Synthesis, Structure and Biological Activity of Some Hybrid Benzimidazole / Quinoline Derivatives

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The synthesis, X-ray crystal structure and antimycobacterial activity of 3-(2-ethoxy-2-oxoethyl)-1-(2-oxo-2-(pyridin-2-ylamino)ethyl)-1H-benzo[d]imidazol-3-ium bromide are reported. The synthesis is direct and efficient, the structure of compound was proven by elemental and spectral analysis, the X-ray spectrum including. The compound crystallizes in the space group Pbca (orthorhombic) with a = 20.6941(2) Å, b = 8.4233(11) A, c = 24.1005(3) A, α = 90°, β= 90°, γ= 90°, V= 4201.02(9) and Z = 8. Accurate molecular parameters for the heterocyclic system were obtained from intensity data collected at 293 K. The tested hybrid derivatives have an excellent solubility in microbiological medium (>200 μM), which is very promising from the pharmacological properties point of view, but no antimycobacterial activity.

Keywords: hybrid benzimidazole / quinoline, X-ray, solubility microbiological medium, antimycobacterial activity

During the last decades, azaheterocyclic compounds, especially the five and six member rings, have received considerable attention due to their important applications from synthetic points of view as well as from pharmacological and industrial point of view [1, 2]. Thus, diazines and intermediaries derivatives (and their ylides) are valuable intermediaries in a large variety of synthesis, these including alkylation, acylation, quaternization, cycloadditions, organometallic, and so on [3-21]. On the other hand, azaheterocyclic compounds have a large variety of applications in agriculture (herbicidal activity and grow up factor for plants) [22-25], medicinal chemistry (anticancer, antimicrobials, anti-inflammatory, antihypertensive, diuretics, antithrombotics, anticoagulants, antidepressant, anxiolytics, anticonvulsant, analgesic) [26-38], optoelectronics and material chemistry (fluorescent derivatives, sensors and biosensors, lasers, semiconductors and ionic and liquid crystal properties) [39-53].

As part of our ongoing research in the field of nitrogen heterocycles with antimycobacterial activity [26,27, 32,33,54] and their structure elucidation using X-ray measurements [55-58], we decided to synthesize a hybrid benzimidazole / quinoline derivative, to analyze through X-ray the structure, to test its antimycobacterial activity.

Experimental part

All the reagents and solvents employed were of the best grade available and were used without further purification. Melting points were determined using an electrothermal apparatus (MELTEMP II) and are uncorrected. X-Ray analysis was recorded with an Agilent SuperNova Dual diffractometer equipped with a Cu (Kα radiation) fine-focus sealed X-ray tube and a graphite monochromator. A suitable crystal was selected and mounted on the SuperNova, Eos diffractometer. Intensity data were collected using Cu-Kα radiation (λ= 1.5418 A), the crystal was kept at 293.00 K during data collection. All H atoms were located in difference electron density maps and were included in idealized positions in a riding model with isotropic thermal parameters equal to 1.2 times those of their parent atoms. In the final cycles of refinement, least-squares weights of the form $w = 1/[\sigma^2(F_o)^2 + (0.0387P)^2 + 0.0691P]$, $P = (F_o^2 + 2F_c^2)/3$ were employed. Crystallographic data for 3-(2-ethoxy-2-oxoethyl)-1-(2-oxo-2-(pyridin-2-ylamino)ethyl)-1-benzo[d]imidazol-3-ium bromide **4** are listed in table 1. CCDC 1470403, contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK: fax: (internat.) +44-1223/336-033; Email: deposit@ccdc.cam.ac.uk].

Computing details

Data Collection: CrysAlisPro, Agilent Technologies, Version 1.171.36.28 (release 01-02-2013 CrysAlis171 .NET). Using Olex2 [60], the structure was solved with the Superflip [61] structure solution program using Charge Flipping and refined with the ShelXL [62] refinement package using Least Squares minimization.

Results and discussions

The title compound was synthesized using a direct and efficient setup procedure, described elsewhere [59]. Thus, the *N*-acylation of 8-aminoquinoline **1** with 2-chloroacetyl chloride is leading to the corresponding acylamine **2**. Subsequent treatment of acylamine **2** with benzimidazole is leading to the derivative **3**, *via* an *N*-alkylation reaction of the NH- benzimidazolic moiety. In the last step, a quaternization reaction of *N*-benzimidazole atom with ethylbromoacetate, is leading to the desired hybrid benzimidazole / quinoline derivative **4**, (scheme 1).

