SHORT PAPER

J. Chem. Research (S), 2000, 336–338

Synthesis, spectral studies and biological activity of 4′-oxothiazolidinyl benzimidazoles

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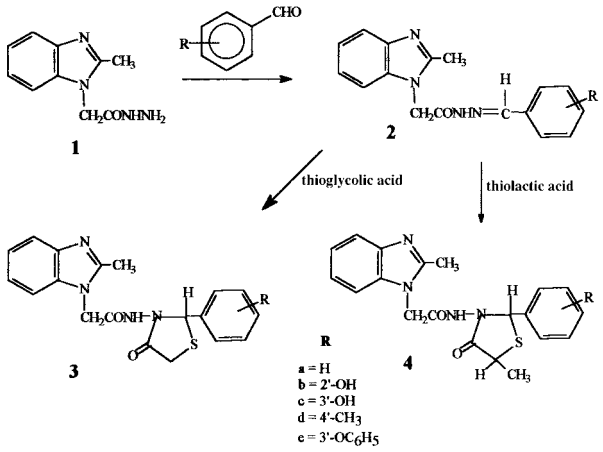
New 2-methyl-1-[(2′-substituted phenyl-4′-oxothiazolidinyl)aminocarbonylmethyl)]-1*H*-benzimidazoles (**3**) and 2-methyl-1-[(2′-substituted phenyl-5′-methyl-4′-oxothiazolidinyl) aminocarbonylmethyl]-1*H*-benzimidazoles (**4**) are synthesized, characterized and evaluated for their antimicrobial and antitubercular activity.

In pharmacological studies of benzimidazole and its derivatives it has been shown to possess a variety of activities including anthelmintic[1] and antimicrobial[2–4] 4-Oxothiazoldines and their 5-arylmethylene derivatives also possesses a variety of therapeutic activities[5–7]. Therefore, it was thought of interest to combine two of the above-mentioned rings together in a molecular framework to see the additive effects of these rings towards the biological activities.

In our earlier publication[8] we reported some biologically active 1-[(4.(4′-substituted)-phenyl-3-alkyl/aralkyl-thio-4*H*-1,2,4-triazol-5-yl)methyl]-2-methyl-1*H*-benzimidazoles. In this paper we report the synthesis of new 2-methyl-1-[(2′-substituted phenyl-4′-oxothiazolidinyl)aminocarbonylmethyl]-1*H*-benzimidazoles (**3**) and 2-methyl-1-[(2′-substituted phenyl-5′-methyl-4′-oxothiazolidinyl) aminocarbonylmethyl]-1*H*-benzimidazoles (**4**) (Scheme 1). These new compounds are evaluated for their antimicrobial and antitubercular activity.



