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POTENT ANTIINFLAMMATORY 3-THIAZOLE-4(5)-ACETIC ACIDS OF 1,2-BENZISOTHIAZOLE

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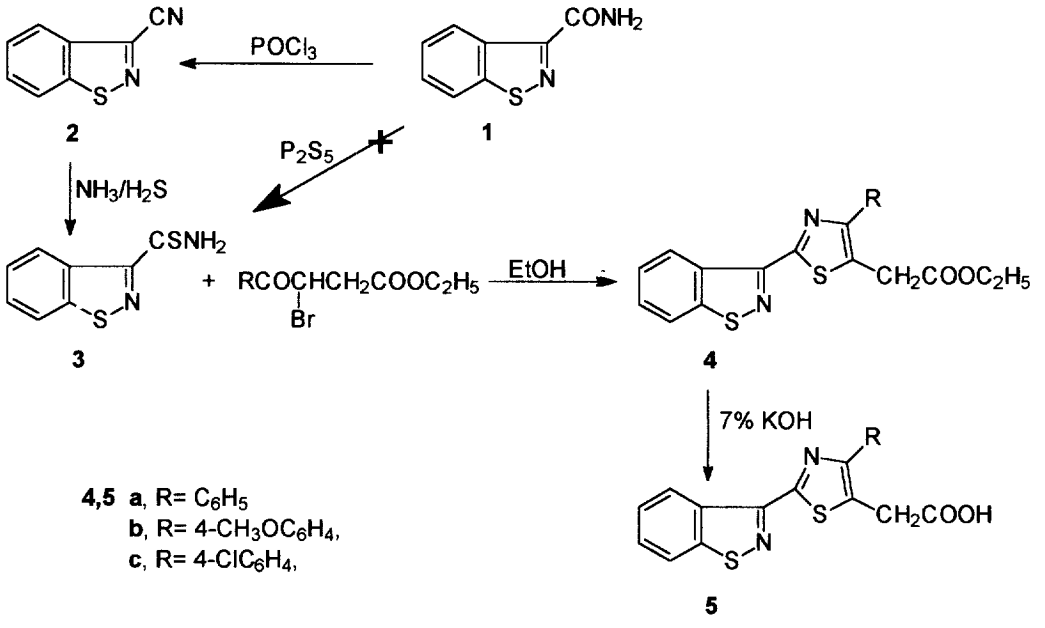
Abstract : A number of 1,2-benzisothiazole derivatives, having 2-thiazolyl-4(5)-acetic acid moiety attached to position-3 of 1,2-benzisothiazole nucleus, were prepared and evaluated as antiinflammatory agents. Some of these were found to possess excellent level of antiinflammatory activity in carrageenin-induced rat paw edema assay.

The search for more effective antiinflammatory agents has led medicinal chemists to explore a wide variety of chemical structures[1,2]. A majority of these compounds, especially those with proven clinical efficacy, are acidic in nature such as aspirin, indomethacin, flufenamic acid, ibuprofen, etc., or β-diketones such as phenylbutazone, etc. Since the discovery of aspirin, much efforts have been devoted to the development of acidic Non-Steroidal Antiinflammatory Drugs (NSAIDs) and some of these, having an acetic acid grouping[3,4] are found to possess significant antiinflammatory activity. Although these drugs reduce symptoms of chronic inflammatory disease but they are by no means free from irritant side effects[5]. Therefore, investigations of new antiinflammatory agents are still continuing with a hope to find an ideal NSAID. The carrageenin-induced rat paw edema model has been used as a popular model for preliminary screening for such antiinflammatory agents[6].

During the last two decades, several kinds of biological activities have been claimed for 1,2-benzisothiazoles[7,8]. It's 5- and 3-acetic acid derivatives possess some antiinflammatory activity[9]. Some thiazole-4(5)-acetic acid derivatives are also known to possess antiinflammatory activity[10], e.g. fenclozic acid has significant level of activity, but has to be withdrawn due to hepatotoxicity observed in many cases[11]. Appreciation of these findings, coupled with our ongoing interest in the synthesis and evaluation of 1,2-benzisothiazole derivatives as antiinflammatory agents[12] and as a part of our ongoing programme[13] to develop NSAIDs, we undertook the synthesis of some acidic derivatives of thiazolyl-1,2-benzisothiazoles. The present communication reports the potent antiinflammatory activity of some 2-(1,2-benzisothiazol-3-yl)-4(5)-thiazole acetic acids and their ethyl esters.

