VERSITA

ACTA CHEMICA IASI, **21**, 9-18 (2013)

DOI: 10.2478/achi-2013-0002

Diazolium Salts with Dihydroxyacetophenone Skeleton with Anticipated Anticancer and Antibacterial Activity

Dorina Mantu,[a] Eliza Ene,[a] Vasilichia Antoci[a] and Ana Maria Zbancioc[b*]

[a]*Department of Chemistry, "Al.I. Cuza" University Iasi, 11 Carol I Bd, Iasi 700506, Romania*

[b]*"Gr.T. Popa" University of Medicine and Pharmacy, Iasi, School of Pharmacy, Str. Universitatii 16, 700115 Iasi, Romania*

Abstract: We report herein a feasible study concerning design, syntheses and structure of some new diazolium salts with dihydroxyacetophenone skeleton of anticipated anticancer and antimicrobial activity. The syntheses of the desired imidazolium dihydroxyacetophenone salts occur smoothly, *via* an *N*-alkylation reaction, with good to excellent yields. The structure of the newly compounds were assigned without doubts by elemental and spectral analysis: IR, ^{1}H NMR, ^{13}C NMR, 2D-COSY, 2D-HETCOR (HMQC), long range 2D-HETCOR (HMBC).

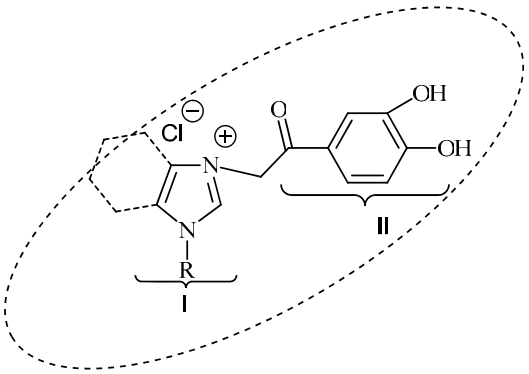
Keywords: *N*-Alkylation; Imidazole; Dihydroxyacetophenone; Antibacterial; Anticancer.

Introduction

* Dr. Ana Maria Zbancioc, e-mail: sweetyanamaria@yahoo.com

During the last decades diaza heterocycles, especially imidazol, pyrimidine, pyridazine and phthalazine, became leading structures in medicinal chemistry, opto-electronics and agriculture.[1] Diazines and diazols have demonstrated a large variety of biological activities, which include antibacterial and antifungal,[2-6] antituberculosis,[7,8] anticancer,[9,10] etc. It is also highly recognized that diazines and diazols have potential applications in opto-electronics, especially in the field of highly fluorescent derivatives,[11-13] compounds with liquid crystal and ionic liquids properties[14-16] and semiconductors.[17] Herbicidal activity and grow up factor for plants are also reviewed.[18-20]

Dihydroxyacetophenone is one of the most used classes of building blocks in supramolecular chemistry[21] and it was proved that some azine salts with dihydroxyacetophenone skeleton could have biological activity.[22] The emphasis of this work was to synthesize new diazolium salts with dihydroxyacetophenone skeleton taking into consideration their potential utilisation as dipoles in cycloaddition reactions[23-28] as well as their potential biological activity. In this respect a rational drug design (Scheme 1) show as that a combination of the two moieties, imidazole (**I**) and dihydroxyacetophenone (**II**), will be beneficial for biological activity, especially for anticancer and antibacterial activity. In related cases[7,9,22] part **II** was responsible for anticancer activity and the molecule as a whole for antimicrobial activity.

