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# SYNTHESIS OF NEW 1,2,3-TRIAZOLE-LINKED QUINAZOLINONE DERIVATIVES PER CLIK CATALYZED BY COPPER

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## ABSTRACT

This study presents, a series of new 1,2,3-triazole-linked quinazolinone derivatives **6a-f** obtained regioselectively in good yields, were synthesized in the multistep process. In the first step, 2-aminobenzimidazole **1** reacted with ethyl 2-oxocyclohexanecarboxylate **2** to form **3** which then proporgylated with propargyl bromide to form **4**. Finally, **4** was subjected to Click chemistry with various azides **5a-f** in the presence of a $CuSO_4.5H_2O$ + sodium ascorbate mixture in dimethylformamide at room temperature to obtain 2 + 3 cycloaddition products **6a-f**. All these new compounds synthesized were characterized by FT-IR, $^1$H-NMR and $^{13}$C-NMR.

## KEYWORDS

Click reaction, Copper catalyst, 1,2,3-Triazole. Quinazolinone.

## INTRODUCTION

Nitrogenous heterocycles are one of the most preferred structures [i] in medicinal chemistry for drug discovery. Among the various N-heterocycles, 1,2,3 triazole and quinazolinone are the two most common ring systems found in small molecule drugs [ii] approved by the FDA.

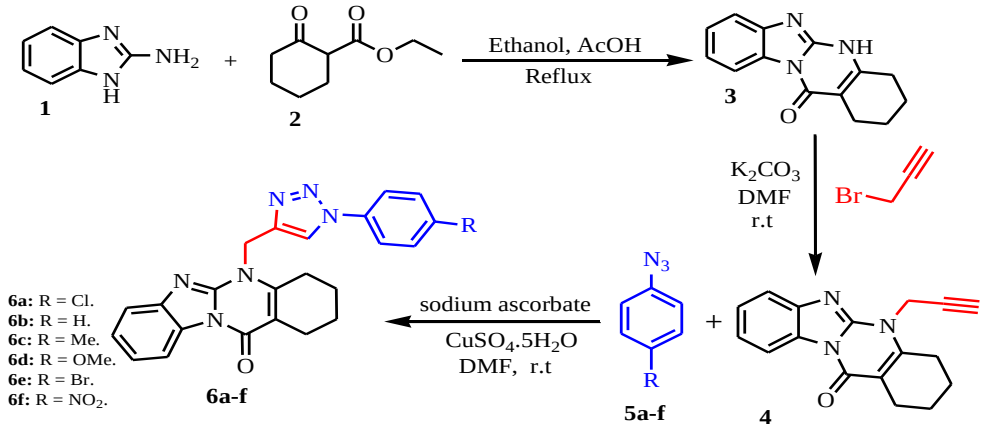
1,2,3-Triazoles and their derivatives play an important role in organic chemistry, medicinal chemistry, dyes and agrochemicals due to their chemical properties and structure, they contain high aromatic stabilization and great dipole moment [iii] and actively participate in hydrogen bonding and are also easily soluble in water, easy synthesis by click chemistry, [iv,v] useful and important for the construction of bioactive molecules, For example, some compounds of triazole exhibit a broad spectrum of pharmacological activities such as anti-inflammatory, [vi] antimicrobial, [vii] antibacterial, [viii] antiviral, [ix] anti-allergic, [x] antifungal, [xi] antimalarial, [xii]

anti-proliferative, [xiii] anti-HIV, [xiv,xv] anti-cancer, [xvi] and anti-tuberculosis. [xvii,xviii] Likewise, the quinazolinone backbone is an important class of nitrogenous heterocyclic compounds exhibiting biological activities such as anticancer, [xix] antibacterial, [xx] antifungal, [xxi] analgesic,[xxii] anti-inflammatory, [xxiii] anticonvulsant, [xxiv] antitumor and antiviral.[xxv]
On the other hand, the quinazolinone nucleus linked to 1,2,3-triazole by copper-catalyzed click reactions at specific ring positions of bi- or tri-heterocyclic molecules has received high consideration due to biological properties remarkable, such as anticancer, antibacterial and antidiabetic. For example, B.Banerji et al [xxvi] described the synthesis of triazole-substituted quinazoline hybrid molecules promising anticancer agents. S. Gatadi, [xxvii] et al developed the synthesis 1,2,3-triazole linked 4(3H)-Quinazolinones as potent antibacterial agents against multidrug-resistant Staphylococcus aureus. Therefore, the synthesis of 1,2,3-triazole bound to quinazolinone has gained advantage in organic synthesis as well as in medicinal chemistry. In this context, we were interested in the synthesis of new 1,2,3-triazole - quinazolinone derivatives **6a-f** linked by the click reactions catalyzed by copper (scheme 1).