Scheme 1

2-Methylbenzimidazole-1-acetic acid hydrazide (**1**) was prepared from 2-methyl-benzimidazole according to a reported procedure.[8] The reaction of compound **1** and benzaldehyde afforded 2-methyl-1-(benzylidenehydrazinoaminocarbonylmethyl)-1*H*-benzimidazole (**2a**). The reaction of **2a** with thioglycolic acid and thiolactic acid in dry benzene gave the corresponding 2-methyl-1-[2′-phenyl-4′-oxothiazolidinyl)aminocarbonylmethyl]-1*H*-benzimidazole (**3a**) and 2-methyl-1-[2′-phenyl-5′-methyl-4′-oxothiazolidinyl)aminocarbonylmethyl]-1*H*-benzimidazole (**4a**). The IR spectrum of the compound **2a** showed –NH–stretching vibrations at 3425 cm^{-1} and –CO–group stretching at 1685 cm^{-1}. While in **3a** –NH–group stretching at 3434 cm^{-1} and –CO–group stretching at 1725 cm^{-1} and 1685 cm^{-1} (for two –CO–groups) and in **4a**, –NH–stretching at 3441 cm^{-1} and –CO–stretching at 1713 cm^{-1} and 1683 cm^{-1} (for two –CO–groups). the ^{1}H NMR spectra showed singlet at δ 5.00 ppm for one proton of –N=CH–, while it is shifted downfield at δ 5.79 ppm and δ 5.77 in **3a** and **4a** respectively due to the chiral nature of carbon. Further it is concluded that, the singlet at δ at 5.45 ppm for two protons of $–NCH_2CO–$ in **2a**, but it is shifted upfield at δ 4.88 and δ 4.87 ppm in **3a** and **4a** respectively. Singlet at δ 2.48 ppm for three protons of $–CH_3$ (position 2) in **2a** but in both **3a** and **4a** it is considerably shifted upfield at δ 2.35 ppm. Compound **3a,** showed double doublet at δ 3.74 ppm (*J*=16 Hz) and δ 3.90 ppm (*J*-16 Hz) for two protons of $–COCH_2S–$. This is due to the prochiral nature of $–CH_2–$ group and which is integrating for two protons. Compound **4a** showed double quartet at δ 4.03 ppm (*J*=7 Hz) and δ 4.15 ppm (*J*=7 Hz) for one proton of $–CHCH_3–$ and double doublet at δ 1.46 ppm (*J*-7 Hz) and δ 1.51 ppm (*J*=7 Hz) for three protons of $–CHCH_3$. This is due to the two stereoisomers present which are 2,5-*cis* and *trans*. In compound **2a** a singlet is obtained at δ 9.62 ppm for one proton of –CONH–, but in compounds **3a** and **4a** it is shifted downfield at δ 10.74 and 1079 ppm respectively (D_2O exchangeable). Finally in compound **2a** the aromatic range is observed as multiplet between δ 6.82–8.18 ppm but in **3a** and **4a** it is observed between δ 7.09–7.51 ppm.

The ^{13}C NMR spectra of compound **3a** show peaks at δ 13.19, 29.15, 44.00 and 61.52 for the carbons of $–CH_3$ (position 2), $–CH_2S–$, $–NHC_2$ and –SCHN– respectively. The carbonyl carbons are observed at δ 166.03 and 168.83 ppm for $–CH_2CO–$ and –NCOC– respectively. The peak at δ 152.32 for –NC=N– of benzimidazole and aromatic carbons are observed between δ 109.49 and δ 142.09 ppm. Similarly in **4a**, peaks at δ 13.18, 19.31, 43.99, 60.21 and 60.47 ppm for the carbons of $–CH_3$ (position 2), $–CH_3$, $–NCH_2–$, –CHS– and –SCHN– respectively. The carbonyl carbons observed at δ 166.02 and 171.73 ppm for $–CH_2CO–$ and –NCOC– respectively. The peak at δ 152.28 pm for –NC=N– of benzimidazole ring and aromatic carbons are observed between δ 109.49 and 142.28 ppm. The mass spectra (EI) of compound **3a** and **4a** shows molecular ion peak, *m/z* at 366 and 380 respectively. Fragmentation pattern of compound **3a**: 366 (M^+, 5%), 292(8%), 221(5%), 173(8%), 145(100%, base peak), 131(15%), 117(9%), 91(15%), 77(40%) and compound **4a**: 380(M^+, 5%), 292(10%), 178(5%), 173(10%), 145(100% base peak), 131(20%), 117(12%), 91(17%), 77(50%).

Biological activity

The compounds **3a–3e** and **4a–4e** are screened for their antibacterial[9] activity against pathogenic organisms S. aureus, and S. typhi and antifungal[10] activity against C. Albicans, T.

