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Research Article

SYNTHESIS OF 2-(4-SEC-BUTYL-PHENYL)-PROPIONIC ACID-PYRROLIDIN-2-YLCARBAMOYL METHYL ESTER DERIVATIVES AS ANTI-INFLAMMATORY POTENTIAL

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ABSTRACT

Synthesis of 2-(4-sec-butyl-phenyl)-propionic acid-pyrrolidin-2-ylcarbamoyl methyl ester with bio-isosteric concept for ibuprofen with enhancing anti-inflammatory potential. Ibuprofen on refluxing with 2-amino pyridine in chloroacetyl chloride in presence of glacial acetic acid gave 2-(4-sec-butyl-phenyl)-propionic acid-pyrrolidin-2-yl-carbamoyl methyl ester, which can be used as a prodrug for ibuprofen. Derivatives on treatment with (various cycloamino moieties such as morpholine, pyrrolidine, hydrazine hydrate etc.) gave compounds and structures of all these compounds were confirmed on the basis of their analytical and spectral data. The title compounds were characterized by their spectral (I.R., ^{1}H NMR, Mass Spectroscopy) and elemental analysis. Some of these compounds have shown significant anti-inflammatory activity.

Keywords: Ibuprofen, b2-(4-sec-butyl-phenyl)-propionic acid-pyrrolidin-2-ylcarbamoyl methyl ester, anti-inflammatory activity.

INTRODUCTION

Ibuprofen uses the Musculoskeltal systems of the human body. It belongs to the phenylpropionic acid derivatives which belongs to the arylalkalonic acid, the largest group of anti-inflammatory agents. In contrast to previous serendipitous discovery the modern research was aimed to design and synthesize new compounds as a rationale for anti-inflammatory drug design. From the several side chain substituted derivatives of ibuprofen, flurbiprofen has emerged as the most interesting compound.[1] Several attempts to modulate the anti-inflammatory activity through manipulation of the aromatic ring have been reported. Early efforts to modulate the activity of ibuprofen regarded the substitution of the aromatic ring. Most of them which have passed the clinical stages include: nabumetone and sulindac[2]. Amongst the ring modified derivatives this category of compounds lacks 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[3,4]. According to the, Belliotti et al. the pharmaceutical compositions may also contain a K^+/H^+-ATPase inhibitors such as omeprazole[5]. Amongst the side chain modified derivatives, S-triazines derivatives have been found to possess good diuretic and saluretic activities along with have been

extensively used as therapeutic agents such as: Sulfasymazine, Irsoglandin, Troclosene K and Prometryn[6,7,8]. 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[9,10]. Therefore, the analogs were prepared from it by using this type of bio-isosterism with ibuprofen for evaluating the anti-inflammatory activity.

EXPERIMENTAL

The melting points were determined by thieles's tube method using liquid paraffin and were uncorrected. The Infrared (IR) spectra were recorded on a Shimdzu (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 (in cm^{-1}). Proton –NMR spectra were recorded on Brucker multinuclear FT NMR spectrometer model AV-400 MHz using deuterated- chloroform containing tetramethylsilane(Me4Si) as internal standard (chemical shifts in δ, ppm). 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.

Synthesis of 2-(4-sec-butyl-phenyl)-propionic acid-pyridin-2-yl-carbamoyl methyl ester (4) (Bio-isosteric esterification of Ibuprofen)

Ibuprofen, (4.85 mmol) was dissolved in glacial acetic acid and chloro acetyl chloride (22.14mmole) was added drop wise with constant stirring to the solution. Then, 2 amino pyridine (10.63 mmol) 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 solid material which separated during heating was collected by filteration and crystallized from ethanol to yield **4**. The brown coloured crystalline solid was formed which are further used for the preparation of **5a, 5b, 5c, 5d, 5e, 5f**.

Synthesis of 2-(4-sec-butyl-phenyl)-propionic acid-pyrolidino-3-yl-carbamoyl methyl ester (5a)

The intermediate (2.05 mmol) and pyrolidine (14.08 mmol) was refluxed for 6 hrs and reaction was monitored with the help of T.L.C. The reaction mixture was cooled to room temperature and poured into ice water to complete the precipitation. The solid was filtered off and recrystallized from ethanol to give the title compound **5a**.

Synthesis of 2-(4-sec-butyl-phenyl)-propionic acid-morpholino-2-yl-carbamoyl methyl ester (5b)

The intermediate (2.05 mmol) and morpholine (11.90 mmol) was refluxed for 4 h and reaction was monitored with the help of T.L.C. The reaction mixture was left overnight and then poured into ice cold water to complete precipitation. The solid was filtered off and recrystallized from methanol to give the title compound **5b**.

