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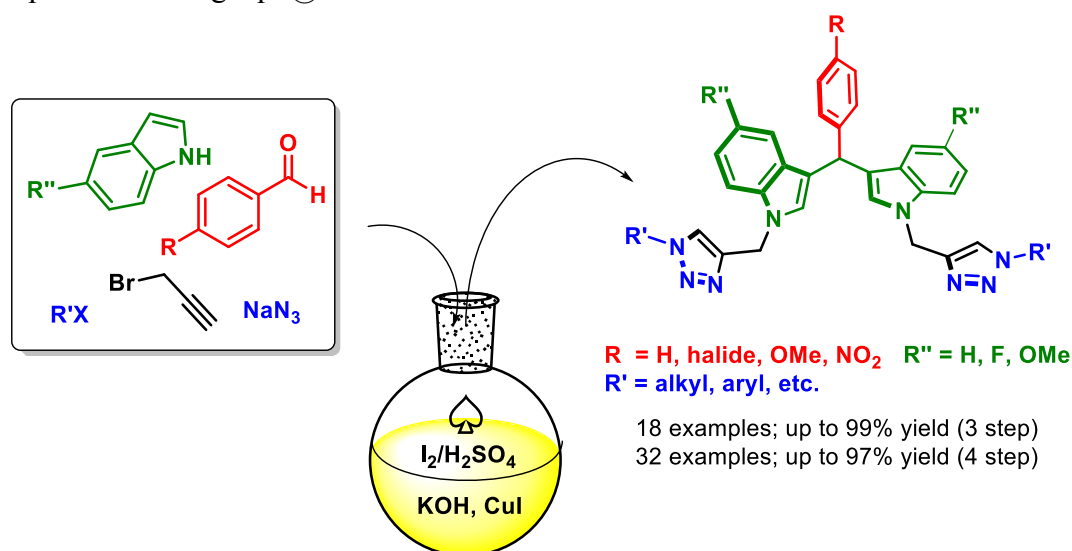
One pot approach for the synthesis of bis-indole-1,4-disubstituted-1,2,3-triazoles

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Abstract: A new strategy for the synthesis of bis-indoletriazoles was developed using a sequential one-pot four-step procedure *via* I₂ and H₂SO₄-SiO₂ catalyzed Friedel-Crafts reactions of indole with aldehyde followed by *N*-alkylation with propargyl bromide, azidation and copper(I)-catalyzed azide alkyne cycloaddition (CuAAC). The reaction proceeded smoothly at room temperature in a short time and a series of bis-indoletriazoles were obtained in good to excellent yields proving the generality of this one-pot methodology.

Key words: Bis-indoletriazoles; Friedel-Crafts; CuAAC; One-pot

Introduction

Indole and triazole are important structural ring systems in pharmacological and agrochemical compounds with various biological properties.¹ Recently, bis-indole has received considerable attention in medicinal chemistry as a main structural scaffold of bioactive natural

products and synthetic drugs.² Combination of indole or bis-indole and triazole into a single compound for improving the biological efficacy or libraries of analogues for structure-activity studies has been reported.³ These synthetic compounds exhibited a broad spectrum of biological activities including antitubercular, anti-adipogenic, antibacterial and anticancer activities (Figure 1).⁴⁻⁸

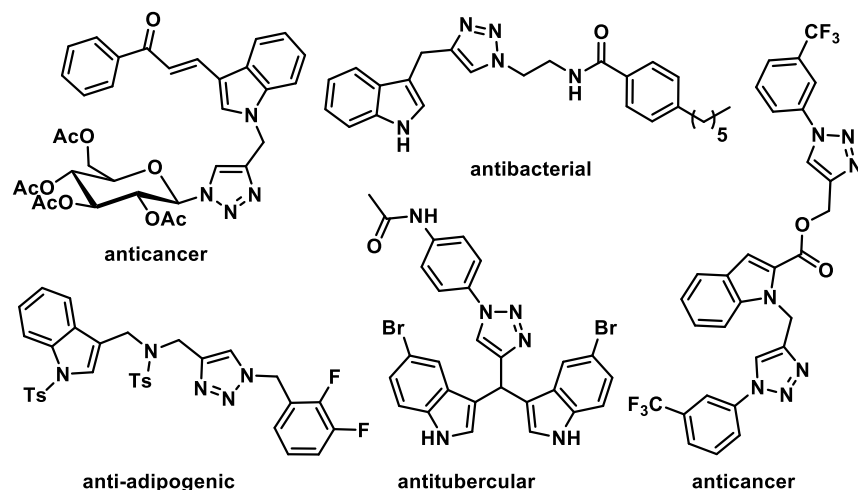


Figure 1 Structure of bioactive compounds containing indole and triazole moieties

Despite the structural diversity and the variety of biological activities observed in indoletriazole compounds, no convenient approach to the synthesis has been disclosed. The previous synthesis reported by Perumal³ employed separated steps for their preparation which are both time and cost consuming. Therefore, this work aimed to develop an efficient strategy to complete an entire multi-step sequence in a single pot for the synthesis of bis-indoletriazoles eliminating the need for work-up and product isolation between successive synthetic steps.

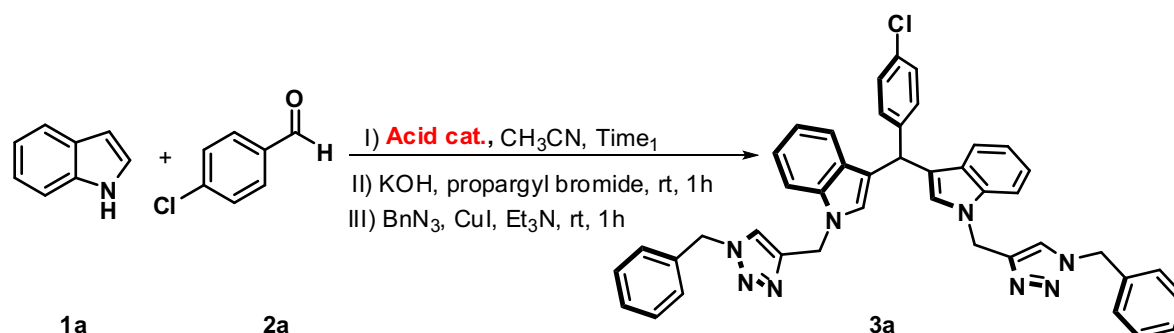
The synthesis of bis-indole-1,4-disubstituted-1,2,3-triazoles derivatives was designed *via* Friedel-Crafts reactions, *N*-propargylation, azidation and the CuAAC reaction as a sequential one-pot four-step reaction resulting in a high-yielding, scalable, and convergent approach.

Results and Discussion

Firstly a possible one-pot three-step method was investigated for preparing bisindole-triazole by screening Brønsted and Lewis acids as catalysts for Friedel-Crafts reactions of indole **1a** (2.2 equiv.) and *p*-chlorobenzaldehyde **2a** in acetonitrile for in situ generation of bisindole (Table 1). Then the *N*-propargylation step was carried out with propargyl bromide for 1 h using KOH as a base in the presence of acetonitrile to give products in high yield.

Changing to other bases such as NaOH or NaH gave a low yield of product. In the same pot, CuAAC reaction of the resulting *N*-propargylindole with benzyl azide for 1 h at room temperature was carried out to obtain product **3a**.

Table 1. Optimization Studies for the synthesis of **3a** via a one-pot three-step reaction.



Entry	Acid cat. (equiv)	Time ₁ (min)	Yield (%) ^a
1	I ₂ (0.2)	20	58
2	ZnCl ₂ (0.2)	20	23
3	FeCl ₃ (0.2)	24 (h)	48
4	Bi(OTf) ₃ (0.2)	30	90
5 ^b	H ₂ SO ₄ -SiO ₂	20	66
6 ^b	Amberlyst 15	60	95
7^b	H₂SO₄-SiO₂ /I₂ (0.15)	15	98
8 ^b	H ₂ SO ₄ -SiO ₂ /ZnCl ₂ (0.15)	30	39
9 ^b	H ₂ SO ₄ -SiO ₂ /FeCl ₃ (0.15)	15	82
10 ^c	KHSO ₄ (1.0)	60	58

^aReaction conditions: **1a** (0.44 mmol), **2a** (0.2 mmol), KOH (1.9mmol), CuI (0.06mmol), propargyl bromide (0.6 mmol), Et₃N (0.6 mmol), BnN₃ (0.6 mmol) and CH₃CN (0.6 mL)

^bAmount of acid catalyst (H₂SO₄-SiO₂ or Amberlyst 15) = 20 mg

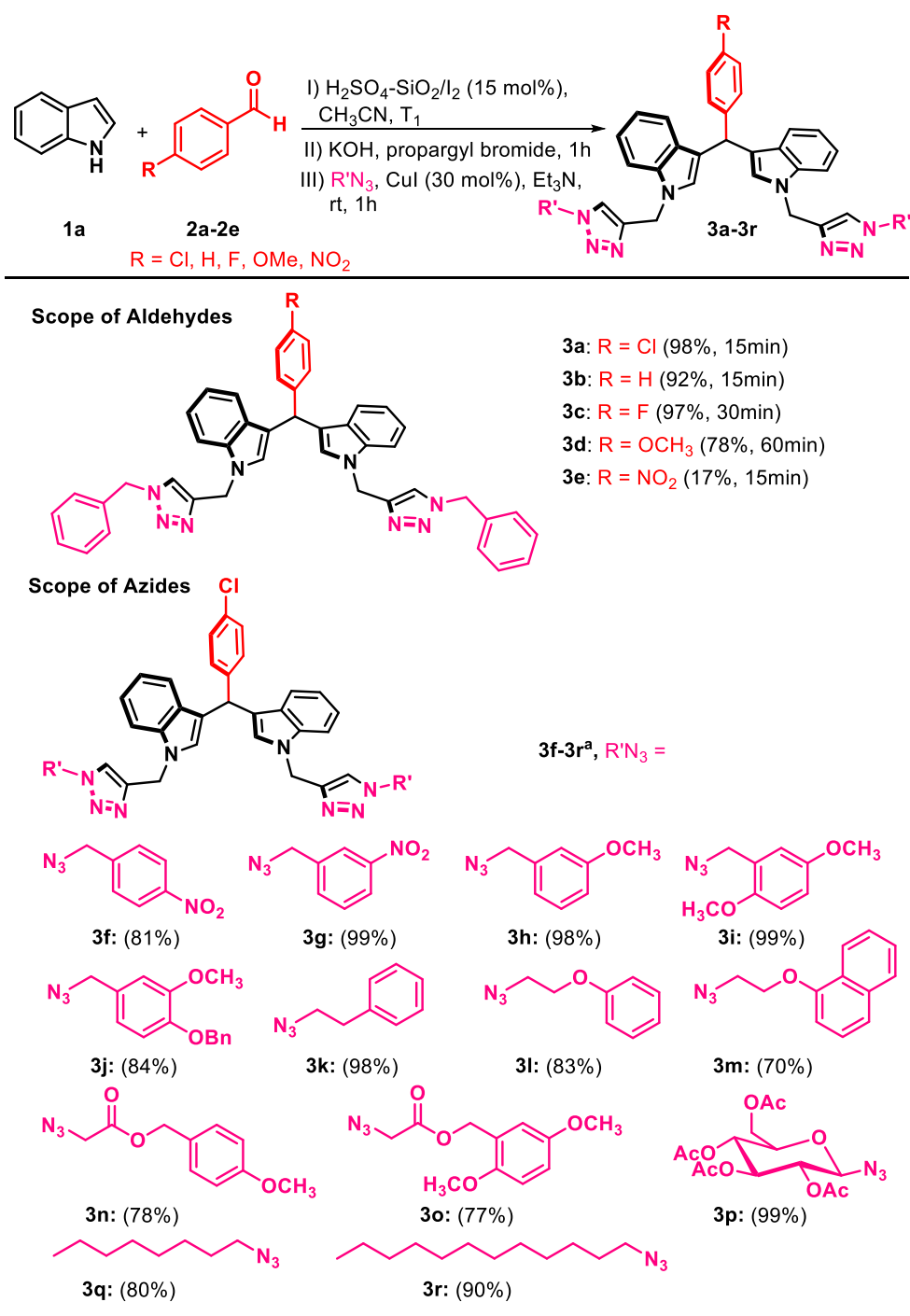
^cUsing KHSO₄ in MeOH (Perumal's conditions)³, no reaction was observed in the second step.