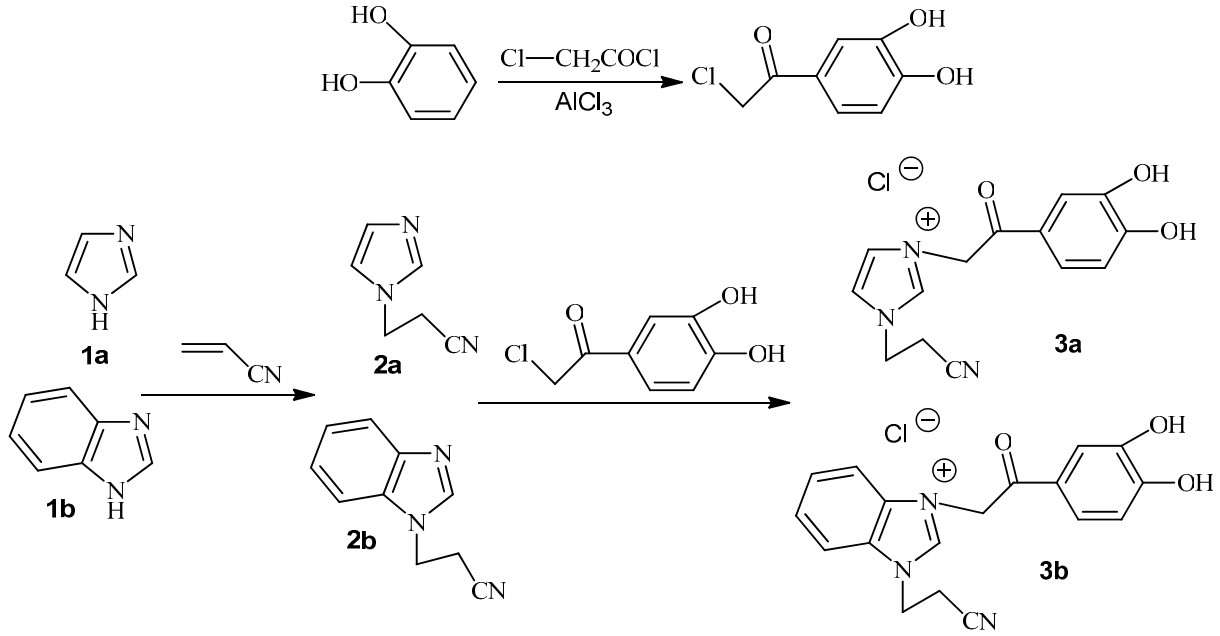


Scheme 1

Results and discussions

In accordance with our goal, we decided to study the influence concerning syntheses and biological activity of rationally substituted imidazols. The syntheses of the desired imidazolium salts occured in several steps. In the first step we synthesized the dihydroxyacetophenone part, namely 2-chloro-3',4'-dihydroxyacetophenone, using a Friedel - Crafts acylation reaction of pyrochatecol with haloacylchloride. In a subsequent step, we carried out the *N*-cyanoethylation of the acidic nitrogen from imidazol derivatives (imidazole and benzimidazole) *via* Michael addition of acrylonitrile. Full details concerning this synthesis was presented ealsewere.[29]

In the last step of synthesis we combined the two main parts of our designed molecule, imidazolium salts with dihydroxyacetophenone skeleton, using the quaternization reaction of the second nitrogen atom from imidazole with 2-chloro-3',4'-dihydroxyacetophenone (Scheme 2).



Scheme 2

The structures of the new compounds were assigned by elemental and spectroscopic analysis: IR, ^{1}H NMR, ^{13}C NMR, 2D-COSY, 2D-HETCOR (HMQC), long range 2D-HETCOR (HMBC). If we consider compound 1-(2-cyanoethyl)-3-[(3,4-dihydroxyphenyl)-2-oxo-ethyl]-1*H*-imidazol-3-ium chloride (**3a**) as representative, detailed organic structural analysis proved without doubts its structure.

In the IR spectra the most important signals are those one furnished by the stretching vibrations of hydroxyl, cyano and carbonyl ketone group. The hydroxyl appears as a medium (to strong) broad band centred to 3159 cm^{-1}, which is characteristic for phenols with strong intramolecular hydrogen bonding. To 2250 cm^{-1} (medium to strong) appears the characteristic band for cyano group. The carbonyl ketone group appears as a sharp strong band to 1681 cm^{-1}, which is characteristic for alkyl – aryl ketones.

