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Synthesis of novel benzimidazolium salts of biologically active chalcogenylacetic acids

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Novel potentially biologically active benzimidazolium-based salts, some of them being ionic liquids, were synthesized by the reaction between substituted benzimidazoles and biologically active acetic acid derivatives $RYCH_2CO_2H$ (R = Ar, 3-indolyl; Y = O, S).

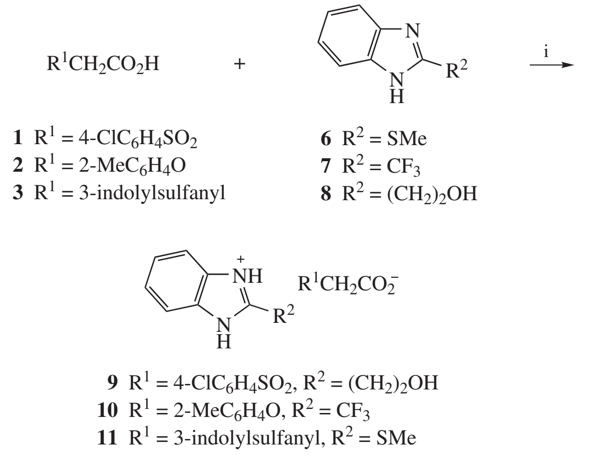
Over the last time, the ever-growing fundamental and practical importance of ionic liquids (ILs)[1(*a*)] has stimulated the research interest in their biological activity, toxicity and biodegradation in enviroment.[1]

Earlier,[2] we synthesized a library of pharmaceutically active, nontoxic protic hydroxyalkylammonium ILs: $R^1_n(HOCHR^2CH_2)_{3-n}N^+H{\cdot}RYCH_2CO_2^-$ (R = Ar, indolyl; Y = O, S, SO_2). These compounds comprising the cations of biogenic 2-hydroxyethylamines and anions of biologically active (het)arylchalcogenylacetic acids[2(*h*),(*i*),3,4] possess high pharmacological activity, considerably exceeding or different from that of the initial cation and anion precursors.

In continuation of our research related to the design of novel potentially pharmacologically active ILs, we have focused our efforts to benzimidazolium-derived ones (BzimILs). Benzimidazole moiety is found in certain natural products such as vitamin B_{12}[5] or alkaloids.[6] Its derivatives represent an important class of bioactive molecules used in drug design.[7]

Unlike imidazolium-based ILs, BzimILs are less studied. Among the known representatives of BzimILs are such drugs as 2-benzylbenzimidazolium chloride (dibazol, bendazol) showing vasodilating and spasmolytic effects, and 2-ethylthiobenzimidazolium bromide (bemithyl, metaprot), an antihypoxant.[8] 1-Alkoxymethyl-3-(nicotionylaminomethyl)benzimidazolium chlorides possess antimicrobial properties.[9] All these compounds consist of bioactive benzimidazolium cation and inactive inorganic anion (Cl^-, Br^-).

In the present work, a series of new type of potentially pharmacologically active salts and BzimILs have been synthesized by the reaction of 4-chlorophenylsulfonyl- (**1**), 2-methylphenyloxy- (**2**), 3-indolylsulfanyl- (**3**) and 2-methyl-4-chlorophenyloxyacetic (**4**) acids (biologically active acids) with commercially available 1,2-dimethyl- (anti-fungals)[7(*b*)] (**5**), 2-methylsulfanyl- (antihypoxant)[8] (**6**), 2-trifluoromethyl- (antiparasitic activity)[7(*p*)] (**7**) and 2-hydroxyethyl- (antiamoebic activity)[7(*q*)] (**8**) benzimidazoles (Schemes 1, 2). Compounds **9**–**15** are viscous liquids or powders, well soluble in water, alcohols and acetone. Structure and composition of compounds **9**–**15** have been proved by IR, ^1H, ^{13}C, ^{15}N NMR spectroscopy and elemental analysis.[†] A significant upfield shift of ^{15}N NMR δ_N (N=C) signals observed, for example, for **11** (protic BzimIL) by –100 ppm and for **12**, **13** (alkylated salts and BzimILs) by –50 ppm as compared to the starting benzimidazoles indicates that these compounds contain quaternized nitrogen atom ^+NH (**11**) or $^+NR_3$ (**12**, **13**).[10]



1 $R^1 = 4\text{-}ClC_6H_4SO_2$
2 $R^1 = 2\text{-}MeC_6H_4O$
3 R^1 = 3-indolylsulfanyl

6 $R^2 = SMe$
7 $R^2 = CF_3$
8 $R^2 = (CH_2)_2OH$

9 $R^1 = 4\text{-}ClC_6H_4SO_2$, $R^2 = (CH_2)_2OH$
10 $R^1 = 2\text{-}MeC_6H_4O$, $R^2 = CF_3$
11 R^1 = 3-indolylsulfanyl, $R^2 = SMe$

Scheme 1 *Reagents and conditions*: i, MeOH, 65 °C, 1–3 h.

