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# Synthesis and antiinflammatory activity of some 3-(2-thiazolyl)-1,2-benzisothiazoles

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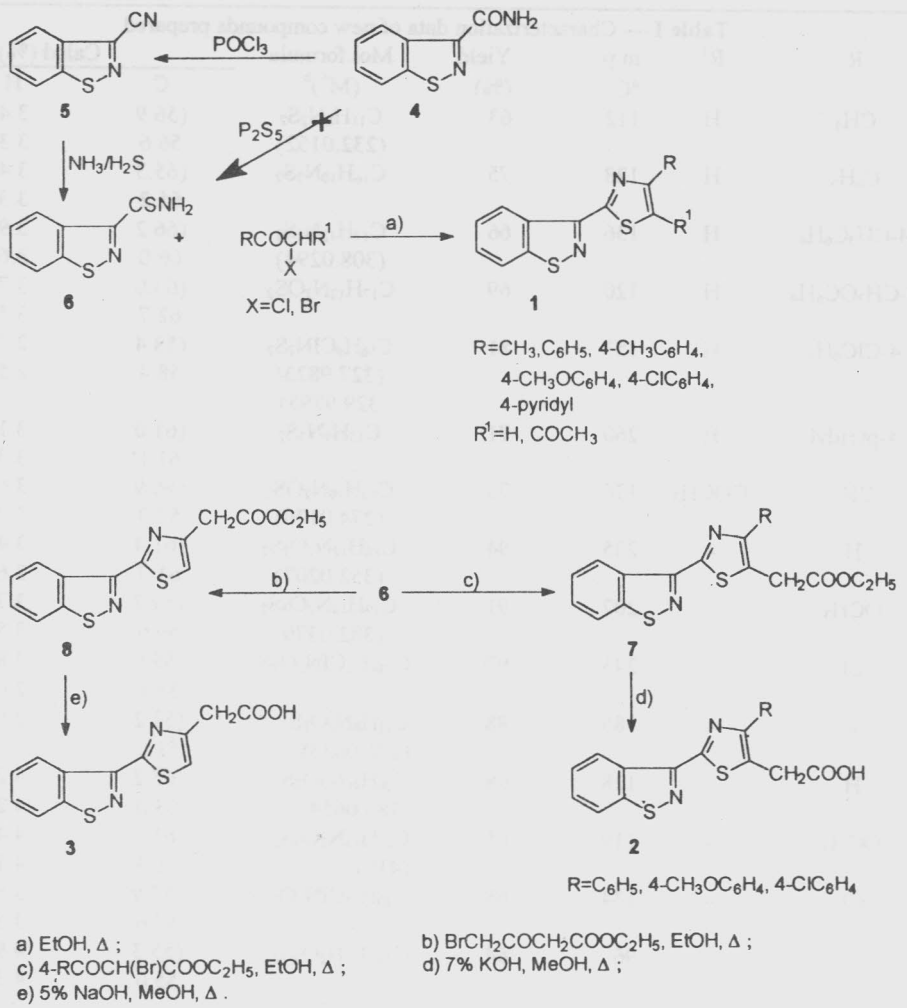
Four types of benzisothiazole derivatives, 3-(4-alkyl/aryl-2-thiazolyl)/1,2-benzisothiazoles **1a-f** 3-(4-aryl-5-carboxymethyl-2-thiazolyl)-1,2-benzisothiazoles **2**, 3-(4-carboxymethyl-2-thiazolyl)-1,2-benzisothiazole **3** and 3-(5-acetyl-4-methyl-2-thiazolyl)-1,2-benzisothiazole **1g** have been synthesized as potential antiinflammatory agents. All the target compounds and some selected intermediates have been assayed for their antiinflammatory activity. some of these compounds possess excellent level of antiinflammatory activity.

