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Synthesis of some new hydrazide–hydrazones, thiosemicarbazides and thiazolidinones as possible antimicrobials

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Introduction

A considerable number of hydrazide–hydrazone derivatives have been reported to demonstrate tuberculostatic [1, 2], antibacterial and antifungal [3] activities. Mercaptoimidazole derivatives have also been reported to show bactericidal and fungicidal activity [4–7]. In an earlier communication we reported on 4,5-diphenyl-2-mercaptoimidazole derivatives and tested their antimicrobial activity [8]. In continuation of our work on the synthesis of imidazoles of pharmaceutical interest, we report here on the synthesis, characterization and antimicrobial evaluation of new [4,5-bis(4-methoxyphenyl)-1*H*-imidazole-2-yl]-mercaptoacetic acid derivatives.

Chemistry

The synthesis of the new compounds was carried out as outlined in scheme 1. The starting compounds **1**, **2**, **3** were prepared according to the literature methods. Thus 4,5-bis(4-methoxyphenyl)-1*H*,3*H*-imidazole-2-thione **1** [9] was reacted with chloroacetic acid in alkaline medium to afford [4,5-bis(4-methoxyphenyl)-1*H*-imidazole-2-yl]mercaptoacetic acid **2** [8]. Treatment of **2** with acetic anhydride gave 5,6-bis(4-methoxyphenyl)imidazo[2,1-*b*]thiazole-3-one **3** [10]. This compound was reacted with hydrazine hydrate in boiling ethanol to furnish [4,5-bis(4-methoxyphenyl)-1*H*-imidazole-2-yl]mercaptoacetic acid hydrazide **4**. Compound **4** readily condensed with aromatic aldehydes to yield the corresponding hydrazones **4a–k**. Compound **4** also reacted with appropriate alkyl / aryl isothiocyanates in ethanol to give thiosemicarbazides **5a** and **5b**. These compounds were cyclized with ethyl α-bromoacetate in the presence of anhydrous sodium acetate to yield the corresponding 4-thiazolidinone derivatives **6a** and **6b**. Some characteristics of the compounds are presented in table I.

Results and discussion

The structures of all compounds were confirmed by UV, IR, ^{1}H-NMR, mass spectra and elemental analyses. The IR spectrum of **4** showed the NH bands at 3320, 3260 and 3140, and the amide C=O band at 1650 cm^{-1}. The same groups of **4a–k** absorbed in the 3210–3100 and 1670–1650 cm^{-1} regions. The ^{1}H-NMR spectrum of **4** showed four resonances at 4.39, 4.41, 9.43 and 12.50 ppm which disappeared on deuteration and were assigned to the NH_2 and NH groups of hydrazide and the NH of imidazole, respectively. The ^{1}H-NMR spectra of **4a–k** revealed the existence of two isomers in DMSO-d_6. It is proposed that in these compounds, restricted rotation about the C=N linkage as well as the partial double bond character of the amide C–N bond and hydrogen bonding between the hydrazide NH proton and sulfur atom led to the formation of *E* and *Z* isomers. Thus the resonances associated with the SCH_2, N=CH, CONH and imidazole NH protons were observed as two singlets. The percentage of each isomer was

