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Facile synthesis of novel bistriazolonaphthalenes *via* click chemistry

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ABSTRACT

A series of novel 1,2,3-triazole linked naphthols were prepared in excellent yields via regioselective and efficient copper(I)-catalyzed 1,3-dipolar cycloaddition of naphtholpropargylic ester with bisalkylazides. Structures of all the new synthesized compounds were characterized by ^{1}H NMR, ^{13}C NMR, IR and mass spectra.

Keywords: Naphtholpropargylicester, bisalkylazides, 1,3-dipolar cycloaddition, regioselective, bistriazolonaphthalenes

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INTRODUCTION

The chemistry of triazoles has received considerable attention in recent years due to their wide range of biological activities. Triazole derivatives are known to exhibit various pharmacological properties such as antimicrobial [1], anti-inflammatory [2], cytotoxic [3], anticonvulsant [4], analgesic [5] and antiviral [6]. Triazoles have also been incorporated in a wide variety of therapeutically interesting drugs including H1/H2 histamine receptor and antimycotic drugs like fluconazole, itraconazole and voriconazole. On the other hand, heterocycles containing the naphthol nucleus also exhibit various biological activities. For instance 2-naphthol derivatives have been reported as potential cognition enhancers [7]. 2-Substituted-1-naphthol derivatives were shown to inhibit the activities of cyclooxygenase and 5-lipooxygenase. 1-Naphthol derivatives were found to possess potent antiamnesic activity. The pharmacological importance of both triazoles and naphthol moiety has promoted us to synthesize a series of novel naphthalene derivatives containing a 1,2,3-triazole ring with enhanced biological significance. To the best of our knowledge there is no report on the synthesis of trizole using naphthol skeleton as chemical backbone. The synthetic route utilized the “click reaction” which is Cu(I) catalyzed [3+2] cycloaddition popularized by Sharpless and Meldal as the key transformation to build up the triazole ring [8, 9]. Click chemistry consists of a set of powerful, highly reliable and selective reaction conditions and simple workup [10]. Herein, we report the facile regioselective synthesis of a series of 12 naphthol based triazoles employing click reaction.

MATERIALS AND METHODS

General: The reagents and solvents were of analytical grade and were used without further purification unless otherwise mentioned. Thin layer chromatography (TLC) was carried out on aluminum sheets coated with silica gel 60 F254 (Merck). TLC plates were inspected under UV light. Micro-analytical data were obtained by employing a Perkin-Elmer 240c analyzer. IR spectra (KBr pellets) were recorded with a Perkin-Elmer-1700 spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were measured on a Varian INOVA-500 spectrometer. The following abbreviations have been used to explain the observed multiplicities: s, singlet; d, doublet; t, triplet; m, multiplet. Coupling constants have been assigned and listed without duplication in the ^{1}H NMR description of the synthesized compounds. Electron spray-mass spectra were recorded on an LCQ system (Finngan MAT, USA) using methanol as the mobile phase. Melting points were recorded on a Polmon MP 96.

General procedure for the synthesis of bisazides (II_{a-f})
Dissolve one equivalent of terminal dibromoalkane **(I_{a-f})** and four equivalents of sodium azide in DMF and stir the reaction mixture at 80°C for 6h. After completion of the reaction as indicated by the disappearance of starting compounds on TLC, remove the DMF in vacuo and add ice cold water. This upon extraction with chloroform yields the pure compound.

1,8-diazidooctane (II_f)
BP: 215°C; ^{1}H NMR (400MHz, $CDCl_3$): δ 1.40 (m, 8H), 1.63 (m, 4H), 3.27 (t, 4H, *J* = 7.2Hz).

General procedure for the synthesis of naphtholpropargylicesters (V_{1-2})
To a solution of α-naphthol **(III_1)** or 4-methoxy naphthol **(III_2)** (0.01 mol) taken in DMF (10 mL), K_2CO_3 (0.02 mol) and propargylbromide **(IV)** (0.013 mol) were added. The resulting solution was stirred at 80°C for 6h. After completion of the reaction as indicated by TLC, DMF was removed in vacuo and water was added. The resulting product was extracted with $CHCl_3$ (3×20 mL). The solvent was concentrated under reduced pressure. The crude product was purified by column chromatography using hexane:ethylacetate (8:2) as eluent to afford the pure compound.