The search for more effective non-steroidal antiinflammatory drugs (NSAIDs) has led medicinal chemists to explore a wide variety of chemical structures. A majority of these compounds, especially those with proven clinical efficacy, are acidic in nature such as aspirin, indomethacin, flufenamic acid, ibuprofen, etc. Since the discovery of aspirin, much efforts have been concentrated to the development of acedic NSAIDs and some of these, having an acetic acid grouping[1,2] are found to possess significant antiinflammatory activity. Appreciation of these findings and as a part of our ongoing programme[3,4] towards the development of NSAIDs, coupled with the observation that several 1,2-benzisothiazoles and their 1,1-dioxides possess good antiinflammatory activity[5], our attention has been directed on the variation of the 1,2-benzisothiazole moiety by introducing heterocyclic systems bearing acetic acid function with a view to synthesize new analogues with improved antiinflammatory activity[6]. In this communication, we report the synthesis of a few series of compounds such as 3-(4-alkyl or arylthiazol-2-yl)-1,2-benzisothiazoles **1a-f**, 3-(5-acetyl-4-methylthiazol-2-yl)-1,2-benzisothiazole **1g**, 3-(4-aryl-5-carboxymethyl-thiazol-2-yl)-1,2-benzisothiazoles **2** and 3-(4-carboxymethylthiazol-2-yl)-1,2-benzisothiazole **3**. These compounds have been synthesized following the reaction sequence shown in Scheme I.

The conventional method for preparing thioamides by treating the corresponding amides with phosphorus pentasulphide failed to give the hitherto unknown thioamide **6** from 1,2-benzisothiazole-3-carboxamide **4**. So, the required thiocarboxamide **6** was prepared from 1,2-benzisothiazole-3-carboxamide **4** through the 3-cyano compound **5**. The carboxamide **4** on treatment with phosphoryl chloride afforded 1,2-benzisothiazole-3-carbonitrile **5**[7] which on treatment with hydrogen sulphide and ammonia gas in ethanol gave 1,2-benzisothiazole-3-thiocarboxamide **6** in 72% yield. The structure of **6** was established by IR and mass spectra. The IR spectrum displayed peaks at 3342, 3273, 3184 (NH str.) and 1622 $cm^{-1}$ (NH bend.). Moreover, the absorption peak due to CN in the IR spectrum of carbonitrile **5** was absent in the IR spectrum of **6**. The mass spectrum of **6** showed the molecular ion $[M]^+$ at m/z 193.9977 (calcd Mol. wt 193.9978). Condensation of **6** with chloroacetone, phenacyl bromides and 1-acetyl-1-bromoacetone according to the well known Hantzsch thiazole synthesis gave **1** in 66-81% yields (Table I).

Compound **6** on condensation with various ethyl β-aroyl-β-bromopropionates gave 3-(4-aryl-5-carbethoxymethylthiazol-2-yl)-1,2-benzisothiazoles **7** in good yields (65-68%, cf. Table I) which on alkaline hydrolysis in methanol followed by acidification afforded the corresponding acids **2** in 91-97% yields (Table I). The IR spectra of all the esters **7** showed an intense peak at 1730 $cm^{-1}$ (C=O). The hydrolysed acids **2** exhibited apart




**Scheme I**

from a band at 1695 $cm^{-1}$ (C=O), a broad band in the region 2800-2600 $cm^{-1}$ due to hydrogen bonded OH stretching. The characteristic triplet-quartet pattern present in the $^1H$ NMR spectra of **7** was absent in the $^1H$ NMR spectra of **2**. The signal for $CH_2$ protons of $CH_2COOH$ group in **2** and **7** appeared as a singlet at δ3.9.

1,2-Benzisothiazole-3-thiocarboxamide **6** also underwent condensation with ethyl γ-bromoacetoacetate smoothly in ethanolic solution giving the required 3-(4-carbethoxymethylthiazol-2-yl)-1,2-benzisothiazole **8** in 64% yield which on basic hydrolysis with 5% sodium hydroxide in methanol afforded the corresponding acetic acid **3**. The IR spectrum of the ester **8** showed a band at 1725 $cm^{-1}$ (C=O), whereas the acid showed peaks at 1695 (C=O) and a broad peak in the region 2800-2600 $cm^{-1}$ (hydrogen bonded OH of acid). The signal due to $CH_2$ protons of $CH_2COOH$ group appeared as singlet at δ 3.8 in the $^1H$ NMR spectra of **3** and **8.**

