¹H AND ¹³C NMR SPECTRAL ASSIGNMENTS AND X-RAY CRYSTALLOGRAPHY OF N-(3-(1H-IMIDAZOL-1-YL)PROPYL)-2-PHENYLQUINAZOLIN-4-AMINE

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ABSTRACT

N-(3-(1H-Imidazol-1-yl)propyl)-2-phenylquinazolin-4-amine (**2**) was obtained by nucleophilic substitution of 1-(3-aminopropyl)-imidazole over 4-chloro-2-phenylquinazoline (**1**) with DMF/TEA at room temperature. The precursor and product were characterized by NMR spectroscopy. The structure of the title compound was confirmed by X-ray diffraction methods. The quinazoline fragment (**2**) is essentially planar and makes a dihedral angle of 66.35 ° with the imidazole plane. In the crystal packing the molecules are associated by two strong intermolecular NH...N hydrogen bonds with graph-set motif R₂²(16). These pairs are linked by two π - π interactions.

INTRODUCTION

Quinazoline derivatives are known to possess remarkable anti-inflammatory activity as NOS-II^{1,2} and PDE-4³ inhibitors, among others. They are also found to show broncho-dilatory⁴ and anti-allergic⁵ properties. In addition, these compounds also have a therapeutic benefit as an anti-invasive agent with potential for activity in early and advanced solid tumors, metastatic bone disease and leukemias^{6,7}. Based on the importance of these molecules, our attention was attracted towards synthesis of novel quinazoline derivatives in order to find new biologically active molecules.

Quinazoline derivatives are synthesized mainly starting from anthranilic acid^{8,9}, benzonitrile¹⁰ and so on with an appropriate substituent to have specific functionality and activity. In continuation of our efforts towards synthesis of molecules with potential biological activity we have synthesized a new series of 2-aryl-4-amino-quinazoline derivatives¹¹.

RESULTS AND DISCUSSION

Substitution of chlorine on 4-chloro-2-phenylquinazoline **1** (Scheme 1), with 1-(3-aminopropyl)-imidazole in TEA and DMF at room temperature for 4 h, generated N-(3-(1H-imidazol-1-yl)propyl)-2-phenylquinazolin-4-amine **2** with good yield (84%). Okano¹² and Yokoyama¹³, carried out this reaction under slightly different conditions, reporting lower yields for similar structures.

Scheme 1. Reagents and reaction conditions in synthesis of **2**.

The complete ¹H and ¹³C NMR assignments of compounds **2**, based on one- and two-dimensional NMR experiments (e.g. Figure 1a; gives the atom numbering), is shown in Table 1.

Figure 1: a) Numbering scheme of N-(3-(1H-imidazol-1-yl)propyl)-2-phenylquinazolin-4-amine b) COSY, c) NOESY principal correlations and d). HMBC.

In the COSY experiment (Fig. 2b) of **2**, we can see the interactions between the amine proton H11 with protons H18a and H18b and H19 with H20 of the alkylic chain. In addition, the correlations of imidazole protons H24/H25 have been observed too. The NOESY (Fig 2c) show the interaction of H11 (NH) with H5. This data is consistent with the band at 3227 cm⁻¹ (N-H) observed in the IR spectra. Further, interactions between H19/H20, H20/H25 and H24/H25 can be observed. In the HMBC experiment (Fig. 2d) the following interactions were observed: C4/H11 (NH), C4/H18, C20/H22, C20/H25 and C22/H24. These results allow us to confirm the incorporation of the radical 1-(3-aminopropyl)-imidazole at C4 position in **2**.

Table: ^1H and ^{13}C chemical shifts and 2D-NMR correlation data of compound **2**.

