Synthesis of benzofuran analogs of fenamates as non steroidal antiinflammatory agents

Balasaheb Y Mane1*, Y S Agasimundin2 & B Shivakumar2
1SVPM’s College of Pharmacy, Malegaon BkII, Baramati 413 115, India
2Department of Pharmaceutical Chemistry, S.C.S. College of Pharmacy Harpanahalli 583 131, India
E-mail: balasahebmane24@rediffmail.com

Received 5 January 2009; accepted (revised) 15 September 2009

A series of benzofuran analogs of anthranilic acid derivatives are synthesized. All the new compounds have been characterized by spectral data and elemental analyses and screened for antiinflammatory activity. Compounds 3e, 4e, 4g and 5g are found to possess antiinflammatory activity comparable to that of standard diclofenac sodium.

Keywords: Benzofuran, anthranilic acid, antiinflammatory activity

The fenamates are a class of NSAIDs that have common structural features of an n-arylanthranilic acid such as mefenamic acid, meclofenamic acid and flufenamic acids1-3. These are the first line therapeutic agents for the clinical treatment of various inflammatory disorders4. In view of this, several anthranilic acid derivatives have been prepared for investigation of antiinflammaotry activity. Many such compounds were found to possess potent antiinflammatory5-7, cardiovascular8 and analgesic9 activities. Anthranilic acid derivatives are known to act by blocking the metabolism of anthranilic acid by the enzyme cyclooxygenase (CO) and thereby the production of prostaglandins. Inhibiting CO may also increases the conversion of arachidonic acid to proinflammatory leukotrienes via the enzyme 5-lipoxygenase (5-LO). The replacement of the carboxylic acid functionality with tetrazole not only retained the CO inhibitory activity of the parent but also inhibited 5-LO (Ref. 10). Literature survey shows that modification of carboxylic group in anthranilic acid markedly modulates the activity11.

Compounds containing benzofuran nucleus are widely distributed in nature amongst the plant kingdom. Such compounds are often associated with useful biological and pharmacological activities. This stimulated to synthesise benzofuran analogs of anthranilic acid derivatives in which benzene moiety of anthranilic acid is replaced by benzofuran moiety.

Ethyl 3-hydroxybenzofuran-2-carboxylate 1 was prepared by single pot synthesis12,13 from methyl salicylate and diethylbromomalonate. The reaction of this with various aromatic amines at 90-95°C in presence of catalytic amount of Conc. hydrochloric acid produced ethyl 3-arylaminbenzofuran-2-carboxylate 3a-h, while the reaction at reflux temperature gave 3-hydroxybenzofuran-2-carboxanilides 2a-h. Hydrolysis of esters 3a-h using ethanolic potassium hydroxide gave the corresponding carboxylic acids, some of these are unstable and undergoes decomposition so isolated as potassium salt. Finally, compounds 3a-h were converted into carbohydrazides 5a-h by reaction with hydrazine hydrate at room temperature Scheme 1. IR spectra of 3a-h exhibited an absorption band in the region 3350-3440 cm\(^{-1}\) due to NH and strong band in the region of 1666-1685 cm\(^{-1}\) due to ester carbonyl. \(^1\)H NMR spectra of 3a-h revealed a signal at \(\delta\) 7.0-7.92 as a multiplet corresponding to aromatic protons, a quartet at \(\delta\) 2.0 corresponding to two protons due to CH\(_2\) group, a deuterium exchangeable broad singlet at \(\delta\) 1.6 due to NH proton and a triplet at \(\delta\) 1.2 corresponding to three protons of CH\(_3\) group. IR spectra of 5a-h exhibited an absorption band in the region 3326-3340 cm\(^{-1}\) due to NHNH\(_2\) and strong band in the region of 1666-1685 cm\(^{-1}\) due to ester carbonyl. \(^1\)H NMR spectra of 5a-h revealed a signal at \(\delta\) 1.8 as a broad singlet corresponding to three protons of CH\(_2\) group, a deuterium exchangeable broad singlet at \(\delta\) 1.6 due to NH proton and a triplet at \(\delta\) 1.2 corresponding to three protons of CH\(_3\) group. IR spectra of 5a-h exhibited an absorption band in the region 3326-3340 cm\(^{-1}\) due to NHNH\(_2\) and strong band in the region of 1614-1630 cm\(^{-1}\) due to carbonyl. \(^1\)H NMR spectra of 5a-h revealed a signal at \(\delta\) 1.8 as a broad singlet corresponding to three protons of NHNH\(_2\), a broad singlet at \(\delta\) 4.0 corresponding to one of NH and a multiplet at \(\delta\) 7.0-8.0 corresponding to aromatic protons Table I.

