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Synthesis, structural characterization, crystallographic analysis and antibacterial properties of some nitrosuryl triazolo[3,4-*b*]-1,3,4-thiadiazines

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Summary — A series of 1-(5-nitro-2-furyl)-2-bromo-3-aryl-2-propen-1-ones has been prepared through dehydrobromination of 2,3-dibromo-1-(5-nitro-2-furyl)-3-arylpropan-1-ones. Condensation of 1-(5-nitro-2-furyl)-2-bromo-3-aryl-2-propen-1-ones with 4-amino-5-mercapto-1,2,4-triazoles afforded a new class of 6-(5-nitro-2-furyl)-7-arylidene-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazines. The structures of the condensation products are fully confirmed by analytical, IR, NMR and mass spectral data. The formation of 1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazepines rather than 1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazepines in the above condensation has also been confirmed by X-ray crystallographic analysis. The newly synthesized compounds have been screened for their *in vitro* antibacterial activity against Gram-positive and Gram-negative bacteria.

Microbial agent / nitrosuran heterocycle / 1,2,4-triazole derivative

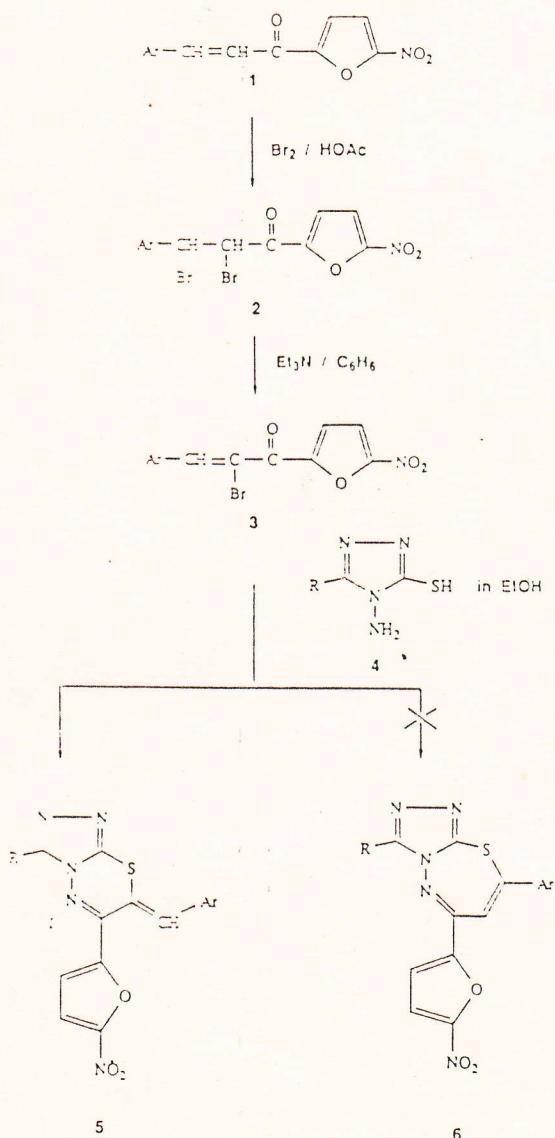
Introduction

Various 1,2,4-triazoles and the *N*-bridged heterocycles derived from them are found to be associated with diverse pharmacological activity [1–15]. The analgesic, antiasthmatic, diuretic, antihypertensive, anticholinergic, antibacterial, antifungal, antiinflammatory, hypoglycemic, antitubercular and antiviral properties are exhibited by various *N*-bridged heterocycles derived from a variety of 4-amino-5-mercaptop-1,2,4-triazoles, and have made them as important chemotherapeutic agents. Synthesis and reactions of 4-amino-5-mercaptop-1,2,4-triazoles have been reported by Temple [16]. The 1,2,4-triazole nucleus has recently been incorporated into a wide variety of therapeutically interesting drug candidates including H₁ histamine receptor blockers, cholinesterase inhibitors, CNS stimulants, antianxiety agents and analgesics [17]. Apart from these, certain 4-amino-5-

mercaptop-1,2,4-triazoles are used as efficient analytical reagents for the gravimetric estimation of metals such as silver, copper and gold [18].

