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Synthesis and antibacterial activity studies of 6-methoxyquinazoline-triazole hybrid derivatives

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Abstract: The Click reaction between the electronically divergent triazole compounds 4-((l-(4-(*tert*-butyl)benzyl)-*1H*-l,2,3-triazol-4-yl)methoxy)-5-methoxy-2-nitrobenzamides (**8a-e**) with different aldehydes using $Na_2S_2O_4$ in DMSO was performed to obtain hybrid of quinazolinone-triazole derivatives (**10a-o**). All the synthesized compounds were fully characterized on the basis of their detailed spectral studies and screened for their antibacterial activities strains using paper disc method. The compounds (**10 a-o**) were evaluated for their antibacterial activity against human pathogenic organism *Escherichia Coli*, *Staphylococcus aureus* (**Table 1**). The investigation of antibacterial screening data reveal that **10e**, **10f**, **10g**, **10j** and **10n** were highly active against E. *coli*, where as **10b**, **10d**, **10j, 10k** and **10o** showed least activity. Compounds **10b**, **10e**, **10f**, **10g**, **10i**, **10k** and **10n** showed high activity against S. *aureus*, where as compounds **10d**, **10j**, **10o** showed least activity. Compounds **10c**, **10h**, **10l** and **10o** were inactive against both organisms employed.

Key words: The Click reaction; methoxyquinazolinone-triazole; reductive cyclization.

1. Introduction

Quinazolinone derivatives widely occur in natural products, and they show a diverse range of useful biological and pharmacological activities[1-2]. The quinazolinone derivatives exhibit many central nervous system (CNS) effects, such as analgesic, anti-parkinsonian, CNS depressant, and CNS stimulant activities; they also act as psychotropic, hypnotic, cardiotonic, and antihistamine agents and possess cardiovascular activity (including antihypertensive, antiarrhymic, vasodilatory, and lipid-lowering effects) and antiinflammatory activity (including inhibition of cyclooxygenase activity and leukocyte function)[3-4]. They are also potent antibacterial, antifungal, antiviral, antimycobacterial, and antimalarial agents and possess anthelmintic activity. Quinazolinone derivatives are used as inhibitors of various enzymes, and these enzymes include monoamine oxidase, aldose reductase, tumor necrosis

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factor R, and thymidylate synthase[5-7]. Therefore, they are interesting as structural scaffolds and have been assigned as privileged structures in drug development.

Triazole compounds contain three nitrogen atoms in the five-membered aromatic azole ring. They are readily able to bind with a variety of enzymes, and receptors in biological system *via* diverse non-covalent interactions, and thus display versatile biological activities. The related research in triazole-based derivatives as medicinal drugs has been an extremely active topic, and numerous excellent achievements have been acquired[8-9]. Triazole compounds have an importance as medicinal drugs, including antifungal, anticancer, antibacterial, antitubercular, antiviral, anti-inflammatory and analgesic, anticonvulsant, antiparasitic, antidiabetic, anti-obesitic, antihistaminic, anti-neuropathic, and antihypertensive as well as other biological activities[10-11].

Molecular hybridization is a novel inception in drug design and development based on the combination of pharmacophoric moieties of different biologically active compounds to produce a new hybrid system with improved affinity and efficacy, when compared to the parent drugs[12-14]. Additionally, this strategy can result in compounds presenting modified selectivity profile, different and/or dual modes of action and reduced undesired side effects. In chemical synthesis, click chemistry is generating substances quickly and reliably by joining small units together[15]. Click chemistry is not a single specific reaction, but describes a way of generating products that follows examples in nature, which also generates substances by joining small modular units. So, in this paper, we described new innovative hybrid compounds through click chemistry, exhibiting anti-bacterial properties.

As part of our continuous interest in developing novel routes for C-C and C-hetero bond formations for the construction of divergent heterocycles[16-21], herein we demonstrate a clean and convenient click reaction between the electronically divergent triazole compounds 4-((l-(4-(*tert*-butyl)benzyl)-*1H*-l,2,3-triazol-4-yl)methoxy)-5-methoxy-2-nitrobenzamides (**8a-e**) with different aldehydes using $Na_2S_2O_4$ in DMSO to obtain hybrid of quinazolinone-triazole derivatives (**10a-o**).

2. Results and discussion

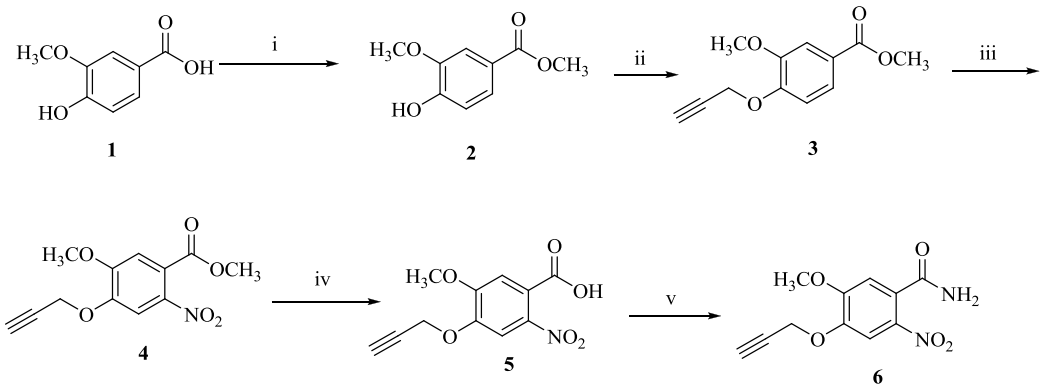
We have successfully synthesized fifteen novel compounds (**10a-o**) in good yields *via* preparation of 4-((l-(4-(*tert*-butyl) benzyl)-*1H*-l,2,3-triazol-4-yl) methoxy)-5-methoxy-2-nitrobenzamide (**8a-e**) by employing the reaction sequences shown in both **Figure 1** and **2**.