**Antiinflammatory activity.** Compounds **1-3,6** and **7** were tested for their antiinflammatory activity by acute carrageenin-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 carrageenin solution into the left hind paw. The compounds were administered at a dose of 100 mg/kg orally one hour before or intraperitoneally half an hour before carrageenin injection. The paw volume of the limbs was measured with a volume differential meter immediately before and 2 hr and 3.5 hr after carrageenin injection. In every set of experiments,

**Table I** — Characterization data of new compounds prepared

| Compd[a] | R | $R^1$ | m.p. °C | Yield (%) | Mol.formula $(M^+)^b$ | Calcd (%) (Found) C | H | N |
|---|---|---|---|---|---|---|---|---|
| **1a** | $CH_3$ | H | 112 | 63 | $C_{11}H_8N_2S_2$ | (56.9 | 3.4 | 12.1) |
| | | | | | (232.0152) | 56.6 | 3.3 | 12.2 |
| **1b** | $C_6H_5$ | H | 128 | 75 | $C_{16}H_{10}N_2S_2$ | (65.3 | 3.4 | 9.5) |
| | | | | | | 65.2 | 3.3 | 9.4 |
| **1c** | 4-$CH_3C_6H_4$ | H | 136 | 66 | $C_{17}H_{12}N_2S_2$ | (66.2 | 3.9 | 9.1) |
| | | | | | (308.0294) | 66.0 | 3.6 | 9.0 |
| **1d** | 4-$CH_3OC_6H_4$ | H | 120 | 69 | $C_{17}H_{12}N_2OS_2$ | (63.0 | 3.7 | 8.6) |
| | | | | | | 62.7 | 3.5 | 8.6 |
| **1e** | 4-$ClC_6H_4$ | H | 153 | 81 | $C_{16}H_9ClN_2S_2$ | (58.4 | 2.7 | 8.5) |
| | | | | | (327.9823/ 329.9795) | 58.4 | 2.5 | 8.3 |
| **1f** | 4-pyridyl | H | 260 | 71 | $C_{15}H_9N_3S_2$ | (61.0 | 3.1 | 14.2) |
| | | | | | | 61.1 | 3.3 | 14.3 |
| **1g** | $CH_3$ | $COCH_3$ | 176 | 75 | $C_{13}H_{10}N_2OS_2$ | (56.9 | 3.6 | 10.2) |
| | | | | | (274.0176) | 57.0 | 3.7 | 10.0 |
| **2a** | H | – | 235 | 94 | $C_{18}H_{12}N_2O_2S_2$ | (61.4 | 3.4 | 8.0) |
| | | | | | (352.0207) | 61.7 | 3.6 | 8.1 |
| **2b** | $OCH_3$ | – | 207 | 91 | $C_{19}H_{14}N_2O_3S_2$ | (59.7 | 3.7 | 7.3) |
| | | | | | (382.0379) | 59.6 | 3.5 | 7.0 |
| **2c** | Cl | – | 245 | 97 | $C_{18}H_{11}ClN_2O_2S_2$ | (55.9 | 2.8 | 7.2) |
| | | | | | | 55.6 | 2.6 | 7.5 |
| **3** | – | – | 185 | 88 | $C_{12}H_8N_2O_2S_2$ | (52.2 | 2.9 | 10.1) |
| | | | | | (276.0033) | 52.3 | 3.1 | 10.0 |
| **7a** | H | – | 128 | 68 | $C_{20}H_{16}N_2O_2S_2$ | (63.2 | 4.2 | 7.4) |
| | | | | | (380.0654) | 63.0 | 4.2 | 7.3 |
| **7b** | $OCH_3$ | – | 119 | 65 | $C_{21}H_{18}N_2O_3S_2$ | (61.5 | 4.4 | 6.8) |
| | | | | | (410) | 61.4 | 4.1 | 6.7 |
| **7c** | Cl | – | 134 | 68 | $C_{20}H_{15}ClN_2O_2S_2$ | (57.9 | 3.6 | 6.8) |
| | | | | | | 57.6 | 3.5 | 6.5 |
| **8** | – | – | 96 | 64 | $C_{14}H_{12}N_2O_2S_2$ | (55.3 | 4.9 | 9.2) |
| | | | | | | 55.0 | 4.3 | 9.2 |

[a]All the compounds were crystallized from ethanol.
[b]Correct masses were found by HRMS

one group of fats 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 the rabit cornea[9]. The results are given in Table II.