In the screening of acid and Lewis acid in Friedel-Crafts step,⁹ molecular iodine (I₂) was initially investigated and the first step reaction was completed within 20 minutes affording the desired product **3a** in 58% yield after *N*-propargylation and click reactions (Table 1, entry 1). Using ZnCl₂, FeCl₃ or H₂SO₄-SiO₂¹⁹ as catalyst, low to moderate yields of product were obtained (entries 2, 3 and 5). Changing the catalyst to Bi(OTf)₃ and Amberlyst 15, the yield of **3a** was increased to 90-95% (entries 4 and 6), however, the reaction with Amberlyst 15 required longer reaction times. Using H₂SO₄ supported on Silica-gel mixed with 15mol % Lewis acid had an improved the reaction efficiency compared with the reaction without H₂SO₄-SiO₂ (entries 5, and 7–9). H₂SO₄-SiO₂/I₂ was found to be the most effective catalyst producing

3a with a 98% yield in a short reaction time (entry 7). On the basis of these findings, entry 7 was selected as an optimal condition for synthesizing other analogues. It should be noted that, the reaction failed to give the desired product in our one pot procedure when employing Perumal's conditions (KHSO₄ as Lewis acid in MeOH)³. Applying KHSO₄ as Lewis acid to our one pot process gave 58% yield of product. Employing aliphatic aldehydes such as propanal as the substrate instead of aromatic aldehydes under the conditions in entry 7, the reaction gave 28% yield of product.

With the optimized reaction conditions, a range of aromatic aldehydes and alkyl azides were investigated. The results are summarized in Table 2, and a variety of aldehyde derivatives **2a-2e** bearing either electron-donating groups such as 4-methoxy and electron-withdrawing groups such as 4-chloro, 4-fluoro and 4-nitro at the *para* position of benzaldehyde gave the desired products **3a-3e** in 17–98% yields. Benzaldehyde **2b**, 4-Cl-benzaldehydes **2a** and 4-F-benzaldehydes **2c** gave excellent yields of bisindole-triazole products. Electron-donating groups (*p*-methoxybenzaldehyde) exhibited a slightly lower reactivity in the Friedel-Crafts step to afford **3d** in 78% yield after stirring for 60 min. In contrast the strong functionalized electron-deficient aldehyde **2e** was smoothly reacted with indole **1a** in the first step (with observation on TLC) but gave low reactivity with propargyl bromide in the *N*-propargylation step which led to **3e** in poor yield.

A variety of organoazides bearing substituted benzyl, ether and esters functionalized with alkyl, long chain aliphatic alkyl and tetra-*O*-acetyl-glucosyl groups were investigated and the reactions generally proceeded smoothly, affording the corresponding products **3f-3r** in good to excellent yields. With these successful results for the one-pot three-step Friedel-Crafts *N*-propargylation and CuAAC reactions for the synthesis of bis-indole-1,4-disubstituted-1,2,3-triazole derivatives, the next step was to extend the procedure to a one-pot four-step reaction. that can be better utilizing the reactions by reduce process in preparation the exposure-azides by in situ preparation from corresponding alkyl halides and sodium azide in the reactor.¹⁰⁻¹⁵ The results are shown in Table 3.

Table 2 The range of aldehydes and alkyl azides studied..

Reaction conditions: **1a** (0.44 mmol), aldehyde (0.2 mmol), KOH (1.9 mmol), propargyl bromide (0.6 mmol), CuI (0.06 mmol), Et₃N (0.6 mmol), R'N₃ (0.6 mmol) and CH₃CN (0.6 mL)

^aT₁ = 15 min

Table 3. Optimization Studies for the synthesis of **4a** via the one-pot four-step reaction

Entry	Cu-cat. (35 mol%)	Solvent	T ₃ (h)	4a (%) ^a
1	CuSO ₄ ·5H ₂ O/NaAsc	CH ₃ CN	3	18
2	CuI	CH ₃ CN	3	34
3	CuI	CH ₃ CN	3	79 ^b
4	CuI	DMF	1	84^b
5	CuI	THF	2	83 ^b
6	CuI	DCE	3	trace ^b
7	CuI	H ₂ O	3	39 ^b
8	CuI	PEG-400	24	58 ^b

^aReaction conditions: KOH (1.9 mmol), propargyl bromide, Et₃N, BnBr and NaN₃ (0.6 mmol) and CH₃CN (0.6 mL)

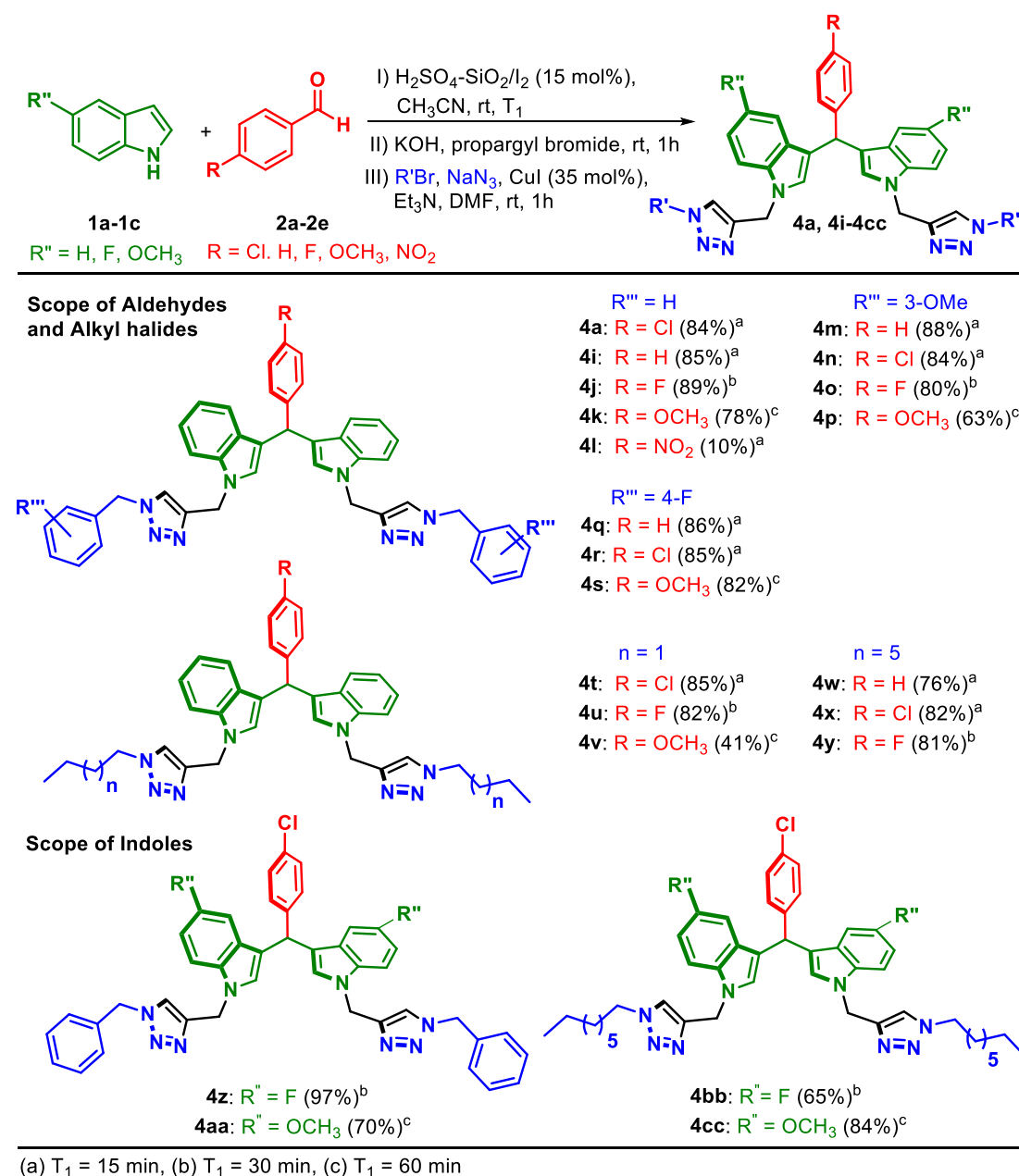
^bMixed of benzyl bromide and NaN₃ in solvent previously added to reaction.

Chemical structures of R-X or R-OMs groups for products 4b-4h are shown below the table:

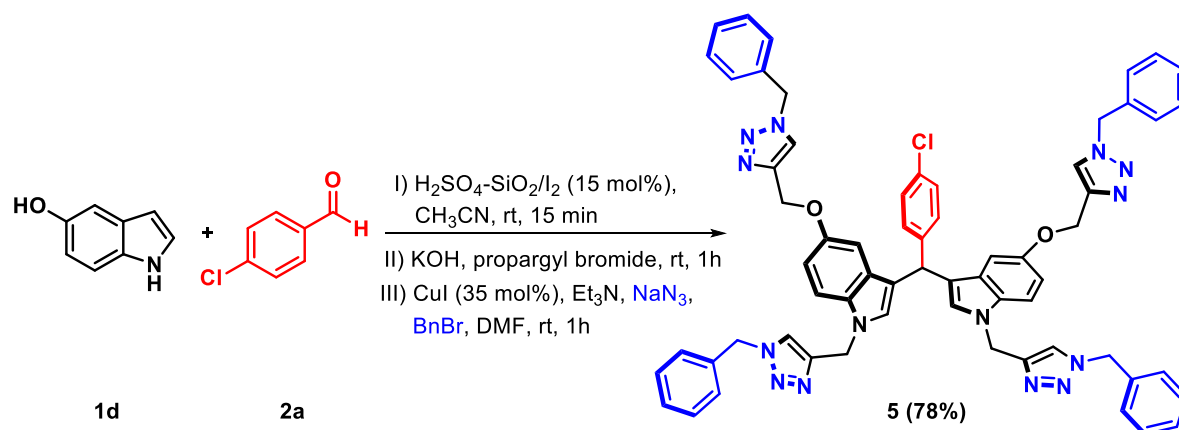
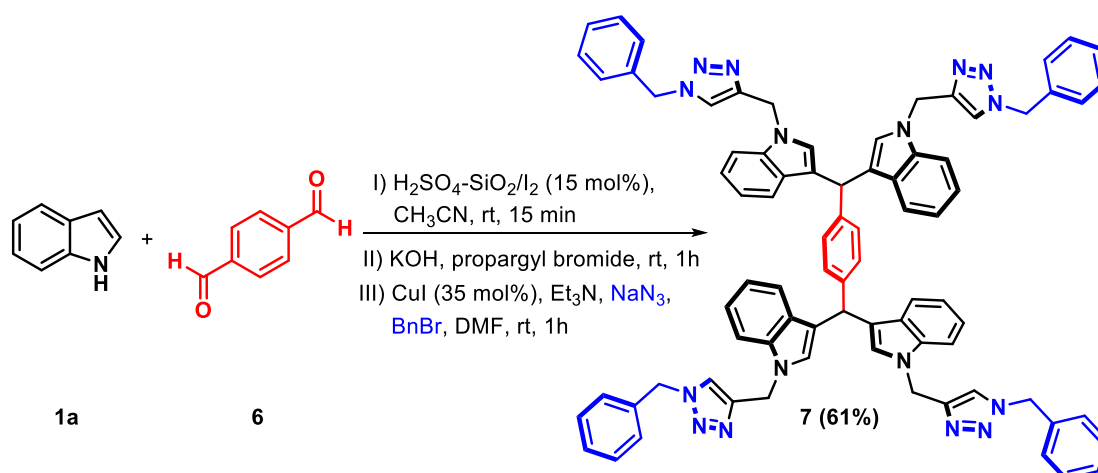
- 4b:** (76%) R-X = 4-bromobenzyl
- 4c:** (68%) R-X = 4-bromobenzyl with NO₂ at 3-position
- 4d:** (90%) R-OMs = CH₃I
- 4e:** (59%) R-OMs = 4-nitrobenzyl
- 4f:** (84%) R-OMs = 4-bromobenzyl with a cyclohexyl group
- 4g:** (11%) R-OMs = 2-naphthyl
- 4h:** (19%) R-OMs = 1-hexyl

The optimal conditions for the one-pot four-step synthesis of bisindoletriazole was studied and it was found that including the additional step of azidation required the solvent to be changed to DMF in the final step. DMF proved to be the best choice over acetonitrile, THF, water and PEG-400, providing a high yield of product in a short reaction time. Moreover, using alkyl halide in the azidation step was found to give yields of bisindoletriazole products **4a-4f** higher than alkyl mesylate as shown in Table 3.

