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SYNTHESIS AND ANTIINFLAMMATORY ACTIVITY OF SOME 3-HETEROCYCLYL-1,2-BENZISOTHIAZOLES

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ABSTRACT : A number of 3-heterocyclyl-1,2-benzisothiazoles, having 1,3,4-oxadiazole, 1,3,4-thiadiazole and 1,2,4-triazole ring systems attached to position-3 of 1,2-benzisothiazole nucleus, were prepared and evaluated as antiinflammatory agents.

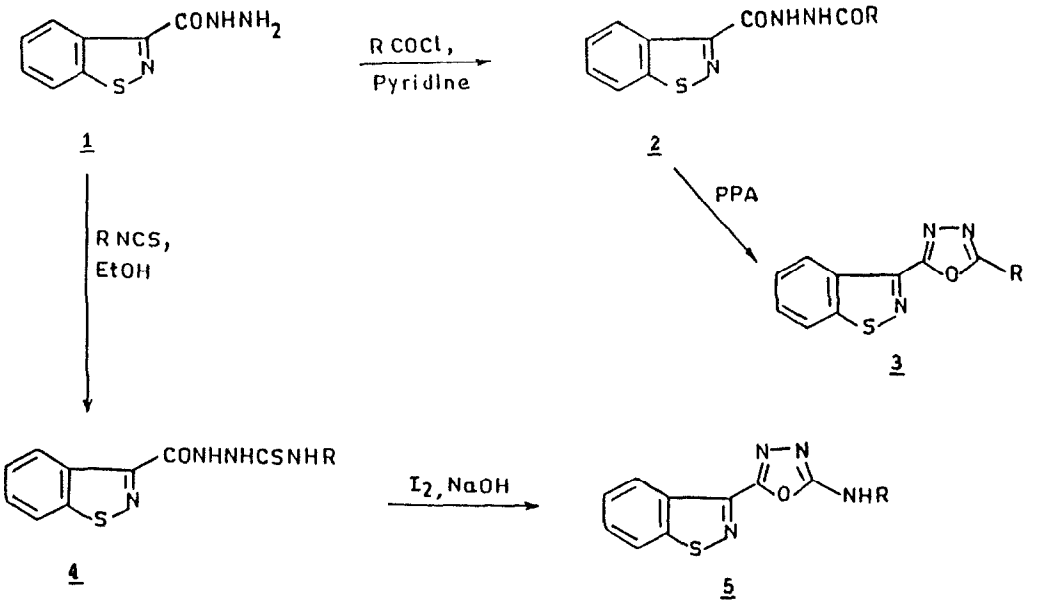
Currently, there is a considerable therapeutic interest in novel antiinflammatory drugs with a mode of action different from that of the classical acidic nonsteroidal antiinflammatory drugs (NSAIDs), mainly for use in patients with arthritis of varying degree of severity. The classical NSAIDs do not prevent progression of such a disease and are subject to irritant side effects[1]. The most prevalent side effect of the use of NSAIDs is the occurrence of gastrointestinal damage with gastric upset and irritation being the major problems. Therefore, investigations of new antiinflammatory agents are still a challenge. The carrageenin-induced rat paw edema model has been used as a popular assay for such antiinflammatory agents[2] which are primarily cyclooxygenase (CO) inhibitors[3]. Over 20 years ago, Juby et. al.[4] found that the fenamate analogues where the carboxylic acid function was replaced by a tetrazole, possess antiinflammatory properties. Recently, Boschelli et. al.[5] reported that the replacement of the carboxylic acid functionality with heterocycles, such as 1,3,4-oxadiazoles, 1,3,4-thiadiazoles, etc., results in the conversion of NSAIDs into balanced dual inhibitors of cyclooxygenase and 5-lipoxygenase.

Appreciation of the above results and the observation that several 1,2-benzisothiazoles and their 1,1-dioxides have been reported to exhibit good antiinflammatory activity[6,7], stimulated our interest in the synthesis of some 1,2-benzisothiazole derivatives with five and six membered N, S, and/or O containing heterocyclic systems attached to 3-position of 1,2-benzisothiazole nucleus.