2-(4-sec-butyl-phenyl)- propionic acid hydrazin-carbonyl methyl ester (5c)

The intermediate (2.05 mmol) and hydrazine hydrate (2.06 mmol) was refluxed for 5 h and reaction was monitored with the help of T.L.C. The reaction mixture was cooled to room temperature and poured into ice water to complete the precipitation. The solid was filtered off and recrystallized from ethanol to give the title compound **5c**.

2-(4-sec-butyl-phenyl)-propionic acid-imidazolo-3-yl-carbamoyl methyl ester (5d)

The intermediate (2.05 mmol) and imidazole (0.15 mmol) was refluxed for 8 h and reaction was monitored with the help of T.L.C. ,then left to cool for complete precipitation. The solid product was filtered and recrystallized from ethanol to give the compound **5d**.

2-(dimethylamino)-2-oxoethyl2-4(4-isobutyl phenyl) propanoate(5e)

The intermediate (2.05 mmol) and dimethyl (22.22 mmol) was refluxed for 4 h and reaction was monitored with the help of T.L.C. ,then left to cool the reaction mixture overnight and poured into ice –cold water to complete the

precipitation. The solid product was filtered off and recrystallized from ethanol **5e**.

2-diethylamino)-2-oxoethyl-2-4(4-isobutyl phenyl) propanoate (5f)

The intermediate (2.05 mmol) and diethyl 13.69 (mmol) was refluxed for 5 h and reaction was monitored with the help of T.L.C. The reaction mixture was cooled to room temperature and poured into ice water to complete the precipitation. The solid was filtered off and recrystallized from ethanol to give the title compound **5f**.

Pharmacological Activity

The anti-inflammatory activity screening was carried out by using paw edema method as described by Ther, Linder and Vogel against albino rats of either sex taken from animal house and fed with standard diet and water *ad libitum* and permission for conducting these experiments was obtained from Institution Animal Ethical Committee. The animal house was maintained at the temperature 26-28°C and relative humidity was about 65-68%.

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 LD_{50} 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.

All the compounds at the dose of 3 mg/kg were dissolved in sodium CMC solution and were administered intravenously. The animals 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 compounds was evaluated by comparing the results with those obtained by dosing the reference standard, Ibuprofen.

RESULT AND DISCUSSION

The ibuprofen derived compound is consistent with the desired structures which were confirmed by the spectral data Table3. The anti-inflammatory activity was determined as the percentage of inhibition of inflammation and the results are expressed as the percentage of inhibition table 1.

Scheme 1

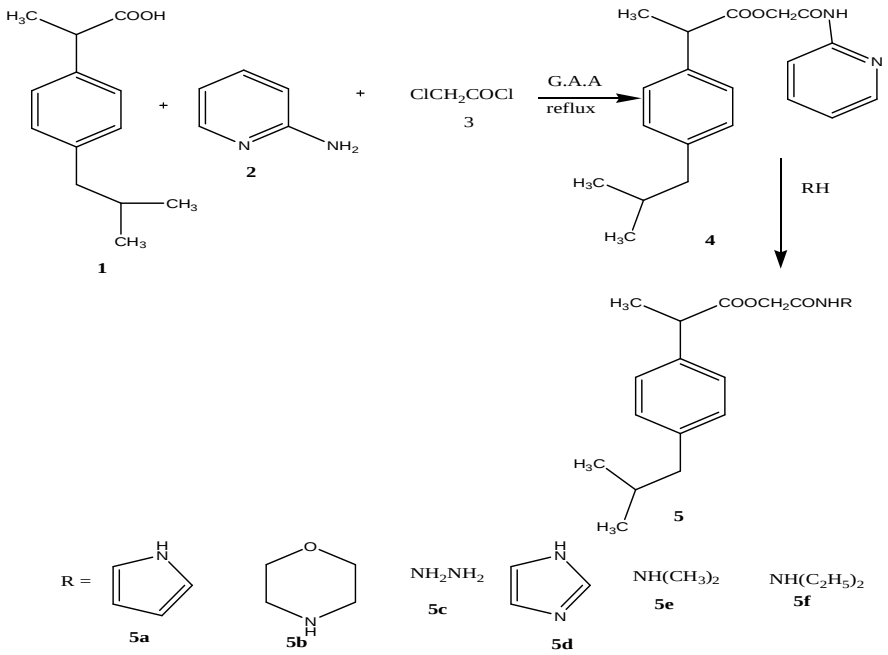

Table 1: Anti-inflammatory activity of some ibuprofen derived compounds

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.	5a	6	255	0.072±0.019	78
4.	5b	6	193	0.317±0.337	80
5.	5c	6	270	0.100±0.000	82
6.	5d	6	253	0.100±0.071	76
7.	5e	6	255	0.320±0.023	77
8	5f	6	258	0.100±0.032	68

