# Synthesis of phenylimidazo thiazolo benzocycloheptene derivatives as potential antiinflammatory agent-IV[†]

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**Abstract :** New heterocyclic systems namely 10-phenyl-6,7-dihydro-5H-benzo[6,7] cyclohepta[1,2-d][1,3]thieazoles **4a-c** have been synthesized via the reaction of 2-(2-imino-1,4,5,6-tetrahydro-2H-benzo[7,8]cyclohepta[d][1,3] thiazol)-1-phenyl-1-propen-1-ol (**3a-c**) intermediates with phenacyl bromide, in good yields. All these compounds (**4a-c**) exhibit significant antiinflammatory activity.

## Introduction

A number of biologically interesting polynuclear compounds incorporating a fused thiophene ring viz. Thiasteroids,[1] analogues of indole alkaloids,[2,3] carcinogenic compounds[4] etc., consists of six-membered ring annelated to thiophene. But examples of polycondensed systems incorporating a thiophene, imidazole or thiazole ring fused to a seven membered ring (viz benosuberones and benzazepines) are sparse. In continuation of our previous studies[5-7] in the synthesis of biologically active fused heterocycles we have synthesized the hitherto unreported phenylimidazo thiazolobenzocycloheptene derivaties **4a-c** starting from the 6,7,8,9-tetrahydro-5H-benzocycloheptene-5-ones **1a-c**[8] and their analgesic and antiinflammatory activities studied in the present investigation.

## Chemistry

Reaction of the tetrahydro benzocycloheptenones (**1a-c**) with thiourea and iodine were heated under reflux to give expected 5,6-dihydro-4H-benzo[3,4]cyclohepta[d][1,3] thiazol-2-amines (**2a-c**) as colourless needles (60-65%).[7,9] Cyclization of (**2a-c**) with phenacyl bromide at room temperatur resulted in 2-(2-imino-1,4,5,6 tetrahydro2H-benzo[7,8]cyclohepta [d][1,3] thiazol-1-yl)-1-phenyl-1-propen-ols (**3a-c**) as the intermediiate products (67-68%). Subsequently compounds (**3a-c**) were assigned the enol form and gave 10-phenyl-6,7-dihydro-5H-benzo[6,7]cyclohepta[1,2-d] imidazo [2,1-*d*][1,3] thiazoles (**4a-c**, 90-92%)

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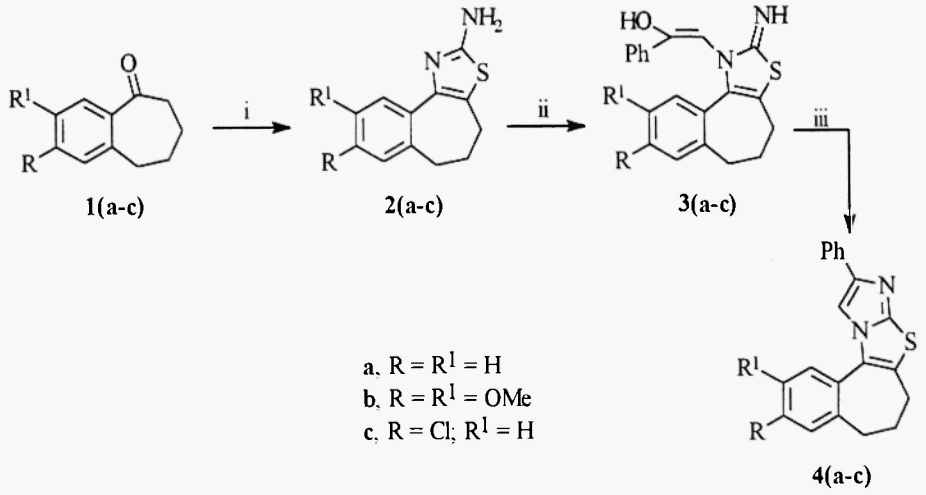
heating in ethanol (**Scheme-1**). Their structures were established by $^1$H NMR, IR and elemental analysis. These compounds (**4a-c**) were tested for their analgesic and antiinflammatory activities.




**Reagents and Conditions.** i) $H_2NCSNH_2$, $I_2$, EtOH, reflux; ii) $PhCOCH_2Br$, EtOH, RT, overnight; iii) EtOH, reflux, 6 hrs.