## EXPERIMENTAL

### Materials

All chemicals were obtained from Sigma Aldrich and were used without further purification. Thin layer chromatography (TLC) was done on silica gel TLC aluminium plates (E. Merck Kieselgel 60 F-254) and were visualized by exposure to UV-light at 254 nm or iodine vapor for few seconds. FT-IR spectra were recorded on a Bruker ATR spectrophotometer and the values are expressed in $cm^{-1}$. Melting point in °C was determined in open capillaries using Electrothermal melting point apparatus Stuart MPS-10. $^{1}H$ and $^{13}C$ NMR spectra were acquired on a Bruker AQS-AVANCE spectrometer (400 MHz) at 25°C using DMSO-$d_6$ as solvent. Chemical shifts (δ) are reported in parts per million (ppm) relative to the internal standard tetramethylsilane (TMS, δ = 0.00 ppm).




**Scheme 1**. synthesis of new 1,2,3-triazole-linked quinazolinone derivatives (6a-f).

### General procedure for the synthesis of 1,3,4,5-tetrahydrobenzo[4,5]imidazo[2,1-*b*]quinazolin-12(2*H*)-one ( 3 )

The ethyl 2-oxocyclohexanecarboxylate **1** (1eq) with 2-aminobenzimidazoles **2** (1eq) was dissolved in ethanol (30 ml) and added a catalytic amount of acetic acid in a round bottom flask (100 ml). The reaction mixture was heated at reflux for 8 hours. When the yellowish product was observed and the reaction completed (monitored by TLC), the reaction mixture was cooled, and the separated solid was filtered, dried and recrystallized from ethanol to afford compound **3** which was used for next step.

**General procedure for the synthesis of 5-(prop-2-yn-1-yl)-1,3,4,5-tetrahydrobenzo[4,5]imidazo[2,1-*b*]quinazolin-12(2*H*)-one ( 4 )**

Propargyl bromide (1.2 eq) was added slowly to a stirring mixture of quinazolinone **3** (1eq ) and $K_2CO_3$ (2 eq) in dry DMF (20 ml), The reaction mixture was allowed to stir at room temperature for 10 hours. The progress of the reaction and purity of the compounds was checked by TLC. After completion of the reaction, the reaction mixture was poured in to ice cold water to obtain pure product **4** which was used for next step without any further purification.

**Synthesis of aryl azides (5a–f)**.

A mixture of substituted aniline (1 eq) in 6M HCl is heated at 45°C for 30 min. Transfer the mixture to an ice bath and maintain the temperature between 0-5°C. The diazonium salt thus obtained will be added drop by drop to a second solution consisting of CH3COONa.H2O (60 g) and sodium azide (1.1 eq) dissolved in distilled water (150 mL), leave the mixture under magnetic stirring for 45 min. filter the solid obtained, wash well with distilled water. Recrystallize from diethyl ether to obtain azides sufficiently pure for further use.

**General procedure for the synthesis of ( 6a-f )**

A mixture of **4** (1eq) and (1eq) of different azide derivatives **5a-f** (1eq ) individually in the presence of $CuSO_4.5H_2O$ (10 mol%), sodium ascorbate (20 mol%) and DMF (20 ml) as solvent were stirred at room temperature in a flask round bottom (50 ml) for 2 h and the completion of the reactions was monitored by TLC. After completion of the reaction, the reaction mixtures were poured in ice cold water and neutralized with acetic acid individually to obtain the cycloaddition products **6a-f** in good yields.

