Synthesis and Antiinflammatory Activity of Some 1,4-Dihydro-3-methyl-1-(2-thiazolyl)pyrazolo[4,3-*c*][1,2]benzothiazine 5,5-Dioxides

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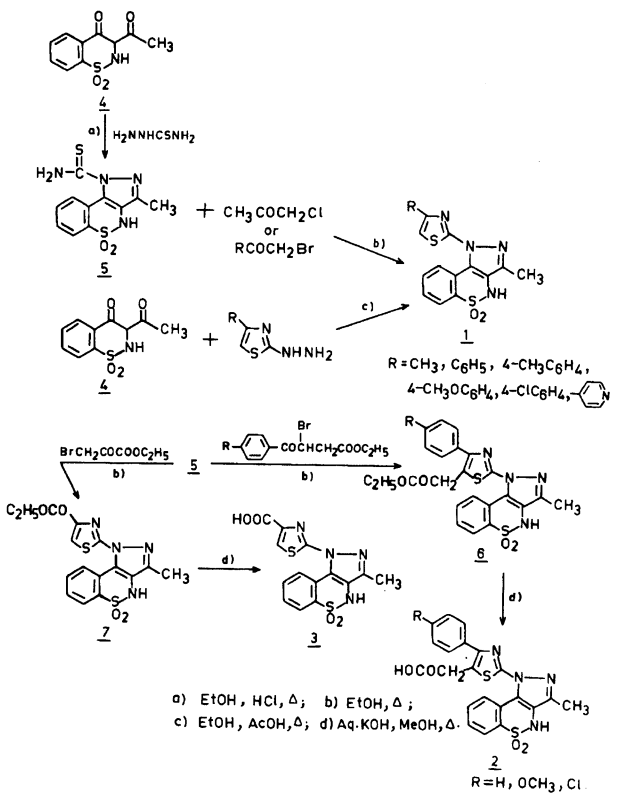
Synopsis. Condensation of 1,4-dihydro-3-methyl-1-thiocarbamoylpyrazolo[4,3-*c*][1,2]benzothiazine 5,5-dioxide with various phenacyl bromides, ethyl 3-aroyl-3-bromopropionates, and ethyl bromopyruvate afforded 1,4-dihydro-3-methyl-1-(2-thiazolyl)pyrazolo[4,3-*c*][1,2]benzothiazine-5,5 dioxides, which were also prepared by an alternate route in order to confirm their structure, were tested for antiinflammatory activity by carrageenan-induced rat paw edema test. The compounds have shown moderate to good activity.

Several 1,2-benzothiazine 1,1-dioxides have been reported to possess clinical level of antiinflammatory activity.[1,2] This activity is also associated with many thiazole derivatives.[3,4] It was therefore considered worthwhile to synthesize compounds with both the moieties in the same molecule and screen them for antiinflammatory activity. We report in this paper the synthesis and antiinflammatory activity of three types of such compounds namely, 1-(4-alkyl or aryl-2-thiazolyl)-1,4-dihydro-3-methylpyrazolo[4,3-*c*][1,2]benzothiazine 5,5-dioxides (**1**), 1-(4-aryl-5-carboxymethyl-2-thiazolyl)-1,4-dihydro-3-methylpyrazolo[4,3-*c*][1,2]benzothiazine 5,5-dioxides (**2**) and 1-(4-carboxy-2-thiazolyl)-1,4-dihydro-3-methylpyrazolo[4,3-*c*][1,2]benzothiazine 5,5-dioxide (**3**). These compounds have been synthesized according to the reaction sequence shown in Scheme 1.



Scheme 1.

