Synthesis and biological evaluation of some *N*-substituted indoles

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Abstract

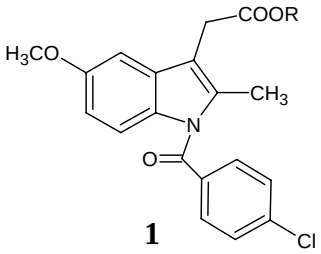
The esterification of 1-alkyl/aryl-3-ethoxy carbonyl-5-hydroxy-2-methyl indoles **(1a-g)** with ethyl chloroacetate and ethyl chloroformate, afforded ethyl 5-(ethoxycarbonyl) methoxy]-1-alkyl/aryl-2-methyl-indole-3-carboxylate **(2a-g)** and 3-(ethoxycarbonyl)-1-alkyl/aryl-2-methyl-1*H*-indol-5-yl ethyl carbonate **(3a-g)** respectively. The reaction of **1b-g** with monochloroacetic acid and 2-chloropropionic acid afforded the corresponding indole acetic acid **(4b-g)** and propanoic acid **(5b-g)** derivatives respectively. These newly synthesized compounds were evaluated *in vivo* for potential anti-inflammatory and analgesic activities and the results were compared with indomethacin. These analogues were administered p.o. at a dose level of 20 mg/kg.

Keywords: N-Substituted indole analogues, synthesis, anti-inflammatory activity, analgesic activity

Introduction

The indole ring system is probably the most important heterocycle in nature. Owing to the great structural diversity of biologically active indoles,[1-3] it is not surprising that the indole ring system has become an important structural component in many pharmaceutical agents. This is exemplified by the amino acid tryptophan, hormones serotonin and melatonin, the psychotropic drug LSD, the antitumour agent vinblastine[4]. Chai et al. synthesized some new ethyl 6-bromo-5-hydroxy-1*H*-indole-3-carboxylates and disclosed their favorable anti-HBV[5] activities. Indomethacin,[6] Etodolac[7] and Tenidap[8] are NSAIDs, and have been shown to exert anti-inflammatory effects. Tenidap is an inhibitor of prostaglandin interleukin-1[9] production in the body used for the treatment of rheumatoid arthritis and osteoarthritis. It also inhibits both

enzymes cyclooxygenase and 5-lipoxygenase,[10] which convert arachidonic acid into prostaglandin and leukotrienes[11] and exhibit superior activity compared to indomethacin. The major mechanism of action by which nonsteroidal anti-inflammatory drugs (NSAIDs) exhibit anti-inflammatory activity involves the inhibition of cyclooxygenase (COX) derived prostaglandin (PG) synthesis.[12, 13] PGs in addition to being undesirable effectors of inflammatory reactions, also exerts important physiological functions such as gastrointestinal cytoprotection and vascular homeostasis.[14,15] Chronic use of NSAIDs is associated with alterations in gastrointestinal integrity and function,[16] which results in the development of gastric ulcers and bleeding. Synthetic approaches based on NSAIDs have been taken with the aim of improving their profile where the action of NSAID is in lowering the prostaglandin production through inhibition of cyclooxygenase (COX). Recently a number of selective inhibitors of COX-2 were shown to possess anti-inflammatory activity with little or no gastric side effects.[17,18] Several alkyl-substituted propanoic acids of indomethacin were prepared by Black et al.[19] It was found that the alkyl, aryl, aralkyl and heterocyclic esters **(Figure 1)** and amides **(Figure 2),** which are modified from indomethacin, exhibit high potency and selectivity[20].



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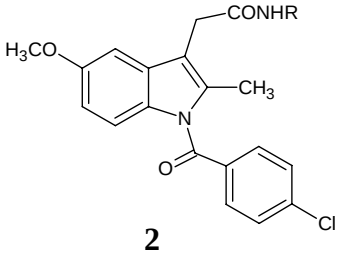

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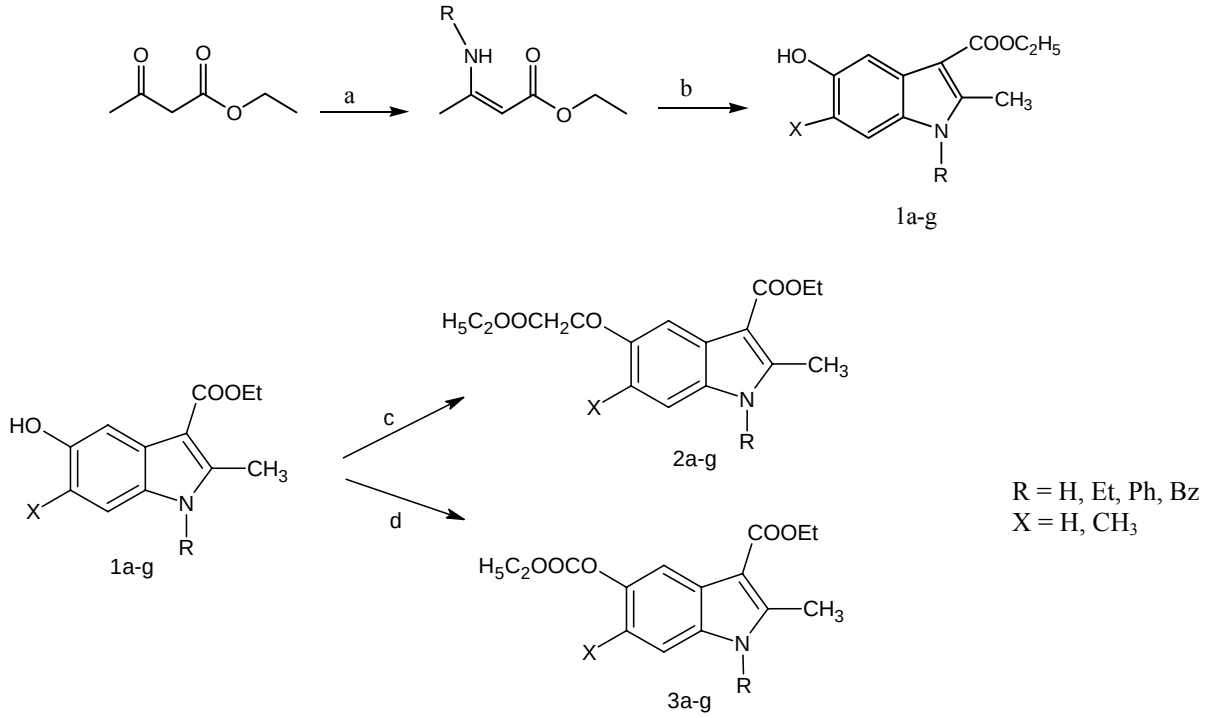
Based on these facts and in continuation of research work on the synthesis of indole analogues,[21] here we report the synthesis of a series of new N-substituted indole analogues from Nenitzescu method, which may result in interesting biological activities. The biological activity and structure-activity relationship (SAR) of the newly synthesized compounds were evaluated compared to indomethacin and some of them were found to possess potent anti-inflammatory and analgesic activities.

