A Facile One-Pot Route for the General Synthesis of Triazole Linked Chiral 2-Substituted Benzimidazoles

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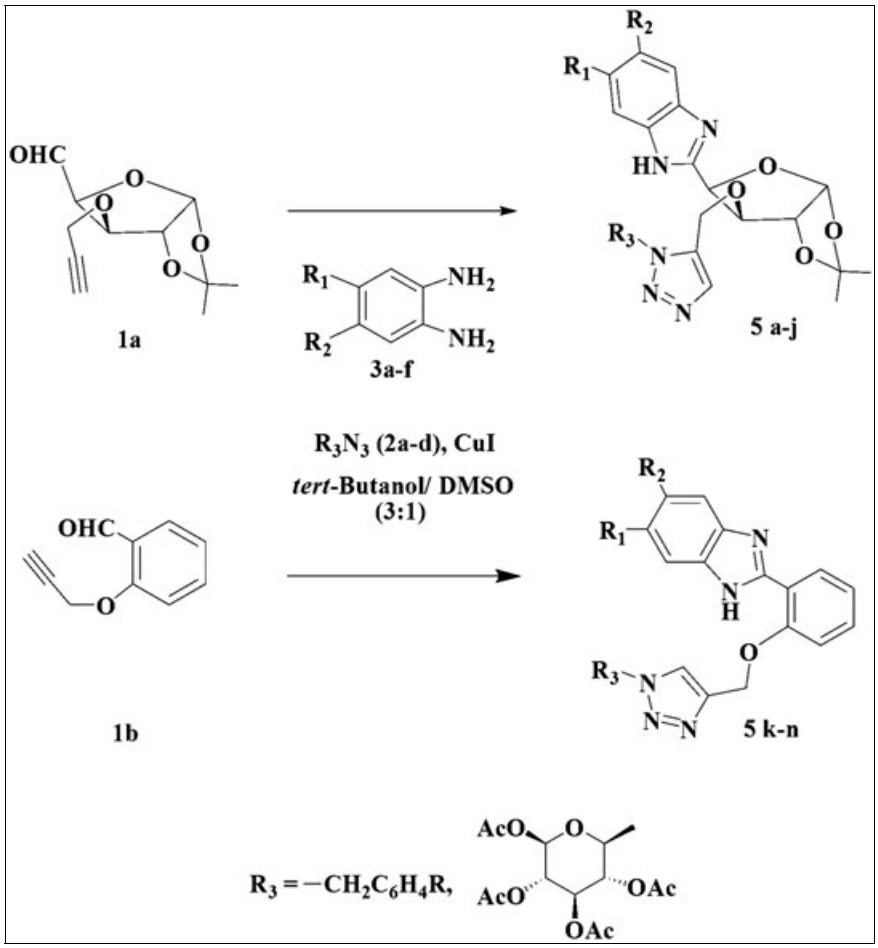

One-pot protocol for the synthesis of novel class of triazole linked 2-sugar and 2-aryl substituted benzimidazoles has been developed. The rapid and simple method involves copper (I) catalyzed simultaneous formation of benzimidazole and triazole rings at room temperature and in high yield.

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INTRODUCTION

The great success of copper (I) accelerated version of Huisgen 1,3-dipolar cycloaddition [1,2], generating selectively 1,4-substituted triazoles rests in its generality, successful application in varied systems [3,4], and chemically inertness of triazole to different reactions, that is, oxidation, reduction, and hydrolysis [4]. It has been employed to functionalize nanoparticles [5], carbon nanotubes [6], solid surfaces [7], and synthetic polymers [8] and even ligation of porphyrin ring to fullerene [9]. The reaction has also been employed in biological systems for bacterial cell surface labeling [10] and conjugation of biological polymers to viruses [11].

Benzimidazole analogs are well known for their application as pharmaceuticals [12]. Recent studies have broadened their scope for further utilization in recognizing specific sequences of DNA [13], chemo sensing [14], and

corrosion science [15]. These attributes of benzimidazole may be exploited for functionalizing different substrates with the benzimidazole scaffold [16] to produce materials with novel properties, through a triazole moiety. This brings forth the importance of synthesis of molecules containing both benzimidazole and triazole rings.

Few examples of compounds containing both benzimidazole and triazole rings are known [17]; however, their synthesis involves multistep conversions. Syntheses of benzimidazoles involving condensation of aromatic 1,2 diamines with aldehydes, carboxylic acids, or acid chlorides are well documented in literature [18]. Drastic reaction conditions are used and the formation of undesired by-products is the major drawbacks. Exploration of metal catalyzed ring closure of 2-azidoaryl imines [19] and intramolecular C-N bond formation of ortho aryl halides using either copper or palladium catalysts [20] provided improved procedures for benzimidazole synthesis. Metal catalyzed processes also include use of H_2O_2/CAN [21a], $TiCl_4$ [21b], $ZrOCl_2$ [21c], $In(OTf)_3$ [21d], $Sc(OTf)_3$ [21e], $Yb(OTf)_3$ [21f], $VO(acac)_2$-$CeCl_3$ [22], $Cu(OTf)_2$ [23a], and Cu(II) complex [23b] for direct condensation of aromatic 1,2 diamines with aldehydes at room temperature. CuI catalyzed [24] formation of benzimidazole as an intermediate at elevated temperature and CuI catalyzed click chemistry are reported separately, but there are no reports of combining click chemistry with such cyclization reaction. In this report, we disclose a one-pot procedure for CuI mediated simultaneous formation of benzimidazole and triazole rings.