In a recent communication [19], 2 of us reported the synthesis of several diaryl-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazepines by condensing α-bromochalcones with 3-substituted 4-amino-5-mercaptop-1,2,4-triazoles in the presence of ethanolic potassium hydroxide. Prompted by the biological properties of 1,2,4-triazoles and as a part of our general search for chemotherapeutically important nitrosuran heterocycles [20–25], we decided to study the reaction between 1-(5-nitro-2-furyl)-2-bromo-3-arylpropen-1-ones 3 in the presence of 3-substituted 4-amino-5-mercaptop-1,2,4-triazoles 4 with a view to synthesizing a new series of nitrosuryl triazolo[3,4-*b*]thiadiazepines 6 (scheme 1). However, the condensation products are now identified as 7-arylidene-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazines 5 based on their analytical and spectral data. Thus in the present paper we report the synthesis and structural characteristics of a new series of nitrosuryl-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazines 5 along with their antibacterial activity.

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Received: 1992.



Scheme 1.

Chemistry

Dibromopropanones **2** were prepared according to the procedure [25] reported by us earlier. Dehydrobromination of these dibromides **2** according to the standard literature methods [26] resulted in the formation of α -bromopropenones **3** rather than the acetylenic ketones. These α -bromopropenones were then condensed with 3-substituted 4-amino-5-mercaptop-1,2,4-triazoles in the presence of anhydrous sodium acetate in ethanol to give the condensation products which are now characterized as 3-substituted 6-(5-nitro-2-furyl)-7-arylidene-1,2,4-triazolo-[3,4-*b*]-1,3,4-thiadiazines **5** rather than the anticipated 3-substituted 6-(5-nitro-2-furyl)-8-aryl-1,2,4-triazolo[3,4-*b*]-1,3,4-

thiadiazepines **6** by analytical and spectral data. The structure of one of the condensation products **5a** was also confirmed by X-ray crystallographic analysis. The aminomercaptotriazoles carrying alkyl, aryl and aryloxymethyl substituents at position 3 were prepared according to literature procedures [17, 22].

Results and discussion

The characterization data of α -bromopropenones **3** are given in table I. The fact that only one molecule of hydrogen bromide was eliminated during dehydrobromination was confirmed by the positive Lassaigne's and Beilstein's tests on compounds **3a** and **3k**. Examination of the NMR spectrum of α -bromopropenone **3a** and **3k** showed an olefinic proton signal at δ 8.2 and 8.33 respectively, thus confirming the assigned structure **3** for the dehydrobrominated products. That the dehydrobrominated products are α -bromopropenones is also evident from mass spectral studies. The mass spectrum of **3e** showed a molecular ion peak at *m/z* 335/337, consistent with its molecular formula $C_{14}H_{10}BrNO_2$, while that of **3k** showed a molecular ion peak at 355 in agreement with its molecular formula $C_{14}H_9BrClNO_2$. The *M* + 2 and *M* + 4 peaks were also observed in the spectrum of **3k**. Further, the molecular ions of **3c** and **3e** underwent loss of a bromine radical to give intense fragment ion peaks at *m/z* 276 and 256, respectively. The formation of α -bromopropenones rather than acetylenic ketones in these dehydrobrominations implies that the hydrogen at C-2 in propanones **2** is more acidic than the hydrogen at C-3 and is easily abstracted by the base. Due to the alkaline sensitivity of nitrofurans, bases stronger than triethylamine could not be employed for the dehydrobromination.

The reaction of α -bromopropenones **3** with triazoles **4** in ethanolic medium employing sodium acetate as a base yielded yellowish / orange condensation products, which are now characterized as 3-substituted 6-(5-nitro-2-furyl)-7-arylidene-1,2,4-triazolo-[3,4-*b*]-1,3,4-thiadiazines **5** rather than 3-substituted 6-(5-nitro-2-furyl)-8-aryl-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazepines **6** on the basis of NMR and mass spectral data. The characterization data of these condensation products **5** are given in table II.

