

Copper - Alumina Catalyzed Regioselective Synthesis of Novel 1, 4-Disubstituted 1, 2, 3-Triazoles from Phenylpropanolamines by Click Chemistry Approach

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Abstract: A series of some novel phenylpropanolamino-1, 4-disubstituted-1, 2, 3-triazoles have been synthesized with regioselectivity in good to excellent yields using a reusable heterogeneous CuI/Al₂O₃ (5%) catalyst via Click chemistry approach. The reaction conditions were well optimized. All synthesized compounds have been characterized using IR, Mass and NMR techniques. The antimicrobial activities of synthesized compounds were screened against ten bacteria and two fungi using in vitro well method. Among the synthesized triazoles compound **9a** shows potent antimicrobial activity.

Key Words: Phenylpropanolamine, click chemistry, 1,3-dipolar cycloaddition, regioselectivity, azidation, antimicrobial activity.

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I. Introduction

1.1 Biologically importance of Phenylpropanolamines

Phenylpropanolamine (PPA) as a synthetic precursor which was reported by Mannich and Jacobsen in year of 1910 and well known for their psychoactive properties as well as decongestant, stimulant and anorectic effects.¹⁻³ The first patent on phenylpropanolamine was published in 1939 and used as over the counter (OTC) drugs for decongestant for about 40 years.⁴ Many countries has been regulated the usage of PPA due to its adverse effects related to stroke, cardiovascular and psychiatric disorders.^{5, 6} Hence, the development of structurally modified PPAs with minimum adverse effect is one of the important tasks for researchers. Even Though there are several routes to synthesis of this molecule have been reported, the product isolated is a racemate and required chemical resolution to obtain the desired optical antipode. Such structurally modified PPA showed multiple biological activities such as cardiovascular, antitussive, antimicrobial, and antibiotic.^{7,8}

The above pictures show graphic representation of the vicinal chiral carbons stereochemistry present in PPA (**Figure 1**). The development of substituted PPA as active pharmaceutical ingredient (API) is illustrative as for example, Atenolol as a cardioselective β -blocker, propranolol as a drug for reducing the oxygen demand of the heart, metoprolol as a β_1 receptor blocker to reduce high blood pressure are representative examples for molecules containing the PPA structural unit.⁹⁻¹²

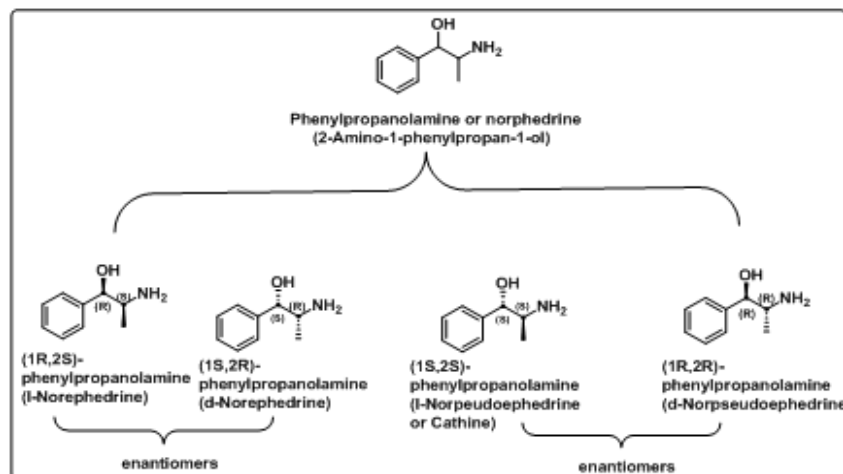


Figure 1 Stereoisomers of phenylpropanolamine.

Iwamoto and Hartung¹³ modified mescaline, 2-(3,4,5-trimethoxyphenyl)-ethanamine, a naturally occurring alkaloid with psychotropic effects was modified structurally and prepared various derivatives of it as PPA analogs (**Figure 2**). These analogs of PPA were found to be less toxic than mescaline and exhibited better physiological responses. Synthesis of phenylpropanolamine and its enantiomers are well documented in literature. It was synthesized using general chemical synthetic methods and biosynthetic methods.¹⁴

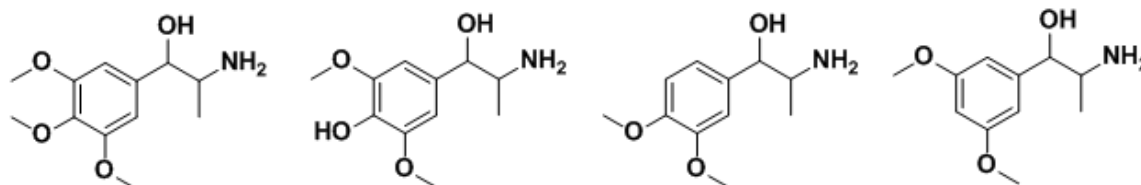
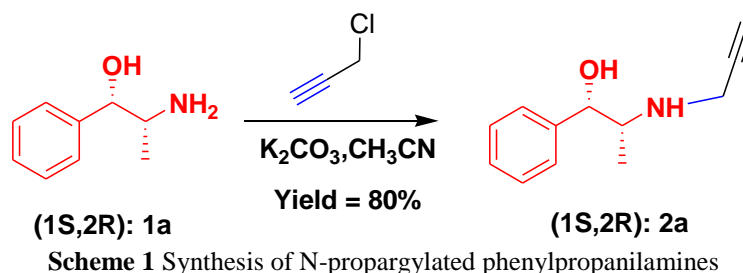


Figure 2 Few mescaline analogs of phenylpropanolamine.