In the ^{1}H-NMR, the most deshielded signals are those of the hydrogen from hydroxyl groups which appear to 10.44 ppm (s, broaded, 1H: OH from

14-th position) respectively to 9.70 ppm (s, broaded, 1H: OH from 13-th position). These protons are followed by the protons from imidazole ring: 9.34 ppm (s, 1H: H_2), 7.99 ppm (s, 1H: H_4) and 7.80 ppm (s, 1H: H_5). The H_2 appears at so low magnetic field, due to the deshielding effect induced by the two neighbourhood nitrogens (one being with positive charge). To 6.01 ppm (s, 2H: H_9), appear the methylene protons, due to the powerful deshielding effect induced by the positive nitrogen and dihydroxybenzoyl group. The three protons from the phenyl rings appear to 7.02 – 7.00 ppm (d, $J_{15,16}$ = 8.0 Hz, 1H: H_{15}) and 7.47 – 7.45 ppm [d (overlapped peaks), 2H: H_{16}, H_{12}). The protons from cyanoethyl group appear to 4.66 – 4.63 ppm (t, $J_{6,7}$ = 6.4 Hz, 2H: H_6) respectively to 3.33 – 3.30 ppm (t, $J_{7,6}$ = 6.4 Hz, 2H: H_7), in accordance with their surroundings.

The ^{13}C-NMR spectrum also confirmed the proposed structures. Thus in the case of compound (**3a**) the most important signals are those of the carbonyl carbon (C_{10}), cyano carbon (C_8), aromatic carbons bearing hydroxyl groups (C_{13}, C_{14}) and imidazole carbons (C_2, C_4, C_5). The carbonyl carbon (C_{10}) is the most deshielded (δ= 189.13 ppm), characteristic for alkyl-aryl ketone. The carbonyl carbon is followed in the spectrum by the aromatic carbons bearing hydroxyl groups: to 152.14 ppm appear C_{14} (*para* carbonyl, *orto* hydroxyl) while to 145.70 ppm appear C_{13} (*meta* carbonyl, *orto* hydroxyl). The cyano carbon (C_8) appear at typical chemical shift for this type of carbon, 117.178 ppm (CN). The imidazole carbons appear also very deshielded, according with their environment: C_2 to 137.83 ppm [α-nitrogens (from position 1 and 5), one being positive charged], C_4 to 125.34 ppm (α- positive charged nitrogen, α- carbon C_5) and, finally, C_5 to 122.01 ppm (α- nitrogen from 1 possition, α- carbon C_4); also the relative intensity of the carbons are in according with the proposed structure.

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

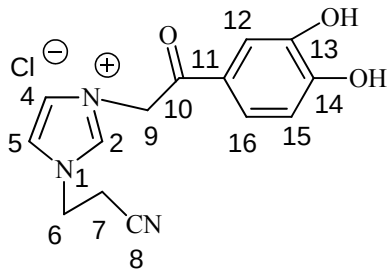
Experimental

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 and were uncorrected. The ^{1}H and ^{13}C NMR spectra, and two-dimensional experiments 2D-COSY, 2D-HETCOR (HMQC), long range 2D-HETCOR (HMBC) were recorded on a Bruker Avance 400 DRX spectrometer operating at 400 MHz. The following abbreviations were used to designate chemical shift multiplicities: s = singlet, d = doublet, t = triplet, m = multiplet, br = broad. The IR spectra were recorded on a FTIR Shimadzu Prestige 8400s spectrophotometer. Analyses indicated by symbols of the elements or functions were within ± 0.4% of the theoretical values.

General procedure for synthesis of imidazolium salts

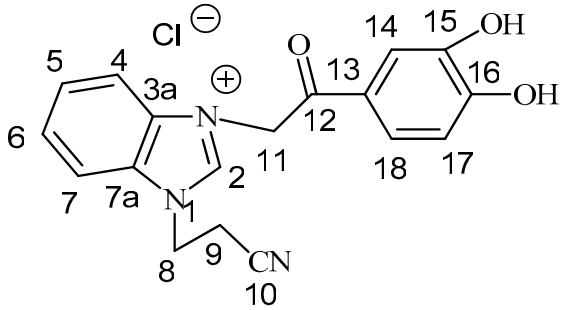
Imidazole derivatives (1 mmol) were dissolved in 10 mL dry acetone. A solution of 2-chloro-3',4'-dihydroxyacetophenone (0.186 g, 1 mmol) in 30 mL dry acetone was added dropwise, under stirring. The reaction mixtures were stirred for 150 hours at room temperature. The obtained salts were filtered of under vacuum, washed 2 times with 5 mL of dry acetone and dried in vacuo. The crude products were purified by recrystallization from dry acetone.