The PMR spectral data of **4** of the condensation products **5b**, **5k**, and **5m** are in agreement with the assigned structures for these compounds. In the PMR spectrum of **5b**, a 3-proton singlet appeared at δ 2.55. The singlet due to the olefinic proton was shifted downfield and merged with the doublet due to one of the nitrofuran β -protons and appeared as a multiplet at δ 7.1, while the signals due to the other nitrofuran β proton and the aromatic protons appeared as multiplets at δ 7.4 integrating for 6 protons. The downfield

Table I. Characterization data of compounds **3**

H-NMR (δ , ppm), 5.85 (s, H, aromatic, β -Cl), 276/256 (ΔM , Br).

Chemical shift attributed to furfuryl α -proton and assigned structure of α -bromopropenones. The condensation products is mass spectra peaks at *m/z* 335/337, integrating with

Table I. Characterization data of 1-(5-nitro-2-furyl)-2-bromo-3-aryl-2-propen-1-ones 3.

Compound no	Ar	Yield (%)	mp (°C)	Colour	Halo-chromism	IR (cm ⁻¹)		Analysis (%)		
						vC=O	vNO ₂ , asym sym	C	H	N
3a*	3,4-Methylene-dioxyphenyl	79	149–51	Yellow	Dark blue	1665	1545 1350	46.10 45.90	2.02 2.18	3.76 3.82
3b	2-Nitro-4,5-methylene dioxyphenyl	60	151–53	Yellow	Light red	1670	1550 1345	40.98 40.87	1.76 1.70	6.70 6.81
3c*	4-Chlorophenyl	78	129	Greyish yellow	Blood red	1660	1530 1380	43.91 43.76	2.08 1.96	3.72 3.93
3d	2,4-Dichlorophenyl	74	119–122	Green	Rose red	1670	1540 1360	39.62 39.89	1.48 1.53	3.66 3.88
3e*	p-Tolyl	68	103–105	Greyish yellow	Dark red	1660	1530 1365	50.12 50.00	3.04 2.98	4.02 4.17
3f	2-Bromo-4-methylphenyl	70	129	Yellow	Rose red	1660	1530 1375	40.36 40.48	2.14 2.17	3.51 3.37
3g	2-Methyl-4-bromophenyl	77	156–158	Pale yellow	Rose red	1665	1540 1335	40.44 40.48	2.21 2.17	3.46 3.37
3h	2-Chloro-4-methylphenyl	65	121–123	Yellow	Rose red	1665	1535 1350	45.18 45.34	2.41 2.43	3.90 3.78
3i	2-Methyl-4-chlorophenyl	76	129–132	Yellow	Dark red	1665	1580 1350	45.41 45.34	2.46 2.43	3.60 3.78
3j	p-Anisyl	71	161–163	Yellow	Dark red	1665	1535 1340	47.81 47.72	2.79 2.84	3.91 3.97
3k**	Phenyl	62	106	Greyish yellow	Dark red	1645	1520 1350	48.39 48.44	2.46 2.48	4.41 4.34

*¹H-NMR (CDCl₃): δ, 8.2 (s, 1H, -C=CH-), 7.67 (d, 1H, J = 3.5 Hz, furan proton), 7.2–7.4 (m, 5H, aromatic and furan protons), 5.85 (s, 1H, -O-CH₂-O-). **¹H-NMR (CDCl₃): δ, 8.33 (s, 1H, -C=CH-), 7.8–8.1 (m, 2H, aromatic protons), 7.38–7.6 (m, 2H, aromatic and furan protons). ¹ MS, m/e (% abundance) 355 (50, M⁺), 357 (70, M + 2), 359 (20, M + 4), 320/322 (44, M-Cl), 276/278 (100/33, M-Br). ² MS, m/e (% abundance) 355 (18, M⁺), 337 (16, M + 2), 320/322 (52, M-CH₃), 256 (100, M-Br).

Chemical shift of the olefinic proton at δ 7.1 could be attributed to the combined anisotropic effect of the 2-furyl and phenyl rings. The NMR spectra of 5k, 5n and 5p were also consistent with the assigned structures. The typical carbonyl absorption of α-bromopropenones disappeared in the IR spectra of the condensation products. Further evidence in support of the thiadiazine structure for the condensation products is obtained from the mass spectral data. The mass spectra of 5b, 5j, and 5k showed molecular ion peaks at m/z 387, 463 and 443, respectively, consistent with their molecular formulae, C₁₆H₁₀ClN₂O₃S.