1.2 Results and discussion

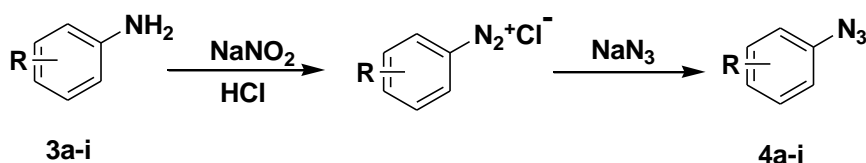
1.2.1 Synthesis of *N*-alkyl derivatives of Phenylpropanolamines

We started our synthesis by preparing the starting materials *N*-propargylated phenylpropanilamines (**2a-2b**) from Phenylpropanolamines (**1a-1b**) in presence of propargyl chloride and potassium carbonate in acetonitrile (**Scheme 1**). The reaction yielded *N*-propargylated phenylpropanilamines as a sole product with a yield around 80%.



1.2.2 Synthesis of azides from arylamines.

Synthesis of various arylazides (**4**) was prepared by the reaction of arylamines (**3**) with sodium nitrite and sodium azide in strong acidic condition. (**Scheme 2**) The yield of the arylazide **4a-i** from 70-90%.



1.2.3 Preparation of catalyst CuI/Al₂O₃

Neutral alumina (100g) and copper iodide (10g) and methanol (300 mL) were mixed and heated for 1.0 hour 55 to 60 °C. Methanol was distilled off completely and the free flowing white powder was dried at 75 °C for 6 hours. The obtained catalyst was stored under nitrogen.

1.2.4 Synthesis of 1, 4-disubstituted 1, 2, 3-triazoles.

Optimization of Reaction Condition

We initiated our study to synthesis of phenylpropanolamines tethered 1,4-disubstituted 1,2,3-triazoles by click reaction of aryl azide **4a** with *N*-propargylated phenylpropanilamines **2a** under catalyst (CuI) at room temperature for 8 to 10 hours. The reaction process was monitored by TLC and the reaction yielded the preferred triazole **5a** in 82% (**Scheme 3, Table 1**, entry 1). Having obtained the triazole products in moderate yield, we next varied the reaction conditions in order to improve the yield. We have changed the catalyst from CuI to CuBr, the yield of the reaction was reduced to 22%. (**Table 1**, entry 2), furthermore increasing quantity of CuI catalyst to 20 mol% slightly increased to 85% and decreasing the catalyst loading to 5 mol% the yield lower to 56%. (**Table 1**, entry 3-4). Then we have reduced the reaction time to 8 h, getting the same 85% yield (**Table 1**, entry 5). We have fixed catalyst CuI 10 mol% and change the solvents such as H₂O, EtOH, *n*-BuOH, *n*-BuOH/H₂O (1:1), EtOH/H₂O (1:1) and MeOH/THF/H₂O (1:1:1) the yield was not improved. (**Table 1**, entry

6-11). Even though Cu(I) catalyzed CUAAC reaction shows moderate to good yield but it has some drawbacks like difficulty to removal of traces of copper from the triazoles and Cu(I) catalyst used in the reaction cannot be recycled and reusable. Then we tested the heterogeneous copper catalyst (CuI/Al₂O₃), the maximum yield 96% was obtained when 5% CuI and 5% Al₂O₃ were used. Bases such as diisopropylethylamine (DIPEA), triethylamine (TEA) and potassium hydroxide were used and better yield was noticed with DIPEA (**Table 1**, entry 14). Finally, we found that (CuI/Al₂O₃) was the most effective catalyst for the selective formation of the desired product in terms of both reaction time and yield.