Although the compounds tested do not follow any general pattern in exhibiting AI activity, certain observations are worthmentioning. Most of the compounds show higher inhibition when administered intraperitoneally as compared to the oral route. The activity decreases rapidly with the passage of time as inhibition measured after 2 hr period is generally more than that observed after 3.5 hr indicating thereby that these compounds are rapidly metabolised in the system. Amongst the target compounds the highest activity was exhibited by compound **2c** (inhibition 75% p.o.) followed by **3** with inhibition of 64% (p.o.). Moreover, the compound **2c** had quite high activity (69% inhibition) even at dose level of 50 mg/kg. This is somewhat expected because these compounds (**2c** and **3**) belong to the family of heterocyclyalkanoic acids. The high activity puts these compounds in a class of potential NSAIDS and therefore they have been marked for detailed pharmacological screening. The order of activity shown by the compounds within the series **2** i.e. **2c>2b>2a** is in confirmation of our earlier observation that compounds with chloro or methoxy substituents show higher activity[10]. Another compound **6** has

**Table II** — Antiinflammatory activity of compounds **1-3,6,7** on oral (p.o.) and intraperitoneal (i.p.) administration

| Compd | % inhibition | | | |
|---|---|---|---|---|
| | oral (p.o.) | | intraperitoneal (i.p.) | |
| | 2 hr | 3.5 hr | 2 hr | 3.5 hr |
| **1a** | 32 | 22 | ND | ND |
| **1b** | 7 | 23 | 12 | N |
| **1c** | 9 | N | N | N |
| **1d** | 30 | 7 | 64 | 30 |
| **1e** | 17 | 35 | N | N |
| **1f** | 6 | N | 43 | 29 |
| **1g** | N | 7 | 20 | N |
| **2a** | 15 | 19 | 45 | 7 |
| **2b** | 36 | 33 | 40 | 24 |
| **2c*** | 75 | 62 | 78 | 67 |
| | 69** | 61 | 76 | 64 |
| **3** | 64 | 46 | 55 | 64 |
| **6** | 67 | 61 | 45 | 30 |
| **7a** | 7 | 11 | ND | ND |
| **7b** | 20 | 29 | 34 | 30 |
| **7c** | 34 | 22 | 24 | 13 |
| **Ibuprofen** | 62 | 65 | 70 | 74 |

Each value is the mean of four animals.
N≤10% inhibition
ND denotes not done.
*Value is the mean of eight animals.
**Percent inhibition at 50 mg/kg.

shown activity comparable with that of ibuprofen and has also been chosen for detailed pharmacological study.

## Experimental Section

**General.** Melting points were determined in open capillaries in a sulphuric acid-bath and are uncorrected. IR spectra were scanned as nujol mulls on a Perkin-Elmer 842 infrared spectrophotometer ($\nu_{max}$ in $cm^{-1}$). $^1H$ NMR spectra were recorded on a Perkin-Elmer R-32 (90 MHz) instrument (chemical shifts in δ, ppm) using TMS as internal standard, and mass spectra at 70 eV on MS-12, DS-55 and MS 30/DS 50S mass spectrometers.

1,2-Benzisothiazole-3-carboxamide **4**[11], ethyl β-aroyl-β-bromopropionates[12], ethyl γ-bromoaceto-acetate[13] and 1-acetyl-1-bromoacetone[14] were prepared according to the literature methods.

**1,2-Benzisothiazole-3-carbonitrile 5.** 1,2-Benzisothiazole-3-carboxamide **4** (1.78 g, 0.01 mole) was placed in a round bottomed flask and phosphoryl chloride (5 mL) added to it. The reaction mixture turned hot with the dissolution of the carboxamide. The solution was then refluxed for 1 hr, cooled and poured into cold water. The resulting solid was filtered, dried under vacuum, and crystallized from ethanol, mp 91°C (Lit[7], mp 83-85°C), yield 1.3 g (81%); IR : 2234 (C-N str.).