A range of aldehydes, indoles and alkyl halides were examined using the one-pot four-step reaction and the results are summarized in **Table 4**. Using benzyl bromide in the azidation step, a variety of substituted benzaldehydes were investigated and they gave just as good yields of benzyltriazole-bisindoles **4a** and **4i-4l** as the one-pot three-step method in **Table 1** except nitrobenzaldehyde **2e**.

Table4. Range of aldehydes, indoles and alkyl halides studied.

Next the a range of substituted methoxy- and fluoro-benzaldehydes were studied together with a number of substituted benzyl bromides and compounds **4m-4s** were obtained in high yields. Using aliphatic bromide in the azidation step such as *n*-butyl and *n*-octyl bromide, compounds **4t-4y** were produced in moderate to high yields. Fluoroindole and Methoxyindole were also investigated and performed well to yield the corresponding products **4z-4cc** in good to excellent yields under the one-pot conditions.

Scheme 1. One-pot four-step synthesis of **5** using 5-hydroxyindole**Scheme 2.** One-pot four-step synthesis of **7** using terephthalaldehyde

Furthermore, the one-pot four-step reaction is applicable for the synthesis of bis-indole tetra-triazoles and tetraindole-tetratriazole derivatives¹⁶⁻¹⁸ (Schemes 1 and 2). The reaction of *p*-chlorobenzaldehyde **2a** and 5-hydroxyindole **1d** smoothly proceeded by using the one-pot procedure to give **5** in good yields. When indole was treated with terephthalaldehyde under the optimized conditions, tetraindole-tetratriazole **7** was obtained in good yields proving the efficiency of the one-pot method.

Conclusions

An efficient protocol was developed for the sequential one-pot four-step synthesis of bis-indole-1,4-disubstituted-1,2,3-triazoles from Friedel-Crafts reactions using $\text{H}_2\text{SO}_4\text{-SiO}_2/\text{I}_2$ as a Lewis acid catalyst, N-propargylation and azides generated in situ from alkyl halides and sodium azide followed by the final step click reaction. The reactions gave high yields of

product under mild conditions and are compatible with many functional groups, which can save time and cost and only requires chromatographic purification of the final product, making this process even more user friendly and safe.

Experimental section

General information: All chemicals were purchased from commercial sources and used without further purification. ^1H and $^{13}\text{C}\{^1\text{H}\}$ NMR spectra were recorded on a BRUKER AVANC 400 and 100 MHz instrument. All spectra were measured in CDCl_3 solvent and chemical shifts are reported as δ values in parts per million (ppm) relative to tetramethylsilane (δ 0.00 ppm) or CDCl_3 ($\delta(^1\text{H})$, 7.26; $\delta(^{13}\text{C})$, 77.0 ppm) as an internal standard. Data are reported as follows; chemical shift (multiplicity, integrated intensity or assignment, coupling constants in Hz, assignment). High-resolution mass spectra (HRMS) data were obtained with a Finnigan MAT 95. Infrared spectra were determined on a PERKIN ELMER FT/IR-2000S spectrophotometer and are reported in wave number (cm^{-1}). Analytical thin-layer chromatography (TLC) was conducted on precoated TLC plates; silica gel 60F-254 [E. Merck, Darmstadt, Germany]. Silica gel columns for open-column chromatography utilized silica gel 60 PF254 [E. Merck, Darmstadt, Germany]. Melting points were measured using a Melting point apparatus (Griffin) and are uncorrected. Sulphuric acid immobilized on silica gel ($\text{H}_2\text{SO}_4\text{-SiO}_2$) were prepared according to the literature procedure¹⁸.

General procedure for one-pot three-step bis-indole triazoles derivatives: For the first step, a stirred solution of indole **1** (1.1 mmol) in CH_3CN (1 mL) was mixed with the aldehyde **2** (0.5 mmol). Then I_2 powder (9.5 mg, 0.075 mmol) and $\text{H}_2\text{SO}_4\text{-SiO}_2$ (20 mg) was added while the stirring was continued at room temperature. TLC showed the conversion was complete. In the second step KOH (266.5 mg, 4.75 mmol) and propargyl bromide (0.1 mL, 1.5 mmol) was added at room temperature and the stirring was continued for 1 h. The reaction mixture was filtered to remove salt and the solvent of the filtrate was evaporated to dryness. The reaction mixture was then re-dissolved in CH_3CN (1 mL). Finally, alkyl azide (1.5 mmol), CuI (33.3 mg, 0.175 mmol) and Et_3N (0.2 mL, 1.5 mmol) was added to the reaction mixture and stirred at

room temperature for 1 h. After completion of the reaction it was quenched with saturated cool aqueous $\text{Na}_2\text{S}_2\text{O}_3$ (10 mL) and was extracted with ethyl acetate (3 x 10 mL). The organic phase was collected and washed with water (3 x 5 mL), then dried with anhydrous Na_2SO_4 , filtered and evaporated in *vacuo*. The crude product was purified by silica gel column chromatography (SiO_2 , 40-50% EtOAc/*n*-Hexane as eluent) to afford bis-indole-1,4-disubstituted-1,2,3-triazoles **3**.

3,3'-(4-chlorophenylmethylene)-bis-indole-((1-benzyl-1,2,3-triazol-4-yl)methyl) 3a: 98% yield (0.1365 g) as a pink solid; m.p. 182-183 °C; R_f = 0.13 (40% EtOAc/*n*-Hexane); IR (KBr): 3135, 3052, 2922, 2851, 1634, 1489, 1466, 1332, 804, 736 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.36-7.25 (m, 10H), 7.20-7.12 (m, 10H), 7.07 (s, 2H), 6.94 (t, J = 7.6 Hz, 2H), 6.59 (s, 2H), 5.79 (s, 1H), 5.40 (s, 4H), 5.29 (s, 4H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 145.0, 142.2, 136.5, 134.4, 131.7, 129.8, 128.9, 128.6, 128.3, 127.8, 127.4, 127.1, 121.8, 121.5, 119.8, 119.1, 118.4, 109.6, 53.9, 41.8, 39.4; HRMS (ESI) m/z $\text{C}_{43}\text{H}_{35}\text{ClN}_8$ ($\text{M}+\text{H}$) $^+$ calcd 699.2751, found 699.2752.

3,3'-(phenylmethylene)-bis-indole-((1-benzyl-1,2,3-triazol-4-yl)methyl) 3b³: CAS Number 1174761-01-3; 92% yield (0.1220 g) as a pink solid; m.p. 94-96 °C; R_f = 0.48 (50% EtOAc/*n*-Hexane); IR (KBr): 3135, 3054, 2923, 2851, 1611, 1480, 1466, 1332, 736 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.34-7.29 (m, 12H), 7.23-7.12 (m, 9H), 7.05 (s, 2H), 6.92 (t, J = 7.6 Hz, 2H), 6.59 (s, 2H), 5.82 (s, 1H), 5.40 (s, 4H), 5.30 (s, 2H), 5.29 (s, 4H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 145.1, 143.6, 136.5, 134.4, 128.9, 128.6, 128.5, 128.2, 127.8, 127.6, 127.1, 126.1, 121.7, 121.6, 119.9, 119.0, 118.9, 109.5, 53.9, 41.9, 40.0.

3,3'-(4-fluorophenylmethylene)-bis-indole-((1-benzyl-1,2,3-triazol-4-yl)methyl) 3c: 97% yield (0.1530 g) as a pink solid; m.p. 102-103 °C; R_f = 0.54 (50% EtOAc/*n*-Hexane); IR (KBr): 3135, 3052, 2922, 2851, 1634, 1506, 1466, 1332, 1221, 736 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.33-7.25 (m, 10H), 7.21-7.09 (m, 8H), 7.04 (s, 2H), 6.91 (t, J = 7.6 Hz, 2H), 6.88 (t, J = 8.8

Hz, 2H), 6.55 (s, 2H), 5.77 (s, 1H), 5.38 (s, 4H), 5.27 (s, 2H), 5.26 (s, 2H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 161.2 (d, $J = 243.0$ Hz), 144.9, 139.4 (d, $J = 3.0$ Hz), 136.5, 134.4, 129.8 (d, $J = 8.0$ Hz), 128.9, 128.5, 127.7, 127.4, 127.0, 121.8, 121.5, 119.8, 119.0, 118.7, 114.8 (d, $J = 21.0$ Hz), 109.5, 53.9, 41.8, 39.2; HRMS (ESI) m/z $\text{C}_{43}\text{H}_{35}\text{FN}_8\text{Na}$ ($\text{M}+\text{Na}$) $^+$ calcd 705.2866, found 705.2870.

3,3'-(4-methoxyphenylmethylene)-bis-indole-((1-benzyl-1,2,3-triazol-4-yl)methyl) 3d³:

CAS Number 1174761-04-6; 78% yield 0.1240 g) as an orange solid; m.p. 153-155 °C; $R_f = 0.38$ (50% EtOAc/*n*-Hexane); IR (KBr): 3137, 3052, 2923, 2851, 1610, 1509, 1465, 1331, 1265, 737 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.36-7.28 (m, 10H), 7.20-7.10 (m, 8H), 7.05 (s, 2H), 6.92 (t, $J = 7.6$ Hz, 2H), 6.77 (d, $J = 8.8$ Hz, 2H), 6.58 (s, 2H), 5.77 (s, 1H), 5.40 (s, 4H), 5.30 (s, 2H), 5.29 (s, 2H), 3.78 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 157.8, 145.2, 136.6, 135.8, 134.4, 129.4, 128.9, 128.6, 127.8, 127.4, 127.0, 121.7, 121.5, 120.0, 119.3, 118.9, 113.5, 109.5, 55.0, 53.9, 41.9, 39.1.

3,3'-(4-nitrophenylmethylene)-bis-indole-((1-benzyl-1,2,3-triazol-4-yl)methyl) 3e: 17%

yield (0.0247 g) as a yellow solid; m.p. 181-182 °C; $R_f = 0.22$ (50% EtOAc/*n*-Hexane); IR (KBr): 3133, 3054, 2923, 2852, 1660, 1497, 1519, 1466, 1344, 743 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 8.08 (d, $J = 8.4$ Hz, 2H), 7.42 (d, $J = 8.4$ Hz, 2H), 7.37-7.28 (m, 10H), 7.20-7.15 (m, 6H), 7.12 (s, 2H), 6.96 (t, $J = 7.2$ Hz, 2H), 6.63 (s, 2H), 5.92 (s, 1H), 5.42 (s, 4H), 5.30 (s, 4H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 151.6, 146.5, 144.9, 136.6, 134.4, 129.3, 129.1, 128.8, 127.9, 127.3, 127.2, 123.6, 122.2, 121.6, 119.6, 119.4, 117.4, 109.7, 54.1, 42.0, 40.0; HRMS (ESI) m/z $\text{C}_{43}\text{H}_{35}\text{N}_9\text{O}_2\text{Na}$ ($\text{M}+\text{Na}$) $^+$ calcd 732.2811, found 732.2808.

3,3'-(4-chlorophenylmethylene)-bis-indole-((1-(4-nitrobenzyl)-1,2,3-triazol-4-yl)methyl)

3f: 81% yield (0.1278 g) as a red solid; m.p. 109-111 °C; $R_f = 0.05$ (40% EtOAc/*n*-Hexane); IR (KBr): 3127, 3042, 2922, 2851, 1609, 1489, 1522, 1466, 1347, 804, 734 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 8.13 (d, $J = 8.8$ Hz, 4H), 7.33-7.26 (m, 8H), 7.23-7.10 (m, 8H), 6.93 (t, $J = 7.6$

Hz, 2H), 6.65 (s, 2H), 5.79 (s, 1H), 5.48 (s, 4H), 5.30 (s, 4H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 147.9, 145.4, 142.2, 141.4, 136.5, 131.8, 129.8, 128.4, 128.3, 127.5, 127.1, 124.1, 122.0, 121.9, 119.9, 119.2, 118.6, 109.5, 52.9, 41.8, 39.4; HRMS (ESI) m/z $\text{C}_{43}\text{H}_{33}\text{ClN}_{10}\text{O}_4\text{Na}$ ($\text{M}+\text{Na}$) $^+$ calcd 811.2272, found 811.2278.