Results and Discussion

Chemistry

The synthesis of target compounds ethyl 5-ethoxycarbonyl-N-substituted-indole-3-carboxylate derivatives were obtained as described in Scheme 1. The required starting materials 1-alkyl/aryl-3-ethoxy carbonyl-5-hydroxy-2-methyl indoles were prepared by Nenitzescu[22] method i.e., the treatment of different alkyl/aryl amines with ethyl acetoacetate to form ethyl *β*-alkyl/aryl amino crotonates. The resulting crotonates on reaction with 1,4-benzoquinone/toluoquinone in

dichloroethane under nitrogen atmosphere produced the desired 1-alkyl/aryl-5-hydroxy-2-methyl-3- ethoxycarbonyl indoles[23] **(1a-g)**. The esterification of these 5-hydroxy indoles **(1a-g)** with ethyl chloroacetate and ethyl chloroformate, in presence of anhydrous K_2CO_3 and KI in dry acetone afforded ethyl 5-[(ethoxycarbonyl)methoxy]-1-alkyl/aryl-2-methyl-1*H*indole-3-carboxylate **(2a-g)** and 3-(ethoxycarbonyl)-1-alkyl/aryl-2-methyl-1*H*-indol-5-yl ethyl carbonate **(3a-g)** respectively (Scheme 1)**.**

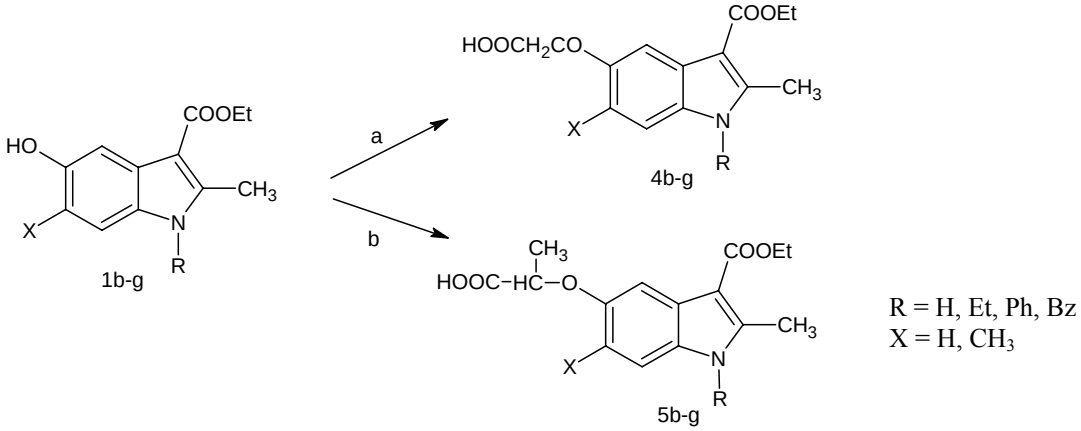


Scheme 1. Reagents and conditions: (a) RNH_2, 45 ^oC ; (b) 1,4-benzoquinone /toluoquinone, $ClCH_2CH_2Cl$, reflux; (c) $ClCH_2COOEt$, acetone, K_2CO_3, KI, reflux; (d) ClCOOEt, acetone, K_2CO_3, KI, reflux.

In the IR spectrum of **2a**, the absorption due to indole NH stretching was observed at 3423 cm^{-1}, the carbonyl of carboxylates appeared at 1741 & 1681 cm^{-1}. The absorption due to –O-CH_2- group appeared at 1589 cm^{-1}. The ^1H NMR ($CDCl_3$) of **2a**, shows two triplets in the region at 1.2-1.4 δ and 1.4-1.5 δ due to -CH_2CH_3 groups present at position-3 and at position-5 respectively. A singlet was observed at 2.75 δ due to the methyl group. Two quartets were observed in the region at 4.2-4.3 δ and 4.4-4.5 δ due to the corresponding -CH_2CH_3 groups at position-3 and position-5 of indole. Another singlet appeared at 4.55 δ due to the methylene protons. The aromatic protons appeared as multiplet at 6.8-7.6 δ. The H of indole NH was appeared as singlet at 8.5 δ. The IR spectrum of **3c** showed bands at 1727 & 1677 cm^{-1} due to the ester carbonyl groups. The ^1H NMR ($CDCl_3$) spectrum showed signals at 1.3-1.4 δ as triplet and another triplet at 1.4-1.5 δ was observed due to -CH_2CH_3 groups present at position-3 and

position-5 respectively. Also two quartet signals were observed at 4.1-4.2 δ and 4.3- 4.4 δ corresponds to -CH_2CH_3 group present at position-3 and position-5 of indole. A singlet was observed due to the protons of methyl group at 3.0 δ. Aromatic protons were appeared as multiplet in the region 6.65-7.4 δ.

The reaction of **1b-g** with monochloro acetic acid and 2-chloropropionic acid afforded the corresponding indole acetic acid **(4b-g)** and propanoic acid **(5b-g)** derivatives (Scheme 2)**.**



Scheme 2. Reagents and conditions: (a) $ClCH_2COOH$, EtOH, Et_3N, reflux; (b) $CH_3CH(Cl)COOH$, EtOH, Et_3N, reflux.

In the IR spectra of **4c** it exhibited the absorption bands at 3310 cm^{-1} due to carboxylic group and at 1670 & 1648 cm^{-1} due to the carbonyl groups. The ^1H NMR of compound **4c** in $CDCl_3$, exhibited undistinct triplet at 1.5 δ and quartet at 4.4 δ corresponding to the ethyl group of carboxylic ester at position-3. Protons of methyl group at position-2 of indole moiety resonated at 2.2 δ as a singlet. The methylene protons of acetic acid moiety showed a sharp singlet at 2.6 δ. The aromatic protons have resonated from 6.6-7.7 δ. The NMR data obtained are in agreement with the proposed structure.

In the IR spectra of **5b** it exhibited the absorption bands at 3340 cm^{-1} due to carboxylic group and at 1720 & 1710 cm^{-1} due to the carbonyl groups. The ^1H NMR of compound **5b** in $CDCl_3$ exhibited a singlet corresponding to methyl protons present at position-2 of the indole moiety at 2.75 δ. The methyl protons of propanoic acid moiety showed doublet at 1.7 δ. The signals corresponding to six protons of two ethyl groups, one at position-1 and another due to ethyl carboxylate at position-3 of indole is noticed by the appearance of merged triplet at 1.2-1.5 and quartet at 4.1-4.4 δ. The signal due to OH proton was observed at 10.4 δ and an undistinct quartet was noticed at 6.8-6.85 δ due to the methine proton of propanoic acid. The aromatic cluster is seen from 7.0-7.5 δ. All these data are in agreement with the structure assigned to the molecule.

