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Selective Synthesis of 2-(1,2,3-Triazoyl) Quinazolinones through Copper-Catalyzed Multicomponent Reaction

Manoela Sacramento [1], Luís Pedro A. Piúma [1], José Edmilson R. Nascimento [1], Roberta Cargnelutti [2], Raquel G. Jacob [1], Eder João Lenardão [1] and Diego Alves [1,*]

[1] Laboratório de Síntese Orgânica Limpa, LASOL—CCQFA, Universidade Federal de Pelotas, UFPel, P.O. Box 354, Pelotas 96010-900, RS, Brazil; manoelasacramento@hotmail.com (M.S.); luisppiuma@gmail.com (L.P.A.P.); jedmilsonrn@gmail.com (J.E.R.N.); raquelgjacob@yahoo.com.br (R.G.J.); elenardao@uol.com.br (E.J.L.)

[2] Departamento de Química, CCNE, Universidade Federal de Santa Maria, UFSM, Santa Maria 97105-900, RS, Brazil; roberta.cargnelutti@ufsm.br

* Correspondence: diego.alves@ufpel.edu.br

Abstract: We describe here our results from the copper-catalyzed three component reaction of 2-azidobenzaldehyde, anthranilamide and terminal alkynes, using Et_3N as base, and DMSO as solvent. Depending on the temperature and amount of Et_3N used in the reactions, 1,2,3-triazolyl-quinazolinones or 1,2,3-triazolyl-dihydroquinazolinone could be obtained. When the reactions were performed at 100 °C using 2 equivalents of Et_3N, 1,2,3-triazolyl-dihydroquinazolinone was formed in 82% yield, whereas reactions carried out at 120 °C using 1 equivalent of Et_3N provided 1,2,3-triazolyl-quinazolinones in moderate-to-good yields.

Keywords: 1,2,3-triazoles; quinazolinones; copper catalysis; cycloaddition; multicomponent

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1. Introduction

Nitrogen heterocyclic compounds are among the most representative chemical architectures, and they are found in several natural products and commercial drugs. Quinazolinones are important members of the *N*-heterocycles, and they are building blocks in numerous natural products and widely used in the preparation of synthetic bioactive compounds, especially in the pharmaceutical industry [1]. Quinazolinones derivatives exhibit a wide range of pharmacological activities, including antimicrobial and antitubercular [2], anti-inflammatory [3], antiviral [4], anticancer [5], anti-Alzheimer [6], antimalarial [7], among others [8,9] (Figure 1).

Due to the pharmacological importance of the quinazolinone moiety, in recent years the development of new synthetic methods to access this class of compounds has attracted attention in organic synthesis. Generally, the quinazolinones are synthesized by the condensation of *o*-aminobenzamides with aldehydes [10], phenylacetic acid [11] and alcohols [12,13]. Other important protocols include carbon-supported acid-catalyzed cascade coupling of isatoic anhydrides with amides and aldehydes [14], oxidative annulation of alcohols with *o*-aminoarylnitriles [15], and Cu-catalyzed oxidative annulation of anilines, alkylamines and aldehydes [16].

Recently, the use of copper catalysis in the synthesis of quinazolinones has received much attention. An example was reported by Akhlaghinia et al. [17], who described an efficient protocol for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones using Cu(I) functionalized with aminated 3-glycidyloxypropyltrimethoxysilane with thiosemicarbazide [SBA-16/GPTMS-TSC-Cu(I)] as a catalyst in the condensation of 2-aminobenzamide and an aldehyde under solvent-free conditions (Figure 2A). In 2020, Suresh et al. [18] reported the copper-catalyzed oxidative synthesis of quinazolinones in the presence of the reusable catalyst based in $Cu_3(BTC)_2$ (BTC = 1,3,5-benzene tricarboxylate) under mild condition, as

shown in Figure 2B. There remains, however, a need for in-depth research on the synthesis of highly functionalized quinazolinones from various substrate combinations.

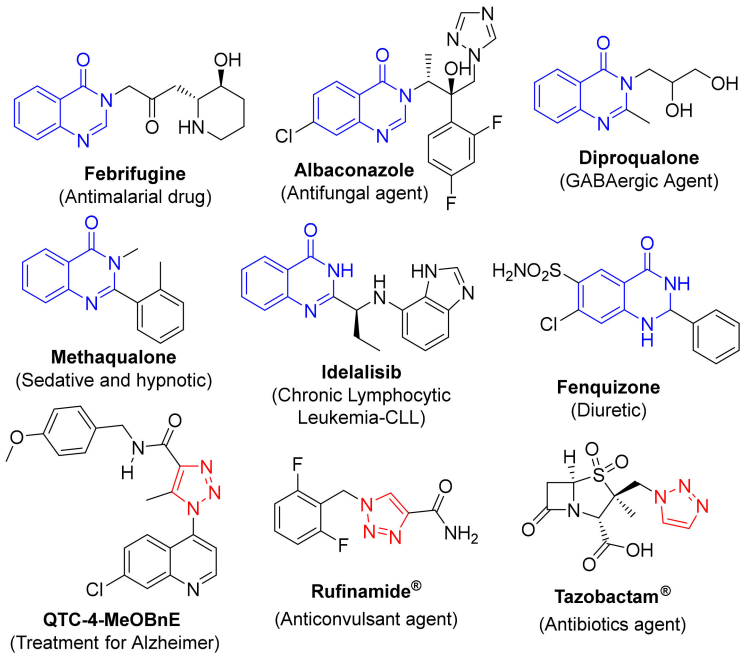


Figure 1. Quinazolinones and 1,2,3-triazoles with pharmacological activities.