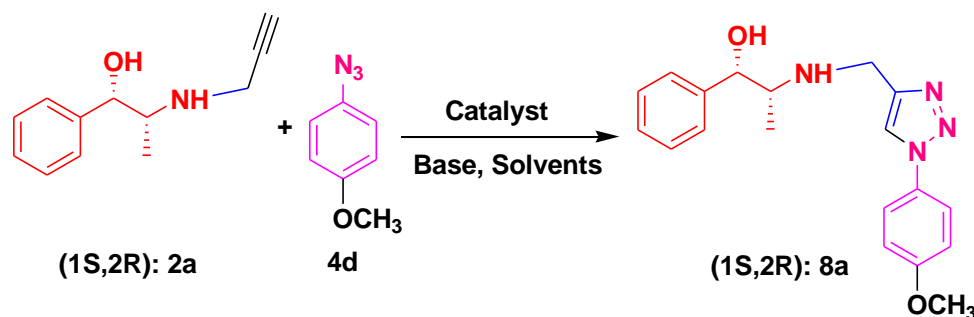


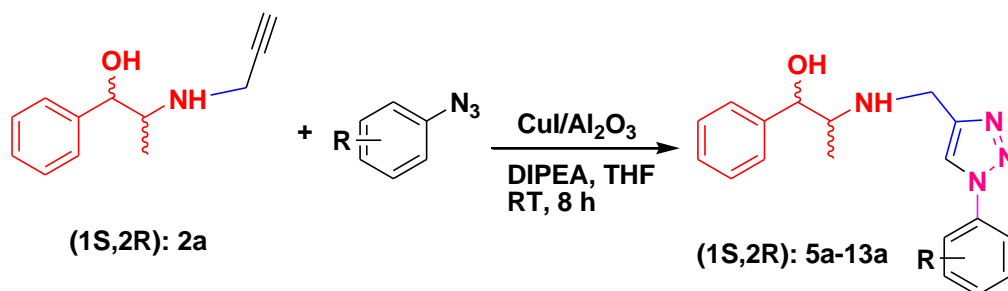
Table 1 Optimization of Reaction Condition^a

Entry	Catalyst (mol %)	Base (50 mol %)	Solvent	Time (h)	8a Yield (%) ^b
1	CuI (10)	DIPEA	THF	12	82
2	CuBr (10)	DIPEA	THF	12	22
3	CuI (20)	DIPEA	THF	12	85
4	CuI (5)	DIPEA	THF	12	56
5	CuI (10)	DIPEA	THF	8	85
6	CuI (10)	DIPEA	H ₂ O	8	58
7	CuI (10)	DIPEA	EtOH	8	Trace
8	CuI (10)	DIPEA	n-BuOH	8	75
9	CuI (10)	DIPEA	n-BuOH/H ₂ O 1:1	8	80
10	CuI (10)	DIPEA	EtOH/H ₂ O 1:1	8	35
11	CuI (10)	DIPEA	MeOH/THF/H ₂ O 1:1:1	8	82
12	10% CuI/Al ₂ O ₃ 5%	DIPEA	THF	8	90
13	10% CuI/Al ₂ O ₃ 10%	DIPEA	THF	8	92
14	5% CuI/Al₂O₃ 5%	DIPEA	THF	8	95
15	5% CuI/Al ₂ O ₃ 5%	TEA	THF	8	Trace
16	CuI (10)	TEA	THF	8	Trace
17	CuI (10)	KOH	n-BuOH	8	Trace
18	CuI (20)	KOH	n-BuOH	8	Trace
19	5% CuI/Al ₂ O ₃ 5%	KOH	n-BuOH	8	Trace
20	5% CuI/Al ₂ O ₃ 5%	DIPEA	H ₂ O	8	86

^aReaction Conditions: N-Propargylated phenylpropanolamines **2a** (1.0 mmol), Phenylazide **4d** (1.0 mmol) and various Catalyst, solvents and Base. ^bIsolated Yields after recrystallization in Acetone.

The structures of phenylpropanolamines tethered 1, 2, 3-triazoles **8a** was elucidated by using IR, ¹H and ¹³C NMR and mass spectral data. Characteristic IR bands at 3300 and 2969 cm⁻¹ represents the –NH stretching and aliphatic stretching respectively. In ¹H NMR spectrum of compound **8a**, the doublet at δ 0.86 ppm (*J* = 8.0 Hz) and singlet at δ 3.86 ppm were attributed to CH₃ and OCH₃ respectively. The triplet at δ 2.82 ppm (*J* = 8.0 Hz) and doublet at δ 5.17 ppm (*J* = 4.0 Hz) were assigned to proton at 1*S* and 2*R* carbons respectively. Finally peak at δ 8.45 ppm was attributed to triazole ring proton. The structure was further confirmed with ¹³C NMR, peaks at 56.0, 115.3 and 159.6 were attributed to OCH₃, and triazole ring carbons. The mass spectrum revealed the molecular ion peak (M⁺+1) at *m/z* 339.

Once the reaction conditions were optimized, the catalytic efficiency of the developed protocol using equimolar amounts of N-propargylated phenylpropanolamines **2a** (1.0 mmol), phenylazide **4a-i** (1.0 mmol) and 5 mol% of CuI/Al₂O₃ at room temperature in THF was investigated (**Table 1**). The products were confirmed on the basis of NMR and mass spectrometry. Under the optimized conditions, all the given reactions showed clean conversion and provided a library of 1,4-disubstituted 1,2,3-triazoles derivatives (**5a–13a**) in good to excellent yields (85–96%). The results are summarized in **Figure 3**.



Scheme 4 Synthesis of phenylpropanolamines tethered 1,2,3-triazoles from derivatives 5a-13a.