Anti-inflammatory and analgesic activity

The test compounds listed in Tables 1-2 were screened for anti-inflammatory and analgesic activity. Table-1 reports, the results obtained with compounds synthesized to investigate the anti-inflammatory effect of N-substituted indole analogues. The 1st, 5th and 6th positions of indole have been modified to study the SAR of ethyl 5-hydroxy-2-methyl indole-3-carboxylate. The indomethacin which is used as reference standard drug at a dose level of 20 mg/kg. The ethyl 5-hydroxy-2-methyl indole-3-carboxylate was substituted with hydrogen, ethyl, phenyl and benzyl groups at positon-1 and the hydroxyl group at position-5 was converted to $–OCH_2COOC_2H_5$, $-OCOOC_2H_5$, $-OCH_2COOH$ and $–OCH(CH_3)COOH$ groups. The position-6 was modified with hydrogen and CH_3 groups.

Table 1. Anti-inflammatory activity results of compounds

Compd	Substituents		Dose	Inhibition of paw edema after					(%) Inhibition after	
	R	**X**	(mg/Kg) b.w.	**½ h**	**1 h**	**2 h**	**3 h**	**4 h**	**2 h**	**4 h**
Control	_	_	Tween 80, 1%	0.175 (± 0.017)	0.3 (± 0.0183)	0.458 (± 0.0271)	0.475 (± 0.0524)	0.5 (± 0.0447)	_	_
Std. Indomethacin	_	_	20	0.108 (± 0.0154)	0.133 (± 0.0211)	0.092** (± 0.0154)	0.133 (± 0.0247)	0.217 (± 0.0211)	80.1	56.4
2a	H	H	20	0.173 (± 0.080)	0.292 (± 0.0153)	0.416 (± 0.0288)	0.466 (± 0.0211)	0.4583 (± 0.0238)	9.2	8.34
2b	Et	H	20	0.167 (± 0.010)	0.283 (± 0.0167)	0.425 (± 0.0112)	0.45 (± 0.0318)	0.492 (± 0.0154)	7.2	1.6
2c	Ph	H	20	0.1083 (±0.0201)	0.15 (± 0.0183)	0.125** (± 0.0171)	0.2 (± 0.0129)	0.342 (± 0.0238)	72.7	31.6
2d	Bz	H	20	0.1583 (± 0.0154)	0.2166 (± 0.0105)	0.4 (± 0.0129)	0.45 (± 0.0186)	0.475 (± 0.0112)	12.7	5.0
2e	H	CH_3	20	0.1333 (± 0.0105)	0.2167 (± 0.0105)	0.3083* (± 0.0083)	0.4 (± 0.0223)	0.475 (± 0.0112)	32.7	5.0
2f	Ph	CH_3	20	0.1167 (± 0.0105)	0.1667 (± 0.0105)	0.15** (± 0.0183)	0.1917 (± 0.0083)	0.3167 (± 0.0105)	67.3	36.7
2g	Bz	CH_3	20	0.0917 (± 0.0083)	0.1333 (± 0.0105)	0.25 (± 0.0223)	0.4083 (± 0.0083)	0.45 (± 0.0183)	45.4	10.0
3a	H	H	20	0.167 (± 0.0105)	0.275 (± 0.0112)	0.375 (± 0.0112)	0.4333 (± 0.0167)	0.475 (± 0.0112)	18.2	5.0
3b	Et	H	20	0.15 (± 0.0129)	0.2 (± 0.0129)	0.275* (± 0.0171)	0.2917 (± 0.0154)	0.375 (± 0.0171)	40.0	25.0

Table 1. Continued

Compd	Substituents		Dose	Inhibition of paw edema after					(%) Inhibition after	
	R	**X**	(mg/Kg) b.w.	**½ h**	**1 h**	**2 h**	**3 h**	**4 h**	**2 h**	**4 h**
3c	Ph	H	20	0.125 (± 0.0112)	0.2 (± .000)	0.25* (± 0.0223)	0.4083 (± 0.0083)	0.45 (± 0.0183)	45.4	10.0
3d	Bz	H	20	0.15 (± 0.0223)	0.233 (± 0.0211)	0.4083 (± 0.0083)	0.4367 (± 0.0128)	0.4833 (± 0.0167)	10.9	3.34
3e	H	CH_3	20	0.14 (± 0.0193)	0.233 (± 0.0166)	0.3667 (± 0.0167)	0.45 (± 0.0183)	0.475 (± 0.0113)	19.98	5.0
3f	Ph	CH_3	20	0.1167 (± 0.017)	0.175 (± 0.0113)	0.275* (± 0.0113)	0.4033 (± 0.0226)	0.4583 (± 0.0083)	40.0	8.34
3g	Bz	CH_3	20	0.15 (± 0.0224)	0.25 (± 0.0183)	0.333* (± 0.0167)	0.4333 (± 0.0105)	0.4667 (± 0.0105)	27.3	6.6
4b	Et	H	20	0.1667 (± 0.0167)	0.2833 (± 0.0167)	0.42 (± 0.010)	0.45 (± 0.0183)	0.5 (± 0.0224)	8.4	3.3
4c	Ph	H	20	0.1583 (± 0.0201)	0.2083 (± 0.0201)	0.1667* (± 0.0167)	0.3166 (± 0.0105)	0.475 (± 0.0214)	63.6	5.0
4d	Bz	H	20	0.1667 (± .0105)	0.2083 (± 0.0153)	0.3833 (± 0.0167)	0.45 (± 0.0223)	0.4833 (± 0.0167)	16.4	3.3
4e	H	CH_3	20	0.1083 (± 0.0083)	0.1583 (± 0.0083)	0.3167 (± 0.0211)	0.3666 (± 0.0247)	0.4583 (± 0.0154)	30.9	8.3
4f	Ph	CH_3	20	0.0916 (±0.0083)	0.15 (± 0.0183)	0.25* (± 0.0183)	0.3833 (± 0.0105)	0.4667 (± 0.0105)	45.4	6.7
4g	Bz	CH_3	20	0.142 (± 0.020)	0.2 (± 0.0183)	0.2417* (± 0.0201)	0.233 (± 0.0211)	0.3833 (± 0.0105)	47.3	23.3
5b	Et	H	20	0.1833 (± 0.0167)	0.2667 (± 0.0105)	0.3833 (± 0.0105)	0.5 (± 0.0183)	0.492 (± 0.0201)	16.4	1.7
5c	Ph	H	20	0.1333 (± 0.0247)	0.225 (± 0.0112)	0.1833* (±0 .0105)	0.3 (± 0.0183)	0.3583 (± 0.020)	60.0	28.3
5d	Bz	H	20	0.175 (± 0.0112)	0.2583 (± 0.0271)	0.3733 (± 0.0235)	0.4083 (± 0.0154)	0.4583 (± 0.0185)	18.5	8.3
5e	H	CH_3	20	0.15 (± 0.0129)	0.2416 (± 0.020)	0.3583 (± 0.0153)	0.4417 (± 0.0201)	0.4833 (± 0.0105)	21.8	3.3
5f	Ph	CH_3	20	0.10 (± 0.0183)	0.1583 (± 0.0083)	0.1667** (± 0.0105)	0.25 (± 0.013)	0.333 (± 0.0105)	63.6	33.4
5g	Bz	CH_3	20	0.1667 (± 0.0167)	0.2083 (±0.0083)	0.2167** (± 0.0167)	0.2917 (± 0.0083)	0.3417 (± 0.0238)	52.7	31.7

Significance levels *P< 0.05, **P< 0.01 compared with respective control (ANOVA followed by Dunnett's test). Each value represents ± SE (n = 6).