Table 2: Physico-Chemical data

Compound	Molecular Formula	Molecular Weight	Melting Point (°C)	(%) Yield
4	$C_{20}H_{24}N_2O_3$	340.42	90	72.90
5a	$C_{19}H_{27}N_2O_3$	331.43	95	73.85
5b	$C_{19}H_{27}N_2O_4$	347.43	100	70.87
5c	$C_{15}H_{22}N_2O_3$	278.35	85	63.15
5d	$C_{18}H_{23}N_3O_3$	329.39	120	67.42
5e	$C_{17}H_{25}NO_3$	291.39	110	60.90
5f	$C_{19}H_{29}NO_3$	319.44	115	55.68

Table 3: Spectral analysis

Compound	I.R (cm^{-1})	^1H NMR (δ, ppm)and MS	Elemental Analysis			
			C	H	N	O
4	880.8 cm^{-1} (C-H, bending), 1418.5 cm^{-1} (C-O-H, bending). 1291.2 cm^{-1} (stretching C-(C=O)-O, stretching), 3081.9 cm^{-1} (C-H, aliphatic),1569.2 cm^{-1} (C-N, aromatic).	8.32(d, 1H, -CC*H*CH-), 7.91(t, 2H, - CCHC*H*C*H*-), 8.49(d, 1H, -CHC*H*N-). MS : m/e = 340.18 (M^+, 100%).	70.56	7.11	8.23	14.10
5a	1401.8 cm^{-1} (C-N, stretching), 2977.5 cm^{-1} (C-H, methylene), 3405 cm^{-1} (N-H, aliphatic), 3401.4 cm^{-1} (N-H, stretching).	4.85(t, 1H, -NCH_2-), 1.93(t, 2H, pyrolidino-CHC$H_2$$CH_2$-), 1.64 (t, 2H, pyrolidino-CH_2C$H_2$$CH_2$-), 2.80 (t, 2H, pyrolidino-CH_2N-). MS : m/e= 331.43(M^+, 100%).	68.85	8.21	8.45	14.48
5b	1237.1 cm^{-1} (C-O-C, stretching), 1043.5 cm^{-1} (symmetric stretch of six membered ring), 3416.5 cm^{-1} (C-H, cyclic), 1257.3 cm^{-1} (C-O, stretching), 2961.0 cm^{-1} (β diketones).	3.77(d, 2H, Morpholino -CHCH_2O-), 3.69(t, 2H, Morpholino –OC$H_2$$CH_2$-), 2.92 (t, 2H, Morpholino-NCH_2-), 4.97 (t, 1H, -NC*H*). MS : m/e= 347.43(M^+, 100%).	65.68	7.83	8.06	18.42
5c	1401.8 cm^{-1}(C-N, stretching), 656.3 cm^{-1} (medium band of primary amine), 3315.7 cm^{-1} (N-H, symmetrical vibration), 1291.2 cm^{-1}(C=O)-O, stretching).	8.0(t, 1H, N*H*-), 2.0 (d, 2H,NH_2). MS : m/e= 278.16 (M^+, 100%).	64.73	7.97	10.06	17.24
5d	1653.5(C=N ring stretch), 3081.0(C-H Stretch)	1.40(s, 1H, -C*H*N-), 7.5(s, 1H, NC*H*N-). MS : m/e= 329.39 (M^+, 100%).	65.00	7.04	12.76	14.57
5e	3088.1(C-H stretch), 1422.0(C-N stretch)	3.24(quartet, 4H, -CH_2), 1.20 (dd, 6H, -CH_3). MS : m/e= 291.18 (M^+, 100%).	70.07	8.65	4.81	16.47
5f	3084.6(C-H stretch), 1406(C-N stretch)	2.90(s, 6H, -CH_3-). MS: m/e= 319.21 (M^+, 100%).	71.00	9.15	4.38	15.03

CONCLUSION

Evaluation of anti-inflammatory activity reveals that all the synthesized compounds were consistent with their activity. In the series of ibuprofen derived compounds, all have shown significant anti-inflammatory activity in comparison to reference drug, ibuprofen at 50 mg/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 the 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 profiles and maximal therapeutic benefits.

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