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Note

Heterocyclic systems containing bridgehead nitrogen atom : Synthesis and biological activities of some substituted *s*-triazolo[3,4-*b*] [1,3,4]thiadiazoles

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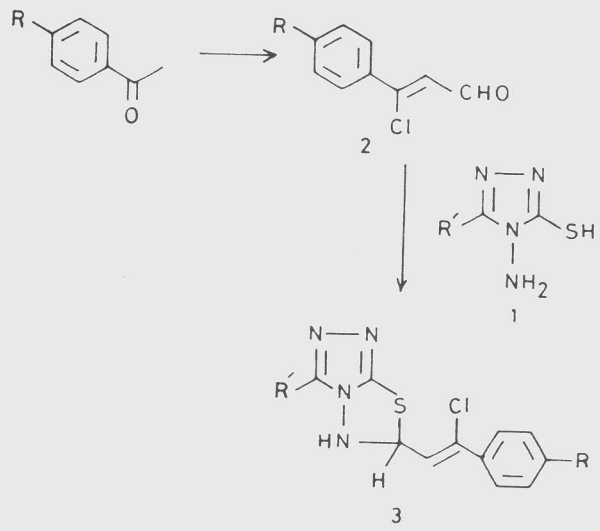
Various 3-alkyl/aryl-6-(2-chloro-2-substituted-phenyl ethenyl)-5, 6-dihydro-*s*-triazolo [3,4-*b*][1,3,4]-thiadiazoles **3** have been synthesised by the condensation of 3-substituted-4-amino-5-mercapto-1,2,4-triazoles **1** with various substituted β-chlorocinnamaldehydes **2** in benzene containing a catalytic quantity of *p*-TsOH using Dean-Stark apparatus. Structures of thiadiazoles **3** have been established on the basis of analytical and spectral data. The thiadiazoles **3** have been assessed for antiinflammatory, antibacterial and antifungal activities.

Substituted 1,2,4-triazoles and the *N*-bridged heterocycles derived from them amongst the various heterocycles that have received considerable attention during the last two decades as potential bioactive agents[1-10]. In continuation of our work on the synthesis of biologically active nitrogen and sulphur containing heterocycles[11-14], we have synthesised triazolo-thiadiazole system which may be viewed as a cyclic analogue of two very important components, i.e. thiosemicarbazide[15] and biguanide[16], which often display diverse biological activities. It has been reported[17] that some of their derivatives exhibit pronounced analgesic, antiasthmatic, diuretic, antihypertensive, antibacterial, antifungal, antiinflammatory, antitubercular and antiviral activities.

Prompted by these observations, we report



3a ; R' = 4' - $OMeC_6H_4$, R = Cl
b ; R' = - $CH_2C_6H_5$, R = Cl
c ; R' = 2' - $CH_3C_6H_4$, R = Cl
d ; R' = CH_3 , R = Cl
e; R' = C_2H_5, R = Cl
f; R' = C_3H_7, R = Cl
g; R' = 4' - $OMeC_6H_4$, R = OMe
h ; R' = - $CH_2C_6H_5$, R = OMe
i ; R' = 2' - $CH_3C_6H_4$, R = OMe
j ; R' = CH_3 , R = OMe
k ; R' = C_2H_5 , R = OMe
l ; R' = C_3H_7 , R = OMe
m ; R' = 4' - $OMeC_6H_4$, R = Br
n ; R' = $CH_2C_6H_5$, R = Br
o ; R' = 2' - $CH_3C_6H_4$, R = Br
p ; R' = CH_3 , R = Br
q ; R' = C_2H_5 , R = Br
r ; R' = C_3H_7 , R = Br

herein the synthesis of 3-alkyl/aryl-6- (2-chloro-2-substituted-phenyl ethenyl)-5,6-dihydro-*s*-triazolo-[3,4-*b*] [1,3,4]thiadiazoles **3** by the condensation of 3-alkyl/aryl-4-amino-5-mercapto-1,2,4-triazoles **1** with various substituted β-chlorocinnamal-dehydes **2** in benzene containing catalytic quantity of *p*-TsOH using Dean-Stark apparatus[18]. Most of the reactions of β-chlorocinnamaldehydes have been used for the synthesis of condensed heterocyclic systems where vinylic chlorine atom has been displaced. The present reaction involves the condensation of CHO group only and retains the vinylic chlorine atom in the resultant compounds **3**, to study the effect of this vinylic chlorine atom on the biological activities.