Table 2. Analgesic activity results of some synthesized compounds

Compd	Substituents		Dose (mg/Kg)	Mean value ± S.E. at different time interval (in seconds)					Percent analgesia	
	R	X		0	30	60	90	120	60	120
Control (Tween-80, 1%)	_	_	Tween 80, 1%	2.5 (± 0.2236)	2.5 (± 0.2236)	2.667 (± 0.2108)	2.667 (± 0.2108)	2.667 (± 0.2108)	_	_
Standard (Diclofenac sodium)	_	_	20	2.67 (± 0.2108)	5.667** (± .2108)	8.833** (± 0.1667)	7.333** (± 0.2108)	3.667 (± 0.2108)	69.8	27.2
2c	Ph	H	20	4.3 (± 0.395)	4.667* (± 0.2108)	7.833** (± 0.3073)	6.333** (± 0.2108)	3.50 (± 0.2236)	65.95	23.8
2e	H	CH_3	20	2.5 (± 0.2236)	2.667 (± 0.2108)	2.833 (± 0.3073)	2.50 (± 0.2236)	2.5 (± .2236)	5.85	-
2f	Ph	CH_3	20	3.5 (± 0.15)	5.333** (± 0.333)	8.5** (± 0.2236)	6.5** (± 0.2236)	3.667 (± 0.2108)	68.62	27.2
3b	Et	H	20	2.66 (± 0.2106)	2.667 (± 0.2108)	2.833 (± 0.3073)	2.5 (± 0.2236)	2.5 (± 0.2236)	5.85	_
3c	Ph	H	20	2.5 (± 0.2236)	2.5 (± 0.2236)	2.667 (± 0.2108)	2.667 (± 0.2108)	2.667 (± 0.2108)	_	_
3f	Ph	CH_3	20	3.2 (± 0.098)	3.333 (± 0.2108)	5.333 * (± 0.2108)	3.333 (± 0.2108)	2.667 (± 0.2108)	49.99	_
4c	Ph	H	20	2.0 (± .2206)	2.5 (± 0.2236)	2.833 (± 0.1667)	2.5 (± 0.2236)	2.67 (± 0.2108)	5.85	_
4g	Bz	CH_3	20	2.20 (± 0.09)	3.333 (± 0.2108)	5.5 * (± 0.2236)	4.333 * (± 0.2108)	2.833 (± 0.1667)	51.50	5.85
5c	Ph	H	20	4.05 (± 0.44)	5.0 * (± 0.3651)	7.333** (± 0.2108)	6.167** (± .3073)	3.5 (± 0.2236)	63.63	23.8
5f	Ph	CH_3	20	3.5 (± 0.09)	5.333** (± 0.333)	7.833** (± 0.3073)	6.33 ** (± 0.2108)	3.667 (± 0.2108)	65.95	27.72

Significance levels *P< 0.05, **P< 0.01 compared with respective control (ANOVA followed by Dunnett's test). Each value represents ± SE (n= 6).

It has been observed from the table, the anti-inflammatory results of the indole analogues with N-phenyl substitution has shown good activity. Here 2c with inhibition of 72.7 %, 2f with 67.3 %, 4c with 63.6 %, 5c with 60 % and 5d with 63.6 % obtained at 2 hr. Amongst substitutions at position-5 of indole, substitution with $–OCH_2COOC_2H_5$ group found to be more active than others. It is also observed that to have a more activity, there must be a $–CH_2-$ group

present between –O- and -$COOC_2H_5$. If –CH_2- group is removed, then the activity decreases significantly. However, more interesting observation made during our studies was, if –CH_2- is substituted with CH_3 group as in propanoic acid, the activity of resulting molecule enhances considerably.

Indole having N-benzyl substitution and hydrogen and methyl group at position-6 has also shown good activity [2g-68 %, 3g-40 %, 4g-47.3 % and 5g-52.7 % at 2 hrs]. Amongst these compounds, the compound having CH_3 substitution at position-6 has enhanced the activity over the hydrogen substitution. Compounds having –$OCH_2COOC_2H_5$ group at position-5 has shown good activity over the other groups but in comparison with indomethacin they found to be less active. The indole analogues having N-H and N-ethyl substitution were found to be less active. Hence, Indole derivatives having N-phenyl substitution and –$OCH_2COOC_2H_5$ group at position-5 is more active compared to other compounds and these are important for the activity.

Table-2 reports the analgesic activity of some selected compounds. The result indicates that, the indole-N substituted with phenyl and benzyl group has shown good activity. Here the percent analgesia of 2c is 65.9 %, 2f is 68.6 %, 5c is 63.6 % and 5f is 65.9 % at 60 min. In the N-phenyl series, compounds having –$OCH_2COOC_2H_5$ substitution at position-5, hydrogen and methyl groups at position-6 showed better activity. The other compounds have shown less activity compared to the standard drug diclofenac sodium.

Conclusions

This study clearly demonstrates that the substitution of N-phenyl and N-benzyl on the indole ring were crucial for the anti-inflammatory and analgesic activity. Another interesting aspect of this study is that, both potency and spectrum of N-substituted indoles are depending on the substitution at position-5. It has been observed that oxomethylene (OCH_2) group is essential to retain the activity. In 3rd series when –CH_2 group was removed the activity was lost but, when it was substituted with methyl group as in 5th series there was very less reduction in the activity. When –$OCH_2COOC_2H_5$ group is replaced by -OCH_2COOH group, these compounds showed little reduction in the activity. Hence, the oxomethylene group is found to be essential to retain the activity preferably with the attachment of ester over the acid group. Even when, the activities of N-phenyl and N-benzyl substituted compounds were compared, the N-phenyl is more active than N-benzyl with hydrogen or methyl group at position-6. It has been observed that, in N-benzyl substituted indoles with methyl substitution at position-6 is responsible for enhancing the activity over hydrogen substitution at position-6.

Experimental Section

General Procedures. Melting points were taken in open capillary method and are uncorrected. All chemicals were purchased from Aldrich and S D Fine chemicals. ^{1}H NMR spectra in $CDCl_3$ or DMSO-d$_6$ were recorded on AMX-400 (MHz) spectrophotometer and chemical shifts are expressed in ppm (δ) with trimethylsilane as internal standard. Mass spectra were recorded on a GC-LC/MS (expressed in m/z), 5970 spectrophotometer.