Esterification of vanillic acid **1** was carried out by using catalytic amount of concentrated H_2SO_4 in methanol at reflux temperature to obtain methyl vanilate **2** which was converted to propargyl ether **3** in 85% yield by treating with propargyl bromide and K_2CO_3 in acetone at reflux temperature for 6h. Compound **3** was nitrated by using conc. HNO_3 at -5 °C for 3 h affording the corresponding nitro ester **4** in 90% yield as a yellow solid (**Figure 1**). Hydrolysis of this nitro ester was carried out by using 10% aqueous NaOH solution in THF and water which gave acid **5** in 95% yield as a pale yellow solid. The resulting acid was converted to its acid chloride by refluxing in thionyl chloride. After removal of excess thionyl chloride, the obtained acid chloride was treated with aqueous ammonia solution at 0 °C afforded amide **6** in 85% yield as a white solid.

The reaction sequence employed for the synthesis of title compounds is shown in (**Figure 2**). The Click reaction of the azide compound **7** and *O*-propargylated 2-nitrobenzamide **6** was carried out by using $CuSO_4.5H_2O$ and sodium ascorbate in *tert*-butanol, THF and water as a solvent at room temperature for 8 h afforded triazole compound **8** in 80% yield. The structure of the key intermediates (**8a-e**) was well established from their spectral data. For compound **8a**, IR spectrum showed charteristic $–NO_2$ asymmetric and symmetric stretching around at 1574, 1485 and 1345, 1268 cm^{-1} respectively. Carbonyl amide appeared at 1697 cm^{-1} as can be understood from IR spectrum. Characteristic olefinic próton from triazole group appeared at 7.43 (s, 1H) and benzylic and *O*-methylene prótons appeared at 5.53 (s, 2H) and 5.27 (s, 2H), respectively from NMR studies. ESI mass of **8a** showed *m/z*= 440 corresponding to (M^++H).

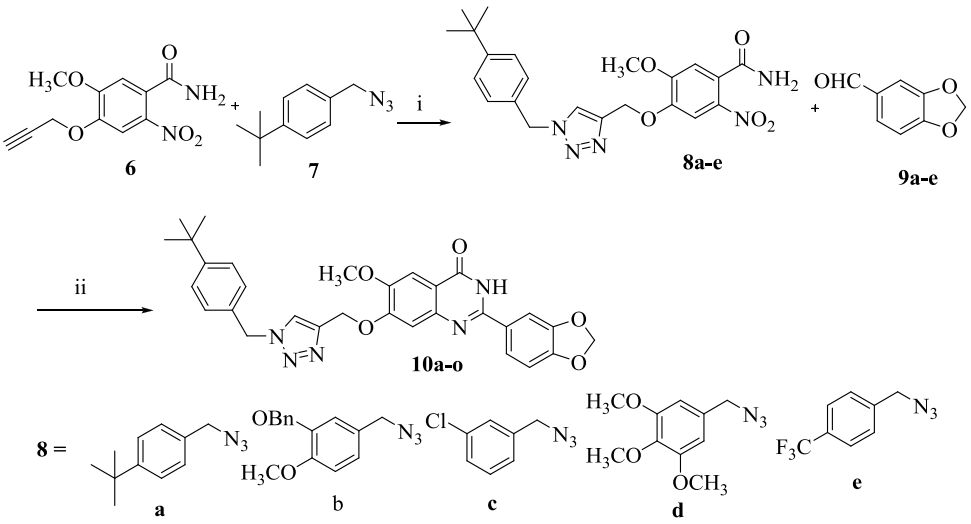
The stirred solution of triazole of 2-nitrobenzamide was reacted with different aldehydes by using $Na_2S_2O_4$ in DMSO at 100 °C for 3-4 hours to afford hybrid of quinazolinone-triazoles **10** (**a-o**) in 75-85% yields (**Table-1**). For compound **10a**, aromatic characteristic IR stretching appeared at 3041

cm^{-1} and amide stretching at 1677 cm^{-1}. ESI mass of **10a** showed *m/z*= 540 corresponding to (M^{+}+H). Cyclization of quinazolinone ring is confirmed by the disappearance of aldehydic proton as confirmed from TLC and NMR spectra.



Reagents and conditions: (i) MeOH, cat. Cone. H2SO4, reflux, 8 h, 95%(ii) propargyl bromide, K2CO3, acetone, reflux, 6 h, 85% (iii) cone. HNO3, -5 °C, 90% (iv) THF:H2O, 10% NaOH, 6 h, r.t., 95% (v) (a) SOC12, reflux, 2 h (b) aqueous ammonia sol. THF, 0 °C to r.t. 85%.

