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Synthesis and antimicrobial activity of some 1,2,4-triazole-3-mercaptoacetic acid derivatives

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Abstract

Ethyl 5-(2-furyl)-4-ethyl-1,2,4-triazole-3-mercaptoacetate (**2**), 5-(2-furyl)-4-ethyl-1,2,4-triazole-3-mercaptoacetic acid hydrazide (**3**) and a series of new *N*-alkylidene/arylidene-5-(2-furyl)-4-ethyl-1,2,4-triazole-3-mercaptoacetic acid hydrazides (**4a–f**) were synthesized and evaluated for in vitro antibacterial activity against *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* and antifungal activity against *Candida albicans* ATCC 10231 using the disk diffusion and microdilution methods. Compound **4f** showed antibacterial activity against some bacteria. The in vitro antimycobacterial activity of the new compounds against *Mycobacterium tuberculosis* $H_{37}Rv$ was evaluated employing the BACTEC 460 radiometric system. The highest inhibition observed was 61% at > 6.25 μg/ml.

Keywords: 1,2,4-Triazoles; Antibacterial activity; Antifungal activity; Antimycobacterial activity

1. Introduction

Triazole derivatives have been reported to exhibit antibacterial [1–15], antifungal [1–3,16–19] and antimycobacterial [20–24] properties. *N*-Benzylidene derivatives of acid hydrazides are also associated with diverse biological activities [25–27]. In continuation of our work on the synthesis of heterocycles of pharmaceutical interest [28–32] we report here synthesis, characterization and antimicrobial evaluation of new 1,2,4-triazole-3-mercaptoacetic acid derivatives.

2. Chemistry

The key intermediate, 4-ethyl-2,4-dihydro-5-(2-furyl)-3*H*-1,2,4-triazole-3-thiones (**1**) was prepared according to Ref. [33].

Treatment of **1** with ethyl bromoacetate afforded **2**, which readily yielded **3** on reaction with hydrazinium hydroxide. Condensation of **3** with aromatic aldehydes gave **4a–f** (Table 1 and Scheme 1) [27]. Analytical and spectral data (IR, ^{1}H NMR, MS) confirmed the proposed structures.

IR spectra showed the N–H bands of **3** at 3321 and 3107 cm^{-1} and the N–H and O–H bands of **4a–f** in the 3482–3108 cm^{-1} regions. The C=O groups of **2**, **3** and **4a-f** absorbed in the 1739, 1671, 1705–1662 cm^{-1} regions, respectively. Absorptions in the 1548–1487 cm^{-1} region were assigned to the C=N and C=C functions of **2** and **3**. Additional bands which appeared in the spectra of the condensation products (**4a–f**) in the 1617–1593 cm^{-1} region were attributed to the exocyclic C=N function. The ^{1}H NMR spectrum of **3** (DMSO-d_6) displayed two resonances (δ 9.27 and δ 4.17) which were assigned to the NH and NH_2 groups of the hydrazide, respectively. The ^{1}H NMR spectra of **4a** and **4d** revealed the presence of two isomers in a ratio of 2.5:1 in DMSO-d_6 as supported by the NH, N=CH, and SCH_2 protons resonating as double singlets at about 11.94/11.84–11.59, 8.66–8.38/8.17–7.86 and 4.45–4.44/4.11–4.06 ppm [27,34]. It is assumed that the N=CH double bond restricts rotation and gives rise to the formation of *E* and *Z* isomers with the *E* isomer dominating. The EIMS of compounds **3** and **4d** showed

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Table 1
Physical constants of compounds **2**, **3** and **4a–f**

