

Synthesis of 4-chloro-6-methoxy-2-methyl-3-nitroquinoline

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Abstract. 4-Chloro-6-methoxy-2-methyl-3-nitroquinoline (1) was synthesized from 4-methoxyaniline through three steps including Cyclization, Nitrification and Chlorination. The structure of the target product (1) was confirmed by ¹H NMR and MS. This method started with cheap raw materials was of simple experimental operation and mild reaction conditions. It was suitable for large scale pilot study and the yield of the product is achieved to 85%.

Introduction

PI3K/Akt/mTOR signaling pathway plays an important role in tumor cell proliferation, survival, resistance to apoptosis, angiogenesis and metastasis, and resistance to radiotherapy and chemotherapy. Therefore, it is closely related with human multiple tumors. In other words, mTOR is a vital substrate along this pathway. The development of targeted therapies against mTOR led to the approval of allosteric inhibitors, for the treatment of cancers [1]. However, it remains an unresolved issue that the suboptimal duration of response is in unselected patients [2]. In view of that awaits further investigation and in multiple tumour types, there are being actively investigated for numerous novel therapies against critical nodes of this pathway in the clinic [3]. So many boffins prepared a series of quinoline derivatives, and they research their differential tissue staining and tumor growth retardation to determine antitumor activity [4-5].

With the efforts of a large number of scientific research workers [6], a series of PI3K/mTOR inhibitors have come out and showed excellent anti-tumor activity and many quinazoline derivatives which exhibited potential biological activities, such as 6-methoxy-2-methyl-3,5-dinitro-N-phenylquinolin-4-amine (2), N-[4-(1-Adamantyl)phenyl]-2-[3-(4-methoxyphenyl)-2-oxo-2H-[1,2,4]triazino[2,3-c]quinazolin-6-ylthio]acetamides (3) [7], 3-hydroxy-8-methoxy-4-methyl-9-nitro-3H-imidazo[4,5-c]quinoline-2-carboxylic acid (4) have been confirmed (Fig.1). In recent years, the product of quinolone inhibitors such as NVP-BEZ235 in tumor applications has been reported, including chemotherapy and drug combination. It is combined with other molecular targeted drugs and radiotherapy combined therapy and so on [8-12].

4-Chloro-6-methoxy-2-methyl-3-nitroquinoline (1) is a key intermediate for the synthesis of quinoline inhibitors. In this paper, we summarized and optimized the synthetic methods of compound 1 according to the literature [13]. We designed and optimized the synthetic methods make it more suitable for industrial production.