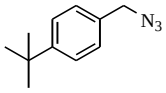
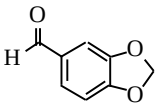
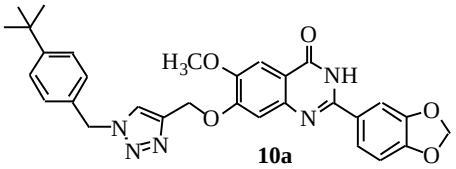
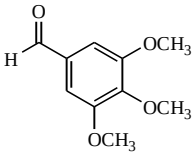
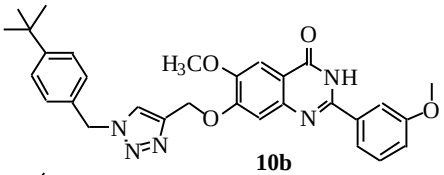
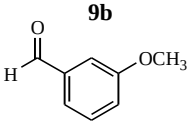
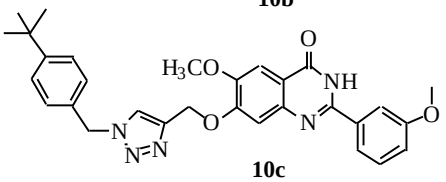
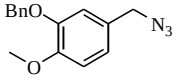
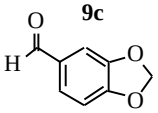
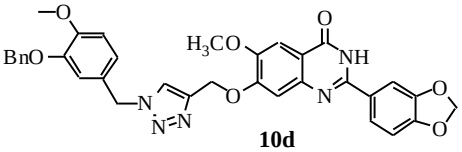
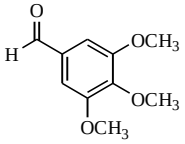
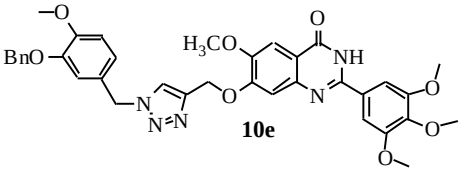
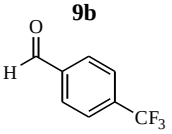
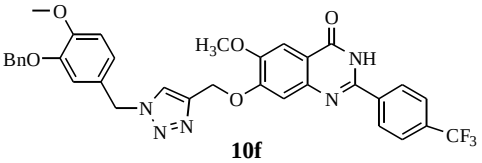
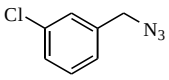
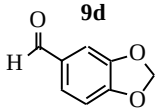
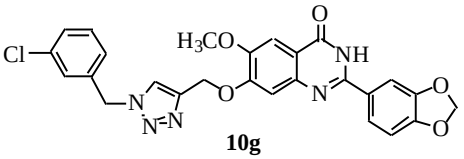
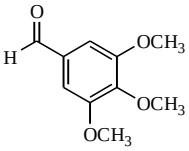
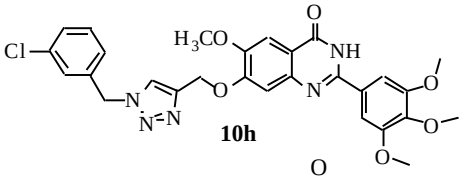
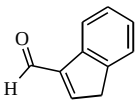
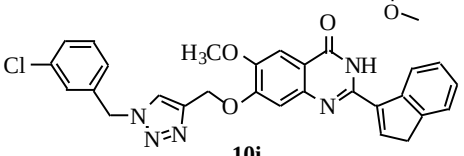
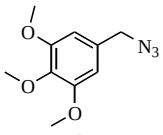
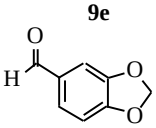
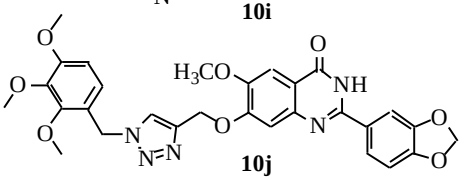
Figure 1. Synthesis of 5-methoxy-2-nitro-benzamide **(6)**

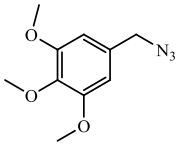
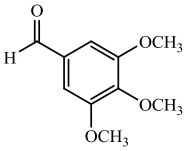
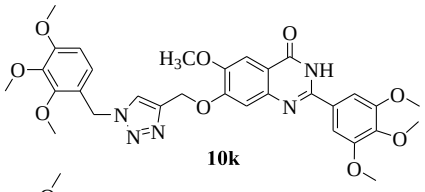
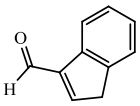
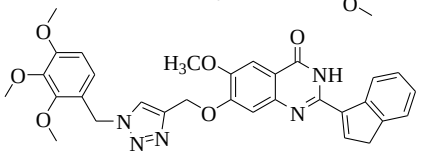
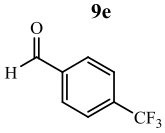
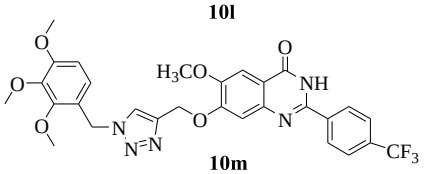
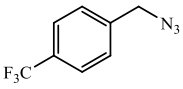
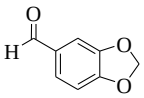
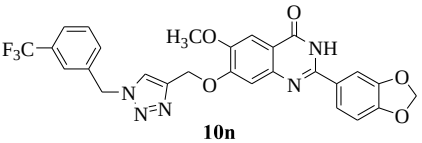
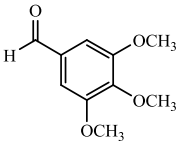
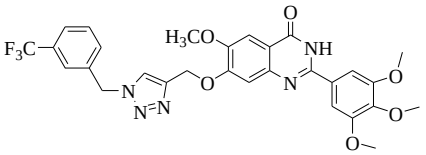


Reaction conditions: (i) benzyl azides (1 mmol), compound 51 (1 mmol), CuSO4.5H2O, (10 mol%), sodium ascorbate (10 mol%), ter. Butanol, water, RT; (ii) o-nitrobenzamide (1 mmol), benzaldehyde (1 mmol), Na2S2O4, (2 mmol), DMSO (5 mL), 100 °C

Figure 2. Synthesis of title compounds **(10a-o)**

Table 1. Synthesis of quinazolinone-triazoles **10 (a-o)**

***o*-Nitrobanzamide**	**Aldehyde**	**Quinazolinone**	**Yield (%)**
 **8a**	 **9a**	 **10a**	85
8a	 **9b**	 **10b**	80
8a	 **9c**	 **10c**	79
 **8b**	 **9a**	 **10d**	80
8b	 **9b**	 **10e**	81
8b	 **9d**	 **10f**	78
 **8c**	 **9a**	 **10g**	83
8c	 **9b**	 **10h**	80
8c	 **9e**	 **10i**	78
 **8d**	 **9a**	 **10j**	81

o-Nitrobanzamide	Aldehyde	Quinazolinone	Yield (%)[a]
 **8d**	 **9b**	 **10k**	80
8d	 **9e**	 **10l**	75
8d	 **9d**	 **10m**	77
 **8e**	 **9a**	 **10n**	80
8e	 **9b**		82

[a] Isolated yields.

Antibacterial Activity

All the newly prepared compounds (**10a-o**) were screened for the antibacterial activity is done by the paper disc method[22]. Organisms used: *Escherichia coli* (MTCC 443), (Gram-negative) *Staphylococcus aureus* (MTCC 096), (Gram-positive).