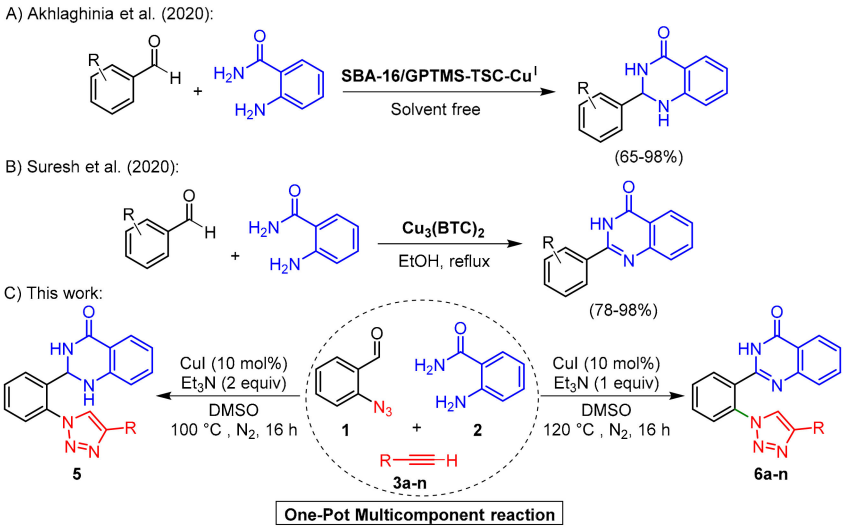


Figure 2. Recent examples of the copper-catalyzed synthesis of quinazolinones and this work.

In this sense, substituted 1,2,3-triazoles are an important and useful class of heterocycles and have received considerable attention because of their application in organic synthesis, medicinal chemistry, and materials science [19–24]. For instance, the hybrid molecule containing quinoline and 1,2,3-triazole nucleus, 1-(7-chloroquinolin-4-yl)-*N*-(4-methoxybenzyl)-5-methyl-1*H*-1,2,3-triazole-4 carboxamide (QTC-4-MeOBnE **A**), exerts therapeutic effect through multiple pathways involved in AD (Figure 1) [25,26]. Other examples are Rufinamide® [27] and Tazobactam® [28], that having anticonvulsant and antibiotic activities, respectively (Figure 1). Some 1,2,3-triazole-based compounds have shown antibacterial [29–31], anticancer [32], antifungal [33,34], antiviral [35], among others [36,37]. Efficient methods to access highly functionalized 1,2,3-triazoles include the copper-catalyzed azide-alkyne cycloaddition (CuAAC) reaction [38,39] and

the organocatalyzed [3+2] cycloaddition reactions via the generation of enamines, also known as Ramachary-Bressy-Wang organocatalytic azide-ketone [3+2]-cycloaddition (OrgAKC) [40–42]. Both CuAAC and OrgAKC are a powerful synthetic tool, due to simple reaction conditions, broader substrate scope and high atom economy.

Hybrid molecules containing the combination of quinazolinones and 1,2,3-triazoles, leads to compounds with promising pharmacological activities, such as antihistaminic [43], anticancer [44] antitubercular [2], antimicrobial [2], antihypertensive [45], and for the treatment of Alzheimer's disease [46]. Continuing our studies on the synthesis of new functionalized 1,2,3-triazoles, and due to the pharmacological importance of the 1,2,3-triazoyl-quinazolinones scaffold, we describe herein the synthesis of a range of new 2-(1,2,3-triazoyl)quinazolin-4(3*H*)-ones by a copper-catalyzed multicomponent reaction of 2-azidobenzaldehyde **1**, anthranilamide **2** and terminal alkynes **3** (Figure 2C).

2. Results

The original objective of this work was the synthesis of ten-membered heterocycles fused to a triazole ring (**4**), as a continuation of our previous works on the synthesis of medium-sized rings [47]. Thus, aiming to prepare the bicyclic triazole **4**, a mixture of 2-azidobenzaldehyde **1** (0.5 mmol), anthranilamide **2** (0.5 mmol) and phenylacetylene **3a** (0.5 mmol) in the presence of CuI (10 mol%) as a catalyst and Et_3N (2 equivalents) as a base, in DMSO (1.5 mL) and under N_2 atmosphere was stirred at 100 °C (Figure 3). However, after 16 h of reaction, the only isolated product was the triazoyl-2,3-dihydroquinazolinone **5a**, which was isolated in 82% yield. The structure of **5a** was confirmed after fully characterization by high- and low-resolution mass spectrometry, ^1H and ^{13}C NMR analysis (data are described in Supplementary Materials).

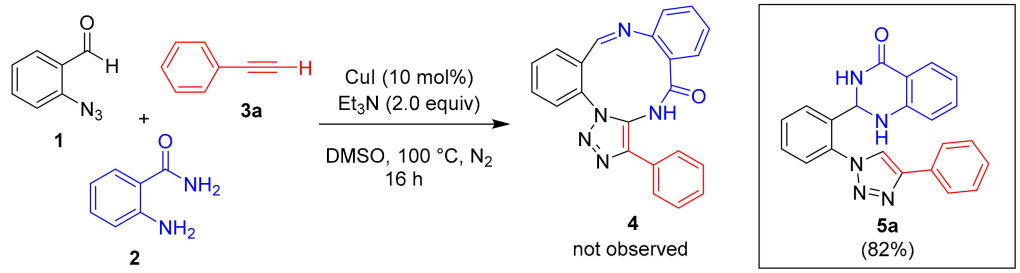
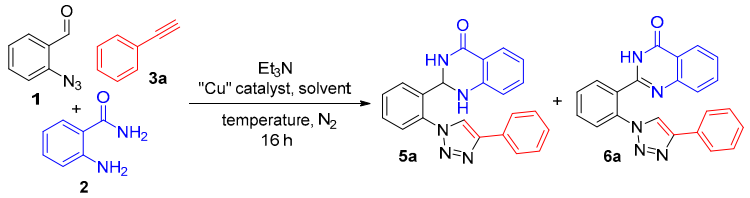


Figure 3. Synthesis of triazoylquinazolinone **5a**.

After confirming the identity of compound **5a**, and checking in the literature the importance and versatility of the quinazolinone nucleus, our efforts were aimed at optimizing the reaction described in Figure 3. For this purpose, freshly prepared 2-azidobenzaldehyde **1** (0.5 mmol), anthranilamide **2** (0.5 mmol) and phenylacetylene **3a** (0.5 mmol) were used as standard substrates, and different copper(I) and copper(II) salts, as well as a diversity of solvents and temperatures were evaluated (Table 1).

Table 1. Optimization of the reaction conditions [a].



