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Note

Synthesis and biological activities of some 2-substituted phenyl-3-(3-alkyl/aryl-5,6-dihydro-*s*-triazolo-[3,4-*b*][1,3,4]thiadiazol-6-yl)indoles

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Some 2-substitutedphenyl-3-(3-alkyl/aryl-5,6-dihydro-*s*-triazolo [3 4-*b*] [1,3,4]thiadiazol-6-yl) indoles **3** have been synthesised by the condensation of 2-arylindole-3-aldehydes **1** with 3- substituted-4-amino-5-mercapto-1,2,4-triazoles **2** in DMF containing *p*-TsOH as catalyst. Their structures have been established on the basis of analytical and spectral data. The indoles **3** have been assessed for antiinflammatory, antibacterial and antifungal activities.

It is known in literature that large number of biologically active compounds possess indole[1-3] nucleus. It is also known that if an active nucleus is linked to another nucleus, the resulting molecule may possess greater potential for biological activity. The indole nucleus plays an important role as common denominator for various biological activities. Indole itself has been found to possess fungicidal[4], bactericidal[5] and herbicidal activities[6-8]. Likewise, 1,3,4-thiadiazole ring is associated with broad spectrum of biological activities by virtue of incorporating toxophoric N=C-S linkage. A triazolo-thiadiazole system may be viewed as a cyclic analogue of two very important components — thiosemicarbazide and biguanide which often display diverse biological activities.

In continuation of our work on heterocycles[9-11] of biological interest and guided by the observation that many a time the combination of two or more heterocyclic nuclei enhances the biological profile manyfold than its parent nuclei, we synthesised the title compounds **3** bearing 1,3,4-thiadiazole, 1,2,4-triazole and indole moieties in a single molecular frame work and evaluated their antiinflammatory, bactericidal and fungicidal activities.

The required 2-arylindole-3-aldehydes **1** were synthesised from 2- arylindoles by formylation with $POCl_3$ and DMF[12]. The 2- arylindoles were synthesised starting from substituted acetophenones which on heating with phenylhydrazine gave hydrazones followed by cyclisation with PPA to give 2- arylindoles[13]. The 3-aryl-4-amino-5-mercapto-1,2,4-triazoles were prepared following the method of Reid and Heindel[14] and 3-alkyl-4-amino-5-mercapto-1,2,4-triazoles were prepared from thiocarbohydrazide by cyclisation in appropriate aliphatic acids[15]

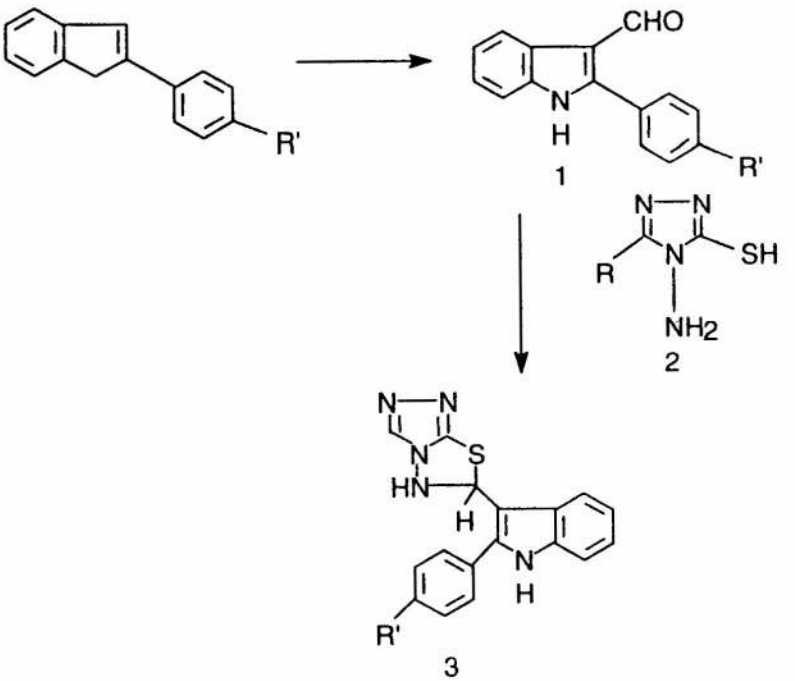
The structural assignments of **3** are based on IR and PMR data. The PMR spectra of **3a-t** exhibited broad singlet peaks at δ5.2-5.6 and 9.7-9.9, exchangeable with D_2O due to 5- N*H* and the indole N*H* protons. A singlet at δ5.8-6.1 was assigned to 6-C*H* protons, whereas, aromatic protons showed a multiplet at δ6.9-8.4. Their IR spectra exhibited absorption bands at 3150-3300 cm^{-1} due to NH group. The sharp band that appeared around 1615 cm^{-1} was due to C=N group. The bands that appeared at 1685 (C=O), 3210, 3150 (NH_2) and 1130 cm^{-1} (C=S) respectively for the starting aldehydes **1** and triazoles **2** were absent in the newly formed compounds **3a-t**. The PMR spectra of **3a-t** also showed the absence of peak at δ12.8-13.1 attributable to SH proton (exchangeable with D_2O) of the starting mercaptoaminotriazole **2**.

