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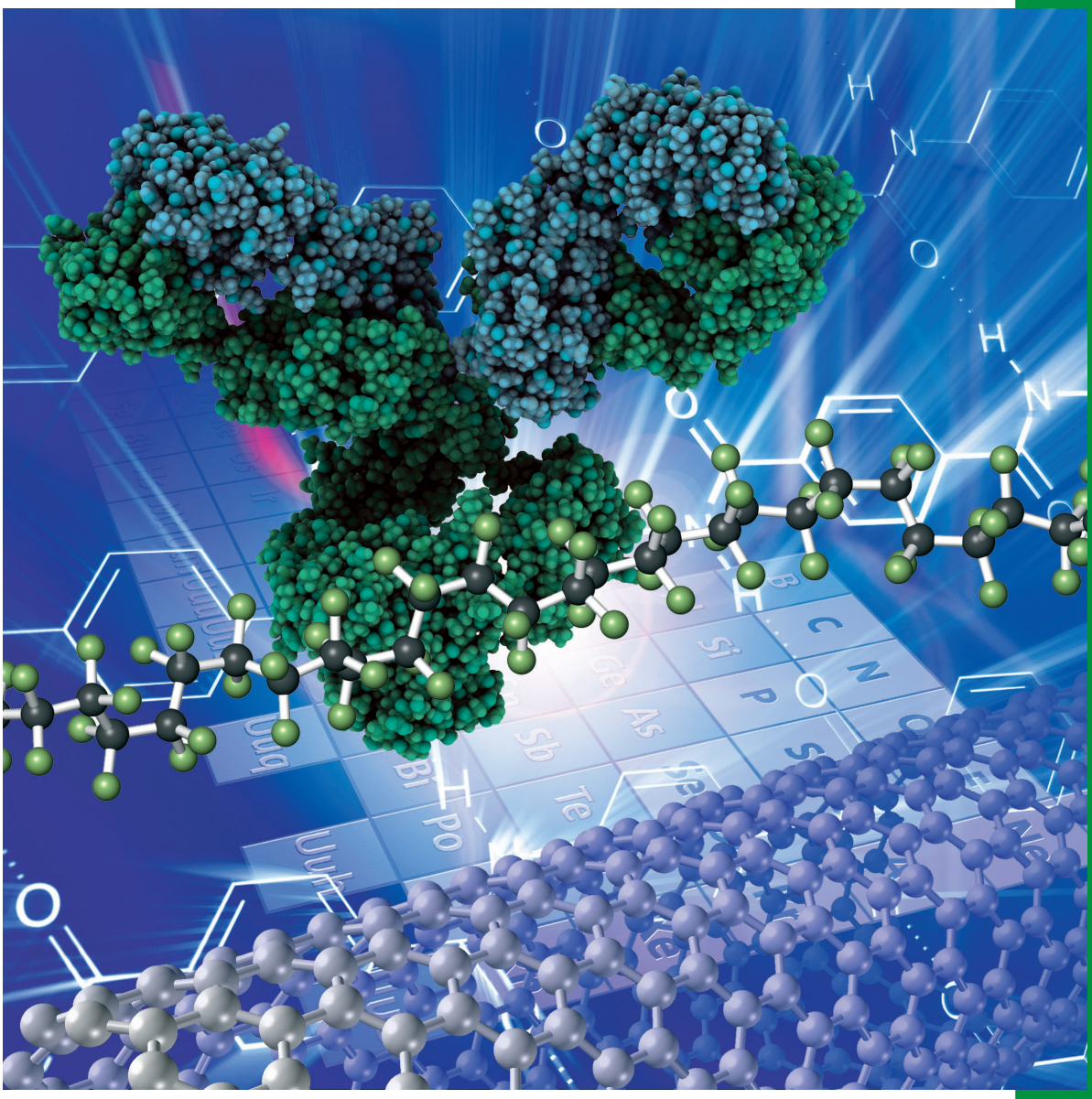

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Copper(I)-Catalyzed Azide-Alkyne Cycloaddition Microwave-Assisted: Preparation of 7-(4-Substituted-1*H*-1,2,3-Triazol-1-yl)-Fluoroquinolones

Hiram Hernández-López,[a] Socorro Leyva-Ramos,*[b] Rosa Delia Moncada-Martínez,[a] Jesús Adrián López,[c] and Jaime Cardoso-Ortiz[a]

Nowadays, the pharmaceutical industry faces the challenge of innovating and increasing the productivity of new medicines due to the increasing multidrug resistance among bacteria, viruses and fungi. The main objective of the present study is connected quinolone and triazole molecules to enhance and broad antibacterial spectrum as well as to have multiple mechanisms of action. Preparation of 4-substituted-1*H*-1,2,3-triazol-1-yl in C-7 of 6-fluoro- and 6,8-difluoro-quinolone ring is showed. The synthesis involved the preparation of intermediate ethyl 7-azide-1-ethyl-fluoroquinolone-3-carboxylate, followed by copper(I)-catalyzed azide-alkyne cycloaddition to give 13 derivatives. The cycloaddition was carried out by two different methods, where it was observed that the microwave radiation was the best reaction condition, obtaining a range of yields of 47–93%, at 140 °C, 125W_{max} for 10 minutes. Therefore, this methodology provided an easy pathway to synthesize a library of fluoroquinolones coupled to 1,2,3-triazole, still unexplored.