3,3'-(4-chlorophenylmethylene)-bis-indole-((1-(3-nitrobenzyl)-1,2,3-triazol-4-yl)methyl)

3g: 99% yield (0.1570 g) as a pink solid; m.p. 105-108 °C; R_f = 0.06 (40% EtOAc/*n*-Hexane); IR (KBr): 3137, 3053, 2925, 2852, 1612, 1530, 1465, 1350, 806, 741 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 8.22-8.16 (m, 2H), 8.05 (s, 2H), 7.57-7.50 (m, 4H), 7.32 (t, J = 7.6 Hz, 4H), 7.23-7.12 (m, 8H), 6.95 (t, J = 7.2 Hz, 2H), 6.63 (s, 2H), 5.80 (s, 1H), 5.53 (s, 4H), 5.32 (brs, 4H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 148.3, 145.4, 142.2, 136.5, 133.8, 131.7, 130.1, 129.8, 128.3, 127.4, 127.1, 123.6, 122.6, 121.9, 119.8, 119.2, 118.6, 109.5, 52.8, 41.7, 39.4; HRMS (ESI) m/z $\text{C}_{43}\text{H}_{33}\text{ClN}_{10}\text{O}_4\text{Na}$ ($\text{M}+\text{Na}$) $^+$ calcd 811.2272, found 811.2282.

3,3'-(4-chlorophenylmethylene)-bis-indole-((1-(3-methoxybenzyl)-1,2,3-triazol-4-

yl)methyl) 3h: 98% yield (0.1485 g) as a pink solid; m.p. 98-100 °C; R_f = 0.14 (50% EtOAc/*n*-Hexane); IR (KBr): 3135, 3052, 2923, 2851, 1602, 1490, 1465, 1332, 1264, 777, 742 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.33 (d, J = 8.4 Hz, 2H), 7.31 (d, J = 8.0 Hz, 2H), 7.25 (t, J = 8.0 Hz, 2H), 7.20 (brs, 4H), 7.15 (t, J = 7.6 Hz, 2H), 7.11 (s, 2H), 6.95 (t, J = 7.6 Hz, 2H), 6.87 (dd, J = 8.4, 1.6 Hz, 2H), 6.76 (t, J = 7.6 Hz, 2H), 6.70 (brs, 2H), 6.62 (s, 2H), 5.81 (s, 1H), 5.36 (s, 4H), 5.29 (s, 4H), 3.73 (s, 6H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 160.0, 145.0, 142.2, 136.5, 135.8, 131.7, 130.1, 129.8, 128.3, 127.5, 127.1, 121.9, 121.6, 120.0, 119.8, 119.1, 118.4, 114.0, 113.4, 109.6, 55.2, 53.9, 41.9, 39.4; HRMS (ESI) m/z $\text{C}_{45}\text{H}_{39}\text{ClN}_8\text{O}_2\text{Na}$ ($\text{M}+\text{Na}$) $^+$ calcd 781.2782, found 781.2777.

3,3'-(4-chlorophenylmethylene)-bis-indole-((1-(2,3-dimethoxybenzyl)-1,2,3-triazol-4-

yl)methyl) 3i: 99% yield (0.1692 g) as a pink solid; m.p. 94-95 °C; R_f = 0.17 (50% EtOAc/*n*-Hexane); IR (KBr): 3139, 3053, 2923, 2851, 1613, 1505, 1465, 1331, 1228, 808, 742 cm^{-1} ; ^1H

NMR (400 MHz, CDCl₃) δ 7.33 (d, J = 8.4 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 7.20 (s, 4H), 7.17-7.11 (m, 4H), 6.94 (t, J = 7.6 Hz, 2H), 6.83 (dd, J = 8.8, 2.0 Hz, 2H), 6.78 (d, J = 8.8 Hz, 2H), 6.66 (brs, 2H), 6.61 (s, 2H), 5.80 (s, 1H), 5.39 (s, 4H), 5.29 (s, 4H), 3.67 (s, 6H), 3.64 (s, 6H); ¹³C{¹H} NMR (100 MHz, CDCl₃) δ 153.6, 151.1, 144.5, 142.4, 136.6, 131.7, 129.9, 128.3, 127.5, 127.2, 123.6, 122.0, 121.8, 119.8, 119.1, 118.3, 115.8, 114.7, 111.7, 109.7, 55.7, 55.6, 49.1, 42.0, 39.5; HRMS (ESI) m/z C₄₇H₄₃ClN₈O₄Na (M+Na)⁺ calcd 841.2993, found 841.2997.

3,3'-(4-chlorophenylmethylene)-bis-indole-((1-(4-benzyloxy-3-methoxybenzyl)-1,2,3-triazol-4-yl)methyl) 3j: 84 % yield (0.1627 g) as a red solid; m.p. 94-95 °C; R_f = 0.15 (40% EtOAc/*n*-Hexane); IR (KBr): 3139, 3053, 2923, 2851, 1633, 1515, 1466, 1332, 1265, 784, 737 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.45-7.27 (m, 14H), 7.20 (s, 4H), 7.14 (t, J = 7.6 Hz, 2H), 7.08 (s, 2H), 6.94 (t, J = 7.2 Hz, 2H), 6.82 (d, J = 8.0 Hz, 2H), 6.74-6.67 (m, 4H), 6.60 (s, 2H), 5.79 (s, 1H), 5.31 (s, 4H), 5.28 (s, 4H), 5.13 (s, 4H), 3.76 (s, 6H); ¹³C{¹H} NMR (100 MHz, CDCl₃) δ 150.0, 148.5, 145.0, 142.3, 136.7, 136.6, 131.8, 129.9, 128.5, 128.3, 127.9, 127.5, 127.3, 127.2, 121.9, 121.4, 120.5, 119.9, 119.1, 118.4, 113.9, 111.5, 109.6, 71.0, 56.0, 53.9, 42.0, 39.5; HRMS (ESI) m/z C₅₉H₅₁ClN₈O₄Na (M+Na)⁺ calcd 993.3619, found 993.3629.

3,3'-(4-chlorophenylmethylene)-bis-indole-((1-phenylethyl-1,2,3-triazol-4-yl)methyl) 3k: 98 % yield (0.1489 g) as a pink solid; m.p. 83-85 °C; R_f = 0.16 (40% EtOAc/*n*-Hexane); IR (KBr): 3136, 3057, 2924, 2853, 1612, 1488, 1465, 1333, 804, 742 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.31 (t, J = 8.8 Hz, 4H), 7.24 (s, 4H), 7.20-7.12 (m, 8H), 7.02-6.94 (m, 6H), 6.85 (s, 2H), 6.60 (s, 2H), 5.82 (s, 1H), 5.27 (brs, 4H), 4.45 (t, J = 7.0 Hz, 4H), 3.09 (t, J = 7.2 Hz, 4H); ¹³C{¹H} NMR (100 MHz, CDCl₃) δ 144.3, 142.3, 136.8, 136.6, 131.8, 129.9, 128.7, 128.5, 128.4, 127.6, 127.2, 127.0, 121.9, 119.9, 119.2, 118.4, 109.6, 51.6, 42.0, 39.5, 36.6; HRMS (ESI) m/z C₄₅H₃₉ClN₈Na (M+Na)⁺ calcd 749.2884, found 749.2887.

3,3'-(4-chlorophenylmethylene)-bis-indole-((1-phenoxyethyl-1,2,3-triazol-4-yl)methyl) 3l:

83 % yield (0.1252 g) as a pink solid; m.p. 92-94 °C; R_f = 0.17 (50% EtOAc/*n*-Hexane); IR (KBr): 3140, 3052, 2923, 2851, 1599, 1489, 1466, 1333, 1242, 790, 740 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.37-7.29 (m, 6H), 7.27-7.13 (m, 10H), 7.00 (t, J = 7.6 Hz, 2H), 6.96 (t, J = 7.2 Hz, 2H), 6.72 (d, J = 8.4 Hz, 4H), 6.64 (s, 2H), 5.83 (s, 1H), 5.31 (s, 4H), 4.62 (t, J = 4.8 Hz, 4H), 4.26 (t, J = 4.8 Hz, 4H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 157.6, 144.6, 142.3, 136.6, 131.7, 129.9, 129.5, 128.3, 127.5, 127.2, 122.8, 121.9, 121.6, 119.9, 119.1, 118.5, 114.5, 109.6, 66.0, 49.6, 41.9, 39.4; HRMS (ESI) m/z $\text{C}_{45}\text{H}_{39}\text{ClN}_8\text{O}_2\text{Na}$ ($\text{M}+\text{Na}$) $^+$ calcd 781.2782, found 781.2779.

3,3'-(4-chlorophenylmethylene)-bis-indole-((1-naphthyloxyethyl-1,2,3-triazol-4-yl)methyl)

3m: 45 % yield (0.0767 g) as a red solid; m.p. 106-108 °C; R_f = 0.04 (50% EtOAc/*n*-Hexane); IR (KBr): 3133, 3053, 2923, 2851, 1632, 1581, 1464, 1333, 1269, 794, 740 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.91 (d, J = 8.4 Hz, 2H), 7.79 (d, J = 8.4 Hz, 2H), 7.48-7.42 (m, 4H), 7.37-7.27 (m, 10H), 7.16-7.07 (m, 6H), 6.96 (t, J = 7.6 Hz, 2H), 6.69 (d, J = 7.6 Hz, 2H), 6.61 (s, 2H), 5.74 (s, 1H), 5.28 (s, 4H), 4.71 (t, J = 4.8 Hz, 4H), 4.39 (t, J = 4.8 Hz, 4H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 153.3, 144.9, 142.2, 136.6, 134.4, 131.7, 129.9, 128.3, 127.6, 127.5, 127.2, 126.6, 125.6, 125.6, 125.2, 122.6, 122.0, 121.3, 121.2, 120.0, 119.2, 118.5, 109.5, 105.0, 66.3, 49.7, 41.9, 39.4; HRMS (ESI) m/z $\text{C}_{53}\text{H}_{43}\text{ClN}_8\text{O}_2\text{Na}$ ($\text{M}+\text{Na}$) $^+$ calcd 881.3095, found 881.3087.

3,3'-(4-chlorophenylmethylene)-bis-indole-((1-(4-methoxybenzyldiacetyl)-1,2,3-triazol

-4-yl)methyl) 3n: 78 % yield (0.1352 g) as a pink solid; m.p. 78-79 °C; R_f = 0.10 (50% EtOAc/*n*-Hexane); IR (KBr): 3140, 3052, 2934, 2838, 1751, 1614, 1516, 1465, 1333, 1249, 804, 742 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.34 (d, J = 7.2 Hz, 2H), 7.33 (d, J = 7.6 Hz, 2H), 7.24-7.22 (m, 8H), 7.19 (s, 2H), 7.16 (t, J = 7.5 Hz, 2H), 6.98 (t, J = 7.6 Hz, 2H), 6.86 (d, J = 8.4 Hz, 4H), 6.64 (s, 2H), 5.83 (s, 1H), 5.34 (s, 2H), 5.33 (s, 2H), 5.10 (s, 4H), 5.02 (s, 4H),

3.79 (s, 6H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 166.0, 159.9, 145.0, 142.3, 136.5, 131.7, 130.3, 129.8, 128.3, 127.4, 127.1, 126.5, 123.0, 121.9, 119.8, 119.1, 118.6, 114.0, 109.5, 67.7, 55.1, 50.6, 41.7, 39.3; HRMS (ESI) m/z $\text{C}_{49}\text{H}_{43}\text{ClN}_8\text{O}_6\text{Na}$ ($\text{M}+\text{Na}$) $^+$ calcd 897.2892, found 897.2899.

3,3'-(4-chlorophenylmethylene)-bis-indole-((1-(2,3-dimethoxybenzyl)diacetyl)-1,2,3-

triazol-4-yl)methyl) 3o: 77 % yield (0.1434 g) as a pink solid; m.p. 95-96 °C; R_f = 0.07 (50% EtOAc/*n*-Hexane); IR (KBr): 3143, 3053, 2922, 2851, 1754, 1633, 1505, 1466, 1333, 1223, 805, 738 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.34 (d, J = 8.4 Hz, 4H), 7.26-7.22 (m, 6H), 7.16 (t, J = 7.2 Hz, 2H), 6.98 (t, J = 7.6 Hz, 2H), 6.86-6.79 (m, 6H), 6.65 (s, 2H), 5.83 (s, 1H), 5.35 (s, 2H), 5.34 (s, 2H), 5.20 (s, 4H), 5.06 (s, 4H), 3.76 (s, 6H), 3.74 (s, 6H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 166.1, 153.4, 151.8, 145.3, 142.2, 136.6, 131.8, 130.0, 128.4, 127.6, 127.2, 123.6, 123.1, 122.0, 119.9, 119.2, 118.8, 116.2, 114.5, 111.6, 109.6, 63.5, 56.0, 55.7, 50.8, 41.9, 39.4; HRMS (ESI) m/z $\text{C}_{51}\text{H}_{47}\text{ClN}_8\text{O}_8\text{Na}$ ($\text{M}+\text{Na}$) $^+$ calcd 957.3103, found 957.3101.