The pH of the medium prepared from above ingredients was adjusted to 7.0. The medium was sterilized in the autoclave at 121 ^{0}C (15 lbs) pressure for 15 min. The medium was cooled to 45 -50 ^{0}C and poured in 20 ml volume in each petridish and allowed to solidify. Detailed medium composition was given in supporting information part.

Testing equipments

Tubes of uniform size, paper disc and petridishes were employed.

Maintenance of sterility

All required apparatus were sterilized before use and necessary precautions were taken to avoid contamination.

Preparation of sample solutions

The testing sample 2 mg was dissolved in 2 ml of DMSO. This gives the concentration of the sample as 1000 µg/ml. Different dilute solutions such as 200 µg/ml, 100 µg/ml, 50 µg/ml were prepared from the sample solution.

Antibacterial testing

After solidification of media, petriplates inoculated with actively growing culture of *Escherichia coli* and *Staphylococcus aureus* separately as follows. Filter paper discs of 5 mm diameter

were dipped in the test solution of different concentrations. After drying the disc, it was kept on Antibiotic med-3 agar in petriplates seeded with 1ml bacterial culture of *Escherichia coli* and *Staphylococcus aureus* and incubated for 24 hrs at 37 ^{0}C.

Discussion

After solidification of media, petriplates inoculated with actively growing culture of *Escherichia coli* and *Staphylococcus aureus* separately as follows. Filter paper discs of 5 mm diameter were dipped in the test solution of different concentrations. After drying the disc, it was kept on Antibiotic med-3 agar in petriplates seeded with 1 ml bacterial culture of *Escherichia coli* and *Staphylococcus aureus* and incubated for 24 hrs at 37 ^{0}C, After 24 hours the petridishes were checked for growth inhibition zone. The presence of clear zone of growth inhibition around the paper disc indicated the inhibition of growth of organism. The compound was considered to be active. The antibacterial activity of the compounds tested is given in **Table-2**.

Table 2. Antibacterial activity

	Escherichia coli (Gram-negative) (Conc. µg/ml)			**Staphylococcus aureus (Gram-positive) (Conc. µg/ml)**		
Compound	200	100	50	200	100	50
10a	22	21		12	21	9
10b	12	14	12	31	24	22
10c	11	13	8	-	14	7
10d	-	-	11	18	-	11
10e	18	19	30	28	18	23
10f	12	12	22	23	32	22
10g	23	19	17	11	19	17
10h	11	-	-	22	-	-
10i	22	11	17	13	11	17
10j	13	-	11	14	-	11
10k	14	11	11	26	29	19
10l	12	6	8	3	6	8
10m	3	6	9	22	6	9
10n	22	18	19	11	18	19
10o	11	12	12	-	12	12
			Ciprofloxacin			
(100 µg/disc)			20		21	

The compounds 10 (a-o) were evaluated for their antibacterial activity against human pathogenic organism *Escherichia Coli* (G_{-ve}), *Staphylococcus aureus* (G_{+ve}). The investigation of antibacterial screening data reveal that **10e**, **10f**, **10g**, **10j** and **10n** were highly active against E. *coli*, where as **10b**, **10d**, **10j, 10k** and **10o** showed least activity. Compounds **10b**, **10e**, **10f**, **10g**, **10i**, **10k** and **10n** showed high activity against S. *aureus*, where as compounds **10d**, **10j**, **10o** showed least activity. Compounds **10c**, **10h**, **10l** and **10o** were inactive against both organisms employed. The relationship between the structure of the synthesized compounds and the antimicrobial effectiveness was looked into assess the role of pharmacophore. Groups bearing 3,4-benzyloxy, methoxy substituted aryl or chloro substituted aryl azides (**10 g**, **10i**) and -CF_3 or trimethoxy aryl aldehydes and piperanal displayed good antibacterial activity against the both the organisms (**10 e, 10f and 10n**).

3. Experimental Section

All the used reactants, reagents and solvents were obtained from commercial sources and were of analytical grade. Melting points were determined by open capillary method. ^{1}H NMR (DMSO-d_6 300

MHz) and ^{13}C NMR (DMSO-d_6, 125 MHz) were recorded on Bruker Avance Spectrometer 300 MHz and TMS as internal standard (chemical shifts and ppm). Mass spectra were recorded on a VG micromass70-70H instrument. The purity of the compounds was checked by TLC on silica gel plates using a mixture of *n*-hexane and ethyl acetate.

3.1. General procedure for the synthesis of compounds (8a-e):

To a solution mixture of *t*-butanol/H_2O in a ratio of 1:1 (30 mL), compound **6** (2 g, 8.00 mmol), was added, followed by addition of $CuSO_4.5H_2O$ (0.199 g, 0.8 mmol) and sodium ascorbate (0.316 g, 1.6 mmol). The reaction mixture was stirred at room temperature for 10 min. A solution of l-(azidomethyl)-4-(*tert*-butyl) benzene **7a** (1.19 g, 8.00 mmol) in *t*-butanol was added dropwise to the reaction mixture and stirred at room temperature for 6 h (**Scheme 2**). After completion of the reaction the reaction mixture was diluted with CH_2C1_2 (60 mL) and washed with water (2 x 30 mL), dried over anhydrous sodium sulphate and the solvent was concentrated under vacuo resulted in the crude material which was recrystallized in EtOH to get pure compound **8a** in (2.91 g, 83%) yield.

3.1.1. 4-((1-(4-(tert-butyl)benzyl)-1H-1,2,3-triazol-4-yl)methoxy)-5-methoxy-2-nitrobenzamide (8a): m.p. 142-144 °C; IR (KBr) ν_{max}: 3163, 3041, 2962, 2821, 2646, 2105, 1697, 1595, 1574, 1485, 1454, 1410, 1345, 1268, 1074, 918, 748, 688 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.30 (s, 9H, *t*-butyl), 3.92 (s, 3H, -OCH_3), 5.27 (s, 2H, -OCH_2), 5.53 (s, 2H, -NCH_2), 7.24 (d, 2H, *J*= 8.30 Hz), 7.39 (d, 2H, *J* = 8.30 Hz), 7.43 (s, 1H, =CH azole), 7.80 (s, 1H), 8.06 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 30.14, 33.58, 54.20, 56.23, 59.34, 111.74, 112.80, 118.87, 120.05, 126.51, 129.75, 138.19, 145.41, 149.29, 151.27, 157.50, 164.62; MS (ESI) *m/z*: 440 (M^++H).