Atom No.	^1H NMR, multiplicity, $J(\text{H,H})$ (Hz) ^a	COSY ^b	NOESY ^c	^{13}C -APT NMR ^a	HMBC ^d
1	-	-	-	-	-
2	-	-	-	159.1	-
3	-	-	-	-	-
4	-	-	-	159.6	-
5	8.24 [H-5, d, $J(5,6) = 8,2$]	5(6)	5(6)	122.7	5(C: 4, 7, 9, 10)
6	7.49 [H-6, m]	6(5, 7)	-	125.2	6(C: 5, 8, 9, 10)
7	7.77 [H-7, m]	7(6, 8)	-	132.6	7(C: 8)
8	7.77 [H-8, m]	8(7)	-	127.8	8(C: 7, 9, 10)
9	-	-	-	149.9	-
10	-	-	-	113.8	-
11	8.34 [H-11, t, $J(11,18) = 5.4$]	11(18)	5	-	11(C: 4)
12	-	-	-	138.5	-
13	8.44 [H-13, m]	13(14)	13(14)	127.8	13(C: 2, 15)
14	7.49 [H-14, m]	14(13, 15)	14(13, 15)	128.2	14(C: 12)
15	7.49 [H-15, m]	15(14, 16)	15(14, 16)	130.0	-
16	7.49 [H-16, m]	16(15, 17)	16(15, 17)	128.2	16(C: 12)
17	8.44 [H-17, m]	17(16)	17(16)	127.8	17(C: 2, 15)
18	3.66 [H-18 _(a,b) , t, $J(18,19) = 7.0$]	18(11, 19)	18(19)	37.6	18(C: 4, 19, 20)
19	2.18 [H-19 _(a,b) , p, $J(19,18-20) = 6.9$]	19(18, 20)	19(18, 20)	30.2	19(C: 18, 20)
20	4.14 [H-20 _(a,b) , t, $J(20,19) = 6.8$]	20(19)	20(19,22,25)	44.0	20(C: 18, 19, 22, 25)
21	-	-	-	-	-
22	7.70 [H-22, s]	-	22(20)	137.3	22(C: 20, 24, 25)
23	-	-	-	-	-
24	6.94 [H-24, s]	24(25)	-	128.3	24(C: 22)
25	7.25 [H-25, s]	25(24)	25(20)	119.4	25(C: 20, 22, 24)

^a In ppm from TMS; ^b H-H COSY, ^c H-H NOESY and ^d H-C HMBC interactions.

The theoretical study of Molecular mechanic (MM2)¹⁴ shows that **2** (Fig. 2) presents a more stable conformation (33.316275 Kcal/mol) when the quinazoline moiety is coplanar with the phenyl radical at C2, which is consistent with the structure obtained by X-ray diffraction. On the other hand, the imidazole ring and C20 appears in a conformation with an anti-disposition respect to N11.

Figure 2. Theoretical conformation of **2**: Energy= 33.316275 Kcal/mol (Grad. 0.095603).

The crystal structure was determined by single crystal X-ray diffraction. In the title compound, Fig.3, the quinazoline fragment is essentially planar (rms deviation 0.037 Å) and makes a dihedral angle of 66.35 ° with the imidazole plane. All the quinazoline systems are oriented almost perpendicular to the $[-1\ 0\ 1]$ direction. In the crystal packing the molecules are associated by two

strong intermolecular $\text{NH}\cdots\text{N}$ hydrogen bonds with graph-set motif¹⁵ $R_2^2(16)$, as in the bromo-substituted quinazoline analog¹⁶, Fig. 4. Between these pairs, π - π interactions are present ($\text{Cg4}\cdots\text{Cg2}^i$ 3.6050(7) Å; $\text{Cg4}\cdots\text{Cg3}^i$ 3.7229(7) Å; symmetry code (i) $-x+2, -y+2, -z+2$; Cg2, Cg3 and Cg4 are the centroids of rings (N25,C10,C11,C16,N17,C18), (C11-C16) and (C19-C20), respectively). The packing of these pairs in the crystal is shown in Fig. 5. A number of $\text{C-H}\cdots\text{N}$ and $\text{C-H}\cdots\pi$ interactions is also present (Table 2)

Figure 3. Ortep drawing with 50 percent probability ellipsoids.