General method for the preparation of ethyl 5-[(ethoxycarbonyl) methoxy]-1-alkyl/aryl-2-methyl-1-*H*-indole-3-carboxylate (2 a-d)

To a mixture of 1-alkyl/aryl-3-ethoxycarbonyl-5-hydroxy-2-methyl indole **(1a-d)** (0.1mol) and ethylchloroacetate (0.15 mol) in 50 ml dry acetone was treated with anhydrous K_2CO_3 (300mg) and allowed to reflux for 40 h. The reaction mixture was then filtered and washed thoroughly with acetone and the solvent was evaporates. The crude product was purified by recrystallisation from ethanol to afford the desired compounds as white crystals.

Ethyl 5-[(ethoxycarbonyl) methoxy]-2-methyl-1-*H*-indole-3-carboxylate (2a). Yield-80 %, M.P.-100-102 ^{o}C, IR (KBr): *v*, 3423, 1741, 1681, 1589 cm^{-1}, ^{1}H NMR ($CDCl_3$): δ, 1.2-1.4 (t, 3H, CH_3CH_2), 1.4-1.5 (t, 3H, CH_3CH_2), 2.75 (s, 3H, CH_3), 4.2-4.3 (q, 2H, CH_2CH_3), 4.4-4.5 (q, 2H, CH_2CH_3), 4.55 (s, 2H, CH_2), 6.8-7.6 (m, ArH), 8.5 (s, indole NH), ESIMS: (m/z) 425.8. Anal. Calcd. for $C_{16}H_{19}NO_5$ (%): C, 62.94; H, 6.27; N, 4.59. Found: C, 62.85; H, 6.15; N, 4.48.

Ethyl 5-[(ethoxycarbonyl) methoxy]-1-ethyl-2-methyl-1-*H*-indole-3-carboxylate (2b). Yield-60%, M.P.-170 ^{o}C, IR (KBr): *v*, 1739, 1639, 1620 cm^{-1}, ^{1}H NMR ($CDCl_3$): δ, 1.3-1.38 (t, 6H, $2CH_3CH_2$), 1.43-1.48 (t, 3H, CH_3CH_2), 1.7 (s, 3H, CH_3), 4.14-4.16 (q, 2H, CH_2CH_3), 4.2-4.4 (q, 4H, $2CH_2CH_3$), 4.7 (s, 2H, CH_2), 7.0-7.6 (m, ArH), LCMSD: m/z 333.3. Anal. Calcd. for $C_{18}H_{23}NO_5$: C, 64.85; H, 6.95; N, 4.20. Found: C, 64.72; H, 6.86; N, 4.35.

Ethyl 5-[(ethoxycarbonyl) methoxy]-2-methyl-1-phenyl-1-*H*-indole-3-carboxylate (2c). Yield-75 %, M.P.-142-145 ^{o}C, IR (KBr): *v*, 1750, 1680,1620 cm^{-1}, ^{1}H NMR($CDCl_3$) : δ, 1.3-1.4 (t, 3H, CH_3CH_2), 1.4-1.5 (t, 3H, CH_3CH_2), 2.7 (s, 3H, CH_3), 4.3-4.4 (q, 2H, CH_2CH_3), 4.45-4.55 (q, 2H, CH_2CH_3), 6.7-7.6 (m, ArH), LCMSD: m/z 382.8, Anal. Calcd. for $C_{22}H_{23}NO_5$: C, 69.28; H, 6.08; N, 3.67. Found: C, 69.14; H, 6.18; N, 3.59.

Ethyl 5-[(ethoxycarbonyl) methoxy]-1-benzyl-2-methyl-1-*H*-indole-3-carboxylate (2d). Yield-75 %, M.P.-268-270 ^{o}C, IR (KBr): *v*, 1839, 1763, 1618 cm^{-1}, ^{1}H NMR ($CDCl_3$): δ, 1.3-1.4 (t, 3H, CH_3CH_2), 1.45-1.5 (t, 3H, CH_3CH_2), 2.7 (s, 3H, CH_3), 4.25- 4.35 (q, 2H, CH_2CH_3), 4.35-4.5 (q, 2H, CH_2CH_3), 4.7 (s, 2H, CH_2), 5.3 (s, 2H, CH_2), 6.7-7.6 (m, ArH), ESIMS: (m/z) 396.2, Anal. Calcd. for $C_{23}H_{25}NO_5$: C, 69.86; H, 6.37; N, 3.54. Found: C, 69.75; H, 6.29; N, 3.46.

General method for the preparation of ethyl 5-[(ethoxycarbonyl)methoxy]-1-alkyl/aryl -2,6-dimethyl-1-*H*-indole-3-carboxylate (2 e-g)

To a mixture of 1-alkyl/aryl-3-ethoxycarbonyl-5-hydroxy-2,6-dimethyl indole **(1e-g)** (0.1mol) and ethylchloro acetate (0.15 mol) in 50 ml dry acetone was treated with anhydrous K_2CO_3

(300mg). The mixture was allowed to reflux for 40 h. Then it was filtered and washed thoroughly with acetone and the solvent was evaporated. The product thus obtained was purified by recrystallisation from ethanol to afford the white crystalline compound.

Ethyl 5-[(ethoxycarbonyl) methoxy]-2,6-dimethyl-1-*H*-indole-3-carboxylate (2e). Yield-80%, M.P.-120-122 ^{o}C , IR (KBr): *v*, 3265, 1751, 1665, 1550 cm^{-1}, ^{1}H NMR ($CDCl_3$): δ, 1.25-1.48 (2t, 6H, $2CH_3CH_2$), 2.4 (s, 3H, CH_3), 2.7 (s, 3H, CH_3), 4.2-4.4 (2q, 4H, $2CH_2CH_3$), 4.7 (s, 2H, CH_2), 6.9 (s, 4′-ArH), 7.3 (s, 7′-ArH), 7.6 (s, indole NH), LCMSD: m/z 320.2. Anal. Calcd. for $C_{17}H_{21}NO_5$: C, 63.94; H, 6.63; N, 4.39. Found: C, 63.82; H, 6.58; N, 4.24.

Ethyl 5-[(ethoxycarbonyl) methoxy]-1-pheyl-2,6-dimethyl-1-*H*-indole-3-carboxylate (2f). Yield -70%, M.P.-116-118 ^{o}C , IR (KBr): *v*, 1755, 1682, 1628 cm^{-1}, ^{1}H NMR ($CDCl_3$): δ, 1.25-1.45 (2t, 6H, $2CH_3CH_2$), 2.35 (s, 3H, CH_3), 2.73 (s, 3H, CH_3), 4.2-4.4 (2q, 4H, $2CH_2CH_3$), 4.8 (s, 2H, CH_2), 6.7-7.5 (m, ArH), LCMSD: m/z 395.6. Anal. Calcd. for $C_{23}H_{25}NO_5$: C, 69.86; H, 6.37; N, 3.54. Found: C, 69.97; H, 6.26; N, 3.44.