Introduction

Quinolones and its derivatives form an important class of compounds, which are widely used in medicine, mainly as antibacterial agents, but also as antidiabetic, antitumor, antitubercular, antimalarial, antiviral, and anti-HIV agents,[1-6] as a result of activity, significant tissue penetration, and convenient routes of administration. Intense research for potent fluoroquinolone derivatives has been possible due to modifications in the quinolone nucleus through the addition of different substituents at the N-1, C-5, C-6, C-7, and C-8, and the formation of fused rings, between the 5 and 6, 6 and 7, or 7 and 8 positions.[7,8] The most successful compounds developed are based on modifications at C-7, and it has been found that the spectrum, level of antibacterial activity, inhibition of DNA gyrase or topoisomerase IV, and cell permeability are highly affected by the nature of the C-7 substituent group. Substituents that have been studied included: medium-sized *N*-heterocyclic ring (5- and 6-membered),[9,10] *N*-substituted piperazine,[11,12] linear substituents with one or two heteroatoms (-$NHNH_2$, -NHR, -$NHCH_2CH_2NH_2$), methyl-, chloro-, and 1,2,3-triazole-derivatives.[13-18] The 1,2,3 moiety does not occur in nature, although the synthetic molecules containing 1,2,3-triazole unit show diverse biological activities including anti-obesity, antiallergic, antibacterial, antiparasitic, herbicidal, fungicidal, and anti-HIV.[19-23] 1,2,3-triazole moieties are stable to metabolic degradation, oxidative/reductions conditions, and are capable of dipole-dipole interactions and hydrogen bonding, which can be favourable in the binding of biomolecular targets and for solubility.[24,25]

In order to cover those exploratory biological needs, a strategy of synthesis of triazole-fluoroquinolone pharmacophore library that involve a low time of reaction, good yields without use of inert atmosphere, and minimal purification, is required. The purpose of this investigation is to provide a more advantageous method for the synthesis of 7-(4-substituted-1*H*-1,2,3-triazol-1-yl)-fluoroquinolones. The derivatives were prepared by conventional as well as microwave irradiation.

Results and Discussion

The copper-catalyzed azide-alkyne cycloaddition (CuAAC) reaction is well suited to many solution-phase applications with the simple use of Cu(I) salts, either added directly or generated by reduction of Cu(II) or oxidation of Cu(0).[26] The reaction is quantitative, regioselective, thermodynamic and kinetically favorable. On preliminary results, the ethyl 7-azide-1-ethyl-6,8-difluoroquinolone-3-carboxylate **1**, and ethyl 7-azide-1-ethyl-6-fluoroquinolone-3-carboxylate **2** were prepared from 2,3,4-trifluoro-, or 3,4-difluoro-aniline, according to the literature method.[27] Azide fluoroquinolone **1**, was first synthesized and used for the CuAAC by CuI and NaOH (0.5 N).[28, 29] The Cu(I) species may either be introduced as performed complexes, but

[a] *Dr. H. Hernández-López, R. D. Moncada-Martínez, Dr. J. Cardoso-Ortiz*
Unidad Académica de Ciencias Químicas, Universidad Autónoma de Zacatecas, Carretera Zacatecas-Guadalajara km 6, Ejido la Escondida s/n, Zacatecas, Zacatecas, 98160, México
[b] *Dr. S. Leyva-Ramos*
Facultad de Ciencias Químicas, Universidad Autónoma de San Luis Potosí, Av. Manuel Nava 6, Zona Universitaria, San Luis Potosí, San Luis Potosí, 78210, México
E-mail: sleyva@uaslp.mx
[c] *Dr. J. A. López*
Unidad Académica de Ciencias Biológicas, Universidad Autónoma de Zacatecas, Av. Preparatoria s/n, Col Hidráulica. Zacatecas, Zacatecas98068, México