We describe here a rapid and efficient three-component one-pot synthesis of triazole linked chiral 2-substituted benzimidazoles, involving simultaneous formation of benzimidazole and triazole rings at room temperature. We chose the *O*-propargylated aldehyde **1a** derived from diacetone glucose for our study because of the promising pharmacological properties of benzimidazole analogs, featuring chiral substituents at C-2 position [25]. Moreover, the biological activity of such chiral diheterocyclic compounds is still unexplored. The methodology was also found applicable for aromatic aldehydes.

RESULTS AND DISCUSSION

Compounds **1a** and **1b** were synthesized from diacetone glucose and salicylaldehyde, respectively, as reported earlier [26]. To begin with, we took up the synthesis of the **5 k** for which we chose the substrates **1b**, *o*-phenylenediamine (**2a**), and benzyl azide (**3a**) as the reactants. These were stirred at room temperature in the presence of CuI, using *tert*-butanol as solvent at optimal reaction conditions (Scheme 1). The results revealed that the reaction did not proceed in absence of copper (I). However, the reaction when carried out in the presence of 5 mol % CuI yielded only 50% of the desired product **5 k** (Table 1, entry 2). The most remarkable yield of 85% was obtained when the reaction was performed using 10 mol % of CuI (entry 3). No further improvement in yield was observed using larger amounts of CuI. Other copper catalysts such as CuCl, CuBr, Cu_2O, and CuOAc were also evaluated and found to be less efficient. The yield was drastically reduced when carried out under nitrogen atmosphere, indicating involvement of aerial oxidation.

To investigate the role of copper, we also tried a stepwise synthesis of **5k** (Scheme 2). It revealed that benzimidazole formation did not proceed in absence of catalyst but with CuI as catalyst, 85% yield was achieved in 1.5 h. The 1,2,3-triazole formation step was completed within 1 h using CuI. The low overall yield (~76%) of **5k** by stepwise synthesis justifies the need for a one-pot procedure that is simple and with high yield.

To elaborate the scope of this new methodology, we chose the *O*-prorargylated aldehyde **1a** to react with various derivatives of *o*-phenylenediamine (**3a–f**) and several organic azides (**2a–d**). In all cases, the reaction went smoothly under the same experimental conditions and at high yield. The results, summarized in Table 2, revealed that the diamines with electron-donating substituents were the suitable substrates, but those with electron-withdrawing groups displayed less reactivity (entries 4 and 5). We used 2-*O*-(prop-2-ynyl) salicylaldehyde (**1b**) as a different type of substrate, to check the versatility of this methodology (**5k–n**), and in these cases also the yields were excellent. 2-*O*-(prop-2-ynyl) salicylic acid (**1c**) was also employed to test the effect of replacing the CHO group with a COOH group, but produced low yield even after 10 h.

CONCLUSION

In summary, we have developed a new one-pot reaction protocol for the general synthesis of triazole linked chiral benzimidazoles. The reaction is fast and is carried out under mild conditions. CuI used in the reaction procedure plays a dual role in promoting the aldehyde for oxidative cyclization and activating the carbon–carbon triple bond to undergo 1,3-cycloaddition. This protocol may also have interesting implications in the construction of structurally diverse benzimidazole molecules and in ligation of the benzimidazole scaffold to different substrates, using triazole as the linker.

EXPERIMENTAL

All solvents were purified according to standard methods. Melting points were determined with a capillary melting point apparatus and are uncorrected. ESI-MS (positive) was conducted using LC-ESI-Q-TOF micro mass spectrometer. Optical rotations were measured with a Perkin Elmer model 241-MC automatic

Scheme 1. One-pot synthesis of triazole linked 2-substituted benzimidazoles.