The required 4 - amino-3-aryl-5-mercapto-1,2,4-triazoles were synthesised following the method of Reid and Heindel[19] and 3-alkyl-4-amino-5-mercapto-1, 2, 4-triazoles were synthe-sised from thiocarbohydrazides by cyclisation in appropriate aliphatic acids[20]. The substituted β-chlorocinnamaldehydes were prepared by

Vilsmeyer-Haack reaction[21] of substituted acetophenones.

The structural assignments of **3** are based on IR and ^{1}H NMR data. The IR spectra of **3a-r** showed sharp bands near 1600 and 3200-3400 cm^{-1} due to C=N and NH group. The bands that appeared at 3210, 3150 (NH_2), 1130 cm^{-1} (C=S) and 1610 cm^{-1} (C=O), respectively for the starting triazoles **1** and β-chlorocinnamaldehydes **2** were absent in the newly formed compounds **3a-r**. The ^{1}H NMR spectra of **3a-r** exhibited broad singlet peaks at δ 5.8-6.0 exchangeable with D_2O, due to NH proton, whereas, 6-CH proton appeared as doublet at δ 6.4-6.5. The -C*H*=C proton appeared as doublet buried in the aromatic region.^{1}HNMR spectra of **3a-r** also showed the absence of peaks at δ 5.5-5.6 due to NH_2 protons present in triazoles. A broad signal of one proton intensity at δ 12.8-13.1 attributed to SH proton (exchangeable with D_2O) was also absent in their ^{1}HNMR spectra.

Antiinflammatory activity

The compounds were tested for their antiinflammatory activity by acute carrageenam-induced Oedema test model in rats[22] and exhibited mild to moderate activity ranging from 9.63 to 39.21% taking phenylbutazone as standard which showed 58% inhibition (cf. Table I).

Antibacterial and antifungal activities

The antibacterial activity of **3a-r** was determined *in vitro* using paper disc method against two pathogenic microorganisms viz., *E. coli* (Gram-negative and *S. aureus* (Gram-positive) at 200 μg/mL and 100 μg/mL concentrations respectively, in the nutrient agar media. The compounds **3a-r** were not significantly active towards these bacteria.

Similarly, the antifungal screening of **3a-r** was carried out *in vitro* by paper disc method against two fungi viz., *A. niger* and *C. albicans* and they did not show significant antifungal activity as well.

Experimental Section

All melting points were taken on Buchi melting point apparatus and are uncorrected. Homogeniety of the compounds was routinely checked on silica gel-G TLC plates using benzene-ethyl acetate (4:1) as eluant. IR spectra (ν_{max} in cm^{-1}) were recorded on Shimadzu - 435 Spectrophotometer using KBr disc and ^{1}H NMR spectra in $CDCl_3$/$CDCl_3$ +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.

6-[2-Chloro-2-(4-chlorophenyl)ethenyl]-3- (4-me-thoxyphenyl)-5,6-dihydro-*s*-triazolo[3,4-