1-(Prop-2-ynyloxy)naphthalene (V_1)
BP: 198°C; IR (KBr, cm^{-1}): 3055, 2919, 2123, 1628, 1580, 1508, 1462, 1401, 1368, 1271, 1234, 1157, 1098, 1069; ^{1}H NMR (400MHz, $CDCl_3$): *δ* 2.50 (t, 1H, *J* = 2.4Hz), 4.82 (d, 2H, *J* = 2.4 Hz), 6.88 (d, 1H, *J* = 7.6Hz), 7.35 (t, 1H, *J* = 7.6 Hz), 7.47 (m, 3H), 7.77 (m, 1H), 7.28 (m, 1H); ^{13}C NMR (400MHz, DMSO-d_6): 56.2, 75.8, 77.0, 77.3, 77.6, 78.8, 105.6, 121.3, 122.2, 126.7, 127.6, 134.7, 153.4; Mass (ES): *m/z* 182[M]$^+$, 183[M+H]$^+$.

1-Methoxy-4-(prop-2-ynyloxy)naphthalene (V_2)
MP: 68-70°C; IR (KBr, cm^{-1}): 3068, 2933, 2129, 1628, 1593, 1468, 1391, 1365, 1274, 1239, 1154, 1096, 1020; ^{1}H NMR (400MHz, DMSO-d_6): *δ* 2.53 (t, 1H, *J* = 2.4Hz), 3.96 (s, 3H), 4.84 (d, 2H, *J* = 2.4Hz), 6.71 (d, 1H, *J* = 8.4Hz), 6.87 (d, 1H, *J* = 8.4Hz), 7.52 (m, 2H), 8.22 (m, 2H); ^{13}C NMR (400MHz, $CDCl_3$): 55.7, 56.6, 75.3, 76.7, 79.0, 102.8, 105.7, 121.8, 125.9, 126.1, 126.3, 126.5, 147.3, 150.2. Mass (ES): *m/z* 212 [M]$^+$, 213[M+H]$^+$.

General experimental procedure for the synthesis of bisnaphthalotriazoles (VI_{1-2a-f})
Compound **V_{1-2}** (2 mmol) and bisazides **(II_{a-f})** (1 mmol) were dissolved in 10 mL of DMF. To this mixture, aqueous solutions of $CuSO_4.5H_2O$ (25mg, 0.1 mmol) and sodium ascorbate (39mg, 0.2 mmol) were added and stirred at 80°C for appropriate time (table 1). The reaction mixture was poured into 25 mL of water and was extracted with $CHCl_3$ (3×25mL). The organic layers were combined washed with water (20 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated in vacuo to give the crude product. The crude product was purified by column chromatography using hexane:ethylacetate (9:1% to 6:4%) as eluent to afford the pure product.

1,2-Bis(4((naphthalen-1-yloxy)methyl)-1H-1,2,3-triazol-1-yl)ethane (VI_{1-a})
MP: 180-182°C; IR (KBr, cm^{-1}): 3055, 2921, 1628, 1579, 1507, 1461, 1400, 1367, 1269, 1233, 1157, 1098, 1069; ^{1}H NMR (400MHz, DMSO-d_6): *δ* 4.56 (s, 4H), 5.24 (s, 4H), 6.95 (d, 2H, *J* = 7.6Hz), 7.48 (m, 10H), 7.81 (m, 2H), 8.28 (m, 2H); ^{13}C NMR (400MHz, DMSO-d_6): 56.3, 78.8, 79.6, 106.5, 121.8,121.9, 125.1, 125.3, 125.7, 126.5, 126.9, 127.9, 143.4, 153.0; Mass (ES): *m/z* 476 [M]$^+$, 477 [M+H]$^+$.