Antiinflammatory activity

The compounds were tested for their antiinflammatory activity by acute carrageenam-induced oedema in rat paw and exhibited activity ranging from 8.12 to 19.80% taking phenylbutazone as standard which showed 58% inhibition (cf Table I).

Antibacterial and antifungal activities

The antibacterial activity of some of the compounds was determined *in vitro* using paper disc method against two pathogenic micro-organisms



3a : R = 4 - MeOC6H4	, R' = H	3k : R = CH3	, R' = CH3
b : R = CH2C6H5	, R' = H	l : R = C2H5	, R' = CH3
c : R = 2-MeC5H5	, R' = H	m : R = C3H5	, R' = CH3
d : R = C6H5	, R' = H	n : R = 4-MeO 6H5	, R' = Cl
e : R = CH3	, R' = H	o : R = CH 2C6H5	, R' = Cl
f : R = C2H5	, R' = H	p : R = 2-MeC 6H5	, R' = Cl
g : R = C3H5	, R' = H	q : R = C 6H5	, R' = Cl
h : R = CH2C6H5	, R' = CH3	r : R = CH3	, R' = Cl
i : R = 2-MeC5H4	, R' = CH3	s : R = C2H5	, R' = Cl
j : R = C6H5	, R' = CH3	t : R = C3H7	, R' = Cl

viz., *Eschericia coli* (Gram-negative) and *Staphylococcus aureus* (Gram-positive) at 200 μg/mL and 100 μg/mL concentrations respectively, in the nutrient agar media.

Out of the test compounds, **3a**, **3d**, **3g** and **31** exhibited a low degree of inhibition against *S. aureus* and *E.Coli*.

Similarly, the antifungal screening of some of the compounds was carried out *in vitro* by paper disc method against two fungi viz., *Aspergillus niger* and *Candida albicans*. Out of the test compounds, **3a**, **3g**, **3j** and **31** exhibited mild to moderate inhibition against *A. niger* and *C. albicans*.

Experimental Section

Melting points were determined in open capillaries in a sulphuric acid-bath and are uncorrected. Homogeniety of the compounds was routinely checked on silica gel-G TLC plates using benzene-ethylacetate (7:3) as eluant. IR spectra (υ max in cm^{-1}) were recorded on Shimadzu -435 spectrophotometer using KBr disc and ^{1}HNMR spectra in $CDCl_3$ and $CDCl_3$ + DMSO-d_6 (Chemical shifts in δ, ppm) on varian T-60A and EM-390 spectrometers (60 MHz and 90 MHz) using TMS as internal standard. Compounds were analysed for C, H and N and