Figure 4. View along the $[-1\ 0\ 1]$ direction. Two adjacent centrosymmetric dimers are depicted showing the π - π interaction between the dimers.

Figure 5. View along the b axis showing the packing.

Table 2. Hydrogen-bond geometry ($\text{\AA}$, $^\circ$).

$D-H\cdots A$	$D-H$	$H\cdots A$	$D\cdots A$	$D-H\cdots A$
$N9-H9\cdots N2^i$	0.88	2.10	2.9057(15)	152
$C1-H1\cdots N25^{ii}$	0.95	2.57	3.4785(15)	160
$C4-H4\cdots Cg3^{iii}$	0.95	2.90	3.527(2)	125
$C6-H6B\cdots Cg4^{ii}$	0.99	2.74	3.657(2)	154

Symmetry codes: (i) $-x+1, -y+2, -z+1$; (ii) $x-1, y, z$; (iii) $-x+2, -y+2, -z+1$.

EXPERIMENTAL

Melting points were determined on a Kofler-type apparatus and are uncorrected. The IR were taken on a Perkin-Elmer 200 spectrophotometer with KBr. NMR spectra were collected in DMSO- d_6 or $CDCl_3$ on a Varian Unity Inova 500 MHz spectrometer equipped with a microflow probe from Protasis. Mass spectra were recorded on a Micromass-LCT Premier Time-of-Flight electrospray (ESI) spectrometer with interface system Acquity UPLC (Ultra Performance Liquid Chromatography). Crystallographic analyses were made in an Agilent SuperNova, Dual, Cu, Atlas Diffractometer with CuK α radiation. TLC was performed on Al Si gel Merck 60 F254 and TLC plates were visualized by spraying with phosphomolybdic acid reagent and heating. Commercially available, laboratory grade reagents were used without further purification.

General Procedure

To a solution containing 1.0 g (4.2 mmol) of 4-chloro-2-phenylquinazoline (**1**) in 10 ml of DMF and 1.2 ml of TEA (8.6 mmol), 0.7 ml of 1-(3-aminopropyl)-imidazole (5.9 mmol) was added¹². After 4 hours of reaction at room temperature, 30 ml of water were added forming a white precipitate, which was filtered at vacuum and dried at 105 $^\circ\text{C}$, obtaining 1.15 g (84% yield) of N-(3-(1H-imidazol-1-yl)propyl)-2-phenylquinazolin-4-amine (**2**). The crude product was crystallized in acetone giving colorless crystals (m.p. 146-148 $^\circ\text{C}$).

4-Chloro-2-phenylquinazoline 1:

IR (cm^{-1}): 3026 and 3056 ($C_{\text{Ar-H}}$); 1546, 1566 ($C=N$); 1589, 1615 ($C_{\text{Ar-C}}_{\text{Ar}}$), 1076 ($C_{\text{sp}^2}-\text{Cl}$).

$^1\text{H-NMR}$ ($CDCl_3$, 500 MHz) (ppm): 8.60 (2H, m, H13; H17), 8.26 (1H, d, $J=8.29$ Hz, H5), 8.10 (1H, d, $J=8.45$ Hz, H8), 7.94 (1H, dd, $J=1.29$; 7.15; 8.37 Hz, H7), 7.67 (1H, ddd, $J=0.89$; 7.22; 8.09 Hz, H-6), 7.53 (3H, m, (H14, H15, H16).

$^{13}\text{C-NMR}$ ($CDCl_3$, 125.7 MHz (ppm): 131.3 (C15), 128.8 (C14, C16), 128.9 (C17, C13), 136.8 (C12), 162.7 (C4), 160.3 (C2), 128.4 (C6), 134.9 (C7), 125.9 (C5), 129.1 (C8), 122.6 (C10), 152.1 (C9).