Scheme 1 depicts the two step conversion of hydrazide (1) into 2-substituted-1,3,4-oxadiazoles (3, 5). The diacylhydrazines (2) were prepared from hydrazide (1)[8] in good yield by the reaction of various acyl and aroyl chlorides. The cyclodehydration of 2 was effectively used by using polyphosphoric acid (PPA) at 140-150° C for 2 hr to provide 1,3,4-oxadiazoles (3) in moderate yield. 1-(1,2-Benziso-

thiazole-3-carbonyl)-4-substituted thiosemicarbazides (4) were prepared in good yield by the condensation of hydrazide (1) with ethyl and phenyl isothiocyanates following the procedure of Silberg and Cosma[9]. The thiosemicarbazides (4) were cyclized to 2-substituted amino-1,3,4-oxadiazoles (5) by the reaction of iodine in potassium iodide solution in the presence of dilute sodium hydroxide. We found

Scheme 1

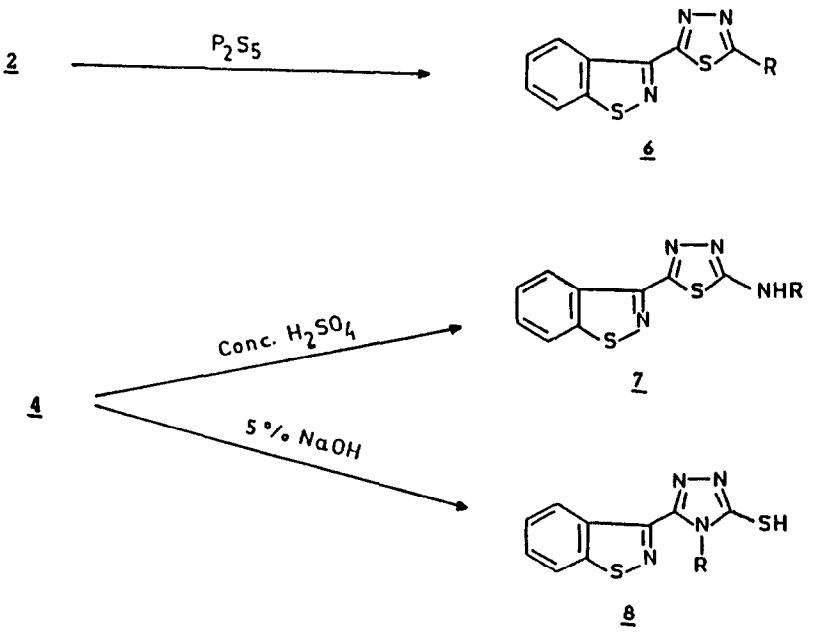


2, 3, 4, 5 a, R = CH_3 d, R = 4-ClC_6H_4
b, R = C_2H_5 e, R = 4-$CH_3OC_6H_4$
c, R = C_6H_5

that the target compounds 3c, 5b and 5c possess antiinflammatory activity comparable to that of the standard drug, ibuprofen, in carrageenin-induced rat paw edema assay (Table 1).

The activity shown by 1,3,4-oxadiazoles (3, 5) prompted us to synthesize the corresponding thiadiazole and triazole analogues. The 2-substituted-1,3,4-thiadiazole derivatives were prepared in moderate yield by the treatment of 2 with P_2S_5 at 150-160° C under partial vacuum. Cyclization of 4 with concentrated sulphuric acid afforded 2-substituted amino-1,3,4-thiadiazole derivatives in good yield. Ring closure of aryl thiosemicarbazides in alkaline medium is a well known method for the synthesis of s-triazoles[10]. Cyclization in 5% sodium hydroxide gave 3-mercapto-4H-1,2,4-triazoles (8) in moderate yield (Scheme 2). The competitive formation of isomeric 2-aminothiadiazoles

Scheme 2



6, 7, 8, a, R = C_2H_5
b, R = C_6H_5

is completely prevented by operating in strong alkali.Only compound 8a was found to be active having activity approaching to ibuprofen while all other compounds were mildly active or inactive (Table 1).