3-Acetyl-2,3-dihydro-4*H*-1,2-benzothiazin-4-one 1,1-dioxide (**4**)[5] was obtained by the ring expansion reaction of 2-acetonylsaccharin.[6] Compound **4**, on treatment with thiosemicarbazide, afforded 1-thiocarbamoyl-1,4-dihydro-3-methylpyrazolo[4,3-*c*][1,2]benzothiazine 5,5-dioxide (**5**) in 61% yield. The IR spectrum of **5** displayed peaks at 3440, 3260, 3160 cm^{-1} (NH str.), 1610 cm^{-1} (NH bend.) and 1350, 1175 cm^{-1} (SO_2 str.). Moreover the peak due to C=O in the IR spectrum of 3-acetyl compound (**4**) was absent in the IR spectrum of **5**. Condensation of **5** with chloroacetone or phenacyl bromides gave **1** in 59—66% yield (Table 1). In order to confirm the structure of compounds **1**, they were also synthesized by an alternate route by the condensation of 3-acetyl-2,3-dihydro-4*H*-1,2-benzothiazin-4-one 1,1-dioxide (**4**) with 4-aryl-2-hydrazinothiazoles[7] in 57—61% yield.

Compound **5**, on condensation with various ethyl 3-aroyl-3-bromopropionates, gave 1-(4-aryl-5-ethoxycarbonylmethyl-2-thiazolyl)-1,4-dihydro-3-methylpyrazolo-[4,3-*c*][1,2]benzothiazine 5,5-dioxides (**6**) in good yields (62—71%, cf. Table 1) which on alkaline hydrolysis in methanol followed by acidification afforded the corresponding acids (**2**) in 88—93% yield (Table 1). The IR spectra of all the esters (**6**) showed an intense peak between 1737—1722 cm^{-1} (C=O str.) apart from peaks between 3260—3122 cm^{-1} (NH str.) and 1320—1311, 1179—1160 cm^{-1} (SO_2 str.). The hydrolyzed acids (**2**) show apart from a band between 1714—1699 cm^{-1} (C=O str.), a broad band in the region 2800—2600 cm^{-1} (hydrogen bonded O–H str.) and peaks between 3210—3103 (NH str.), 1331—1317, 1164—1151 cm^{-1} (SO_2 str.). The characteristic triplet–quartet pattern present in the ^1H NMR spectra of esters (**6**) was absent in the ^1H NMR spectra of **2**. The CH_2 protons of CH_2COOH group in **2** appear as a singlet at $\delta=3.7$.

Condensation of **5** with ethyl bromopyruvate proceeded smoothly in ethanolic solution giving the required 1-(4-ethoxycarbonyl-2-thiazolyl)-1,4-dihydro-3-methylpyrazolo[4,3-*c*][1,2]benzothiazine 5,5-dioxide (**7**) in 69% yield which on alkaline hydrolysis in methanol afforded the corresponding acid (**3**). The IR spectrum of ester (**7**) showed a band at 1720 cm^{-1} (C=O str.), whereas the acid (**3**) showed a peak at 1694 cm^{-1} (C=O

Table 1. Characterization Data of New Compounds Prepared (**1**, **2**, **6**)

Compd[a]	R	Mp	Yield	Mol. formula	Found (%) (Calcd)		
		°C	%	(M^+)[b]	C	H	N
1a	CH_3	214	62	$C_{14}H_{12}N_4O_2S_2$ (332.0255)	50.9 (50.6)	3.8 (3.6)	16.6 (16.9)
1b	C_6H_5	233	66,61[c]	$C_{19}H_{14}N_4O_2S_2$ (394.0459)	58.2 (57.9)	3.9 (3.6)	14.0 (14.2)
1c	4-$CH_3C_6H_4$	253	66,59[c]	$C_{20}H_{16}N_4O_2S_2$ (408.0643)	58.6 (58.8)	4.1 (3.9)	13.6 (13.7)
1d	4-$CH_3OC_6H_4$	220	59,57[c]	$C_{20}H_{16}N_4O_3S_2$ (424.0386)	56.9 (56.6)	4.0 (3.8)	13.3 (13.2)
1e	4-ClC_6H_4	285	61,58[c]	$C_{19}H_{13}ClN_4O_2S_2$	53.5 (53.2)	3.1 (3.0)	13.4 (13.1)
1f	4-Pyridyl	280	62	$C_{18}H_{13}N_5O_2S_2$	54.7 (54.7)	3.3 (3.3)	18.0 (17.7)
6a	H	180	71	$C_{23}H_{20}N_4O_4S_2$ (480.0618)	57.2 (57.5)	4.4 (4.2)	11.5 (11.7)
6b	OCH_3	176	62	$C_{24}H_{22}N_4O_5S_2$ (510.0952)	56.3 (56.5)	4.5 (4.3)	11.2 (11.0)
6c	Cl	208	70	$C_{23}H_{19}ClN_4O_4S_2$	53.9 (53.6)	3.7 (3.7)	11.0 (10.9)
2a	H	235	90	$C_{21}H_{16}N_4O_4S_2$	56.0 (55.8)	3.7 (3.5)	12.7 (12.4)
2b	OCH_3	202	93	$C_{22}H_{18}N_4O_5S_2$	54.5 (54.8)	3.6 (3.7)	11.5 (11.6)
2c	Cl	298	88	$C_{21}H_{15}ClN_4O_4S_2$	52.1 (51.8)	3.2 (3.1)	11.7 (11.5)