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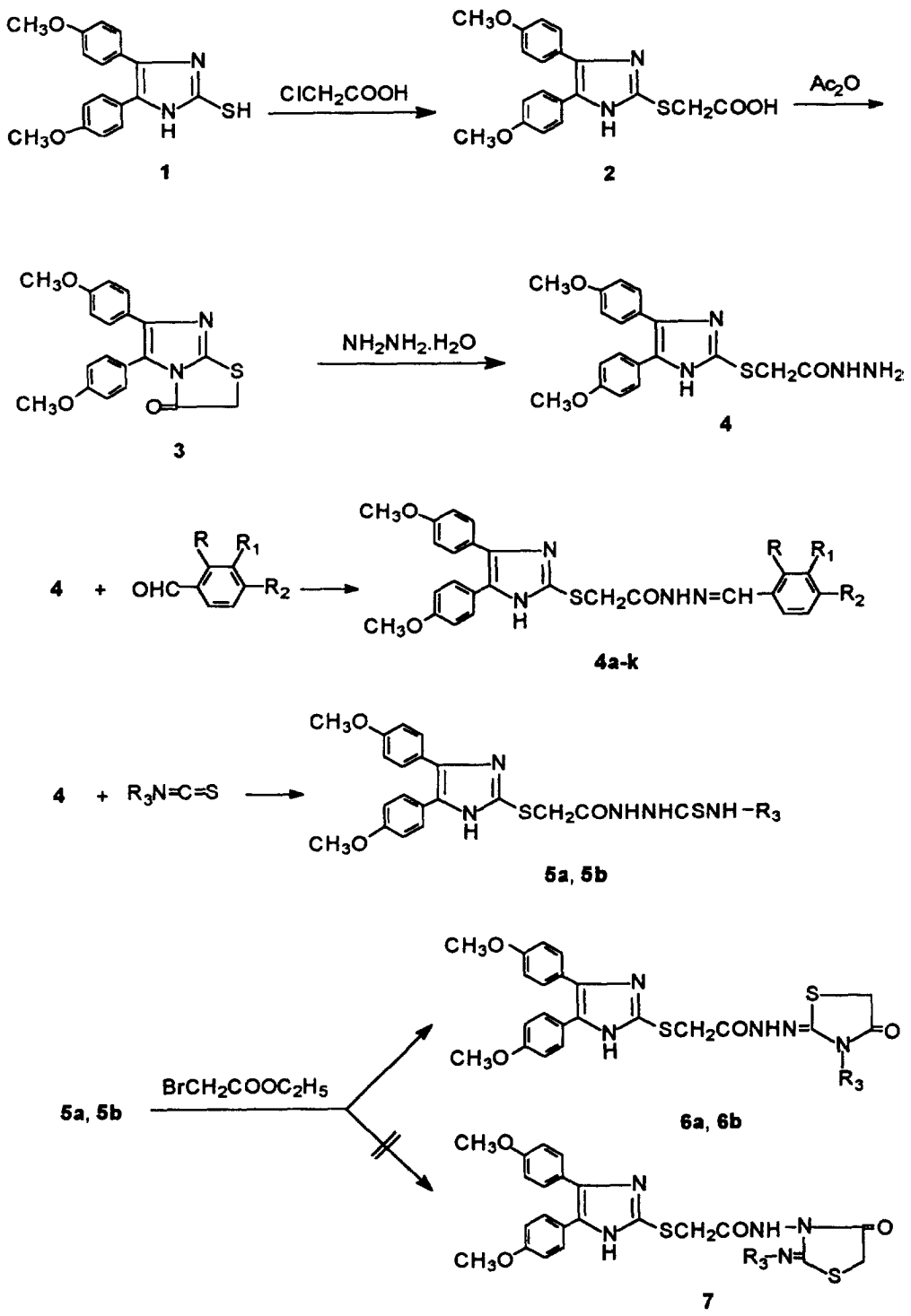

Scheme 1. Structures of compounds **1**–**4**, **4a**–**k**, **5a**, **5b**, **6a**, **6b** and **7**.

Table I. Some characteristics of the studied compounds.

Compound	*R*	R_1	R_2	R_3	*Mp (°C)*	*Yield (%)*	*Formula (molecular mass)*
4	–	–	–	–	127–131	97	$C_{19}H_{20}N_4O_3S$·1/2 EtOH (407.48)
4a	H	H	H	–	181–182	63	$C_{26}H_{24}N_4O_3S$ (472.54)
4b	OH	H	H	–	207–209	64	$C_{26}H_{24}N_4O_4S$ (488.54)
4c	H	H	OCH_3	–	180–181	66	$C_{27}H_{26}N_4O_4S$ (502.57)
4d	H	OCH_3	OH	–	204–205	48	$C_{27}H_{26}N_4O_5S$ (518.57)
4e	H	OC_2H_5	OH	–	215–217	64	$C_{28}H_{28}N_4O_5S$ (532.59)
4f	H	H	$N(CH_3)_2$	–	205–207	63	$C_{28}H_{29}N_5O_3S$ (515.61)
4g	H	H	F	–	198–199	69	$C_{26}H_{23}FN_4O_3S$ (490.53)
4h	H	H	Cl	–	192–199	46	$C_{26}H_{23}ClN_4O_3S$ (506.99)
4i	H	H	Br	–	131–133	56	$C_{26}H_{23}BrN_4O_3S$ (551.43)
4k	H	H	NO_2	–	141–143	84	$C_{26}H_{23}N_5O_5S$·H_2O (535.56)
5a	–	–	–	C_3H_5	138–139	78	$C_{23}H_{25}N_5O_3S_2$·H_2O (501.61)
5b	–	–	–	C_6H_5	141–144	79	$C_{26}H_{25}N_5O_3S_2$·1/2H_2O (528.63)
6a	–	–	–	C_3H_5	127–128	92	$C_{25}H_{25}N_5O_4S_2$·H_2O (541.63)
6b	–	–	–	C_6H_5	202–204	80	$C_{28}H_{25}N_5O_4S_2$·H_2O (577.68)