3,3'-(4-chlorophenylmethylene)-bis-indole-((1-(β -tetraacetylglucose)-1,2,3-triazol-4-yl)

methyl) 3p: 99 % yield (0.2326 g) as a red solid; m.p. 122-124 °C; R_f = 0.10 (50% EtOAc/*n*-Hexane); IR (KBr): 3138, 3054, 2926, 2853, 1755, 1613, 1489, 1466, 1368, 1224, 805, 742 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.42 (s, 1H), 7.40 (s, 1H), 7.36 (d, J = 8.0 Hz, 2H), 7.33 (d, J = 7.6 Hz, 2H), 7.31-7.22 (m, 4H), 7.20 (t, J = 7.2 Hz, 2H), 7.03 (t, J = 7.6 Hz, 1H), 7.02 (t, J = 7.2 Hz, 1H), 6.71 (s, 1H), 6.68 (s, 1H), 5.85 (s, 1H), 5.79 (d, J = 8.8 Hz, 2H), 5.40-5.30 (m, 8H), 5.21 (t, J = 9.6 Hz, 2H), 4.27 (ddd, J = 12.8, 8.4, 5.2 Hz, 2H), 4.11 (brd, J = 12.4 Hz, 2H), 3.96 (brdd, J = 10.0, 3.6 Hz, 2H), 2.05 (s, 6H), 2.04 (s, 6H), 2.02 (s, 3H), 2.00 (s, 3H), 1.72 (s, 3H), 1.68 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 170.4, 169.9, 169.3, 168.7, 168.7, 145.5, 145.4, 142.3, 136.6, 136.6, 131.8, 130.0, 128.4, 127.7, 127.6, 127.3, 122.0, 120.3, 120.2, 120.0, 119.99, 119.3, 119.28, 118.7, 118.66, 109.6, 109.56, 85.6, 85.57, 75.2, 75.1, 72.6,

70.1, 70.0, 67.7, 67.6, 61.5, 61.47, 41.9, 41.8, 39.5, 20.6, 20.5, 19.9, 19.8; HRMS (ESI) m/z $C_{57}H_{59}ClN_8O_{18}Na$ (M+Na)⁺ calcd 1201.3534, found 1201.3534.

3,3'-(4-chlorophenylmethylene)-bis-indole-((1-octhyl-1,2,3-triazol-4-yl)methyl) 3q: 80 % yield (0.1183 g) as a red oil; R_f = 0.36 (40% EtOAc/*n*-Hexane); IR (KBr): 3133, 3053, 2925, 2854, 1633, 1488, 1466, 1332, 804, 740 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H), 7.25-7.22 (m, 4H), 7.18 (t, J = 7.6 Hz, 2H), 7.10 (s, 2H), 7.00 (t, J = 7.6 Hz, 2H), 6.65 (s, 2H), 5.84 (s, 1H), 5.33 (s, 4H), 4.22 (t, J = 7.2 Hz, 4H), 1.84-1.79 (m, 4H), 1.27-1.24 (m, 20H), 0.87 (t, J = 7.2 Hz, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 144.4, 142.2, 136.5, 131.6, 129.8, 128.2, 127.4, 127.1, 121.8, 121.3, 119.7, 119.0, 118.3, 109.5, 50.2, 41.9, 39.4, 31.5, 30.0, 28.8, 28.7, 26.2, 22.4, 13.9; HRMS (ESI) m/z $C_{45}H_{55}ClN_8Na$ (M+Na)⁺ calcd 765.4136, found 765.4135.

3,3'-(4-chlorophenylmethylene)-bis-indole-((1-dodecyl-1,2,3-triazol-4-yl)methyl) 3r: 90 % yield (0.1532 g) as a brown oil; R_f = 0.35 (30% EtOAc/*n*-Hexane); IR (KBr): 3133, 3055, 2925, 2854, 1614, 1489, 1466, 1333, 803, 741 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 7.6 Hz, 2H), 7.26 (d, J = 8.4 Hz, 2H), 7.23 (d, J = 8.8 Hz, 2H), 7.18 (t, J = 7.6 Hz, 2H), 7.09 (s, 2H), 7.00 (t, J = 7.2 Hz, 2H), 6.64 (s, 2H), 5.84 (s, 1H), 5.33 (s, 4H), 4.22 (t, J = 7.2 Hz, 4H), 1.80 (quin, J = 7.6 Hz, 4H), 1.24 (brs, 36H), 0.88 (t, J = 6.8 Hz, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 144.5, 142.3, 136.6, 131.8, 129.9, 128.3, 127.5, 127.2, 121.9, 121.3, 119.8, 119.1, 118.4, 109.6, 50.3, 42.0, 39.5, 31.8, 30.1, 29.5, 29.4, 29.3, 29.2, 28.9, 26.4, 14.0; HRMS (ESI) m/z $C_{53}H_{71}ClN_8Na$ (M+Na)⁺ calcd 877.5388, found 877.5384.

General procedure for one-pot four-step bis-indole triazoles derivatives: The first step, a stirred solution of indole **1** (1.1 mmol) in CH_3CN (1 mL) was mixed with aldehyde **2** (0.5 mmol), I_2 powder (9.5 mg, 0.075 mmol) and $H_2SO_4-SiO_2$ (20 mg) at room temperature. TLC showed the conversion was complete. In the second step KOH (266.5 mg, 4.75 mmol) and

propargyl bromide (0.1 mL, 1.5 mmol) was added at room temperature and the stirring was continued for 1 h. The reaction mixture was filtered to remove salt and the solvent of the filtrate was evaporated to dryness. The reaction mixture was re-dissolved in DMF (0.50 mL). A solution of NaN₃ (97.5 mg, 1.5 mmol) and alkyl halide **3** (1.5 mmol) in DMF (0.5 mL) was added while stirring at room temperature. Finally, CuI (33.3 mg, 0.175 mmol), Et₃N (0.2 mL, 1.5 mmol), and solution of alkyl azide was added and stirring was continued at room temperature for 1 h. After completion of the reaction, it was quenched with saturated cool aqueous Na₂S₂O₃ and extracted with ethyl acetate (3x10 mL). The organic phase was collected and washed with water (3x5 mL), then dried with anhydrous Na₂SO₄, filtered and evaporated in *vacuo*. The crude product was purified by silica gel column chromatography (SiO₂, 40-50% EtOAc/Hexane as eluent) to afford bis-indole-1,4-disubstituted-1,2,3-triazoles **4**.

3,3'-(4-chlorophenylmethylene)-bis-indole-((1-methyl-1,2,3-triazol-4-yl)methyl) 4d: 90 % yield (0.1999 g) as a brown solid; m.p. 97-99 °C; R_f = 0.03 (50% EtOAc/*n*-Hexane); IR (KBr): 3138, 3052, 2922, 2851, 1633, 1488, 1466, 1333, 804, 739 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.34 (t, J = 7.6 Hz, 4H), 7.25-7.21 (m, 4H), 7.18 (t, J = 7.6 Hz, 2H), 7.10 (s, 2H), 7.00 (t, J = 7.6 Hz, 2H), 6.64 (s, 2H), 5.83 (s, 1H), 5.32 (s, 2H), 5.31 (s, 2H), 3.97 (s, 6H); ¹³C{¹H} NMR (100 MHz, CDCl₃) δ 144.7, 142.2, 136.5, 131.7, 129.8, 128.3, 127.4, 127.1, 122.5, 121.8, 119.8, 119.1, 118.4, 109.5, 41.8, 39.4, 36.5; HRMS (ESI) m/z C₃₁H₂₇ClN₈Na (M+Na)⁺ calcd 569.1945, found 569.1942.

3,3'-(4-chlorophenylmethylene)-bis-indole-((1-(4-nitroxybenzyl)diacetyl)-1,2,3-triazol-4-yl)methyl) 4e: 59 % yield (0.2651 g) as a red solid; m.p. 98-100 °C; R_f = 0.10 (50% EtOAc/*n*-Hexane); IR (KBr): 3144, 3055, 2922, 2851, 1759, 1608, 1522, 1489, 1466, 1347, 1195, 805, 738 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.16 (d, J = 8.4 Hz, 4H), 7.42 (d, J = 8.4 Hz, 4H), 7.34 (d, J = 7.6 Hz, 2H), 7.32 (d, J = 7.6 Hz, 2H), 7.25-7.20 (m, 6H), 7.14 (t, J = 7.2 Hz, 2H), 6.97 (t, J = 7.6 Hz, 2H), 6.44 (s, 2H), 5.83 (s, 1H), 5.34 (s, 2H), 5.33 (s, 2H), 5.25 (s,

4H), 5.12 (s, 4H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 165.8, 147.6, 145.0, 142.3, 141.4, 136.4, 131.6, 129.8, 128.4, 128.2, 127.4, 127.0, 123.7, 123.1, 121.8, 119.8, 119.1, 118.5, 109.5, 66.0, 50.4, 41.6, 39.2; HRMS (ESI) m/z $\text{C}_{47}\text{H}_{37}\text{ClN}_{10}\text{O}_8\text{Na}$ ($\text{M}+\text{Na}$) $^+$ calcd 927.2382, found 927.2379.

3,3'-(4-chlorophenylmethylene)-bis-indole-((1-(menthlyldiacetyl)-1,2,3-triazol-4-yl)methyl)

4f: 84 % yield (0.3846 g) as a red solid; m.p. 112-113 °C; R_f = 0.15 (30% EtOAc/*n*-Hexane); IR (KBr): 3139, 3054, 2956, 2870, 1746, 1613, 1489, 1465, 1334, 1220, 803, 740 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.35 (d, J = 8.0 Hz, 2H), 7.34 (d, J = 7.6 Hz, 2H), 7.27-7.22 (m, 6H), 7.18 (t, J = 7.6 Hz, 2H), 6.99 (t, J = 7.6 Hz, 2H), 6.65 (s, 2H), 5.83 (s, 1H), 5.36 (s, 4H), 5.02 (t, J = 4.5 Hz, 4H), 4.74 (td, J = 10.8, 4.4 Hz, 2H), 1.96 (brd, J = 12.0 Hz, 2H), 1.77-1.62 (m, 8H), 1.34 (brt, J = 12.0 Hz, 2H), 1.10-0.99 (m, 2H), 0.97 (d, J = 11.6 Hz, 6H), 0.86 (d, J = 6.8 Hz, 6H), 0.71 (d, J = 6.8 Hz, 6H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 165.6, 145.0, 142.2, 136.5, 131.7, 129.9, 128.3, 127.5, 127.1, 123.0, 121.9, 119.8, 119.1, 118.5, 109.6, 76.8, 50.8, 46.6, 41.8, 40.5, 39.4, 33.8, 31.2, 26.1, 23.2, 21.8, 20.6, 16.2; HRMS (ESI) m/z $\text{C}_{53}\text{H}_{63}\text{ClN}_8\text{O}_4\text{Na}$ ($\text{M}+\text{Na}$) $^+$ calcd 933.4558, found 933.4569.

3,3'-(4-chlorophenylmethylene)-bis-indole-((1-penthyl-1,2,3-triazol-4-yl)methyl) 4h: 19 %

yield (0.0635 g) as a red solid; m.p. 77-79 °C; R_f = 0.10 (30% EtOAc/*n*-Hexane); IR (KBr): 3134, 3054, 2927, 2856, 1614, 1489, 1466, 1333, 804, 749 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.35 (d, J = 8.0 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H), 7.24 (d, J = 4.0 Hz, 4H), 7.18 (t, J = 8.0 Hz, 2H), 7.10 (s, 2H), 7.00 (t, J = 7.6 Hz, 2H), 6.64 (s, 2H), 5.84 (s, 1H), 5.33 (brs, 4H), 4.22 (t, J = 7.2 Hz, 4H), 1.81 (quin, J = 7.6 Hz, 4H), 1.35-1.26 (m, 8H), 0.87 (t, J = 7.2 Hz, 6H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 144.6, 142.3, 136.6, 131.8, 129.9, 128.4, 127.5, 127.2, 121.1, 121.4, 119.9, 119.1, 118.5, 109.6, 50.3, 42.0, 39.5, 29.8, 28.4, 22.0, 13.8; HRMS (ESI) m/z $\text{C}_{39}\text{H}_{43}\text{ClN}_8\text{Na}$ ($\text{M}+\text{Na}$) $^+$ calcd 681.3197, found 681.3207.