C₂₂H₁₄ClN₂O₃S and C₂₂H₁₄N₂O₃S. Molecular ion peaks in the spectra of 5b and 5k were found to be the base peaks.

The *in situ* generation of α-bromopropenones 3 and their subsequent condensation with aminomercapto-triazoles 4 also yielded the triazolo-thiadiazines 5. In a typical experiment involving the condensation of 2 (Ar = phenyl, p-chlorophenyl) and 4 (R = CH₃) the final condensation products obtained by these 2 different routes were found to be identical as evidenced by their melting point and mixed melting point. Attempts to synthesize the triazolo-thiadiazines 5 by a one-pot reaction of aminomercaptotriazoles 4 with

Table II. Characterization data of 3-substituted 6-(5-nitro-2-furyl)-7-arylidene-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazines 5.

Compound no	R	Ar	Yield (%)	mp (°C)	Colour	Analysis (%)			Table No
						Found [calc]	C	H	
							C	H	
5a	Methyl	Phenyl	90	257–259	Yellow	54.41 [54.39]	3.18 3.11	19.73 19.83]	
5b*	Methyl	4-Chlorophenyl	52	239–241	Yellow	49.42 [49.55]	2.53 2.58	18.20 18.06]	
5c	Methyl	2,4-Dichlorophenyl	63	201–202	Yellow	45.36 [45.49]	2.08 2.13	16.71 16.58]	
5d	Methyl	<i>p</i> -Tolyl	57	248–250	Yellow	55.61 [55.58]	3.49 3.54	19.10 19.07]	Mixed me MAMT: 3- amino-5-m
5e	Ethyl	Phenyl	68	224	Brownish yellow	55.49 [55.58]	3.51 3.54	19.21 19.07]	Table IV. A l param sd's are gi
5f	Ethyl	4-Chlorophenyl	50	233	Yellow	50.76 [50.81]	2.87 2.98	17.58 17.43]	
5g	Ethyl	<i>p</i> -Tolyl	78	233–234	Yellow	56.76 [56.69]	4.02 3.94	18.33 18.37]	Atom
5h	Ethyl	3,4-Methylene-dioxyphenyl	50	212–213	Orange yellow	52.58 [52.55]	3.19 3.16	17.00 17.03]	01 0.1 02 0.20
5i	<i>p</i> -Tolyl	Phenyl	70	236–237	Yellow	61.43 [61.54]	3.51 3.49	16.38 16.32]	03 0.2 V1 0.1 V2 0.20
5j*	<i>p</i> -Tolyl	4-Chlorophenyl	54	234–236	Yellow	57.20 [56.95]	2.96 3.02	15.08 15.10]	V3 0.19 V4 0.21 V5 0.2
5k*	<i>p</i> -Tolyl	<i>p</i> -Tolyl	46	224–226	Yellow	62.41 [62.30]	3.91 3.83	15.68 15.80]	C1 -0.31 C2 -0.11 C3 -0.02
5l	Phenyl	4-Chlorophenyl	45	233–234	Yellow	55.86 [56.06]	2.65 2.67	15.65 15.57]	C4 -0.11 C5 -0.31
5m**	<i>p</i> -Tolyloxy-methyl	4-Chlorophenyl	81	193–195	Yellow	56.06 [55.92]	3.31 3.24	14.01 14.18]	C6 -0.40 C7 -0.02 C8 0.09
5n	<i>p</i> -Tolyloxy-methyl	<i>p</i> -Tolyl	67	175–176	Yellow	60.91 [60.88]	4.08 4.01	14.69 14.80]	C9 0.16 C10 0.17
5o	<i>p</i> -Tolyloxy-methyl	2,4-Dichlorophenyl	51	177–178	Yellow	52.31 [52.27]	2.69 2.84	13.20 13.25]	C11 0.22 C12 0.16 C13 0.13

*¹H-NMR (CDCl₃): δ 7.4 (m, 5H, aromatic protons and furan β-proton), 7.1 (singlet, merged with a doublet, 2H, *J* = 3.5 Hz vinylic and furan β-proton), 2.55 (s, 1H, -CH₂-). MS, m/e (% abundance), 387/389 (100), 35, M⁺, 209 (18), 186 (15), 77 (10), *MS, m/e (% abundance), 463/465 (100/33, M⁺), 276 (30), 136 (38), 117 (38), 88 (100). ¹H-NMR (CDCl₃): δ 8.1 (d, 2H, *J* = 7.5 Hz aromatic protons), 7.25–7.5 (m, 9H, aromatic, vinylic and furan β-protons), 2.36 (s, 6H, Ar-CH₂-). MS, m/e (% abundance), 387/389 (100), 35, M⁺, 209 (18), 186 (15), 77 (10).