Entry	Et_3N (mmol)	Catalyst (10 mol%)	Solvent	Temp. (°C)	Yield (%) [b]	Ratio [c] 5a:6a
1	1	CuI	DMSO	100	82	1:0
2	1	CuBr	DMSO	100	21	1:0
3	1	CuCl	DMSO	100	27	1:0

Table 1. *Cont.*

Entry	Et_3N (mmol)	Catalyst (10 mol%)	Solvent	Temp. (°C)	Yield (%) [b]	Ratio [c] 5a:6a
4	1	$CuBr_2$	DMSO	100	n.f.	–
5	1	$CuCl_2$	DMSO	100	n.f.	–
6	1	$Cu(OAc)_2 \cdot H_2O$	DMSO	100	38	1:0
7 [d]	1	CuI	DMSO	100	81	1:0
8 [e]	1	CuI	DMSO	100	31	1:0
9	1	CuI	1,4-dioxane	100	36	1:0
10	1	CuI	DMF	100	NF	1:0
11	1	CuI	PEG-400	100	58	1:0
12	1	CuI	Toluene	100	61	1:0
13 [f]	1	CuI	DMSO	100	65	1:0
14	1	CuI	DMSO	80	60	1:0
15	1	CuI	DMSO	120	88	1:0.5
16	1	CuI	DMSO	140	90	1:0.7
17	0.5	CuI	DMSO	120	87	0:1
18	0.5	CuI	DMSO	100	66	0.2:1
19	0.5	–	DMSO	120	NF	–

[a] Reaction using 2-azidobenzaldehyde **1** (0.5 mmol), anthranilamide **2** (0.5 mmol) and phenylacetylene **3a** (0.5 mmol) in the presence of copper salt as catalyst, Et_3N as base, in 1.5 mL of solvent fo 16 h. [b] Yield of **5a** + **6a**. [c] Determined by ^1H NMR. [d] Used 20 mol% of CuI. [e] Used 5 mol% of CuI. [f] Reaction using 2.0 equiv of phenylacetylene **3a**. NF = not formed.

When the same conditions of Figure 3 (Table 1, entry 1) were performed using other copper(I) salts, such as CuBr and CuCl, it was observed a significant decrease in the yield of product **5a**, from 82% to 21% and 27%, respectively (Table 1, entry 1 vs. entries 2–3). When copper(II) salts like $CuBr_2$, $CuCl_2$, and $Cu(OAc)_2 \cdot H_2O$ were tested, only the latter afforded the expected product **5a**, in 38% yield (Table 1, entries 4–6). By increasing the amount of the best catalyst (CuI) to 20 mol%, the yield of **5a** was the same, whereas when we decrease the catalyst charge to 5 mol%, a decrease in the yield to 31% was observed (Table 1, entry 7–8). By fixing 10 mol% of CuI as catalyst, the following studies were intended to verify which would be the best solvent for the reaction. When 1,4-dioxane was used, the product **5a** was obtained in 36% yield (Table 1, entry 9), while no product was observed when N,N-dimethylformamide (DMF) was used as solvent (Table 1, entry 10). Polyethylene glycol (PEG-400) and toluene were also tested, affording the product **5a** in 58% and 61% yield, respectively (Table 1, entries 11,12). These outcomes indicate that DMSO is the best solvent for the synthesis of **5a**. When a large excess of phenylacetylene **3a** was used (2.0 equiv), compound **5a** was obtained in 65% yield, a lower yield than that observed using an equivalent amount (Table 1, entry 13 vs. entry 1). A decrease in the reaction performance was observed at 80 °C instead of 100 °C, with product **5a** being obtained in 60% yield (Table 1, entry 14). Notably, when higher temperatures were evaluated (120 and 140 °C), the formation of the aromatic quinazolin-4(3H)-one **6a** was detected (Table 1, entries 15–16). The overall yield refers to the mixture of compounds **5a** and **6a** as this cannot be separated by column chromatography. The mixture of products could be observed in the ^1H NMR spectrum of the crude reaction.

Our next aim was then establishing an optimal condition to selectively lead to the formation of the aromatic quinazolinone **6a**. Firstly, the amount of base was reduced in order to verify its influence in the oxidation stage; using equivalent amount of Et_3N at 120 °C, the aromatic product **6a** was exclusively obtained in 87% yield (Table 1, entry 17). However, both the selectivity and the yield were diminished when the temperature was reduced to 100 °C (66% yield; **5a**:**6a** ratio: 0.2:1) (Table 1, entry 18 vs. entry 17). Finally, the role of the catalyst was verified, the formation of products **5a** and **6a** was not observed in the absence of CuI (Table 1, entry 19). Compound **6a**, once isolated, was characterized by high- and low-resolution mass spectrometry, ^1H and ^{13}C NMR, and X-ray diffraction

analysis (data are described in Supplementary Materials). Selected bond lengths (Å) and angles (°) for compound **6a** are summarized in Table S2 (Supplementary Materials).

Thus, with the best condition to prepare the triazoylquinazolin-4(3H)-one **6a** in hand (Table 1, entry 16), this methodology was expanded to the reaction of 2-azidobenzaldehyde **1** and anthranilamide **2** with a variety of alkyl and aryl terminal alkynes **3a-n** (Figure 4).