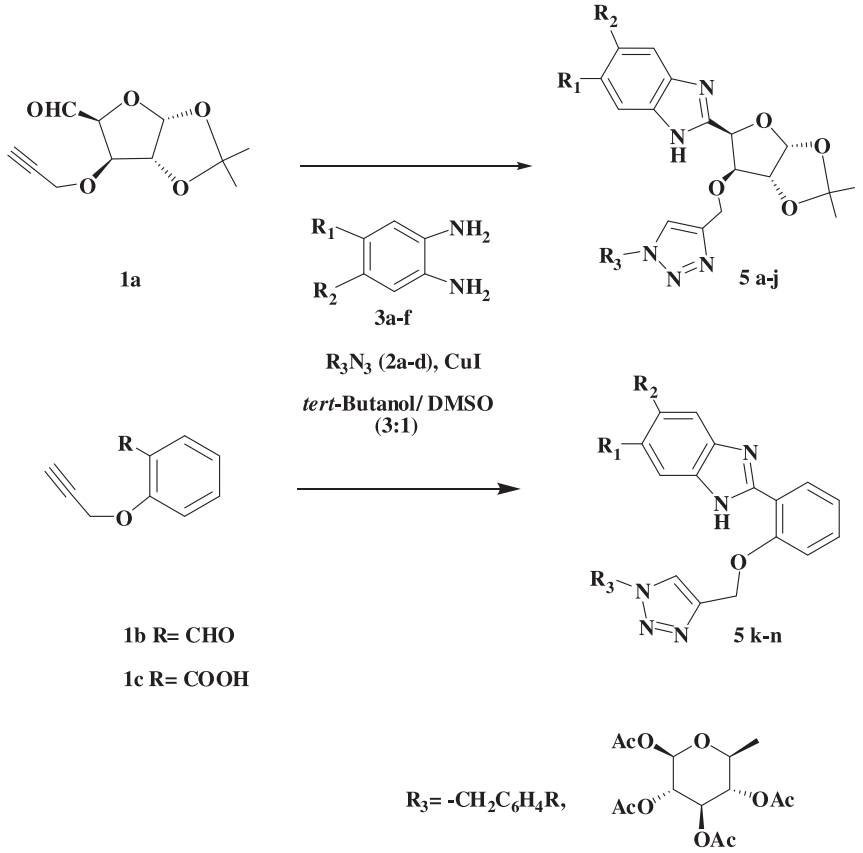


Table 1

Optimization of reaction conditions: effect of amount of the catalyst on **5k**.

Entry[a]	Catalyst	Amount of catalyst (mol %)	Yield of **5k**[b] (%)
1	None	0	No reaction
2	CuI	5	50
3	**CuI**	**10**	**85**
4[c]	CuI	20	5
5	CuCl	20	20
6	CuBr	20	30
7	Cu_2O	20	5
8	CuOAc	20	10

Boldface letters in entry 3 indicates the best reaction conditions.
[a]All the reactions were performed using **1a**, **2a**, and **3a** in *tert*-butanol as solvent, at room temperature in air for 1.5 h.
[b]Yield of pure products after column chromatography.
[c]Performed under N_2 atmosphere.

Scheme 2. Stepwise synthesis of triazole linked 2-substituted benzimidazoles.

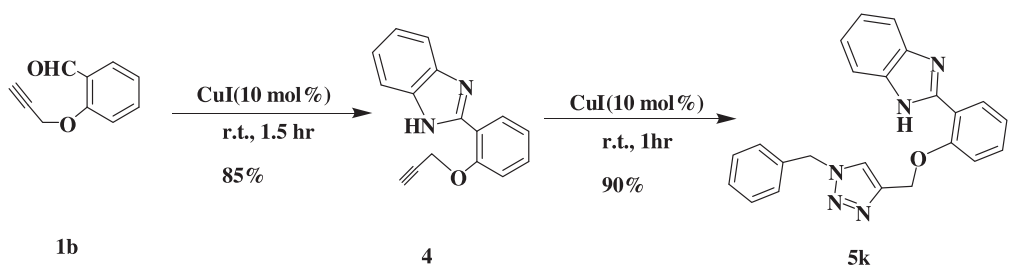
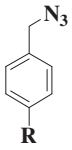
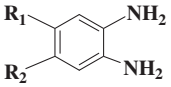
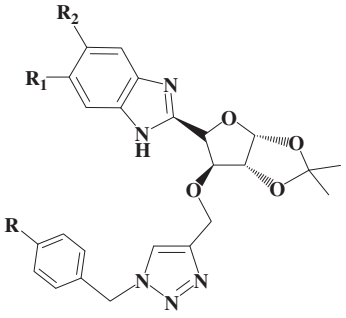
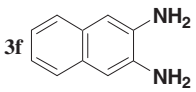
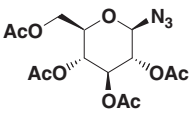
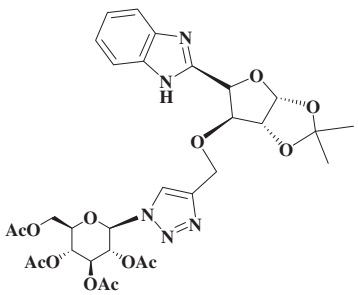
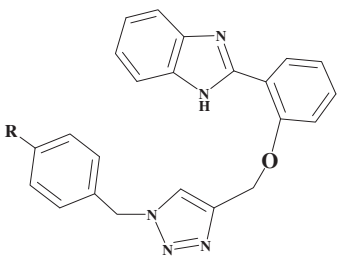
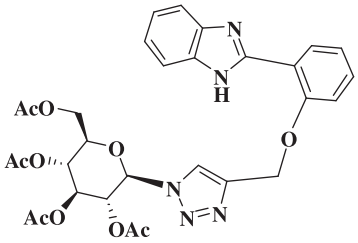


