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RESEARCH ARTICLE

NOVEL SYNTHESIS AND ANTI-INFLAMMATORY ACTIVITY OF SCHIFF BASES OF KETOPROFEN HAVING HETEROCYCLIC MOIETY

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ABSTRACT

A new series of two Schiff bases of ketoprofen having heterocyclic moiety have been synthesized in present investigation. We have tested the anti-inflammatory activities of the synthesized compounds in vivo by using carrageenan induced edema model, using ketoprofen as standard. The safety of these newly synthesized derivatives is reflected by toxicity studies.

Key Words: Heterocyclic moiety, Schiff bases, Carrageenan, Anti-inflammatory.

INTRODUCTION

Arachidonic acid (AA) stored in cell membranes is metabolized by two enzymatic families namely cyclooxygenases (Cox-1,-2 and -3) and lipooxygenases (5-, 8-, 12- and 15-Lox). These enzymes convert AA into prostaglandins, prostocyclines and lecuotrienes, which are involved in physiological processes as well as pathological responses such as inflammation formation (Funk, 2001). Currently used nonsteroidal anti-inflammatory drugs (NSAIDs) act through the nonselective inhibition of cyclooxygenase isoform (Cox-1 and Cox-2) and show some side effects including gastrointestinal activity , which appears to occur as a result of the inhibition of cox-1isoenzyme which is involved in many physiological processes including gastric cytoprotection **(**Meyer *et al.*, 2000). Moreover, cox inhibition alone may lead to upregulation of the 5-Lox pathway, causing various side effects especially in the GI tract and kidney **(**Charlier *et al.*, 2003). Therefore developing potential drugs with high analgesics and anti-inflammatory activity lacking the general side-effects of currently used NSAIDs is still a debate.

We have been long interested in developing biologically active molecule having heterocyclic moiety with potent anti-inflammatory activity and devoid of GI side effects (Banoglu *et al.*, 2003). Our recent studies indicated that Schiff bases of ketoprofen alleviated the pain and suppressed the induced inflammation. Furthermore the toxicity studies were carried out to determine their safety profile of newly synthesized compounds (3a and 3b).