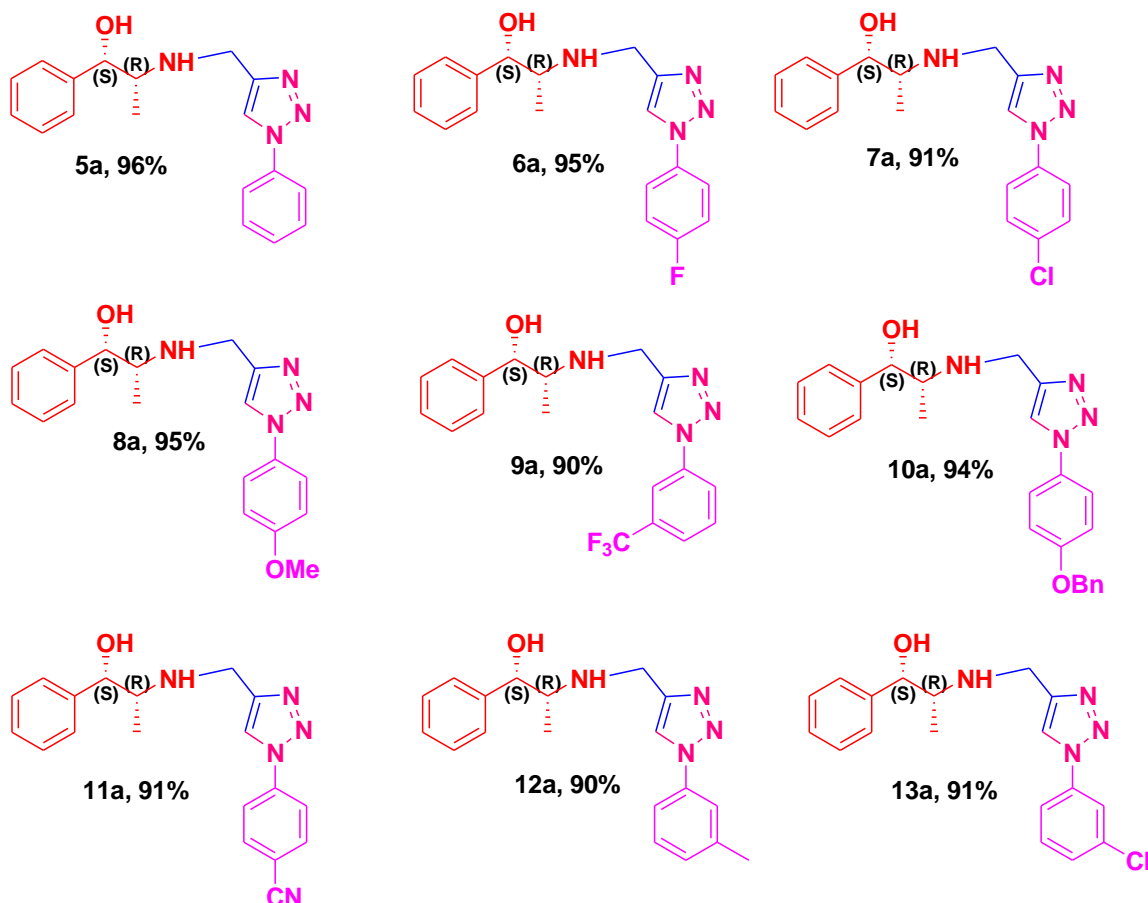


Figure 3 Structure of phenylpropanolamines tethered 1,2,3-triazoles from derivatives 5a-13a.

1.2.5 Recovery and reuse of catalyst CuI/Al₂O₃

To display greener environment of our protocol, the recyclability of (CuI/Al₂O₃) was tested. After completion of the reaction, the reaction mixture was centrifuged to remove the catalyst. The residual catalyst thus obtained was washed with ethyl acetate, followed by drying for 4 h at 110 °C. In our study, the catalyst was recycled upto 5 times and found satisfactory yields in-between 87 % and 96 %. (Table 2)

Table: 2 Recyclability of (CuI/Al₂O₃) tested in the synthesis of 8a^a

Entry	Catalytic run	Catalyst recovery ^b	Yield ^c (%)
1	1	97	95
2	2	92	94
3	3	88	92
4	4	86	90
5	5	82	87

^a 5.0 mol% CuI/Al₂O₃ was used for the reaction.

^b The recovered catalyst was used under identical conditions as those in the first run.

^c Isolated yield of the product 8a.

1.3 Experimental

1.3.1 Materials and methods

All chemicals were purchased from Sigma-Aldrich Pvt Ltd. Analytical Thin layer chromatography (TLC) was carried out using pre-coated Merck TLC Silica gel 60 F254 and spots were detected using Ultra-Violet light.

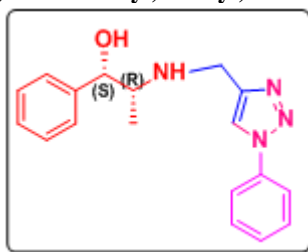
1.3.2 Equipments and analytical instruments

Melting points were measured using a Veego melting point apparatus model VMP-PM. IR spectra were recorded (KBr pellet) on a Shimadzu Prestige 21 FTIR instrument in the range of 4000 to 400 cm^{-1} . ^1H NMR and ^{13}C NMR spectra were recorded using a Bruker-Avance 300 MHz FT-NMR spectrometer (400 and 100 MHz, respectively) using DMSO-d_6 as solvent and TMS as internal standard. Low resolution mass spectra were recorded on an Agilent 6110LC/MS mass spectrophotometer using the ESI mode. The elemental analysis was done (sample thoroughly dried under vacuum) using a Thermo Fischer Flash 1112 Series elemental analyzer.