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

Compd	Yield (%)	m.p. °C	Mol.formula	Found (Calc.) (%) C	H	N	^{1}HNMR ($CDCl_3$/$CDCl_3$ + DMSO-d_6) δ , ppm	Antiinflammatory activity (% Inhibition)
3a	59	220-21	$C_{18}H_{14}Cl_2N_4OS$	53.37 (53.33	3.41 3.45	13.79 13.82)	3.9 (s, 3H, -OCH_3) , 5.9 (bs , 1H , NH), 6.5 (d,1H ,CH) , 6.9 - 8.0 (m,8H, Ar-H and d buried 1H , -CH = C)	31.42
3b	58	166-67	$C_{18}H_{14}Cl_2N_4S$	55.50 (55.52	3.64 3.59	14.36 14.39)	4.2 (s,2H,Ar-CH_2) , 5.7 (bs,1H,NH), 6.4(d,1H,CH), 7.0 - 8.0 (m, 9H, Ar-H and d buried 1H, - CH = C)	12.0
3c	65	233	$C_{18}H_{14}Cl_2N_4S$	55.49 (55.52	3.57 3.59	14.37 14.39)	2.3 (s,3H, -CH_3) ,5.9(bs,1H,NH), 6.5 (d,1H,CH),6.9 - 8.1(m, 8H, Ar-H and d buried 1H, -CH =C)	38.57
3d	69	228 - 29	$C_{12}H_{10}Cl_2N_4S$	45.97 (46.00	3.15 3.19	17.93 17.89)	2.3(s,3H, -CH_3), 5.8(bs,1H,NH), 6.5 (d,1H,CH), 7.3 - 7.8 (m,4H, Ar-H and d buried 1H, -CH =C)	9.63
3e	65	183	$C_{13}H_{12}Cl_2N_4S$	47.69 (47.70	3.64 3.66	17.07 17.12)	1.3 (t,3H, -CH_2-CH_3), 2.8 (q, 2H,-CH_2CH_3), 5.9(bs, 1H,NH) , 6.4(d,1H,CH), 7.5 - 8.0 (m, 4H, Ar-H and d buried 1H, -CH =C)	26.0