## RESULTS AND DISCUSSION

In this work, the synthesis of 5-((1-( substituted phenyl)-1*H*-1,2,3-triazol-4-yl) methyl)-1,3,4,5-tetrahydrobenzo[4,5]imidazo[2,1-*b*]quinazolin-12(2*H*)-one derivatives **6a–f** involved several steps as shown in ( scheme1). In the first step, the compound **3** was prepared by condensation of the compound ethyl 2-oxocyclohexanecarboxylate **1** (1 eq ) with 2-aminobenzimidazoles **2** (1 eq ) in ethanol and a catalytic amount of acetic acid at reflux temperature. Further, in the second step compound **3** undergo propargylation with propargyl bromide in the presence of $K_2CO_3$ in dimethylformamide with stirring at room temperature to obtain product **4**, aryl azide derivatives **5a–f** were prepared at from their respective anilines by diazotization with sodium nitrite under acidic conditions followed by nucleophilic displacement with sodium azide. Finally, compounds **6a–f** was obtained by reaction of 1,3-dipolar cycloaddition of alkyne **4** with aromatic azides **5a–f** in the presence of $CuSO_4.5H_2O$ and reducing agent sodium ascorbate in dimethylformamide with stirring at room temperature. This "click" reaction gives a 1,4-disubstituted triazolyl **6a–f** derivatives regioselectively with good yields.

**Table 2.** synthesis of new 1,2,3-triazole-linked quinazolinone derivatives (6a-f).

| Compounds | **R** | **Yield (%)** | **mp(°C )** |
|---|---|---|---|
| **6a** | Cl | 89 | 224-226 |
| **6b** | H | 81 | 210-212 |
| **6c** | Me | 82 | 218-220 |
| **6d** | OMe | 87 | 236-238 |
| **6e** | Br | 88 | 222-224 |
| **6f** | $NO_2$ | 82 | 226-228 |

## Characterization

### FT-IR spectroscopic analysis

The IR spectra of compounds **6a–f** show characteristic bands at 2978-3081 $cm^{-1}$, 1683-1728 $cm^{-1}$, 1562 -1616 $cm^{-1}$, 1456-1498 $cm^{-1}$.which can be attributed respectively to =C-H, C=O, C=N, C=C.

### $^{1}$H-NMR spectroscopic analysis

In $^{1}$H NMR, the spectra of all the synthesized compounds **6a–f** show signals at 1.56 - 2.92 ppm were assigned for the $CH_2$ protons. A singlet at 4.93-5.39 ppm for aliphatic $CH_2$. Aromatic protons resonate in the region of 6.69 - 8.71 ppm. The triazol signal (C=CH-N) appears at 8.63-8.80 ppm in all compounds **6a-f** . In addition, the $^{1}$H-NMR spectrum of (**6c)** reveals the presence of a singlet at 3.20 ppm corresponding to the Me methyl group, and the $^{1}$H-NMR spectrum of (**6d)** reveals the presence of a singlet at 3.83 ppm corresponding to the O-Me methoxy group.

All spectral data from FTIR, $^{1}$H-NMR and $^{13}$C-NMR confirmed the structure of the 1,2,3-triazole-linked quinazolinone derivatives **6a-f**.