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† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

Table 1

Sr. no.	R	Antibacterial		Antifungal			Antituberculolis
		S. aureus	*S. typhi*	*C albicans*	*T. tubrum*	*T. mentagrophytes*	$H_{37}Rv$
3a	H	++	+	–	++	++	++
3b	2′-OH	++	++	+	++	+++	+++
3c	3′-OH	+	–	–	+	–	–
3d	4′-CH_3	–	–	–	–	–	++
3e	3′-OC_6H_5	–	–	+	+	+	++
4a	H	++	++	+	++	++	++++
4b	2′-OH	++	+	++	+	++++	++++
4c	3′-OH	++	+	–	+	–	–
4d	4′-CH_3	–	+	+	–	+	+
4e	3′-OC_6H_5	++	–	+	++	++	++++

–, No activity; +, 200 μg/ml; ++, 100 μg/ml; +++, 50 μg/ml; ++++, 25 μg/ml.

rubrum and T. metagrophytes by using tube dilution technique. Also the compounds **3a–3e** and **4a–4e** are screened for their *in vitro* antitubercular[11] activity against $H_{37}R_v$ strain of Mycobacterium tuberculosis. The screening results exhibit the minimum inhibitory concentration (MIC) against the microorganisms in the range 25–200 μg/ml and are given in Table 1.

Experimental

General: Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded in KBr on a Perkin-Elmer FTIR-1600 spectrophotometer, NMR spectra on a Bruker AMX (500 MHz) spectrometer using TMS as an internal standard in DMSO-d_6 (chemical shifts in δ, ppm). Mass spectra were recorded on Jeol JMS-D300. TLC was run on Silica gel-G plates and spots were visualized by iodine vapours and/or UV light at 254 and 360 nm.

2-Methyl-1-(benzylidenehydrazinaminocarbonylmethyl)-1H-benzimidazole (**2a**): A solution of 2-methylbenzimidazole-1-acetic acid hydrazide (**1**) (0.1 mol) in dry methanol (50ml) and benzaldehyde (0.1 mol) was refluxed on a water bath for about 5–6 hours. The reaction mixture was cooled, separated solid was filtered, washed with small amount of cold methanol and recrystallized in methanol. M.p. 232–233°C; yield 92%. MS (EI), *m/z* 292 (found: C, 70.00; H, 5.81; N, 19.06 $C_{17}H_{16}N_4O$ requires C, 69.84; H, 5.52; N, 19.16).

Similarly **2b–2e** are synthesized and their characterization data are given below.

2b (R= 2′-OH): m.p. 302–330°C (d) (aq. DMF); Yield 89%; λ_{max}/cm^{-1}: 3441, 3174, 2950, 1680, 1613, 1517, 1417; ^{1}H NMR: δ 2.48 (s, 3H, CH_3), δ 5.01 (s, 1H, CH), δ 5.45 (s, 2H, CH_2), δ 9.64 (s, 1H, NH), δ 11.74 (s, 1H, OH) and δ 6.82–8.15 (m, 8H, ArH.) (D_2O exchangeable) MS (EI), *m/z* 308 (found: C, 66.00; H, 5.19; N, 18.02. $C_{17}H_{16}N_4O_2$ requires C, 66.22; H, 5.23; N, 18.17).

2c (R= 3′-OH): m.p. 290–291°C (d) (MeOH); yield 87%: ν_{max}/cm^{-1}: 3441, 3181, 2955, 1680, 1612, 1578, 1529, 1466; ^{1}H NMR: δ 2.38 (s, 3H, CH_3) δ 5.15 (s, 1H, CH), δ 5.52 (s, 2H, CH_2), δ 9.85 (s, 1H, NH), δ 11.48 (s, 1H, OH) and δ 6.87–8.05 (m, 8H, ArH.) (D_2O exchangeable) (found: C, 66.32; H, 5.15; N, 18.25. $C_{17}H_{16}N_4O_2$ requires C, 66.22; H, 5.23; N, 18.17).