Structures

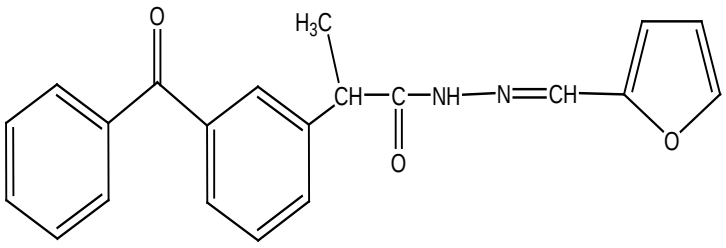

Figure 3a: 2-(3-benzoylphenyl)-N'-(furan-2-ylmethylene) propane hydrazide

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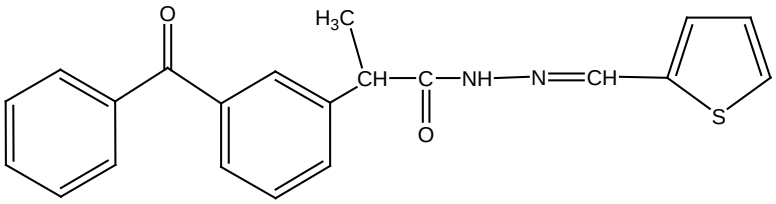
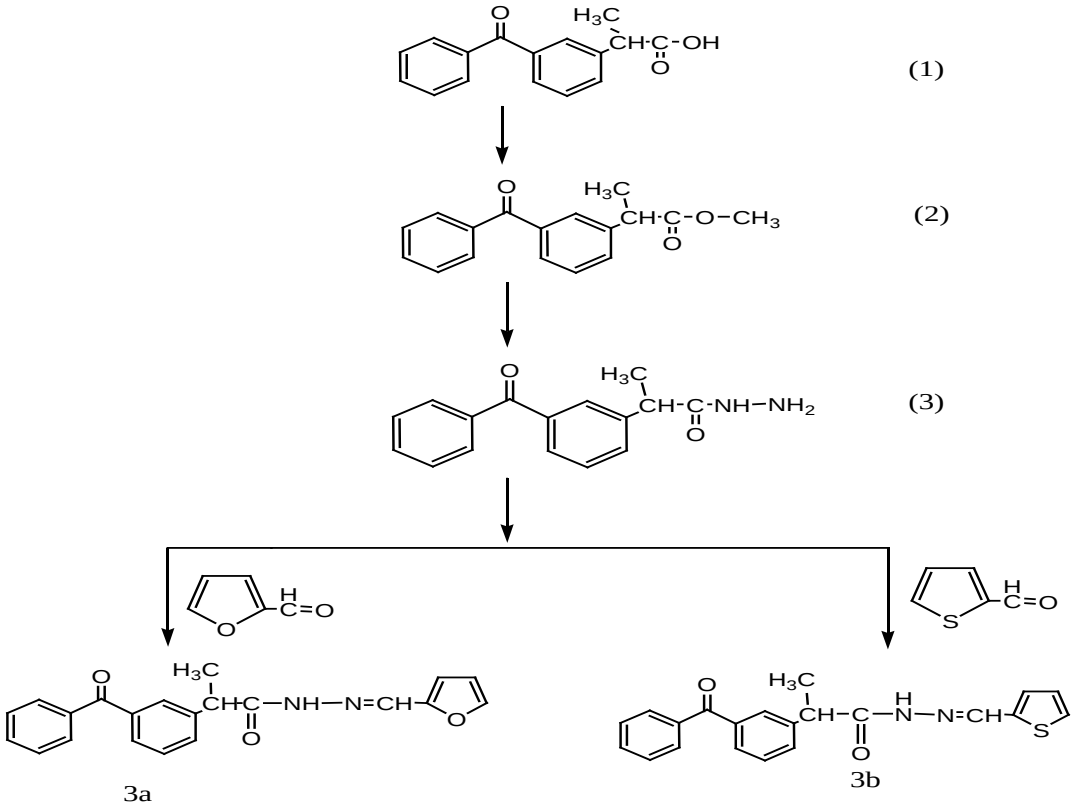


Figure 3b: 2-(3-benzoylphenyl)-N'-(thiophene-2-ylmethylene) propane hydrazide

RESULTS AND DISCUSSION

Schiff bases of ketoprofen (1) have heterocyclic moiety [furan (3a) and thiophene (3b)] were prepared from ketoprofen (Scheme 1).

Scheme 1



Ketoprofen (1) was prepared (Mitra *et al.*, 1988) and subsequent esterification, hydrazinolysis was carried out by the known method as reported in the literature **(**Carter *et al.*, 1999; Mazaleyrat *et al.*, 1999).The anti inflammatory activity of 3a and 3b were studied in vivo for their percent inhibition of edema in the carrageenan model of inflammation in rats using the method illustrated by Winter et al **(**Winter *et al.*, 1962).

The percent inhibition of edema was calculated against the control on the basis of experimental data. Statistical analysis revealed that anti-inflammatory activity of 3a and 3b was better in comparison to standard drug ketoprofen. The percent inhibitions of 3a and 3b at the end of three hours were 82.00 and 83.00 respectively. The low toxicity of synthesized compounds was evident from the observation that there was no mortality in mice at doses up to 1000 mg/kg.

MATERIALS AND METHODS

All melting points were determined in open capillary tube and are uncorrected. IR spectra were recorded on a Perkin Elmer FTIR spectrometer. ^{1}H NMR spectra were recorded on Bruker FT 300 MHz using deuterated solvents, TMS as internal reference and chemical shifts are expressed in δ ppm. All reactions were monitored by TLC using Merck pre-coated silica gel plates and spots were visualized against UV light. All reagents and solvents were purchased from Aldrich Chemicals and used as supplied without any further purification.