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these conditions did not generate favorable results, even when a variety of solvents (MeOH, CH_3CN, DMSO, DMF, H_2O/acetone, H_2O/CH_3CN) were used in combination with other bases as DIPEA or TEA, or when the temperature was increased to 140 °C.[26] It is possible that the poor stability of Cu^{I} and its rapid oxidation to Cu^{II} does not allow catalyzed the cycloaddition reaction,[30, 31] which led to the fluoroquinolone azide being easily broken with the irreversible loss of N_2, producing singlet nitrene that generated secondary products by selective O–H or N–H insertion with CH_3OH or DEA respectively or proton abstraction.[32] However, triazole ring was obtained when the catalyst CuI was exchanged for a mixture of $CuSO_4$ and sodium ascorbate in solid form, obtaining low yields (Table 1, entry 2); but when catalyst was used in a solution system, $CuSO_4$ (1 M) and sodium ascorbate (7.5%),[33-35] the yields increased to 80% with 5 days of reaction (Table 1, entry 3). On the other hand, temperatures below 50 °C did not proceed, temperatures above it were not made to prevent the formation of nitrene group in the quinolone ring by thermolysis. When the reaction time was extended to 10 days, no differences in yields were observed.

Furthermore, the strategy of synthesis of a series of 7-(4-substituted)-triazolyl-6,8-difluoroquinolones by CuAAC reaction (table 3) was possible in medium efficiency and a simple work-up procedure. With a one-pot reaction starting from the appropriate azide **1** and alkyne-derivative **3a-j**, the Cu(I) catalyst was prepared *in situ* by copper sulphate (II) and sodium ascorbate. After heating the reaction mixture at 50 °C for one weak in DMF, the triazole product **4a-i** was isolated by simple filtration and recrystallization with CH_3CN and yields ranging from 41% to 78%. The structures of triazole **4a-i** obtained, were confirmed by lack of the band in 2127 cm^{-1} of N_3 and the increment of bands in the region of 1620 to 1450 cm^{-1} due to aromatic and triazole C=C bonds. The stretching absorptions bands for C–N appeared as multiple bands around 1300 to 1000 cm^{-1} in the IR spectrum. The ^{1}H NMR spectra exhibited a single peak between 8.68 and 7.83 ppm, and the ^{13}C NMR spectra showed two signals in the range of 156.60-151.06 and 136.60-122.02 ppm for the triazolinic ring. Compound **5j** could not characterize by ^{13}C NMR due to its low solubility in DMSO-d_6.

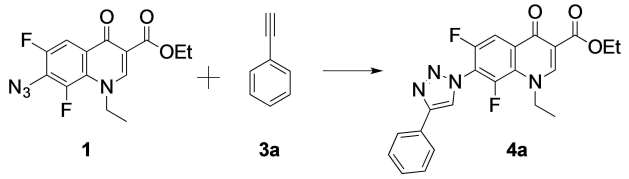
The fragmentation pattern of the synthesized triazole-fluoroquinolone, showed the formation of several ions, which were generated through elimination of C_2H_4 (transforming ester to carboxylic acid), as well as the loss of CO_2, CO, OH, C_2H_4 (in *N*-1 position), and in some cases (**4a**, **4b**, **4i**, **5g**), the triazole ring was disrupted into azide-fluoroquinolone. This triazole ring fragmentation is consistent with the retro-cycloaddition 1,3-dipolar reaction observed under ultrasonic or ultraviolet conditions.[36, 37]

Microwave radiation was used as an alternative route proposed to a drastic reduction in the reaction time, minimize cumbersome work-up, and get better yield.[38-40] Microwave radiation uses relatively low energy that is non-ionizing and cannot break chemical bonds; it can only make molecules rotate. Conventional heating is slow, relying on convection currents and thermal conductivity, whereas microwave heating is fast and occurs on a molecular level. In the preliminary proofs, the 50 °C was maintained as maximum temperature to avoid decomposition of azide group, situations in which the formation of triazole was not achieved when was used solvent such as toluene, *n*-hexane, and even free solvent conditions (use of phenylacetylene as reactant and solvent).[39] High temperatures such as 78 °C allowed a 25% yield in 10 minutes with DMF, but potency during the reaction decreased to 20 W. However, conditions of 125W_{max}, 140 °C, and 10 minutes allowed a yield of 80% (Table 2).

Use of protic solvents increased the synthesis of by-products, while CH_3CN with close vessel and automatic control of pressure, showed a 54% yield without further purifications (table 2, entry 5), which allows to explore the reaction and modify just the time interval, increasing the yields of **4a-i** and **5g-j** when the radiation is used for 2 minutes, then cooling, 2 minutes then cooling, and 2 minutes then cooling.

Thus, the synthesis of several triazole-quinolones **4a-i** and **5g-j** was achieved under microwave heat in good yields, ranging between 47 to 93% (Table 3), and decreasing the

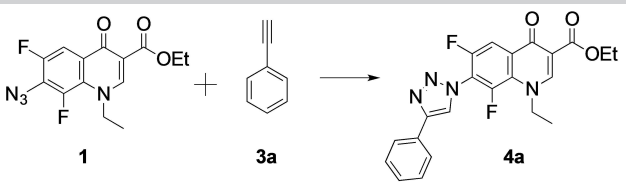
Table 1. Heat convection for the synthesis of 7-triazolyl-fluoroquinolone by CuAAC.