a) All the compounds were crystallized from ethanol. b) Correct masses were found by HRMS. c) Yield by method B.

str.) and a broad band in the region 2800—2600 cm^{-1} (hydrogen bonded O–H str. of acid) besides other peaks.

Antiinflammatory Activity. The compounds (**1**—**3**) were tested for antiinflammatory activity by acute carrageenan-induced rat paw edema test.[8] The compounds were administered as suspension in gum acacia (1% w/v) in normal saline. Male albino Charles Foster rats weighing between 110 and 140 g were divided into groups of four each. Edema was induced by injecting 0.1 ml of carrageenan solution into the left hind paw. The compounds were administered at a dose of 100 mg kg^{-1} orally one hour before or intraperitoneally half an hour before carrageenan injection. In every set of experiments, one group of rats was kept as control and administered only the vehicle 1% gum acacia, whereas another group received a standard drug (Ibuprofen) for comparison. The results were evaluated as percent inhibition as compared with the control group. Local irritant action was tested by applying different concentrations of test compounds on rabit cornea.[9] The results are given in Table 2.

Table 2. Antiinflammatory Activity of Compounds **1**—**3** on Oral (p.o.) and Intraperitoneal (i.p.) Administration[a]

Compd	Percent inhibition			
	(p.o.)		(i.p.)	
	2 h	3.5 h	2 h	3.5 h
1a	19	—	34	35
1b	17	5	61	47
1c	—	—	30	37
1d	—	5	61	40
1e	7	22	65	64
1f	36	22	53	34
2a	32	19	66	46
2b	41	16	53	40
2c	34	22	38	29
3	30	12	53	59
Ibuprofen	62	65	70	74

a) Each value is the mean of four anomals.—Denotes inhibition below 5%.

Although the compounds tested do not follow any general pattern in exhibiting AI activity, certain observations are worth mentioning. Most of the compounds show higher inhibition when administered intraperitoneally as compared to the oral route. The activity reduces rapidly with the passage of time as inhibition measured after 2 h period is generally more than that observed after 3.5 h indicating thereby that these compounds are rapidly metabolised in the system. Compounds of the series **2** showed moderate activity with inhibition varying from 32—41% (p.o.). Compounds belonging to the series **1** were less active; the highest activity was shown by compound **1f** with 36% inhibition (p.o.). Compound **3** showed inhibition of 30% (p.o.).

Experimental

Melting points were determined in open capillaries in a sulfuric acid bath and are uncorrected. IR spectra were scanned as Nujol mulls on a Perkin–Elmer 842 infrared spectrophotometer (ν_{max} in cm^{-1}). ^1H NMR spectra were recorded on a Perkin–Elmer R-32 (90 MHz) instrument using TMS as internal standard and mass spectra at 70 eV on MS-12, DS-55 and MS.30/DS 50S mass spectrometer.

