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RESEARCH ARTICLE

Synthesis and Evaluation of Ibuprofen Derived Analogs as Potential Anti-Inflammatory Agents

Dobhal, Y.*, Gupta, R., Kaur, I.

Sardar Bhagwan Singh (P.G) Institute of Biomedical Sciences and Research, Dehradun, India.

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ABSTRACT

In the present study four ibuprofen analogs having anti-inflammatory potential synthesized with a series of chemical reactions up to final derivative such as 2-(4-sec-butyl-phenyl)-propionic acid-pyridin-2-ylcarbamoylmethyl ester with bio-isosteric concept form ibuprofen. Ibuprofen on refluxing with 2-amino pyridine in chloroacetyl chloride in presence of glacial acetic acid synthesize 2-(4-sec-butyl-phenyl)-propionic acid-pyridin-2-yl-carbamoyl methyl ester, which can be used as a prodrug for ibuprofen. Derivative on treatment with various cycloamino moieties such as morpholine, pyrrolidine, hydrazine hydrate gave compounds. Structure of all these compounds were confirmed on the basis of their analytical and spectral data. The compounds were characterized by IR and elemental analysis. Some of these compounds have shown significant anti-inflammatory activity.

KEYWORDS

Ibuprofen, 2- amino pyridine, Chloroacetyl chloride, Glacial acetic acid, 2-(4-sec-butyl-phenyl)-propionic acid-pyridin-2-yl-carbamoyl methyl ester, Anti-inflammatory activity

INTRODUCTION

The hall marks of inflammation was first described by Celsus-Aulus (Aurelius) Cornelius, a Roman physician and medical writer in 30B.C.to 45 A.D. the Greek word “Phlegmon” was used to describe internal inflammatory lesions. The inflammation (Latin-*inflammare*: to set on fire) is stereotyped i.e. a similar sequence of events occurs in a variety of tissue sites in response to a diversity of injuries.[1] The inflammation is a localized protective response elicited by destruction of tissues that serves to destroy, dilute or wall off both the injurious agents and the injured tissues, which can be provoked by physical, chemical and biological agents, including mechanical trauma, exposure to excessive amount of sunlight, X-rays and radioactive materials, corrosive chemicals, extremes of heat and cold and infectious agents such as bacteria, viruses and other pathogenic microorganisms,[2,3] Moreover, inflammation is of two types: one is acute inflammation which involves polymorphonuclear neutrophil leukocytes and other is chronic inflammation which involves monocytes, macrophages, lymphocytes and plasma cells. A measurable historical perspectives showed that the Cornelius Celsus (1st century AD Rome) postulated the cardinal sign of inflammation as redness (*Rubor*), swelling (*Tumor*), heat (*Calor*), pain (*Dolor*) and loss of function (*Functio laesa*).[4,5]

Ibuprofen belongs to the phenylpropionic acid derivatives which belong to the arylalkalonic acid, the largest group of anti-inflammatory agents. In contrast to previous serendipitous discovery the modern research was aimed to

***Address for Correspondence:**
Yogita Dobhal
SBSPGI, Balawala,
Dehradun, India.
E-Mail Id: yogita_sharma05@rediffmail.com

design and synthesize new compounds as rationale for anti-inflammatory drug design. From the several side chain substituted derivatives and manipulation of aromatic ring of ibuprofen and flurbiprofen has emerged as the most interesting compound for the anti-inflammatory activity.[6] Early efforts to modulate the activity of ibuprofen regarded the substitution of the aromatic ring.[7] Most of them which have passed the clinical stages include: nabumetone and sulindac. Amongst the ring modified derivatives, compounds lack the common characteristic features of ibuprofen like compounds. The only compound that has been studied includes thiadiazole or oxadiazole derivatives. These compounds have substituted hydroxamate side chains and acceptable acid additions or base salts which makes the pharmaceutical compositions. The 2-amino pyridine has been chosen as a moiety for anti-inflammatory action due to the presence of the lactam-lactim type of tautomerism which makes the nitrogen containing compounds most beneficial for the pharmacological activities. The pyridine nucleus and the benzene nucleus both are known to exhibit the phenomenon of ring equivalence. So, 2-amino pyridine was rationally used for designing of compounds.[8] Therefore, the analogs were prepared from it by using this type of bio-isosterism with ibuprofen for evaluating the anti-inflammatory activity.

MATERIALS AND METHOD

The melting points were determined by thieless tube method using liquid paraffin and were uncorrected. The Infrared (I.R.) spectra were recorded on a Shimadzu (Japan) 8400 S FTIR spectrophotometer model using nujol and potassium bromide and on Perkin Elmer RX1 using potassium bromide cell for liquid sample and potassium bromide pellets for solid samples. The purity of compounds was established by Thin Layer Chromatography (T.L.C). Iodine was used to develop the T.L.C. plates. All the solvents were distilled prior to use according to standard procedures.

Anhydrous potassium carbonate was used as a drying agent.