1,3-Bis(4-((naphthalen-1-yloxy)methyl)-1H1,2,3,-triazol-1-yl)propane (VI_{1-b})
MP: 166-168°C; IR (KBr, cm^{-1}): 3057, 2925, 1579, 1461, 1395, 1268, 1237, 1155, 1097, 1068, 1020;^{1}H NMR (400MHz, DMSO-d_6): *δ* 2.23 (m, 2H), 4.40 (t, 2H, *J* = 6.4Hz), 4.49 (t, 2H, *J* = 6.8Hz), 5.40 (s, 2H), 5.42 (s, 2H), 6.97 (td, 2H, J^1= 4.4Hz, *J* = 4.8Hz), 7.40 (tt, 4H, J^1 = 2.4Hz, *J* = 7.6Hz), 7.48 (m, 4H), 7.68 (s, 2H), 7.81 (t, 2H, *J* = 6.8Hz), 8.25 (dd, 2H);^{13}C NMR (400MHz, DMSO-d_6): 30.1, 46.8, 61.7, 79.1, 105.7, 120.3, 121.5, 124.8, 125.2, 125.9, 126.4, 127.4, 127.4, 142.9, 153.4; Mass (ES): *m/z* 490 [M]$^+$, 491 [M+H]$^+$.

1,4-Bis(4((naphthalene-1-yloxy)methyl)-1H-1,2,3-triazol-1yl)butane (VI_{1-c})
MP:78-80°C; IR (KBr, cm^{-1}): 3086, 2942, 2871, 1673, 1630, 1580, 1509, 1459, 1393, 1271, 1342, 1157, 1101, 1057; ^{1}H NMR (400MHz, DMSO-d_6): δ 2.07 (m, 4H), 4.43 (t, 4H, *J* = 7.2), 5.42 (s, 4H), 6.97 (d, 2H, *J* = 7.6, 7.39 (t, 4H, *J* = 7.6, 7.48 (m, 4H), 7.67 (s, 2H), 7.81 (d, 2H, *J* = 7.6), 8.26 (d, 2H, *J* = 7.6); ^{13}C NMR (400MHz, DMSO-d_6): 27.3, 49.2, 62.2, 106.3, 120.7, 122.0, 124.9, 125.4, 125.7, 126.6, 126.9, 127.9, 134.5, 143.3, 153.9; Mass (ES): *m/z* 504[M]$^+$, 505[M+H]$^+$.

1,5-Bis(4((naphthalen-1-yloxy)methyl)-1H-1,2,3-triazol-1-yl)pentane (VI_{1-d})
MP: 178-180°C; IR (KBr, cm^{-1}): 3057, 2945, 1674, 1628, 1578, 1507, 1461, 1395, 1268, 1237, 1177, 1154, 1097, 1052, ^{1}H NMR (400MHz, DMSO-d_6): *δ* 1.97 (m, 6H), 4.31 (t, 4H, *J* = 6.8Hz), 5.37 (s, 4H), 6.94 (d, 2H, *J* = 7.6Hz),

7.49 (m, 7H), 7.59 (s, 2H), 7.79 (d, 2H *J* = 7.2Hz), 7.99 (s, 1H), 8.24 (d, 2H, *J* = 7.2Hz); ^{13}C NMR (400MHz, DMSO-d_6): 23.2, 29.5, 49.6, 50.8, 62.2, 106.2, 120.7, 122.0, 124.8, 125.4, 125.7, 126.5, 126.9, 127.9, 143.2, 153.9; Mass (ES): *m/z* 518[M]$^+$, 519[M+H]$^+$.

1,6-Bis(4((naphthalene-1-yloxy)methyl)-1H-1,2,3-triazol-1yl)hexane (VI$_{1-e}$)
MP: 148-150^{o}C; IR (KBr, cm^{-1}): 3081, 2945, 1629, 1577, 1506, 1460, 1387, 1268, 1148, 1096, 1050; ^{1}H NMR (400MHz, DMSO-d_6): δ 1.34 (m, 8H), 4.34 (t, 4H, *J* = 7.2Hz), 5.40 (s, 4H), 6.96 (d, 2H, *J* = 7.6Hz), 7.38 (t, 4H, *J* = 7.6Hz), 7.44 (m, 4H), 7.61 (s, 2H), 7.79 (d, 2H, *J* = 7.6Hz), 8.25 (d, 2H, *J* = 7.6Hz); ^{13}C NMR (400MHz, DMSO-d_6): 25.1, 29.4, 50.4, 61.7, 105.8, 120.2, 121.5, 124.2, 124.9, 125.2, 126.0, 126.4, 127.4, 134.0, 142.7, 153.4; Mass (ES): *m/z* 532 [M]$^+$, 533 [M+H]$^+$, 534 [M+2]$^+$.