3-Acetyl-2,3-dihydro-4*H*-1,2-benzothiazin-4-one 1,1-dioxide (**4**),[5] 4-aryl-2-hydrazinothiazoles,[7] ethyl 3-aroyl-3-bromopropionates,[10] and ethyl bromopyruvate[11] were prepared according to literature methods.

1, 4- Dihydro- 3- methyl- 1- thiocarbamoylpyrazolo [4,3-*c*][1,2]benzothiazine 5,5-Dioxide (5). A mixture of 3-acetyl-2,3-dihydro-4*H*-1,2-benzothiazin-4-one 1,1-dioxide (**4**; 2.39 g, 0.01 mol) and thiosemicarbazide (0.91 g, 0.01 mol) in ethanol (50 ml) containing a few drops of concd hydrochloric acid was heated under reflux for 6 h. The solution was evaporated to the half volume and cooled. The solid which separated out was collected, dried and crystallized from ethanol, mp 201—202 °C, yield 1.8 g (61%); IR 3440, 3260, 3160 (NH str.), 1610 (NH bend), 1350, 1175 cm^{-1} (SO_2 str.); ^1H NMR ($CDCl_3$) δ=2.4 (s, 3H, CH_3), 7.8—8.3 (m, 5H, Ar-H and ring NH), 9.4 (bs, $CSNH_2$). Found: C, 44.8; H, 3.3; N, 19.0%. Calcd for $C_{11}H_{10}N_4O_2S_2$: C, 44.9; H, 3.4; N, 19.0%.

1- (4- Phenyl- 2- thiazolyl)- 1, 4- dihydro- 3- methylpyrazolo[4,3- *c*][1,2]benzothiazine 5,5-Dioxide (1b). Method A. A mixture of 1-thiocarbamoyl-1,4-dihydro-3-methylpyrazolo[4,3-*c*][1,2]benzothiazine 5,5-dioxide (**5**; 1.47 g, 0.005 mol) and phenacyl bromide (1.0 g, 0.005 mol) in ethanol (30 ml) was heated under reflux for 6 h. The volume was reduced to half and the solid which separated out was collected by filtration and treated with sodium hydrogencarbonate solution (2%). The product was collected by filtration, washed with water, dried, and crystallized from ethanol, mp 233 °C, yield 1.3 g (66%); IR 3270 (NH str.), 1320, 1178 cm^{-1} (SO_2 str.); ^1H NMR (DMSO-d_6/$CDCl_3$) δ=2.35 (s, 3H, CH_3), 7.1—8.1 (m, 1OH, Ar-H, thiazole 5-H and ring NH), 8.5—8.7 (m, 1H, Ar-H). MS: $M^{+\cdot}$ at m/z 394.0459. Calcd for $M^{+\cdot}$, 394.0569.

Method B. A mixture of 2-hydrazino-4-phenylthiazole (1.16 g, 0.005 mol) and 3-acetyl-2,3-dihydro-4*H*-1,2-benzothiazin-4-one 1,1-dioxide (**4**; 1.19 g, 0.005 mol) in ethanol (30 ml) containing few drops of glacial acetic acid was heated under reflux for 6 h. After cooling, the separated solid was collected by filtration, dried, and crystallized from ethanol, mp 233 °C, yield 1.2 g (61%). Mixed melting point with the sample obtained by method A undepressed and IR spectra superimposable.

Other compounds in the series were similarly prepared and are listed in Table 1.

1- (Ethoxycarbonylmethyl- 4- phenyl- 2- thiazolyl)- 1, 4- dihydro- 3- methylpyrazolo[4, 3- *c*][1, 2]benzothiazine 5,5-Dioxide (6a). To a solution of **5** (1.47 g, 0.005 mol) in ethanol (25 ml) was added a solution of ethyl 3-benzoyl-3-bromopropionate (1.43 g, 0.005 mol) in ethanol (20 ml). The reaction mixture was refluxed for 4 h cooled and kept overnight. The crystalline solid which separated out was collected by filtration and treated with sodium hydrogencarbonate solution (2%). The product was collected by filtration, washed with water, dried, and crystallized from ethanol, mp 180 °C, yield 1.8 g (71%); IR 3122 (NH str.), 1737 (C=O str.), 1320, 1165 cm^{-1} (SO_2 str.); ^1H NMR (DMSO-d_6/$CDCl_3$) δ=1.2 (t, 3H, $CH_2COOCH_2CH_3$), 2.25 (s, 3H, CH_3), 3.8 (s, 2H, $CH_2COOC_2H_5$), 4.1 (q, 2H, $COOCH_2CH_3$), 7.1—8.6 (m, 10H, Ar-H and ring NH). MS: $M^{+\cdot}$ at m/z 480.0618. Calcd for $M^{+\cdot}$, 480.0937.