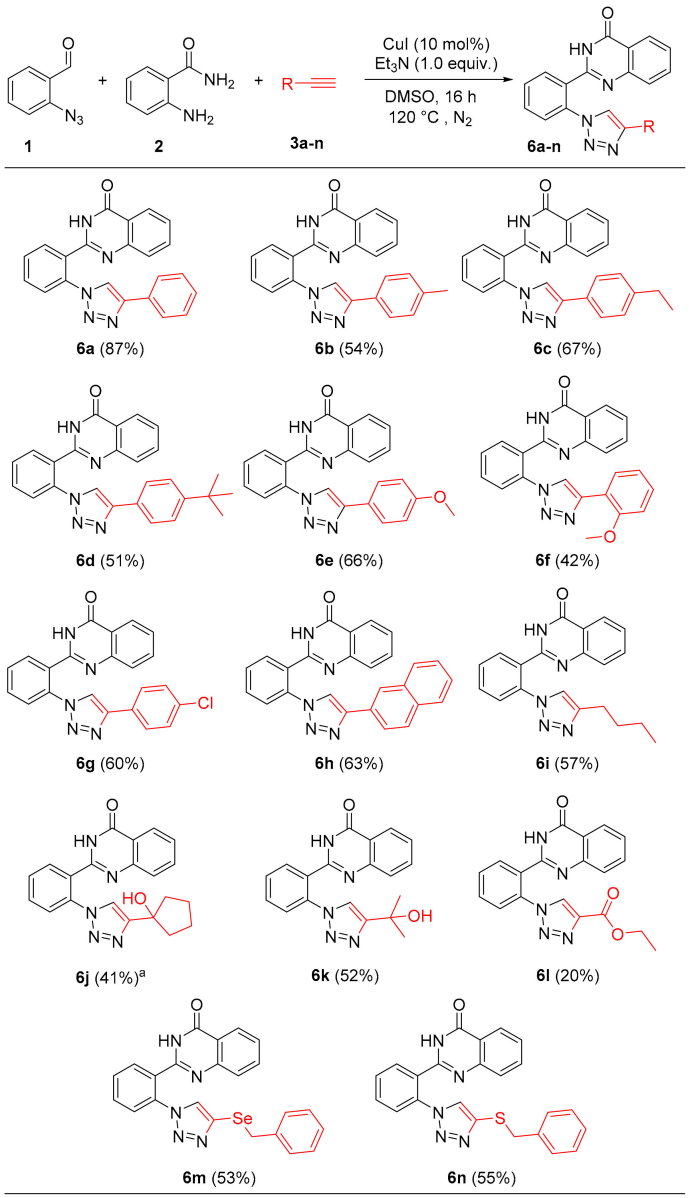


Figure 4. Reaction scope to obtain triazoylquinazolin-4(3H)-ones **6a-n**. Reactions performed using 2-azidobenzaldehyde **1** (0.5 mmol), anthranylamide **2** (0.5 mmol), terminal alkynes **3a-n** (0.5 mmol), CuI (10 mol%), and Et_3N (0.5 mmol) in DMSO (1.5 mL) at 120 °C under N_2 atmosphere for 16 h. Yields of isolated product after column chromatography. [a] Obtained as a mixture of **5j** and **6j**.

When analyzing the results shown in Figure 4, it is observed that the developed protocol tolerates a range of substituents in the alkynes counterpart. For instance, the variation of the groups at the para-position of the pendent phenyl ring, did not influence in the reactivity, and both electron-donating and electron-withdrawing substituents afforded the expected product **6** in around the same average yield. For instance, the electron-rich compounds **6b** (R = 4-Me), **6c** (R = 4-Et), **6d** (R = 4-^{t}Bu), and **6e** (R = 4-OMe) were obtained respectively in 54%, 67%, 51% and 66% yield, while the electron-poor one **6g** (R = 4-Cl) was isolated in 60% yield (Figure 4). The presence of an ortho-substituent, however, caused

a decrease in the yield, probably due a slightly steric hindrance compared to the para-substituted analogs, and compound **6f** (R = 2-OMe) was obtained in 42% yield. A good result was obtained starting from 2-ethynylnaphthalene (**3h**), with the desired product **6h** being obtained in 63% yield, while the aliphatic 1-hexyne (**3i**) afforded **6i** in 57% yield after reaction with **1** and **2**. The effect of the presence of different functional groups in the alkyne evaluated. Propagyl alcohols **3j** and **3k** satisfactorily reacted to afford the respective products **6j** and **6k** in 41% and 52%, respectively. In the case of 1-ethynylcyclopentanol (**3k**), an inseparable mixture of aromatic (**6j**) and non-aromatic (**5j**) products was obtained. The method was suitable also to ethyl propiolate (**3l**); however the expected product **5l** was obtained in only 20% yield, with the formation of several by-products. Interestingly, alkynyl selenide **3m** and alkynyl sulfide **3n** could be converted to the respective selenium- and thio- derivatives **5m** and **5n** in 53% and 55% yield, respectively.

Thus, based on our results, and on studies described in the literature [38,47–51], a plausible mechanism for the multicomponent synthesis of quinazolinones functionalized with 1,2,3-triazoles **6** was proposed (Figure 5). Firstly, the triazole nucleus is formed, through the reaction between the terminal alkyne **3**, Et_3N and CuI, generating the copper acetylide intermediate **A**. Then, intermediate **A** reacts with 2-azidobenzaldehyde (**1**), through the complexation of the nucleophilic nitrogen from azide with the metal, forming of intermediate **B**. The β-vinylidene attack of copper(I) acetylide to the terminal electrophilic nitrogen of the azide occurs, affording the unstable six-membered ring **C**, which undergoes a ring contraction to give the copper triazoyl **D** [38]. After a protolysis step, the intermediate **E** is formed and the copper catalyst is regenerated in the catalytic cycle. In the sequence, a condensation reaction occurs by the nucleophilic attack of the nitrogen atom of the amino group of the anthranilamide (**2**) to the carbonyl of intermediate **E**, eliminating a water molecule and affording the intermediate **F**. Then, an intramolecular cyclization reaction occurs after a nucleophilic attack from the amide nitrogen to the imine carbon, forming the triazoyl-2,3-dihydroquinazolinone **5**, which is oxidized in the reaction media [52–54] to the more stable aromatic quinazolin-4(3H)-one **6** (Figure 5).