1,8-Bis(4-((naphthalen-1-yloxy)methyl)-1H-1,2,3-triazol-1-yl)octane (VI$_{1-f}$)
MP: 90-92^{o}C; IR (KBr, cm^{-1}): 3053, 2936, 1664, 1629, 1577, 1507, 1462, 1390, 1304, 1266, 1235, 1175, 1155, 1096, 1067, 1052; ^{1}H NMR (400MHz, DMSO-d_6): δ 1.23 (m, 8H), 1.81 (m, 4H), 4.36 (t, 4H, *J* = 6.4Hz), 5.33 (s, 4H), 7.18 (d, 2H, *J* = 7.2Hz), 7.52 (m, 8H), 7.87 (d, 2H, *J* = 8Hz), 8.12 (d, 2H, *J* = 7.6Hz), 8.34 (s, 2H); ^{13}C NMR (400MHz, DMSO-d_6): 30.9, 33.3, 34.8, 54.5, 61.1, 67.0, 111.0, 125.5, 126.7, 130.1, 130.5, 131.1, 131.6, 132.6, 139.2, 147.9, 158.7; Mass (ES): *m/z* 560 [M]$^+$, 561 [M+H]$^+$.

1,2-Bis(4-((4-methoxynaphthalen-1-yloxy)methyl)-1H-1,2,3-triazol-1-yl)ethane (VI$_{2-a}$)
MP: 163-165^{o}C; IR (KBr, cm^{-1}):3071, 2936, 1667, 1629, 1595, 1467, 1381, 1274, 1240, 1156, 1098, 1048; ^{1}H NMR (400MHz, DMSO-d_6): δ 3.91 (s, 6H), 4.96 (s, 4H), 5.21 (s, 4H), 6.85 (d, 2H, *J* = 8.8Hz), 7.02 (d, 2H, *J* = 8.4Hz), 7.53 (m, 4H), 8.10 (m, 4H), 8.19 (s, 2H); ^{13}C NMR (400MHz, DMSO-d_6): 54.3, 60.5, 67.0, 83.9, 108.2, 110.3, 126.5, 126.6, 129.4, 130.7, 130.7, 130.9, 148.4, 152.4, 154.2; Mass (ES): *m/z* 536 [M]$^+$, 537 [M+H]$^+$.

1,3-Bis(4-((4-methoxynaphthalen-1-yloxy)methyl)-1H-1,2,3-triazol-1-yl)propane(VI$_{2-b}$)
MP: 76-78^{o}C; IR (KBr, cm^{-1}): 3073, 2935, 1725, 1628, 1594, 1462, 1384, 1272, 1239, 1156, 1097;^{1}H NMR (400MHz, DMSO-d_6): δ 0.85 (m, 2H), 3.92 (s, 6H), 4.45 (s, 4H), 5.27 (s, 4H), 6.87 (d, 2H, *J* = 7.6Hz), 7.08 (d, 2H, *J* = 7.2Hz), 7.51 (m, 4H), 8.10 (s, 4H), 8.35 (s, 2H);^{13}C NMR (400MHz, DMSO-d_6): 35.4, 38.1, 52.0, 60.7, 62.6, 67.3, 108.7, 110.8, 126.6, 126.7, 129.6, 130.7, 130.9, 131.0, 152.5, 154.2; Mass (ES): *m/z* 550 [M]$^+$,551 [M+H]$^+$.

1,4-Bis(4-((4-methoxynaphthalen-1-yloxy)methyl)-1H-1,2,3-triazol-1-yl)butane(VI$_{2-c}$)
MP: 98-100^{o}C; IR (KBr, cm^{-1}): 3080, 2952, 1630, 1596, 1461, 1384, 1273, 1241, 1156, 1100;^{1}H NMR (400MHz, DMSO-d_6): δ 1.87 (m, 4H), 3.36 (s, 6H), 4.43 (s, 4H), 5.26 (s, 4H), 6.86 (d, 2H, *J* = 8.4Hz), 7.06 (d, 2H, *J* = 8.4Hz), 7.53 (m, 4H), 8.11 (m, 4H), 8.30 (s, 2H);^{13}C NMR (400MHz, DMSO-d_6): 32.0, 53.9, 60.7, 67.2, 84.3, 108.9, 110.9, 126.6, 126.7, 129.6, 130.7, 130.9, 131.1, 131.1, 152.5, 154.1; Mass (ES): *m/z* 564 [M]$^+$, 565 [M+H]$^+$.