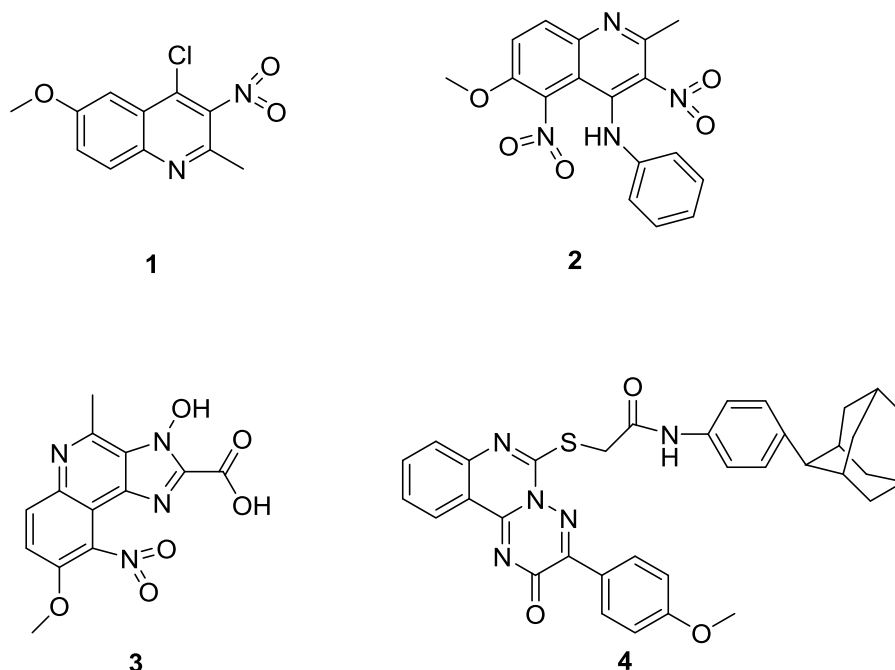


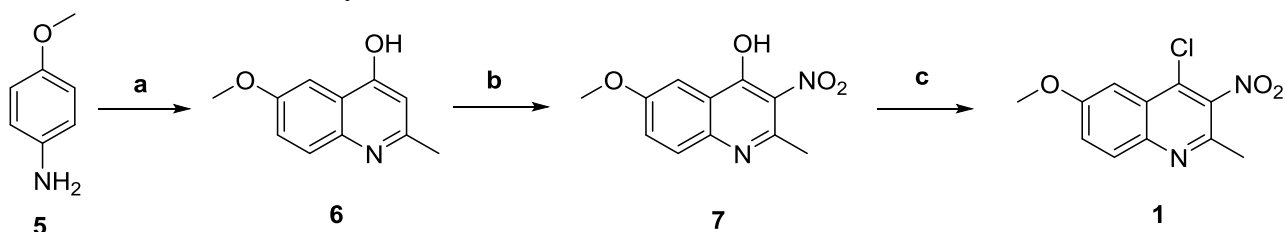
Figure 1. Structures and the representative compounds in study

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). 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 Compound 1

Reagents and Conditions: (a) Ethyl acetoacetate, polyphosphoric acid, 170 °C, 1 h; (b) Propionic acid, nitric acid, 125 °C, 2 h; (c) Phosphorus oxychloride, N, N-Dimethylformamide, 110 °C, 1 h.

Preparation for 6-methoxy-2-methylquinolin-4-ol (6). To the mixture of 4-methoxyaniline (4.0 g, 32.9 mmol), ethyl acetoacetate (14.0 mL), polyphosphoric acid (16.0 g, 47.3 mmol) was added drop-wise with stirring maintaining the temperature at 170 °C and keep the temperature for 1 h, after completion of reaction as indicated by TLC. After the reaction was finished, the filtrate mixed with ice water was stirred for 1h and filtration. The filtrate cake was dried to obtain a yellow solid (1.8 g, 45.2%). ESI-MS m/z : 191.0(M+H) +

Preparation for 6-methoxy-2-methyl-3-nitroquinolin-4-ol (7). The solution of compound 6

1.8 g (10.5 mmol) in 100mL propionic acid was stirred and the mixture of 4.4mL nitric acid and 4.7mL propionic acid was added dropwise for 1h at room temperature. Raise the temperature to 125°C. Then the mixture was reacted for 2 h and filtered by solid. The solid was washed with saturated NaHCO_3 solution for 1h at 0°C, filtration and the filte cake was dried to obtain a yellow powdery solid (1.2 g, 70%). ESI-MS m/z : 236.0(M+H)⁺

Preparation for 4-chloro-6-methoxy-2-methyl-3-nitroquinoline (1). The solution of compound **7** 1.2 g (5.4 mmol) in 36.2 mL POCl_3 was stirred and 2 drops DMF was added into the solution. Then the mixture was reacted for 2h at 110°C. The solution was concentrated under reduced pressure to afford a yellow solid. The solid was washed with saturated NaHCO_3 solution for 1h at 0°C, filtration, and the filte cake was dried to obtain a milk white solid (1.1 g, 85.0%). ESI-MS m/z : 255.0(M+H)⁺. ¹H NMR (400 MHz, CDCl_3) δ 8.05 (d, J = 9.2 Hz, 1H), 7.66 (dd, J = 9.2, 2.5 Hz, 1H), 7.48 (d, J = 2.4 Hz, 1H), 3.99 (s, 3H), 2.64 (d, J = 5.0 Hz, 3H).