The structure of the compound was proved by elemental (C, H, N) and spectral analysis (IR, ^{1}H NMR, ^{13}C NMR, 2D-COSY, 2D-HMQC and 2D-HMBC) being in accordance with the proposed structure, and was presented elsewhere [59]. In order to establish unequivocally the structure of compound **4**, the X-ray data analysis was performed. Pink needles crystals of compound **4** were obtained by crystallization from absolute ethanol. Compound **4** crystallizes in the Pbca orthorhombic space group, with cell parameters and structure refinement

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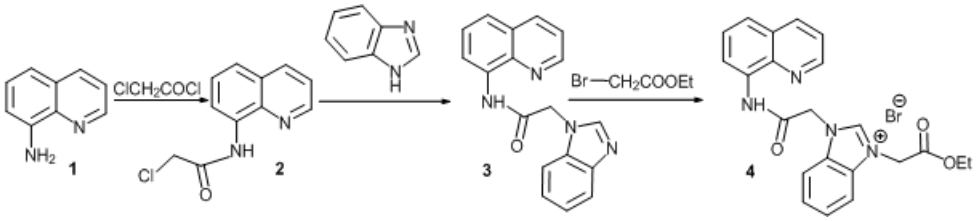

Scheme 1
Synthesis of hybrid benzimidazole / quinoline derivative **4**

Chemical formula	$C_{22}H_{21}N_4O_3Br$
Formula weight	469.34
Crystal Color	Pink
Crystal System	Orthorhombic
Space Group	Pbca
Lattice Parameters:	
Cell Lengts (Å):	
a	20.6941(2)
b	8.4233(11)
c	24.1005(3)
Cell angles (°):	
α	90
β	90
γ	90
Volume	4201.02(9)
Z value	8
ρ_{calc} (mg/mm^3)	1.484
F(000)	1920.0
μ(Cu Kα)	2932
Reflections collected	16123
Data/restraints/parameters	3990/0/272
Final R indexes [I > 2σ(I)]	$R_1 = 0.0361$, $wR_2 = 0.1015$
Goodness of Fit on F^2	1.033

Table 1
CRYSTAL AND EXPERIMENTAL DATA

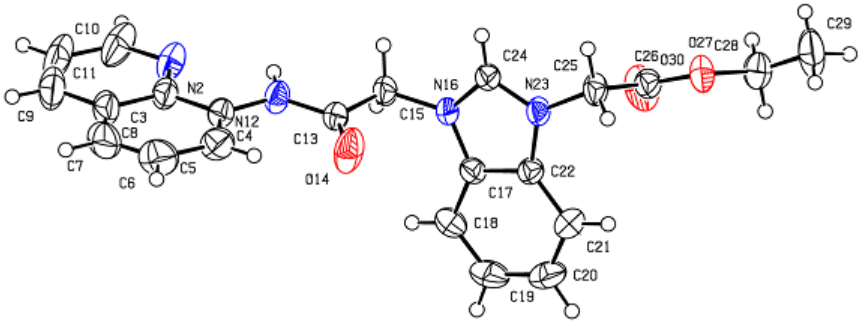

Fig. 1. The molecular structure of $C_{22}H_{21}BrN_4O_3$. Displacement ellipsoids are drawn at 50% probability level. H atoms are presented as small spheres of arbitrary radius

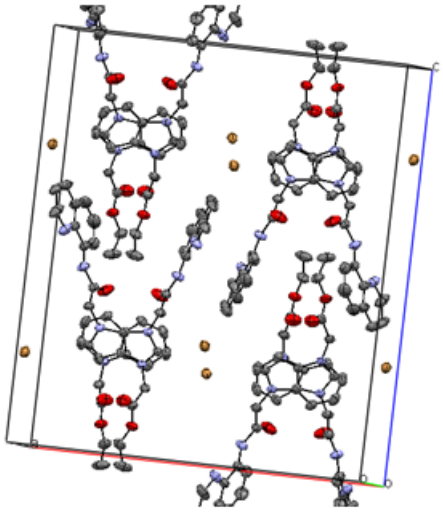

Fig. 2. Part of the crystal structure of $C_{22}H_{21}BrN_4O_3$

details given in table 1.The X-ray structure of the title compound with the atom numbering scheme is shown in figure 1.

We may notice from the X-ray structure (fig.1) and data from table 2, that the benzimidazole moiety is almost perpendicular to the acyl-aminoquinoline, with the bromide atom in the proximity of quinoline ring. Also, the amide carbonyl group linked to quinoline moiety and the COOEt carbonyl group linked to benzimidazole ring are in the opposite site. The data from table 2 reveals that the bonds from the aminoquinoline and benzimidazole moiety are as length in between the single C–C (C–N respectively) and double C=C (C=N respectively) bonds.

The crystal structure packing of compound **4** (fig. 2), shows an interesting Y shape of molecules, with the tail of a Y molecule into the bowl of another Y molecule. Full information concerning X-ray structure could be found in the Cambridge Crystallographic Data Centre, the CCDC 1470403.