Comp.	R/X	Yield (%)	M.p. (°C)	Formula (mol. wt.)	Analysis
2	OC_2H_5	53	167–168	$C_{12}H_{15}N_3O_3S{\cdot}H_2O$ (299.35)	C, H, N
3	$NHNH_2$	65	159–160	$C_{10}H_{13}N_5O_2S$ (267.31)	C, H, N
4a	$C_6H_4OCH_3$(3-)	81	84–85	$C_{18}H_{19}N_5O_3S$ (385.45)	C, H, N
4b	$C_6H_4OCH_3$(4-)	82	148–149	$C_{18}H_{19}N_5O_3S$ (385.45)	C, H, N
4c	$C_6H_4NO_2$(3-)	65	184–185	$C_{17}H_{16}N_6O_4S$ (400.42)	C, H, N
4d	$C_6H_4NO_2$(4-)	53	193–194	$C_{17}H_{16}N_6O_4S$ (400.42)	C, H, N
4e	C_6H_3(OH)Br(2,5-)	63	204–205	$C_{17}H_{16}BrN_5O_3S$ (450.33)	C, H, N
4f	5-nitro-2-furylethenyl	54	219–220	$C_{17}H_{16}N_6O_5S{\cdot}2H_2O$ (452.45)	C, H, N

the molecular ions at *m/z* 267 and *m/z* 400 with different intensities. The molecules fragmented via the routes proposed for similar structures [5,27,35,36]. The fragment at *m/z* 195 was the base peak and was formed as shown in Schemes 2 and 3.

3. Results and discussion

The newly synthesized compounds were evaluated for in vitro antimicrobial activity against *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* and *Candida albicans* ATCC 10231 using the disk diffusion and microdilution methods [37]. As can be seen in Table 2, only compound **4f** showed antibacterial activity against *S. aureus* ATCC 6538, *S. epidermidis* ATCC 12228, *E. coli* ATCC 8739, *S. flexneri* and *S. typhi*. The active entry **4f** was compound incorporating the 5-nitro-2-furyl moiety which stressed the importance of this residue in antibacterial action [35]. The antimicrobial screen was further extended to include *Mycobacterium tuberculosis* $H_{37}Rv$. Primary screening was conducted at 6.25 μg/ml against the microorganism in BACTEC 12B medium using the BACTEC 460 radiometric system [38]. Only compound **3** was inactive against *M. tuberculosis* $H_{37}Rv$ whereas compounds **2** and **4a–f** showed varying degrees of inhibition in the primary screen (Table 3).

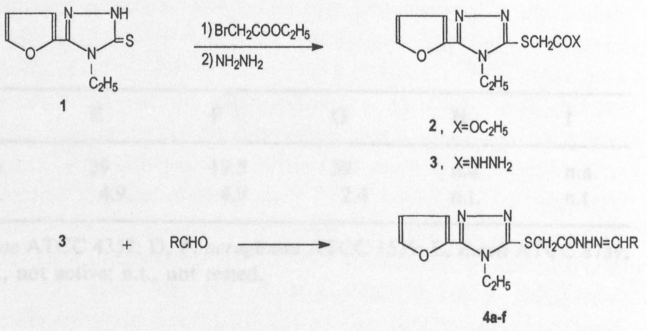
4. Experimental

4.1. Chemistry

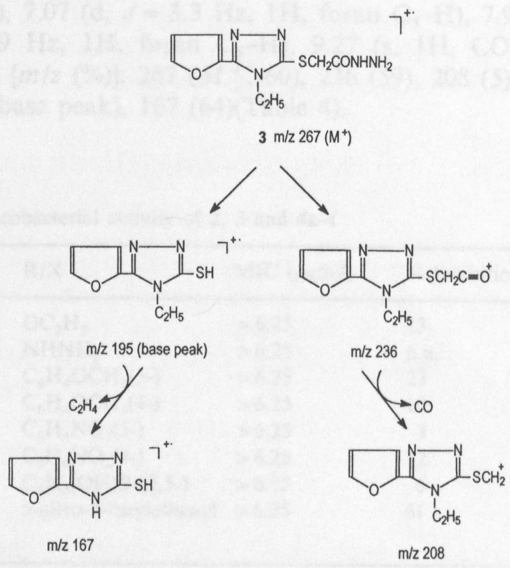
Elemental analyses were performed on a Carlo Erba 1106 elemental analyzer. Melting points (m.p.) were determined on a Büchi 530 apparatus in open capillary tubes and are uncorrected. IR spectra were run on KBr tablets, using a Perkin–Elmer 1600 FTIR spectrometer. ^1H NMR spectra were recorded on a Bruker AC 200 (200 MHz) instrument using tetramethylsilane as internal standard. EIMS were performed on a VG Zab Spec (70 eV) instrument.

