Imidazolium Salts with Dihydroxyacetophenone Skeleton with Anticipated Anticancer Activity. II

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We report herein a feasible study concerning syntheses and structure of some diazolium salts with dihydroxyacetophenone skeleton of anticipated anticancer activity. A fast, general and facile method for preparation of 1,3-diazol salts via N-alkylation reactions under conventional heating and microwave irradiation is presented. The microwaves remarkably accelerated these N-alkylations, the reaction times decreased dramatically, the reaction conditions were milder, the consumed energy decreased considerably and the amount of used solvents was reduced substantially. Consequently, the microwave assisted alkylation of imidazole derivatives could be considered eco-friendly. The structure of the newly compounds were assigned without doubts by elemental and spectral analysis: ^{1}H NMR, ^{13}C NMR, 2D-COSY, 2D-HETCOR (HMQC), long range 2D-HETCOR (HMBC).

Keywords: Imidazole, benzimidazole, microwave, synthesis, anticancer

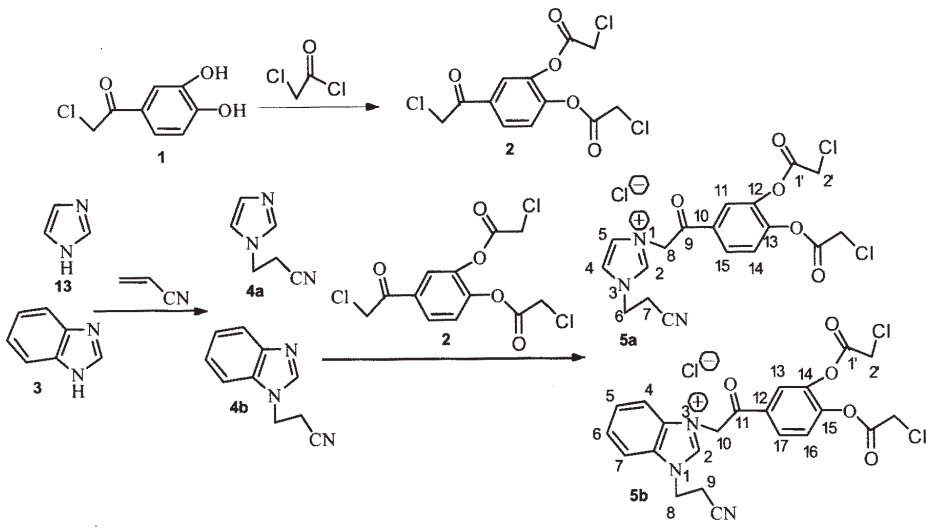
During the last decades azaheterocycles became representative structure types in medicinal chemistry, opto-electronics and agriculture [1-8]. Diazols, especially imidazole, benzimidazole and their analogues, usually possess diverse biological activities like antibacterial and antifungal [9], antituberculosis [10], anticancer [11,12], etc. Despite the progresses made by modern medical science in cancer therapy, neoplasm is still one of the most merciless diseases ever known by humans. As far cancer therapy, DNA alkylating agents remain an important class of drugs used in chemotherapy [11,12], since the introduction of the nitrogen mustards more than fifty years ago.

Synthesis of azaheterocyle by conventional heating, have some major disadvantages, including long reaction times, high energy consumption and the need for large amounts of solvents, etc [13-19]. During the last decades, microwave (MW) irradiation became an increasingly valuable tool in organic chemistry, in a large variety of syntheses [20-26].

In extension of our work in the field of biologically active compounds, we report here the synthesis and structural characterization of imidazolium salts with dihydroxy-acetophenone skeleton of anticipated anticancer and antimicrobial activity (scheme 1).

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. The ^{1}H- and ^{13}C-NMR spectra and two-dimensional 2D-COSY, 2D-HETCOR (HMQC), long range 2D-HETCOR (HMBC) experiments were recorded on a Bruker Avance 400 DRX spectrometer operating at 400/100 MHz. Chemical shifts are given in ppm (δ-scale), coupling constants (*J*) in Hz. The microanalyses were in satisfactory agreement with the calculated values: C, ± 0.15; H, ± 0.10; N, ± 0.30. For the microwave irradiation we used a monomode reactor STAR SYSTEM-2, CEM corporation (800 W).



Scheme 1
Reaction pathway to obtain imidazolium salts with dihydroxyacetophenone skeleton

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*General procedure for syntheses of imidazolium salts with dihydroxyacetophenone skeleton (**5**) under conventional thermal heating*

1-(2-Cyano-ethyl)-1*H*-imidazole (**4a**) (10 mmol, 1.21 g), respectively 1-(2-cyano-ethyl)-1*H*-benzimidazole (**4a**) (10 mmol, 1.71 g), were dissolved in 30 mL dry acetone. Chloro-acetic acid 2-(2-chloro-acetoxy)-5-(2-chloro-acetyl)-phenyl ester (**2**) (10 mmol, 3.40 g), in 10 mL dry acetone, was then added. The resulting mixture was stirred at room temperature for 150 h. The solvent was removed on rotary evaporator and the obtained salts were washed with ether. No other purification was required.