3,3'-(phenylmethylene)-bis-indole-((1-(3-methoxybenzyl)-1,2,3-triazol-4-yl)methyl) 4m: 88 % yield (0.3193 g) as a pink solid; m.p. 87-89 °C; R_f = 0.16 (40% EtOAc/*n*-Hexane); IR (KBr): 3138, 3054, 2923, 2851, 1602, 1492, 1466, 1323, 1265, 743 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.35-7.27 (m, 6H), 7.27-7.19 (m, 5H), 7.14 (t, J = 7.2 Hz, 2H), 7.08 (s, 2H), 6.93 (t, J = 7.6 Hz, 2H), 6.86 (d, J = 8.0 Hz, 2H), 6.75 (d, J = 7.6 Hz, 2H), 6.69 (brs, 2H), 6.62 (s, 2H), 5.84 (s, 1H), 5.35 (s, 4H), 5.28 (s, 4H), 3.73 (s, 6H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 160.0, 145.2, 143.7, 136.6, 135.9, 130.1, 128.5, 128.2, 127.7, 127.2, 126.1, 121.8, 121.6, 120.0, 119.0, 114.1, 113.4, 109.5, 55.2, 53.9, 42.0, 40.0; HRMS (ESI) m/z $\text{C}_{45}\text{H}_{40}\text{N}_8\text{O}_2\text{Na}$ ($\text{M}+\text{Na}$) $^+$ calcd 747.3172, found 747.3180.

3,3'-(4-fluorophenylmethylene)-bis-indole-((1-(3-methoxybenzyl)-1,2,3-triazol-4-yl)methyl) 4o: 80 % yield (0.2966 g) as a pink solid; m.p. 91-92 °C; R_f = 0.10 (50% EtOAc/*n*-Hexane); IR (KBr): 3136, 3052, 2922, 2851, 1602, 1506, 1466, 1332, 1265, 1221, 740 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.32 (d, J = 8.4 Hz, 2H), 7.29 (d, J = 8.4 Hz, 2H), 7.27-7.19 (m, 4H), 7.14 (t, J = 7.6 Hz, 2H), 7.08 (s, 2H), 6.94 (t, J = 8.0 Hz, 2H), 6.91 (t, J = 8.8 Hz, 2H), 6.86 (dd, J = 8.0, 2.0 Hz, 2H), 6.75 (d, J = 7.6 Hz, 2H), 6.69 (brs, 2H), 6.59 (s, 2H), 5.80 (s, 1H), 5.37 (s, 4H), 5.29 (s, 4H), 3.73 (s, 6H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 161.1 (d, J = 243.0 Hz), 159.8, 144.9, 139.3 (d, J = 3.0 Hz), 136.5, 135.8, 129.9, 129.8 (d, J = 8.0 Hz), 127.4, 127.0, 121.7, 121.6, 119.8, 119.77, 119.0, 118.7, 114.8 (d, J = 21.0 Hz), 113.9, 113.4, 109.5, 55.0, 53.7, 41.7, 39.2; HRMS (ESI) m/z $\text{C}_{45}\text{H}_{39}\text{FN}_8\text{O}_2\text{Na}$ ($\text{M}+\text{Na}$) $^+$ calcd 765.3078, found 765.3075.

3,3'-(4-methoxyphenylmethylene)-bis-indole-((1-(3-methoxybenzyl)-1,2,3-triazol-4-yl)methyl) 4p: 63 % yield (0.2376 g) as an orange solid; m.p. 89-91 °C; R_f = 0.16 (50% EtOAc/*n*-Hexane); IR (KBr): 3137, 3053, 2923, 2851, 1603, 1509, 1466, 1332, 1264, 739 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.32 (d, J = 8.0 Hz, 2H), 7.30 (d, J = 8.0 Hz, 2H), 7.26-7.22 (m, 2H), 7.18 (d, J = 8.4 Hz, 2H), 7.13 (t, J = 8.0 Hz, 2H), 7.06 (s, 2H), 6.92 (t, J = 7.6 Hz,

2H), 6.86 (dd, $J = 8.4, 2.0$ Hz, 2H), 6.80-6.73 (m, 4H), 6.68 (brs, 2H), 6.59 (s, 2H), 5.77 (s, 1H), 5.37 (s, 4H), 5.30 (s, 2H), 5.29 (s, 4H), 3.78 (s, 3H), 3.72 (s, 6H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 160.0, 157.9, 145.2, 136.6, 135.9, 135.8, 130.1, 129.4, 127.7, 127.1, 121.7, 121.6, 120.0, 119.95, 119.4, 119.0, 114.1, 113.6, 113.4, 109.5, 55.2, 55.1, 53.9, 42.0, 39.2; HRMS (ESI) m/z $\text{C}_{46}\text{H}_{42}\text{N}_8\text{O}_3\text{Na}$ ($\text{M}+\text{Na}$) $^+$ calcd 777.3278, found 777.3272.

3,3'-(phenylmethylene)-bis-indole-((1-(4-fluorobenzyl)-1,2,3-triazol-4-yl)methyl) 4q:

86 % yield (0.3019 g) as a pink solid; m.p. 103-104 °C; $R_f = 0.16$ (40% EtOAc/*n*-Hexane); IR (KBr): 3134, 3054, 2923, 2851, 1608, 1509, 1465, 1332, 1225, 741 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.34-7.12 (m, 15H), 7.04 (s, 2H), 7.02 (t, $J = 8.4$ Hz, 4H), 6.93 (t, $J = 7.2$ Hz, 2H), 6.60 (s, 2H), 5.82 (s, 1H), 5.37 (s, 4H), 5.30 (s, 4H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 162.8 (d, $J = 246.0$ Hz), 145.4, 143.7, 136.6, 130.2 (d, $J = 3.0$ Hz), 129.8 (d, $J = 8.0$ Hz), 128.5, 128.2, 127.7, 127.2, 126.2, 121.8, 121.5, 120.0, 119.1, 119.06, 116.4 (d, $J = 21.0$ Hz), 109.5, 53.3, 42.0, 40.0; HRMS (ESI) m/z $\text{C}_{43}\text{H}_{34}\text{F}_2\text{N}_8\text{Na}$ ($\text{M}+\text{Na}$) $^+$ calcd 723.2772, found 723.2779.

3,3'-(4-chlorophenylmethylene)-bis-indole-((1-(4-fluorobenzyl)-1,2,3-triazol-4-yl)methyl) 4r:

85 % yield (0.3109 g) as a pink solid; m.p. 96-98 °C; $R_f = 0.10$ (40% EtOAc/*n*-Hexane); IR (KBr): 3127, 3054, 2921, 2850, 1644, 1510, 1466, 1332, 1224, 785, 742 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.31 (t, $J = 8.0$ Hz, 4H), 7.21-7.13 (m, 10H), 7.08 (s, 2H), 7.02 (t, $J = 8.8$ Hz, 4H), 6.95 (t, $J = 7.6$ Hz, 2H), 6.60 (s, 2H), 5.79 (s, 1H), 5.37 (s, 4H), 5.30 (brs, 4H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 162.8 (d, $J = 247.0$ Hz), 145.2, 142.3, 136.6, 131.8, 130.3 (d, $J = 3.0$ Hz), 129.9, 129.8 (d, $J = 8.0$ Hz), 128.4, 127.5, 127.1, 121.9, 121.5, 119.9, 119.2, 118.5, 116.0 (d, $J = 22.0$ Hz), 109.6, 53.3, 41.9, 39.5; HRMS (ESI) m/z $\text{C}_{43}\text{H}_{33}\text{ClF}_2\text{N}_8\text{Na}$ ($\text{M}+\text{Na}$) $^+$ calcd 757.2382, found 757.2395.

3,3'-(4-methoxyphenylmethylene)-bis-indole-((1-(4-fluorobenzyl)-1,2,3-triazol-4-

yl)methyl) 4s: 82 % yield (0.3480 g) as an orange solid; m.p. 96-97 °C; $R_f = 0.18$ (50% EtOAc/*n*-Hexane); IR (KBr): 3133, 3052, 2927, 2852, 1609, 1509, 1465, 1332, 1247, 1225,

742 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.32 (t, $J = 8.5$ Hz, 4H), 7.20-7.11 (m, 8H), 7.05 (s, 2H), 7.02 (t, $J = 8.4$ Hz, 4H), 6.93 (t, $J = 7.2$ Hz, 2H), 6.78 (d, $J = 8.4$ Hz, 2H), 6.60 (s, 2H), 5.77 (s, 1H), 5.36 (s, 4H), 5.29 (brs, 4H), 3.78 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 162.8 (d, $J = 247.0$ Hz), 157.9, 145.4, 136.6, 135.8, 130.3 (d, $J = 3.0$ Hz), 129.8 (d, $J = 8.0$ Hz), 129.4, 127.7, 127.1, 121.8, 121.5, 120.0, 119.4, 119.0, 116.0 (d, $J = 22.0$ Hz), 113.6, 109.5, 55.1, 53.3, 42.0, 39.2; HRMS (ESI) m/z $\text{C}_{44}\text{H}_{36}\text{F}_2\text{N}_8\text{O Na}$ ($\text{M}+\text{Na}$) $^+$ calcd 753.2878, found 753.2881.

3,3'-(4-chlorophenylmethylene)-bis-indole-((1-buthyl-1,2,3-triazol-4-yl)methyl) 4t: 85 % yield (0.2933 g) as a brown solid; m.p. 82-83 $^\circ\text{C}$; $R_f = 0.14$ (40% EtOAc/*n*-Hexane); IR (KBr): 3135, 3051, 2924, 2852, 1633, 1489, 1466, 1332, 804, 740 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.35 (d, $J = 8.0$ Hz, 2H), 7.34 (d, $J = 7.6$ Hz, 2H), 7.25 (d, $J = 8.8$ Hz, 2H), 7.23 (d, $J = 8.8$ Hz, 2H), 7.18 (t, $J = 7.6$ Hz, 2H), 7.09 (s, 2H), 7.00 (t, $J = 7.6$ Hz, 2H), 6.64 (s, 2H), 5.84 (s, 1H), 5.33 (brs, 4H), 4.23 (t, $J = 7.2$ Hz, 4H), 1.79 (quin, $J = 7.6$ Hz, 4H), 1.29 (sex, $J = 7.6$ Hz, 4H), 0.92 (t, $J = 7.2$ Hz, 6H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 144.4, 142.2, 136.5, 131.6, 129.8, 128.2, 127.4, 127.1, 121.8, 121.3, 119.7, 119.0, 118.3, 109.5, 49.8, 41.8, 39.4, 31.9, 19.4, 13.2; HRMS (ESI) m/z $\text{C}_{37}\text{H}_{39}\text{ClN}_8\text{Na}$ ($\text{M}+\text{Na}$) $^+$ calcd 653.2884, found 653.2887.

3,3'-(4-fluorophenylmethylene)-bis-indole-((1-buthyl-1,2,3-triazol-4-yl)methyl) 4u: 82 % yield (0.2656 g) as a pink solid; m.p. 82-83 $^\circ\text{C}$; $R_f = 0.18$ (40% EtOAc/*n*-Hexane); IR (KBr): 3135, 3051, 2924, 2851, 1633, 1506, 1466, 1332, 1220, 739 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.35 (d, $J = 8.4$ Hz, 4H), 7.29-7.26 (m, 2H), 7.18 (t, $J = 7.6$ Hz, 2H), 7.09 (s, 2H), 7.00 (t, $J = 7.6$ Hz, 2H), 6.95 (t, $J = 8.4$ Hz, 2H), 6.63 (s, 2H), 5.85 (s, 1H), 5.33 (s, 4H), 4.23 (t, $J = 7.2$ Hz, 4H), 1.79 (quin, $J = 7.6$ Hz, 4H), 1.29 (sex, $J = 7.2$ Hz, 4H), 0.92 (t, $J = 7.6$ Hz, 6H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 161.2 (d, $J = 242.0$ Hz), 144.4, 139.4 (d, $J = 3.0$ Hz), 136.6, 129.8 (d, $J = 8.0$ Hz), 127.5, 127.1, 121.8, 121.3, 119.8, 119.0, 118.7, 114.8 (d, $J = 21.0$

Hz), 109.5, 49.9, 41.8, 39.2, 32.0, 19.5, 13.2; HRMS (ESI) m/z $C_{37}H_{39}FN_8Na$ ($M+Na$)⁺ calcd 637.3179, found 637.3179.