**Scheme-1**

**Analgesic and antiinflammatory activities**

Analgesic and antiinflammatory activities of the compounds **4a-c** were determined by Turner[10] writhing test[11] and rat-paw edema test.[12] The inhibition of edema was recorded on a plethysmometer (UGO BASILE make) and expressed as % inhibition. The results are given in **Table 1**. Compounds **4a-c** showed 32-34% inhibitiion in rats while aspirin and phenyl butazone at the same dose (100 mg/kg, p.o) produced 17% and 39% inhibition of 1% carrageenan-induced inflammation, respectively. The per cent protection for each compound was calculated using the following formula:

$$\% \text{ protection} = 100 - \frac{\text{No. of writhes in test}}{\text{No of writhes in control}} \times 100$$

All the new compounds (**4a-c**) exhibited significant antiinflammatory activity comparable with that of phenylbutazone. Especially chloro substituent

showed highest activity than methoxy. However, they were found to possess weak analgesic action with reference to aspirin.

**Table-1**. Evaluation of analgesic and antiinflammatory activities of compounds **4a-c**

| Compound | Analgesic action (% protection of pain) | | Antiinflammatory action (% inhibition) |
|---|---|---|---|
| | Tail clip | Writhing | (Rat paw edema) |
| **4a** | 13 | 11 | 32 |
| **4b** | 12 | 12 | 32 |
| **4c** | 14 | 16 | 34 |
| Aspirin (100 mg/kg) | 55 | 46 | 17 |
| Phenylbutazone (100 mg/kg) | 30 | 26 | 39 |

The results were of two observations. Values of 20% inhibition of significant ($p>0.01$) greater were

**Experimental section**

Melting points were determined in open glass capillaries on a polmon melting point apparatus and are uncorrected. $^1$H NMR spectra were recorded on a Gemini (200 MHz) spectrometers (chemical shifts are recorded in δ, ppm); internal standard was TMS and IR spectra were recorded in KBr on a Perkin-Elmer bio-spectrometer. Elemental analyses were carried out with a Carlo Erba model 1106 Elemental Analyzer.

**Preparation of 2a-c - General Procedure.** A mixture of **1a** (15 mmol), thiourea (5 mmol) and iodine (15 mmol) was refluxed for 48 hr in abs. ethanol (50 mL). At this point TLC showed only a slight change in the substrate. After prolonged refluxing (4 to 5 days until TLC showed the absence of the ketone) the resulting hydride was dissolved in hot water. The solution was filtered while hot and the clear filterate was neutralized with a strong solution of ammonia. The resulting precipitate was washed with water and crystallized from ethanol.

**5,6-Dihydro-4H-benzo[3,4]cyclohepta[d][1,3]thiazol-2-amine (2a)**. Yield 60%, pale yellow, m.p. 250°C (lit.,[7] m.p. 250°C); IR (Kbr) : υ 3380 cm$^{-1}$; $^1$H NMR (DMSO-$d_6$) : δ 2.18-2.40 (m, 2H, 5-H), 2.61-2.85 (m, 4H, 4 & 6-H), 5.35 (br.s, 2H, $NH_2$, $D_2O$ exchangeable) and 6.50-7.25 (m, 4H, Ar-H).

**8,9-Dimethoxy-5,6-dihydro-4H-benzo[3,4]cyclohepta[d][1,3]thiazol-2-amine (2b)**. Yield 63%, pale yellow crystals, m.p. >290°C (lit.,[7] m.p. >290°C); IR (KBr) : υ 3385 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) : δ 2.15-2.30 (m, 2H, 5-H), 2.60-2.85 (m, 4H, 4 & 6-H), 5.35 (br.s, 2H, $NH_2$, $D_2O$ exchangeable), 3.90 (s, 3H, OMe), 3.95 (s, 3H, OMe), 6.50 (s, 1H, 7-H) and 7.25 (s, 1H, 10-H).

**8-Chloro-5,6-dihydro-4H-benzo[3,4]cyclohepta[d][1,3]thiazol-2-amine (2c)**. Yield 65%, pale yellow prisms, m.p. >290°C (lit.,[7] m.p. >290°C); IR (KBr) : υ 3388 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) : δ 2.20-2.41 (m, 2H, 5-H), 2.60-2.85 (m, 4H, 4 & 6-H), 5.33 (br.s, 2H, $NH_2$, $D_2O$ exchangeable) and 6.48-7.22 (m, 3H, Ar-H).

**Preparation of 3a-c - General procedure.** A mixture of **2a** (12 mmol) and phenacyl bromide (12 mmol) in 50 mL ethanol was allowed to stand at room temperature overnight. The crystals, which separated, were collected by filtration and washed with a small amount of ethanol.