Table 2

CuI catalyzed one-pot synthesis of triazole linked 2-substituted benzimidazoles (**5a–n**).[a]

Entry	Substrate	Azides	Aromatic diamines	Product[b]	Yield[c]
					
1	**1a**	**2a**(R = H)	**3a**(R_1 = H, R_2 = H)	**5a**	**85**
2	**1a**	**2a**	**3b**(R_1 = CH_3, R_2 = H)	**5b**	**77**
3	**1a**	**2a**	**3c**(R_1 = CH_3, R_2 = CH_3)	**5c**	**74**
4	**1a**	**2a**	**3d**(R_1 = Cl, R_2 = Cl)	**5d**	**72**
5	**1a**	**2a**	**3e**(R_1 = COPh, R_2 = H)	**5e**	**69**
6	**1a**	**2a**		**5f**	**80**
7	**1a**	**2b** (R = CH_3)	**3a**	**5g**	**82**
8	**1a**	**2c** (R = NO_2)	**3a**	**5h**	**75**
					
9	**1a**	**2d**	**3a**	**5i**	**74**
10	**1a**	**2d**	**3b**	**5j**	**72**
					
11	**1b**	**2a**	**3a**	**5k**	**92**
12	**1b**	**2b**	**3a**	**5l**	**88**
13	**1b**	**2c**	**3a**	**5m**	**82**
					

(*Continued*)

Table 2
(Continued)

Entry	Substrate	Azides	Aromatic diamines	Product[b]	Yield[c]
14	**1b**	**2d**	**3a**	**5n**	**80**
15[d]	**1c**	**2a**	**3a**	**5k**	**40**
16[d]	**1c**	**2b**	**3a**	**5l**	**45**

[a]Reaction conditions: propargylated aldehyde (1 mmol), *o*-phenylenediamine derivatives (1 mmol), organic azide (1 mmol), 15 mL *tert*-butanol, CuI (0.1 mmol), and 1.5 h at room temperature.
[b]All products were characterized by IR, NMR, and mass spectroscopy.
[c]Yield refers to pure products by column chromatography.
[d]Performed at 50°C for 10 h.

polarimeter for solutions in a 1-dm cell. The NMR spectra were taken on a BRUKER 300/600 DPX spectrometer operating at 300/600 MHz for ^{1}H and 75/150 MHz for ^{13}C, respectively, with tetramethylsilane (TMS) as an internal standard and the chemical shifts are reported in δ units. All the chemicals were purchased from Aldrich Chemical Ltd (USA). The values of chemical shifts (δ) were given in parts per million and coupling constants (*J*) in hertz. The following NMR abbreviations were used: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and dd (doublet of doublet).

Procedure for synthesis of 4. Propargylated aldehyde **1b** (1 mmol) and *o*-phenylenediamine derivatives (1 mmol) were taken in a 25-mL RB flask and dissolved in 10 mL of *tert*-butanol. CuI (0.1 mmol) was then added and the mixture was stirred at room temperature. After completion of the reaction (1.5 h, monitored by TLC), the solvents were removed in a rotary evaporator. The crude mass was diluted with ethyl acetate and washed thoroughly with water. Finally, the compound was purified by column chromatography to obtain **4** as a light yellow solid: ^{1}H NMR (300 MHz, $CDCl_3$) : δ 2.67(t, 1H), 4.97(d, $J = 2.4$ Hz, 2H), 7.15–7.18 (m, 1H), 7.21–7.23 (m, 1H), 7.27–7.31 (m, 3H), 7.42–7.48 (m, 1H), 7.51(brs, 1H), 7.83 (brs, 1H), 8.61 (dd, $J_1 = 8.1$ Hz, $J_2 = 1.6$ Hz, 1H), 10.59 (brs, 1H); HRMS (ESI): *m/z* calcd for $C_{16}H_{12}N_2O$ [M], $[M + Na]^+ = 271.0847$, found 271.0836.

Procedure for conversion of 4 to **5k**. 2-(2-(prop-2-ynyloxy) phenyl)-1H-benzo[d]imidazole **4** (1mmol) and benzyl azide (1 mmol) were taken in a 25-mL RB flask and dissolved in 10 mL of *tert*-butanol. CuI (0.1 mmol) was then added and the mixture was stirred at room temperature. After completion of the reaction (1.0 h, monitored by TLC), the solvents were removed in a rotary evaporator. The crude mass was diluted with ethyl acetate and washed thoroughly with water. Finally, the compound was purified by column chromatography to obtain **5k** as a light yellow gum.

General procedure for synthesis of 5a–n. Propargylated aldehyde (**1a** or **1b**, 1 mmol), *o*-phenylenediamine derivatives (1 mmol), and organic azide (1 mmol) were taken in a 50-mL RB flask and dissolved in 15 mL of *tert*-butanol. CuI (0.1 mmol) was then added and the mixture was stirred at room temperature. After completion of the reaction (1.5 h, monitored by TLC), the solvents were removed in a rotary evaporator. The crude mass was diluted with ethyl acetate and washed thoroughly with water. Finally, the compound was purified by column chromatography using suitable solvent system. The products were characterized by spectroscopic and analytical analysis (^{1}H, ^{13}C NMR, and HR ESI-MS).