1,5-Bis(4-((4-methoxynaphthalen-1-yloxy)methyl)-1H-1,2,3-triazol-1-yl)pentane (VI$_{2-d}$)
MP: 120-122^{o}C; IR (KBr, cm^{-1}): 2939, 1627, 1593, 1461, 1384, 1271, 1237, 1156, 1096, 1050; ^{1}H NMR (400MHz, DMSO-d_6): δ 1.56 (m, 2H), 1.89 (m, 4H), 3.92 (s, 6H), 4.41 (m, 4H), 5.25 (s, 4H), 6.87 (m, 2H), 7.08 (m, 2H), 7.52 (t, 4H, *J* = 2Hz), 8.11 (m, 4H), 8.32 (d, 2H, *J* = 8.8Hz); ^{13}C NMR (400MHz, DMSO-d_6): 28.3, 32.9, 34.2, 54.4, 55.7, 60.5, 67.3, 108.3, 110.5, 126.5, 126.7, 130.7, 130.7, 130.8, 131.0, 152.5, 154.2; Mass (ES): *m/z* 578 [M]$^+$, 579 [M+H]$^+$.

1,6-Bis(4-((4-methoxynaphthalen-1-yloxy)methyl)-1H-1,2,3-triazol-1-yl)hexane (VI$_{2-e}$)
MP: 148-149^{o}C; IR (KBr, cm^{-1}): 3073, 2928, 2094, 1660, 1630, 1595, 1465, 1388, 1273, 1241, 1157, 1101, 1090, 1046; ^{1}H NMR (400MHz, DMSO-d_6): δ 1.42 (m, 4H), 1.63 (m, 4H), 3.96 (s, 6H), 4.39 (m, 4H), 5.36 (s, 4H), 6.70 (m, 2H), 6.87 (m, 2H), 7.26 (s, 2H), 7.51 (m, 4H), 8.22 (m, 4H); ^{13}C NMR (400MHz, DMSO-d_6): 25.6, 26.1, 28.6, 29.9, 49.7, 50.9, 56.0, 62.6, 104.2, 106.3, 121.8, 122.0, 125.9, 126.2, 126.3, 147.8, 149.4; Mass (ES): *m/z* 592 [M]$^+$, 593 [M+H]$^+$.

1,8-Bis(4-((4-methoxynaphthalen-1-yloxy)methyl)-1H-1,2,3-triazol-1-yl)octane (VI$_{2-f}$)
MP: 138-140^{o}C; IR (KBr, cm^{-1}): 3057, 2933, 2854, 1699, 1656, 1590, 1463, 1387, 1345, 1271, 1237, 1156, 1098, 1079; ^{1}H NMR (400MHz, DMSO-d_6): δ 1.22 (m, 8H), 1.80 (m, 4H), 3.91 (s, 6H), 4.35 (s, 4H), 5.26 (s, 4H), 6.86 (d, 2H, *J* = 8Hz), 7.07 (d, 2H, *J* = 8Hz), 7.51 (s, 4H), 8.09 (s, 4H), 8.29 (s, 2H); ^{13}C NMR (400MHz, DMSO-d_6): 30.9, 33.3, 34.8, 54.7, 60.4, 67.2, 108.2, 110.4, 126.4, 126.6, 126.6, 130.7, 130.7, 130.8, 130.9, 131.0, 152.5, 154.2; Mass (ES): *m/z* 620 [M]$^+$, 621 [M+H]$^+$.

RESULTS AND DISCUSSION

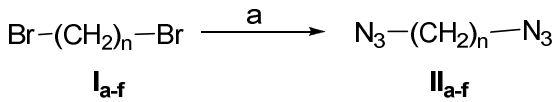
The present investigation focuses on the development of a few triazolonaphthalenes starting from naphthols. The regioselective synthesis of 1,2,3-triazolo naphthalenes involves 3 steps 1) Synthesis of bisalkylazides (Scheme-I), 2) propargylation of naphthols, 3) click reaction of propargylated naphthols with bisalkylazides (Scheme-II).