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

Compd	Yield	m.p °C.	Mol. formula	Found (Calc.) (%)			^{1}HNMR($CDCl_3$/$CDCl_3$+DMSO-d_6)	Antiinflammatory activity
3f	60	138	$C_{14}H_{14}Cl_2N_4S$	49.25 (49.26	4.09 4.10	16.39 16.42)	1.1(t ,3H,-CH_2CH_3) ,1.9(m,2H,-$CH_2CH_2CH_3$), 2.8(t,2H, -$CH_2CH_2CH_3$), 5.9(bs,1H,NH), 6.4(d,1H,CH),7.5 - 8.0 (m,4H,Ar-H and d buried 1H , -CH=C)	15.66
3g	62	185-86	$C_{19}H_{17}ClN_4O_2S$	56.90 (56.92	4.21 4.24	13.96 13.98)	3.9 (s,6H,2x-OCH_3), 5.9(bs,1H,NH), 6.4(d,1H,CH), 6.9 - 8.0(m, 8H, Ar-H and d buried 1H,-CH=C)	31.42
3h	65	169	$C_{19}H_{17}ClN_4OS$	59.27 (59.29	4.38 4.42	14.63 14.56)	3.8(s,3H,-OCH_3), 4.3(s,2H,Ar-CH_2), 5.9(bs,1H,NH),6.4(d,1H,CH),6.8-8.0 (m, 9H, Ar-H and d buried 1H,-CH=C)	31.42
3i	60	210-11	$C_{19}H_{17}ClN_4OS$	59.25 (59.29	4.37 4.42	14.59 14.56)	2.3(s,3H,-CH_3),3.9(s,3H,-OCH_3), 5.8(bs,1H,NH),6.3(d,1H,CH),6.8-8.0 (m, 8H, Ar-H and d buried 1H,-CH=C)	10.0
3j	65	214	$C_{13}H_{13}ClN_4OS$	50.61 (50.56	4.17 4.21	18.14 18.15)	2.2(s,3H,-CH_3), 3.9(s,3H,-OCH_3), 5.9(bs,1H,NH) , 6.5(d,1H,CH),6.7-8.0 (m, 4H, Ar-H and d buried 1H, -CH=C)	39.21
3k	62	192-93	$C_{14}H_{15}ClN_4OS$	52.05 (52.09	4.61 4.65	17.38 17.36)	1.3(t,3H,-CH_2CH_3), 2.9(q, 2H,-CH_2CH_3), 3.9(s,3H,-OCH_3),5.9(bs,1H,NH),6.4 (d,1H,CH) , 6.8-8.0 (m, 4H, Ar-H and d buried 1H, -CH=C)	22.4
3l	50	121	$C_{15}H_{17}ClN_4OS$	53.46 (53.49	5.01 - 5.05	16.68 16.64)	1.1(t,3H,-$CH_2CH_2CH_3$),2.0(m,2H,-$CH_2CH_2CH_3$), 2.9(t,2H,-$CH_2CH_2CH_3$),3.9(s,3H,-OCH_3),5.8 (bs,1H,NH),6.4(d,1H,CH),6.8-8.0(m, 4H, Ar-H and d buried 1H, -CH=C)	33.73
3m	75	240	$C_{18}H_{14}BrClN_4OS$	48.01 (48.05	3.08 3.11	12.47 12.45)	3.9(s,3H,-OCH_3),5.9(bs,1H,NH),6.5 (d,1H,CH), 6.9-8.1 (m, 8H, Ar-H and buried IH,-CH=C)	18.29
3n	70	154-55	$C_{18}H_{14}BrClN_4S$	49.80 (49.82	3.20 3.22	12.95 12.91)	4.3(s,2H,Ar-CH_2), 5.9(bs,1H,NH),6.4 (d,1H,CH),7.0-8.0 (m, 8H, Ar-H and d buried 1H,-CH=C)	11.72
3o	68	228-29	$C_{18}H_{14}BrClN_4S$	49.80 (49.82	3.24 3.22	12.90 12.91)	2.3(s,3H,-CH_3),5.9(bs,1H,NH),6.5 (d,1H,CH), 7.0-8.1 (m, 8H, Ar-H and d buried 1H,-CH=C)	37.5
3p	84	219	$C_{12}H_{10}BrClN_4S$	40.25 (40.27	2.76 2.79	15.65 15.66)	2.2(s,3H,-CH_3),5.9(bs,1H,NH),6.5 (d,1H,CH),7.4-8.0(m, 4H, Ar-H and d buried 1H,-CH=C)	22.6
3q	80	186-87	$C_{13}H_{12}BrClN_4S$	42.03 (41.99	3.20 3.23	15.04 15.07)	1.3 (t,3H,-CH_2CH_3), 2.9 (q,2H,-CH_2CH_3), 5.9(bs,1H,NH), 6.4(d,1H,CH), 7.6-8.0 (m, 4H, Ar-H and d buried 1H,-CH=C)	12.0
3r	72	143	$C_{14}H_{14}BrClN_4S$	43.52 (43.57	3.60 3.63	14.55 14.52)	1.1(t,3H,-$CH_2CH_2CH_3$),1.9(m,2H,-$CH_2CH_2CH_3$), 2.9(t,2H,-$CH_2CH_2CH_3$),5.9(bs,1H,NH), 6.4 (d,1H,CH),7.4-8.0(m,4H, Ar-H and d buried 1H,-CH=C)	34.3

***b*][1,3,-4]thiadiazole 3a : General procedure.** An equimolar mixture of 4-amino-5-mercapto-3- (4-methoxyphenyl)-*s*-triazole (1.11g, 0.005 mole), *p*-chloro-β-chlorocinnamaldehyde (1.0 g, 0.005 mole), *p*-TsOH (20 mg) in dry benzene (75 mL) was heated under reflux for 10 hr using Dean-Stark device for the separation of evolved water. The solvent was removed and the residue extracted with chloroform (75mL). The organic layer was washed with water (2×50 mL), dried over anhyd. Na_2SO_4 and the solvent evaporated. The residue obtained, was crystallised from MeOH as white needles (1.19 g), m.p. 220-21°C.

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

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