**2-(2-Imino-1,4,5,6-tetrahydro-2H-benzo[7,8]cyclohepta[d][1,3]thiazoi-1-yl)-1-phenyl-1-ethene-1-ol (3a).** Yield 68%, m.p. 281.2°C; IR (KBr) : υ 3390, 3360, 2910, 2850 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) : δ 2.15-2.30 (m, 2H, 5-H), 2.60-2.85 (m, 4H, 4 & 6-H), 7.14 (s, 1H, =CH), 8.66 (br, s, 1H, =NH), 8.64 (s, 1H, OH) and 6.50-7.44 (m, 9H, Ar-H); (Found : C, 72.15; H, 6.00; N, 8.00. Calcd. for $C_{21}H_{21}N_2OS$ : C, 72.17; H, 6.06; N, 8.01%).

**2-(2-Imino-8,9-dimethoxy-1,4,5,6-tetrahydro-2H-benzo[7,8]cyclohepta[d][1,3] thiazol-1-yl)-1-phenyl-1-ethene-1-ol (3b).** Yield 67%, m.p. 260°C (dec.); IR (KBr) : υ 3385, 2910, 2860 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) : δ 2.18-2.33 (m, 2H, 5-H), 2.60-2.88 (m, 4H, 4 & 6-H), 7.18 (s, 1H, =CH), 8.78 (br, s, 1H, =NH), 8.76 (s, 1H, OH), 3.95 (s, 3H, -OMe), 4.00 (s, 3H, -OMe), 6.48 (s, 1H, 7-H), 7.23 (s, 1H, 10-H), 6.25-7.25 (m,5H, Ar-H). (Found : C, 67.51; H, 5.90; N, 6.79. Calcd. for $C_{23}H_{24}N_2O_3S$ : C, 67.62; H, 5.92; N, 6.88%).

**2-(8-Chloro-2-imino-1,4,5,6-tetrahydro-2H-benzo[7,8]cyclohepta[d][1,3] thiazol-1-yl)-1-phenyl-1-ethene-1-ol (3c).** Yield 67%, m.p. 242°C (dec.); IR (KBr) : υ 3398, 3355, 3905, 3855 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$) : δ 2.17-2.23 (m, 2H, 5-H), 2.60-2.86 (m, 4H, 4 & 6-H), 7.20 (s, 1H, =CH), 8.70 (br, s, 1H, =NH), 8.77 (s, 1H, -OH) and 6.65-7.46 (m, 8H, Ar-H). (Found : C, 65.60; H, 5.25; N, 7.30. Calcd. for $C_{21}H_{20}ClN_2OS$ : C, 65.69; H, 5.25; N, 7.29%).

**Preparation of 4a-c - General Procedure.** A suspension of **3a** (20 mmol) in 60 mL ethanol was heated under reflux for 6 hr after cooling, the rystals which separated were collected by filtration.

**10-Phenyl-6,7-dihydro-5H-benzo[6,7]cyclohepta[1,2,-d]imidazo[2,1-b] [1,3]thiazole (4a)**. Yield 92%, colourless crystals; m.p. 238.2°C; $^1$H NMR (DMSO-$d_6$) : δ 2.18-2.37 (m, 2H, 6-H), 2.66-2.87 (m, 4H, 5 & 7-H). (Found : C, 75.90; H, 5.00; N, 8.81. Calcd. for $C_{20}H_{16}N_2S$ : C, 75.91; H, 5.10; N, 8.85%).

**2,3-Dimethoxy-10-phenyl-6,7-dihydro-5H-benzo[6,7]cyclohepta[1,2,-d] imidazo[2,1-b][1,3]thiazole (4b)**. Yield 90%, buff white powder; m.p. 280°C (dec.); $^1$H NMR (DMSO-$d_6$) : δ 2.15-2.31 (m, 2H, 6-H), 2.61-2.85 (m, 4H, 5 & 7-H), 7.56 (s, 1H, 11-H), 3.99 (s, 3H, -OMe), 4.10 (s, 3H, -OMe), 6.49 (s, 1H, 4-H), 7.22 (s, 1H, 1-H) and 6.25-7.40 (m, 5H, Ar-H). (Found : C, 68.10; H, 5.71; N, 7.96. Calcd. for $C_{20}H_{20}N_2O_2S$ : C, 68.15; H, 5.72; N, 7.94%).

**3-Chloro-10-phenyl-6,7-dihydro-5H-benzo[6,7]cyclohepta[1,2,-d] imidazo[2,1-b][1,3]thiazole (4c)**. Yield 93%, pale yellow needles; m.p. 268°C; $^1$H NMR (DMSO-$d_6$) : δ 2.17-2.33 (m, 2H, 6-H), 2.68-2.86 (m, 4H, 5 & 7-H), 7.55 (s, 1H, 11-H), 6.45-7.25 (m, 8H, Ar-H). (Found : C, 68.44; H, 4.29; N, 7.99. Calcd. for $C_{20}H_{15}ClN_2S$ : C, 68.46; H, 4.31; N, 7.98%).

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