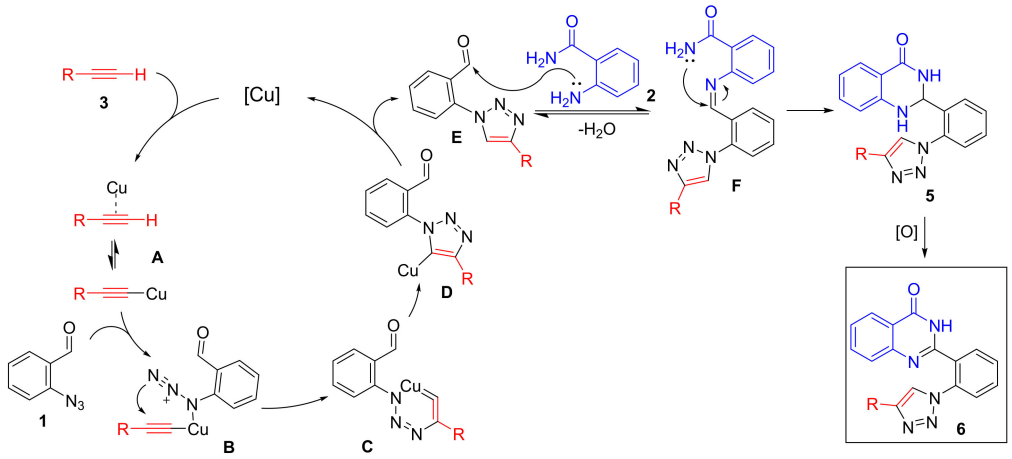


Figure 5. Proposed mechanism for the formation of triazoylquinazolin-4(3H)-one **6**.

3. Materials and Methods

3.1. General Information

The reactions were monitored by TLC carried out on Merck silica gel (60 F_{254}) by using UV light as visualizing agent and 5% vanillin in 10% H_2SO_4 and heat as developing agents. Baker silica gel (particle size 0.040–0.063 mm) was used for flash chromatography. Hydrogen nuclear magnetic resonance spectra (^{1}H NMR) were obtained at 400 MHz on Bruker DPX 400 spectrometer. Spectra were recorded in DMSO-*d6* solutions. Chemical shifts are reported in ppm, referenced to tetramethylsilane (TMS) as the external reference. Coupling constants (*J*) are reported in Hertz. Abbreviations to denote the multiplicity of a particular signal are s (singlet), d (doublet), dd (double doublet), t (triplet), q (quartet),

quin (quintet), sex (sextet) and m (multiplet). Carbon-13 nuclear magnetic resonance spectra (^{13}C NMR) were obtained at 100 MHz on Bruker DPX 400 spectrometer. Chemical shifts are reported in ppm, referenced to the solvent peak of DMSO-*d6*. Low-resolution mass spectra were obtained with a Shimadzu GC-MS-QP2010 mass spectrometer. High resolution mass spectra (HRMS) were recorded on a Bruker Micro TOF-QII spectrometer 10416. The collection of X-ray diffraction data of compound 6a was performed on a Bruker D8 Quest diffractometer equipped with a Photon 100 detector, Incoatec microfocus Montel optic X-ray tube with Cu-Kα radiation (1.54178 Å). Structure solutions and refinements were done through direct methods, with the SHELX program package [55,56]. Hydrogen atoms were included in the refinement at calculated positions. The graphical representation of the crystal structure was performed using the DIAMOND program (version 4.6.0) [57]. The crystallographic information file (CIF) for the compound 6a was deposited at the Cambridge Crystallographic Data Centre (CCDC) under identification number 2106971. Crystal data and more details of the data collection and refinement of 6a is provided in Table S1 (Supplementary Materials).

3.2. General Procedure for the Synthesis of Triazoylquinazolin-4(3H)-ones **6a–n**

In a test tube was added 2-azidobenzaldehyde (1, 0.5 mmol), anthranilamide (2, 0.5 mmol), CuI (10 mol%). Then, DMSO (1.5 mL) was added, followed by triethylamine (0.5 mmol) and the terminal alkyne **3a–n** (0.5 mmol). The system was heated to 120 °C under a nitrogen atmosphere and magnetic stirring for 16 h. Afterwards, the organic phase was received in water (20 mL), extracted with dichloromethane (3 × 10 mL), dried with $MgSO_4$, and concentrated on a rotary evaporator followed by a vacuum pump. Finally, a purification by column chromatography of silica gel as a stationary phase, and a mixture of hexanes/ethyl acetate as eluent (50/50) was performed, providing the desired products **6a–n** (20–87%).

4. Conclusions

In this work, an efficient method was developed for the synthesis of a series of unprecedented quinazolinones functionalized with 1,2,3-triazoles in modrate to good yields. The reaction involves a 1,3-dipolar cycloaddition between terminal alkynes and 2-azidobenzaldehyde, to obtain the triazole nucleus, followed by a cyclocondensation with anthranilamide to form the quinazolinone nucleus, which is oxidized in situ to the aromatic product. Fourteen new compounds (**6a–n**) were obtained in yields from 20 to 87%, presenting in their structure different substituents with a diversity of functional groups, including aryl, naphthyl, alkyl, ester, alcohol, as well as sulfide and selenide.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/catal11101170/s1, ^{1}H and ^{13}C NMR spectra of all compounds. Table S1. Crystallographic and structure refinement data for compound **6a**, Figure S1. Ellipsoid representations (50% probability) of **6a**, Figure S2. Molecular structure of **6a** determined by single-crystal X-ray crystallography, Table S2. Selected bond lengths (Å) and angles (°) of both independent molecules present in the compound **6a**.

Author Contributions: Conceptualization, J.E.R.N., R.G.J., E.J.L. and D.A.; methodology, J.E.R.N., L.P.A.P., M.S. and R.C.; investigation, J.E.R.N., L.P.A.P. and M.S.; resources, E.J.L. and D.A.; data curation, J.E.R.N., R.C., E.J.L. and D.A., writing—original draft preparation, J.E.R.N. and M.S.; writing—review and editing, R.C., E.J.L. and D.A.; visualization, R.C., R.G.J., E.J.L. and D.A.; supervision, R.G.J., E.J.L. and D.A.; funding acquisition, R.G.J., E.J.L. and D.A. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: The authors declare no conflict of interest.

