Synthesis of *N*-4-(4-chloro-3-trifluoromethyl-phenyl)-7-methoxy-Quinazoline - 4, 6- diamine

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Abstract. *N*-4- (4 - chloro- 3 –trifluoromethyl –phenyl) -7 – methoxy – quinazoline -4, 6-diamine (1) exhibited potential biological activities in medicine, 4-chloro-7-fluoro-6-nitro-quinazoline (2) is an important intermediate in compound 1. In this work, a rapid synthetic method for compound 1 was established. The compound 1 was synthesized from the commercially available 4-chloro-7-fluoro-6-nitro-quinazoline 2 through three steps including substitution with phenylamine, nucleophilic substitution reaction and reduction reaction. The structures were confirmed by ^{1}HNMR. Furthermore, the synthetic method was optimized.

Introduction

Cancer is a disease caused by normal cells changing so that they grow in an uncontrolled way. Although many anti-tumor drugs and surgeries are available, the slow efficacy of the anti-tumor drugs and the cancer recurrence are still problems[1-2]. In recent years, there were many small molecule anticancer drugs had been reported. Among them, many molecules contained the 4-chloro-7-fluoro-6-nitro-quinazoline (2). Therefore, design and synthesis of 4-chloro-7-fluoro-6-nitro-quinazoline (2) derivative as small molecule inhibitors played a great role in the study of anticancer drugs.

Many quinazoline derivatives which exhibited potential biological activities, such as (3 – chloro -4 –fluoro –phenyl) - (3 ,4 –dimethoxy –phenyl) - (7-fluoro-6-nitro-quinazolin-4-yl)-amine (3) [3], (7 –fluoro -6 –nitro –quinazolin -4- yl) - (4 –phenoxy –phenyl)- amine (4) [4], [1 - (3-fluoro - benzyl)- 1 H – indazol -5 –yl] - (7 - fluoro- 6- nitro - quinazolin -4-yl) -amine (5) [5], (3 - ethyny l – phenyl) - (7 – fluoro – 6 – nitro – quinazolin – 4 – yl) - amine (6), (5-chloro-benzo[1, 3] dioxol - 4 - y l) - (7 - fluoro - 6 - nitro - quinazolin - 4 - yl) - amine (7) [6], [3-chloro-4-(pyridin-2-ylmethoxy)-phenyl]-(7-fluoro-6-nitro-quinazolin-4-yl)-amine (8)[7], these quinazoline derivatives showed excellent biological activity.

Most of the synthetic methods of *N* – 4 - (4 –chloro -3 –trifluoromethyl –phenyl)-7 –methoxy – quinazoline – 4 ,6 -diamine (1) which reported in the literature have the drawbacks, such as lower yield and complicated reaction conditions[8-10]. 4-chloro-7-fluoro-6-nitro-quinazoline (2) is a key intermediate for synthesizing *N* -4 -(4-chloro -3-trifluoromethyl –phenyl)-7-methoxy -quinazoline-4, 6 - diamine (1). Therefore, the optimization of the synthetic route and methods of 4-chloro-7-fluoro-6-nitro-quinazoline (2) is necessary. The structures of representative compounds were shown in Fig. 1 and Fig 2.