3.1.2. 4-((1-(3-(Benzyloxy)-4-methoxybenzyl)-1H-1,2,3-triazol-4-yl)methoxy)-5-methoxy nitroben zamide (8b): m.p. 163-165 °C; IR (KBr) ν_{max}: 3187, 3035, 2905, 2852, 2122, 1888, 1733, 1599, 1489, 1411, 1383, 1324, 1249, 1040, 796, 769, 698 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.79 (s, 3H, -OCH_3), 3.81 (s, 3H, -OCH_3), 5.17 (s, 2H, -OCH_2), 5.25 (s, 2H, -OCH_2), 5.53 (s, 2H, -NCH_2), 6.94-7.19 (m, 8H), 7.45 (s, 1H), 7.77 (s, 1H), 8.08 (s, 1H); ^{13}C NMR (75 MHz,DMSO-d_6): δ 54.55, 55.72, 56.23, 59.34, 70.63, 112.80, 114.11, 118.87, 120.05, 122.99, 127.71, 127.69, 127.72, 134.70, 135.89, 136.65, 145.41, 149.38, 150.79, 157.48, 164.65; MS (ESI) *m/z*: 520 (M^++H).

3.1.3. 5-Methoxy-2-nitro-4-((1-(4-(chloro)benzyl)-1H-l,2,3-triazol-4-yl)methoxy) benzamide (8c): m.p.: 155-157 °C; IR (KBr) ν_{max}: 3174, 3042, 2922, 2854, 2556, 2311, 2119, 1692, 1609, 1571, 1494, 1420, 1305, 1282, 1261, 1216, 1166, 1076, 914, 812, 772, 666 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.81 (s, 3H, -OCH_3), 5.24 (s, 2H, -OCH_2), 5.51 (s, 2H, -NCH_2), 7.19 (d, 2H), 7.39 (d, 2H), 7.42 (s, 1H), 7.45 (s, 1H), 8.15 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 54.18, 56.21, 59.32, 111.76, 112.81, 118.89, 120.06, 129.15, 130.64, 131.51, 134.68, 135.89, 145.41, 151.27, 157.50, 164.68; MS (ESI) *m/z*: 418 (M^++H).

3.1.4. 5-Methoxy-2-nitro-4-((1-(3,4,5-trimethoxybenzyl)-lH-1,2,3-triazol-4-yl)methoxy)benzamide (8d): m.p. 161-163 °C; IR (KBr) ν_{max}: 3172, 3045, 2964, 2848, 2625, 2100, 1695, 1607, 1520, 1578, 1369, 1285, 1254, 1212, 818, 875, 765, 732 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.76 (s, 3H), 3.83 (s, 9H), 5.25 (s, 2H, -OCH_2), 5.53 (s, 2H, -NCH_2), 6.57 (s, 2H), 7.41 (s, 1H), 7.45 (s, 1H), 8.15 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 54.89, 56.16, 56.23, 60.62, 106.80, 111.74, 112.80, 118.87, 120.05, 136.95, 139.39, 145.41, 151.27, 153.69, 157.50, 164.82; MS (ESI) *m/z*: 474 (M^++H).

3.1.5. 5-Methoxy-2-nitro-4-((1-(4-(trifluoromethyl)benzyl)-1H-l,2,3-triazol-4-yl)methoxy) benzamide (8e): m.p. 184-186 °C; IR (KBr) ν_{max}: 3182, 3136, 2922, 2852, 1677, 1603, 1563, 1528, 1484, 1445, 1347, 1321, 1306, 1267, 1250, 1178, 1031, 942, 834, 770, 687 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.78 (s, 3H, -OCH_3), 5.24 (s, 2H, -OCH_2), 5.53 (s, 2H, -NCH_2), 7.44 (s, 1H), 7.46 (s, 1H), 7.73 (d, 2H, *J* = 7.55 Hz), 8.06 (d, 2H, *J* = 7.55 Hz), 7.81 (s, 1H), 8.15 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 54.20, 56.23, 59.34, 111.74, 112.80, 118.87, 119.98, 120.05, 126.04, 127.12, 126.21, 126.39, 126.56, 130.56, 130.63, 134.25, 135.89, 145.25, 145.41, 151.27, 157.50, 164.62; MS (ESI) *m/z*: 452 (M^++H).

3.2. General procedure for the synthesis of title compounds (10a-o):

3.2.1. 2-(benzo[d][1,3]dioxol-5-yl)-7-((1-(4-(tert-butyl)benzyl)-1H-1,2,3-triazol-4-yl)methoxy)-6-methoxyquinazolin-4(3H)-one (10a):

To a stirred solution of compound **8a** (0.10 g, 0.22 mmol) and anisaldehyde (0.036 g, 0.242 mmol) in dimethyl sulfoxide (3 ml) was added sodium dithionite (0.087 g, 0.44 mmol) and reaction mixture was heated at 100 °C for 2-3 h (**Scheme 2**). After completion of the reaction, reaction mixture was poured in ice/water and resulted precipitate was filtered out, recrystallized in EtOH to get pure white solid product **10a** (0.096 g, 85%) yield. m.p.: 145-147 °C; IR (KBr) ν_{max}: 3185, 3130, 3041, 2922, 2852, 1677, 1603, 1563, 1528, 1484, 1445, 1347, 1321, 1306, 1267, 1250, 1178, 1031, 942, 834, 770, 687 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.29 (s, 9H), 3.77 (s, 3H, -OCH_3), 5.23 (s, 2H, -OCH_2), 5.53 (s, 2H, -NCH_2), 5.90 (s, 2H), 6.78 (d, 2H), 6.92 (d, 2H), 7.44 (s, 1H), 7.35-7.62 (m, 4H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 30.12, 33.60, 54.21, 56.22, 59.36, 101.10, 107.16, 107.24, 108.45, 111.38, 113.64, 118.87, 120.10, 120.90, 126.51, 129.75, 138.19, 142.74, 145.41, 147.52, 149.29, 151.34, 154.27, 162.75; MS (ESI) *m/z*: 540 (M^++H).