1.3.3 Experimental procedure for the synthesis of phenylpropanolamines tethered 1,2,3-triazoles 5a-13a.

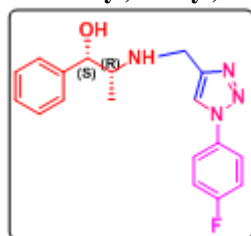
N-propargylated phenylpropanilamines **2a** (10 mmol) was added to solution of Azide **4a-i** (10 mmol) taken in the THF solvent followed by diisopropylethylamine (1.2 equiv.) and catalyst ($\text{Cu}/\text{Al}_2\text{O}_3$ 5 mol%) at room temperature for 8 to 10 hours. Completion of the reaction was monitored by TLC (mobile phase: 20% methanol in dichloromethane). After the completion of reaction, catalyst was removed by filtration and washed with water and solvents then used for recycle. Filtrate was concentrated in rotavapor. Work up with ethyl acetate (50 mL) and organic layer separated. Organic layer was washed with water (20 mL), dried over sodium sulfate and concentrated completely to get semi solid. The semi solid was triturated with acetone (5 mL), filtered and dried at 60 $^\circ\text{C}$ under vacuum to get the compound **5a-13a**.

(1S,2R)-1-phenyl-2-(((1-phenyl-1H-1,2,3-triazol-4-yl)methyl)amino)propan-1-ol **5a**.



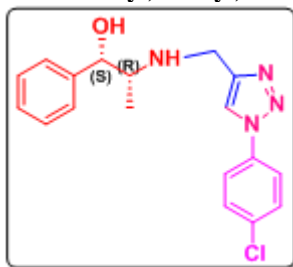
Pale brown solid, Yield 96%, Mp: 121-124 $^\circ\text{C}$, IR (KBr, cm^{-1}): 3307, 3135, 3065, 2972, 2853, 1599, 1509, 1501, 1449, 1419, 1229, 1140, 1075, 996, 985, 911, 902, 832, 760, 702, 691, 520; ^1H -NMR (400 MHz, DMSO-d_6); δ_{H} (ppm) 0.83 (s, 3H), 2.72 (bs, 1H), 3.89 (s, 2H), 4.74 (s, 1H), 5.15 (s, 1H), 7.16-7.25 (m, 1H), 7.34-7.36 (m, 4H), 7.57-7.64 (m, 3H), 7.96-7.98 (m, 2H), 8.62 (s, 1H); ^{13}C -NMR (100 MHz, CDCl_3); δ_{C} (ppm) 14.6, 42.3, 63.1, 73.6, 112.7, 117.5, 120.6, 127.4, 128.5, 133.9, 142.3; ESI-MS: m/z calcd for $\text{C}_{18}\text{H}_{20}\text{N}_4\text{O}$ $[\text{M}]^+$: 308.38, found: 309.0.

(1S,2R)-2-(((1-(4-fluorophenyl)-1H-1,2,3-triazol-4-yl)methyl)amino)-1-phenylpropan-1-ol **6a**.



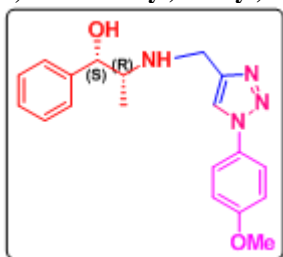
Brown solid, Yield 91%, MP: 138-141 $^\circ\text{C}$, IR (KBr, cm^{-1}): 3308, 3136, 3095, 2973, 2911, 2853, 1888, 1650, 1603, 1560, 1515, 1492, 1452, 1425, 1375, 1226, 1189, 1154, 1076, 1044, 993, 901, 838, 738, 699, 610, 529; ^1H -NMR (400 MHz, CDCl_3); δ_{H} (ppm) 0.89 (s, 3H), 2.17 (s, 1H), 3.92-4.27 (m, 2H), 4.96 (s, 1H), 7.32-7.46 (m, 5H), 7.84-7.87 (m, 2H), 7.94-8.17 (m, 2H), 8.17 (s, 1H); ^{13}C -NMR (100 MHz, CDCl_3); δ_{C} (ppm) 14.4, 42.2, 63.4, 73.5, 112.7, 117.4, 120.7, 127.3, 128.6, 133.8, 142.0; ESI-MS: m/z calcd for $\text{C}_{18}\text{H}_{19}\text{FN}_4\text{O}$ $[\text{M}]^+$: 326.15, found: 327.0.

(1S,2R)-2-(((1-(4-chlorophenyl)-1H-1,2,3-triazol-4-yl)methyl)amino)-1-phenylpropan-1-ol 7a.