The values obtained for these compounds in carrageenin-induced rat paw edema assay upon oral (p.o.) and intraperitoneal (i.p.) administration 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 standardf drug (ibuprofen) for comparison. Local irritant action was tested by applying different concentrations of test compounds on rabbit cornea[11]. The screening data permit us to discern some general observations about structure activity relationship amongst various series of compounds.

In general, the compounds tested show somewhat higher activity when administered intraperitoneally Ii.p.) as compared to the oral route (p.o.). This is the case with the standard drug, ibuprofen, also. Compounds with high activity show higher inhibition when measured 2 hour after the carrageenin injection as compared to that measured after 3.5 hour. This behaviour is opposite to that of ibuprofen and may be attributed to the rapid metabolisation of the compounds in the system.

Amongst oxadiazoles (3, 5), compounds 3c and 5c having unsubstituted phenyl ring, show the highest activity and the activity decreases as the phenyl ring is modified by methoxy and chloro substituents. Oxadiazoles in general, show higher activity as compared to thiadiazoles and triazoles. We are continuing to prepare more heterocyclic analogues of 1,2-benzisothiazole and their detailed pharmacological studies will be discussed in further reports.

Table 1

Compound	% inhibition[12]			
	oral (p.o.)		intraperitoneal (i.p.)	
	2 hr	3.5 hr	2 hr	3.5 hr
3a	43	21	69	42
3b	N	18	N	N
3c	60	32	60	48
3d	13	24	50	33
3e	21	29	45	33
5a	N	N	67	60
5b	53	29	65	42
5c	56	27	67	48
5d	14	N	48	40
5e	28	33	59	50
6a	N	12	N	N
6b	N	22	21	10
7a	34	25	59	50
7b	8	10	62	48
8a	57	32	64	50
8b	N	N	81	60
ibuprofen	62	65	70	74

N = 10% inhibition

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REFERENCES AND NOTES

1. Gemmell, D. K.; Cottney, J.; Lewis, A. J. *Agents Actions* **1979**, *9*, 107.
2. Van Arman, C. G. *Handb. Exp. Pharmacol.* **1979**, *50*, 75.
3. Winter, C. A.; Risley, E. A.; Nuss, G. W. *Proc. Soc. Exp. Biol. Med.* **1962**, *111*, 544.
4. Juby, P. F.; Hudyma, T. W.; Brown, M. *J. Med. Chem.* **1968**, *11*, 111.
5. Boschelli, D. H.; Connor, D. T.; Hoefle, M.; Bornemeier, D. A.; Dyer, R. D. *Bio. Med. Chem. Lett.* **1992**, *2*, 69.
6. Amoretti, L.; Morini, G.; Zappia, L.; Coruzzi, G. *Ateneo Pharmense Acta Nat.* **1977**, *13*, 477; *Chem. Abstr.* **1978**, *88*, 69188b.
7. Wade P. C.; Vogt, R. B. *U. S. Pat.* **1979**, 4,147,798; *Chem. Abstr.* **1979**, *91*, 20491t.
8. Stolle, R.; Geisel, W.; Badstubner, W. *Chem. Ber.* **1925**, *58*, 2095.
9. Silberg, A.; Cosma, N. *Acad. Rep. Populare Romine Filiala Cluj. Studii Cercetari Chim.* **1959**, *10*, 151; *Chem. Abstr.* **1960**, *54*, 8794g.
10. Sherman, W. R. *J. Org. Chem.* **1961**, *26*, 88.
11. Luduena, F. P.; Hoppe, J. O. *Pharma. Exp. Ther.* **1952**, 104.
12. The procedure used to determine the inhibition has been described previously, see: Sawhney, S. N.; Sharma, P. K.; Gupta, A.; Singh, G. B.; Bani, S. *Indian J. Chem.* **1992**, *31B*, 421.