Synthesis of 7-(benzyloxy)-4-chloro-6-methoxyquinazoline

Min Wang[1],Ping Wang[1, a,*], Yiqiang OuYang[1], Linxiao Wang[1],Qingjun Li[1], Si Gao[1], Shan Xu[1, b,*]

School of Pharmacy, Jiangxi Science & Technology Normal University, Nanchang 330013, China

[*a] 439711557@qq.com, [*b] shanxu9891@126.com

Keywords: 7-(Benzyloxy)-4-chloro-6-methoxyquinazoline;Vandetanib;Synthesis

Abstract.7-(Benzyloxy)-4-chloro-6-methoxyquinazoline (**1**) was synthesized from methyl 4-hydroxy-3-methoxybenzoate (**2**) through five steps including substitution, nitration, reduction, cyclization and chlorination.Its structure was confirmed by ^{1}H NMR and MS spectrum. The total yield of the five steps was 29.2%.

Introduction

Cancer is one of the major diseases that threaten human health. The incidence of cancer is the second only to cardiovascular and cerebrovascular diseases, and it's mortality rate is the highest among all diseases[1]. According to the World Health Organization (WHO) statistics, the death of cancer patients reached 7.6 million. It has been predicted that the world will have 21.4 million new cases by 2030 [2] . Although a series of antitumor drugs and surgeries are available, the slow efficacy of the antitumor drugs and the cancer recurrence are still problems [3] . Therefore, searching for highly efficient and safe chemotherapeutic agents for treating cancer remains desirable.

Quinazoline compounds are one kind of effective EGFR inhibitors[4], such as Gefitinib(**a**),Erlotinib(**b**) and Lapatinib(**c**),which own the structure of quinazoline. So they are drugs with good anti-tumor activity [5-6].The compound **1** is a quinazoline compound. It is an important intermediate in the synthesis of Vandetanib[7-12]. The structures of those compounds were shown in Fig. 1.

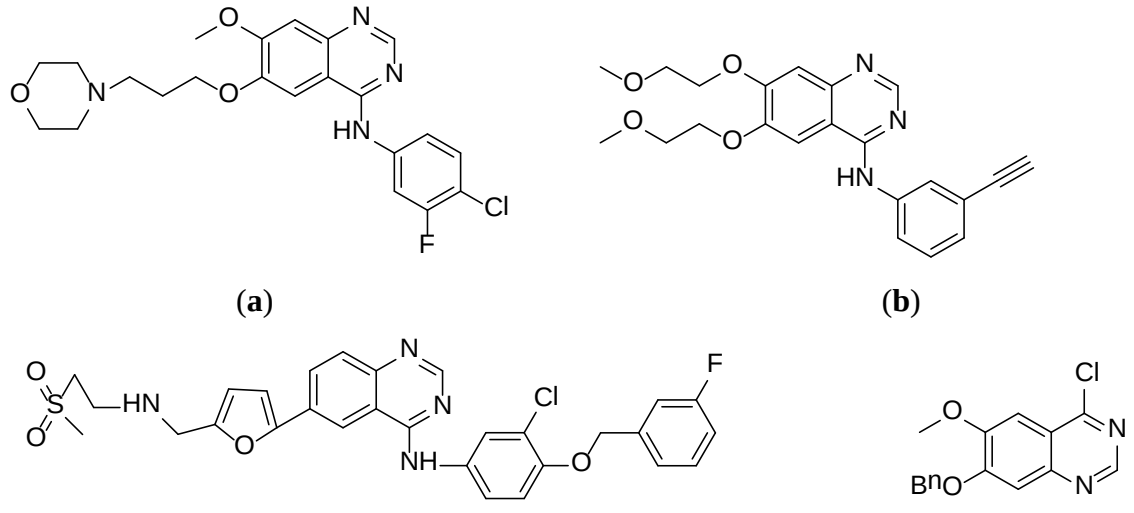


Fig. 1 Sructures of drugs containing quinoline necleus

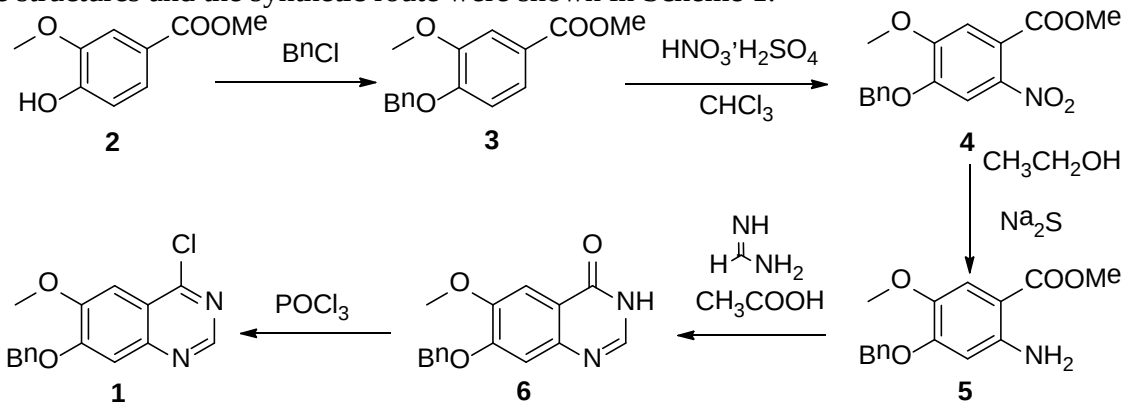
Materials and methods

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

Methyl 4-(benzyloxy)-3-methoxybenzoate(3)

BnCl (3.5mL,30mmol), K_2CO_3 (4.14g,30mmol) and methyl 4-hydroxy-3-methoxybenzoate (5.46g,30mmol) was added to DMF(15mL). Heated to 100^{o}C and stirred for 7h.After colling to room temperature, the reactant was added to 100ml ice-water mixture slowly. The product was filtered off and dried to afford 7.91g methyl 4-(benzyloxy)-3-methoxybenzoate(**3**).yield:97%.