calculated using the integral values of the peak pairs and in line with the literature findings, the dominating isomer was assigned to the *E* isomer [11, 12]. The percentage of *E* and *Z* isomers was in the range of 69–51% and 49–31%, respectively.

IR spectra of **5a** and **5b** exhibited characteristic broad N–H bands in the 3190–3160 cm^{-1} region and the amide C=O band at 1690 and 1680 cm^{-1}. In the ^{1}H-NMR spectra of **5a** and **5b** the CH_2 protons appeared as singlets at 3.84 and 3.90 ppm. Furthermore, in **5a** the N^4–H proton of the thiosemicarbazide moiety appeared at 8.21 ppm as a triplet (J = 5.56 Hz) and in **5b** the same proton was observed at 9.71 ppm as a singlet. NHCS, NHCO and imidazole NH

protons resonated at 9.40, 9.76, 10.24, 10.43 and 12.51, 12.53 ppm, respectively. All the N–H protons readily exchanged with deuterium.

When **5a** and **5b** reacts with ethyl α-bromoacetate there is a possibility of formation of two products (**6** and **7**), depending upon the ene-thiol form of **5a** and **5b** (scheme 1). Since the TLC analysis of the products (**6a** and **6b**) showed a single spot, to distinguish between **6** and **7**, **6b** was hydrolyzed by refluxing with HCl–ethanol. The hydrolysis product, 3-phenyl-2,4-dioxo-thiazolidine, confirmed the structure of **6** [13, 14]. The IR spectra of **6a** and **6b** showed two C=O bands at 1680, 1685 and 1720, 1740 cm^{-1}. The former was attributed to the amide C=O stretching and the latter to the cyclic C=O stretching which was particularly diagnostic for thiazolidinone formation. In the ^{1}H-NMR spectra of **6a** and **6b**, exocyclic and endocyclic SCH_2 protons appeared at 4.02, 4.07 and 4.11, 4.13 ppm as singlets and the CONH and imidazole NH proton resonated at 10.70, 11.10 and 12.00, 12.15 ppm as singlets. After cyclization, absence of resonances assigned to the N^1–H and N^2–H protons of the thiosemicarbazides **5a** and **5b** provided confirmatory evidence of thiazolidinone formation.

The EI–MS of **4a–k** showed molecular ions (except **4a**) of different intensity. Compounds **4a–k** fragmented via the common routes, the first and second of which involved the cleavage of the CO–NH or the N–N bond and hydrogen transfer; the third, loss of CH_2=C=O and N_2. The cleavage of the CO–NH bond and migration of the NH proton of the imidazole ring to the nitrogen of the arylidene hydrazine moiety gave the fragment at *m/z* 352 and $Ar–CH=N–NH_2]^{+\cdot}$. Direct cleavage of the CO–NH bond gave the fragment at *m/z* 353 and Ar–CH=N–NH^+. The *m/z* 312 ion, the base peak in all compounds except **4k**, was formed as the S–CH_2 and CO–NH bonds were cleaved and the hydrogen of the NH group migrated to the sulfur atom and the molecule lost CH_2=C=O.