References

1. Auti, P.S.; George, G.; Paul, A.T. Recent advances in the pharmacological diversification of quinazoline/quinazolinone hybrids. *RSC Adv.* **2020**, *10*, 41353–41392. [CrossRef]
2. Pandey, S.K.; Yadava, U.; Upadhyay, A.; Sharma, M.L. Synthesis, biological evaluation and molecular docking studies of novel quinazolinones as antitubercular and antimicrobial agents. *Bioorg. Chem.* **2021**, *108*, 104611. [CrossRef]
3. Abdel-Aziz, A.A.-M.; Abou-Zeid, L.A.; ElTahir, K.E.H.; Ayyad, R.R.; El-Sayed, M.A.-A.; El-Azab, A.S. Synthesis, anti-inflammatory, analgesic, COX-1/2 inhibitory activities and molecular docking studies of substituted 2-mercapto-4(3*H*)-quinazolinones. *Eur. J. Med. Chem.* **2016**, *121*, 410–421. [CrossRef]
4. Brown, E.C.; Kong, T.; McNulty, J.; D'Aiuto, L.; Williamson, K.; McClain, L.; Piazza, P.; Nimgaonkar, L.V. Discovery of potent antiviral (HSV-1) quinazolinones and initial structure-activity relationship studies. *Bioorg. Med. Chem. Lett.* **2017**, *27*, 4601–4605. [CrossRef]
5. Gatadi, S.; Pulivendala, G.; Gour, J.; Malasala, S.; Bujji, S.; Parupalli, R.; Shaikh, M.; Godugu, C.; Nanduri, S. Synthesis and evaluation of new 4(3*H*)-quinazolinone derivatives as potential anticancer agentes. *J. Mol. Struct.* **2020**, *1200*, 127097. [CrossRef]
6. Decker, M. Novel inhibitors of acetyl- and butyrylcholinesterase derived from the alkaloids dehydroevodiamine and rutaecarpine. *Eur. J. Med. Chem.* **2005**, *40*, 305–313. [CrossRef] [PubMed]
7. Zhu, S.; Chandrashekar, G.; Meng, L.; Robinson, K.; Chatterji, D. Febrifugine analogue compounds: Synthesis and antimalarial evaluation. *Bioorg. Med. Chem.* **2012**, *20*, 927–932. [CrossRef] [PubMed]
8. Alagarsamy, V.; Chitra, K.; Saravanan, G.; Solomon, V.R.; Sulthana, M.T.; Narendhar, B. An overview of quinazolines: Pharmacological significance and recent developments. *Eur. J. Med. Chem.* **2018**, *151*, 628–685. [CrossRef] [PubMed]
9. He, D.; Wang, M.; Zhao, S.; Shu, Y.; Zeng, H.; Xiao, C.; Lu, C.; Liu, Y. Pharmaceutical prospects of naturally occurring quinazolinone and its derivatives. *Fitoterapia* **2017**, *119*, 136–149. [CrossRef]
10. Gupta, R.; Arora, G.; Yadav, Y.; Dixit, R.; Srivastavab, A.; Sharma, R.K. A magnetically retrievable copper ionic liquid nanocatalyst for cyclooxidative synthesis of 2-phenylquinazolin-4(3*H*)-ones. *Dalton Trans.* **2021**, *50*, 890–898. [CrossRef]
11. To, T.A.; Vo, Y.H.; Nguyen, H.T.T.; Ha, P.T.M.; Doan, S.H.; Doan, T.L.H.; Li, S.; Le, H.V.; Tu, T.N.; Phan, N.T.S. Iron-catalyzed one-pot sequential transformations: Synthesis of quinazolinones via oxidative Csp^3-H bond activation using a new metal-organic framework as catalyst. *J. Catal.* **2019**, *370*, 11–20. [CrossRef]
12. Kerdphon, S.; Sanghong, P.; Chatwichien, J.; Choommongkol, V.; Rithchumpon, P.; Singh, T.; Meepowpan, P. Commercial copper-catalyzed aerobic oxidative synthesis of quinazolinones from 2-aminobenzamide and methanol. *Eur. J. Org. Chem.* **2020**, 2730–2734. [CrossRef]
13. Wang, Y.; Meng, X.; Chen, G.; Zhao, P. Direct synthesis of quinazolinones by heterogeneous $Cu(OH)_X$/OMS-2 catalyst under oxygen. *Catal. Commun.* **2018**, *104*, 106–111. [CrossRef]
14. Zhang, X.; Luo, C.; Chen, X.; Ma, W.; Li, B.; Lin, Z.; Chen, X.; Li, Y.; Xie, F. Direct synthesis of quinazolinones *via* the carbon-supported acid-catalyzed cascade reaction of isatoic anhydrides with amides and aldehydes. *Tetrahedron Lett.* **2021**, *66*, 152835. [CrossRef]
15. Wang, Q.; Lv, M.; Liu, J.; Li, Y.; Xu, Q.; Xu, Z.; Cao, H. Efficient synthesis of quinazolinones by transition-metal-free direct aerobic oxidative cascade annulation of alcohols with *o*-aminoarylnitriles. *ChemSusChem* **2019**, *12*, 3043–3048. [CrossRef] [PubMed]
16. Liang, Y.; Tan, Z.; Jiang, H.; Zhu, Z.; Zhang, M. Copper-catalyzed oxidative multicomponent annulation reaction for direct synthesis of quinazolinones via an imine-protection strategy. *Org. Lett.* **2019**, *21*, 4725–4728. [CrossRef]
17. Erfan, M.A.; Akhlaghinia, B.; Ghodsinia, S.S.E. An efficient green protocol for synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones using SBA-16/GPTMS-TSC-Cu^I under solvent-free conditions. *ChemistrySelect* **2020**, *5*, 2306–2316. [CrossRef]
18. Latha, G.; Devarajan, N.; Suresh, P. Framework copper catalyzed oxidative synthesis of quinazolinones: A benign approach using $Cu_3(BTC)_2$ MOF as an efficient and reusable catalyst. *ChemistrySelect* **2020**, *5*, 10041–10047. [CrossRef]
19. Rani, A.; Singh, G.; Singh, A.; Maqbool, U.; Kaur, G.; Singh, J. CuAAC-ensembled 1,2,3-triazole-linked isosteres as pharmacophores in drug discovery: Review. *RSC Adv.* **2020**, *10*, 5610–5635. [CrossRef]
20. Jain, A.; Piplani, P. Exploring the chemistry and therapeutic potential of triazoles: A comprehensive literature review. *Mini Rev. Med. Chem.* **2019**, *19*, 1298–1368. [CrossRef]
21. Mantoani, S.P.; Andrade, P.; Chierrito, T.P.C.; Figueredo, A.S.; Carvalho, I. Potential triazole-based molecules for the treatment of neglected diseases. *Curr. Med. Chem.* **2019**, *26*, 4403–4434. [CrossRef]
22. Asif, M. Pharmacological activities of triazole analogues as antibacterial, antifungal, antiviral agents. *Pharm. Sci. Asia* **2017**, *44*, 59–74. [CrossRef]