Table I—Characterisation data and antiinflammatory activity of **3a-t**

Compd	m.p. (°C)	Yield (%)	Mol. formula	Antiinflammatory activity (% inhibition)
3a	227-28	62	$C_{24}H_{19}N_5OS$	-
3b	203-04	58	$C_{24}H_{19}N_5S$	-
3c	220-22	69	$C_{24}H_{19}N_5S$	19.41
3d	231-32	79	$C_{23}H_{17}N_5S$	8.12
3e	220-22	85	$C_{18}H_{15}N_5S$	17.11
3f	195	75	$C_{19}H_{17}N_5S$	12.62
3g	217-18	77	$C_{20}H_{19}N_5S$	9.70
3h	203	55	$C_{25}H_{21}N_5S$	NT
3i	224-25	53	$C_{25}H_{21}N_5S$	19.41
3j	233-34	63	$C_{24}H_{19}N_5S$	19.80
3k	210-11	58	$C_{19}H_{17}N_5S$	19.41
3l	224	70	$C_{20}H_{19}N_5S$	16.50
3m	213-14	74	$C_{21}H_{21}N_5S$	12.62
3n	275-76	83	$C_{24}H_{18}ClN_5OS$	16.68
3o	260-61	72	$C_{24}H_{18}ClN_5S$	12.53
3p	237	58	$C_{24}H_{18}ClN_5S$	18.0
3q	287-88	65	$C_{23}H_{16}ClN_5S$	12.8
3r	311-12	63	$C_{18}H_{14}ClN_5S$	9.8
3s	302-03	72	$C_{19}H_{16}ClN_5S$	14.0
3t	307-08	79	$C_{20}H_{18}ClN_5S$	15.0

Nt = Not tested

- = nil activity

the values were found within ± 0.5% of the theoretical values. The compounds displayed expected spectral characteristics. However, only those spectral data which have a direct relevance to the structural assignments are described here.

2-Phenylindole-3-aldehyde 1a : General procedure $POCl_3$ (23 g, 0.15 mole) was added dropwise with constant stirring to DMF (20mL) at 5-10°C 2-Phenylindole (19.3g, 0.1 mole) in DMF (30mL) was added dropwise during 10 min. The reaction mixture was allowed to attain room temperature and then stirred at 50-60°C in an oil bath for 5 hr. After cooling, the reaction mixture was poured over ice-cold saturated aq. NaOAc solution. The solid obtained was filtered, washed with water, dried and crystallised from EtOAc: pet.ether as shining crystals (16.0g), m.p. 250°C; IR (KBr) : 3290 (NH), 1685 (C=O); PMR ($CDCl_3$) : δ7.0 - 7.85 (m,9H,Ar-*H*), 8.6 (bs,1H, indole N*H*), 10.2 (s,1H,-C*H*O).

2-*p*-Methylphenylindole-3-aldehyde 1b. Shining crystals (15.6g), m.p. 238-39°C; IR (KBr) : 3295 (NH), 1680 (C=O); PMR ($CDCl_3$) : δ 2.37 (s,3H,-CH_3), 6.9 - 7.8 (m,8H,Ar- *H*), 8.7 (bs, 1H, indole N*H*), 10.2 (s, 1H C*H*O).

2-*p*-Chlorophenylindole-3-aldehyde 1c. Shining crystals (15.0g), m.p. 298-99°C; IR (KBr) : 3300 (NH), 1685 (C=O); PMR ($CDCl_3$) : δ 7.2 - 7.85 (m,8H,Ar-*H*), 8.7 (bs,1H,indole N*H*), 10.2 (s,1H, C*H*O).

2-Phenyl-3-[3-(4-methoxyphenyl)-5,6-dihydro-*s*-triazolo[3,4-*b*] [1,3,4] thiadiazol-6-yl]indole 3a : General procedure. An equimolar mixture of 4-amino-5-mercapto-3-(4-methoxyphenyl)-*s*- triazole (1.11g, 0.005 mole), 2-phenylindole-3-aldehyde (1.10g, 0.005mole), and *p*-TsOH (20 mg) in dry DMF (30mL) was stirred at 70-80°C for 14hr. It was cooled and poured over crushed ice. The solid separated was filtered, washed with water, dried and crystallised from acetic acid as white crystals (62%), m.p. 227-28°C; IR : 3285 (NH, stretch), 1605 (C=N stretch), 1575 (C=C stretch), 1470 (C-N stretch), 1275 (C-O-C asymmetric stretch),. 1055 (C-O-C symmetric stretch) and 695cm^{-1} (C-S stretch); PMR ($CDCl_3$) : δ3.91 (s,3H,-OCH_3), 5.56 - 5.58 (bs, 1H,N*H*), 6.0(s,1H,C*H*), 7.05-8.4 (m,13H,Ar-*H*), 9.75 (s,1H,indole N*H*).

Compounds **3b-t** were prepared similarly and their characterisation data are given in Table I.

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