1-(2-Cyanoethyl)-3-[(3,4-dihydroxyphenyl)-2-oxo-ethyl]-1H-imidazol-3-ium chloride **(3a)**:



It was obtained according with the general procedure from 0.133 g imidazole. Yield 39%. Mp 317-318 °C. IR (KBr, cm^{-1}): 3159 (O-H), 3045 (C-H arom.), 2960 (C-H aliph.), 2250 (CN), 1681 (C=O ketone), 1606, 1593, 1568, 1515, 1456 (C=C, C=N arom.). ^{1}H-RMN (DMSO-d_6, δ, ppm): 3.33 – 3.30 (t, $J_{7,6}$ = 6.4, 2H: H_7), 4.66 – 4.63 (t, $J_{6,7}$ = 6.4, 2H: H_6), 6.01 (s, 2H: H_9), 7.02 – 7.00 (d, $J_{15,16}$ = 8.0, 1H: H_{15}), 7.47 – 7.45 (d (overlapped peaks), 2H: H_{16}, H_{12}), 7.80 (s, 1H: H_5), 7.99 (s, 1H: H_4), 9.34 (s, 1H: H_2), 9.70 (s, broaded, 1H: OH from 13-th position), 10.44 (s, broaded, 1H: OH from 14-th position). ^{13}C-RMN (TMS, DMSO-d_6, δ, ppm): 18.72 (C_7), 44.58 (C_6), 55.00 (C_9), 115.06 (C_{12}), 11.58 (C_{15}), 117.178 (CN), 121.63 (C_{16}), 122.01 (C_5), 124.54 (C_{11}), 125.34 (C_4), 137.83 (C_2), 145.70 (C_{13}), 152.14 (C_{14}), 189.13 (C_{10}, ketone).

1-(2-Cyanoethyl)-3-[(3,4-dihydroxyphenyl)-2-oxo-ethyl]-1H-benzimidazol-3-ium chloride **(3b)**:



It was obtained according with the general procedure from 0.188 g imidazole. Yield 85%. Mp 318-320 °C. IR (KBr, cm^{-1}): 3431 (O-H), 3066 (C-H arom.), 2981 (C-H aliph.), 2247 (CN), 1678 (C=O ketone), 1604, 1560, 1521 (C=C, C=N arom.). ^{1}H-RMN (DMSO-d_6, δ, ppm): 3.36 (s, 2H:

H_9), 5.00 (s, 2H: H_8), 6.35 (s, 2H: H_{11}), 7.03 – 7.01 (d, $J_{17,18}$ = 8.0, 1H: H_{17}), 7.50 (s, 1H: H_{14}), 7.58 – 7.56 (d, $J_{18,17}$ = 8.0, 1H: H_{18}), 7.76 – 7.68 (m (overlapped peaks), 2H: H_5, H_6), 8.05 – 8.03 (d, $J_{7,6}$ = 7.6, 1H: H_7), 8.26 – 8.24 (d, $J_{4,5}$ = 8.0, 1H: H_4), 9.67 (s, broaded, 1H: OH from 15-th position), 9.89 (s, 1H: H_2), 10.41 (s, broaded, 1H: OH from 16-th position). ^{13}C-RMN (TMS, DMSO-d_6, δ, ppm): 18.08 (C_9), 42.43 (C_8), 52.70 (C_{11}), 113.84 (C_7), 114.07 (C_4), 115.19 (C_{14}), 115.46 (C_{17}), 117.84 (C_{18}), 121.96 (C_{13}), 125.35 (CN), 126.69 (C_6), 126.92 (C_5), 130.45 (C_{7a}), 131.88 (C_{3a}), 143.84 (C_2), 145.62 (C_{15}), 152.19 (C_{16}), 188.86 (C_{12} ketone).

Conclusions

Herein we report a feasible study concerning design, syntheses and structure of some new diazolium salts with dihydroxyacetophenone skeleton of anticipated anticancer and antimicrobial activity. The syntheses of the desired imidazolium salts occur smoothly, in several steps, with good to excellent yields. The structures of the newly compounds were assigned without doubts by elemental and spectral analysis: IR, ^{1}H NMR, ^{13}C NMR, 2D-COSY, 2D-HETCOR (HMQC), long range 2D-HETCOR (HMBC). A rational drug design suggests us that these compounds could have anticancer and antimicrobial activity.

Acknowledgements

Authors are thankful to CNCS Bucharest, Romania, project PN-II-DE-PCE-2011-3-0038, no. 268/05.10.2011, for financial support.

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