Thiosemicarbazides (**5a** and **5b**) fragmented via three prominent pathways [15, 16] to afford the fragments at *m/z* 384 and $R_4N=C=S]^{+\cdot}$ by NHNH–CS bond cleavage and hydrogen transfer; at *m/z* 353 and $R_4NH–C\equiv S^+$ by CO–NH bond rupture and at *m/z* 312 by cleavage of the S–CH_2 bond, hydrogen transfer and losses of CH_2=C=O and N_2H_2.

Microbiology

The antibacterial, antifungal and antimycobacterial activities of all the compounds were tested against different bacteria (*Staphylococcus aureus* ATCC 6538, *Staphylococcus epidermidis* ATCC 12228, *Klebsiella pneumoniae* ATCC 4352, *Pseudomonas aeruginosa* ATCC 1539, *Escherichia coli* ATCC 8739, *Shigella flexneri, Salmonella typhi, Proteus mirabilis, Mycobacterium tuberculosis* H37Rv) and the yeast *Candida albicans* ATCC 10231 by using the methods indicated in the *Experimental protocols*. None of the compounds showed significant activity against the selected microorganisms.

Experimental protocols

Chemistry

Melting points were determined with a Büchi 530 melting point apparatus in open capillaries, and are uncorrected. IR(KBr) and ^{1}H-NMR (DMSO–d_6) spectra are recorded on a Perkin–Elmer 577 (Grating) and Bruker AC 200 (200 MHz) instruments, respectively. EIMS (70 eV) and CIMS (CH_4) were run at Pennsylvania State University, PA, USA and Sittingbourne Research Centre, UK, respectively. Microanalyses were performed on Perkin–Elmer 240 and Carlo Erba 1106 elemental analyzers.

[4,5-bis(4-Methoxyphenyl)imidazole-2-yl]mercaptoacetic acid hydrazide ***4***

Compound **3** (0.005 mol) and 0.01 mol of H_2N-NH_2•$2H_2O$ were refluxed in 10 mL ethanol for 20 min and allowed to cool. The crystals thus formed were filtered and recrystallized from ethanol. UV (C_2H_5OH, nm): 280 (ε: 16300), 237 (ε: 16415); IR (KBr, cm^{-1}): 3320, 3260 and 3140 (NH imidazole and hydrazide), 1650 (C=O, amide); ^{1}H-NMR (DMSO–d_6, δ, ppm): 1.00 (3H, t, J = 6.98 Hz, CH_3CH_2OH), 3.43 (2H, q, CH_3CH_2OH), 3.74 and 3.77 (6H, 2s, $2CH_3O$), 4.34 and 4.36 (2H, 2s, CH_2S), 4.38 and 4.41 (2H, 2s, NH_2), 6.85 and 6.96 (4H, dd, J = 8.63 Hz, anisyl-$C_{3,5}$-H), 7.31 and 7.38 (4H, dd, J = 8.56 Hz, anisyl $C_{2,6}$-H), 9.43 (1H, s, CONH), 12.50 (1H, s, imidazole-NH).

[4,5-bis(4-Methoxyphenyl)imidazol-2-yl]mercaptoacetic arylidenehydrazides ***4a–k***

A solution of **4** (0.005 mol) in ethanol and an appropriate aromatic aldehyde (0.005 mol) were heated under reflux for 3 h. The product that formed after cooling was filtered and recrystallized from ethanol. **4f**: UV (C_2H_5OH, nm): 348 (ε: 29854), 304 (ε: 27224), 237 (ε: 29028); IR (KBr, cm^{-1}): 1660 (C=O, amide); ^{1}H-NMR (DMSO–d_6, δ, ppm): 2.91 and 2.96 (6H, 2s, $N(CH_3)_2$), 3.72 and 3.76 (6H, 2s, 2 CH_3O), 3.89 and 3.40 (2H, 2s, SCH_2), 6.62 and 6.73 (2H, 2d, J = 8.73, 8.71 Hz, arylidene-$C_{3,5}$-H), 6.81 and 6.92 (4H, 2d, J = 8.75, 8.54 Hz, anisyl-$C_{3,5}$-H), 7.27 and 7.38 (4H, 2d, J = 8.75, 8.54 Hz, anisyl-$C_{2,6}$-H), 7.46 (2H, d, J = 8.51, arylidene-$C_{2,6}$-H), 7.86 and 8.00 (1H, 2s, N=CH), 11.25 and 11.57 (1H, 2s, CONH), 12.42 and 12.50 (1H, 2s, imidazole NH).