*General procedure for syntheses of imidazolium salts (**5**) under MW irradiation*

Caution! It is hazardous to rapidly heat reactions under MW irradiation. Therefore, caution should be exercised when conducting reactions of this type.

Chloro-acetic acid 2-(2-chloro-acetoxy)-5-(2-chloro-acetyl)-phenyl ester (**2**) (10 mmol, 3.40 g), in 15 mL dry acetone, was placed in the reaction vessel (Pyrex glass or quartz; for parallel synthesis both cells of the STAR reactor could be used, in which case the irradiation power of reactor has to be double). 1-(2-Cyano-ethyl)-1*H*-imidazole (**4a**) (10 mmol, 1.21 g), respectively 1-(2-cyano-ethyl)-1*H*-benzimidazole (**4a**) (10 mmol, 1.71 g), was then added. The tubes are then placed in the microwave cell and heated for 5 min stirring of the reaction mixture is desirable. When the stirring device is not accessible, it could be replaced with nitrogen continuously bubbled into the reaction system. Once the heating cycle is complete, the tube was cooled to ambient temperature, removed from the reactor, and the imidazolium salts (**5**) were processed as indicated under conventional thermal heating.

3-{2-[3,4-Bis-(2-chloro-acetoxy)-phenyl]-2-oxo-ethyl}-1-(2-cyano-ethyl)-1*H*-imidazol-3-ium chloride (5a). Dirty white oil. **^{1}H-NMR (DMSO-d$_6$, δ, ppm):** 3.27 (2H: H_7, t, $J_{7,6}$ = 6.4); 4.56 (4H: $H_{2'}$, s); 4.63 (2H: H_6, t, $J_{6,7}$ = 6.4); 6.00 (2H: H_8, s); 7.01 (1H: H_{14}, d, $J_{14,15}$ = 8.0); 7.52 – 7.36 (2H: H_{15}, H_{11}, m); 7.79 (1H: H_4, s); 7.97 (1H: H_5, s); 9.32 (s, 1H: H_2, s). **^{13}C-NMR (DMSO-d$_6$, δ, ppm):** 18.66 (C_7), 44.50 (C_6), 59.57 ($C_{2'}$), 60.78 (C_8), 114.75 (C_{15}), 115.61 (CN), 117.77 (C_5), 121.62 (C_{11}), 122.01 (C_4), 124.55 (C_{10}), 125.33 (C_{14}), 137.86 (C_2), 145.74 (C_{12}), 152.22 (C_{13}), 174.24 ($C_{1'}$, CO, keto-ester), 189.13 (CO, ketone).

3-{2-[3,4-Bis-(2-chloro-acetoxy)-phenyl]-2-oxo-ethyl}-1-(2-cyano-ethyl)-1*H*-benzoimidazol-3-ium chloride (5b). Brown oil. **^{1}H-NMR (DMSO-d$_6$, δ, ppm):** 3.28 (2H: H_9, t, $J_{9,8}$ = 6.4); 4.49 (4H: $H_{2'}$, s); 4.81 (2H: H_8, t, $J_{8,9}$ = 6.4); 5.60 (2H: H_{10}, s); 7.52 (1H: H_{16}, d, $J_{16,17}$ = 8.4); 7.80 – 7.68 [(2H: H_5, H_6, m (overlaped peaks)]; 7.85 (1H: s, H_{13}); 8.05 – 7.98 [(2H: H_7, H_{17}, m (overlaped peaks)]; 8.20 (1H: H_4, d, $J_{4,5}$ = 8.0); 10.00 (s, 1H: $H_{2'}$, s). **^{13}C-NMR (DMSO-d$_6$, δ, ppm):** 18.10 (C_9), 42.54 (C_8), 56.37 (C_{10}), 58.24 ($C_{2'}$), 113.72 (C_4), 114.04 (C_7), 117.36 (C_{17}), 121.42 (CN), 124.12 (C_{13}), 125.86 (C_5), 126.12 (C_6), 127.05 (C_{12}), 130.18 (C_{16}), 131.47 (C_{7a}), 131.94 (C_{3a}), 142.12 (C_{14}), 143.72 (C_2), 146.51 (C_{15}), 169.21 ($C_{1'}$,CO, keto-ester), 189.61 (CO, ketone).

Results and discussions

In a preliminary communication [12], we synthesized a series of dihydroxyacetophenone derivatives with antimicrobial and anticancer activity. According to our goal, we decided to study the influence concerning syntheses and biological activity of rationally substituted imidazolium salts with dihydroxyacetophenone skeleton. The reaction pathway to imidazolium salts with dihydroxyacetophenone skeleton involves several types of reactions: acylation, *N*-cyanoethylation and quaternization, (scheme 1).