Compound 5a. Yellow gum; $[\alpha]_D^{26}$ −39.97 (C 0.12, $CHCl_3$); IR (KBr, cm^{-1}): 3140, 2985, 2931, 1438, 1378, 1317, 1219, 1080, 1036, 856, 749; ^{1}H NMR (300 MHz, $CDCl_3$) : δ 1.36 (s, 3H), 1.55 (s, 3H), 4.26 (d, $J = 12.3$ Hz, 1H), 4.35 (d, $J = 3.0$ Hz, 1H), 4.58 (d, $J = 12.0$ Hz, 1H), 4.74 (d, $J = 3.6$ Hz, 1H), 5.23–5.34 (m, 2H), 5.59 (d, $J = 3.0$ Hz, 1H), 6.07 (d, $J = 3.6$ Hz, 1H), 6.71 (s, 1H), 7.11–7.17 (m, 2H), 7.25–7.29 (m, 2H), 7.33–7.44 (m, 5H), 9.92 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.24, 26.77, 53.93, 64.07, 77.67, 82.86, 83.69, 105.15, 112.56, 122.23, 127.97, 128.64, 128.96, 134.32, 144.17, 149.61; HRMS (ESI): *m/z* calcd for $C_{24}H_{25}N_5O_4$ $[M + H]^+ = 448.1985$, found 448.1983.

Compound 5b. Yellow gum; $[\alpha]_D^{26}$ −24.28 (C 0.12, $CHCl_3$); IR (KBr, cm^{-1}): 2924, 2856, 1713, 1450, 1377, 1219, 1080, 1036, 858, 805, 754; ^{1}H NMR (300 MHz, $CDCl_3$) : δ 1.36 (s, 3H), 1.55 (s, 3H), 2.49 (s, 3H), 4.25–4.34 (m, 2H), 4.57 (d, $J = 12.0$ Hz, 1H), 4.74 (d, $J = 3.3$ Hz, 1H), 5.24–5.36 (m, 2H), 5.56 (d, $J = 2.7$ Hz, 1H), 6.07 (d, $J = 3.6$ Hz, 1H), 6.74 (s, 1H), 7.08–7.14 (m, 3H), 7.33–7.35 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.57, 26.22, 26.74, 53.90, 64.02, 77.65, 82.86, 83.62, 105.09, 112.50, 122.27, 124.02, 127.89, 128.61, 128.93, 129.03, 134.36, 144.20, 149.17; HRMS (ESI): *m/z* calcd for $C_{25}H_{27}N_5O_4$ $[M + H]^+ = 462.2141$, found 462.2139.

Compound 5c. Yellow gum; $[\alpha]_D^{26}$ −23.20 (C 0.12, $CHCl_3$); IR (KBr, cm^{-1}): 3140, 2931, 1452, 1378, 1218, 1162, 1080, 1031, 856, 720; ^{1}H NMR (300 MHz, $CDCl_3$) : δ 1.35 (s, 3H), 1.55 (s, 3H), 2.38 (s, 6H), 4.24–4.32 (m, 2H), 4.55 (d, $J = 12.3$ Hz, 1H), 4.73 (d, $J = 3$ Hz, 1H), 5.23–5.36 (m, 2H), 5.55 (d, $J = 2.4$ Hz, 1H), 6.07 (d, $J = 3.3$ Hz, 1H), 6.75 (s, 1H), 7.11–7.12 (m, 2H), 7.32–7.38 (m, 5H), 9.62 (brs, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 20.35, 26.28, 26.80, 53.94, 64.06, 77.64, 82.93, 83.58, 105.09, 112.55, 122.31, 127.90, 128.66, 128.98, 129.08, 134.42, 144.26, 148.53; HRMS (ESI): *m/z* calcd for $C_{26}H_{29}N_5O_4$ $[M + H]^+ = 476.2298$, found 476.2347.

Compound 5d. Yellow gum; $[\alpha]_D^{26}$ −22.82 (C 0.19, $CHCl_3$); IR (KBr, cm^{-1}): 3139, 2984, 2933, 1502, 1450, 1379, 1219, 1162, 1080, 1035, 857, 721; ^{1}H NMR (300 MHz, $CDCl_3$) : δ 1.36 (s, 3H), 1.55 (s, 3H), 4.30 (d, $J = 12.3$ Hz, 1H), 4.35 (d, $J = 2.7$ Hz, 1H), 4.62 (d, $J = 12.3$ Hz, 1H), 4.74 (d, $J = 3.3$ Hz, 1H), 5.34–5.45 (m, 2H), 5.53 (d, $J = 2.7$ Hz, 1H), 6.06 (d, $J = 3.6$ Hz, 1H), 6.91 (s, 1H), 7.18–7.19 (m, 2H), 7.36–7.38 (m, 5H), 10.18 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.16, 26.71, 54.08, 63.81, 77.32, 82.56, 83.47, 105.12, 112.64, 122.06, 126.37, 127.69, 127.94, 128.04, 128.79, 129.05, 134.08, 136.79, 143.99, 144.46, 151.80; HRMS (ESI): *m/z* calcd for $C_{24}H_{23}Cl_2N_5O_4$ $[M + H]^+ = 516.1205$, found 516.2072.