3,3'-(4-methoxyphenylmethylene)-bis-indole-((1-buthyl-1,2,3-triazol-4-yl)methyl) 4v: 41 % yield (0.1278 g) as an orange solid; m.p. 80-81 °C; R_f = 0.20 (50% EtOAc/*n*-Hexane); IR (KBr): 3134, 3053, 2926, 2853, 1610, 1509, 1465, 1332, 1247, 741 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, J = 8.0 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 7.23 (d, J = 8.4 Hz, 2H), 7.16 (t, J = 7.2 Hz, 2H), 7.06 (s, 2H), 6.98 (t, J = 7.6 Hz, 2H), 6.81 (d, J = 8.4 Hz, 2H), 6.64 (s, 2H), 5.82 (s, 1H), 5.33 (brs, 2H), 5.32 (brs, 2H), 4.22 (t, J = 7.6 Hz, 4H), 3.78 (s, 3H), 1.78 (quin, J = 7.6 Hz, 4H), 1.28 (sex, J = 7.6 Hz, 4H), 0.91 (t, J = 7.6 Hz, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 157.9, 144.8, 136.7, 135.9, 129.5, 127.7, 127.2, 121.8, 121.3, 120.1, 119.4, 119.0, 113.6, 109.5, 55.2, 50.1, 42.1, 39.2, 32.1, 19.6, 13.4; HRMS (ESI) m/z $C_{38}H_{42}N_8ONa$ ($M+Na$)⁺ calcd 649.3379, found 649.3383.

3,3'-(phenylmethylene)-bis-indole-((1-octhyl-1,2,3-triazol-4-yl)methyl) 4w: 76 % yield (0.2695 g) as a red oil; R_f = 0.27 (40% EtOAc/*n*-Hexane); IR (KBr): 3133, 3056, 2927, 2856, 1613, 1493, 1466, 1333, 741 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, J = 7.6 Hz, 2H), 7.33 (d, J = 8.0 Hz, 4H), 7.29-7.21 (m, 3H), 7.16 (t, J = 7.6 Hz, 2H), 7.06 (s, 2H), 6.98 (t, J = 7.2 Hz, 2H), 6.65 (s, 2H), 5.87 (s, 1H), 5.33 (s, 4H), 4.21 (t, J = 7.2 Hz, 4H), 1.83-1.78 (m, 4H), 1.26-1.24 (m, 20H), 0.87 (t, J = 7.2 Hz, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 144.6, 143.6, 136.5, 128.5, 128.1, 127.6, 127.2, 126.1, 121.7, 121.3, 119.9, 118.9, 109.5, 50.2, 41.9, 40.0, 31.5, 30.0, 28.8, 28.7, 26.2, 22.4, 13.9; HRMS (ESI) m/z $C_{45}H_{56}N_8Na$ ($M+Na$)⁺ calcd 731.4526, found 731.4518.

3,3'-(4-fluorophenylmethylene)-bis-indole-((1-octhyl-1,2,3-triazol-4-yl)methyl) 4y: 81 % yield (0.2372 g) as a red oil; R_f = 0.34 (40% EtOAc/*n*-Hexane); IR (KBr): 3133, 3054, 2927, 2856, 1602, 1506, 1466, 1333, 1221, 741 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, J = 8.4 Hz, 4H), 7.29-7.27 (m, 2H), 7.17 (t, J = 7.2 Hz, 2H), 7.09 (s, 2H), 7.00 (t, J = 7.2 Hz, 2H), 6.95

(t, $J = 8.4$ Hz, 2H), 6.64 (s, 2H), 5.85 (s, 1H), 5.33 (brs, 4H), 4.21 (t, $J = 7.2$ Hz, 4H), 1.84-1.78 (m, 4H), 1.26-1.24 (m, 20H), 0.87 (t, $J = 7.2$ Hz, 6H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 161.3 (d, $J = 243.0$ Hz), 144.6, 139.4 (d, $J = 3.0$ Hz), 136.6, 129.9 (d, $J = 8.0$ Hz), 127.5, 127.2, 121.8, 121.4, 119.9, 119.0, 118.8, 114.9 (d, $J = 21.0$ Hz), 109.6, 50.3, 42.0, 39.3, 31.6, 30.1, 28.9, 28.8, 26.3, 22.5, 14.0; HRMS (ESI) m/z $\text{C}_{45}\text{H}_{55}\text{FN}_8\text{Na}$ ($\text{M}+\text{Na}$) $^+$ calcd 749.4431, found 749.4434.

3,3'-(4-chlorophenylmethylene)-bis-5-fluoro-indole-((1-benzyl-1,2,3-triazol-4-yl)methyl)

4z: 97 % yield (0.1419 g) as a pink solid; m.p. 133-135 °C; $R_f = 0.36$ (40% EtOAc/*n*-Hexane); IR (KBr): 3132, 3066, 2924, 2853, 1620, 1488, 1455, 1321, 1270, 796, 729 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.35-7.33 (m, 6H), 7.24-7.16 (m, 10H), 7.10 (s, 2H), 6.91-6.86 (m, 4H), 6.62 (s, 2H), 5.63 (s, 1H), 5.43 (s, 4H), 5.28 (s, 2H), 5.27 (s, 2H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 157.5 (d, $J = 233.0$ Hz), 144.8, 141.5, 134.4, 133.3, 132.1, 129.8, 129.0, 128.7, 128.7, 128.6, 127.9, 127.7 (d, $J = 9.0$ Hz), 121.5, 118.0 (d, $J = 5.0$ Hz), 110.5 (d, $J = 6.0$ Hz), 110.4 (d, $J = 23.0$ Hz), 104.7 (d, $J = 23.0$ Hz), 54.1, 42.2, 39.5; HRMS (ESI) m/z $\text{C}_{43}\text{H}_{33}\text{ClF}_2\text{N}_8\text{Na}$ ($\text{M}+\text{Na}$) $^+$ calcd 757.2382, found 757.2384.

3,3'-(4-chlorophenylmethylene)-bis-5-methoxy-indole-((1-benzyl-1,2,3-triazol-4-

yl)methyl) 4aa: 70 % yield (0.2667 g) as a pink solid; m.p. 133-135 °C; $R_f = 0.15$ (40% EtOAc/*n*-Hexane); IR (KBr): 3132, 3066, 2924, 2853, 1620, 1488, 1455, 1321, 1270, 796, 729 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.34-7.31 (m, 6H), 7.22 (d, $J = 8.8$ Hz, 2H), 7.20-7.16 (m, 8H), 7.09 (s, 2H), 6.82 (dd, $J = 8.8, 2.4$ Hz, 2H), 6.72 (dd, $J = 2.4$ Hz, 2H), 6.72 (s, 1H), 6.58 (s, 2H), 5.68 (s, 1H), 5.41 (s, 4H), 5.25 (s, 2H), 5.24 (s, 2H), 3.65 (s, 6H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 153.8, 145.2, 142.2, 134.5, 132.0, 131.8, 129.9, 129.0, 128.7, 128.4, 128.0, 127.9, 121.6, 117.8, 111.7, 110.4, 102.3, 55.9, 54.1, 42.2, 39.5; HRMS (ESI) m/z $\text{C}_{45}\text{H}_{39}\text{ClN}_8\text{O}_2\text{Na}$ ($\text{M}+\text{Na}$) $^+$ calcd 781.2782, found 781.2788.

3,3'-(4-chlorophenylmethylene)-bis-5-fluoro-indole-((1-octyl-1,2,3-triazol-4-yl)methyl)

4bb: 65 % yield (0.1008 g) as a yellow oil; R_f = 0.45 (40% EtOAc/*n*-Hexane); IR (KBr): 3135, 3080, 2927, 2856, 1623, 1488, 1456, 1321, 1182, 795, 736 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.29-7.22 (m, 6H), 7.11 (s, 2H), 6.92-6.88 (m, 4H), 6.67 (s, 2H), 5.67 (s, 1H), 5.34 (d, J = 16.0 Hz, 2H), 5.29 (d, J = 16.0 Hz, 2H), 4.24 (t, J = 7.2 Hz, 4H), 1.83-1.80 (m, 4H), 1.26-1.24 (m, 20H), 0.86 (t, J = 6.8 Hz, 6H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 157.5 (d, J = 234.0 Hz), 144.3, 141.5, 133.3, 132.1, 129.8, 128.7, 128.5, 127.7 (d, J = 9.0 Hz), 121.3, 117.9 (d, J = 5.0 Hz), 110.5 (d, J = 9.0 Hz), 110.3 (d, J = 26.0 Hz), 104.7 (d, J = 24.0 Hz), 50.4, 42.3, 39.6, 31.6, 30.1, 28.9, 28.8, 26.3, 22.5, 14.0; HRMS (ESI) m/z $\text{C}_{45}\text{H}_{53}\text{ClF}_2\text{N}_8\text{Na}$ ($\text{M}+\text{Na}$) $^+$ calcd 801.3947, found 801.3951.

3,3'-(4-chlorophenylmethylene)-bis-5-methoxy-indole-((1-octyl-1,2,3-triazol-4-yl)methyl)

4cc: 84 % yield (0.1340 g) as a pink solid; m.p. 142-143 $^\circ\text{C}$; R_f = 0.41 (40% EtOAc/*n*-Hexane); IR (KBr): 3133, 3080, 2927, 2855, 1621, 1488, 1452, 1318, 1217, 798, 734 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.26-7.23 (m, 6H), 7.10 (s, 2H), 6.83 (dd, J = 8.8, 2.0 Hz, 2H), 6.75 (d, J = 1.6 Hz, 2H), 6.62 (s, 2H), 5.71 (s, 1H), 5.29 (brs, 4H), 4.22 (t, J = 7.6 Hz, 4H), 3.68 (s, 6H), 1.82-1.79 (m, 4H), 1.26-1.24 (m, 20H), 0.87 (t, J = 6.8 Hz, 6H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 153.7, 144.6, 142.2, 132.0, 131.8, 129.9, 128.4, 128.0, 127.9, 121.3, 117.8, 111.6, 110.4, 102.3, 55.9, 50.3, 42.3, 39.6, 31.6, 30.2, 29.0, 28.8, 26.4, 22.5, 14.0; HRMS (ESI) m/z $\text{C}_{47}\text{H}_{59}\text{ClN}_8\text{O}_2\text{Na}$ ($\text{M}+\text{Na}$) $^+$ calcd 825.4347, found 825.4341.

3,3'-(4-chlorophenylmethylene)-bis-5-(1-benzyl-1,2,3-triazol-4-yl-methyl)-indole-((1-benzyl-1,2,3-triazol-4-yl)methyl)

5: According for general procedure of one-pot four-step, a stirred solution of indole **1d** (146.5 mg, 1.1 mmol) in CH_3CN (1 mL) was mixed with aldehyde **2a** (70.0 mg, 0.5 mmol). In the second step KOH (266.5 mg, 4.75 mmol) and propargyl bromide (0.2 mL, 2.5 mmol) was added at room temperature and the stirring was continued for 1 h, NaN_3 (162.5 mg, 2.5 mmol), benzyl bromide (0.3 mL, 2.5 mmol), CuI (66.6 mg, 0.35

mmol) and Et₃N (0.4 mL, 2.5 mmol) in final step. The crude product was purified by silica gel column chromatography (SiO₂, 40% EtOAc/*n*-Hexane as eluent) to give of product **5** as a brown solid (417.8 mg, 78%); m.p. 108-110 °C; *R_f* = 0.24 (40% EtOAc/*n*-Hexane); IR (KBr): 3137, 3064, 2924, 2853, 1619, 1487, 1456, 1329, 1195, 798, 729 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.41 (s, 2H), 7.33-7.30 (m, 12H), 7.24-7.19 (m, 6H), 7.17-7.13 (m, 10H), 6.83 (dd, *J* = 8.8, 2.0 Hz, 2H), 6.80 (d, *J* = 2.0 Hz, 2H), 6.58 (s, 2H), 5.62 (s, 1H), 5.45 (s, 4H), 5.37 (s, 4H), 5.23 (s, 4H), 4.98 (s, 4H); ¹³C{¹H} NMR (100 MHz, CDCl₃) δ 152.4, 144.9, 144.8, 142.1, 134.6, 134.6, 132.3, 131.7, 129.9, 129.0, 128.98, 128.7, 128.6, 128.4, 128.0, 127.9, 122.5, 121.7, 117.8, 112.4, 110.4, 104.0, 63.0, 54.1, 54.0, 42.1, 39.6; HRMS (ESI) *m/z* C₆₃H₅₃ClN₁₄O₂Na (M+Na)⁺ calcd 1095.4062, found 1095.4058.

