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Synthesis of Novel 4(3*H*)-Quinazolinones with 1,2,3-Triazoles Moiety Conjugated by Schiff Base

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We describe the synthesis of a novel quinazolin-4(3*H*)-ones *i.e.*, (E)-3-[4-{4-(hydroxymethyl)-1*H*-1,2,3-triazol-1-yl}benzylideneamino]-7-fluoro-2-methylquinazolin-4(3*H*)-one (**7**). Treatment of 4-(4-(hydroxymethyl)-1*H*-1,2,3-triazol-1-yl)benzaldehyde, which is synthesized *via* a click reaction of 4-azidobenzaldehyde and alkyne, with 3-amino-7-fluoro-2-methylquinazolin-4(3*H*)-one afforded the corresponding product in toluene catalyzed by $TiCl_4$. *in vitro* Cytotoxic activity of compound **7** against human hepatoma hepg2 cells is evaluated.

Keywords: Quinazolin-4(3*H*)-ones, Cytotoxic activity, Schiff base, 1,2,3-Triazoles.

INTRODUCTION

1,2,3-Triazoles are one of the most interesting motifs with widespread applications in pharmaceuticals and agrochemicals[1]. Since the copper-catalyzed 1,3-dipolar cycloaddition was discovered by Sharpless in 2001, both the types and the synthesis of 1,2,3-triazoles have increased rapidly. Compounds containing the 1,2,3-triazole moiety are known to exhibit various biological activities such as antibacterial[2], herbicidal, anti-fungicidal[3], antiallergic[4], and anti-HIV activities[5], as well as selective b3 adrenergic receptor agonist[6].

Quinazolines are important heterocycles that attracted much attention due to their wide range of pharmaceutical and biological activities[7-11]. Many researches revealed that quinazolin-4(3*H*)-ones, especially the 2,3-disubstituted derivatives, possess significant biological activities including antifungal, anticonvulsant and anti-inflammatory activities[12-14]. In particular, quinazolinones are found to be more potent compared with the oxidizes, fully aromatic quinazolines[15,16].

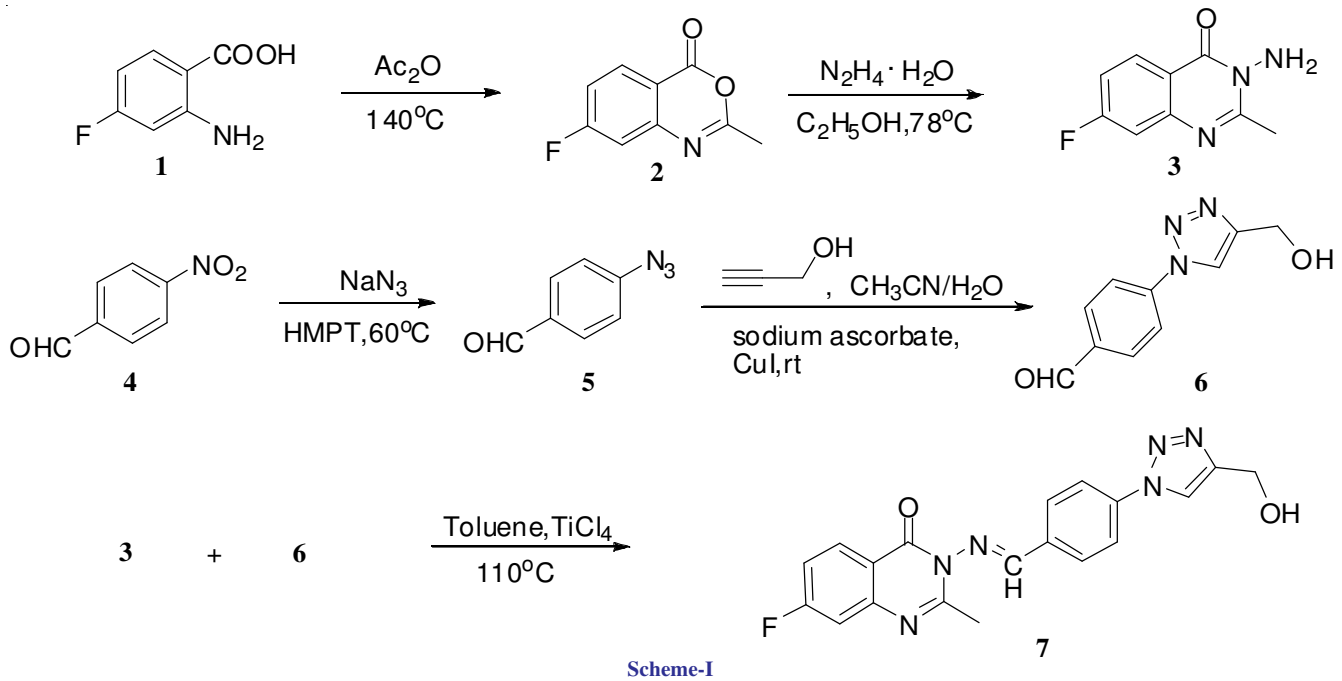
Recently studies show that substitution by aryl or heteroaryl group at C-2 or N-3 position of the quinazolinones markedly enhances the anti-inflammatory activity[17]. From this view of point, we introduce 1,2,3-triazoles biologically active fragment to the N-3 positon of the quinazolinones, with the expectation to identify novel molecules with higher antiinflammatory activity. To the best of our knowledge, quinazolines with 1,2,3-triazoles moiety conjugated by Schiff base haven't been reported so far. In this paper, we also describe a facile method for the synthesis of (E)-3-[4-{4-(hydroxymethyl)-1*H*-1,2,3-triazol-1-yl}benzylideneamino]-7-fluoro-2-methylquinazolin-4(3*H*)-one easily available 2-amino-4-fluorobenzoic acid (**1**) and 4-nitrobenzaldehyde (**4**) (**Scheme-I**).