**1,2-Benzisothiazole-3-thiocarboxamide 6.** 1,2-Benzisothiazole-3-carbonitrile **5** (1.6 g, 0.01 mole) was dissolved in ethanol (20 mL). Ammonia gas was passed through the solution till saturated, followed by passing of the dry hydrogen sulphide gas. The product 1,2-Benzisothiazole-3-thiocarboxamide **6** crystallized out rapidly on standing of the reaction mixture for sometime at room temperature, filtered, washed with cold ethanol, dried and crystallized from ethanol mp 98°C, yield 1.4 g (72%); IR: 3342, 3273, 3184 (NH str.), 1622 (NH bend.); $^1H$ NMR ($CDCl_3$): 7.2-7.6 (m, 2H, Ar-H), 7.6-7.9 (m, 1H, Ar-H), 8.3-8.8 (bs, NH), 9.1-9.4 (m, 1H, Ar-H); MS: $M^+$ at m/z 193.9977; Calcd Mol. wt. 193.9978. Anal. Calcd for $C_8H_6N_2S_2$: C,49.5; H, 3.1; N, 14.4. Found: C, 49.0; H, 3.3; N, 14.0%.

**3-[ 4-(*p*-Toluyl)thiazol--2-yl ]-1,2-benzisothiazole 1c.** A mixture of 1,2-Benzisothiazole-3-thiocarboxamide **6** (1.94 g, 0.01 mole) and *p*-methylphenacyl bromide (2,13 g, 0.01 mole) in ethanol (50 mL) was refluxed for 6 hr. The volume was reduced to half and the solid which separated out was filtered and treated with aqueous ammonia. The product was collected by filteration, washed with water, dried and crystallized from ethanol, mp 136°C, yield 2.0 g (66%); IR: No absorption in the region 3400-3100 and 1800-1650 (NH and C=O absent); $^1H$ NMR ($CDCl_3$) : 2.4 (s, 3H, $CH_3$), 7.1-8.1 (m, 8H, Ar-H and thiazole 5-H), 9.1-9.4 (m, 1H, Ar-H); MS : $M^+$ at m/z 308.0294; Calcd Mol. wt. 308.0447.

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

**3-[ 4-(*p*-Anisyl)-5-carbethoxymethylthiazol-2-yl ]-1,2-benzisothiazole 7b.** To a solution of 1,2-benzisothiazole-3-thiocarboxamide **6** (1.94 g, 0.01 mole) in ethanol (25 mL) was added a solution of ethyl β-(*p*-anisoyl)-β-bromopropionate (2.85 g, 0.01 mole) in ethanol (25 mL). The reaction mixture was refluxed for 4 hr, cooled and kept overnight. The crystalline solid which separated out was filtered, washed with sodium bicarbonate solution (2%) and then with water, dried and crystallized from ethanol, mp 119°C, yield 2.7 g

(65%); IR : 1730 (C=O str. of $COOC_2H_5$); $^1H$ NMR ($CDCl_3$) : 1.25 (t, 3H, $COOCH_2CH_3$), 3.8 (s, 3H, $OCH_3$), 3.9 (s, 2H, $CH_2COOC_2H_5$), 4.2 (q, 2H, $COOCH_2CH_3$), 6.8-8.0 (m, 7H, Ar-H); MS : $M^+$ at m/z 410; Calcd mol. wt. 410.

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

**3-[ 4-(*p*-Anisyl)-5-carboxymethylthiazol-2-yl ]-1,2-benzisothiazole 2b**. To a solution of 3-[ 4-(*p*-anisyl)-5-carbethoxymethylthiazol-2-yl ]-1,2-benzisothiazole **7b** (4.10 g, 0.01 mole) in methanol (20 mL) was added potassium hydroxide solution (7%, 20 mL) and the mixture heated under reflux for 1 hr. After cooling, the solution was filtered from any undissolved matter and the filtrate acidified with glacial acetic acid. The product so obtained was filtered, washed with water, dried and crystallized from ethanol, mp 207°C, yield 3.48 g (91%); IR : 2800-2600 (hydrogen bonded OH of COOH), 1694 (C=O str.); $^1H$ NMR (DMSO-$d_6$ $CDCl_3$) : 3.8 (s, 3H, $OCH_3$), 3.9 (s, 2H, $CH_2COOH$), 6.7-8.1 (m, 7H, Ar-H), 8.9-9.2 (m, 1H, Ar-H),; MS: $M^+$ at m/z 382.0379; Calcd Mol. wt. 382.0451.

