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Synthesis and Spectral Characterization of 4,7-Dichloro-6-nitroquinazoline

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Abstract: Afatinib is a 4-anilinoquinazoline tyrosine kinase inhibitor (TKI) in the form of a dimaleate salt which is indicated for the treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC). The most scalable route for the synthesis of this drug was reported in two Boehringer Ingelheim patents, in which the title compound, 4,7-dichloro-6-nitroquinazoline (**IV**), is an important intermediate. Compound **IV** is also present in a number of synthetic pathways for various 4,7-disubstituted quinazoline derivatives displaying high therapeutic potential. However, no detailed characterization of this popular compound has been reported, possibly due to its high instability. In this paper, **IV** was prepared in an overall yield of 56.1% by a 3-step process (condensation, nitration, and chlorination) from 2-amino-4-chlorobenzoic acid (**I**). The target compound has been for the first time fully characterized by melting point, mass-spectrometry, FT-IR, ^{1}H-NMR and ^{13}C-NMR spectroscopies.

Keywords: afatinib; 2-amino-4-chlorobenzoic acid; 4,7-dichloro-6-nitroquinazoline; quinazoline

1. Introduction

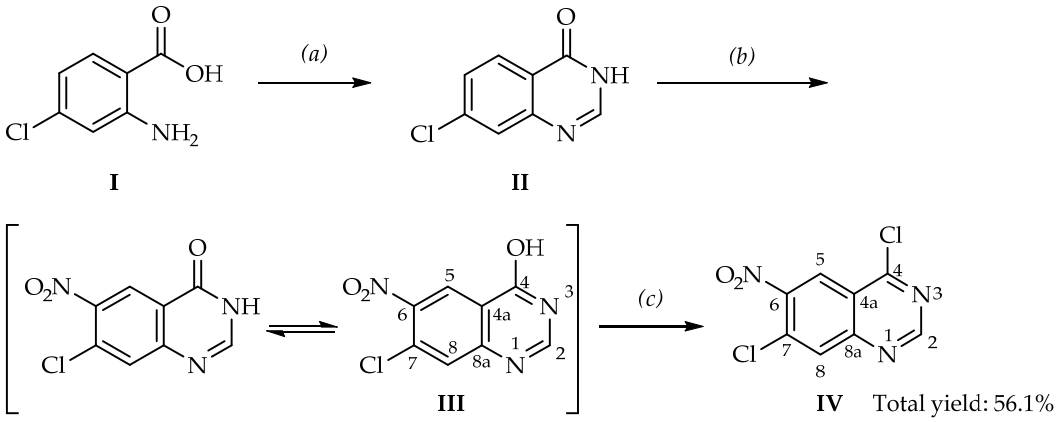
Quinazoline and quinazolinones scaffolds are present in a diverse range of biologically active compounds with huge therapeutic potential, including anticancer, antimicrobial, antiviral, antituberculosis, antifungal, antimalarial, anti-inflammatory, analgesic, and antidiabetic properties [1–4]. Many quinazoline derivatives, in particular the 4-anilinoquinazolines such as gefitinib, erlotinib, lapatinib, vandetanib, icotinib, afatinib and dacomitinib are approved as tyrosine kinase inhibitors (TKI) for the treatment of different cancers in targeted therapies [5,6]. Among those, afatinib dimaleate is a powerful second-generation TKI, irreversibly binding to both EGFR (epidermal growth factor receptor) and HER2 (human epidermal growth factor receptor 2). It is an approved anticancer drug marketed under the brand names Giotrif® (EU, Japan, Taiwan and Canada) and Gilotrif® (USA). It is indicated for patients with specific types EGFR mutation-positive non-small cell lung cancer [7,8].

The synthetic route to afatinib dimaleate can be derived from two Boehringer Ingelheim patents, comprising 10 reactions [9–14]. In that synthetic procedure, the compound 4,7-dichloro-6-nitroquinazoline (**IV**, CAS Registry number 162012-71-7) is a highly reactive intermediate. However, it was used in situ and thus no characterization was available. Similarly, in other synthetic routes of other bioactive quinazoline derivatives reported by SciFinder and Reaxys, compound **IV**

was also synthesized and used directly in the next step without characterization [15–36], or only partially characterized by ^{1}H-NMR [37]. The most detailed characterization of **IV** includes a melting point analysis, ^{1}H-NMR and ^{13}C-NMR spectroscopies, and an elemental analysis [38]. However, it appears that the reported NMR data for **IV** in this paper are close to those of the starting material (7-chloro-6-nitroquinazolin-4(3*H*)-one, **III**), indicating the possibility of a hydrolysis reaction which converts **IV** back to the starting material. In addition, the given elemental analysis did not present the percentage of each element, which offers no clarification over the identity of this compound. In this paper, compound **IV** has been for the first time fully characterized by melting point, mass-spectrometry, FT-IR, ^{1}H-NMR and ^{13}C-NMR spectroscopies.