Compound 5e. Yellow gum; $[\alpha]_D^{26}$ −32.82 (C 0.24, $CHCl_3$); IR (KBr, cm^{-1}): 3063, 2932, 2359, 1651, 1619, 1446, 1375, 1320, 1218, 1163, 1077, 1030, 888, 852, 720; ^{1}H NMR (300 MHz, $CDCl_3$) : δ 1.35 (s, 3H), 1.54 (s, 3H), 4.29 (d, $J = 12$ Hz, 1H), 4.38 (brs, 1H), 4.59 (d, $J = 12$ Hz, 1H), 4.73 (d, $J = 3.3$ Hz, 1H), 5.29–5.40 (m, 2H), 5.59 (brs, 1H), 6.05

(d, J = 3.3 Hz, 1H), 6.91 (s, 1H), 7.14 (brs, 2H), 7.29–7.30 (m, 4H), 7.46–7.51 (m, 3H), 7.58 (d, J = 7.2 Hz, 1H), 7.81–7.83 (m, 3H), 10.50 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.14, 26.70, 53.93, 63.85, 77.57, 82.65, 83.50, 105.14, 112.55, 122.23, 124.93, 127.84, 128.11, 128.62, 128.94, 129.91, 132.03, 134.18, 138.08, 144.03, 196.64; HRMS (ESI): *m/z* calcd for $C_{31}H_{29}N_5O_5$ $[M+H]^+$ = 552.2247, found 552.2253.

Compound 5f. Yellow gum; $[\alpha]_D^{26}$ −46.58 (C 0.19, $CHCl_3$); IR (KBr, cm^{-1}): 3140, 2986, 2931, 2360, 1647, 1455, 1435, 1375, 1271, 1218, 1163, 1078, 1035, 859, 747, 709; ^{1}H NMR (600 MHz, $CDCl_3$) : δ 1.37 (s, 3H), 1.56 (s, 3H), 4.32 (d, J = 12.0 Hz, 1H), 4.46 (d, J = 3 Hz, 1H), 4.63 (d, J = 12.6 Hz, 1H), 4.76 (d, J = 3 Hz, 1H), 5.12 (s, 2H), 5.66 (d, J = 3 Hz, 1H), 6.12 (d, J = 3.6 Hz, 1H), 6.60 (s, 1H), 6.90 (d, J = 7.2 Hz, 2H), 7.17–7.20 (m, 2H), 7.23–7.26 (m, 3H), 7.44–7.47 (m, 2H), 7.97–7.98 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.21, 26.78, 53.79, 64.15, 77.97, 82.79, 83.92, 105.35, 112.65, 122.23, 123.99, 127.78, 127.89, 128.49, 128.81, 130.34, 134.14, 144.13, 154.39; HRMS (ESI): *m/z* calcd for $C_{28}H_{27}N_5O_4$ $[M+H]^+$ = 498.2197, found 598.2187.

Compound 5g. Yellow gum; $[\alpha]_D^{26}$ −38.38 (C 0.20, $CHCl_3$); IR (KBr, cm^{-1}): 3139, 2985, 2933, 1441, 1378, 1316, 1218, 1163, 1080, 1039, 854, 748; ^{1}H NMR (600 MHz, $CDCl_3$) : δ 1.34 (s, 3H,), 1.53 (s, 3H,), 2.34 (s, 3H,), 4.25 (d, J = 12.0 Hz, 1H), 4.36 (d, J = 2.5 Hz, 1H,), 4.57 (d, J = 12.2 Hz, 1H), 4.72 (d, J = 3.5 Hz, 1H), 5.21–5.28 (m, 2H), 5.60 (d, J = 2.6 Hz, 1H), 6.04 (d, J = 3.5 Hz, 1H), 6.74 (s, 1H), 7.02 (d, J = 6.0 Hz, 2H), 7.13 (d, J = 4.8 Hz, 2H), 7.26–7.27 (m, 2H), 7.56 (brs, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 21.13, 26.30, 26.83, 53.82, 64.09, 77.54, 82.89, 83.65, 105.20, 112.67, 122.12, 122.70, 128.10, 129.68, 131.30, 138.64, 145.69, 149.54; HRMS (ESI): *m/z* calcd for $C_{25}H_{27}N_5O_4$ $[M+H]^+$ = 462.2141, found 462.2139.

