

Synthesis and Anti-inflammatory Activity of [2-(Benzothiazol-2-ylimino)-4-oxo-3-phenylthiazolidin-5-yl]-acetic Acid Derivatives

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요약. 소염작용을 가진 일련의 싸이아졸리딘아세트산 유도체들을 싸이오유레이와 말레산무수물로부터 합성하고 분광학적인 방법으로 구조를 확립하였다. 또한 이 화합물들의 소염작용을 표준시약인 디클로페낙 소듐과 비교한 결과 어느 정도의 효과를 가지고 있음을 검정하였다.

주제어: 소염제, 싸이아졸리딘아세트산 유도체, 소염작용, 항염증

ABSTRACT. A synthetic method for the title compounds (**2a-o**) was carried out. The title compounds (**2a-o**) were prepared by the condensation of various thioureas and maleic anhydride. Anti-inflammatory activities *in vivo* were evaluated and compared with standard drug diclofenac sodium. Some compounds showed moderate activity. The structures of all the new compounds were established on the basis of ¹H NMR and IR spectral data.

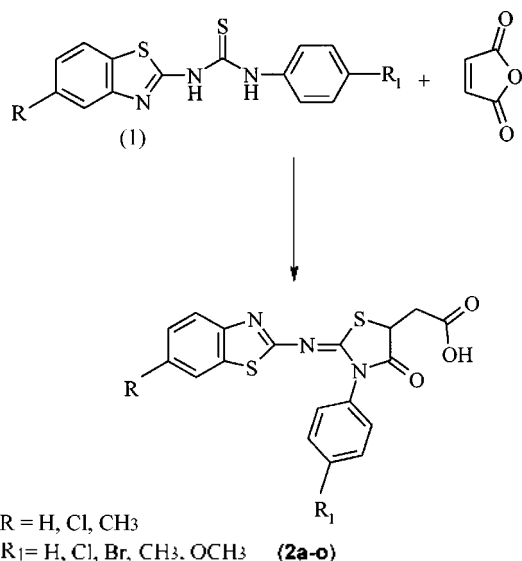
Keywords: Anti-Inflammatory, Synthesis, [2-(Benzothiazol-2-ylimino)-4-oxo-3-phenylthiazolidin-5-yl]-acetic Acid, Thiazolidinylacetic Acid

INTRODUCTION

Following the discovery of indomethacin, a large number of aryl and heterocyclic acetic acids have been synthesized and many of them have shown significant anti-inflammatory activity.^{1,2,3} Potent anti-inflammatory activities have been reported in number of aryl thiazole¹⁵ and benzothiazole⁶ derivatives. Thiazolidones also shows antimicrobial,⁷ anticonvulsant,⁸ antibacterial,⁹ fungicidal¹⁰ and congeners as central nervous system active agents.¹¹ In view of the fact, imino thiazolidones were synthesized in our labora-

tory and were found to possess significant anti-inflammatory activity as compared to that of diclofenac sodium.

Many other methods are available in literature for synthesis of thiazolidones but not by using maleic anhydride with thiourea. Although Tivadi *et al.*¹² reported a reaction between symmetrical thioureas with maleic anhydride to synthesis such type of compounds. Here we wish report the synthesis of title compounds (**2a-o**) by the condensation of maleic anhydride with heterocyclic thiourea (1) in ethanol (Scheme 1). The newly synthesized com-



Scheme 1.

pounds were tested for anti-inflammatory activity according to the method reported by Winter *et al.*¹³ In albino wistar rats employing the Carageenan induced rat paw edema test model. Percentage reduction in the inflammation after 3hrs of administration of Carageenan and the test compound was compared with that of the animals administrated with Carageenan and the reference standard diclofenac sodium (*Table 1*).

From the activity data it was observed that the test compounds showed tendency to cause more or less fall in edema as compared with the control. However amongst all compounds tested, compounds (**2c, j, o**) were found to exhibit high activity. It was observed that compound having methoxy group at *p*-position of phenyl ring exhibited the maximum percent inhibition of edema.