2. Results and Discussion

The target compound **IV** was prepared in three steps from 2-amino-4-chlorobenzoic acid (**I**) in an overall yield of 56.1% (Scheme 1). The synthetic procedures were based on references [30,33,39] with some changes.



Scheme 1. Synthesis of 4,7-dichloro-6-nitroquinazoline (**IV**). *Reagents and conditions* (*yield*): (**a**) HCO-NH_2, reflux at 160 °C (82.3%); (**b**) HNO_3/H_2SO_4 (84.7%); (**c**) $SOCl_2$/DMF at 100 °C (91.3%).

Compound **IV** is an imidoyl halide (also known as imidyl or iminochlorides), a group of highly reactive organic compounds widely used as synthetic tools to produce a variety of compounds. It is often not necessary to isolate imidoyl halides because in situ generation and subsequent reactions can afford the desired derivatives in high yields [40–42]. In fact, our experimental observations demonstrate that **IV** is extremely sensitive to moisture and can be readily hydrolyzed giving back the starting material **III**. This phenomenon could explain the reason why the NMR-data in the aforementioned article [38] are so close to those of the starting material **III**. These data are presented in Tables 1 and 2.

Table 1. Reported and our data for ^{1}H-NMR spectroscopies of **III** and **IV.**

Signals	δ (ppm) for Compound III				δ (ppm) for Compound IV		
	Ref [30] (in DMSO-d_6)	Ref [43] (in DMSO-d_6)	Ref [39] (in DMSO-d_6)	Our Data (in DMSO-d_6)	Ref [38] (in DMSO-d_6)	Ref [37] (in DMSO-d_6)	Our Data (in $CDCl_3$)
OH or NH forms	3.30 * (br.s, 1H, NH form)	12.79 (br.s, 1H, OH form)	12.79 (br.s, 1H, OH form)	12.73 (br.s, 1H, OH form)	NA **	NA	NA
H-5	8.53 (s, 1H)	8.69 (s, 1H)	8.67 (s, 1H)	8.64 (s, 1H)	8.60 (s, 1H)	9.56 (s, 1H)	9.18 (s, 1H)
H-2	8.28 (s, 1H)	8.32 (s, 1H)	8.31 (s, 1H)	8.27 (s, 1H)	8.27 (s, 1H)	8.71 (s, 1H)	8.76 (s, 1H)
H-8	7.97 (s, 1H)	8.03 (s, 1H)	8.01 (s, 1H)	7.97 (s, 1H)	7.85 (s, 1H)	8.28 (s, 1H)	8.30 (s, 1H)

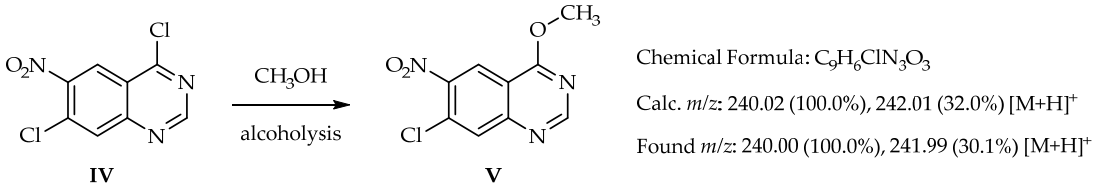
*: The signal is overlapped with water signal at 3.33 ppm in DMSO-d_6. ** NA: not available.

Table 2. Reported and our data for ^{13}C-NMR spectroscopies of **III** and **IV**.