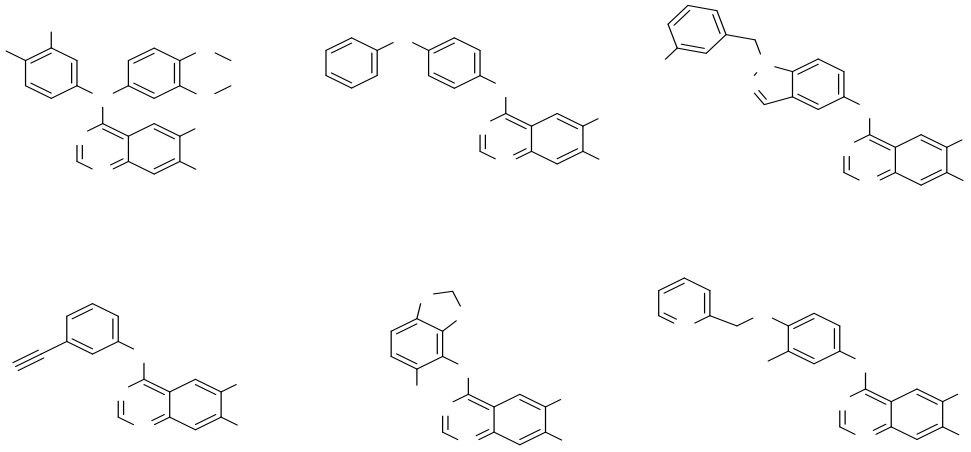


Fig.1 Structures of some drugs or active compounds containing quinazoline

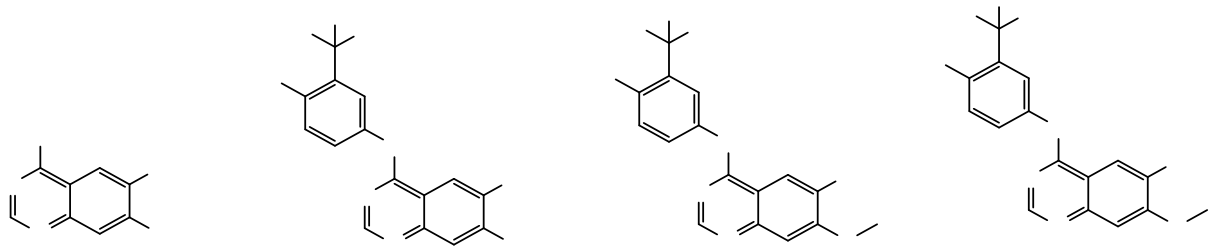


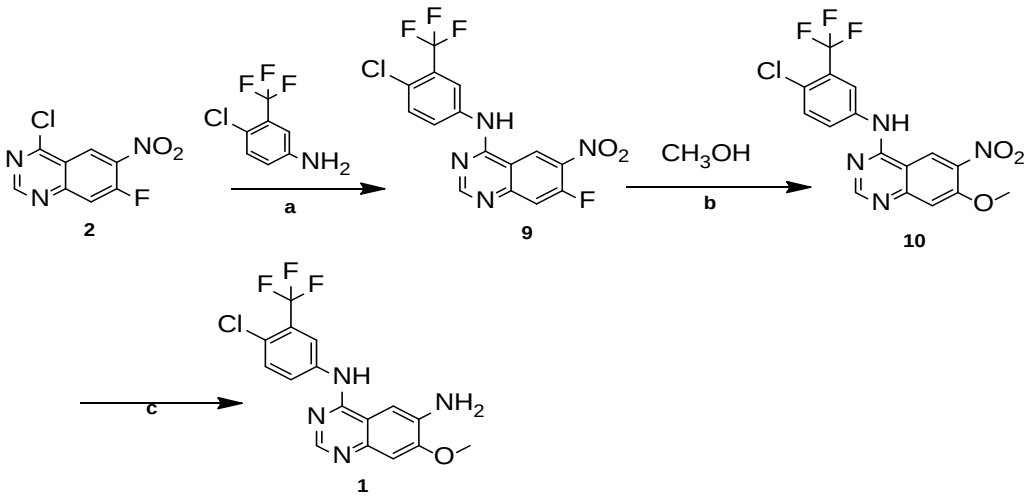
Fig. 2 Structures of some representative compounds containing quinazoline motif and the target compounds 9 ,10 and 1

Materials and methods

NMR spectra were performed using Bruker 400 MHz spectrometers (Bruker Bioscience, Billerica, MA, USA) with TMS as an internal standard. Mass spectra (MS) were taken in ESI mode on Agilent 1100 LC–MS (Agilent, Palo Alto, CA, USA). Elemental analysis was determined on a Carlo-Erba 1106 Elemental analysis instrument (Carlo Erba, Milan, Italy). All the materials were obtained from commercial suppliers and used without purification, unless otherwise specified. Yields were not optimized. TLC analysis was carried out on silica gel plates GF254 (Qindao Haiyang Chemical, China).

Synthesis of compounds

The structures and the synthetic route were shown in Scheme 1.



Scheme 1. The synthetic route of compounds 9, 10 and 1

Reagents and conditions:(a)Acetonitrile, Triethylamine, r. t, 1.5 h; (b)Methanol, 50 percent sodium hydroxide, 70 ℃, 1 h; (c)Ethanol, Hydrazine hydrate, Activated carbon, Ferric chloride, 80 ℃, 1.5 h.

