Asian Journal of Chemistry Vol. 16, No. 2 (2004), 823–826

Synthesis and Pharmacological Evaluation of 4-Hydroxybenzothiophene-6-carboxylic Acid Derivatives as NSAIDs

MAHESH ATTIMARAD* and G. BAGAVANT
Department of Pharmaceutical Chemistry, Al-Ameen College of Pharmacy
Hosur Road, Bangalore-560 027, India

4-Hydroxybenzothiophene-6-carboxylic acid and its derivatives were synthesized *via* Stobbe condensation and Friedel Crafts cyclization and they were found to possess anti-inflammatory and analgesic activities.

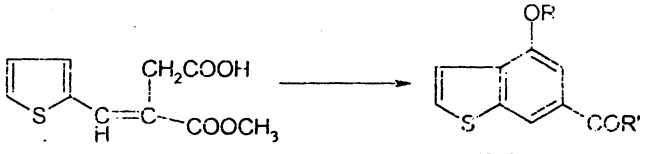
Key Words: Synthesis, Benzothiophene, Anti-inflammatory and Analgesic activities, NSAID.

INTRODUCTION

Various derivatives of benzothiophenes[1-4] and some compounds with glycolic acid[5] moiety were reported to exhibit analgesic and anti-inflammatory activities. Other studies described the derivatization of the carboxylate function of some NSAIDs as hydroxamates to provide dual inhibitors of both cyclo-oxygenase and 5-lipoxygenase[6]. These observations stimulated the synthesizing of the title compounds possessing benzothiophene ring, acidic sites and hydroxamic acid group to evaluate their anti-inflammatory and analgesic activities.

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. The IR spectrum were run on Shimadzu FT IR spectrophotometer in KBr pellets. ^{1}H NMR and ^{13}C NMR were obtained using JEOL GSX-400 FT NMR 400 MHz in $CDCl_3$/DMSO-d_6 solvent using TMS as internal reference. Mass spectra were recorded by Jeol-JMS-300 spectrometer at 70 eV. The compounds were analyzed for C, H and N analysis and the values were found within ±0.4% of the calculated values.



(1) (2-7)

Scheme 1

E-3-Methoxycarbonyl-4-(2-thienyl)buta-3-enoic acid (1): A mixture of thiophene 2-aldehyde (11.2 g, 9.3 mL, 0.1 mol) dimethyl succninate (14.6 g, 13 mL, 0.1 mol) in dry *t*-butanol (15 mL) was added gradually during 1 h to a solution of potassium *t*-butoxide [potassium (4.4 g, 0.11 mol) and dry *t*-butanol (75 mL)] at 0–5°C. The mixture was stirred at room temperature for 4 h. Then it was acidified to Congo red with 4 N HCl, 100 mL was added and 50–70 mL distilled off under reduced pressure. A reddish oil separated on cooling; it was extracted with ether. Butenoic acid was extracted into sodium bicarbonate solution from the ether phase. The sodium bicarbonate layer was acidified with 4 N HCl and the orange to red viscous oil was taken into ether, dried and distilled off the solvent to yield acid-ester. Yield: 80%, m.p. 112–114°C (lit[7]. m.p. 116–117°C).

Methyl 4-acetoxybenzothiophene-6-carboxylate (2): The above acid-ester **(1)** (5 g) was added to a mixture of anhydrous sodium acetate (2.5 g) and acetic anhydride (25 mL) and left overnight at room temperature with occasional shaking; the temperature was then gradually raised to 70–80°C during 2 h and maintained there for a further 4 h, then poured into water and the oily material obtained was crystallized from light petroleum (b.p. 60–80°C) to give the acetoxy ester **(2)** as yellow needles. Yield: 48%, m.p. 82–84°C.

IR cm^{-1} (KBr): 3080 ν(Ar—H), 1755 ν($OCOCH_3$), 1710 ν($COOCH_3$), 1560 ν(ArC=C), 1200 ν(O—C=O). ^1H NMR: 2.40 (s, 3H, $OCOCH_3$), 3.91 (H, 3H, $COOCH_3$), 7.25 (d, 1H, Ar—H), 7.60 (d, 1H, Ar—H), 7.75 (s, 1H, ar—H), 8.45 (s, 1H, Ar—H).