Table-I. List of compounds obtained by the reaction of propargylicnaphtholesters (V_{1-2}) with various bisalkylazides (II_{a-f})

S.No	Compound	R	n	Time (h)	Yield (%)
1	**VI_{1-a}**	H	2	3.5	72
2	**VI_{1-b}**	H	3	7.0	82
3	**VI_{1-c}**	H	4	6.5	79
4	**VI_{1-d}**	H	5	9.0	81
5	**VI_{1-e}**	H	6	9.5	92
6	**VI_{1-f}**	H	8	10.0	90
7	**VI_{2-a}**	OCH_3	2	4.5	79
8	**VI_{2-b}**	OCH_3	3	5.0	81
9	**VI_{2-c}**	OCH_3	4	6.5	69
10	**VI_{2-d}**	OCH_3	5	10.5	78
11	**VI_{2-e}**	OCH_3	6	7.0	72
12	**VI_{2-f}**	OCH_3	8	6.5	92

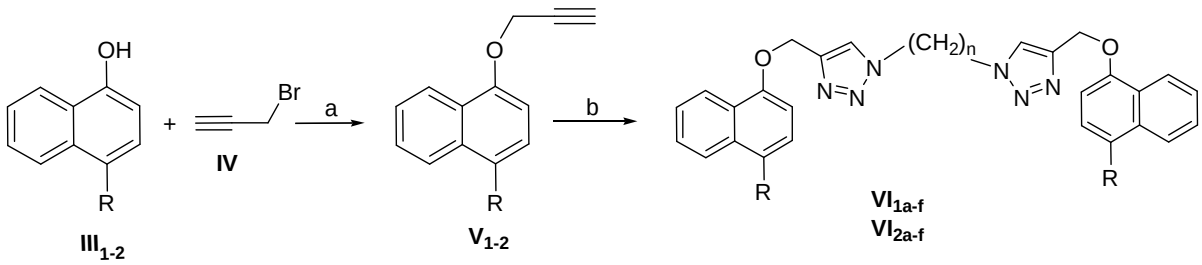
Bisalkylazides **(II_{a-f})** were freshly generated by the reaction of dibromoalkane **(I_{a-f})** with sodium azide in DMF in good yields. Schematic representation of this is shown in scheme-I. Naphthols **(III_{1-2})** on reaction with propargyl bromide **(IV)** in presence of K_2CO_3 provided propargylnaphtholesters **(V_{1-2})**. The structure of compound V_1 and V_2were confirmed by appearance of propargylic and terminal alkyne protons at δ 4.82, 4.84, and 2.50, 2.53 respectively, in the ^{1}H NMR spectrum. The IR spectra of these compounds exhibited a new weak absorption maximum at around 2100 cm^{-1} characteristic of $\upsilon_{c\equiv c}$, indicating the formation of propargylicesters.

Scheme I: Synthesis of bis alkyl azides (II_{a-f})



*Reagents and conditions: a = NaN_3, DMF, 80°C; Where n = 2-**a**, 3-**b**, 4-**c**, 5-**d**, 6-**e**, 8-**f**.*

Scheme II: Synthesis of bisnaphtholotriazoles ($VI_{1-2-a-f}$)



*Reagents and conditions: a = K_2CO_3, DMF, 80°C, 24h.; b= $N_3(CH_2)_nN_3$ $CuSO_4.5H_2O$, sodium ascorbate, DMF, 80°C, 24h; Where R = H-1, R = OCH_3-2; n - **a** -2, **b** -3, **c** - 4, **d** -5, **e** - 6, **f** – 8.*

The third step of the synthesis was the click reaction propargylicesters of naphthalenes **(V_1**and **V_2)** react with bisalkylazides **(II_{a-f})** in presence of aq. $CuSO_4.5H_2O$ and sodium ascorbate in DMF to give 1,2,3-triazolonaphthalenes **(VI_{1-2a-f})** in excellent yields as shown in scheme-II. The formation of triazole ring was unequivocally established by characteristic chemical shift value of the triazolyl proton which resonated between δ 8.19-8.34 ppm. Reaction time and respective yield of the synthesized triazolonaphthalene are depicted in Table-I.

CONCLUSION

In summary, we report a short and convenient synthesis of novel bis 1,2,3-triazolonaphthalesters using the Cu(I)-catalyzed alkyne-azide cycloaddition reaction. These products are under investigation for their biological activities.

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