EXPERIMENTAL

Synthesis of methyl-2-(3-benzoylphenyl)propanoate (2)

A mixture of 2-(3-benzoylphenyl)propionic acid (0.01 mole) (1), methanol (0.05 mole) and catalytic amount of concentrate HCl (0.5 mL) was refluxed for 8 hours. Excess of methanol was removed under distillation and the content were rendered basic (pH 8) by sodium carbonate. The reaction mixture was cooled, filtered and the crude product was isolated.

Recrystallized from methanol (yield 63%). m.p. 66-68 °C,

^{1}H NMR (DMSO-d_6) δ: 1.54 (s, 3H, CH_3), 3.80 (q, 1H, CH), 7.30-7.77 (m, 9H, Ar-H)

IR ν max cm^{-1} (KBr): 1764, 1644, 1620

Anal: $C_{17}H_{16}O_3$

Synthesis of methyl-2-(3-benzoylphenyl) propane hydrazide (3)

A mixture of methyl-2-(3-benzoylphenyl) propanoate (0.01 mole) (2), 99% 100% hydrazine hydrate(0.012 mole), methanol (50 mL) was refluxed for 4 hours, Excess of methanol was removed under distillation. The reaction mixture was cooled, filtered and the crude product was isolated.

Recrystallized from methanol (yield 66%). m. p. 215-216, °C,

^{1}H NMR (DMSO-d_6) δ: 1.52 (s, 3H, CH_3), 2.20 (s, 2H, NH_2) 3.90 (q, 1H, CH), 7.31-7.78 (m, 9H, Ar-H), 8.01(s, 1H, NH)

IR ν max cm^{-1} (KBr):1711, 1640, 1621, 1656

Anal: $C_{16}H_{16}N_2O_3$

Synthesis of 2-(3-benzoylphenyl)-N'-(furan-2-ylmethylene) propane hydrazide (3a)

A mixture of 2-(3-benzoylphenyl) propane hydrazide (0.01 mole) (3), furan-2- carboxyaldehyde (0.01 mole) and methanol (50 ml) was refluxed for 4 hours. Excess of methanol was removed under distillation. The reaction mixture was cooled, filtered and the crude product was isolated.

Recrystallized from methanol (yield 60%). m. p. 219°C (d),

^{1}H NMR (DMSO-d_6) δ: 1.55 (s, 3H, CH_3), 3.90 (q, 1H, CH), 7.50 (s, 1H, NH_2), 6.30-7.40 (m, 3H, furan ring), 7.42-7.94 (m, 9H, Ar-H), 8.12(br, s, 1H, NH)

IR ν max cm^{-1} (KBr): 1700, 1655, 1600, 1490

Anal: $C_{21}H_{18}N_2O_3$

Synthesis of 2-(3-benzoylphenyl)-N'-(thiophene-2-ylmethylene) propane hydrazide (3b)

A mixture of 2-(3-benzoylphenyl) propane hydrazide (0.01 mole) (3), thiophene-2-carboxyaldehyde (0.01 mole) and methanol (50 ml) was refluxed for 5 hours. Excess of methanol was removed under distillation. The reaction mixture was cooled, filtered and the crude product was isolated.

Recrystallized from methanol (yield 51%). m. p. 231°C,

^{1}H NMR (DMSO-d_6) δ: 1.56 (s, 3H, CH_3), 3.91 (q, 1H, CH), 7.52 (s, 1H, NH_2), 6.29-7.36(m, 3H, thiophene ring), 7.44-7.94 (m, 9H, Ar-H), 8.14(br, s, 1H, NH)