Ethyl 5-[(ethoxycarbonyl) methoxy]-1-benzyl-2,6-dimethyl-1-*H*-indole-3-carboxylate (2g). Yield -75%, M.P.198-199 ^{0}C, IR (KBr): *v*, 1780, 1687, 1600 cm^{-1}, ^{1}H NMR ($CDCl_3$): δ, 1.2-1.4 (2t, 6H, $2CH_3CH_2$), 2.42 (s, 3H, CH_3), 2.7 (s, 3H, CH_3), 4.25-4.5 (2q, 4H, $2CH_2CH_3$), 4.65 (s, 2H, CH_2), 6.8-7.3 (m, ArH), LCMSD: m/z 410.1. Anal. Calcd. for $C_{24}H_{27}NO_5$: C, 70.40; H, 6.65; N, 3.42. Found: C, 70.31; H, 6.54; N, 3.31.

General method for the preparation of 3-(ethoxycarbonyl)-1-alkyl/aryl-2-methyl-1-*H*-indol-5-yl ethyl carbonate (3 a-d)

To a mixture of 1-alkyl/aryl-3-ethoxycarbonyl-5-hydroxy-2-methyl indole **(1a-d)** (0.1 mol) and ethylchloro formate (0.15 mol) in 50 ml dry acetone was treated with anhydrous K_2CO_3 (300 mg) and allowed to reflux for 40 h. The reaction mixture was then filtered and washed thoroughly with acetone. The solvent was evaporated, the product thus separated was purified by recrystallisation from ethanol to afford the white crystalline compound.

3-(Ethoxycarbonyl)-2-methyl-1-*H*-indol-5-yl ethyl carbonate (3a). Yield-50%, M.P.-90 ^{o}C, IR (KBr): *v*, 3070, 1760, 1680, 1625 cm^{-1}, ^{1}H NMR (DMSO): δ, 1.35-1.4 (t, 6H, $2CH_3CH_2$), 3.0 (s, 3H), 4.0-4.4 (q, 4H, $2CH_2CH_3$), 7.4-7.8 (m, ArH), 8.2 (s, indole NH), ESIMS: m/z 292.0. Anal. Calcd. for $C_{15}H_{17}NO_5$: C, 61.85; H, 5.88; N, 4.81. Found: C, 61.96; H, 5.95; N, 4.93.

3-(Ethoxycarbonyl)-1-ethyl-2-methyl-1-*H*-indol-5-yl ethyl carbonate (3b). Yield–60%, M.P.-90-92 ^{o}C, IR (KBr): *v*, 1757, 1678 cm^{-1}, ^{1}H NMR (DMSO): δ, 1.2-1.4 (t, 9H, $3CH_3CH_2$), 3.3 (s, 3H), 4.2-4.4 (q, 6H, $3CH_2CH_3$), 7.4-7.9 (m, ArH). LCMSD: m/z 392.5. Anal. Calcd. for $C_{17}H_{21}NO_5$: C, 63.94; H, 6.63; N, 4.39. Found: C, 63.86; H, 6.76; N, 4.27.

3-(Ethoxycarbonyl)-1-pheyl-2-methyl-1-*H*-indol-5-yl ethylcarbonate (3c). Yield–55%, M.P.-92-93 ^{o}C, IR (KBr): *v*, 1727, 1677, 1584 cm^{-1}, ^{1}HNMR ($CDCl_3$): δ, 1.3-1.4 (t, 3H, CH_3CH_2), 1.4-1.5 (t, 3H, CH_3CH_2), 3.0 (s, 3H, CH_3), 4.1-4.2 (q, 2H, CH_2CH_3), 4.3-4.4 (q, 2H, CH_2CH_3), 6.65-7.4 (m, ArH), ESIMS (FAB): m/z, 369. Anal. Calcd. for $C_{21}H_{21}NO_5$: C, 68.65; H, 5.76; N, 3.81. Found: C, 68.53; H, 5.67; N, 3.70.

3-(Ethoxycarbonyl)-1-benzyl-2-methyl-1-*H*-indol-5-yl ethyl carbonate (3d). Yield–65%, M.P.- 98-100 ^{o}C, IR (KBr): *v*, 1780, 1680, 1600 cm^{-1}, ^{1}H NMR ($CDCl_3$): δ, 1.3-1.5 (t, 6H, $2CH_3CH_2$), 2.8 (s, 3H, CH_3), 4.2-4.4 (q, 4H, $2CH_2CH_3$), 4.7 (s, 2H, CH_2), 6.8-7.4 (m, ArH), LCMSD: m/z 380.8. Anal. Calcd. for $C_{22}H_{23}NO_5$: C, 69.28; H, 6.08; N, 3.67. Found: C, 69.33; H, 5.91; N, 3.55.

General method for the preparation of 3-(ethoxycarbonyl)-1-alkyl/aryl-2,6-dimethyl-1-*H*-indol-5-yl ethyl carbonate (3 e-g)

To a mixture of 1-alkyl/aryl-3-ethoxycarbonyl-5-hydroxy-2-methyl indole **(1 e-g)** (0.1 mol) and ethylchloro formate (0.15 mol) in 50 ml dry acetone was treated with anhydrous K_2CO_3 (300 mg) and allowed to reflux for 40 h. The reaction mixture was then filtered and washed thoroughly with acetone and the solvent was evaporated to get the product. The product thus obtained was purified by recrystallisation from ethanol to afford the white crystalline compound.

3-(Ethoxycarbonyl)-2,6-dimethyl-1-*H*-indol-5-yl ethyl carbonate (3e). Yield–60%, M.P.-118-120 ^{o}C, IR (KBr): *v*, 3295, 1760, 1720, 1595 cm^{-1}, ^{1}H NMR ($CDCl_3$): δ, 1.35-1.55 (t, 6H, $2CH_3CH_2$), 2.45 (s, 3H, CH_3), 2.6 (s, 3H, CH_3) 4.4-4.55 (q, 4H, $2CH_2CH_3$), 7.3-8.0 (m, ArH), ESIMS: m/z 305.4. Anal. Calcd. for $C_{16}H_{19}NO_5$: C, 62.94; H, 6.27; N, 4.59. Found: C, 63.07; H, 6.35; N, 4.66.

3-(Ethoxycarbonyl)-1-phenyl-2,6-dimethyl-1-*H*-indol-5-yl ethyl carbonate (3f). Yield–70%, M.P.- 96-98 ^{o}C, IR (KBr): *v*, 1725, 1650, 1626 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ, 1.4-1.55 (t, 6H, $2CH_3CH_2$), 2.5 (s, 3H, CH_3), 2.7 (s, 3H, CH_3), 4.35-4.55 (q, 4H, $2CH_2CH_3$), 7.4-8.3 (m, ArH), LCMSD: m/z 381.6. Anal. Calcd. for $C_{22}H_{23}NO_5$: C, 69.28; H, 6.08; N, 3.67. Found: C, 69.12; H, 6.21; N, 3.75.

3-(Ethoxycarbonyl)-1-benzyl-2,6-dimethyl-1-*H*-indol-5-yl ethyl carbonate (3g). Yield–70%, M.P.-125 ^{o}C, IR (KBr): *v*, 1730, 1680, 1545 cm^{-1}, ^{1}H NMR (DMSO): δ, 1.4-1.5 (t, 6H, $2CH_3CH_2$), 2.55 (s, 3H, CH_3), 2.7 (s, 3H, CH_3), 4.4-4.6 (q, 4H, $2CH_2CH_3$), 4.75 (s, 2H, CH_2), 7.0-7.5 (m, ArH), LCMSD: m/z 318.5. Anal. Calcd. for $C_{23}H_{25}NO_5$: C, 69.86; H, 6.37; N, 3.54. Found: C, 69.77; H, 6.45; N, 3.41.