EXPERIMENTAL

The melting points were taken in open capillary and are uncorrected. Purity of the compounds was checked by T.L.C. IR spectra were recorded on JASCO spectrophotometer using KBr pellets. ¹H NMR spectra were recorded in CDCl₃ on a sophis-

ticated multinuclear FT-NMR spectrophotometer model Ac-300 F (Bruker) 300 MHz using TMS as an internal standard. Satisfactory microanalysis ($\pm 0.4\%$ of the calculated values) was obtained for all the compounds.

General procedure for the synthesis of [2-(6-substituted benzothiazol-2-ylimino)-4-oxo-3-phenyl-thiazolidin-5-yl]acetic acids (**2 a-o**)

In a 100 ml round bottom flask fitted with reflux condenser and a CaCl₂ guard tube, substituted heterocyclic thiourea (**1**) (0.01 mol) and maleic anhydride (0.01 mol) in ethanol (25 ml) were refluxed on a water bath for 20 hrs. Excess of the solvent was removed under vacuum. The solid was dried and recrystallized from ethanol.

Anti-inflammatory activity

Anti-inflammatory activity of all title compounds was carried out by carageenan-induced rat paw edema test as described by Winter *et al.*¹³ it is not needed.

Carageenan-induced rat paw edema test-Albino rats of either sex (150-200 g) were divided into different groups, each containing six individuals. Animals were fasted for 12 h before experiment and only water was allowed. While the first group was a control one and received vehicle (Tween 80 in propylene glycol (10%, v/v), 0.5 mL per rat), the second group received diclofenac sodium 10 mg kg⁻¹ body mass. All the remaining groups received orally the test compounds at the same dose. All the suspensions for oral dose were prepared in the vehicle mentioned above and administered in a constant volume of 0.5 mL per rat.

After one hour of the administration of the test compound and diclofenac sodium 0.1 mL of 1% w/v suspension of carageenan was injected in to the subplanatar of left paw of control and test animals. Immediately, the paw volume was measured using plethysmometer (initial paw volume), there after the paw volume was measured every half an hour till three hours. The difference between initial and subsequent readings gave the edema volume for the corresponding time. Percentage inhibition was calculated (*Table 1*).

Table 1. Characterization data and anti-inflammatory activity of compounds (2a-o)