4-Hydroxybenzothiophene-6-carboxylic acid (3): The acetoxy ester **(2)** (3.2 g) was dissolved in 80 mL of alcoholic (15% v/v) potassium hydroxide (10%). It was refluxed for 2 h and cooled. Acidification precipitated the hydroxy acid, which was filtered dried and crystallized from acetone-benzene. Yield; 88%, m.p. 243–244°C.

IR cm^{-1} (KBr): 3377 ν(O—H), 3020 ν(Ar—H), 1660 ν(—C=O—). ^1H NMR: 7.3 (s, 1 H, Ar—H), 7.52 (d, J-5.22 cps, 1H, Ar—H), 7.81 (d, J-5.45 cps, 1H, Ar—H), 8.05 (s, 1H, Ar—H), 10.38 (s, 1H, phenolic OH), 12.8 (s, 1H, COOH).

6-Carboxy-4-benzothiophenoxyacetic acid (4): To a solution of the hydroxy acid **(3)** (1 g) in 33% NaOH solution (3.5 mL), a 50% solution of aq., chloroacetic acid solution 2.5 mL was added. The test tube was stoppered loosely and warmed gently on a water bath for 1 h. After cooling, the contents were acidified with HCl and the precipitated aryloxy acetic acid **(4)** was filtered, dried and crystallized from aq. ethanol. Yield: 66%, m.p. 276–277°C.

IR cm^{-1} (KBr): 3100 ν(Ar—H), 3080–2900 ν(COO—H), 1680 ν(—C=O—), 1670 and 1560 ν(ArC=C—). ^1H NMR: 4.92 (s, 2H, CH_2), 7.25 (s, 1H, Ar—H), 7.55 (d, J-5.60 cps, 1H, Ar—H), 7.93 (d, J-5.56 cps, 1H, Ar—H), 8.27 (s, 1H, Ar—H), 13.10 (s, 2H COOM). ^{13}C NMR: Found: C_2- 130.478, C_3-120.035, C_{3a}-133.376, C_4-152.128, C_5-105.402, C_6-128.035, C_7-117.748, C_{7a} 140.572, C_8-167.329, C_9-65.044, C_{10}-170.026.

Methyl 4-hydroxybenzothiophene-6-carboxylate (5): Methyl 4-hydroxy-benzothiophene-6-carboxylate **(5)** was prepared by esterifying the acid with diazomethane. Yield; 91%. m.p. 142°C.

IR cm^{-1} (KBr): 300 ν((O—H), 3020 ν(Ar—H), 1660 ν(—C=O—), 1610,

1574, ν(ArC=C—). ^{1}HNMR: (s, 3H, $COOCH_3$), 7.3 (s, 1H, Ar—H), 7.52 (d, J-5.22 cps, 1H, Ar—H), 7.81 (d, J-5.45 cps, 1H, Ar—H), 8.05(s, IR Ar—H), 10.38 (s, 1H, phenolic OH).

The same compound was also obtained by mild hydrolysis of acetoxy ester **(2)** with 10% Na_2CO_3 solution.

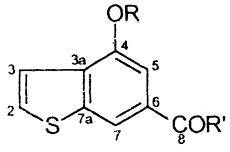
4-Hydroxybenzothiophene-6-hydroxamic acid (6): Hydroxylamine HCl (2 g) and sodium acetate trihydrate (4 g) were dissolved in distilled water and to this solution acetoxy ester **2** (1 g) was added. Ethanol was added dropwise to get a clear solution. The mixture was stirred with warming for 10 min on a water bath and then cooled in ice. The precipitated solid was filtered by suction and crystallized from dilute ethanol. Yield: 83%, m.p. 157°C.

IR (cm^{-1}) KBr: 3300 ν(—N—H—, —O—H—), 1685–1670 ν(—C=O—), 1560 ν(Ar C=C).

4-Hydroxybenzothiophene-6-carboxhydrazide (7): To hydrazine hydrate (1 mL) acetoxy ester **(2)** (1 g) was added in small portions and the mixture was heated gently under reflux for 10 min, then a small quantity of absolute alcohol was added and refluxed for 2 h. Alcohol was distilled off and the residual carboxyhydrazide was crystallized from ethanol. Yield: 90% m.p. 233°C.