(4-chloro-3-trifluoromethyl-phenyl)-(7-fluoro-6-nitro-quinazolin-4-yl)-amine (**9**)

A solution of 4-chloro-7-fluoro-6-nitro-quinazolineand acetonitrile(10 g, 0.044 mol) and 4-chloro-3-trifluoromethyl-phenylamine(10.3 g, 0.053 mol) in acetonitrile(100 mL), then triethylamine(4.4 mL) was added drop-wise at room temperature. The reaction mixture then was stirred at room temperature for 1.5 h, after completion of the reaction (monitored by TLC). The reaction mixture was poured onto water(500 mL), the mixture was then filtered, the filter cake was washed with water, residue was dried to obtain a powdery solid. We can get 14.5 g (4-chloro-3-trifluoromethyl-phenyl)-(7-fluoro-6-nitro-quinazolin-4-yl)-amine (**9**). yield: 85.3%. M.p. 261.4 ℃ -262.5 ℃. ^{1}HNMR (400 MHz, DMSO) δ 10.69 (s, 1H), 9.62 (d, *J* = 7.0 Hz, 1H), 8.80 (s, 1H), 8.40 (s, 1H), 8.25 (d, *J* = 23.4 Hz, 1H), 7.93 (t, *J* = 14.6 Hz, 1H), 7.80 (d, *J* = 8.6 Hz, 1H).

(4-chloro-3-trifluoromethyl-phenyl)-(7-methoxy-6-nitro-quinazolin-4-yl)-amine (**10**)

A solution of (4-chloro-3-trifluoromethyl-phenyl)-(7-fluoro-6-nitro-quinazolin-4-yl)-amine(14.5 g, 0.038 mol) in methyl alcohol(100 mL), then 50 percent sodium hydroxide(4.4 mL) was added drop-wise at room temperature, after stirring and refluxed for 1 h at 70 ℃. After the completion of the reaction (monitored by TLC). The reaction mixture was cooled to room temperature and was poured into sodium bicarbonate solution yielding a precipitate, the mixture then was separated by filtration and washed with water, residue was dried to obtain a powdery solid. We can get 12.2 g (4-chloro-3-trifluoromethyl-phenyl)-(7-methoxy-6-nitro-quinazolin-4-yl)-amine (**10**). yield: 85.3%. M.p. 139.1 ℃ -140.1 ℃. ^{1}HNMR (400 MHz, DMSO) δ 8.76 (s, 1H), 8.00 (s, 1H), 7.82 (s, 1H), 7.59 (s, 1H), 7.38 (d, *J* = 9.1 Hz, 1H), 6.89 (s, 1H), 4.01 – 3.79 (m, 3H), 2.64 (d, *J* = 19.7 Hz, 1H).

***N*-4-(4-chloro-3-trifluoromethyl-phenyl)-7-methoxy-quinazoline-4,6-diamine**(**1**)

A solution of (4-chloro-3-trifluoromethyl-phenyl)-(7-methoxy-6-nitro-quinazolin-4-yl)-amine (12.2 g, 0.031 mol) in ethyl alcohol(100 mL) was stirred at 60 ℃, an appropriate amount of activated carbon (1.84 g) and ferric chloride (1.65 g) were added at the temperature, the mixture was heated to 80 ℃ and 80 percent hydrazine hydrate (4.66 mL) was added to the solution. The reaction mixture then was refluxed for 1.5 h . After the completion of the reaction (monitored by TLC). The mixture was filtered and the precipitate was washed with ethanol. The filtrate was concentrated under reduce pressure and the residue was poured into water with stirred for 30 min. The precipitate was filtered and residue was dried to obtain a powdery solid. We can get 8.5 g *N*-4-(4-chloro-3-trifluoromethyl-phenyl)-7-methoxy-quinazoline-4,6-diamine (**1**). yield: 75.4%. M.p. 258.4 ℃ -259.7 ℃. ^{1}HNMR (400 MHz, DMSO) δ 9.67 (s, 1H), 8.44 (d, *J* = 6.5 Hz, 1H), 8.42 (s, 1H), 8.26 (d, *J* = 8.6 Hz, 1H), 7.68 (d, *J* = 8.8 Hz, 1H), 7.39 (s, 1H), 7.09 (d, *J* = 23.0 Hz, 1H), 5.48 (s, 2H), 3.92 (d, *J* = 38.7 Hz, 3H).

Conclusions

In conclusion, *N*-4-(4-chloro-3-trifluoromethyl-phenyl)-7-methoxy-quinazoline-4,6-diamine (**1)** was synthesized from 4-chloro-7-fluoro-6-nitro-quinazolineand acetonitrile (**8)** through three steps including phenylamine, nucleophilic substitution reaction and reduction reaction. The synthetic method of compound **1** and the reactions conditions were optimized, after optimized, the yield of target compound **1** was higher. Its structure was confirmed by ^{1}HNMR.

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