Comp. No	R	R ₁	M.P.	Yield %	Activity %	IR(KBr)	¹ H NMR-(CDCl ₃)
2a	H	H	195	50	20	2600-3200 (broad. -OH), 1690 (-C=O), 3010(C-CAromatic)	3.2 (d, 2H, -CH ₂ -C-O), 3.9 (t, 1H, -CH-), 7.2-8.5 (m, 9H, ArH), 11.2 (br-s, 1H, -OH)
2b	H	Cl	189	60	21	2600-3200 (broad. -OH), 1695 (-C=O), 2970(C-CAromatic)	3.3 (d, 2H, -CH ₂ -C-O), 3.8 (t, 1H, -CH-), 7.3-8.2 (m, 8H, ArH), 11 (br-s, 1H, -OH)
2c	H	Br	212	70	10	2600-3200 (broad. -OH), 1700 (-C=O), 2970 (C-CAromatic)	3.2 (d, 2H, -CH ₂ -C-O), 3.8 (t, 1H, -CH-), 7.4-8.3 (m, 8H, ArH), 11.1 (br-s, 1H, -OH)
2d	H	CH ₃	205	75	ND	2600-3300 (broad. -OH), 1680 (-C=O), 3000 (C-CAromatic)	2.35 (s, 3H, -CH ₃), 3.2 (d, 2H, -CH ₂ -C-O), 3.8 (t, 1H, -CH-), 7-8.2 (m, 8H, ArH), 11.1 (br-s, 1H, -OH)
2e	H	OCH ₃	171	40	30	2600-2800 (broad. -OH), 1690 (-C=O), 3050 (C-CAromatic)	3.73 (s, 3H, -OCH ₃), 3.24 (d, 2H, -H ₂ C-O), 3.8 (t, 1H, -CH-), 6.7-8.2 (m, 8H, ArH), 11.1 (br-s, 1H, -OH)
2f	Cl	H	189	45	11	2600-3200 (broad. -OH), 1720 (-C=O), 2900 (C-CAromatic)	3.27 (d, 2H, -H ₂ C-O), 3.8 (t, 1H, -CH-), 7.0-8.1 (m, 8H, ArH), 11.00 (br-s, 1H, -OH)
2g	Cl	Cl	178	55	18	2600-3300 (broad. -OH), 1730 (-C=O), 2980 (C-CAromatic)	3.24 (d, 2H, -H ₂ C-O), 3.8 (t, 1H, -CH-), 7.2-8.17 (m, 7H, ArH), 11.00 (br-s, 1H, -OH)
2h	Cl	Br	181	60	ND	2600-2800 (broad. -OH), 1690 (-C=O), 3000 (C-CAromatic)	3.24 (d, 2H, -H ₂ C-O), 3.8 (t, 1H, -CH-), 7.4-8.17 (m, 7H, ArH), 11.00 (br-s, 1H, -OH)
2i	Cl	CH ₃	191	40	15	2600-3300 (broad. -OH), 1746 (-C=O), 2990 (C-CAromatic)	2.3 (s, 3H, -CH ₃), 3.2 (d, 2H, -CH ₂ -C-O), 3.8 (t, 1H, -CH-), 7.1-8.2 (m, 7H, ArH), 11.1 (br-s, 1H, -OH)
2j	Cl	OCH ₃	169	35	35	2600-3300 (broad. -OH), 1734 (-C=O), 3050 (C-CAromatic)	3.73 (s, 3H, -OCH ₃), 3.24 (d, 2H, -H ₂ C-O), 3.8 (t, 1H, -CH-), 6.75-8.17 (m, 8H, ArH), 11 (br-s, 1H, -OH)
2k	CH ₃	H	179	65	18	2600-3300 (broad. -OH), 1690 (-C=O), 3060 (C-CAromatic)	2.3 (s, 3H, -CH ₃), 3.24 (d, 2H, -H ₂ C-O), 3.7 (t, 1H, -CH-), 7.0-8.11 (m, 8H, ArH), 11.1 (br-s, 1H, -OH)
2l	CH ₃	Cl	188	50	20	2600-3300 (broad. -OH), 1710 (-C=O), 3000 (C-CAromatic)	2.35 (s, 3H, -CH ₃), 3.24 (d, 2H, -H ₂ C-O), 3.8 (t, 1H, -CH-), 7.2-8.2 (m, 7H, ArH), 11.2 (br-s, 1H, -OH)
2m	CH ₃	Br	165	50	ND	2600-3300 (broad. -OH), 1704 (-C=O), 3000 (C-CAromatic)	2.3 (s, 3H, -CH ₃), 3.24 (d, 2H, -H ₂ C-O), 3.7 (t, 1H, -CH-), 7.4-8.11 (m, 7H, ArH), 11 (br-s, 1H, -OH)
2n	CH ₃	CH ₃	163	70	ND	2600-3300 (broad. -OH), 1700 (-C=O), 3000 (C-CAromatic)	2.35 (s, 3H, -CH ₃), 3.24 (d, 2H, -H ₂ C-O), 3.8 (t, 1H, -CH-), 7.1-8.11 (m, 7H, ArH), 11 (br-s, 1H, -OH)
2o	CH ₃	OCH ₃	198	40	29	2600-3100 (broad. -OH), 1725 (-C=O), 3000 (C-CAromatic)	2.3 (s, 3H, -CH ₃), 3.7 (s, 3H, -OCH ₃), 3.24 (d, 2H, -H ₂ C-O), 3.8 (t, 1H, -CH-), 6.75-8.11 (m, 7H, ArH), 11 (br-s, 1H, -OH)
Standard	Diclofenac sodium					48	

ND - Not Done

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