3.2.2. 7-((1-(4-(tert-Butyl) benzyl)-1H-1,2,3-triazol-4-yl)methoxy)-6-methoxy-2-(3,4,5-trimethox–yphenyl) quinazolin-4(3H)-one (10b): m.p. 168-169 °C; IR (KBr) ν_{max}: 3186, 3131, 3042, 2923, 2852, 1666, 1607, 1581, 1562, 1498, 1468, 1447, 1341, 1320, 1294, 1263, 1218, 1145, 967, 832, 769, 693, 605 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.29 (s, 9H), 3.77 (s, 3H, -OCH_3), 3.93 (s, 3H, -OCH_3), 4.02 (s, 6H, -OCH_3), 5.22 (s, 2H, -OCH_2), 5.54 (s, 2H, -NCH_2), 6.45-6.51 (m, 2H), 7.32 (s, 1H), 7.41-7.46 (m, 3H), 7.62 (m, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 30.14, 33.58, 54.20, 56.23, 57.32, 59.34, 60.26, 61.49, 105.90, 107.73, 111.26, 113.64, 118.10, 118.87, 126.51, 129.75, 135.47, 138.19, 147.52, 147.83, 147.86, 149.29, 154.26, 154.74, 163.11; MS (ESI) *m/z*: 586 (M^++H).

3.2.3. 7-((1-(4-(tert-Butyl) benzyl)-1H-1,2,3-triazol-4-yl)methoxy)-6-methoxy-2-(3-methoxyphenyl) quinazolin-4(3H)-one (10c): m.p. 170-172 °C; IR (KBr) ν_{max}: 3178, 3033, 2920, 2871, 1680, 1617, 1531, 1467, 1435, 1336, 1253, 1219, 1160, 888, 772, 716, 689, 596 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.29 (s, 9H, *t*-butyl), 3.73 (s, 3H, -OCH_3), 3.78 (s, 3H, -OCH_3), 5.23 (s, 2H, -OCH_2), 5.53 (s, 2H, -NCH_2), 7.26-7.35 (m, 8H), 7.62 (d, 2H), 7.65 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 30.14, 33.58, 55.20, 56.23, 59.34, 107.04, 111.26, 113.64, 114.08, 121.08, 122.98, 126.51, 129.75, 133.15, 138.19, 147.52, 148.28, 148.30, 154.29, 155.84, 163.21; MS (ESI) *m/z*: 526 (M^++H).

3.2.4. 2-(Benzo[d][1,3]dioxol-5-yl)-7-((1-(3-(benzyloxy)-4-methoxybenzyl)-1H-1,2,3-triazol-4yl)meth oxy)-6-methoxyquinazolin-4(3H)-one (10d): m.p. 145-147 °C; IR (KBr) ν_{max}: 3165, 3045, 2962, 2851, 1664, 1595, 1564, 1520, 1469, 1317, 1292, 1265, 1219, 1178, 1034, 943, 883, 831, 772cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.78 (s, 3H), 3.81 (s, 3H), 5.17 (s, 2H, -NCH_2), 5.24 (s, 2H, -OCH_2), 5.54 (s, 2H, -OCH_2O-), 5.89 (s, 2H), 6.73-7.41 (m, 12H), 7.65 (s, 1H), 11.38 (brs, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 54.53, 56.12, 56.23, 59.34, 70.73, 101.08, 107.16, 107.24, 114.94, 118.87, 120.90, 122.62, 127.69, 127.71, 131.67, 135.07, 141.48, 142.74, 147.52, 148.99, 149.24, 149.28, 154.27, 163.01; MS (ESI) *m/z*: 620 (M^++H).

3.2.5.7-((1-(3-(Benzyloxy)-4-methoxybenzyl)-1H-1,2,3-triazol-4-yl)methoxy)-6-methoxy-2(3,4,5-trimethoxyphenyl)quinazolin-4(3H)-one (10e): m.p. 160-163 °C; IR (KBr) ν_{max}: 3167, 3032, 2968, 2853, 1683, 1608, 1583, 1561, 1505, 1491, 1469, 1327, 1255, 1168, 1115, 1037, 933, 897, 862, 822, 772, 695, 664 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.79 (s, 6H), 3.86 (s, 3H), 3.89 (s, 6H), 5.23 (s, 2H, -OCH_2), 5.57 (s, 2H, -NCH_2), 6.81 (d, 1H), 6.96 (s, 1H), 7.07-7.19 (m, 8H), 7.35 (s, 1H), 7.45 (s, 1H), 7.62 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 54.53, 56.14, 56.16, 56.23, 60.62, 70.73, 103.09, 107.16, 113.64, 118.87, 121.88, 122.62, 127.69, 127.71, 131.67, 135.07, 145.41, 147.52, 149.28, 152.94, 154.25, 163.01; MS (ESI) *m/z*: 666 (M^++H).

3.2.6. 7-((1-(3-(Benzyloxy)-4-methoxybenzyl)-1H-1,2,3-triazol-4-yl)methoxy)-6-methoxy-2-(4(triflu oromethyl) phenyl)qumazolin-4(3H)-one (10f): m.p. 186-188 °C; IR (KBr) ν_{max}: 3168, 3033, 2965, 2851, 1684, 1590, 1562, 1511, 1470, 1408, 1344, 1319, 1271, 1245, 1215, 1166, 1126, 1063, 1019, 953, 885, 841, 811, 770, 751, 691, 649, 603 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.78 (s, 3H), 3.81 (s, 3H), 5.27 (s, 2H, -OCH_2), 5.56 (s, 2H, -NCH_2), 7.07-7.18 (m, 8H), 7.35 (s, 1H), 7.45 (s, 1H), 7.62 (s, 1H), 7.74 (d, 2H), 7.98 (d, 2H), 12.63 (brs, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 54.55, 56.11, 56.25, 59.34, 70.73, 107.16, 113.64, 114.94, 118.87, 122.62, 127.69, 127.71, 127.72, 129.01, 129.08, 129.15, 132.70, 135.07, 143.19, 147.52, 149.24, 149.28, 154.27, 163.04 ; MS (ESI) *m/z*: 644 (M^++H).