1-[4,5-bis(4-Methoxyphenyl)-1H-imidazole-2-yl]mercaptoacetyl-4-alkyl/arylthiosemicarbazides ***5a, 5b***

A mixture of **4** (0.01 mol) and an appropriate isothiocyanate (0.01 mol) in 50 mL absolute ethanol was refluxed for 3 h. The crude product thus obtained was filtered and recrystallized from ethanol. **5b**: UV (C_2H_5OH, nm): 276 (ε: 29445), 236 (ε: 30978). IR (KBr, cm^{-1}): 3190 (NH), 1690 (C=O, amide I), 1548 (NHCS, amide II), 1250 (C=S); ^{1}H-NMR (DMSO–d_6, δ, ppm), 3.74 (6H, s, OCH_3), 3.90 (2H, s, SCH_2), 6.82–7.31 (13H, m, C_6H_5, 2 C_6H_4), 9.71 (1H, s, NH-C_6H_5), 9.76 (1H, s, NHCS), 10.43 (1H, s, CONH), 12.53 (imidazole NH).

2-[4,5-bis(4-Methoxyphenyl)imidazole-2-ylmercaptoacetyl]-hydrazone-3-alkyl/aryl-4-thiazolidinones ***6a, 6b***

To a suspension of **5a** or **5b** (0.005 mol) in 20 mL absolute ethanol, 0.84 g (0.005 mol) ethyl α-bromoacetate and 1.64 g (0.02 mol) anhydrous sodium acetate were added. The reaction mixture was refluxed on a water bath for 2 h, cooled, diluted with water and allowed to stand overnight. The precipitate obtained was filtered and recrystallized from ethanol. **6b**: UV (C_2H_5OH, nm): 277 (ε: 35816), 235 (shoulder); IR (KBr, cm^{-1}): 3280 (NH), 1740 (C=O, endocyclic), 1685 (C=O, amide), 1640 (C=N); ^{1}H-NMR (DMSO-d_6, δ, ppm): 3.76 (6H, s, OCH_3), 4.07 (2H, s, SCH_2 exocyclic), 4.13 (2H, s, SCH_2 endocyclic), 6.85–7.38 (13H, m, C_6H_5, 2 C_6H_4-), 11.10 (1H, broad s, CONH), 12.15 (1H, broad s, imidazole NH).

Microbiology

Antimicrobial activity

Disk diffusion method was used for antimicrobial activity. The cultures of bacteria and yeast strains were prepared in 4 mL Mueller–Hinton broth at 37 °C. After 24 h incubation, the turbidity of culture suspension was adjusted with sterile Mueller–Hinton broth in order to obtain a turbidity comparable to a No 1 Mc Farland turbidity standard. One milliliter of this suspension was pipetted onto the Mueller–Hinton Agar plate and distributed evenly over the surface of the medium by gently rocking the plate. Excess suspension was pipetted off. The surface of the medium was allowed to dry for 15 min at room temperature. The 160 mcg compound impregnated disks were applied to the surface of inoculated plates. The petri plates were placed in an incubator at 37 °C. After 18–24 h of incubation, the petri plates were examined and the diameter of the zone of inhibition was measured.

Antimycobacterial activity

M tuberculosis H37Rv strain was prepared as a 7-day-old culture on Löwenstein–Jensen medium and was used to study antimycobacterial activity. This culture was suspended in 4 mL saline with the aid of glass beads. The mixture was shaken with a Vortex mixer for about 1 min. The suspension thus obtained was diluted with saline to give a final concentration of 10^4 CFU/mL.

A solution of all compounds was prepared at concentrations of 200, 100, 50, 25 and 12.5 mcg/mL in a mixture of distilled water/DMSO (1:1), and then 0.25 mL of this solution was added to three tubes containing Löwenstein–Jensen medium. The tubes were inclined and incubated overnight at 37 °C for absorption of the compound into the medium. The final inoculum (0.1 mL) was added to each tube containing the compound and to three other tubes containing the compound-free medium as controls. The tubes were capped, incubated at 37 °C and read weekly for 4 weeks.

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