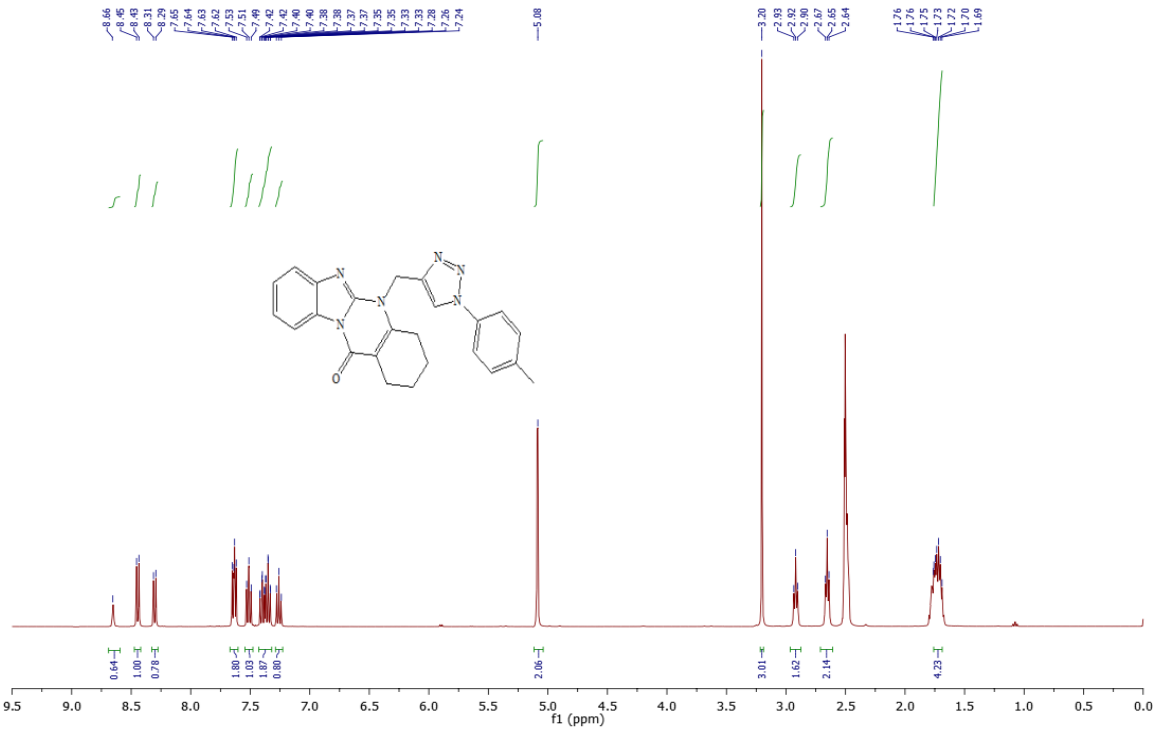



**Fig 1.** The $^{1}$H NMR spectrum of compound **6C** in DMSO-$d_6$ solvent.

### Spectroscopic Data

Data for 1,3,4,5-tetrahydrobenzo[4,5]imidazo[2,1-*b*]quinazolin-12(2*H*)-one (**3**) Yellow powder (yield 79%), m.p. 254-256 °C; FT-IR (νmax in cm-1): 3190 (N-H), 3037 (aromatic C-H), 1725 (C=O), 1613 (C=N),1459 (aromatic C=C); 1H NMR(400 MHz, DMSO-d6, δ in ppm): 8.44 (d, J = 7.9 Hz, 1H), 8.30 (d, J = 8.0 Hz, 1H), 7.51 (t, J = 7.8 Hz, 1H), 7.26 (t, J = 8.2 Hz, 1H), 4.81 (s, 1H) , 2.92 (t, J = 6.3 Hz, 2H), 2.65 (t, J = 6.0 Hz, 2H), 1.76 – 1.69 (m, 4H) ; 13C NMR(100MHz, DMSO-d6, δ in ppm):21.92, 22.14, 22.30, 31.57, 107.12, 115.14, 115.90, 121.72, 122,74, 125,60, 126.44, 141.73, 148 .66, 159.05, (C=O).

Data for 5-(prop-2-yn-1-yl)-1,3,4,5-tetrahydrobenzo[4,5]imidazo[2,1-*b*]quinazolin-12(2*H*)-one (**4**) White powder (yield 85%), m.p. 208-210 °C; FT-IR (νmax in cm-1): 3262 (≡C-H),3035 (aromatic C-H), 2150 (C≡C), 1737 (C=O), 1612 (C=N),1462 (aromatic C=C); 1H NMR(400 MHz, DMSO-d6, δ in ppm): 8.44 (d, J = 7.9 Hz, 1H), 8.30 (d, J = 8.0 Hz, 1H), 7.51 (t, J = 7.8 Hz, 1H), 7.26 (t, J = 8.2 Hz, 1H), 5.17 (s, 2H), 3.31 (t, J = 2.5 Hz, 2H), 2.92 (t, J = 6.3 Hz, 2H), 2.65 (t, J = 6.0 Hz, 2H), 1.76 – 1.69 (m, 4H); 13C NMR(100MHz, DMSO-d6, δ in ppm):21.24, 21.92, 22.14, 25.57, 35.60, 75.95, 76.19, 110.22, 115.90, 117.83, 121.72, 122.74, 125.60, 126.44, 147.40, 148.66, 160.49(C=O).