3.2.7. 7-((1-(3-Chlorobenzyl)-1H-1,2,3-triazol-4-yl)methoxy)-2-(7,7a-dihydrobenzo [d][1,3] dioxo-5-yl)-6-methoxyquinazolin-4(3H)-one (10g): m.p. 214-216 °C; IR (KBr) ν_{max}: 3188, 3031, 2923, 2853, 1684, 1605, 1583, 1563, 1515, 1469, 1405, 1344, 1270, 1243, 1215, 1157, 1133, 1 108, 1073, 1018, 953, 887, 854, 810 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.79 (s, 3H), 5.22 (s, 2H), 5.54 (s, 2H), 5.91 (s, 2H), 6.79 (d, 1H), 6.92 (d, 1H), 7.20 (d, 2H), 7.35 (s, 1H), 7.41-7.47 (m, 5H), 7.58 (d, 2H), 7.62 (s, 1H), 12.27 (brs, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 54.20, 56.23, 59.34, 101.08, 107.16, 107.24, 108.45, 111.38, 113.64, 120.11, 120.90, 129.15, 130.64, 134.68, 145.41, 147.52, 148.98, 151.34, 154.25, 162.79; MS (ESI) *m/z*: 519 (M^++H).

3.2.8. 7-((1-(3-Chlorobenzyl)-1H-1,2,3-triazol-4-yl)methoxy)-6-methoxy-2-(3,4,5-trimethoxy phenyl) quinazolin-4(3H)-one (10h): m.p. 201-203 °C; IR (KBr) ν_{max}: 3176, 3045, 2890, 2837, 1167, 1610, 1552, 1494, 1463, 1438, 1391, 1339, 1297, 1279, 1246, 1204, 1176, 1123, 1074, 1029, 1000, 958, 871, 835, 665 cm^{-1}; ^{1}H NMR (300 MHz,DMSO-d_6): δ 3.79 (s, 3H), 3.83 (s, 9H), 5.22 (s, 2H), 5.53 (s, 2H), 7.12 (s, 2H), 7.21 (d, 2H), 7.35 (s, 1H), 7.43 (s, 1H), 7.58 (d, 2H), 7.62 (s, 1H), 12.22 (brs, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 54.19, 56.16, 56.24, 60.62, 103.09, 107.16, 111.38, 113.64, 118.87, 121.88, 129.15, 130.64, 134.68, 141.36, 141.85, 142.29, 145.41, 147.52, 152.94, 154.27, 162.64; MS (ESI) *m/z*: 564 (M^++H).

3.2.9. 7-((1-(3-Chlorobenzyl)-1H-1,2,3-triazol-4-yl)methoxy)-2-(1-indol-3-yl)-6-methoxy quinazolin-4(3H)-one (10i): m.p. 166-168 °C; IR (KBr) ν_{max}: 3185, 3042, 2981, 2924, 2839, 1679, 1605, 1587, 1555, 1509, 1468, 1415, 1331, 1304, 1292, 1248, 1216, 1175, 1132, 1110, 1073, 1026, 953, 883, 831, 811 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.79 (s, 3H), 4.25 (s, 2H), 5.23 (s, 2H), 5.55 (s, 2H), 7.16-7.36 (m, 5H), 7.46 (s, 1H), 7.56 (d, 2H), 7.59-7.64 (m, 3H), 11.88 (brs, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 38.47, 54.20, 56.23, 59.34, 106.03, 113.46, 118.87, 123.32, 124.38, 127.02, 129.15, 129.75, 130.64, 138.70, 141.25, 141.40, 145.41, 147.76, 154.08, 162.11; MS (ESI) *m/z*: 513 (M^++H).

3.2.10. 2-(Benzo[d][1,3]dioxol-5-yl)-6-methoxy-7-((1-(3,4,5-trimethoxybenzyl)-1H-1,2,3-triazol-.yl) methoxy) quinazolin-4(3H)-one (10j): m.p. 171-173 °C; IR (KBr) ν_{max}: 3144, 3033, 2884, 2819, 2314, 1693, 1550, 1514, 1450, 1393, 1219, 772 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.77 (s, 3H), 3.83 (s, 9H), 5.21 (s, 2H), 5.53 (s, 2H), 5.91 (s, 2H), 6.57 (s, 2H), 6.79 (d, 1H), 6.92 (d, 1H), 7.35 (s, 1H), 7.41 (s, 1H), 7.43 (s, 1H), 7.62 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 54.89, 56.16, 56.23, 60.62, 101.08, 106.80, 107.16, 111.38, 113.64, 118.87, 120.10, 120.90, 136.95, 139.39, 142.74, 147.52, 148.99, 151.34, 153.69, 154.27, 162.76; MS (ESI) *m/z*: 574 (M^++H).

3.2.11. 6-Methoxy-7-((1-(3,4,5-trimethoxybenzyl)-1H-1,2,3-triazol-4-yl)methoxy)-2-(3,4,5-trimethoxy phenyl) quinazolin-4(3H)-one (10k): m.p. 134-136 °C; IR (KBr) ν_{max}: 3185, 3046, 2989, 2978, 2924, 2851, 1680, 1609, 1587, 1506, 1467, 1413, 1357, 1334, 1294, 1244, 1175, 1124, 1080, 1027, 1001, 897, 830, 752, 695, 663, 610 cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6): δ 3.78 (s, 3H), 3.83 (s, 9H), 3.86 (s, 9H), 5.23 (s, 2H), 5.54 (s, 2H), 6.57 (s, 2H), 7.10 (s, 2H), 7.34 (s, 1H), 7.41 (s, 1H), 7.62 (S, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 54.89, 56.23, 56.16, 59.34, 60.62, 103.09, 106.81, 107.16, 111.38, 113.64, 118.87, 121.88, 136.95, 141.36, 141.85, 142.29, 145.41, 147.52, 152.94, 153.69, 154.27, 163.05; MS (ESI) *m/z*: 620 (M^++H).