Table III. Results of debromination of dibromopropanones 2 in the presence of aminomercaptotriazoles 4.

No.	Dibromopropanone used	Triazole used	Propenone obtained	mp* (°C)	% Recovery of propenones
19.73 19.83]	2,3-Dibromo-1(5-nitro-2-furyl)-3-[<i>p</i> -chlorophenyl]-propan-1-one	MAMT	1-(5-Nitro-2-furyl)-3-[<i>p</i> -chlorophenyl]-2-propen-1-one	184	90
18.20 18.06]	2,3-Dibromo-1(5-nitro-2-furyl)-3-[<i>p</i> -chlorophenyl]-propan-1-one	EMAT	1-(5-Nitro-2-furyl)-3-[<i>p</i> -chlorophenyl]-2-propen-1-one	185	85
16.71 16.58]	2,3-Dibromo-1(5-nitro-2-furyl)-3-[<i>p</i> -chlorophenyl]-propan-1-one	PMAT	1-(5-Nitro-2-furyl)-3-[<i>p</i> -chlorophenyl]-2-propen-1-one	184	87
19.10 19.07]	2,3-Dibromo-1-(5-nitro-2-furyl)-3-[<i>p</i> -tolyl]-propan-1-one	MAMT	1-(5-Nitro-2-furyl)-3-[<i>p</i> -tolyl]-2-propen-1-one	178	86

Mixed melting points of both recovered propenones with authentic samples (reference [25]) did not show any depression.
 MAMT: 3-methyl-4-amino-5-mercaptop-1,2,4-triazole; EMAT: 3-ethyl-4-amino-5-mercaptop-1,2,4-triazole; PMAT: 3-phenyl-4-amino-5-mercaptop-1,2,4-triazole.

Table IV. Atomic coordinates and equivalent isotropic thermal parameters for the non-hydrogen atoms of 5a. The *s*'s are given in parentheses.

Atom	X	Y	Z	B(A ²)
S1	0.1573 (3)	0.1852 (1)	0.8672 (2)	0.051 (4)
O1	0.2076 (7)	0.1730 (3)	1.3000 (4)	0.06 (1)
O2	0.267 (2)	0.0795 (6)	1.464 (1)	0.11 (2)
O3	0.256 (1)	0.1393 (4)	1.6212 (6)	0.11 (2)
N1	0.173 (1)	0.2962 (4)	0.7462 (6)	0.06 (2)
N2	0.206 (1)	0.3593 (4)	0.7834 (7)	0.06 (2)
N3	0.1975 (9)	0.3047 (3)	0.9522 (6)	0.04 (1)
N4	0.2145 (9)	0.2918 (3)	1.0818 (6)	0.04 (1)
N5	0.243 (1)	0.1311 (4)	1.5072 (6)	0.06 (2)
C1	-0.310 (2)	-0.0096 (5)	0.7944 (9)	0.07 (3)
C2	-0.117 (2)	0.0073 (5)	0.7987 (8)	0.07 (2)
C3	-0.025 (1)	0.0544 (4)	0.8757 (7)	0.05 (2)
C4	-0.117 (1)	0.0887 (4)	0.9539 (7)	0.05 (2)
C5	-0.312 (1)	0.0707 (4)	0.9522 (8)	0.06 (2)
C6	-0.405 (2)	0.0241 (5)	0.870 (1)	0.07 (3)
C7	-0.027 (1)	0.1387 (4)	1.0383 (7)	0.04 (2)
C8	0.094 (1)	0.1851 (4)	1.0164 (6)	0.05 (2)
C9	0.160 (1)	0.2352 (4)	1.1052 (6)	0.04 (2)
C10	0.171 (1)	0.2652 (4)	0.8502 (7)	0.05 (2)
C11	0.226 (1)	0.3636 (4)	0.9074 (8)	0.05 (2)
C12	0.167 (1)	0.2296 (4)	1.2418 (6)	0.04 (2)
C13	0.133 (1)	0.2727 (4)	1.3264 (7)	0.05 (2)
C14	0.163 (1)	0.2421 (4)	1.4455 (7)	0.05 (2)
C15	0.207 (1)	0.1828 (4)	1.4250 (6)	0.05 (2)
C16	0.260 (1)	0.4208 (4)	0.9874 (9)	0.07 (3)