IR (cm^{-1}) KBr: 3300–3142 ν(—O—H), 3242–3103 ν(—NH_2), 1633 ν(—C=O), 1610 ν(—NH_2 def.), 1572 ν(ArC=C—). MS: m/z 208 (M^+ 20), 177 (100), 149 (42), 121 (15), 69 (17), 40 (23).

Pharmacological Studies: The newly synthesized compounds were screened for anti-inflammatory activity by carrageenan induced rat hind paw oedema method[8] using ibuprofen as standard and analgesic activity by acetic acid induced writhing method in mice[9] against paracetamol as positive control.



Compd. No.	Substitution		m.p. (°C)	Yield (%)	% A.A.	% Analgesic activity
	R	R′				
2	$COCH_3$	OCH_3	82–84	36	43.5	35.3
3	H	OH	243–245	88	44.8	37.0
4	CH_2COOH	OH	276–277	66	52.2	36.4
5	H	OCH_3	142	91	44.0	36.5
6	H	NHOH	157	83	53.7	39.1
7	H	$NHNH_2$	233	90	NS	NS
8	Ibuprofen	—	—	—	68.2	—
9	Paracetamol	—	—	—	—	44.3

% A.A. Anti-inflammatory activity. NS: Not screened. Dosage: 100 mg/kg body weight.

RESULTS AND DISCUSSION

All the compounds show moderately good anti-inflammatory and analgesic activities which indicates that the structure is a good pharmacophoric base. The acetoxy-ester (**2**) shows good anti-inflammatory and analgesic activities indicating the potential prodrug nature of the functional groups. Compound **4** with phenoxyacetic acid group at C-4 and compound **6** with hygroxamic acid group at C-2 have much increased activity to that of the parent hydroxy acid (**3**). Generally the cyclooxygenase inhibitor NSAIDs have single acidic site[10] and the lipoxygenase receptor site of Young[11] has two acidic sites. The good anti-inflammatory activity of compounds **3**, **4** and **6** with two acidic/phenolic sites may be on account of the interaction of either[12] or both acidic sites. The analgesic activity, usually associated with the NSAIDs, is good throughout the series.

ACKNOWLEDGEMENTS

Authors are thankful Prof B.G. Shivananda, Principal, Al-Ameen College of Pharmacy, Bangalore for providing facilities and we are also thankful to Dr. B.H. Patwardhan, U.S.A. Dr. M.K. Gurjar and Dr. N.W. Fadnavis I.I.C.T. for their help in analysis.

REFERENCES

1. P.K. Radl Sen, U.K. Saha and T. Das, *Indian J. Chem.*, **39B**, 334 (2000).
2. J. Svoboda, M. Stadler, A. Jandera, V. Panajotova and M. Kuchar, *Czech. Chem. Commun.*, **65**, 1082 (2000).
3. S.A. Beers and M.P. Wachter, U.S. 5783597 A (1998); *Chem. Abstr.*, **129**, 148904 (1999).
4. A. Dannerberg and G. Muller, PCT Int. Appl. WO 2001074362 Al (2001); *Chem. Abstr.*, **135**, 283227 (2001).
5. A.L. Stefan, D.P. Gerd and K.J. Werner, *J. Med. Chem.*, **37**, 1897 (1994).
6. D.L. Flynn, T.R. Belliotti, A.M. Boctor, D.T. Connor, C.R. Costalan and D.E. Nies, *J. Med. Chem.*, **24**, 518 (1991).
7. S.M. Abdel-Wahhab and N.R. El-Reyyes, *J. Chem. Soc.*, **152**, 3171 (1971).
8. C.A. Winter, E.A. Risley and G.W. Nuss, *Proc. Soc. Exp. Biol. Med.*, **111**, 544 (1962).
9. P.S. Prem, Y.J. Ajit, S. Rao, K.V. Ravindra and D.B. Shridhar, *Expt. Clin. Pharmacol.*, **5**, 601 (1983).
10. T.Y. Shen, *Top. Med. Chem.*, **1**, 29 (1967).
11. R.N. Young, *Adv. Prostaglandin Thromboxane, Leukotrienes Res.*, **19**, 643 (1989).
12. S.G. Kashkedikar and G. Bagavant, *Indian J. Pharm. Sci.*, **51**, 188 (1989).

(*Received*: 03 July 2003; *Accepted*: 09 December 2003) AJC-3275