Conclusions

In conclusion, one novel compound **4** was synthesized from 4-methoxyaniline through three steps. The synthetic route can be used to synthesize 4-chloro-6-methoxy-2-methyl-3-nitroquinoline. The purity of the product was much higher than before. Its structure was confirmed by MS and ¹H NMR spectrum.

Acknowledgments

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References

- [1] Khan K H, Yap T A, Yan L, et al. Targeting the PI3K-AKT-mTOR signaling network in cancer.[J]. Chinese Journal of Cancer, 2013, 32(5):253-265.
- [2] Marone R, Erhart D, Mertz A C, et al. Targeting melanoma with dual phosphoinositide 3-kinase/mammalian target of rapamycin inhibitors.[J]. Molecular Cancer Research, 2009, 7(4):601-613.
- [3] Wan X, Helman L J. The biology behind mTOR inhibition in sarcoma.[J]. Oncologist, 2007, 12(8):1007-1018.
- [4] M. L. Crossley, P. F. Dreisbach, C. M. Hofmann, and R. P. Parker, J.Amer. Chem. SOC., 74,573(1952).
- [5] Nasr M, Abbasi M M, Nabih I. Synthesis of benzoxazino - and naphthoxazinoquinoline derivatives as possible antitumor agents [J]. Journal of pharmaceutical sciences, 1974, 63(8): 1314-1316.
- [6] Abbasi M M, Nasr M, Zoorob H H. Base induced cyclization of some quinolines. Formation of fused nitrogen heterocyclic ring system [J]. Monatshefte für Chemie/Chemical Monthly, 1980, 111(4): 963-969.
- [7] Berest G G, Voskoboynik O Y, Kovalenko S I, et al. Synthesis and biological activity of novel N-cycloalkyl-(cycloalkylaryl)-2-[(3-R-2-oxo-2H-[1, 2, 4] triazino [2, 3-c] quinazoline-6-yl) thio] acetamides[J]. European journal of medicinal chemistry, 2011, 46(12): 6066-6074.
- [8] Roulin D, Waselle L, Dormond-Meuwly A, et al. Targeting renal cell carcinoma with NVP-BEZ235, a dual PI3K/mTOR inhibitor, in combination with sorafenib[J]. Molecular cancer, 2011, 10(1): 1.

- [9] Manara M C, Nicoletti G, Zambelli D, et al. NVP-BEZ235 as a new therapeutic option for sarcomas[J]. *Clinical Cancer Research*, 2010, 16(2): 530-540.
- [10] Kim A, Park S, Lee J E, et al. The dual PI3K and mTOR inhibitor NVP-BEZ235 exhibits anti-proliferative activity and overcomes bortezomib resistance in mantle cell lymphoma cells [J]. *Leukemia research*, 2012, 36(7): 912-920.
- [11] Awasthi N, Yen P L, Schwarz M A, et al. The efficacy of a novel, dual PI3K/mTOR inhibitor NVP - BEZ235 to enhance chemotherapy and antiangiogenic response in pancreatic cancer [J]. *Journal of cellular biochemistry*, 2012, 113(3): 784-791.
- [12] Seixas J D, Luengo-Arratta S A, Diaz R, et al. Establishment of a Structure–Activity Relationship of 1 H-Imidazo [4, 5-c] quinoline-Based Kinase Inhibitor NVP-BEZ235 as a Lead for African Sleeping Sickness[J]. *Journal of medicinal chemistry*, 2014, 57(11): 4834-4848.
- [13] Zhang W, Li Z, Zhou M, et al. Synthesis and biological evaluation of 4-(1, 2, 3-triazol-1-yl) coumarin derivatives as potential antitumor agents[J]. *Bioorganic & medicinal chemistry letters*, 2014, 24(3): 799-807.