Signals	δ (ppm) for Compound III		δ (ppm) for Compound IV	
	Literature	Our Data (in DMSO-d_6)	Ref [38] (in DMSO-d_6)	Our Data (in $CDCl_3$)
C-4	NA	159.3	159.0	163.6
C-2	NA	151.5	150.3	156.9
C-8a	NA	149.6	149.2	151.6
C-6	NA	144.7	144.8	147.5
C-7	NA	130.4	131.1	132.8
C-8	NA	129.4	129.4	132.2
C-5	NA	124.2	124.2	123.5
C-4a	NA	121.7	121.4	122.1

The data in Table 1 indicate that **III** is capable of tautomerism between the lactim (-C(OH)=N-) and lactam (-C(=O)-NH-) forms, displaying a huge difference in chemical shifts between the -OH and the -NH groups (12.79 ppm vs. 3.30 ppm). In the latter form, the -NH- signal is actually overlapped with the water signal if DMSO-d_6 is used and may not be seen in a proton spectrum. As the reported proton chemical shifts for compound **IV** in [38] are similar to those of compound **III** in [30], we suspect that they are of the same chemical compound (Table 1). Indeed, the ^{1}H-NMR values for compound **IV** in [38] do not match up with those of either our data or another paper [37], displaying large chemical shifts' differences of 0.96 ppm, 0.44 ppm, and 0.43 ppm, respectively, for the aromatic hydrogens in DMSO-d_6 [37,38]. We would not expect such large discrepancies in chemical shifts for the same compound using the same NMR solvent (DMSO-d_6). When comparing our ^{1}H-NMR data with those of [37], the differences are −0.38 ppm, 0.05 ppm, and 0.02 ppm, respectively, which indicate a high level of spectral similarities. These slight deviations could potentially originate from the fact that two different NMR solvents (DMSO-d_6 vs. $CDCl_3$) were used [44]. On the other hand, when examining the ^{13}C-NMR data, we found strikingly similar values between **IV** of reference [38] and the starting material **III** (Δδ = 0–0.4 ppm, Table 2). These reported values are different from our ^{13}C-NMR data of **IV** (Δδ = 0.4–5.4 ppm, Table 2). Altogether, both the ^{1}H-NMR and ^{13}C-NMR data combined indicate that the reported NMR data in [38] could potentially be that of the starting material **III**, and not the desired compound **IV**. One possible explanation could be the hydrolysis of the highly reactive compound **IV** back into the starting material **III**, a phenomenon we have observed in our laboratory.

Another interesting fact is that, when measuring mass spectrometry, we not only detected the peak of compound **IV**, but also its methoxy form (compound **V**), which possibly occurs due to alcoholysis by methanol (the solvent in MS). We show this in Scheme 2.



Scheme 2. The formation of 7-chloro-4-methoxy-6-nitroquinazoline (**V**) by alcoholysis with methanol in MS.

On the whole, in the synthesis of **IV**, our control of anhydrous reaction conditions and the appropriate work-up procedures have made it feasible to synthesize and characterize this highly reactive compound for the first time. These data may be useful for further investigations in the synthesis process improvement of afatinib, its analogs and other biologically active quinazoline based compounds. All the mass, FT-IR, ^{1}H-NMR and ^{13}C-NMR spectra are presented in the Supplementary Material File.

3. Materials and Methods

3.1. General Information

The 2-amino-4-chlorobenzoic acid was purchased from Energy Chemical (Zhejiang, China) and used as received. Formamide (99.5%) was purchased from Scharlau Chemie (Barcelona, Spain). Thionyl chloride (99.5%) was purchased from Merck Schuchardt (Hohenbrunn, Germany). Dichloromethane (DCM, 99.5%), sufuric acid (98%) and *N*,*N*-dimethylformamide (DMF, 99.5%) was purchased from Xilong Scientific Co., Ltd. (Shantou, China). Fuming nitric acid (d 1.50 g/mL) was prepared by reaction of solid sodium nitrate and liquid sulfuric acid (98%), following distillation at b.p 82 °C.

The melting point was determined using a SRS EZ-Melt apparatus (Stanford Research Systems, Sunnyvale, CA, USA) and is uncorrected. MS was performed at a EVOQ Qube™ (Bruker, Billerica, MA, USA) or an LTQ Orbitrap XL™ (Thermo Scientific, Waltham, MA, USA) system. FT-IR spectra were recorded by a Perkin Elmer (Waltham, MA, USA) or Shimadzu (Kyoto, Japan) spectrometer. ^{1}H- and ^{13}C-NMR spectra were acquired with a 500 MHz Ascent spectrometer (Bruker, Billerica, MA, USA) using acetone-d_6, DMSO-d_6, or $CDCl_3$ as the solvent. The reaction mixtures were monitored, and the purity of all products was checked by thin-layer chromatography (TLC) on silica gel 60 F_{254} plates (Merck, Darmstadt, Germany).