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

**3-(4-carbethoxymethylthiazol-2-yl)-1,2-benzisothiazole 8**. To an ice cold solution of ethyl γ-bromoactoacetate (2.09 g, 0.01 mole) in ethanol (15 mL) was added a solution of 1,2-benzisothiazole-3-thiocarboxamide **6** (1.94 g, 0.01 mole) in ethanol (20 mL) and the mixture stirred for 15 hr. The unreacted ester was removed on shaking with ether. The aqeous layer was neutralized with aqeous sodium bicarbonate. The solid which separated out was filtered, washed with sodium bicarbonate solution (2% and then with water, dried and crystallized from ethanol, mp 96°C, yield 1.95 g (64%); IR : 1725 (C=O str. of $COOC_2H_5$); $^1H$ NMR ($CDCl_3$): 1.3 (t, 3H, $COOCH_2CH_3$), 3.95 (s, 2H, $CH_2COOC_2H_5$), 4.2 (q, 2H, $COOCH_2CH_3$), 7.2-8.1 (m, 4H, Ar-H and thiazole 5-H), 9.0-9.3 (m, 1H, Ar-H). Anal. Calcd. for $C_{14}H_{12}N_2O_2S_2$: C, 55.3; H, 3.9; N, 9.2. Found: C, 55.0; H, 4.3; N, 9.2%.

**3-(4-carboxymethylthiazol-2-yl)-1,2-benzisothiazole 3**. A suspension of 3-(4-carbethoxymethylthiazol-2-yl)-1,2-benzisothiazole **8**. (1.25 g, 0.005 mole) in sodium hydroxide solution (5%, 25 mL) was refluxed for 2 hr, cooled and diluted with water. It was filtered to remove any undissolved impurity and the filtrate rendered acidic with acetic acid. The solid product, thus obtained, was filtered, washed with water, dried and crystallized from ethanol, mp 185°C, yield 1.2 g (88%); IR : 2800-2600 (hydrogen bonded O-H of COOH), 1695 (C=O str.); $^1H$ NMR (DMSO-$d_6$/$CDCl_3$) : 3.8 (s, 2H, $CH_2COOH$), 6.9-8.1 (m, 4H, Ar-H and thiazole 5-H), 8.8-9.2 (m, 1H, Ar-H); MS : $M^+$ at m/z 276.0033; Calcd. Mol. wt. 275.9758. Anal. Calcd for $C_{12}H_8N_2O_2S_2$: C, 52.2; H, 2.9; N, 10.1. Found: C, 52.3; H, 3.1; N, 10.0%.

**3-(5-Acetyl-4-methylthiazol-2-yl)-1,2-benzisothiazole 1g**. To a solution of 1-acetyl-1-bromoacetone in ethanol (30 mL) was added a solution of 1,2-benzisothiazole-3-thiocarboxamide **6** (1.94 g, 0.01 mole) in ethanol (15 mL) and the mixture refluxed for 3 hr. The crystalline solid which separated out on cooling was filtered and treated with aqeous ammonia. The solid product was collected by filtration, washed with water, dried and crystallized from ethanol, mp 176°C, yield 2.05 g (75%); IR : 1667 (C=O str.); $^1H$ NMR ($CDCl_3$): 2.6 (s, 3H, $CH_3$), 2.85 (s, 3H, $COCH_3$), 7.1-8.1 (m, 3H, Ar-H), 9.0-9.3 (m, 1H, Ar-H); MS : $M^+$ at m/z 274.0176; Calcd. Mol. wt. 274.0240. Anal. Calcd for $C_{13}H_{10}N_2OS_2$: C, 56.9; H, 3.6; N, 10.2. Found: C, 57.0; H, 3.7; N, 10.0%.

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