Scheme 1 depicts the two step conversion of 1,2-benzisothiazole-3-thiocarboxamide (**3**) into thiazole-5-acetic acids (**5**). Unfortunately, the conventional method of preparing thioamides by treating the corresponding amides with phosphorus pentasulphide failed to give thioamide (**3**) from 1,2-benzisothiazole-3-carboxamide (**1**). Therefore, the required thiocarboxamide (**3**) was prepared from **1** through the 3-cyano compound (**2**). The carboxamide (**1**) on treatment with phosphoryl chloride afforded 1,2-benzisothiazole-3-carbonitrile (**2**)[14] which on treatment with hydrogen sulphide and ammonia gas in ethanol gave 1,2-benzisothiazole-3-thiocarboxamide (**3**) in 72% yield. The condensation of **3** with various ethyl β-aroyl-β-bromopropionates[15] according to well known

Scheme 1



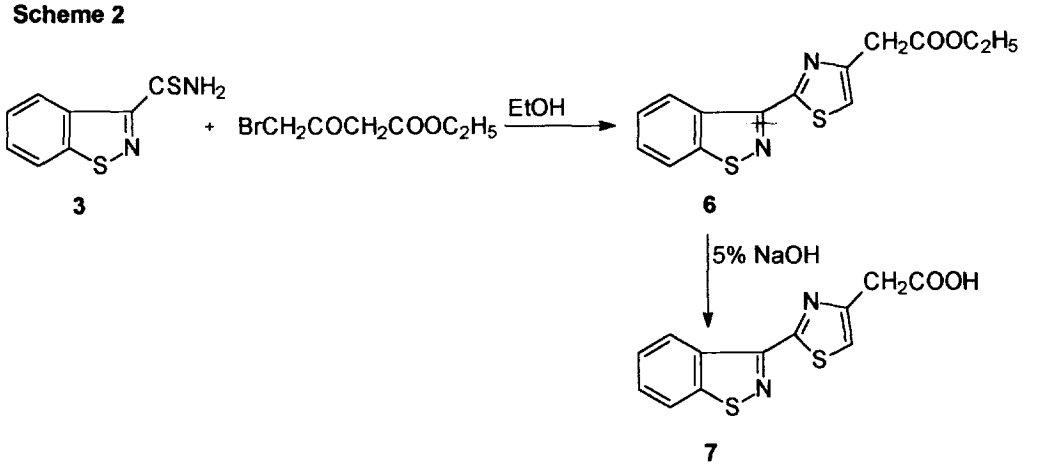
Hantzsch thiazole synthesis gave 3-(4-aryl-5-carbethoxymethylthiazol-2-yl)-1,2-benzisothiazoles (**4**) in good yields. The esters (**4**) on alkaline hydrolysis in methanol followed by acidification afforded the corresponding thiazole-5-acetic acids (**5**) in quantitative yields. We found that compound **5c** possesses excellent level of antiinflammatory activity, higher than that of the standard drug ibuprofen, in carrageenin-induced rat paw edema assay (Table 1).

Prompted by the significant activity of thiazole-5-acetic acids (**5**), we undertook the synthesis of thiazole-4-acetic acid (**7**) (scheme 2). The condensation of thiocarboxamide (**3**) with ethyl γ-bromoacetoacetate[16] proceeded smoothly in ethanolic solution giving 3-(4-carbethoxymethylthiazol-2-yl)-1,2-benzisothiazole (**6**). **6** on hydrolysis with 5% sodium hydroxide in methanol afforded the corresponding thiazole-4-acetic acid (**7**). As expected, compound **7** also showed activity higher than that of ibuprofen.

The values obtained for these compounds in carrageenin-induced rat paw edema assay[17] upon oral (p.o.) and intraperitoneal (i.p.) administration as suspension in gum acacia (1% w/v) in normal saline at 100 mg/kg are presented in Table 1. Each value is the mean of four animals. In every experiment one group of rats was kept as control and another group received a standard drug (ibuprofen) for comparison. Local irritant action was tested by applying different concentrations of test compounds on rabbit cornea[18].

Based on the screening data some general observations are worthmentioning. In general, the compounds tested show somewhat higher activity when administered intraperitoneally (i.p.) as compared to the oral route (p.o.). This is the case with the standard drug, ibuprofen, also. The activity reduces rapidly with the passage of

Scheme 2



time as inhibition measured after 2 hr period is generally more than that observed after 3.5 hr. This behaviour is opposite to that of ibuprofen and may be attributed to the rapid metabolisation of the compounds in the system. Amongst the target compounds, the highest activity has been exhibited by compound **5c** (inhibition 75% p.o.) followed by **7** with inhibition of 64% (p.o.). Moreover the compound **5c** has quite high activity (69% inhibition) even at dose level of 50 mg/kg. This is somewhat expected because these compounds (**5c** & **7**) belong to the family of heterocyclylalkanoic acids. The high activity puts these two compounds in the class of potential NSAIDs and therefore they have been marked for detailed pharmacological screening and the results will be discussed in further reports. The order of activity shown by the compounds within the series **5**, i.e. **5c** > **5b** > **5a**, is in confirmation with our earlier observation that compounds with chloro or methoxy substituents show higher activity[19]. The esters **4**, and **6** were mildly active or inactive.

Table 1 - Antiinflammatory activity of compounds **4-7** on oral (p.o.) and intraperitoneal (i.p.) administration

Compound	% inhibition[20]			
	oral (p.o.)		intraperitoneal (i.p.)	
	2 hr	3.5 hr	2 hr	3.5 hr
4a	N	11	N	N
4b	20	29	34	30
4c	34	22	24	13
5a	15	19	45	7
5b	36	33	40	24
5c*	75	62	78	67
	69[#]	61	76	64
6	18	11	ND	ND
7	64	46	55	64
ibuprofen	62	65	70	74

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

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20. The procedure used to determine the inhibition has been described previously, see reference 12 (b).

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