Methyl 4-(benzyloxy)-5-methoxy-2-nitrobenzoate(4)

4-(benzyloxy)-3-methoxybenzoate(**3**).(2.72g,10mmol) was dissolved in 10mL $CHCl_3$.The mixture of HNO_3(0.67mL,15mmol) and H_2SO_4(0.97mL,18.3mmol) then was added dropwise in ice-bath. Heated to room temperature for 6h.Then ice-water was added to the reaction system, pointed to the water. Choroform layer was washed with staturated bicarbonate solution, with water washing to be neutral. Evaporating the solvent and dried to afford 1.1g methyl 4-(benzyloxy)-5-methoxy-2-nitrobenzoate(**4**).yield:69.4%.ESI-MS m/z: 318.1$(M+H)^+$.

Methyl 2-amino-4-(benzyloxy)-5-methoxybenzoate(5)

4-(benzyloxy)-5-methoxy-2-nitrobenzoate(**4**)(3.17g,10mmol) and Na_2S(4.68g,60mmol) were dissolved in 8mL CH_3CH_2OH, then heated to79^{o}C and stirred for 1.5h.After cooling to room temperature,added 10mL CH_3CH_2OH to the reaction system,filtration,removal of inorganic substances,evaporating the filtrate rotary and dried to afford 2.71g methyl 2-amino-4-(benzyloxy)-5-methoxybenzoate(**5**).yield:94.4%. ESI-MS m/z:288.3$(M+H)^+$.

7-(benzyloxy)-6-methoxyquinazolin-4(3H)-one(6)

Methyl 2-amino-4-(benzyloxy)-5-methoxybenzoate(**5**)(0.3g,1mmol) and formamidine acetate(0.2g,1.4mmol) were dissolved in 7mL CH_3CH_2OH,heated to 79^{o}C and stirred for 6h.Then cooling to room temperature, The product was filtered off and dried to afford 0.24g 7-(benzyloxy)-6-methoxyquinazolin-4(3H)-one(**6**) .yield:85%.

7-(benzyloxy)-4-chloro-6-methoxyquinazoline(1)

5mL $POCl_3$ was added to 7- (benzyloxy) -6-methoxyquinazolin-4(3H)-one(**6**) (0.1g,0.4mmol), heated to 106^{o}C and stirred, when the liquid changed from cloudy to clarify, the reaction was completed. Cooling to room temperature and slowly driping into the ice-water. The product was filtered off and dried to afford 0.096g 7- (benzyloxy) -4-chloro-6 –methoxyquinazoline (1). yield: 80.1%.

Conclusions

In conclusion, the compound **1** is a quinazoline compound. It is an important intermediate in the synthesis of Vandetanib. It was synthesized from methyl 4-hydroxy-3-methoxybenzoate(**2**) through five steps including substitution, nitration, reduction, cyclization and chlorination. Its structure was confirmed by ^{1}H NMR and MS spectrum.

Acknowledgments

We gratefully acknowledge the generous support provided by The National Natural Science Funds (No.80140357) Project supported by the Natural Science Foundation of Jiangxi Province (No. 20142BAB215020) and Program of Key Laboratory of Drug Design and Optimization, Jiangxi Science & Technology Normal University（300098010306）.

Reference

[1] Heron M. Leading causes for 2006. National Vital Statistics Reports, 2010, 58 (14): 1-100

[2] Ahmedin J, Freddie B, Melissa M, Jacques F. Global cancer statistics [J]. A Cancer Journal for Clinicians. 2011, 61(2): 69–90.

[3] Cancer Research UK. New&resources. Worldwide cancer statistics[EB/OL] (2011-9-19)[2012-6-6].

[4] Geroni,Marria,Cristina.A mopholinyl anthracycline derivative combined with protein kinase inhibitors .WO2009016172[P],2009.

[5] Carter,Malcolm,Clive.Bicyclic heteroaromatic compounds as protein tyrosine kinase inhibitors,WO 1999035146[P],1999-08-01.

[6] Kimberly G P,YueMei Z,Malcolm Carter.Optimization and SAR for dual ErbB-1/ErbB-2 tyrosine kinase inhibition in the 6-furanylquinazoline series[J].Bioorganic & Medicinal Chemistry Letters,2006,16(17):4686-4691.

[7] Ning X,Newbery P.Heteroaromatic compounds as PI3 kinase modulators and Methods of use:US,20140234254Al[P].2014-08-21

[8] Wang C,Dong J, Zhang Y,*et al*.Design synthesis and biological evaluation of biphenyl urea derivatives as novel VEGFR-2 inhibitors[J].*Med.Chem.Comm*.,2013(4):1434-1438.

[9] Thomas A P, Stokes E S E, Hennequin L F A.Quinazoline derivatives as VEGF inhibitors:EP,1244647B1[P].2006-06-21.

[10] Gant T G, Sarshar S, Shahbaz M M. Substituted quinazoline inhibitors of growth factor receptor tyrosine kinases:US,201075916A1[P].2010-3-30.

[11]Tasler S, Müller O, Wieber T, et al.Substituted 2-arylbenzothiazoles as ki-nase inhibitors:Hit-to-lead optimization[J].*Bioorganic & Medicinal Chemistry*,2009(18):6728-6737.

[12]Laurent F A H,Elaine S,Elizabeth S,Andrew P T.Preparation of 4-anili-no-piperidingyloxy quinazolines as vascular endothelial growth factor inhibitors:WO,2001032651[P].2001-5-10.