Data for 5-((1-(4-chlorophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-1,3,4,5-tetrahydrobenzo [4,5]imid-azo[2,1-*b*]quinazolin-12(2*H*)-one (**6a**) : White powder (yield 89%), m.p. 224-226°C; FT-IR (νmax in cm-1): 3081 (aromatic C-H), 1683 (C=O), 1591 (C=N),1498 (aromatic C=C), 676 (C-Cl); 1H NMR(400 MHz, DMSO-d6, δ in ppm): 8.68 (s, 1H), 7.96 (d, J = 8.0 Hz, 1H), 7.89 (d, J = 8.0 Hz, 2H), 7.63 (d, J = 8.0 Hz, 1H), 7.56 (d, J = 8.5 Hz, 2H), 7.19 (t, J = 7.8 Hz, 1H), 7.08 (t, J = 7.8 Hz, 1H), 5.07 (s, 2H), 2.86 (t, J = 6.3 Hz, 2H), 2.34 (t, J = 6.3 Hz, 2H), 1.72 – 1.68 (m, 4H) ; 13C NMR(100MHz, DMSO-d6, δ in ppm):20.65, 20.74, 20.85, 27.79, 56.53, 112.58, 115.65, 115.97, 117.40, 119.88, 120.27, 126.31, 127.22, 128.88, 129.51, 130.45, 133.17, 146.41, 147.96, 150.16, 160.62(C=O).
Data for 5-((1-phenyl-1*H*-1,2,3-triazol-4-yl)methyl)-1,3,4,5-tetrahydrobenzo[4,5] imidazo [2,1-*b*]quinazolin-12(2*H*)-one (**6b**) : White powder (yield 81%), m.p. 210-212 °C; FT-IR (νmax in cm-1): 3051 (aromatic C-H), 1726 (C=O), 1584 (C=N),1469 (aromatic C=C);1H NMR(400 MHz, DMSO-d6, δ in ppm): 8.67 (s, 1H), 7.89 (d, J = 8.0 Hz, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.21-7.15 (m, 5H), 6.95(t, J = 6.3 Hz, 1H), 6.83(t, J = 7.8 Hz, 1H), 5.39 (s, 2H), 2.73 (t, J = 8.0 Hz, 2H), 2.42 (t, J = 7.8 Hz, 2H), 1.89 – 1.83 (m, 4H); 13C NMR(100MHz, DMSO-d6, δ in ppm):20.84, 20.96, 28.94, 29.09, 55.83, 111.27, 115.82, 115.86,118.09, 119.16, 121.04, 127.55, 127.67, 129.52, 130.15, 130.45, 130.74, 144.66, 147.83, 150.72, 160.63(C=O).

Data for 5-((1-(*p*-tolyl)-1*H*-1,2,3-triazol-4-yl)methyl)-1,3,4,5-tetrahydrobenzo[4,5]imidazo [2,1-*b*]quinazolin-12(2*H*)-one (**6c**): White powder (yield 82%), m.p. 218-220 °C; FT-IR (νmax in cm-1): 3053 (aromatic C-H), 1726 (C=O), 1584 (C=N),1469 (aromatic C=C); 1H NMR(400 MHz, DMSO-d6, δ in ppm): 8.66 (s, 1H), 8.44 (d, J = 7.9 Hz, 1H), 8.30 (d, J = 8.0 Hz, 1H), 7.63 (dd, J = 8.0, 5.5 Hz, 2H), 7.51 (t, J = 7.8 Hz, 1H), 7.43 – 7.32 (m, 2H), 7.26 (t, J = 8.2 Hz, 1H), 5.08 (s, 2H), 3.20 (s, 3H), 2.92 (t, J = 6.3 Hz, 2H), 2.65 (t, J = 6.0 Hz, 2H), 1.76 – 1.69 (m, 4H); 13C NMR(100MHz, DMSO-d6, δ in ppm):20.74, 20.83, 24.22, 26.07, 29.94, 55.15, 112.56, 115.66, 115.97, 119.91, 121.71, 121.77, 124.60, 126.27, 127.23, 128.87, 129.50, 130.44, 146.64, 148.23,150.16,160.62(C=O).