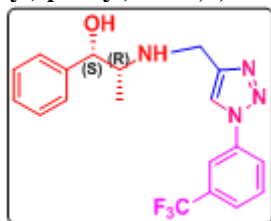
Pale brown solid, Yield 91%, Mp: 172-173°C, IR (KBr, cm^{-1}): 3305, 3138, 3101, 2973, 1501, 1426, 1226, 1093, 1042, 993, 903, 829 and 699; $^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$); δ_{H} (ppm) 0.86 (s, 3H), 2.78 (bs, 1H), 3.88 (s, 2H), 4.70 (s, 1H), 5.18 (s, 1H), 7.19-7.722 (m, 1H), 7.31-7.32 (m, 4H), 7.55-7.69 (m, 2H), 7.93-7.95 (m, 2H), 8.61 (s, 1H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3); δ_{C} (ppm) 14.4, 42.6, 63.2, 73.7, 112.6, 117.4, 120.5, 127.7, 128.4, 133.8, 142.3; ESI-MS: m/z calcd for $\text{C}_{18}\text{H}_{19}\text{ClN}_4\text{O}$ $[\text{M}]^+$: 342.82, found: 343.0.

(1S,2R)-2-(((1-(4-methoxyphenyl)-1H-1,2,3-triazol-4-yl)methyl)amino)-1-phenylpropan-1-ol 8a.



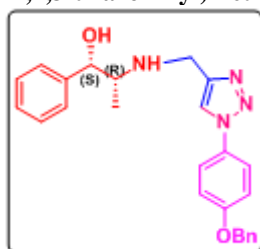
Brown solid, Yield 95%, MP: 148-150°C, IR (KBr, cm^{-1}): 3300, 3136, 2969, 2839, 1519, 1448, 1255, 1227, 1045, 985, 830, 700, 624, 513; $^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$); δ_{H} (ppm) 0.86 (d, $J = 8.0$ Hz, 3H), 2.82 (t, $J = 8.0$ Hz, 1H), 3.86 (s, 3H), 3.89 (s, 2H), 4.70 (s, 1H), 5.17 (d, $J = 4.0$ Hz, 1H), 7.11-7.14 (m, 1H), 7.15-7.23 (m, 1H), 7.28-7.34 (m, 5H), 7.77-7.80 (m, 2H), 8.45 (s, 1H); $^{13}\text{C-NMR}$ (100 MHz, $\text{DMSO-}d_6$); δ_{C} (ppm) 14.9, 42.0, 56.0, 58.2, 74.0, 115.3, 121.2, 122.0, 126.8, 126.9, 128.2, 130.7, 144.3, 148.2, 159.6; ESI-MS: m/z calcd for $\text{C}_{19}\text{H}_{22}\text{N}_4\text{O}_2$ $[\text{M}]^+$: 338.40, found: 339.0.

(1S,2R)-1-phenyl-2-(((1-(3-(trifluoromethyl) phenyl)-1H-1,2,3-triazol-4-yl)methyl)amino) propan-1-ol 9a.



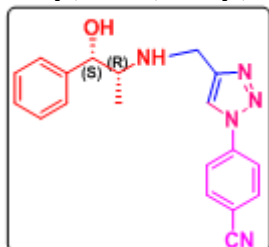
Brown solid, Yield 90%, MP: 123-125°C, IR (KBr, cm^{-1}): 3305, 3135, 3097, 2973, 2841, 2712, 1602, 1565, 1496, 1484, 1426, 1353, 1322, 1227, 1170, 1139, 1130, 1100, 1046, 995, 896, 802, 739, 702, 697, 688, 661, 540, 529; $^1\text{H-NMR}$ (400 MHz, $\text{DMSO-}d_6$); δ_{H} (ppm) 0.87 (d, $J = 8.0$ Hz, 3H), 2.84 (s, 1H), 3.93 (s, 2H), 4.71 (s, 1H), 5.19 (s, 1H), 7.19-7.23 (m, 1H), 7.29-7.35 (m, 4H), 7.86 (d, $J = 8.0$ Hz, 2H), 8.26 (d, $J = 8.0$ Hz, 2H), 8.77 (s, 1H); $^{13}\text{C-NMR}$ (100 MHz, $\text{DMSO-}d_6$); δ_{C} (ppm) 14.9, 42.0, 58.2, 73.9, 116.9, 121.6, 122.7, 124.2, 125.4, 126.8, 128.2, 130.9, 131.2, 131.8, 137.7, 144.3; ESI-MS: m/z calcd for $\text{C}_{19}\text{H}_{19}\text{F}_3\text{N}_4\text{O}$ $[\text{M}]^+$: 376.38, found: 377.0.

(1S,2R)-2-(((1-(4-(benzyloxy) phenyl)-1H-1,2,3-triazol-4-yl)methyl)amino)-1-phenylpropan-1-ol 10a.