Compound 5h. Yellow gum; $[\alpha]_D^{26}$ −24.11 (C 0.18, $CHCl_3$); IR (KBr, cm^{-1}): 3140, 2986, 2934, 1606, 1523, 1440, 1348, 1219, 1164, 1080, 1043, 855, 743; ^{1}H NMR (600 MHz, $CDCl_3$) : δ 1.36 (s, 3H), 1.54 (s, 3H), 4.37 (d, J = 12.5 Hz, 1H), 4.40 (d, J = 2.6 Hz, 1H), 4.64 (d, J = 12.5 Hz, 1H), 4.74 (d, J = 3.5 Hz, 1H), 5.32–5.41 (m, 2H), 5.61 (d, J = 2.6 Hz, 1H), 6.08 (d, J = 3.5 Hz, 1H), 6.78 (s, 1H), 7.23 (d, J = 8.6 Hz, 2H), 7.26–7.27 (m, 2H), 7.56 (brs, 2H), 8.16 (d, J = 8.6 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 26.29, 26.84, 52.91, 64.06, 77.60, 82.83, 83.72, 105.26, 112.81, 122.56, 122.84, 124.20, 128.56, 141.30, 144.72, 147.96, 149.72; HRMS (ESI): *m/z* calcd for $C_{24}H_{24}N_6O_6$ $[M+H]^+$ = 493.1836, found 493.1829.

Compound 5i. Yellow gum; $[\alpha]_D^{26}$ −33.17 (C 0.13, $CHCl_3$); IR (KBr, cm^{-1}): 3147, 2985, 2988, 1753, 1437, 1375, 1225, 1079, 1039, 920, 855, 750, 604; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.38 (s, 3H), 1.57 (s, 3H), 1.85 (s, 3H), 2.10 (s, 9H), 3.89–3.93 (m, 1H), 4.10–4.14 (m, 1H), 4.02 (d, J = 5 Hz, 1H), 4.27 (d, J = 11.4 Hz, 1H), 4.40 (brs, 1H), 4.69 (d, J = 11.7 Hz, 1H), 4.78 (d, J = 3.3 Hz, 1H), 5.07–5.23 (m, 2H), 5.37 (t, J = 9.4 Hz, 1H), 5.66–5.71 (m, 2H), 6.09 (d, J = 3.3 Hz, 1H), 6.86 (s, 1H), 7.37–7.40 (m, 2H), 7.70 (brs, 2H); ^{13}C NMR (150 MHz, $CDCl_3$):δ 20.14, 20.54, 20.69, 26.32, 26.85, 61.47, 64.04, 67.56, 70.48, 72.41, 74.97, 77.68, 82.47, 84.05, 85.46, 105.29, 112.76, 121.08, 123.02, 144.96, 149.49, 169.09, 169.39, 169.81, 170.46; HRMS (ESI): *m/z* calcd for $C_{31}H_{37}N_5O_{13}$ $[M+Na]^+$ = 710.2286, found 710.2296.

Compound 5j. Yellow gum; $[\alpha]_D^{26}$ −25.35 (C 0.22, $CHCl_3$); IR (KBr, cm^{-1}): 3148, 2936, 1753, 1450, 1375, 1225, 1080, 1040, 919, 857, 810, 603; ^{1}H NMR (600 MHz, $CDCl_3$) : δ 1.36 (s, 3H), 1.54 (s, 3H), 1.85 (s, 3H), 2.08 (s, 3H), 2.08 (s, 3H), 2.09 (s, 3H), 2.54 (s, 3H), 3.94–3.96 (m, 1H), 4.14 (dd, J_1 = 12.6 Hz, J_2 = 1.2 Hz, 1H), 4.23 (dd, J_1 = 12.6 Hz, J_2 = 4.8 Hz, 1H), 4.30 (d, J = 12 Hz, 1H), 4.41 (brs, 1H), 4.67 (d, J = 12 Hz, 1H), 4.77 (d, J = 3.6 Hz, 1H), 5.17–5.21 (m, 2H), 5.40 (t, J = 9.5 Hz, 1H), 5.64 (brs, 1H), 5.74 (d, J = 9.6 Hz, 1H), 6.07 (d, J = 3.6 Hz, 1H), 7.10 (s, 1H), 7.19 (d, J = 8.4 Hz, 1H), 7.47 (s, 1H), 7.59 (d, J = 8.4 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$):δ 20.16, 20.53, 20.67, 21.67, 26.31, 26.83, 61.51, 63.85, 67.64, 70.42, 72.43, 75.05, 77.43, 82.54, 83.79, 85.52, 105.52, 112.70, 121.24, 124.55, 133.01, 144.85, 148.82, 169.11, 169.34, 169.80, 170.46; HRMS (ESI): *m/z* calcd for $C_{32}H_{39}N_5O_{13}$ $[M+Na]^+$ = 724.2442, found 724.2442.