General method for the synthesis of 2-(3-(ethoxycarbonyl)-1-alkyl/aryl-2-methyl-1-*H*-indol-5-yloxy)acetic acid (4 b-d)

To the solution of 1-alkyl/aryl-3-ethoxycarbonyl-5-hydroxy-2-methyl indole **(1 b-d)** (0.1mol) in absolute ethanol (20 ml), chloro acetic acid (0.2 mol), few drops of triethyl amine was added. Reaction mixture was refluxed for 6-8 h. The solvent was concentrated and poured on crushed ice, the product thus obtained was collected by filtration and dried. The products were recrystallised from suitable solvent.

2-(3-(Ethoxycarbonyl)-1-ethyl-2-methyl-1-*H*-indol-5-yloxy) acetic acid (4b). Yield-60 %, M.P.-140-143 ^{o}C, IR (KBr): *v*, 3440, 1670, 1657, 1618 cm^{-1}, ^{1}H NMR ($CDCl_3$): δ, 1.4-1.45 (t, 3H, CH_3CH_2), 1.5-1.55 (t, 3H, CH_3CH_2), 3.0 (s, 2H, CH_2), 2.4 (s, 3H, CH_3), 10.2 (br s, OH), 6.8-

7.8 (m, ArH), ESIMS: m/z 305.5. Anal. Calcd. for $C_{16}H_{19}NO_5$: C, 62.94; H, 6.27; N, 4.59. Found: C, 62.81; H, 6.35; N, 4.68.

2-(3-(Ethoxycarbonyl)-1-phenyl-2-methyl-1-*H*-indol-5-yloxy) acetic acid (4c). Yield-65 %, M.P.-155-158 ^oC, IR (KBr): ν, 3310, 1670, 1648, 1615 cm^{-1}, ^1H NMR ($CDCl_3$): δ, 1.5 (t, 3H, CH_3CH_2), 2.2 (s, 3H, CH_3), 2.6 (s, 2H, CH_2), 4.4 (q, 2H, CH_2CH_3), 10.4 (s, OH), 6.6-7.7 (m, ArH), ESIMS: m/z 353.2. Anal. Calcd. for $C_{20}H_{19}NO_5$: C, 67.98; H, 5.42; N, 3.96. Found: C, 67.87; H, 5.54; N, 3.81.

2-(3-(Ethoxycarbonyl)-1-benzyl-2-methyl-1-*H*-indol-5-yloxy) acetic acid (4d). Yield- 63 %, M.P.-135-137 ^oC, IR (KBr): *ν*, 3450, 1750, 1640, 1600 cm^{-1}, ^1H NMR ($CDCl_3$): δ, 1.45 (t, 3H, CH_3CH_2), 2.4 (s, 3H, CH_3), 2.7 (s, 2H, CH_2), 4.5 (q, 2H, CH_2CH_3), 4.7 (s, 2H, CH_2), 10.2 (s, OH), 6.6-7.5 (m, ArH), ESIMS: m/z 368. Anal. Calcd. for $C_{21}H_{21}NO_5$: C, 68.65; H, 5.76; N, 3.81. Found: C, 68.78; H, 5.67; N, 3.68.

General method for the synthesis of 2-(3-(ethoxycarbonyl)-1-alkyl/aryl-2,6-dimethyl-1-*H*-indol-5-yloxy)acetic acid (4 e-g)

The mixture of 1-alkyl/aryl-3-ethoxycarbonyl-5-hydroxy-2,6-dimethyl indole **(1 e-g)** (0.1mol), chloro aceticacid (0.2 mol), absolute ethanol (25 ml), triethyl amine (5 drops) was kept for reflux to about 6-8 h. The solvent was evaporated and poured onto crushed ice. The product thus separated was filtered, dried and recrystallised from suitable solvent to get the pure compound.

2-(3-(Ethoxycarbonyl)-2,6-dimethyl-1-*H*-indol-5-yloxy) acetic acid (4e). Yield- 60 %, M.P.-138-140 ^oC, IR (KBr): *ν*, 3350, 1720, 1658 1600 cm^{-1}, ^1H NMR ($CDCl_3$): δ, 1.45-1.47 (t, 3H, CH_3CH_2), 2.4 (s, 3H, CH_3), 2.7 (s, 3H, CH_3), 2.75 (s, 2H, CH_2), 4.38 (q, 2H, -CH_2CH_3), 10.4 (br s, OH), 6.6-7.3 (m, ArH), 8.3 (s, indole NH), LCMSD: m/z 290.6. Anal. Calcd. for $C_{15}H_{17}NO_5$: C, 61.85; H, 5.88; N, 4.81. Found: C, 61.72; H, 5.76; N, 4.68.

2-(3-(Ethoxycarbonyl)-1-phenyl-2,6-dimethyl-1-*H*-indol-5-yloxy) acetic acid (4f). Yield-63 %, M.P.-150-153 ^oC, IR (KBr): *ν*, 3300, 1723, 1662, 1620 cm^{-1}, ^1H NMR ($CDCl_3$): δ, 1.5-1.6 (t, 3H, CH_3CH_2), 2.4 (s, 3H, CH_3), 2.65 (s, 3H, CH_3), 2.7 (s, 2H, CH_2), 4.4 (q, 2H, -CH_2CH_3), 10.7 (s, OH), 6.6-7.2 (m, ArH), ESIMS: m/z 367.8. Anal. Calcd. for $C_{21}H_{21}NO_5$: C, 68.65; H, 5.76; N, 3.81. Found: C, 68.78; H, 5.67; N, 3.68.

2-(3-(Ethoxycarbonyl)-1-benzyl-2,6-dimethyl-1-*H*-indol-5-yloxy) acetic acid (4g). Yield-60 %, M.P.-157-160 ^oC, IR (KBr): *ν*, 3330, 1730, 1710, 1610 cm^{-1}, ^1H NMR ($CDCl_3$): δ, 1.5-1.6 (t, 3H, CH_3CH_2), 2.3 (s, 3H, CH_3), 2.7 (s, 3H, CH_3), 2.75 (s, 2H, CH_2), 4.35 (q, 2H, -CH_2CH_3), 4.5 (s, 2H, CH_2), 10.75 (s, OH), 6.8-7.2 (m, ArH), ESIMS: m/z 381.4. Anal. Calcd. for $C_{22}H_{23}NO_5$: C, 69.28; H, 6.08; N, 3.67. Found: C, 69.40; H, 6.20; N, 3.55.