The hybrid benzimidazole/quinoline derivative **4**, was evaluated for *in vitro* antimycobacterial activity against *M. tuberculosis H37Rv* (grown under aerobic conditions), as a part of the TAACF TB screening program under direction of the US National Institute of Health, the NIAID division. In the first step, the relative solubility of compound in microbiological medium was measured using turbidity as a measure (30), the tested hybrid derivatives having an excellent solubility in microbiological medium (>200 μM), which is very promising from the pharmacological properties point of view. The IC_{50}, IC_{90} and MIC against *M. tuberculosis H37Rv* under aerobic conditions were determined (31-34), showing that tested compound have no antimycobacterial activity, with an IC_{50}, IC_{90} and MIC > 200μM.

N23	C25	1.456(2)	C20	C21	1.376(3)				
N23	C22	1.392(2)	C20	C19	1.395(4)				
N23	C24	1.329(3)	O27	C26	1.322(3)				
O14	C13	1.206(3)	O27	C28	1.455(3)				
N2	C3	1.356(3)	O30	C26	1.194(3)				
N2	C11	1.327(3)	C18	C17	1.391(3)				
C25	C26	1.509(3)	C18	C19	1.369(4)				
N16	C24	1.330(3)	C4	C5	1.367(3)				
N16	C17	1.388(3)	C10	C9	1.339(5)				
N16	C15	1.454(2)	C10	C11	1.395(5)				
C3	C4	1.421(3)	C6	C5	1.402(4)				
C3	C8	1.417(3)	C6	C7	1.358(5)				
N12	C4	1.406(3)	C15	C13	1.519(3)				
N12	C13	1.344(3)	C9	C8	1.417(4)				
C22	C21	1.391(3)	C28	C29	1.480(4)				
C22	C17	1.385(3)	C8	C7	1.403(5)				
C22	N23	C25	124.60(17)		C5	C4	N12	124.6(2)	
C24	N23	C25	126.31(18)		C9	C10	C11	119.4(3)	
C24	N23	C22	108.84(16)		N16	C17	C18	131.7(2)	
C11	N2	C3	116.9(3)	C22	C17	N16	106.62(16)		
N23	C25	C26	109.93(17)		C22	C17	C18	121.6(2)	
C24	N16	C17	108.76(16)		C7	C6	C5	121.6(3)	
C24	N16	C15	125.16(18)		N16	C15	C13	110.32(17)	
C17	N16	C15	125.90(17)		O27	C26	C25	110.05(18)	
N2	C3	C4	117.9(2)	O30	C26	C25	125.1(2)		
N2	C3	C8	123.2(2)	O30	C26	O27	124.9(2)		
C8	C3	C4	118.9(2)	O14	C13	N12	124.4(2)		
C13	N12	C4	128.07(19)		O14	C13	C15	122.23(18)	
C21	C22	N23	131.67(19)		N12	C13	C15	113.33(18)	
C17	C22	N23	106.25(16)		C18	C19	C20	122.4(2)	
C17	C22	C21	122.07(19)		C4	C5	C6	119.8(3)	
C21	C20	C19	121.7(2)	C10	C9	C8	120.0(3)		
C20	C21	C22	116.0(2)	O27	C28	C29	107.8(2)		
C26	O27	C28	116.43(19)		C9	C8	C3	116.5(3)	
N23	C24	N16	109.52(17)		C7	C8	C3	119.4(2)	
C19	C18	C17	116.1(2)	C7	C8	C9	124.1(3)		
N12	C4	C3	115.1(2)	N2	C11	C10	124.0(3)		
C5	C4	C3	120.3(2)	C6	C7	C8	120.1(2)		

Table 2
SELECTED BOND DISTANCES (Å) AND BOND ANGLES (°)

Conclusions

We report herein the synthesis, X-ray crystal structure and antimycobacterial activity of 3-(2-ethoxy-2-oxoethyl)-1-(2-oxo-2-(pyridin-2-ylamino)ethyl)-1-benzo[d]imidazol-3-ium bromide. The structure of compound was proved unambiguously by elemental and spectral analysis, including the X-ray structure. The compound crystallizes in the space group Pbca with a = 20.6941(2)A, b = 8.4233(11) A, c = 24.1005(3) A, $\alpha = 90°$, $\beta = 90°$, $\gamma = 90°$, V= 4201.02(9) and Z = 8. Accurate molecular parameters for the heterocyclic system were obtained from intensity data collected at 293 K. The tested hybrid derivative have an excellent solubility in microbiological medium (>200 μM), which is very promising from the pharmacological properties point of view, but no antimycobacterial activity.

Acknowledgements: The authors are thankful to CNCSIS Bucuresti, Romania, grant PN-II-DE-PCE-2011-3-0038, no. 268/05.10.2011, for financial support. Authors are thankful to the POSCCE-O 2.2.1, SMIS-CSNR 13984-901, Project no. 257/28.09.2010, CERNESIM, for the X-ray experiments.

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Manuscript received: 11.04.2016