EXPERIMENTAL

Melting points were taken on a Fischer-Johns micro hot-stage apparatus. IR spectra were performed on a Nicollet FT-IR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a VARIAN Mercury plus-300 instrument using tetramethylsilane (TMS) as an internal standard, and DMSO-d_6 or $CDCl_3$ as the solvent at room tempremature. All reagents for synthesis were commercially available and employed as received or purified by standard methods prior to use. All reactions were monitored by TLC with HuanghaiGF 254 silica gel-coated plates. Column chromatography was carried out using 300- to 400-mesh silica gel at medium pressure.

Synthesis of 7-fluoro-2-methyl-4*H*-benzo[d][1,3]-oxazin-4-one (2): A mixture of anthranilic acid 1 (5 g, 32.3 mmol) and acetic anhydride (32.9 g, 323 mmol) was heated at 140 °C for 1 h. After being cooled to 0 °C in an ice bath, the resulting deposits were filtered off and suspended in hexane with stirring, collected by filtration and dried in vacuo to afford compound **2** as a pale yellow solid (5.45 g, 94 %). m.p. 195.4-195.7 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.46 (3H, s), 7.17-7.21 (2H, m), 8.20 (1H, dd, *J* = 9, 6 Hz). - MS (ESI): *m/z* =180 $(M + H)^+$.

Synthesis of 3-amino-7-fluoro-2-methylquinazolin-4(3*H*)-one (3): A mixture of compound 2 (0.90 g, 5 mmol) and hydrazine hydrate (0.75 g, 15 mmol) in ethanol (20 mL)



Scheme-I

was heated at 80 °C for 2 h. After being cooled to room temperature, the resulting precipitates were filtered and recrystallized from ethanol, then vacuum-dried to provide compound **3** as a off-white solid (0.93 g, 96 %). m.p. 153.1-153.7 °C. IR (KBr, ν_{max}, cm^{-1}): ν = 3301, 1670, 1597, 1564, 1501, 1469, 1257. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.68 (s, 3H), 4.87 (s, 2H), 7.13-7.29 (m, 2H), 8.24 (1H, dd, *J* = 6, 9 Hz). ^{13}C NMR (DMSO-d_6, 75 MHz): δ = 21.93, 111.41, 114.41, 116.71, 128.83, 148.70, 156.79, 163.82, 167.15. MS (ESI): *m/z* = 194 $(M + H)^+$. Anal. for $C_9H_8FN_3O$: Calcd. C 55.93, H 4.19, N 21.70; found, C 55.96, H 4.17, N 21.75.

Synthesis of 4-azidobenzaldehyde (5): Sodium azide (2.60 g, 40 mmol) was added to a solution of 4-nitrobenzene of formaldehyde (3.02 g, 20 mmol) in HMPT(20 mL). The mixture was heated at 60 °C for 6 h. After completion, the mixture was cooled to room temperature. Diethyl ether (200 mL) was added to the mixture, then washed it with water (2 × 100 mL) and saturated sodium chloride (100 mL). The organic layer was separated and dried over anhydrous Na_2SO_4. Evaporation of the solvent affords compound **5** as a brown liquid (2.78, 95 %). IR (KBr, ν_{max}, cm^{-1}): ν = 3301, 3288, 2117, 1698. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.18 (d, *J* = 9 Hz, 2H), 7.91 (d, *J* = 10.5 Hz, 2H), 9.97 (s, 1H). MS (ESI): *m/z* = 148 $(M + H)^+$.