The isotropic equivalent displacement parameter $B = 1/3 [U(11) + U(22) + U(33)]$.

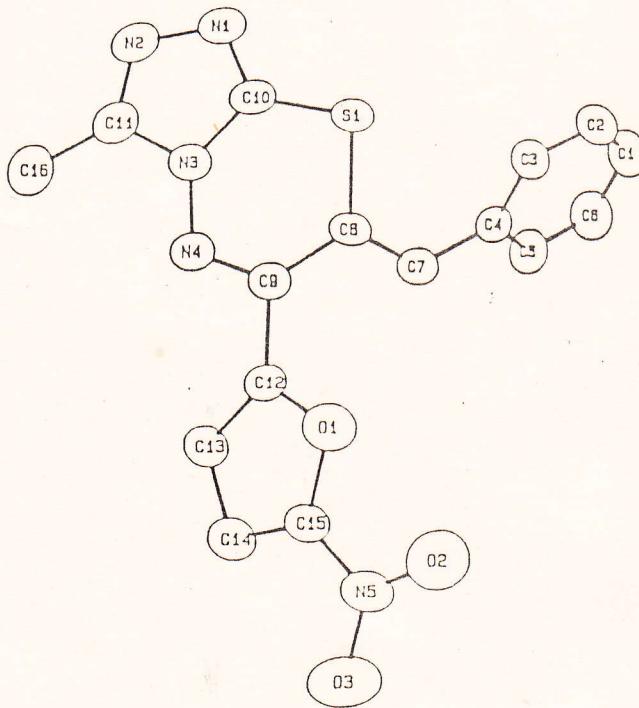


Fig 1. Structure of compound 5a.

dibromides 2 yielded the debrominated compounds, which are now characterized as the parent nitrofuryl propenones 1. Results of such experiments are summarized in table III.

The crystal structure determination of 5a was carried out using the SDP program package [27] on a microVax II computer. The atomic coordinates and equivalent isotropic thermal parameters for all atoms are given in table IV. A perspective view of the mole-

2H, $J = 3.5$ Hz.
 6 (15), 77 (10)
 3.1 (d, 2H, $J = 5$
 (% abundance), 7.0–7.3 (m,

i. Antibacterial activity of compounds 3 and 5.

Compound no	Minimum inhibitory concentration (μg/disk) (diameter of zone of inhibition in mm)*			
	<i>A aer</i>	<i>B sub</i>	<i>E coli</i>	<i>S aur</i>
3a	5 (8.7)	5 (10.5)	5 (11.5)	<5 (11.1)
3b	<5 (12.9)	<5 (11.5)	<5 (14.0)	<5 (17.6)
3c	<5 (13.1)	<5 (13.1)	<5 (14.3)	<5 (12.6)
3d	<5 (13.2)	<5 (14.8)	<5 (15.9)	<5 (12.4)
3e	<5 (9.1)	<5 (9.6)	<5 (9.8)	<5 (12.6)
3f	<5 (8.8)	<5 (9.1)	<5 (10.4)	<5 (11.3)
3g	<5 (10.1)	<5 (9.7)	<5 (11.4)	10 (12.0)
3h	5 (9.2)	5 (9.8)	<5 (10.5)	5 (8.3)
3i	<5 (11.0)	<5 (10.1)	<5 (13.0)	<5 (17.1)
3j	<5 (8.8)	<5 (11.8)	5 (9.3)	<5 (9.6)
3k	5 (11.4)	<5 (9.6)	<5 (12.1)	5 (10.3)
5a	<5 (14.3)	<5 (12.5)	5 (13.1)	<5 (19.4)
5b	<5 (15.3)	<5 (16.0)	5 (8.2)	<5 (17.8)
5c	<5 (12.4)	<5 (14.1)	5 (12.1)	<5 (15.8)
5d	<5 (12.4)	5 (10.9)	10 (10.6)	<5 (7.8)

Table V. (Continued.)