4.1.1. Synthesis of ethyl 5-(2-furyl)-4-ethyl-1,2,4-triazole-3-mercaptoacetate (2)

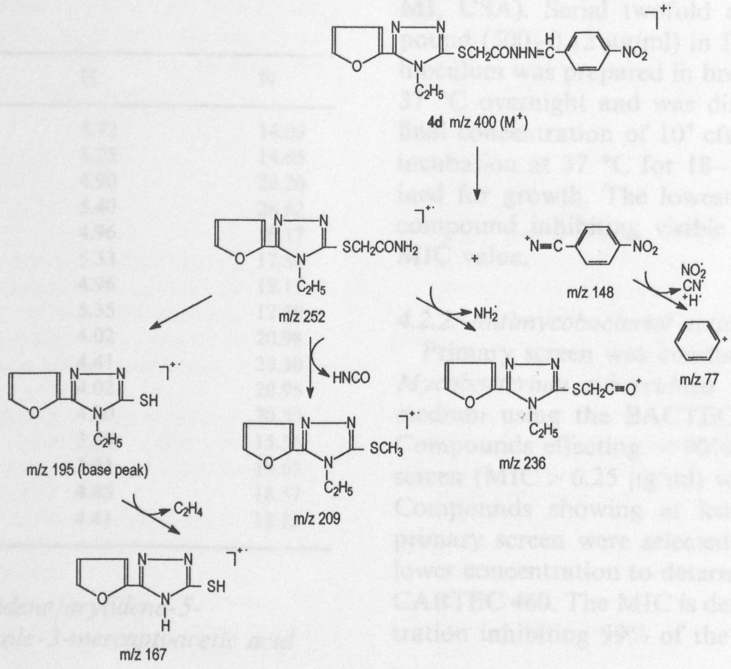
A mixture of **1** (0.01 mol), KOH (0.01 mol), $BrCH_2COOEt$ (0.011 mol) and EtOH (50 ml) was heated under reflux for 2 h. The crystals formed after



Scheme 1. Synthetic routes to compounds **2**, **3** and **4a-f**.



Scheme 2. Proposed mass fragmentation pattern of **3**.



Scheme 3. Proposed mass fragmentation pattern of **4d**.

Table 2
Antimicrobial activity of **4f**

Comp./microorganism [a]	A	B	C	D	E	F	G	H	I
4f	2.4	156	n.a.	n.a.	39	19.5	39	n.a.	n.a.
Cefuroxime Na	1.2	9.8	n.t.	n.t.	4.9	4.9	2.4	n.t.	n.t

[a] A, *S. aureus* ATCC 6538; B, *S. epidermidis* ATCC 12228; C, *K. pneumoniae* ATCC 4352; D, *P. aeruginosa* ATCC 1539; E, *E.coli* ATCC 8739; F, *S. flexneri*; G, *S. typhi*; H, *P. mirabilis*; I, *C. albicans* ATCC 10231; n.a., not active; n.t., not tested.

standing overnight were filtered, washed with H_2O and recrystallized from EtOH to afford **2** (yield = 53%).