Data for 5-((1-(4-methoxyphenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-1,3,4,5-tetrahydrobenzo[4,5] imidazo[2,1-*b*]quinazolin-12(2*H*)-one (**6d**) : White powder (yield 87%), m.p. 236-238 °C; FT-IR (νmax in cm-1): 3069 (aromatic C-H), 1723 (C=O), 1592 (C=N),1456 (aromatic C=C),1311 (O-Me);1H NMR(400 MHz, DMSO-d6, δ in ppm): 8.70 (d, J = 7.9 Hz, 1H), 8.63 (s, 1H), 7.89 (t, J = 7.8 Hz, 1H), 7.82 (d, J = 8.5 Hz, 2H), 7.57 (t, J = 6.0 Hz, 1H), 7.20 (d, J = 5.7 Hz, 1H), 7.05 (d, J = 7.9 Hz, 2H), 4.93 (s, 2H), 3.83 (s, 3H), 2.72 (t, J = 6.3 Hz, 2H), 2.24 (t, J = 6.0 Hz, 2H), 1.69 – 1.56 (m, 4H); 13C NMR(100MHz, DMSO-d6, δ in ppm):20.74, 20.83, 26.07, 27.79, 54.46, 58.62, 112.03, 114.09, 116.86, 117.97, 119.91, 120.27, 121.15, 121.71, 126.27, 127.23, 130.44, 145.95, 148.21, 150.16, 158.36, 160.62(C=O).

Data for 5-((1-(4-bromophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-1,3,4,5-tetrahydrobenzo[4,5] imidazo[2,1-*b*]quinazolin-12(2*H*)-one (**6e**) : White powder (yield 88%), m.p. 222-224 °C; FT-IR (νmax in cm-1): 3067(aromatic C-H), 1710 (C=O), 1616 (C=N),1458 (aromatic C=C), 800 (C-Br); 1H NMR(400 MHz, DMSO-d6, δ in ppm): 8.68 (s, 1H), 7.96 (d, J = 8.0 Hz, 1H), 7.89 (d, J = 8.0 Hz, 2H), 7.63 (d, J = 8.0 Hz, 1H), 7.40 (d, J = 8.0 Hz, 2H), 7.19 (t, J = 7.8 Hz, 1H), 6.71 (t, J = 6.3 Hz, 1H), 5.07 (s, 2H), 2.88 (t, J = 6.0 Hz, 2H), 2.34 (t, J = 6.3 Hz, 2H), 1.77– 1.65 (m, 4H); 13C NMR(100MHz, DMSO-d6, δ in ppm):20.74, 20.83, 26.07, 27.79, 56.81, 112.56, 115.66, 116.95, 118.35, 119.91, 121.71, 124.60, 126.27, 127.23, 128.87, 129.50, 130.44, 144.61, 147.10, 150.16, 160.62(C=O).

Data for 5-((1-(4-nitrophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-1,3,4,5-tetrahydrobenzo[4,5] imi-dazo[2,1-*b*]quinazolin-12(2*H*)-one (**6f**) : White powder (yield 82%), m.p. 226-228 °C; FT-IR (νmax in cm-1): 2978 (aromatic C-H), 1728 (C=O), 1603 (C=N),1469 (aromatic C=C), 1351(C-NO2); 1H NMR(400 MHz, DMSO-d6, δ in ppm): 8.80 (s, 1H), 8.44 (d, J = 7.9 Hz, 1H), 8.30 (d, J = 8.0 Hz, 1H), 7.97 (d, J = 8.0 Hz, 2H), 7.77 (d, J = 8.0 Hz, 2H), 7.51 (t, J = 7.8 Hz, 1H), 7.26 (t, J = 8.2 Hz, 1H), 5.09 (s, 2H), 2.92 (t, J = 6.3 Hz, 2H), 2.65 (t, J = 6.0 Hz, 2H), 1.76 – 1.69 (m, 4H); 13C NMR(100MHz, DMSO-d6, δ in ppm): 20.65, 20.74, 20.85, 27.79, 55.82, 112.58, 114.18, 115.65, 115.97, 119.88, 121.71, 126.31, 127.22, 128.88, 129.51, 133.17, 145.29, 147.33, 150.16, 154.47, 160.62 (C=O).

## CONCLUSION

In conclusion, we have designed and synthesized novel heterocyclic compounds **6a-f** of 1,2,3-triazole functionalized quinazolinone by the reaction of 5-(prop-2-yn-1-yl)-1,3,4,5-tetrahydrobenzo[4,5]imidazo[2,1-*b*]quinazolin-12(2*H*)-one **4** with azides of aryl **5a-f** via copper catalyzed click reactions in the presence of sodium ascorbate, as a base ligand. In addition, the synthesis procedure has many advantages such as short reaction times, easy processing and higher yields, inexpensive catalyst and product purity without by-products.

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