HRESIMS: m/z 241,0536 for $C_{14}H_{10}N_2Cl$ $[M+H]^+$, calculated: m/z 241,0531.

N-(3-(1H-imidazol-1-yl)propyl)-2-phenylquinazolin-4-amine 2:

IR (cm^{-1}): 3227 (N-H); 2929, 2958 ($C_{\text{sp}^3}-\text{H}$); 3112 ($C_{\text{sp}^2}-\text{H}$); 3062 ($C_{\text{Ar-H}}$); 1536, 1573, 1589 ($C=N$); 1618 ($C_{\text{Ar-C}}_{\text{Ar}}$).

$^1\text{H-NMR}$ (DMSO- d_6 , 500MHz): (ppm): 8.44 (2H, m, H13; H17), 8.34 (1H, t, $J=5.35$ Hz, H11), 8.24 (1H, d, $J=8.16$ Hz, H5), 7.77 (2H, m, H7; H8), 7.70 (1H, s, H22), 7.49 (4H, m, H6; H14; H15; H16), 7.25 (1H, s, H25), 6.94 (1H, s, H24), 4.14 (2H, t, $J=6.80$ Hz, H20), 3.66 (2H, t, $J=7.01$ Hz, H18), 2.18 (2H, q, $J=6.89$ Hz, H19).

$^{13}\text{C-NMR}$ (DMSO- d_6 , 125.7 MHz) (ppm): 30.2 (C19), 37.9 (C18), 43.9 (C20), 113.8 (C10), 119.4 (C25), 122.7 (C5), 125.2 (C6), 127.8 (C8), 127.8 (C13, C17), 128.2 (C14, C16), 128.3 (C24), 129.9 (C15), 132.6 (C7), 137.3 (C22), 138.5 (C12), 149.9 (C9), 159.1 (C2), 159.6 (C4).

HRESIMS: m/z 328,1562 for $C_{20}H_{18}N_5$ $[M+H]^+$, calculated: m/z 328,1559.

X-Ray Crystallography

Single crystal analysis data were collected on a Agilent SuperNova, Dual, Cu, Atlas Diffractometer with CuK α radiation. Data collection: *CrysAlis PRO*¹⁷ (Agilent, 2010); cell refinement *CrysAlis PRO*; data reduction: *CrysAlis PRO*. Program used to solve structure program(s) used to refine structure: *SHELXL97*¹⁸; molecular graphics: *OLEX2*¹⁹ software used to prepare material for publication: *OLEX2* and *publCIF*²⁰. Crystal dimension of $C_{20}H_{18}N_5$, 0.7x0.4x0.06 mm; $M_r=329.40$ Dalton; Triclinic $P\bar{1}$; $a=8.0655(3)\text{\AA}$; $b=9.7687(4)\text{\AA}$; $c=11.1588(5)\text{\AA}$; $\alpha=82.287(4)^\circ$; $\beta=78.768(3)^\circ$; $\gamma=88.152(4)^\circ$; $V=854.54(6)\text{\AA}^3$; $Z=2$; $m=0.626\text{mm}^{-1}$. 9864 / 3334 measured/unique reflection with $I>2s(I)$ [$R_{\text{int}}=0.0205$]; $R[F^2>2s(F^2)]$ 0.0402, $wR_2=0.1124$; $S=1.039$; 226 parameters; $Dr_{\text{max}}=0.18\text{e}\text{\AA}^{-3}$ and $Dr_{\text{min}}=-0.22\text{e}\text{\AA}^{-3}$. All H atoms were located in difference maps and their positions and isotropic displacements parameters of 1.2-1.5 times those of the attached atoms. Supplementary information: Crystallographic data (excluding structure factors) for the structural analysis have been deposited in the Cambridge Crystallographic Data Centre, CCDC 911764. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre; Postal Address : CCDC, 12 Union Road, Cambridge CB21EZ, UK, Telephone: (44) 01223 762910, Fax: (44) 01223 336033, e-mail: deposit@ccdc.cam.ac.uk

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