Compound no	Minimum inhibitory concentration (μg/disk) (diameter of zone of inhibition in mm)*			
	<i>A aer</i>	<i>B sub</i>	<i>E coli</i>	<i>S aur</i>
5e	<5 (14.2)	<5 (14.0)	10 (14.0)	<5 (17.8)
5f	<5 (12.1)	<5 (12.1)	20 (11.2)	<5 (14.8)
5g	<5 (9.9)	<5 (11.7)	10 (10.8)	<5 (14.8)
5h	<5 (12.8)	<5 (13.1)	<5 (10.8)	<5 (11.2)
5i	<5 (10.0)	<5 (10.4)	20 (11.2)	<5 (12.5)
5j	<5 (8.9)	5 (8.1)	20 (9.4)	20 (8.8)
5k	<5 (12.3)	<5 (9.4)	10 (8.7)	5 (10.8)
5l	<5 (12.1)	<5 (14.8)	15 (8.3)	<5 (10.1)
5m	20 (7.7)	30 (9.4)	40 (8.1)	20 (9.3)
5n	10 (7.2)	<10 (11.1)	20 (10.5)	10 (8.8)
5o	30 (9.3)	5 (8.4)	5 (8.0)	5 (10.1)
Nitrofurazone (for comparison)	<5 (10.2)	<10 (12.6)	10 (11.1)	<5 (14.4)

*At 37°C after 24 h of incubation. Dehydrated nutrient agar medium was supplied by HiMedia Laboratories Pvt Ltd, Bombay, 400 086, India; *A aer*: *Aerobacter aerogenes*; *B sub*: *Bacillus subtilis*; *E coli*: *Escherichia coli*; *S aur*: *Staphylococcus aureus*. Cultures of the above bacteria were obtained from Kasturba Medical College Hospital, Mangalore.

le as shown in figure 1 reveals that the sulfur atom is in a 6-membered ring rather than a 7-membered ring. The 6-membered ring is in a distorted boat conformation with the S and N4 atoms occupying the *ipso* positions.

*n)**
S aur

<5
(17.8)

<5
(14.8)

<5
(14.8)

<5
(11.2)

<5
(12.5)

20
(8.8)

5
(10.8)

<5
(10.1)

20
(9.3)

10
(8.8)

5
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<5
(14.4)

ent agar
Pvt Ltd.
S aerogenes
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bacteria
ospital.

pharmacology

The α -bromopropenones 3 and triazolothiadiazines 5 were screened for their *in vitro* antibacterial activity against Gram-positive and Gram-negative bacteria employing the disk-diffusion method [28]. Results of such studies are given in table V. From the results it is evident that most of the α -bromopropenones were more active than the corresponding nitrofuryl propenones 1. Among the α -bromopropenones, compound 3d carrying a 2,4-dichlorophenyl substituent possessed excellent antibacterial activity at less than 5 $\mu\text{g}/\text{ml}$ concentration against all the 4 bacteria. Triazolothiadiazines 5, carrying an alkyl substituent at position 3, were found to be the most active ones. Substitution of an alkyl group by an aryloxymethyl group did not enhance the antibacterial activity of triazolothiadiazines 5.

Experimental protocols

Chemistry

Melting points were determined by the capillary method and are uncorrected. The $^1\text{H-NMR}$ spectra of a few selected compounds were recorded on a 90 MHz NMR spectrometer and mass spectra on a Jeol-JMS-D300 mass spectrometer. The R spectra (Nujol mull) were recorded on a Perkin-Elmer 1330 R spectrophotometer. Dibromopropanones 2 were prepared according to the procedures reported earlier by us [25].