2d (R= 4′-OH): m.p. 260–261°C (aq.EtOH); yield 90%; ν_{max}/cm^{-1}: 3419, 3230, 3001, 2880, 1683, 1617, 1520, 1462; ^{1}H NMR: δ 2.28 (s, 3H, Ar–CH_3) δ 2.40 (s, 3H, CH_3), δ 5.21 (s, 1H, CH), δ 5.62 (s, 2H, CH_2), δ 10.06 (s, 1H, NH), and δ 7.01–8.00 (m, 8H, ArH.) (D_2O exchangeable); MS (EI), *m/z* 306 (found: C, 70.48; H, 5.89; N, 18.26 $C_{18}H_{18}N_4O$ requires C, 70.57; H, 5.92; N, 18.29).

2e (R= 3′-OC_6H_5): m.p. 298–299°C (aq. DMF); yield 88%; ν_{max}/cm^{-1}: 3433, 3061, 2927, 2788, 1691, 1567, 1518, 1447; ^{1}H NMR: δ 2.28 (s, 3H, CH_3), δ 5.30 (s, 1H, CH), δ 5.71 (s, 2H, CH_2), δ 9.86 (s, 1H, NH), and δ 6.87–8.08 (m, 13H, ArH.) (D_2O exchangeable); MS (EI), *m/z* 384 (found: C, 71.76; H, 5.30; N, 14.60 $C_{23}H_{20}N_2O_2$ requires C, 71.85; H, 5.24; N, 14.57).

2-Methyl-1-[(2′-phenyl-4′-oxothiazolidinyl)aminocarbonylmethyl]-1H-benzimidazole (**3a**): A mixture of **2a** (0.01 mole) in dry benzene (40ml) and thioglycolic acid (0.01 mole) was refluxed on water bath for about 8–9 hours. The solvent was removed under vacuum and residue obtained was poured into ice water and then neutralized with sodium bicarbonate. Solid separated was filtered, dried and recrystallized in aqueous ethanol. M.p. 242–243; yield 80% (found: C, 62.30; H, 5.01; N, 15.30; S, 8.70 $C_{19}H_{18}N_4O_2S$ requires C, 62.38; H, 4.95; N, 15.29; S, 8.75%).

Similarly **3b–3e** are synthesized and their characterization data are given below.

3b (R= 2′-OH): m.p. 234–235°C (aq. EtOH); yield 83%; ν_{max}/cm^{-1}: 3435, 3203, 1705, 1685, 1595, 1524, 1462, ^{1}H NMR; δ 2.40 (s, 3H, CH_3), δ 3.84, 4.00 (dd, *J*-16 Hz, 2H, CH_2), δ 4.84 (s, 2H, CH_2CO), δ 5.84 (s, 1H, NCHS), δ 10.79 (s, 1H, NH), δ 9.70 (s, 1H, OH) and δ 6.95–8.05 (m, 8H, ArH) (D_2O exchangeable); ^{13}C NMR δ 13.21 (-CH_3, position 2), 29.39 (CH_2S), 43.89 (NHC_2), 60.46 (SCHN), 152.38 (NC=N), 156.58 (C-OH), 166.58 (CH_2CO), 168.84 (NCO) and 108.12–142.12 ppm (11 aromatic carbons); MS (EI), *m/z* 382 (found: C, 59.85; H, 4.70; N, 14.62; S, 8.32 $C_{19}H_{18}N_4O_3S$ requires C, 59.67; H, 4.74; N, 14.65; S, 8.38%).

3c (R= 3′-OH): m.p. 205–206 °C (MeOH); yield 85%; ν_{max}/cm^{-1}: 3433, 3204, 1701, 1683, 1592, 1530, 1462; ^{1}H NMR; δ 2.44 (s, 3H, CH_3), δ 3.90, 4.06 (dd, *J*=16 Hz, 2H, CH_2), δ 4.92 (s, 2H, CH_2CO), δ 5.91 (s, 1H, NCHC), δ 10.71 (s, 1H, NH), δ 9.82 (s, 1H, OH) and δ 7.02–8.00 (m, 8H, Ar) (D_2O exchangeable); MS (EI), *m/z* 382 (found: C, 60.00; H, 4.75; N, 14.58; S, 8.25 $C_{19}H_{18}N_4O_3S$ requires C, 59.67; H, 4.74; N, 14.65; S, 8.38%).