Experimental Section

Melting points were determined in open capillary tubes and are uncorrected. The FT-IR spectra were recorded in KBr on a Shimadzu FTIR-8400S spectrophotometer. \(^1\)H NMR spectra were recorded in CDCl\(_3\) on a Varian Mercury YH-300, using TMS as an internal standard.
Ethyl 3-arylamino-2-carboxylates 3a-h

An intimate mixture of 1 (0.01 mole), aromatic amine (0.011 mole) and a drop of Conc. hydrochloric acid was left overnight at RT and then heated at 90-95°C for 9 hr. The reaction-mixture was cooled and extracted with ether (25 × 2 mL). The organic layer was washed successively with 2N hydrochloric acid and aqueous sodium hydroxide (10%) to remove the unreacted starting material, dried over anhydrous sodium sulphate. Removal of solvents under reduced
pressure gave the product, which was crystallized from aqueous ethanol. The physical and analytical data are mentioned in Table II.

### 3-Arylaminobenzofuran-2-carboxylic acids 4a, 4b, 4c

Compounds 3a, 3b, 3c (0.05 mole) were hydrolyzed by heating under reflux in ethanolic potassium hydroxide (3.5%, 40 mL) just for 3 minutes. The resulting solution was diluted with water, cooled and carefully acidified. The carboxylic acids thus separated were collected and crystallized from suitable solvent. The physical and analytical data are mentioned in Table II.

### Potassium salts of 3-arylaminobenzofuran-2-carboxylic acids 4d-h

Compounds 3d-h were hydrolysed by heating under reflux in ethanolic potassium hydroxide (3.5% 40 mL) for 25 minutes. The potassium salt which separated out as white crystals, on cooling in refrigerator overnight was collected. The physical and analytical data are mentioned in Table II.
NOTES

267

3-Arylaminobenzofuran-2-carbohydrazides 5a-h

A solution of 3a-h (0.005 mole) in ethanol (10 mL) was mixed with excess of hydrazine hydrate (80%) and kept under stirring magnetically at RT for 20 hr. The carbohydrazides which separated out as colourless solid was collected by filtration and crystallized from aqueous ethanol. The physical and analytical data are mentioned in Table II.

Anti-inflammatory activity

Compounds were screened for anti-inflammatory activity by carrageenan induced rat paw edema.
method. Diclofenac sodium was used as standard. Rats were divided into control, standard and different test groups comprising of six animals in each group. They were fasted overnight with free access to water before experiment. In all groups acute inflammation was induced by sub plantar injection of 0.1 mL of freshly prepared 1% suspension of carrageenan in the right hind paw of the rats and paw volume was measured using plethysmometer at 0 hr and 3 hr after carrageenan injection. Rats of test groups were administered orally with test compounds 100 mg/kg and the standard group with diclofenac 100 mg/kg orally in 2% aqueous acacia 1 hr before injection of carrageenan. Control group received only vehicle.

Mean difference in paw volume was measured and percentage of inhibition of edema was calculated and given in Table III.

**Result and Discussion**

In the conversion of ethyl 3-hydroxybenzofuran-2-carboxylate 1 to ethyl 3-arylaminobenzofuran-2-carboxylates 3a-h substituted aromatic amines specially p-substituted aniline gives better yield compared to aniline. The conversion of ethyl 3-arylamino benzofuran-2-carboxylate to ethyl 3-arylamino benzofuran-2-carbohydrazide were carried out at RT which gave good yield. All the new compounds have been screened for antiinflammatory activity and the results are given in Table III. Some of the compounds showed antiinflammatory activity nearly close to that of standard diclofenac sodium. Compounds 4e and 4g which are the potassium salts of the carboxylic acids showed maximum activity because of their solubility in water. The compounds that bear the substituted aniline moiety gave better antiinflammatory activity compared to other compounds.

In conclusion, the conversion of carboxylic acid functionality to esters and carbohydrazides in benzofuran analogs of anthranilic acid maintains better antiinflammatory activity.

**Acknowledgement**

Authors are thankful to Dr. S. Ramchandra Setty, Principal, S.C.S.College of Pharmacy and Mr. R.N.Patil Principal I/C, SVPM’s College of Pharmacy, Malegaon BkII, Baramati for providing laboratory facilities.

**Reference**