Compound 5k. Yellow gum;IR (KBr, cm^{-1}): 3290, 3071, 2952, 1587, 1463, 1393, 1277, 1238, 1121, 1023, 849, 804, 745; ^{1}H NMR (300 MHz, $CDCl_3$) : δ 5.33 (s, 2H), 5.56 (s, 2H), 7.07 (d, J = 8.1 Hz, 1H), 7.16 (t, J = 7.5 Hz, 1H), 7.24–7.30 (m, 4H), 7.37–7.42 (m, 4H), 7.48 (s, 1H), 7.67 (m, 2H), 8.54 (dd, J_1 = 8.0 Hz, J_2 = 1.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$):δ 54.07, 62.53, 112.86, 114.82, 117.63, 121.47, 122.08, 127.70, 127.91, 128.70, 129.00, 129.97, 131.33, 134.19, 137.26, 143.10, 148.79, 155.42; HRMS (ESI): *m/z* calcd for $C_{23}H_{19}N_5O$ $[M+H]^+$ = 382.1668, found 382.1655.

Compound 5l. Yellow gum; IR (KBr, cm^{-1}): 3260, 2926, 1776, 1606, 1462, 1375, 1236, 1168, 1071, 751; ^{1}H NMR (600 MHz, $CDCl_3$) : δ 2.36 (s, 3H), 5.40 (s, 2H), 5.57 (s, 2H), 7.12 (d, J = 8.3 Hz, 1H), 7.21 (m, 5H), 7.33 (m, 2H), 7.44–7.47 (m, 1H), 7.53 (s, 1H), 7.76 (brs, 2H), 8.67 (d, J = 7.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$):δ 21.13, 54.21, 62.92, 113.15, 114.74, 116.81, 121.54, 122.43, 123.39, 128.16, 129.85, 130.19, 131.14, 132.05, 136.30, 138.95, 143.20, 148.33, 155.69; HRMS (ESI): *m/z* calcd for $C_{24}H_{21}N_5O$ $[M+H]^+$ = 396.1824, found 396.1832.

Compound 5m. Yellow solid; mp 130–132°C. IR (KBr, cm^{-1}): 3075, 2926, 1699, 1604, 1521, 1467, 1348, 1285, 1247, 1196, 852, 797, 748; ^{1}H NMR (300 MHz, $CDCl_3$) : δ 5.32 (s, 2H), 5.60 (s, 2H), 7.05 (d, J = 8.1 Hz, 1H), 7.17 (t, J = 7.5 Hz, 1H), 7.24–7.28 (m, 2H), 7.35–7.42(m, 3H), 7.50(s, 1H), 7.65–7.68(m, 2H), 8.19(d, J = 8.4 Hz, 2H), 8.54(d, J = 7.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$):δ 52.68, 62.35, 112.87, 114.58, 116.73, 121.99, 122.08, 122.95, 123.78, 128.29, 129.71, 131.68, 136.50, 141.39, 143.14, 144.62, 147.45, 148.35, 155.30; HRMS (ESI): *m/z* calcd for $C_{23}H_{18}N_6O_3$ $[M+H]^+$ = 427.1519, found 427.1531.

Compound 5n. Light brown solid; mp 115–117°C; $[\alpha]_D^{26}$ −0.69 (C 0.37, $CHCl_3$); IR (KBr, cm^{-1}): 3387, 3095, 2953, 2360, 1752, 1731, 1465, 1444, 1386, 1237, 1140, 1095, 1032, 920, 750, 620, 596; ^{1}H NMR (300 MHz, $CDCl_3$) : δ 1.88 (s, 3H,), 2.06 (s, 3H), 2.07 (s, 3H), 2.08(s, 3H), 4.03–4.08 (m, 1H), 4.15–4.19 (m, 1H), 4.33 (dd, J_1 = 12.8 Hz, J_2 = 4.9 Hz, 1H), 5.26 (t, J = 9.4 Hz, 1H), 5.38–5.51 (m, 4H), 5.94 (d, J = 8.7 Hz, 1H), 7.13–7.27 (m, 4H), 7.42–7.47 (m, 1H), 7.68–7.70 (m, 2H), 7.94 (s, 1H), 8.57–8.60 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$):δ 19.98, 20.39, 20.52, 61.38, 62.31, 67.48, 70.28, 72.28, 74.97, 85.64, 112.73, 114.78, 117.39, 120.93, 122.19, 122.79 130.14, 131.48, 137.10, 143.58, 148.66, 155.32, 168.90, 169.29, 169.77, 170.39; HRMS (ESI): *m/z* calcd for $C_{30}H_{31}N_5O_{10}$ $[M+Na]^+$ = 644.1969, found 644.2017.

General procedure for synthesis of 5a–n from **1c**. 2-*O*-(prop-2-ynyl) salicylic acid (**1c**, 1 mmol), *o*-phenylenediamine derivatives (1 mmol), and organic azide (1 mmol) were taken in a 50-mL RB flask and dissolved in 15 mL of *tert*-butanol. CuI (0.1 mmol) was then added and the mixture was stirred at 50°C for 10 h. The solvents were removed in a rotary evaporator. The crude mass was diluted with ethyl acetate and washed thoroughly with water. Finally,

the compound was purified by column chromatography using suitable solvent system. The products were characterized by spectroscopic and analytical analysis (^{1}H, ^{13}C NMR and HR ESI-MS).

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