3d (R= 4′-CH_3): m.p. 110–111°C (aq.EtOH); yield 88%; ν_{max}/cm^{-1}: 3416, 3012, 1709, 1688, 1580, 1523, 1458; ^{1}H NMR; δ 2.21 (s, 3H, Ar-Ch_3), δ 2.38 (s, 3H, CH_3), δ 3.93, 4.03 (dd, *J*=16 Hz, 2H, CH_2), δ 4.98 (s, 2H, CH_2CO), δ 5.96 (s, 1H, NCHS), δ 10.52 (s, 1H, NH) and δ 6.98–8.00 (m, 8H, ArH) D_2O exchangeable); MS (EI), *m/z* 380 (found: C, 63.10; H, 5.28; N, 14.72; S, 8.38 $C_{20}H_{20}N_4O_2S$ requires C, 63.14; H, 5.30; N, 14.73; S, 8.43%).

3e (R= 3′-OC_5H_5): m.p. 238–239°C (aq.EtOH); yield 87%; ν_{max}/cm^{-1}: 3420, 3019, 1703, 1682, 1578, 1520, 1448; ^{1}H NMR: δ 2.42 (s, 3H, CH_3), δ 3.97, 4.10 (dd, *J*=16 Hz, 2H, CH_2), δ 4.91 (s, 2H, CH_2CO), δ 5.94 (s, 1H, NCHS), δ 10.60 (s, 1H, NH) and δ 6.92–8.21 (m, 13H, ArH) (D_2O exchangeable); ^{13}C NMR δ 13.30 (-CH_3, position 2), 30.01 (CH_2S), 44.09 (NCH_2), 60.25 (SCHN), δ 152.04 (=C–O, Ar), δ 152.90 (–O–C=, Ar), 153.12 (NC=N), 166.23 (CH_2CO), 169.12 (NCO) and 106.82–144.20 ppm (16 aromatic carbons); MS (EI), *m/z* 458 (found: C, 65.52; H, 5.00; N, 12.20; S, 6.97 $C_{25}H_{22}N_4O_3S$ requires C, 65.46; H, 4.84; N, 12.22; S, 7.00%).

2-Methyl-1-[(2′-phenyl-5′-methyl-4′-oxothiazolidinyl)aminocarbonylmethyl]-1H-benzimidazole (**4a**): A mixture of **2a** (0.01 mole) in dry benzene (40ml) and thiolactic acid (0.01 mole) was refluxed on water bath for about 8–9 hours. The solvent was removed under vacuum and residue obtained was poured into ice water and then neutralized with sodium bicarbonate. Solid separated was filtered, dried and recrystallized in aqueous ethanol. M.p. 241–242°C; yield 78%; (found: C, 63.06; H, 5.21; N, 14.62; S, 8.48 $C_{20}H_{20}N_4O_2S$ requires C, 63.14; H, 5.30; N, 14.73; S, 8.43%).

Similarly **4b–4e** are synthesized and their characterization date are given below.

4b (R= 2′-OH): m.p. 222–223°C (aq. EtOH); yield 80%; ν_{max}/cm^{-1}: 3435, 3203, 1705, 1685, 1595, 1524, 1462; ^{1}H NMR: δ 1.48, δ 1.52 (dd, *J*=7 Hz, 3H, $CHCH_3$), δ 2.48 (s, 3H, CH_3), δ 3.98, δ 4.06 (dq, *J*=7 Hz, 1H, $CHCH_3$), δ 4.80 (s, 2H, CH_2CO), δ 5.64 (s, 1H, NCHS), δ 10.81 (s, 1H, NH), δ 9.60 (s, 1H, OH) and δ 6.95–8.02 (m, 8H, ArH) (D_2O exchangeable); ^{13}C NMR δ 13.25 (CH_3, position 2), 19.39 (CH_3), 43.99 (NHC_2), 60.23 (CHS) 60.46 (SCHN), 152.28)(NC=N), 157.72 (C-OH), 166.04 (CH_2CO), 171.74 (NCO) and 109.56–142.12 ppm (11 aromatic carbons); MS (EI), *m/z* 396 (found: C, 60.72; H, 5.08; N, 14.20; S, 8.12 $C_{20}H_{20}N_4O_3$ requires C, 60.59; H, 5.09; N, 14.13; S, 8.09%).