The acylation step is an esterification reaction of ω-chloro-3,4-dihydroxyacetophenone with 2-chloroethanoyl chloride, leading to the chloro-acetic acid 2-(2-chloro-acetoxy)-5-(2-chloro-acetyl)-phenyl ester, **2**. In the next step, we have done the *N*-cyanoethylation of the acidic nitrogen from imidazole and benzimidazole *via* Michael addition of acrylonitrile. The last step of synthesis involves the combination of the two main parts of our imidazolium salts with dihydroxyacetophenone skeleton. In this respect we have done the quaternization reaction (*N*-alkylation) of the second nitrogen atom from *N*-cyanoethyl imidazole derivatives with the chloro-acetic acid 2-(2-chloro-acetoxy)-5-(2-chloro-acetyl)-phenyl ester. Full details concerning acylation and *N*-cyanoethylation were previously reported [12].

Under conventional thermal heating, the quaternization reactions have some disadvantages: moderate yields (72% for **5a**, respectively 64% for **5b**) and long reaction time (120 h). This is why we decided to study the influence of MW concerning the quaternization reactions. The MW assisted reactions were carried out on a monomode reactor, using a constant irradiation power and varying the temperature (the so-called "power control"). The best results were obtained when we used 15% of the full power of the magnetron (800 W). Thus, the obtained data show us that MW induced a remarkable acceleration of reactions, the reaction times decreasing dramatically, from hours to 5 minutes. It is also very important that under MW irradiation the yields are higher (86% for **5a**, respectively 91% for **5b**) and the amount of used solvents is two-fold less. Having in view the advantage of time and of the small amounts of solvent, the quaternization reactions, under MW technologies, could be considered as environmentally friendly.

The structure of compounds was proved by elemental (C, H, N) and spectral analysis (^{1}H NMR, ^{13}C NMR, 2D-COSY, 2D-HETCOR (HMQC), long range 2D-HETCOR (HMBC). Thus, if we consider compound (**5a**) as representative, in the ^{1}H-NMR, the most deshielded signal is that of the hydrogen from the 2-position of imidazole ring, which appears at 9.32 ppm (s, 1H: H_2). The H_2 proton appears at so low magnetic field, due to the deshielding effect induced by the two neighbourhood nitrogens (one being with positive charge). The H_2 proton is followed by the proton from the 5-possition of imidazole ring (α-positive nitrogen, α-carbon), which appears at 7.97 ppm (s, 1H: H_5). At 6.00 ppm (s, 2H: H_8), appear the methylene protons, due to the powerful deshielding effect induced by the positive nitrogen and dihydroxyacetophenone moiety. The methylene protons from ester groups appear also to low magnetic field (comparative with normal alkane), at 4.56 ppm (s, 2H: $H_{2'}$), due to deshielding effect induced by the surroundings substituients: a ketone ester group and a chloride atom. The ^{13}C-NMR spectrum also confirmed the proposed structures. Thus in the case of compound (**5a**) the most important signals are those of the carbonyl carbons, cyano carbon, and imidazole carbons (C_2, C_4, C_5). The carbonyl carbons appear the most deshielded [189.13 (CO, ketone) and 174.24 ($C_{1'}$, CO, keto-ester)], characteristic for alkyl-aryl ketone respectively for esters. The cyano carbon appears at typical chemical shift for this type of carbon, 115.61 ppm (CN). The imidazole carbons appear also very deshielded, according to their environment: C_2 at 137.86 ppm [α-nitrogens (from position 1 and 3), one being positive charged], C_4 at 122.01 ppm (α- positive charged nitrogen, α- carbon C_5) and, finally, C_5

at 117.77 ppm (α- nitrogen from 1 possition, α- carbon C_4). The relative intensities of all carbons are according to the proposed structure.

All the remaining signals from NMR spectra are in accordance with the proposed structure.

Conclusions

In conclusion, we report herein a feasible study concerning syntheses and structure of diazolium salts with dihydroxyacetophenone skeleton of anticipated anticancer activity. The reaction pathway involves the *N*-alkylation reaction of imidazole derivatives. The MW remarkably accelerated the *N*-alkylation reactions, the reaction times decreasing dramatically (from hours to 5 min) and the yields are higher. Taking into consideration the advantages in term of time and of the small amount of the used solvent (under MW the amount of used solvents is two-fold less), the quaternization reactions, under MW technologies, could be considered as environmentally friendly. The structure of the newly compounds were assigned without doubts by elemental and spectral analysis: ^{1}H NMR, ^{13}C NMR, 2D-COSY, 2D-HETCOR (HMQC), long range 2D-HETCOR (HMBC).

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