3.2.12. 2-(1H-Indol-3-yl)-6-methoxy-7-((1-(3,4,5-trimethoxybenzyl)-1H-1,2,3-triazol-4-yl) methoxy) quinazolin-4(3H)-one (10l): m.p. 184-186 °C; IR (KBr) ν_{max}: 3182, 3031, 2987, 2953, 2923, 2853, 1686, 1597, 1565, 1510, 1470, 1379, 1943, 1275, 1253, 1217, 1178, 1159, 1139, 1104, 1078, 1052, 1022, 953, 867, 813, 772, 696, 664 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 3.75 (s, 3H), 3.85 (s, 6H), 3.88 (s, 3H), 4.25 (s, 2H), 5.22 (s, 2H), 5.55 (s, 2H), 6.57 (s, 2H), 7.12 (d, 1H), 7.17 (d, 1H), 7.29 (s, 1H), 7.48 (s, 1H), 7.58 (d, 1H), 7.60 (s, 1H), 7.64 (d, 1H), 11.66 (bs, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 38.47, 54.89, 56.16, 56.23, 60.62, 106.03, 106.80, 113.46, 118.87, 121.32, 124.38, 127.02, 129.75, 139.39, 141.25, 141.40, 145.41, 147.74, 153.69, 154.08, 162.11; MS (ESI) *m/z*: 569 (M^++H).

3.2.13. 6-Methoxy-2-(4-(trifluoromethyl) phenyl)-7-((1-(3, 4, 5-trimethoxybenzyl)-1H-1,2,3- triazol-4-yl)methoxy)quinazolin-4(3H)-one (10m): m.p. 176-178 °C; IR (KBr) ν_{max}: 3178, 3046, 2989, 2924, 2871, 1678, 1612, 1590, 1512, 1469, 1415, 1355, 1331, 1296, 1241, 1170, 1121, 1083, 1029, 1021, 898, 832, 755, 696, 661, 613 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 3.77 (s, 3H), 3.83 (s, 6H), 3.87 (s, 3H), 5.24 (s, 2H), 5.57 (s, 2H), 6.57 (s, 2H), 7.35 (s, 1H), 7.47 (s, 1H), 7.62 (s, 1H), 7.71 (d, 2H), 7.74 (d, 2H), 12.62 (brs, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 54.89, 56.17, 56.23, 60.62, 106.80, 107.16, 111.38, 113.64, 118.87, 120.25, 124.74, 125.09, 125.26, 129.01, 129.08, 132.20, 136.95, 143.19, 145.41, 147.40, 153.69, 154.25, 163.16; MS (ESI) *m/z*: 598 (M^++H).

3.2.14. 2-(Benzo[d][1,3]dioxol-5-yl)-6-methoxy-7-((1-(4-(trifluoromethyl)benzyl)-1H-1,2,3-triazol-4 yl)methoxy)quinazolin-4(3H)-one (10n): m.p. 188-190 °C; IR (KBr) ν_{max}: 3178, 3035, 2989, 2924, 2851, 1680, 1609, 1587, 1506, 1467, 1413, 1357, 1334, 1294, 1244, 1175, 1124, 1080, 1027, 1001, 897, 830, 752, 695, 663, 610 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 3.81 (s, 3H), 5.23 (s, 2H), 5.57 (s, 2H), 6.79 (d,1H), 6.92 (d, 1H), 7.35 (s, 1H), 7.41 (s, 1H), 7.44 (s, 1H), 7.62 (s, 1H), 7.73 (d, 2H), 8.06 (d, 2H), 12.26 (brs, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 54.20, 56.23, 59.34, 101.08, 107.16, 107.24, 108.45, 111.38, 113.64, 112.85, 118.87, 119.98, 120.90, 126.04, 126.39, 126.56, 130.49, 130.56, 130.63, 130.70, 134.25, 145.25, 145.41, 147.52, 148.98, 151.34, 154.27, 162.76; MS (ESI) *m/z*: 552 (M^++H).

3.2.15. 6-Methoxy-7-((1-(4-(trifluoromethyl)benzyl)-1H-1,2,3-triazol-4-yl)methoxy)-2-(3,4,5-trimeth oxyphenyl)quinazolin-4(3H)-one (10o): m.p. 154-156 °C; IR (KBr) ν_{max}: 3178, 3035, 2989, 2884, 2839, 1679, 1605, 1587, 1555, 1509, 1468, 1415, 1331, 1304, 1292, 1248, 1216, 1175, 1132, 1110, 1073, 1026, 953, 883, 831, 811 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 3.79 (s, 3H), 3.83 (s, 3H), 3.86 (s, 6H), 5.22 (s, 2H), 5.55 (s, 2H), 7.11 (s, 2H), 7.34 (s, 1H), 7.45 (s, 1H), 7.73 (d, 2H), 8.06 (d, 2H), 12.13 (brs, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 54.21, 56.15, 56.23, 60.62, 103.09, 107.16, 111.38, 112.85, 113.64, 118.87, 126.04, 126.39, 126.56, 130.49, 130.56, 130.63, 130.70, 134.25, 141.85, 142.29, 145.43, 147.51, 152.94, 154.29, 162.78; MS (ESI) *m/z*: 598 (M^++H).

4. Conclusions

In present study, new derivatives of 4(3*H*)-quinazolinone-l,2,3-triazole hybrids were synthesized by the reductive cyclization approach by using sodium dithionite as an inexpensive, readily available and easily handling catalyst. And the derived compounds were evaluated for anti-bacterial activity.

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Supporting Information

Supporting Information accompanies this paper on http://www.acgpubs.org/OC

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