3.2. Synthetic Procedure

3.2.1. Preparation of 7-Chloroquinazolin-4(3*H*)-one (**II**)

The synthetic procedure for compound II was based on the method described in [39] with some modifications. A mixture of 2-amino-4-chlorobenzoic acid (**I**, 34.30 g, 0.20 mol, 1 equiv.), formamide (125.0 mL, 2.77 mol, 14 equiv.) was aerated with nitrogen, then stirred and refluxed for 1.5 h at 160 °C (the reaction was monitored by TLC with a 9:1 DCM/methanol mixture as eluent). The reaction mixture was cooled to 80 °C, then 500 mL of water was added. The mixture was cooled to −5 °C in 1 h and filtered. The precipitate was washed with water and dried at 60 °C to afford 7-chloroquinazolin-4(3*H*)-one (**II**) as a light brown solid (29.71 g, 82.3%), which was used for the next step without further purification. M.p 251.0–253.0 °C. R_f 0.60 (DCM/methanol, 9:1). MS (ESI$^+$, MeOH), *m*/*z*: found 181.2 and 183.2 $[M + H]^+$, $C_8H_5ON_2Cl$ requires $[M + H]^+$ 181.0 and 183.0. FT-IR (KBr), ν_{max} (cm^{-1}): 3031 (C-H); 2964, 2919 (N-H); 1714 (C=O); 1693 (C=N); 1655, 1606 (C=C). ^{1}H-NMR (acetone-d_6), δ (ppm): 11.82 (br.s, 1H, H-3, NH); 8.17 (d, J = 8,5 Hz, 1H, H-5); 8.09 (s, 1H, H-2); 7.67 (d, J = 2.0 Hz, 1H, H-8); 7.51 (dd, J_1 = 8.5 Hz, J_2 = 2.0 Hz, 1H, H-6). ^{13}C-NMR (acetone-d_6), δ (ppm): 160.6 (C-4); 151.2 (C-8a); 147.3 (C-2); 140.2 (C-7); 128.8 (C-5); 127.7 (C-6); 127.6 (C-8); 122.8 (C-4a).

3.2.2. Preparation of 7-Chloro-6-nitroquinazolin-4(3*H*)-one (7-Chloro-4-hydroxy-6-nitroquinazoline, **III**)

The synthetic procedure for compound **III** was based on [30] with some modifications. Compound **II** (10.83 g, 0.060 mol) and sulfuric acid (120 mL) were added into a 500 mL two-neck round bottom flask. The mixture was cooled to 0 °C on ice and stirred until dissolution. Fuming nitric acid (120 mL) was slowly added to the mixture at 0 °C, and the mixture was stirred for 1.5 h at 30 °C. After completion of reaction as indicated by TLC, 10% NaOH solution was slowly added to the reaction mixture until a precipitate was formed (pH ~7). The mixture was then filtered to furnish a light yellow solid (**III**). The compound was purified by redissolving in HCl (5M) and then neutralizing this solution with NaOH (10%) to pH 6–7 to furnish the pure precipitate which was then filtered, washed with water and dried at 60 °C to furnish 7-chloro-6-nitroquinazolin-4(3*H*)-one (**III**) as a light yellow solid (11.46 g, 84.7%). M.p 263.5–265.0 °C. R_f 0.34 (DCM/methanol, 20:1). MS (ESI$^+$, MeOH), *m*/*z*: found 225.9 $[M + H]^+$, $C_8H_4O_3N_3Cl$ requires $[M + H]^+$ 225.9. FT-IR (KBr), ν_{max} (cm^{-1}): 3452, 3215 (O-H); 3091, 3012 (C-H); 1696 (C=O); 1666, 1612 (C=N); 1523 (C=C); 1336 (NO_2). ^{1}H-NMR (DMSO-d_6), δ (ppm):

12.73 (br.s, 1H, OH); 8.64 (s, 1H, H-5); 8.27 (s, 1H, H-2); 7.97 (s, 1H, H-8). ^{13}C-NMR (DMSO-d_6), δ (ppm): 159.3 (C-4); 151.5 (C-8a); 149.6 (C-2); 144.7 (C-6); 130.4 (C-7); 129.9 (C-5); 124.2 (C-8); 121.7 (C-4a).