23. Bonandi, E.; Christodoulou, M.S.; Fumagalli, G.; Perdicchia, D.; Rastelli, G.; Passarella, D. The 1,2,3-triazole ring as a bioisostere in medicinal chemistry. *Drug Discov. Today* **2017**, *22*, 1572–1581. [CrossRef]
24. Massarotti, A.; Aprile, S.; Mercalli, V.; Del Grosso, E.; Grosa, G.; Sorba, G.; Tron, G.C. Are 1,4- and 1,5-disubstituted 1,2,3-triazoles good pharmacophoric groups? *ChemMedChem* **2014**, *9*, 2497–2508. [CrossRef]
25. Fronza, M.G.; Baldinotti, R.; Fetter, J.; Sacramento, M.; Sousa, F.S.S.; Seixas, F.K.; Collares, T.; Alves, D.; Pratico, D.; Savegnago, L. QTC-4-MeOBnE Rescues Scopolamine-Induced Memory Deficits in Mice by Targeting Oxidative Stress, Neuronal Plasticity, and Apoptosis. *ACS Chem. Neurosci.* **2020**, *11*, 1259–1269. [CrossRef]
26. Fronza, M.G.; Baldinotti, R.; Sacramento, M.; Gutierres, J.; Carvalho, F.B.; Fernandes, M.C.; Sousa, F.S.S.; Seixas, F.K.; Collares, T.; Alves, D.; et al. Effect of QTC-4-MeOBnE Treatment on Memory, Neurodegeneration, and Neurogenesis in a Streptozotocin-Induced Mouse Model of Alzheimer's Disease. *ACS Chem. Neurosci.* **2021**, *12*, 109–122. [CrossRef]
27. Cheng-Hakimian, A.; Anderson, G.D.; Miller, J.W. Rufinamide: Pharmacology, clinical trials, and role in clinical practice. *Int. J. Clin. Pract.* **2006**, *60*, 1497–1501. [CrossRef] [PubMed]
28. Sanders, W.E., Jr.; Sanders, C.C. Piperacillin/Tazobactam: A critical review of the evolving clinical literature. *Clin. Infect. Dis.* **1996**, *22*, 107–123. [CrossRef] [PubMed]
29. Aufort, M.; Herscovici, J.; Bouhours, P.; Moreau, N.; Girard, C. Synthesis and antibiotic activity of a small molecules library of 1,2,3-triazole derivatives. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1195–1198. [CrossRef] [PubMed]
30. Leaver, D.J.; Dawson, R.M.; White, J.M.; Polyzos, A.; Hughes, A.B. Synthesis of 1,2,3-triazole linked galactopyranosides and evaluation of cholera toxin inhibition. *Org. Biomol. Chem.* **2011**, *9*, 8465–8474. [CrossRef]
31. Zhang, B. Comprehensive review on the anti-bacterial activity of 1,2,3-triazole hybrids. *Eur. J. Med. Chem.* **2019**, *168*, 357–372. [CrossRef]
32. Xu, Z.; Zhao, S.-J.; Liu, Y. 1,2,3-Triazole-containing hybrids as potential anticancer agents: Current developments, action mechanisms and structure-activity relationships. *Eur. J. Med. Chem.* **2019**, *183*, 111700. [CrossRef]
33. Lima-Neto, R.G.; Cavalcante, N.N.M.; Srivastava, R.M.; Junior, F.J.B.M.; Wanderley, A.G.; Neves, R.P.; Anjos, A.P. Synthesis of 1,2,3-triazole derivatives and in vitro antifungal evaluation on *Candida* strains. *Molecules* **2012**, *17*, 5882–5892. [CrossRef]
34. Shalini, K.; Kumar, N.; Drabu, S. Advances in synthetic approach to and antifungal activity of triazoles. *Beilstein J. Org. Chem.* **2011**, *7*, 668–677. [CrossRef]
35. Silva, F.C.; Souza, M.C.B.V.; Frugulhetti, I.I.P.; Castro, H.C.; Souza, S.L.O.; Souza, T.M.L.; Rodrigues, D.Q.; Souza, A.M.T.; Abreu, P.A.; Passamani, F.; et al. Synthesis, HIV-RT inhibitory activity and SAR of 1-benzyl-1*H*-1,2,3-triazole derivatives of carbohydrates. *Eur. J. Med. Chem.* **2009**, *44*, 373–383. [CrossRef]
36. Raj, R.; Singh, P.; Singh, P.; Gut, J.; Rosenthal, P.J.; Kumar, V. Azide-alkyne cycloaddition *en route* to 1*H*-1,2,3-triazole-tethered 7-chloroquinoline-isatin chimeras: Synthesis and antimalarial evaluation. *Eur. J. Med. Chem.* **2013**, *62*, 590–596. [CrossRef]
37. Im, C.; Maiti, S.N.; Micetich, R.G.; Daneshtalab, M.; Atchison, K.; Phillips, O.A.; Kunugita, C.J. Synthesis and β-lactamase inhibitory activity of 6-[(1-heteroarylthioethyl-1, 2, 3-triazol-4-yl)-methylene]penam sulfones. *J. Antibiot.* **1994**, *47*, 1030–1040. [CrossRef] [PubMed]
38. Rostovtsev, V.V.; Green, L.G.; Fokin, V.V.; Sharpless, K.B. A stepwise Huisgen cycloaddition process: Copper(I)-catalyzed regioselective "ligation" of azides and terminal alkynes. *Angew. Chem. Int. Ed.* **2002**, *41*, 2596–2599. [CrossRef]
39. Tornøe, C.W.; Christensen, C.; Meldal, M. Peptidotriazoles on solid phase: [1,2,3]-triazoles by regiospecific copper(I)-catalyzed 1,3-dipolar cycloadditions of terminal alkynes to azides. *J. Org. Chem.* **2002**, *67*, 3057–3064. [CrossRef] [PubMed]
40. Ramachary, D.B.; Ramakumar, K.; Narayana, V.V. Amino Acid-Catalyzed Cascade [3+2]-Cycloaddition/Hydrolysis Reactions Based on the Push–Pull Dienamine Platform: Synthesis of Highly Functionalized *N*H-1,2,3-Triazoles. *Chem. Eur. J.* **2008**, *14*, 9143–9147. [CrossRef]
41. Belkheira, M.; El Abed, D.; Pons, J.M.; Bressy, C. Organocatalytic Synthesis of 1,2,3-Triazoles from Unactivated Ketones and Arylazides. *Chem. Eur. J.* **2011**, *17*, 12917–12921. [CrossRef]
42. Danence, L.J.T.; Gao, Y.; Li, M.; Huang, Y.; Wang, J. Organocatalytic Enamide–Azide Cycloaddition Reactions: Regiospecific Synthesis of 1,4,5-Trisubstituted-1,2,3-Triazoles. *Chem. Eur. J.* **2011**, *17*, 3584–3587. [CrossRef] [PubMed]
43. Alagarsamy, V.; Solomon, V.R.; Murugan, M. Synthesis and pharmacological investigation of novel 4-benzyl-1-substituted-4*H*-[1,2,4]triazolo[4,3-*a*]quinazolin-5-ones as new class of H_1-antihistaminic agents. *Bioorg. Med. Chem.* **2007**, *15*, 4009–4015. [CrossRef] [PubMed]
44. Driowya, M.; Leclercq, J.; Verones, V.; Barczyk, A.; Lecoeur, M.; Renault, N.; Flouquet, N.; Ghinet, A.; Berthelot, P.; Lebegue, N. Synthesis of triazoloquinazolinone based compounds as tubulin polymerization inhibitors and vascular disrupting agents. *Eur. J. Med. Chem.* **2016**, *115*, 393–405. [CrossRef] [PubMed]
45. Ram, V.J.; Srimal, R.C.; Kushwaha, D.S.; Mishra, L. Chemotherapeutic agents. XIX. Synthesis of [1,2,4]-Triazoloquinazolinones and related compounds as antihypertensive agents. *J. Prakt. Chem.* **1990**, *332*, 629–639. [CrossRef]
46. Bertelli, L.; Biagi, G.; Giorgi, I.; Livi, O.; Manera, C.; Scartoni, V.; Lucacchini, A.; Giannaccini, G.; Barili, P.L. Substituted 1,2,3-triazolo[1,5-a]quinazolines: Synthesis and binding to benzodiazepine and adenosine receptors. *Eur. J. Med. Chem.* **2000**, *35*, 333–341. [CrossRef]
47. Peringer, F.; Nascimento, J.E.R.; Abib, P.B.; Barcellos, T.; Eycken, E.V.V.; Perin, G.; Jacob, R.G.; Alves, D. Copper-catalyzed multicomponent reactions: Synthesis of fused 1,2,3-triazolo-1,3,6-triazonines. *Eur. J. Org. Chem.* **2017**, *2017*, 2579. [CrossRef]