Spectral data for **2**. IR [ν cm^{-1}, KBr]: 3448 (O–H), 1739 (C=O), 1533, 1515, 1490 (C=N/C=C). ^1H NMR [200 MHz, δ ppm DMSO-d_6]: 1.28 (t, 6H, $2CH_2$–CH_3), 4.04 (s, 2H, SCH_2), 4.17 (q, 4H, $2CH_2$–CH_3), 6.71 (dd, $J = 3.4$, 1.9 Hz, 1H, furan C_4–H), 7.06 (d, $J = 3.3$ Hz, 1H, furan C_3–H), 7.92 (d, $J = 1.1$ Hz, 1H, furan C_5–H)(Table 4).

4.1.2. Synthesis of 5-(2-furyl)-4-ethyl-1,2,4-triazole-3-mercaptoacetic acid hydrazide (3)

A mixture of **2** (0.01 mol), $NH_2NH_2 \cdot H_2O$ (100%) (0.05 mol) and EtOH (40 ml) was heated under reflux for 3 h. The crystallin precipitate was filtered, washed with cold EtOH and recrystallized from EtOH to yield **3** (yield = 65%).

Spectral data for **3**. IR [ν cm^{-1}, KBr]: 3321, 3107 (N–H), 1671 (C=O), 1548, 1516, 1487 (C=N/C=C). ^1H NMR [200 MHz, δ ppm DMSO-d_6]: 1.28 (t, 3H, CH_2CH_3), 3.85 (s, 2H, SCH_2), 4.17 (q, 4H, CH_2CH_3 and $NHNH_2$), 6.72 (dd, $J = 3.3$, 1.6 Hz, 1H, furan C_4–H), 7.07 (d, $J = 3.3$ Hz, 1H, furan C_3–H), 7.93 (d, $J = 0.9$ Hz, 1H, furan C_5–H), 9.27 (s, 1H, CONH). EIMS [m/z (%)]: 267 (M^+, 60), 236 (59), 208 (5), 195 (100, base peak), 167 (64)(Table 4).

Table 3
Antimycobacterial activity of **2**, **3** and **4a–f**

Comp.	R/X	MIC (μg/ml)	% Inhibition [a]
2	OC_2H_5	>6.25	13
3	$NHNH_2$	>6.25	n.a.
4a	$C_6H_4OCH_3$(3-)	>6.25	23
4b	$C_6H_4OCH_3$(4-)	>6.25	18
4c	$C_6H_4NO_2$(3-)	>6.25	3
4d	$C_6H_4NO_2$(4-)	>6.25	12
4e	C_6H_3(OH)Br(2,5-)	>6.25	6
4f	5-nitro-2-furylethenyl	>6.25	61

[a] MIC RMP = 0.25 μg/ml, 97–99% inhibition versus *M. tuberculosis* H_{37}Rv. n.a., not active.

Table 4
Elemental Analysis (calc./found)

Comp	C	H	N
2	48.14	5.72	14.03
	48.40	5.25	14.65
3	44.93	4.90	26.20
	45.36	5.40	26.62
4a	56.09	4.96	18.17
	55.88	5.33	17.50
4b	56.09	4.96	18.17
	56.79	5.35	17.60
4c	50.10	4.02	20.98
	51.48	4.41	20.30
4d	50.10	4.02	20.98
	50.74	4.20	20.50
4e	45.34	3.58	15.55
	45.76	3.83	15.67
4f	45.12	4.45	18.57
	45.30	4.41	18.18

*4.1.3. Synthesis of N-alkylidene/arylidene-5-(2-furyl)-4-ethyl-1,2,4-triazole-3-mercaptoacetic acid hydrazides (**4a–f**)*

A solution of **3** (0.005 mol) in EtOH (40 ml) and the appropriate aldehyde (0.005 mol) was heated under reflux for 4 h. The precipitate obtained from the hot ethanolic solution or after cooling was purified either by washing with hot EtOH or recrystallization from EtOH.