General procedure for one-pot four-step compound 7: The first step, a stirred solution of indole **1a** (117.2 mg, 1.0 mmol) in CH₃CN (0.6 mL) was mixed with terephthalaldehyde **6** (26.8 mg, 0.2 mmol), I₂ powder (10.2 mg, 0.08 mmol) and H₂SO₄-SiO₂ (20 mg) at room temperature. TLC showed the conversion was complete. In the second step KOH (238.4 mg, 4.25 mmol) and propargyl bromide (0.1 mL, 1.3 mmol) was added at room temperature and the stirring was continued for 1 h. The reaction mixture was filtered to remove salt and the solvent of the filtrate was evaporated to dryness. The reaction mixture was redissolved in DMF (0.50 mL). A solution of NaN₃ (84.5 mg, 1.3 mmol) and benzyl bromide (0.2 mL, 1.3 mmol) in DMF (0.5 mL) was added while stirring at room temperature. Finally, CuI (30.5 mg, 0.16 mmol), Et₃N (0.2 mL, 1.3 mmol) and solution of benzyl azide was added and stirring was continued at room temperature for 1 h. After completion of the reaction it was quenched with saturated cool aqueous Na₂S₂O₃ (10 mL) and extracted with dichloromethane (3 x 10 mL). The organic phase was collected and washed with water (3 x 5 mL), then dried with anhydrous Na₂SO₄, filtered and evaporated in *vacuo*. The crude product was purified by silica gel column chromatography (SiO₂, 70% EtOAc/*n*-Hexane as eluent) to afford product **7** as a pink solid

(170.6 mg, 61%); m.p. 221-222 °C; R_f = 0.23 (70% EtOAc/*n*-Hexane); IR (KBr): 3131, 3056, 2923, 2851, 1699, 1497, 1465, 1333, 738 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.31-7.27 (m, 18H), 7.15-7.11 (m, 18H), 7.04 (s, 4H), 6.91 (t, J = 7.2 Hz, 4H), 6.60 (s, 4H), 5.79 (s, 2H), 5.34 (s, 8H), 5.27 (s, 8H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 144.9, 141.5, 136.4, 134.4, 128.8, 128.4, 128.4, 127.6, 127.6, 127.0, 121.6, 119.9, 119.0, 118.8, 109.5, 53.7, 41.7, 39.6; HRMS (ESI) m/z $\text{C}_{80}\text{H}_{66}\text{N}_{16}\text{Na}$ ($\text{M}+\text{Na}$) $^+$ calcd 1273.5554, found 1273.5542.

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ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website, which contains the ^1H and $^{13}\text{C}\{^1\text{H}\}$ NMR spectra for the synthesized compounds (PDF)

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NOTES

There are no conflicts to declare.

REFERENCES

- (1) (a) Keri, R. S.; Patil, S. A.; Budagumpi, S.; Nagaraja, B. M. Triazole: A Promising Antitubercular Agent. *Chem. Biol. Drug Des.* **2015**, *86*, 410-423. (b) Sheng, C.; Che, X.; Wang, W.; Wang, S.; Cao, Y.; Yao, J.; Miao, Z.; Zhang, W. Structure-based design, synthesis, and antifungal activity of new triazole derivatives. *Chem. Biol. Drug Des.* **2011**, *78*, 309-313. (c) Song, P.; Cui, F.; Li, N.; Xin, J.; Ma, Q.; Meng, X.; Wang, C.; Cao, Q.; Gu, Y.; Ke, Y.; Zhang, Q.; Liu, H. Synthesis, Cytotoxic Activity Evaluation of Novel 1,2,3-Triazole Linked Quinazoline Derivatives. *Chinese J. Chem.* **2017**, *35*, 1633-1639. (d) Kumar, P.; Renjitha, J.; Fathimath, Salfeena C. T.; Ashitha, K.T.; Keri, R. S.; Varughese, S.; Somappa, B. S. Antibacterial and antitubercular evaluation of dihydronaphthalenone-indole hybrid analogs. *Chem. Biol. Drug Des.* **2017**, *90*, 703-708.
- (2) (a) Kim, A.; Kim, M. J.; Noh, T. H.; Hong, J.; Liu, Y.; Wei, X.; Jung, J. H. Synthesis and antibacterial evaluation of hamacanthin B analogues. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 5013-5017. (b) Sigala, I.; Ganidis, G.; Thysiadis, S.; Zografos, A. L.; Giannakouros, T.; Sarli, V.; Nikolakaki, E. Lynamycin D an antimicrobial natural product affects splicing by inducing the expression of SR protein kinase 1. *Bioorg. Med. Chem. Lett.* **2017**, *25*, 1622-1629. (c) Yoo, M.; Choi, S. U.; Choi, K. Y.; Yon, G. H.; Chae, J. C.; Kim, D.; Zylstra, G. J.; Kim, E. Trisindoline synthesis and anticancer activity. *Biochem. Biophys. Res. Commun.* **2008**, *376*, 96-99.
- (3) Damodiran, M.; Muralidharan, D.; Perumal, P. T. Regioselective synthesis and biological evaluation of bis(indolyl)methane derivatized 1,4-disubstituted 1,2,3-bistriazoles as anti-infective agents. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3611-3614.
- (4) Danne, A. B.; Choudhari, A. S.; Chakraborty, S.; Sarkar, D.; Khedkar, V. M.; Shingate, B. B. Triazole-Diindolylmethane Conjugates as New Antitubercular Agents: Synthesis, Bioevaluation and Molecular Docking. *MedChemComm* **2018**, *9*, 1114-1130.
- (5) Minvielle, M. J.; Bunders, C. A.; Melander, C. Indole/triazole conjugates are selective inhibitors and inducers of bacterial biofilms. *MedChemComm* **2013**, *4*, 916-919.

- (6) Nagarsenkar, A.; Prajapati, S. K.; Guggilapu, S. D.; Birineni, S.; Sravanti Kotapalli, S.; Ummanni, R.; Babu, B. N. Investigation of triazole-linked indole and oxindole glycoconjugates as potential anticancer agents: novel Akt/PKB signaling pathway inhibitors. *MedChemComm* **2016**, *7*, 646-653.
- (7) Narsimha, S.; Satheesh Kumar, N.; Kumara Swamy, B.; Vasudeva Reddy, N.; Althaf Hussain, S. K.; Srinivasa Rao, M. Indole-2-carboxylic acid derived mono and bis 1,4-disubstituted 1,2,3-triazoles: Synthesis, characterization and evaluation of anticancer, antibacterial, and DNA-cleavage activities. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 1639-1644.
- (8) Rajan, S.; Puri, S.; Kumar, D.; Babu, M. H.; Shankar, K.; Varshney, S.; Srivastava, A.; Gupta, A.; Reddy, M. S.; Gaikwad, A. N. Novel indole and triazole based hybrid molecules exhibit potent anti-adipogenic and antidyslipidemic activity by activating Wnt3a/beta-catenin pathway. *Eur. J. Med. Chem.* **2018**, *143*, 1345-1360.
- (9) (a) Pore, D. M.; Desai, U. V.; Thopate, T. S.; Wadgaonkar, P. P. A mild, expedient, solventless synthesis of bis(indolyl)alkanes using silica sulfuric acid as a reusable catalyst. *Arkivoc* **2006**, *2006*, 75-80. (b) Ramesh, C.; Banerjee, J.; Pal, R.; Das, B. Silica Supported Sodium Hydrogen Sulfate and Amberlyst-15: Two Efficient Heterogeneous Catalysts for Facile Synthesis of Bis- and Tris(1H-indol-3-yl)methanes from Indoles and Carbonyl Compounds. *Adv. Synth. Catal.* **2003**, *345*, 557-559. (c) Sashidhara, K. V.; Kumar, A.; Kumar, M.; Srivastava, A.; Puri, A. Synthesis and antihyperlipidemic activity of novel coumarin bisindole derivatives. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 6504-6507. (d) Shelke, G. M.; Rao, V. K.; Tiwari, R. K.; Chhikara, B. S.; Parang, K.; Kumar, A. Bismuth triflate-catalyzed condensation of indoles with acetone. *RSC Adv.* **2013**, *3*, 22346-22352. (e) Xia, M.; Wang, S. h.; Yuan, W. B. Lewis Acid Catalyzed Electrophilic Substitution of Indole with Aldehydes and Schiff's Bases Under Microwave Solvent-Free Irradiation. *Synth. Commun.* **2004**, *34*, 3175-3182.
- (10) Bénéteau, V.; Olmos, A.; Boningari, T.; Sommer, J.; Pale, P. Zeo-click synthesis: CuI-zeolite-catalyzed one-pot two-step synthesis of triazoles from halides and related compounds. *Tetrahedron Lett.* **2010**, *51*, 3673-3677.
- (11) Dururgkar, K. A.; Gonnade, R. G.; Ramana, C. V. A Cu(I)-promoted one-pot 'SNAr-click reaction' of fluoronitrobenzenes. *Tetrahedron* **2009**, *65*, 3974-3979.
- (12) Dutta, S.; Gupta, S. J.; Sen, A. K. Silver trifluoromethanesulfonate and metallic copper mediated syntheses of 1,2,3-triazole-O- and triazolyl glycoconjugates: consecutive

- glycosylation and cyclization under one-pot condition. *Tetrahedron Lett.* **2016**, *57*, 3086-3090.
- (13) Huang, Y.; Gard, G. L.; Shreeve, J. N. M. One-pot syntheses of 1,2,3-triazoles containing a pentafluorosulfanylalkyl group via click chemistry. *Tetrahedron Lett.* **2010**, *51*, 6951-6954.
- (14) Quan, Z.-J.; Xu, Q.; Zhang, Z.; Da, Y.-X.; Wang, X.-C. Copper-catalyzed click synthesis of functionalized 1,2,3-triazoles with 3,4-dihydropyrimidinone or amide group via a one-pot four-component reaction. *Tetrahedron* **2013**, *69*, 881-887.
- (15) Alonso, F.; Moglie, Y.; Radivoy, G.; Yus, M. Alkenes as azido precursors for the one-pot synthesis of 1,2,3-triazoles catalyzed by copper nanoparticles on activated carbon. *J. Org. Chem.* **2013**, *78*, 5031-5037.
- (16) Huang, S. M.; Hsu, P. C.; Chen, M. Y.; Li, W. S.; More, S. V.; Lu, K. T.; Wang, Y. C. The novel indole compound SK228 induces apoptosis and FAK/Paxillin disruption in tumor cell lines and inhibits growth of tumor graft in the nude mouse. *Int. J. Cancer* **2012**, *131*, 722-732.
- (17) Li, W. S.; Wang, C. H.; Ko, S.; Chang, T. T.; Jen, Y. C.; Yao, C. F.; More, S. V.; Jao, S. C. Synthesis and evaluation of the cytotoxicities of tetraindoles: observation that the 5-hydroxy tetraindole (SK228) induces G(2) arrest and apoptosis in human breast cancer cells. *J. Med. Chem.* **2012**, *55*, 1583-1592.
- (18) Silveira, C. C.; Mendes, S. R.; Villetti, M. A.; Back, D. F.; Kaufman, T. S. CeIII-promoted oxidation. Efficient aerobic one-pot eco-friendly synthesis of oxidized bis(indol-3-yl)methanes and cyclic tetra(indolyl)dimethanes. *Green Chem.* **2012**, *14*, 2912-2921.
- (19) Roy, B.; Mukhopadhyay, B. Sulfuric acid immobilized on silica: an excellent catalyst for Fischer type glycosylation. *Tetrahedron Lett.* **2007**, *48*, 3783-3787.