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) Å, c = 24.1005(3) Å, α = 90°, β = 90°, γ = 90°, V = 4201.02(9) Å³ 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

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 Å), 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/σ²(F²) + (0.0387P)² + 0.0691P, P = (F² + 2F)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].

Results and discussions

The title compound was synthesized using a direct and efficient setup procedure, described elsewhere [59]. Thus, the N-acylation of 8-aminquinoline 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, 1H NMR, 13C 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 Pbcn orthorhombic space group, with cell parameters and structure refinement...
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 IC50, IC90 and MIC against M. tuberculosis H37Rv under aerobic conditions were determined (31-34), showing that tested compound have no antimycobacterial activity, with an IC50, IC90 and MIC > 200 µM.
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 $a = 20.6941(2)\text{Å}$, $b = 8.4233(11)\text{Å}$, $c = 24.1005(3)\text{Å}$, $\alpha = 90^\circ$, $\beta = 90^\circ$, $\gamma = 90^\circ$, $V = 4201.02(9)$ 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.

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References


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