48. Hein, J.E.; Fokin, V.V. Copper-catalyzed azide–alkynecycloaddition (CuAAC) and beyond: New reactivity of copper(i) acetylides. *Chem. Soc. Rev.* **2010**, *39*, 1302–1315. [CrossRef]
49. Liang, L.; Astruc, D. The copper(I)-catalyzed alkyne-azide cycloaddition (CuAAC) "click" reaction and its applications. An overview. *Coord. Chem. Rev.* **2011**, *255*, 2933–2945. [CrossRef]
50. Li, L.; Zang, Z. Development and Applications of the Copper-Catalyzed Azide-Alkyne Cycloaddition (CuAAC) as a Bioorthogonal Reaction. *Molecules* **2016**, *21*, 1393. [CrossRef]
51. Rammah, M.M.; Gati, W.; Mtiraoui, H.; Rammah, M.E.B.; Ciamala, K.; Knorr, M.; Rousselin, Y.; Kubicki, M.M. Synthesis of Isoxazole and 1,2,3-Triazole Isoindole Derivatives via Silver- and Copper-Catalyzed 1,3-Dipolar Cycloaddition Reaction. *Molecules* **2016**, *21*, 307. [CrossRef] [PubMed]
52. Guo, S.; Li, Y.; Tao, L.; Zhang, W.; Fan, X. Rapid assembly of quinazolinone scaffold *via* copper-catalyzed tandem reaction of 2-bromobenzamides with aldehydes and aqueous ammonia: Application to the synthesis of the alkaloid tryptanthrin. *RSC Adv.* **2014**, *4*, 59289–59296. [CrossRef]
53. Hu, B.-Q.; Wang, L.-X.; Yang, L.; Xiang, J.-F.; Tang, Y.-L. Copper-Catalyzed Intramolecular C–C Bond Cleavage To Construct 2-Substituted Quinazolinones. *Eur. J. Org. Chem.* **2015**, 4504–4509. [CrossRef]
54. Upadhyaya, K.; Thakur, R.K.; Shukla, S.K.; Tripathi, R.P. One-Pot Copper(I)-Catalyzed Ligand/Base-Free Tandem Cyclooxidative Synthesis of Quinazolinones. *J. Org. Chem.* **2016**, *81*, 5046–5055. [CrossRef] [PubMed]
55. Sheldrick, G.M. Crystal structure refinement with SHELXL *Acta Crystallogr. Sect. C Struct. Chem.* **2015**, *71*, 3–8. [CrossRef] [PubMed]
56. Sheldrick, G.M. A short history of SHELX. *Acta Crystallogr. Sect. A Found. Crystallogr.* **2008**, *64*, 112–122. [CrossRef]
57. Brandenburg, K.; Putz, H. *Diamond—Crystal and Molecular Structure Visualization*; Crystal Impact: Bonn, Germany, 2014.