1 **3a** **4a**

Entry	Cat (5% mol)	Na-Asc (20% mol)	Solvent	T (°C)	t (day)	Yield (%)
1	$CuSO_4$	Solid	MeOH	50	2	- -
2	$CuSO_4$	Solid	DMF	50	3	16
3	$CuSO_4$ (1 M)	Solution (7.5%)	DMF	50	5	80
4	$CuSO_4$ (1 M)	Solution (7.5%)	DMF	50	10	81
5	$CuSO_4$ (1 M)	Solution (7.5%)	EtOH/ H_2O	rt or 50	1	- -

Table 2. Microwave-assisted for the synthesis of 7-triazol-1-yl-fluoroquinolone by CuAAC.

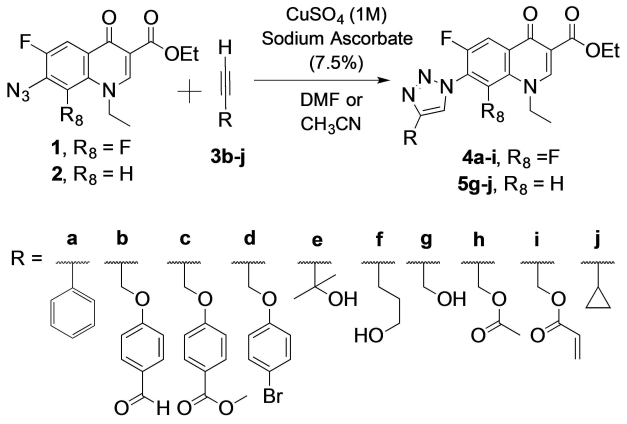


1 **3a** **4a**

Entry	Solvent	T (°C)	t (min)	Yield (%)
1	DMF	80	10	25
2	DMF	140	20	81
3	DMF	140	10	80
4	CH_3CN	80	10	50
5	CH_3CN	140	10	54
6	EtOH	80	10	- -

[a] $CuSO_4 \cdot 7H_2O$ in solution of 1 M (5%mol), Na-Asc in solution at 7.5% (20% mol), were used.

Table 3. Yields obtained under conventional heat and microwave irradiation conditions.



	Yield (%) Convection [a,c]	Microwave [b]		Yield (%) Convection [a,c]	Microwave [b]
4a	78	80[c]	4 h	- -	59[d]
4b	41	51[c]	4i	26	52[d]
4c	56	64[c]	5 g	3	82[d]
4d	59	67[c]	5 h	5	70[d]
4e	70	78[d]	5i	26	93[d]
4f	- -	47[d]	5j	53	65[c]
4 g	54	62[d]			

[a] 50 °C, 5 days. [b] 125 W_{max}, 140 °C, 10 minutes (2 minutes for 3 times). [c] DMF. [d] CH_3CN.

reaction time from a week to 10 minutes. In comparison of fluoroquinolones-triazole linked by piperazine or bicycle ring,[41-43] where the effect of substituents in azido group, are not appreciative, the yields obtained here were similar to the reported in the literature, from 72 to 82%; the use of inert atmospheres[43] or further purifications like chromatographic column[44] were unnecessary, only a simple recrystallization was performed in CH_3CN, avoiding the use of special equipment.

Conclusions

In conclusion, a series of 7-(4-substituted-triazolyl)-quinolones was synthesized by Cu(I)-catalyzed azide/alkyne cycloaddition reaction under heating at 50 °C for one week or microwave-assisted (125W_{max}, 140 °C and 10 minutes) with mild conditions, presenting good yields and less reaction time.

Supporting Information Summary

The azide-fluoroquinolone **1** or **2** (328.6 μmol) was mixed with the alkyne **3a-j** (492.9 μmol, except prop-2-yn-1-ol of **g**: 328.6 μmol), $CuSO_4 \cdot 7H_2O$ 1 M (65.7 μmol) and sodium ascorbate at 7.5% (16.4 μmol) into 3 mL of DMF at 50 °C for 5 days; or microwave conditions: 125W_{max}, 140 °C, 10 minutes with 3 mL of DMF for alkynes **3a-d** and **3j**, or 3 mL of CH_3CN (using automatic control of pressure) for the alkynes 3**e-i**. The brown solution obtained after this time (in both cases) was poured into an ice bath and 10 mL of ice water was added. The precipitate obtained was separated and dried by vacuum filtration. The structure of the compounds **4a-i** and **5g-j** were confirmed by ^1H and ^{13}C NMR, FTIR and MS analyses.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: fluoroquinolone · [1,2,3]-triazolyl derivatives · copper-catalyzed azide-alkyne cycloaddition · nitrogen heterocycle · antibacterial agents

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