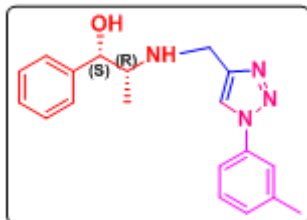
Brown solid, Yield 94%, MP: 127-130°C, IR (KBr, cm^{-1}): 3300, 3141, 3065, 2967, 2872, 2110, 1609, 1594, 1519, 1450, 1378, 1254, 1224, 1173, 1138, 1045, 995, 899, 826, 804, 742, 703, 667, 540; $^1\text{H-NMR}$ (400 MHz, CDCl_3); δ_{H} (ppm) 0.91 (d, $J = 8.0$ Hz, 3H), 2.52 (bs, 2H), 3.06 (s, 1H), 4.12 (q, $J = 12.0$ Hz, 2H), 4.84 (s, 1H), 5.13 (s, 2H), 6.95 (s, 2H), 7.09 (d, $J = 8.0$ Hz, 1H), 7.33-7.35 (m, 4H), 7.37-7.41 (m, 2H), 7.43-7.46 (m, 3H), 7.62 (d, $J = 8.0$ Hz, 2H), 7.82 (s, 1H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3); δ_{C} (ppm) 14.4, 42.1, 58.0, 70.4, 73.3, 115.8, 116.2, 120.0, 122.2, 126.1, 127.2, 127.5, 128.2, 128.3, 128.7, 130.8, 136.3, 141.2, 158.9; ESI-MS: m/z calcd for $\text{C}_{25}\text{H}_{26}\text{N}_4\text{O}_2$ $[\text{M}]^+$: 414.50, found: 415.0.

4-(4-(((1S,2R)-1-hydroxy-1-phenylpropan-2-yl)amino)methyl)-1H-1,2,3-triazol-1-yl)benzonitrile 11a.



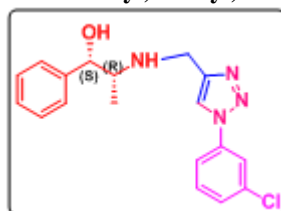
Brown solid, Yield 91%, MP: 138-141°C, IR (KBr, cm^{-1}): 3133, 2919, 2850, 2227, 1607, 1517, 1409, 1330, 1255, 1173, 1045, 990, 841, 835, 739, 699, 652, 554, 547; $^1\text{H-NMR}$ (400 MHz, CDCl_3); δ_{H} (ppm) 0.99 (s, 3H), 2.15 (s, 1H), 3.95-4.22 (m, 2H), 4.93 (s, 1H), 7.33-7.43 (m, 5H), 7.83-7.85 (m, 2H), 7.91-8.11 (m, 2H), 8.17 (s, 1H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3); δ_{C} (ppm) 14.6, 42.3, 63.0, 73.7, 112.5, 117.7, 120.6, 127.5, 128.3, 133.9, 142.1; ESI-MS: m/z calcd for $\text{C}_{19}\text{H}_{19}\text{N}_5\text{O}$ $[\text{M}]^+$: 333.39, found: 334.0.

(1S,2R)-1-phenyl-2-(((1-(m-tolyl)-1H-1,2,3-triazol-4-yl)methyl)amino)propan-1-ol 12a.



Brown solid, Yield 90%, MP: 147-150°C, IR (KBr, cm^{-1}): 3133, 2919, 2227, 1607, 1517, 1409, 1330, 1255, 1225, 1045, 990, 841, 835, 699, 554, 547; $^1\text{H-NMR}$ (400 MHz, CDCl_3); δ_{H} (ppm) 0.91 (d, $J = 8.0$ Hz, 3H), 2.45 (s, 3H), 3.06 (s, 1H), 4.06 (d, $J = 12.0$ Hz, 2H), 4.85 (s, 1H), 7.24 (s, 2H), 7.33-7.38 (m, 4H), 7.40-7.50 (m, 2H), 7.57 (s, 1H), 7.89 (s, 1H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3); δ_{C} (ppm) 14.5, 21.4, 42.1, 58.0, 73.4, 117.6, 119.9, 121.2, 126.1, 127.2, 128.2, 129.5, 129.6, 137.0, 140.0, 141.3, 147.3; ESI-MS: m/z calcd for $\text{C}_{19}\text{H}_{22}\text{N}_4\text{O}$ $[\text{M}]^+$: 322.40, found: 323.0.

(1S,2R)-2-(((1-(3-chlorophenyl)-1H-1,2,3-triazol-4-yl)methyl)amino)-1-phenylpropan-1-ol 13a.



Brown solid, Yield 91%, MP: 107-109°C, IR (KBr, cm^{-1}): 3300, 3141, 3058, 2875, 2708, 1597, 1492, 1431, 1375, 1229, 1141, 1045, 999, 875, 820, 790, 781, 701, 678, 542; $^1\text{H-NMR}$ (400 MHz, CDCl_3); δ_{H} (ppm) 0.93 (d, $J = 4.0$ Hz, 3H), 2.44 (bs, 2H), 3.04 (s, 1H), 4.08 (d, $J = 12.0$ Hz, 2H), 4.82 (s, 1H), 7.25 (s, 2H), 7.33-7.40 (m, 4H), 7.42-7.63 (m, 2H), 7.77 (s, 1H), 7.89 (s, 1H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3); δ_{C} (ppm) 14.3, 42.6, 63.4, 73.2, 118.4, 119.7, 120.7, 126.2, 127.2, 128.2, 128.8, 130.9, 135.6, 137.9, 141.3, 147.8; ESI-MS: m/z calcd for $\text{C}_{18}\text{H}_{19}\text{ClN}_4\text{O}$ $[\text{M}]^+$: 342.82, found: 343.0.