Other compounds in the series were prepared similarly and are listed in Table 1.

1-(5-Carboxymethyl-4-phenyl-2-thiazolyl)-1,4-dihydro-3-methylpyrazolo[4,3-*c*][1,2]benzothiazine 5,5-Dioxide (2a). To a suspension of **6a** (2.40 g, 0.005 mol) in methanol (10 ml) was added potassium hydroxide solution (7%, 10 ml) and the mixture was heated under reflux for 1 h. After cooling, the solution was filtered from undissolved matter and then acidified with glacial acetic acid. The product so obtained was collected by filtration, washed with water, dried, and crystallized from ethanol, mp 235 °C, yield 2.04 g (90%); IR 3103 (NH str.), 2800—2600 (hydrogen bonded O–H str. of COOH), 1714 (C=O str.), 1331, 1151 cm^{-1} (SO_2 str.); ^1H NMR (DMSO-d_6/$CDCl_3$) δ=2.25 (s, 3H, CH_3), 3.8 (s, 2H, CH_2COOH), 7.1—8.5 (m, 1OH, Ar-H and ring NH).

1- (4- Ethoxycarbonyl- 2- thiazolyl)- 1, 4- dihydro- 3- methylpyrazolo[4,3- *c*][1,2]benzothiazine 5,5-Dioxide (7). To a solution of **5** (1.47 g, 0.005 mol) in absolute ethanol (25 ml) was added ethyl bromopyruvate (1.0 g, 0.005 mol). The temperature of the reaction mixture rose to 60 °C rapidly and a yellow color developed. After heating the reaction mixture under reflux for 5 h, the excess of ethanol was distilled off and the contents were treated with dilute ammonia solution and extracted with pet. ether. The solvent was distilled off and the residual product crystallized from pet. ether, mp 238 °C, yield 1.34 g (69%); IR 3120 (NH str.), 1720 (C=O str.), 1331, 1151 cm^{-1} (SO_2 str.); ^1H NMR (DMSO-d_6/$CDCl_3$) δ=1.3 (t, 3H, $COOCH_2CH_3$), 2.25 (s, 3H, CH_3), 4.25 (q, 2H, $COOCH_2CH_3$), 7.2—8.7 (m, 6H, Ar-H, thiazole 5-H and ring NH). Found: C, 49.4; H, 3.8; N, 14.2%. Calcd for $C_{16}H_{14}N_4O_4S_2$: C, 49.2; H, 3.6; N, 14.4%. MS: $M^{+\cdot}$ at m/z 389.9883. Calcd for $M^{+\cdot}$, 390.0468.

1-(4-Carboxy-2-thiazolyl)-1,4-dihydro-3-methylpyrazolo[4,3-*c*][1,2]benzothiazine 5,5-Dioxide (3). It was prepared in an analogous manner as **2**, mp 273 °C, yield 1.6 g (88%); IR 3200 (NH str.), 2800—2600 (hydrogen bonded O–H str. of COOH), 1694 (C=O str.), 1317, 1171 cm^{-1} (SO_2 str.); ^1H NMR δ=2.25 (s, 3H, CH_3), 7.2—8.5 (m, 6H, Ar-H, thiazole 5-H and ring NH). Found: C, 46.2; H, 2.9; N, 15.3%. Calcd for $C_{14}H_{10}N_4O_4S_2$: C, 46.4; H, 2.8; N, 15.5%.

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