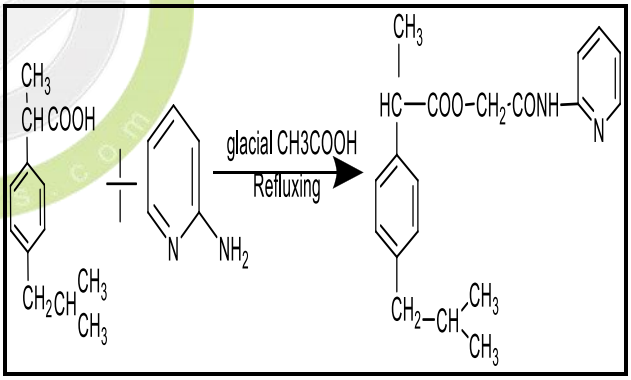
Experimental

Ibuprofen Derived Analogs

Scheme 1: Synthesis of 2-(4-sec-butyl-phenyl)-propionic acid-pyridin-2-yl-carbamoyl methyl ester (Bio-isosteric esterification of ibuprofen)(D1)

Ibuprofen 1gm was dissolved in glacial acetic acid 25ml and chloro acetyl chloride 2.5 ml was added drop wise with constant stirring to the solution. Then, 2- amino pyridine 1 gm was added, continued refluxing on water bath for 12 hours at 90°C and reaction was monitored with the help of T.L.C. The ester of ibuprofen was formed which was used as an intermediate for the preparation of other compounds. The brown colored crystalline liquid provided, yield equal to 42.9% with M.P equal to 90°C.Purity of the compound was confirmed by:

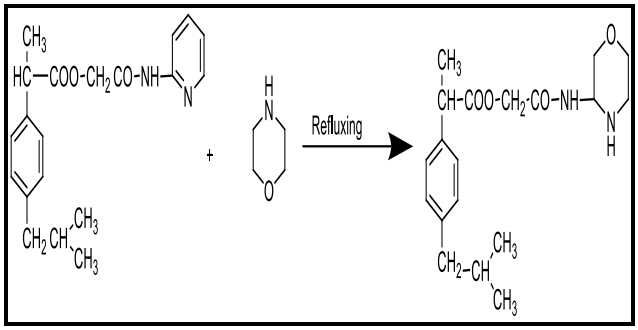
T.L.C (Rf value-0.70) in solvent eluent: Chloroform (85) +Methanol (5)



Scheme 2: Synthesis of 2-(4-sec-butyl-phenyl)-propionic acid-morpholin-3-yl-carbamoyl methyl ester (D2)

The intermediate 4ml and morpholine 2ml was refluxed on water bath for 20 hours at 100°C temperature and reaction was monitored with the help of T.L.C. The dark viscous liquid obtained was obtained, yield equal to 43.85% with M.P equal to 95°C. Purity of the compound was confirmed by:

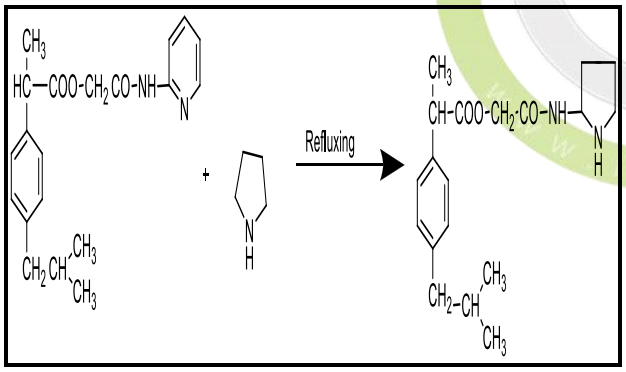
T.L.C (Rf value-0.75) in solvent eluent: Chloroform (85) + Methanol (5)



Scheme 3: Synthesis of 2-(4-sec-butyl-phenyl)-propionic acid-pyrrolidin-2-yl-carbamoyl methyl ester (D3)

The intermediate (4ml) **(21)** and pyrrolidine (6.2ml) was refluxed on water bath for 6 hours at 100°C temperature and reaction was monitored with the help of T.L.C. The liquid obtained was obtained as the target compound, yield equal to 40.87% with M.P equal to 100°C.Purity of the compound was confirmed by:

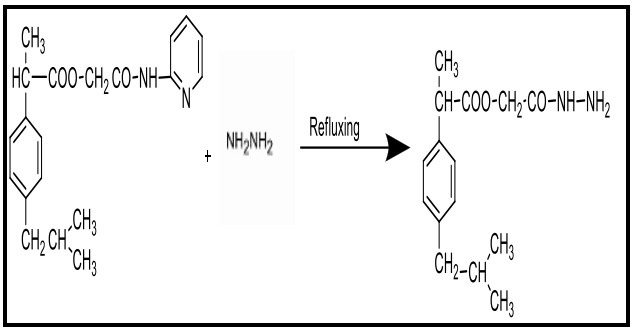
T.L.C (Rf value-0.74) in solvent eluent:Chloroform (85) + Methanol (5)



Scheme 4: 2-(4-sec-butyl-phenyl)-propionic acid hydrazinecarbonyl methyl ester (D4)