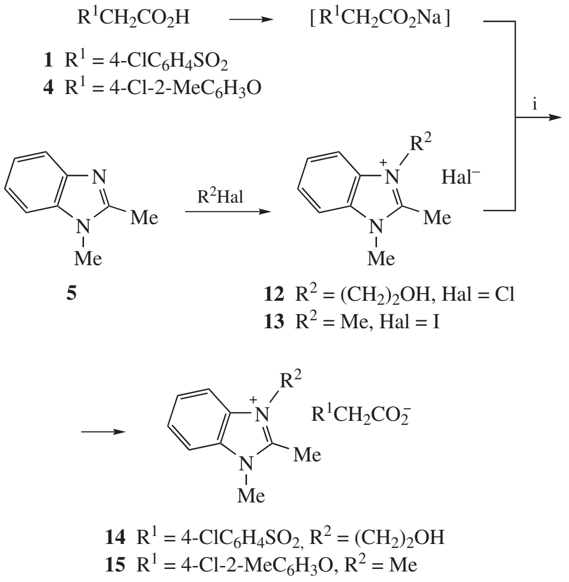
General procedure for the synthesis of protic compounds **9**–**11**. A mixture of benzimidazole derivative (0.01 mol, insoluble in H_2O) and corresponding acid (0.01 mol, insoluble in H_2O) in absolute methanol (25 ml) was stirred at 65 °C for 1–3 h. The solvent was distilled off, and the residue was multiply washed with diethyl ether and dried (24 h) over P_2O_5 at ~0.01 Torr to afford viscous liquids or powders (soluble in water). Compounds **14**, **15** were prepared by the reaction of ion exchange under similar conditions for 7–8 h.

9: yield 92%, colourless powder, mp 55 °C. IR (KBr, ν/cm^{-1}): 1115 (ν_s SO_2), 1323 (ν_{as} SO_2), 1576 (C=N), 1605 (C=O), 2580–2745 (^+NH). ^1H NMR (CD_3OD) δ: 3.68 (s, 2H, $CH_2C{=}N$), 3.78 (s, 2H, CH_2OH), 4.96 (s, 2H, CH_2SO_2), 7.93–7.37 (m, 8H, BzIm, C_6H_4). ^{13}C NMR (CD_3OD) δ: 21.66 ($CH_2C{=}N$), 47.63 (CH_2SO_2), 66.26 (CH_2OH), 147.50–114.19 (BzIm, C_6H_4Cl), 158.14 (C=N), 166.05 (C=O). Found (%): C, 52.59; H, 2.45; Cl, 9.00; N, 7.17. Calc. for $C_{17}H_{17}ClN_2O_5S$ (%): C, 52.24; H, 2.83; Cl, 9.07; N, 7.16.

10: yield 92%, colourless powder, mp 65 °C. IR (KBr, ν/cm^{-1}): 1579 (C=N), 1599 (C=O), 2496–2739 (m, ^+NH). ^1H NMR (D_2O) δ: 2.07 (s, 3H, Me), 4.32 (s, 2H, OCH_2), 7.40–7.03 (m, 8H, BzIm, C_6H_4). ^{13}C NMR (D_2O) δ: 15.28 (Me), 28.20 ($CF_3C{=}N$), 66.89 (CH_2O), 155.81–111.55 (BzIm, C_6H_4), 160.41 (C=N), 170.20 (C=O). Found (%): C, 58.24; H, 4.01; N, 7.91. Calc. for $C_{17}H_{15}F_3N_2O_3$ (%): C, 57.95; H, 4.29; N, 7.95.

11: yield 91%, viscous liquid. IR (KBr, ν/cm^{-1}): 1566 (C=N), 1625 (C=O), 2400–2714 (m, ^+NH). ^1H NMR (D_2O) δ: 2.66 (s, 3H, SMe), 3.36 (s, 2H, SCH_2), 7.68–7.12 (m, 9H, BzIm, Ind). ^{13}C NMR (D_2O) δ: 14.53 (SMe), 40.19 (SCH_2), 140.11–104.42 (BzIm, Ind), 153.45 (C=N), 174.58 (C=O). ^{15}N NMR (D_2O) δ: –245.10 (C=N) [–150.20 (C=N) for initial **6**]. Found (%): C, 58.49; H, 4.40; N, 11.31; S, 16.96. Calc. for $C_{18}H_{17}N_3O_2S_2$ (%): C, 58.19; H, 4.61; N, 11.31; S, 17.26.

[†] NMR spectra were recorded on a Bruker DPX 400 spectrometer (^1H, 400.13 MHz; ^{13}C, 100.61 MHz; ^{15}N, 40.53 MHz, ref. $MeNO_2$) at 25 °C with HMDS as an internal standard in D_2O or CD_3OD. IR spectra were recorded on a Bruker IFS-25 spectrophotometer in KBr. Acids **1**–**4** were synthesized following the general procedure described in ref. 11. Commercially available benzimidazoles **5**–**8** (99.8%) were purchased from Aldrich.