4c (R= 3′-OH): m.p. 248–250°C (aq. MeOH); yield 82%; ν_{max}/cm^{-1}: 3434, 3208, 1704, 1683, 1600, 1528, 1461; ^1H NMR; δ 1.46, δ 1.50 (dd, *J*=7 Hz, 3H, $CHCH_3$), δ 2.44 (s, 3H, CH_3), δ 4.00, δ 4.09 (dq, *J*=7 Hz, 1H, $CHCH_3$), δ 4.89 (s, 2H, CH_2CO), δ 5.68 (S, 1H, NCHC), δ 10.79 (S, 1H, NH), δ 9.63 (S, 1H, OH) and δ 6.80–7.52 (m, 8H, ArH), (D_2O exchangeable); ^{13}C NMR δ 13.28 (CH_3, position 2), 19.36 (CH_3), 44.00 (NHC_2), 60.00 (CHS), 60.45 (SCHN), 152.18 (NC=N), 158.00 (C-OH), 166.08 (CH_2CO), 172.02 (NCO) and 108.98–142.53 ppm (11 aromatic carbons); MS (EI), *m/z* 396 (found: C, 60.96; H, 5.15; N, 14.14; S, 8.12 $C_{20}H_{20}N_4O_3S$ requires C, 60.90; H, 5.11; N, 14.20; S, 8.13%).

4d (R= 4′-CH_3): m.p. 128–129°C (aq. MeOH); yield 79%; ν_{max}/cm^{-1}: 3435, 3208, 1705, 1682, 1608, 1531, 1462; ^1H NMR: δ 1.4, δ 1.49 (dd, *J*=7 Hz, 3H, $CHCH_3$), δ 2.25 (s, 3H, Ar, CH_3), δ 2.38 (s, 3H, CH_3), δ 4.06, δ 4.11 (dq, *J*=7 Hz, 1H, $CHCH_3$), δ 4.80 (s, 2H, CH_2CO), δ 5.87, (s, 1H, NCHS), δ 10.78 (s, 1H, NH) and δ 7.01–8.10 (m, 8H, Ar.) (D_2O exchangeable); MS (EI) *m/z* 394 (found: C, 64.00; H, 5.31; N, 14.35; S, 8.00 $C_{21}{}^{H}{}_{22}N_4O_2S$ requires C, 63.94; H, 5.62; N, 14.20; S, 8.13%).

4e (R= 3′-OC_6H_5): m.p. 225–228°C (aq. EtOH); yield 80%; ν_{max}/cm^{-1}: 3434, 3210, 1706, 1685, 1605, 1530, 1462; ^1H NMR; δ 1.42, δ 1.50 (dd, *J*=7 Hz, 3H, $CHCH_3$), δ 2.42 (s, 3H, CH_3), δ 3.98, δ 4.06 (dq, *J*=7 Hz, 1H, $CHCH_3$), δ 4.92 (s, 2H, Ch_2CO), δ 5.75 (s, 1H, NCHS), δ 10.58 (s, 1H, NH), and δ 6.88–8.12 (m, 13H, Ar.H) (D_2O exchangeable); MS (EI) *m/z* 472 (found: C, 66.00; H, 5.10; N, 12.12; S, 6.82 $C_{26}{}^{H}{}_{26}N_4O_3S$ requires C, 66.08; H, 5.12; N, 11.85; S, 6.78%).

Received 11 February 2000; accepted 10 June 2000
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