Synthesis of 4-[4-(hydroxymethyl)-1*H*-1,2,3-triazol-1-yl]-benzaldehyde (6): A mixture of compound **5** (1.51 g, 10 mmol), 3-hydroxy propyne (0.62 g, 11 mmol), sodium ascorbate (0.40 mg, 2 mmol) and CuI (0.38 g, 2 mmol) in CH_3CN/H_2O (v:v = 9:1, 20 mL) was stirred at room temperature under nitrogen atmosphere for 4 h and filtered. Evaporation of the filtrate afford the solid, solved in ethyl acetate(100 mL), then washed with water (3 × 30 mL) and saturated solution of sodium chloride (30 mL). The organic layer was separated and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave the crude product, recrystallized from acetic ether/*n*-hexane, then vacuum-dried to provide compound **6** as a yellow solid (1.87, 92 %). m.p. 135.3-136.1 °C. IR (KBr, ν_{max}, cm^{-1}): ν = 3405, 1701, 1684, 1621, 1548. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 4.93 (s, 2H), 7.95-8.08 (m, 5H), 10.08 (s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 54.99, 120.13, 121.26, 131.33, 135.59, 140.64, 149.68, 192.18. MS (ESI): *m/z* = 204 $(M + H)^+$. Anal. for $C_{10}H_9N_3O_2$: Calcd. C 59.11, H 4.46, N 20.68; Found: C 59.22, H, 4.49, N 20.59.

Synthesis of (E)-3-[4-{4-(hydroxymethyl)-1*H*-1,2,3-triazol-1-yl}benzylideneamino]-7-fluoro-2-methylquinazolin-4(3*H*)-one (7): A mixture of compound **3** (0.19 g, 1 mmol) and compound **6** (0.20 g, 1 mmol) with a drop of $TiCl_4$ was stirred in toluene (10 mL) at 110 °C for 5 h. After the reaction completed, the solvent was evaporated. The crude product was recrystallized from ethanol, then vacuum-dried to provide compound **7** as a yellow solid (0.32 g, 85 %). m.p. 223.5-234.3 °C. IR (KBr, ν_{max}, cm^{-1}): ν = 3350, 1682, 1595, 1559, 1509, 1482, 1254. ^{1}H NMR (DMSO-d_6, 300 MHz): δ = 2.56 (s, 3H), 4.64 (s, 2H), 7.39-7.47 (m, 2H), 8.16-8.22 (m, 5H), 8.83 (s, 1H), 9.07 (s, 1H). ^{13}C NMR (DMSO-d_6, 75 MHz): δ = 20.60, 54.94, 111.81, 115.04, 117.99, 121.02, 122.22, 129.94, 130.46, 132.04, 139.39, 148.30, 149.50, 154.97, 156.82, 164.01, 167.53. MS (ESI): *m/z* = 379 $(M + H)^+$. Anal. for $C_{19}H_{15}FN_6O_2$: Calcd. C 60.31, H 4, N 22.21; Found: C 60.22, H 3.94, N 22.30.

Synthesis of 4-(hydroxymethyl)-1-[4-(diethoxymethyl) phenyl]-1*H*-1,2,3-triazole (8): A mixture of compound **3** (0.19 g, 1 mmol) and compound **6** (0.20 g, 1 mmol) was stirred in ethanol (10 mL) at 78 °C for 24 h. Evaporation of the solvent gave the crude product, which was subjected to column chromatography (silica gel, EtOAc/petroleum ether = 1/10(v:v)) to afford acetal compound **8** (0.16 g, 57 %) as a pale yellow oily liquids. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.19 (t, 6H), 3.49-3.58 (m, 4H), 4.62 (s, 2H), 5.33 (t, 1H), 5.54 (s, 1H), 7.59 (d, *J* = 8.4 Hz, 2H), 7.90 (d, *J* = 8.4, 2H), 8.67 (s, 1H).

***in vitro* Cytotoxic activity:** The *in vitro* cytotoxicities of compound **1** against human hepatoma hepg2 cell lines were screened. In this study, the hepg2 tumor cells in RPMI1640

medium with 10 % fetal bovine serum were plated in 96-well microtiter plates (4×10^4 cells per well) and allowed to adhere at 37 °C with 5 % CO_2 for 4 h. Then the cells were continuously exposed to the tested compound and the positive references at five different concentrations: 400, 200, 100, 50 and 25 µg mL^{-1}, respectively. Afterwards, the cells were incubated at 37 °C with 5 % CO_2 for 72 h. The cell viability was assessed using a standard MTT assay. The positive reference is 5-fluorouracil.