Scheme 2 *Reagents and conditions*: i, MeOH, 65 °C, 7–8 h.

In summary, a series of novel water-soluble benzimidazolium protic and alkylated salts and ILs has been synthesized from benzimidazole derivatives and biologically active substituted acetic acids. The compounds obtained can be of interest as potentially pharmacological active substances or drug precursors.

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12: yield 89%, viscous liquid. IR (KBr, ν/cm^{-1}): 1590 (C=N), 3390 (OH). ^{1}H NMR (D_2O) δ: 2.40 (s, 3H, NMe), 2.46 (s, 3H, Me), 3.28 (s, 2H, $^+NCH_2$), 3.72 (s, 2H, OCH_2), 7.48–7.10 (m, 4H, BzIm). ^{13}C NMR (D_2O) δ: 11.89 (Me), 28.71 (NMe), 45.39 ($^+NCH_2$), 62.26 (OCH_2), 141.30–109.18 (BzIm), 152.19 (C=N). ^{15}N NMR (D_2O) δ: –190.20 (C=N) [–153.10 (C=N) for initial **5**]. Found (%): C, 58.49; H, 6.97; Cl, 15.26; N, 12.31. Calc. for $C_{11}H_{15}ClN_2O$ (%): C, 58.27; H, 6.66; Cl, 15.63; N, 12.35.

13: yield 97%, colourless powder, mp 135 °C. IR (KBr, ν/cm^{-1}): 1576 (C=N). ^{1}H NMR (D_2O) δ: 2.20 (s, 3H, ^+NMe), 2.38 (s, 3H, MeC=N), 3.27 (s, 3H, NMe), 7.27–6.86 (m, 4H, BzIm). ^{13}C NMR (D_2O) δ: 12.13 (Me), 29.88 (^+NMe), 31.09 (NMe), 133.93–110.64 (BzIm), 151.39 (C=N). ^{15}N NMR (D_2O) δ: – 192.30 (C=N). Found (%): C, 41.90; H, 4.84; I, 44.26; N, 9.70. Calc. for $C_{10}H_{13}IN_2$ (%): C, 41.68; H, 4.54; I, 44.04; N, 9.72.

Compound **14** was obtained by anion exchange reaction of **12** and sodium salt of **1**. For removal of NaCl, the crude product was dissolved in ethanol–water (10 : 1), kept at 0 °C for 72 h, that resulted in precipitation of NaCl which was filtered off. The operation was repeated three times. The solvent was distilled off, the residue was dried *in vacuo* over P_2O_5. Yield 78%, colourless powder, mp 90 °C. IR (KBr, ν/cm^{-1}): 1110 (ν_s SO_2), 1343 (ν_{as} SO_2), 1580 (C=N), 1615 (C=O), 3440 (OH). ^{1}H NMR (D_2O) δ: 2.43 (s, 3H, NMe), 2.51 (s, 3H, Me), 3.71 (s, 2H, $^+NCH_2$), 3.86 (s, 2H, OCH_2), 4.44 (s, 2H, SO_2CH_2), 7.56–6.88 (m, 8H, BzIm, C_6H_4). ^{13}C NMR (D_2O) δ: 12.53 (Me), 29.49 (NMe), 48.20 ($^+NCH_2$), 64.45 (OCH_2), 67.42 (SO_2CH_2), 129.48–110.07 (BzIm, C_6H_4), 156.81 (C=N), 176.41 (C=O). Found (%): C, 54.00; H, 4.68; N, 6.55. Calc. for $C_{19}H_{21}ClN_2O_5S$ (%): C, 53.70; H, 4.98; N, 6.59.

Compound **15** was obtained from **13** and sodium salt of **4**. The removal of NaI was performed similarly as in the synthesis of **14**. Yield 71%, colourless powder, mp 118 °C. IR (KBr, ν/cm^{-1}): 1580 (C=N), 1610 (C=O). ^{1}H NMR (D_2O) δ: 1.96 (s, 3H, Me), 2.31 (s, 3H, ^+NMe), 2.53 (s, 3H, MeC=N), 3.59 (s, 3H, NMe), 4.13 (s, 2H, OCH_2), 7.21–6.53 (m, 7H, BzIm, C_6H_4). ^{13}C NMR (D_2O) δ: 9.86 (*Me*C_6H_3), 11.69 (*Me*C=N), 30.00 (^+NMe), 31.34 (NMe), 66.83 (OCH_2), 133.66–111.96 (BzIm, C_6H_3), 156.25 (C=N), 175.83 (C=O). Found (%): C, 63.59; H, 5.58; Cl, 9.57; N, 7.70. Calc. for $C_{19}H_{21}ClN_2O_3$ (%): C, 63.24; H, 5.86; Cl, 9.82; N, 7.76.