3.2.3. Preparation of 4,7-Dichloro-6-nitroquinazoline (**IV**)

The synthetic procedure for compound IV was based on [33] with some modifications. A mixture of compound **III** (6.09 g, 0.027 mol), thionyl chloride (48.0 mL, 0.661 mol) and *N*,*N*-dimethyl-formamide (0.25 mL) was melted and stirred at 100 °C for 2 h. The reaction mixture was allowed to cool down and excess thionyl chloride was removed by rotary evaporation under reduced pressure. Toluene (40 mL) was added to the residue and the mixture was evaporated again to completely remove volatile matter. The precipitate was washed with diethyl ether and dried in the desiccator to obtain 4,7-dichloro-6-nitroquinazoline (**IV**) as a yellow solid (6.02 g, 91.3%). M.p: 269.0–270.5 °C. R_f: 0.87 (DCM/methanol, 20:1). MS (ESI$^+$, MeOH), *m*/*z*: found 244.4 [M + H]$^+$, 240.00 and 241.99 [methoxy form]; $C_8H_3O_2N_3Cl_2$ requires [M + H]$^+$ 244.0 and 246.0. FT-IR (KBr), ν_{max} (cm^{-1}): 3089 (C-H); 1726, 1645, 1610 (C=N); 1546 (C=C); 1527, 1323 (NO_2). ^{1}H-NMR ($CDCl_3$), δ (ppm): 9.18 (s, 1H, H-2); 8.76 (s, 1H, H-5); 8.30 (s, 1H, H-8). ^{13}C-NMR ($CDCl_3$), δ (ppm): 163.6 (C-4); 156.9 (C-2); 151.6 (C-8a); 147.5 (C-6); 132.8 (C-7); 132.2 (C-8); 123.5 (C-5); 122.1 (C-4a).

Supplementary Materials: Spectral data of starting material **I**, intermediates **II**, **III** and title compound **IV** are available online, Figure S1: FT-IR spectrum of compound 2-amino-4-chlorobenzoic acid (**I**), Figure S2: ^{1}H-NMR spectrum of compound 2-amino-4-chlorobenzoic acid (**I**), Figure S3: ^{13}C-NMR spectrum of compound 2-amino-4-chlorobenzoic acid (**I**), Figure S4: MS spectrum of compound 7-chloroquinazolin-4(3*H*)-one (**II**), Figure S5: FT-IR spectrum of compound 7-chloroquinazolin-4(3*H*)-one (**II**), Figure S6: ^{1}H-NMR spectrum of compound 7-chloroquinazolin-4(3*H*)-one (**II**), Figure S7: ^{13}C-NMR spectrum of compound 7-chloroquinazolin-4(3*H*)-one (**II**), Figure S8: MS spectrum of compound 7-chloro-6-nitroquinazolin-4(3*H*)-one (**III**), Figure S9: FT-IR spectrum of compound 7-chloro-6-nitroquinazolin-4(3*H*)-one (**III**), Figure S10: ^{1}H-NMR spectrum of compound 7-chloro-6-nitroquinazolin-4(3*H*)-one (**III**), Figure S11: ^{13}C-NMR spectrum of compound 7-chloro-6-nitroquinazolin-4(3*H*)-one (**III**), Figure S12: MS spectrum of compound 4,7-dichloro-6-nitroquinazoline (**IV**), Figure S13: FT-IR spectrum of compound 4,7-dichloro-6-nitroquinazoline (**IV**), Figure S14: ^{1}H-NMR spectrum of compound 4,7-dichloro-6-nitroquinazoline (**IV**), Figure S15: ^{13}C-NMR spectrum of compound 4,7-dichloro-6-nitroquinazoline (**IV**).

Author Contributions: T.N.N. and T.H.T. synthesized the compounds. T.N.N. wrote the manuscript. N.S.H.D., V.G.N. and D.L.N. designed the experiments. V.H.N. analyzed spectroscopic data. V.H.N. and N.T.T. edited the manuscript. All authors read and approved the final version of the manuscript.

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