RESULTS AND DISCUSSION

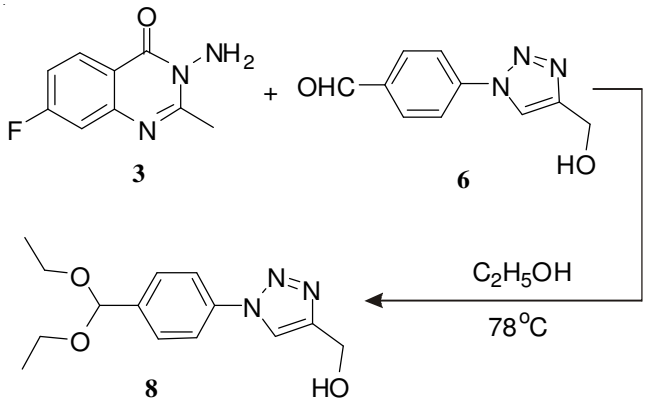
According to a previous reported prodcedure[18], treatment of compound **1** in acetic anhydride at 140 °C afforded compound **2** in a yield of 95 %. Compound **2** reacted with hydrazine hydrate in ethanol gave compound **3** in almost quantitative yield[19]. In the presence of the protonic solvent of HMPT, a clean and complete reaction between 4-nitrobenzaldehyde and sodium azide occurred furnishing product compound **5**. It is notable that the previous protocol for its synthesis of such structure involves diazotization followed by reductive amination, however, this protocol suffers from the self-condensation and results in a low yield[20]. Followed a Huisgen [3+2]-cycloaddition reaction was carried out between compound **5** and alkyne in CH_3CN/H_2O catalyzed by CuI-sodium ascorbate system, affording compound **6** in a high yield of 92 %. Finally, the target product compound **7** was obtained by the reaction of compounds **3** with **6** conducted in toluene. This reaction was examined in differernt solvents to get an insight into the solvent effect. As a result, toluene proved to be the best solvent. However, the reaction proceeded slow and gave only 15 % yield when tried in reflux toluene without catalyst (**Scheme-I**). Therefore, we screened different catalysts to improve the yield and reaction rate. When the reaction was performed in the presence of acetic acid in toluene, it afforded the product compound **7** in 23 % yield. A substantial improvement of the yield (41 %) has been achieved with *p*-toluene sulphonic acid. And the usage of $TiCl_4$ as catalyst led to a dramatic improvement in the rate of the reaction and the yield (85 %) (Table-1, entry 7). It was noteworthy that $TiCl_4$ probably plays two important roles in the course of the reaction: (a) acting as a water-absorbent to induce the reaction equilibrium to the right direction; (b) acting as Lewis acid-catalyst to activate the aldehyde group to accelerate the reaction rate. The whole test was repeated three times.

TABLE-1
OPTIMIZATION OF SYNTHESIS OF COMPOUND **7**[a]

Entry	Solvent	Catalyst	Time (h)	Yield (%)[b]
1	CH_2Cl_2	None	>24	Trace
2	C_2H_5OH	None	>24	Acetal
3	THF	None	>24	Trace
4	Toluene	None	24	15
5	Toluene	TsOH	12	41
6	Toluene	HOAc	12	23
7	Toluene	$TiCl_4$	5	85

[a]Reaction conditions: aldehyde (1 mmol), amine (1 mmol), catalyst (0.1 eq) and solvent (10 mL) under reflux condition; [b]Isolated yields

Furthermore, it's noteworthy that an unwanted aldol condensation product compound **8** (**Scheme-II**) was obtained when ethanol was used as the solvent in the reaction for the expected compond **7**. That was proved by ^{1}H NMR spectroscopy and TLC analysis of the reaction mixture.



Scheme-II

The 2,3-dihydroquinazolin-4(3*H*)-ones (**7**) was screened for its antitumor activity against human hepatoma hepg2 cells (Table-2). The result suggests that compound **7** exibits cytotoxicity on hepg2 cell lines (IC_{50} = 90.74 mg/mL), which is approch to the positive reference 5-fluorouracil (IC_{50} = 93.27 mg/mL), indicating it is worthwhile to be further studied.

TABLE-2
in vitro CYTOTOXIC ACTIVITY OF COMPOUND **7**

Conc. (µg/mL)	% Cytotoxicity against hepg2 cell[a]	Negative contrast
400	76.5	0.21
200	65.04	
100	50.7	
50	43.62	
25	23.5	
IC_{50}	90.74	

[a]Standard (5-fluorouracil) = 93.27 g/mL

Conclusion

In summary, we have developed a facile and efficient procedure for the synthesis of novel compounds (E)-3-(4-(4-(hydroxymethyl)-1*H*-1,2,3-triazol-1-yl)benzylideneamino)-7-fluoro-2-methylquinazolin-4(3*H*)-one easily available 2-amino-4-fluorobenzoic acid compound **7** in high yield. Moreover, quinazolines with 1,2,3-triazoles moiety conjugated *via* schiff base band have't been reported. And in vitro cytotoxicity study exibit that compond **7** showed cytotoxicity on hepg2 cell lines approch to 5-fluorouracil. Current studies in our laboratories aim at further expanding the application scope of this chemistry.

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