IR Vmax cm^{-1} (KBr): 1702, 1656, 1600, 1489

Anal: $C_{21}H_{18}N_2O_2S$ = 346

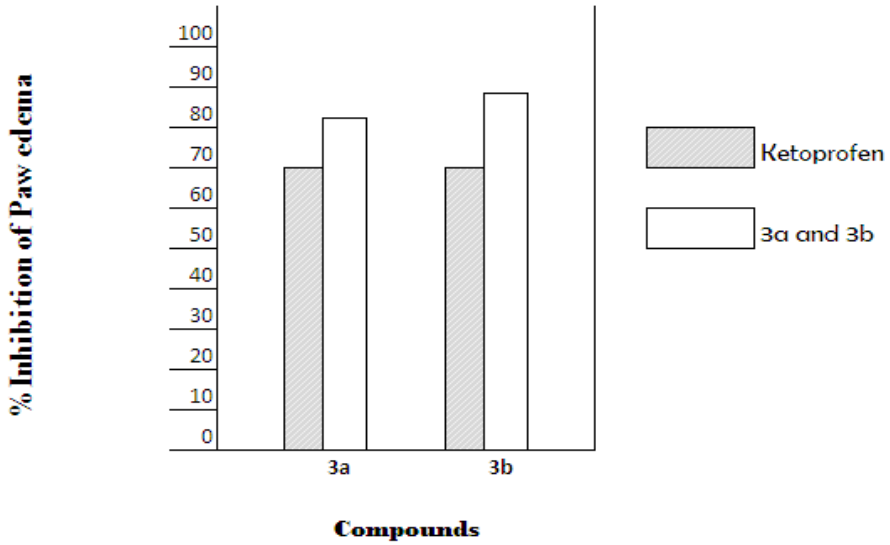


Fig 1 - Comparison of anti-inflammatory activities of 3a and 3b with ketoprofen.

Anti-inflammatory activity

Animals

Sprague-Dawley rats (140-200g) of both sexes were used for the studies. These rats were obtained from the Department of Bio-pharmaceutics, Haffkine Institute, Mumbai. The animals were divided into groups of six each and fasted for 12 hr. before the experiment. The ethical guidelines prescribed for the investigation of animals used in experiments were followed in all test.

Paw edema induced by carrageenan

Carrageenan (0.1ml, %) was administered into the plantar surface of the right hind paw of the animals. The experimental groups, negative control group (0.5% CMC), and positive control group (20 mg/kg ketoprofen were given either the control drug or test compounds orally, one hour prior to the administration of the carrageenan. Before injection of carrageenan, the average volume (V_0) of the right hind paw of each rat was calculated from three readings that did not deviate more than 3%. After injection of the phlogistic agent, the paw volume (V_t) was measured after three hour with the aid of a plethysmometer. The edema was expressed as an increase in the volume of paw and percentage inhibition of acute edema was obtained as follows:

% inhibition = [1-(ΔV experimental/ ΔV control)] × 100

Where $\Delta V = V_t - V_0$ = Mean paw volume

Data analysis

Results are presented as mean ± SEM (Standard error of mean) of six rats. Statistical analysis were performed using one way analysis of varience (ANOVA) followed by Dunnett's test for multiple comparison, using Graph-pad software. P value of $P<0.05$ were taken as significant.

Toxicity study

Acute toxicity of 2-(3-benzoylphenyl)-N'-(furan-2-ylmethylene) propane hydrazide (3a) and 2-(3-benzoylphenyl)-N'-(thiophene-2-ylmethylene) propane hydrazide (3b) was determined in albino mice with the staircase method(Pontiki *et al.*, 2008; Ghosh, 1981). Each group of 5 animals was tested for 24 hours prior to the administration of the test compounds 3a and 3b. The test compounds 3a and 3b administered orally in doses up to 1000 mg/kg and mice were kept under observation for period of 24 hour.

Table 1
In-vivo anti-inflammatory activities of 3a and 3b

Compound	$V_t - V_0$ mean ± SEM	% inhibition of edema at the end of three hours
Ketoprofen	0.09±0.010	70.00
3a	0.008±0.017	82.00
3b	0.126±0.020	83.00

Values expressed as mean ± SEM, n=6 in each group

*P < 0.01 compared with control

CONCLUSION

2-(3-benzoylphenyl)-N'-(furan-2-ylmethylene) propane hydrazide (3a) and 2-(3-benzoylphenyl)-N'-(thiophene-2-ylmethylene) propane hydrazide (3b) synthesized during percent study have shown good anti-inflammatory activity in the carrageenan induced paw edema model. Chemical conversion of ketoprofen to Schiff bases and introduction furan and thophene moiety seems to exhibit better anti-inflammatory activity in comparison to ketoprofen

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