General procedure for α -bromo-1-(5-nitro-2-furyl)-3-aryl-2-propen-1-ones 3
To a solution of 2,3-dibromo-1-(5-nitro-2-furyl)-3-arylpropanones 2 (0.01 mol) in dry benzene (100 ml), a solution of triethylamine (4 g) in dry benzene (30 ml) was added and the reaction mixture was stirred at room temperature for 24 h. The separated triethylamine hydrobromide was removed by filtration. The filtrate was concentrated under reduced pressure and cooled. The precipitated α -bromopropenones 3 were collected by filtration and were further purified by recrystallization from ethanol. The analytical and spectral data of these α -bromopropenones 3 are given in table I.

*General procedure for 3-substituted 6-(5-nitro-2-furyl)-7-aryl-2-one-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazines 5*
A mixture of 3-substituted 4-amino-5-mercaptop-1,2,4-triazole (0.02 mol), α -bromopropenone (3, 0.02 mol) in ethanol (30 ml) and sodium acetate (2.46 g, 0.03 mol) in water (10 ml) was refluxed on a water bath for 2–3 h. The solid mass that separated was collected by filtration, washed with water and recrystallized from dioxane to yield the title compounds 5. The yield, analytical and spectral data of these triazolothiadiazines are given in table II.

One-pot reaction of dibromopropanones 2 with 3-substituted 4-amino-5-mercaptop-1,2,4-triazoles 4
A mixture of dibromopropanone (2, 0.01 mol), triazole (4, 0.01 mol) and triethylamine in ethanol (20 ml) was refluxed on a water bath for 2 h. The resulting clear solution was allowed to stand overnight. Crystals of the propenones 1 separated out. Concentration of the mother liquor gave a second crop of propenones. The combined precipitate was recrystallized from dimethylformamide or acetic acid and the products were identified as the parent 1-(5-nitro-2-furyl)-3-aryl-2-propen-1-ones 1 by their mixed melting points. The recovered propenones also gave positive halochromism test with concentrated sulfuric acid. Details of such experiments are given in table III.

X-ray diffraction analysis

3-Methyl-6-(5-nitro-2-furyl)-7-benzylidene-1,2,4-triazolo-[3,4-*b*]-1,3,4-thiadiazine 5a (molecular formula $C_{16}H_{14}N_2O_2S$) crystallized from a solution of aqueous dimethylformamide in the monoclinic space group $P2_1/n$. The unit-cell parameters are $a = 7.075(3)$, $b = 21.391(5)$, $c = 10.782(3)$ Å, $\beta = 106.12(3)^\circ$, $V = 1567.5$ Å 3 , $Z = 4$, FW = 343.37, $D_{\text{calc}} = 1.45$ g cm $^{-3}$, CuK α ($\lambda = 1.5418$ Å), and $F(000) = 704$. An yellow rectangular crystal of dimensions 1.0 × 0.5 × 0.3 mm was used to collect 3-dimensional intensity data on an Enraf-Nonius CAD-4 diffractometer. Cell parameters were obtained using the setting angles of 25 reflections in the range $20 < \theta < 30^\circ$. Reflections were measured using the $\omega/2\theta$ scan technique. A total of 3209 reflections were collected of which 2252 were unique and significant ($I > 3\sigma$). The structure was solved using the direct methods program SHELX86 [29]. The structural parameters were refined using a full-matrix least-squares refinement procedure with the non-hydrogen atoms were refined anisotropically and the hydrogen atom isotropically. The current R factor is 0.111 with a weighted R-factor of 0.131 for 2252 observed reflections.

Evaluation of antibacterial activity

The antibacterial activity of the test compounds were determined against *B subtilis*, *S aureus*, *A aerogenes* and *E coli* by the disk-diffusion method. Disks measuring 6.25 mm in diameter were punched from No 1 Whatman filter paper. Batches of 100 disks were dispensed to screw-capped bottles and sterilized by dry heat at 140°C for 1 h. Solutions of the test compounds in different concentrations were made by dissolving them in dimethylformamide. One ml of the solution containing 100 times the amount of the chemical required was added to each bottle containing 100 disks. The disks of each concentration were placed in triplicate on nutrient agar medium seeded with fresh bacterial cultures separately. The incubation was carried out at 37°C for 24 h. Nitrofurazone was used as a standard drug and solvent control was kept. Results of such screening studies are reported in table V.

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