_3, D_4 receptors binding affinity by measuring their ability to displace radioligand ([^{3}H]Methylspiperone for D_2 and D_3, [^{3}H]YM-09151-2 for D_4) 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 [^{3}H]8-OH-DPAT, [^{3}H]Ketanserin, [^{3}H]Mesulergine and [^{3}H]LSD binding assay, respectively.