The intermediate 4 ml and hydrazine hydrate 5.5ml was refluxed on water bath for 10 hours at 100°C temperature and reaction was monitored with the help of T.L.C. The liquid obtained was obtained as the target compound, yield equal to 43.15% with M.P equal to 85°C. Purity of the compound was confirmed by:

T.L.C (Rf value-0.75) in solvent eluent: Chloroform (85) + Methanol (5)



Animals

Adult Wister albino rats of either sex weighing up to 200 gm were housed in polypropylene cages and fed with standard diet (Ashirwad Feeds Ltd., Chandigarh, India) and *ad libitum*. The animals were exposed to alternate cycle of 12 h of light and dark. The study protocol was reviewed and approved by the Institution Animal Ethical Committee (Registration no. IAEC/273/CPCSEA/09/I/2256/15) and conforms to the CPCSEA Guidelines for the use and care of experimental animals in research. The animal house was maintained at the temperature 26-28°C and relative humidity was about 65-68%.

Acute Toxicity Study

All the compounds before screening for their pharmacological activity were tested for their toxicity studies. The acute toxicity studies were performed in which a drug is tested to determine LD50 i.e. lethal dose for 50% of mortality in a group of animals. Therefore, from the toxicological data obtained the safest dose for the pharmacological activity was selected as 3mg/kg.[9]

Anti-inflammatory Activity

The anti-inflammatory activity screening was carried out by using paw edema method.[10] All the compounds at the dose of 3 mg/kg body weight were dissolved in sodium C.M.C solution and were administered intravenously. The animal were then injected carrageenan into the sub planter region of the right hind paw of each rat. The paw volumes were recorded by plethysmograph. The efficacy of the compound was evaluated by comparing the results with those obtained by dosing the reference standard, Ibuprofen50 mg/kg body weight.

RESULTS

Table 1: Physico-chemical data of compounds

Compound	Molecular Formula	Molecular Weight	Melting point(°C)	(%) Yield
D1	$C_{20}H_{24}N_2O_3$	340.42	**90**	42.90
D2	$C_{19}H_{28}N_2O_4$	348.44	**95**	43.85
D3	$C_{19}H_{28}N_2O_3$	332.44	**100**	40.87
D4	$C_{15}H_{22}N_2O_3$	278.35	**85**	43.15

Table 2: I.R data of compounds

Compounds	Spectral Data
D1	IR(KBr cm^{-1}):880.8cm^{-1} (C-H, bending) 1418.5 cm^{-1}(C-O-H, bending).1291.2 cm^{-1} C-(C=O)-O, stretching),3081.9cm^{-1}(C-H, Aliphatic), 1569.2cm^{-1}(C-N, aromatic)
D2	IR(KBr cm^{-1}):1237.1cm^{-1}(C-O-C, stretching) 1043.5cm^{-1}(symmetric stretch of six membered ring),3416.5cm^{-1}(C-, stretching),2961.0 cm^{-1}(diketones)
D3	IR(KBr cm^{-1}):1401.8cm^{-1}(C-N, stretching), 29977.5cm^{-1}(C-H, methylene),3405cm^{-1} (N-H, aliphatic),3401.4 cm^{-1}(N-H, stretching)
D4	IR(KBr cm^{-1}):1401.8cm^{-1}(C-N, stretching), 656.3cm^{-1}(medium band of primary amine), 3315.7 cm^{-1}(N-H, symmetrical vibration), 1291.2cm^{-1}(C=O)-O, stretching)

Anti-Inflammatory Activity

The anti-inflammatory activity was determined as the percentage of inhibition of inflammation and the results are expressed as the percentage of inhibition.

Table 3: Anti-inflammatory activity data of compounds

S. No.	Compounds	No. of animals	Average Body weight (gm)	Inflammation (ml)	% inhibition of inflammation
1	Control	6	265	0.470±0.433	5
2	Ibuprofen	6	275	0.058±0.031	75
3	D1	6	255	0.072±0.019	78
4	D2	6	193	0.317±0.337	80
5	D3	6	270	0.100±0.000	82
6	D4	6	253	0.100±0.071	76

CONCLUSION

The preceding discussion would have convinced the reader that the designing and development of potent and efficacious anti-inflammatory drugs is going to be difficult task for medicinal chemist. These surpulous challenging difficulties offered increases the inherent complexity of the problem due to lack of a generally accepted mechanism of action at biological levels are some of the obstacles that still stand in the way of developing novel chemical entities for inflammatory disorders.

Evaluation of anti-inflammatory activity reveals that all synthesized compound were consistent with their activity. In the series of ibuprofen derived compounds D1-D4 have shown significant anti-inflammatory activity in comparison to reference drug, ibuprofen at 50mg/kg. The pyrrolidine derivative of ibuprofen produced through the application of bio-isosteric concept for 2- amino pyridine was most significant. Neverthless, it is that new recently disclosed compounds, seems to be endowed with unprecedented high potency as an anti-inflammatory entities will contribute to elucidate the mechanism of action at physiological level and this research has paved the path for the search of more effective newer anti-inflammatory agents to develop drugs with novel pharmacological profile and maximal therapeutic benefits.

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