Antimicrobial activity

In the present study, the antimicrobial activities of synthesized compounds were screened against ten bacteria and two fungi using *in vitro* well method. The results were summarized below (Table 4.2). In particular, synthesized compounds **9a**, **6a**, **8a**, and **7a** showed promising activity against tested bacteria at 1 mg/mL concentration. Importantly, compound **9a** exhibited potent antimicrobial activity against tested bacteria.

Table 4.2. Antimicrobial activity of synthesized compound using well method (Zone of inhibition in mm) (1 mg/well)

Organism	5a	6a	7a	8a	9a	10a	11a	12a	13a	C
Bacteria										
<i>Enterobacter aerogenes</i>	34	12	14	10	10	-	22	27	14	22
<i>Staphylococcus aureus</i>	32	14	16	13	12	-	16	19	18	14
<i>Staphylococcus epidermidis</i>	24	16	17	14	13	24	28	18	14	26
<i>Staphylococcus aureus</i> MRSA	23	12	18	16	12	28	24	20	16	30
<i>Salmonella paratyphi-B</i>	19	10	16	15	10	19	20	21	17	18
<i>Salmonella typhimurium</i>	21	15	12	13	12	-	19	26	-	24
<i>Proteus vulgaris</i>	19	14	14	17	11	27	26	28	15	30
<i>Micrococcus luteus</i>	28	18	16	14	15	13	16	16	16	26
<i>Klebsiella pneumoniae</i>	25	16	11	16	10	26	21	29	12	20
<i>Shigella flexneri</i>	26	-	13	11	16	29	25	17	18	30
Fungi										
<i>Candida albicans</i>	-	13	13	13	10	-	-	-	15	28
<i>Malassezia pachydermatis</i>	-	16	-	11	12	12	-	-	18	26

II. Conclusion

In summary, the synthesis of some novel phenylpropanolamines tethered 1,2,3-triazoles are reported for the first time. The adducts were obtained by using highly regioselective 1,3-dipolar cycloaddition strategy (click chemistry). Among the synthesized triazoles compound **9a** shows potent antimicrobial activity against tested bacteria., we anticipate that these novel phenylpropanolamines tethered 1,2,3-triazoles will have biological scope for further development .

References

- [1]. (a) Flavahan N. A.; J. Pharmacol. Exp. Ther., 2005, 313, 432–439; (b) Haugeto O. K.; Schroder K. E and Mair I. W.; J. Otolaryngol., 1981, 10, 359–362.
- [2]. (a) Toll K and Graf P.; Rhinology, 2006, 44, 274–277; (b) Maryadele O'Neil J.; The Merck Index: An Encyclopedia of Chemicals, Drugs & Biological, Merck Research Laboratories, NJ, USA, 14th edn, 2006.
- [3]. (a) Declerck I.; Himpens B.; Droogmans G and Casteels R.; Pfluegers Arch., 1990, 417, 117–119; (b) Weinberger M. M., Pediatr. Clin. North Am., 1975, 22, 121–127.
- [4]. (a) Silverman H. I.; Kreger B. E.; Lewis G. P.; Karabelas A.; Paone R and Foley M.; Curr. Ther. Res., 1984, 28, 185–194; (b) Loman J.; Rinkel M and Myerson A.; Am. Heart J., 1939, 18, 89–93.
- [5]. Lake C. R.; Gallant S.; Masson E and Miller P.; Am. J. Med., 1990, 89, 195–208.
- [6]. Walker J. S.; J. Pharm. Sci., 1989, 78, 986–989.
- [7]. Pentel P. R.; Asinger R. W and Benowitz N. L.; Clin. Pharmacol. Ther., 1985, 37, 488–494.
- [8]. Ellenhorn M. J and Barceloux D. G.; Medical Toxicology –Diagnosis and Treatment of Humna Poisoning, Elsevier Science Publishing Co. Inc, New York, NY, 1988, p. 293.
- [9]. Mazumdar K.; Dutta N. K.; Kumar K. A and Dastidar S. G.; Biol. Pharm. Bull., 2005, 28, 713–717.
- [10]. Osswald W and Guimaraes S.; Naunyn-Schmiedeberg's Arch. Pharmacol., 1971, 270, 203–209.
- [11]. Engel J.; Axel K.; Posselt K.; Stroman F and Thiemer K.; Cycloaliphatic ketomaines, US Pat., US4542159, 1985.
- [12]. Wan S. K.; Hoff W and Evans T. R.; Curr. Med. Res. Opin., 1988, 11, 242–253.
- [13]. Iwamoto, H. K.; Hartung, W. H.; J. Org. Chem. 1994, 9, 513.
- [14]. (a) Subrahmanyam, G.; Sunil Vaman, J. U. S. Patent 7414153, 2008; (b) Hyeon-Kyu, L.; Soyeong, K.; Eun, B. C. J. Org. Chem. 2012, 77, 5454.

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