Spectral data for **4a**. IR [ν cm^{-1}, KBr]: 3233 (N–H), 1689 (C=O), 1606, 1576, 1515, 1478 (C=N/C=C). ^{1}H NMR [200 MHz, δ ppm DMSO-d_6]: 1.29 (t, 3H, CH_2CH_3), 3.79, 3.82 (2s, 3H, OCH_3), 4.06, 4.44 (2s, 2H, SCH_2) 4.19 (q, 2H, CH_2CH_3), 6.70 (d, J = 1.2 Hz, 1H, furan C_4–H), 6.96–7.97 (m, 6H, phenyl and furan C_3–H, C_5–H), 8.17, 8.66 (2s, 1H, N=CH), 11.59 (br s, 1H, CONH).

Spectral data for **4d.** IR [ν cm^{-1}, KBr]: 3108 (N–H), 1683 (C=O), 1617, 1545, 1488 (C=N/C=C), 1513 (NO_2), 1341 (NO_2). ^{1}H NMR [200 MHz, δ ppm DMSO-d_6]: 1.29 (t, 3H, CH_2CH_3), 4.11, 4.45 (2s, 2H, SCH_2), 4.20 (q, 2H, CH_2CH_3), 6.68 (d, J = 1.5 Hz, 1H, furan C_4–H), 7.02 (d, J = 3.2 Hz, 1H, furan C_3–H), 7.86–8.38 (m, 6H, N=CH, phenyl and furan C_5–H), 11.84, 11.94 (2s, 1H, CONH). EIMS [m/z (%)]: 400 (M^+, 2), 252 (1), 236 (8), 209 (1), 195 (100, base peak), 167 (20), 148 (4), 77 (3)(Table 4).

4.2. Microbiology

4.2.1. Antimicrobial activity [37]

The disk diffusion method was used for the preliminary antimicrobial evaluation of **2** to **4a–f**. The minimum inhibitory concentration (MIC) of **4f** which showed inhibition in the preliminary tests was determined by the microbroth dilution technique using Mueller–Hinton broth (Difco Laboratories, Detroit, MI, USA). Serial twofold dilutions of the test compound (500–0.12 μg/ml) in DMSO were prepared. The inoculum was prepared in broth which had been kept at 37 °C overnight and was diluted with broth to give a final concentration of 10^5 cfu/ml in the test tray. After incubation at 37 °C for 18–20 h the trays were examined for growth. The lowest concentration of the test compound inhibiting visible growth was taken as the MIC value.

4.2.2. Antimycobacterial activity [38]

Primary screen was conducted at 6.25 μg/ml against *Mycobacterium tuberculosis* $H_{37}Rv$ in BACTEC 12B medium using the BACTEC 460 radiometric system. Compounds effecting < 90% inhibition in the primary screen (MIC > 6.25 μg/ml) were not evaluated further. Compounds showing at least 90% inhibition in the primary screen were selected for further evaluation at lower concentration to determine the actual MIC in the CABTEC 460. The MIC is defined as the lowest concentration inhibiting 99% of the inoculum.

4.2.2.1. BACTEC radiometric method of susceptibility testing. Inocula for susceptibility testing were either from a positive BACTEC isolation vial with a growth index (GI) of 500 or more, or a suspension of organisms isolated earlier on a conventional medium. The culture was well mixed with a syringe and 0.1 ml of a positive BACTEC culture was added to each of the vials containing the test compounds (12.5 μg/ml). The standard vials contained rifampin (RMP) (0.25 μg/ml). A control vial was inoculated with a 1:100 dilution of the culture.

Each vial was tested immediately on a BACTEC instrument to provide CO_2 in the headspace. The vials were incubated at 37 °C and tested daily with a BACTEC instrument. When the GI in the control read at least 30, the increase in GI (ΔGI) from the previous day in the control was compared with that in the drug vial. The following formula was used to interpret the results:

ΔGI control > ΔGI drug = susceptible

ΔGI control < ΔGI drug = resistant

If a clear susceptibility pattern (the difference of ΔGI of control and the drug bottle) was not seen at the time the control GI was 30 the vials were read for 1 or 2 additional days to establish a definite pattern of ΔGI differences.

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