General method for the synthesis of 2-(3-(Ethoxycarbonyl)-1-alkyl/aryl-2-methyl-1-*H*-indol-5-yloxy) propanoic acid (5 b-d)

To the solution of 1-alkyl/aryl-3-ethoxycarbonyl-5-hydroxy-2-methyl indole **(1b-d)** (0.1 mol) in absolute ethanol (20 ml), 2-chloro propionicacid (0.2 mol) and few drops of triethyl amine was added. Reaction mixture was refluxed for 6-8 h. The solvent was concentrated and poured onto

crushed ice, the product thus obtained was collected by filtration and dried. The products were recrystallised from suitable solvent.

2-(3-(Ethoxycarbonyl)-1-ethyl-2-methyl-1-*H*-indol-5-yloxy) propanoic acid (5b). Yield-55 %, M.P.-183-185 ^{o}C, IR (KBr): *v*, 3340, 1720, 1710, 1610 cm^{-1}, ^{1}H NMR ($CDCl_3$): δ, 1.2-1.5 (t, 6H, $2CH_3CH_2$), 1.7 (d, 3H, CH_3CH), 2.75 (s, 3H, CH_3), 4.1-4.4 (q, 4H, $2CH_2CH_3$), 10.4 (s, OH), 6.8-6.85 (m, 1H, $CHCH_3$), 7.0-7.5 (m, ArH). LCMSD (m/z): 319.7. Anal. Calcd. for $C_{17}H_{21}NO_5$**:** C, 63.94; H, 6.63; N, 4.39. Found: C, 63.82; H, 6.55; N, 4.49.

2-(3-(Ethoxycarbonyl)-1-phenyl-2-methyl-1-*H*-indol-5-yloxy) propanoic acid (5c). Yield-58 %, M.P.- 200-203 ^{o}C, IR (KBr): *v*, 3430, 1720, 1650 cm^{-1}, ^{1}H NMR ($CDCl_3$): δ, 1.4-1.6 (t, 3H, CH_3CH_2), 1.8 (d, 3H, CH_3CH), 2.6 (s, 3H, CH_3), 4.4-4.5 (q, 2H, CH_2CH_3), 10.5 (br s, OH), 6.7-6.8 (m, $CHCH_3$), 7.0-7.7 (m, ArH), LCMSD (m/z): 368.1. Anal. Calcd. for $C_{21}H_{21}NO_5$: C, 68.65; H, 5.76; N, 3.81. Found: C, 68.72; H, 5.62; N, 3.95.

2-(3-(Ethoxycarbonyl)-1-benzyl-2-methyl-1-*H*-indol-5-yloxy) propanoic acid (5d). Yield-50%, M.P.-173-175 ^{o}C, IR (KBr): *v*, 3250, 1650, 1630, 1598 cm^{-1}, ^{1}H NMR (DMSO): δ, 1.3-1.4 (t, 3H, CH_3CH_2), 2.0 (d, 3H, CH_3CH), 2.65 (s, 3H, CH_3), 4.4-4.5 (q, 2H, CH_2CH_3), 4.72 (s, 2H, CH_2), 10.4 (br s, OH), 6.6-7.6 (m, $CHCH_3$ and ArH), LCMSD (m/z): 381.6. Anal. Calcd. for $C_{22}H_{23}NO_5$: C, 69.28; H, 6.08; N, 3.67. Found: C, 69.11; H, 5.90; N, 3.85.

General method for the synthesis of 2-(3-(ethoxycarbonyl)-1-alkyl/aryl-2,6-dimethyl-1-*H*-indol-5-yloxy)propanoic acid (5 e-g)

To the solution of 1-alkyl/aryl-3-ethoxycarbonyl-5-hydroxy-2,6-dimethyl indole **(1 e-g)** (0.1 mol) in absolute ethanol (20 ml), 2-chloro propionicacid (0.2 mol) and few drops of triethyl amine were added. The reaction mixture was refluxed for 6-8 h. The solvent was concentrated and poured on crushed ice. The product thus obtained was collected by filtration and dried. The products were recrystallised from suitable solvent.

2-(3-(Ethoxycarbonyl)-2,6-dimethyl-1-*H*-indol-5-yloxy) propanoic acid (5e). Yield-60 %, M.P.-154-156 ^{o}C, IR (KBr): *v*, 3430, 3075, 1700, 1650 cm^{-1}, ^{1}H NMR (DMSO): δ, 1.4-1.45 (t, 3H, CH_3CH_2), 1.5 (d, 1H, CH_3CH), 2.3 (s, 3H, CH_3), 2.55 (s, 3H, CH_3), 4.4-4.45 (q, 2H, CH_2CH_3), 10.0 (s, OH), 6.65 (m, $CHCH_3$), 7.1-7.4 (m, ArH), LCMSD (m/z): 306.1. Anal. Calcd. for $C_{16}H_{19}NO_5$: C, 62.94; H, 6.27; N, 4.59. Found: C, 62.78; H, 6.35; N, 4.70.

2-(3-(Ethoxycarbonyl)-1-phenyl-2,6-dimethyl-1-*H*-indol-5-yloxy)propanoic acid (5f). Yield-65 %, M.P.- 184-186 ^{o}C, IR (KBr): *v*, 3350, 1726, 1680, 1610 cm^{-1}, ^{1}H NMR ($CDCl_3$): δ, 1.42-1.48 (t, 3H, CH_3CH_2), 1.58 (d, 1H, CH_3CH), 2.27 (s, 3H, CH_3), 2.54 (s, 3H, CH_3), 4.4-4.5 (q, 2H, CH_2CH_3), 9.9 (s, OH), 6.7 (m, $CHCH_3$), 7.2-7.6 (m, ArH), LCMSD (m/z): 381.2. Anal. Calcd. for $C_{22}H_{23}NO_5$: C, 69.28; H, 6.09; N, 3.66. Found: C, 69.19; H, 6.22; N, 3.48.

2-(3-(Ethoxycarbonyl)-1-benzyl-2,6-dimethyl-*H*-indol-5-yloxy)propanoic acid (5g). Yield-62 %, M.P.-174-178 ^{o}C, IR (KBr): *v*, 3338, 1730, 1650, 1600 cm^{-1}, ^{1}H NMR ($CDCl_3$): δ, 1.45-1.48 (t, 3H, CH_3CH_2), 1.6 (d, 1H, CH_3CH), 2.3 (s, 3H, CH_3), 2.6 (s, 3H, CH_3), 4.4-4.5 (q, 2H, CH_2CH_3), 4.7 (s, 2H, CH_2), 9.9 (s, OH), 6.9-7.5 (m, $CHCH_3$ and ArH), LCMSD (m/z): 396.2. Anal. Calcd. for $C_{23}H_{25}NO_5$: C, 69.86; H, 6.37; N, 3.54. Found: C, 69.99; H, 6.25; N, 3.41

Pharmacological evaluation

The animals were procured from NIN, Hyderabad, India and were maintained in colony cages at 25 ^{o}C, they fed with standard animal feed and cleared by institutional animal ethics (Reg. No. LCP CPCSEA 346)

Anti-inflammatory activity test. Anti-inflammatory activity was evaluated by the paw edema method,[24] using albino rats of both sexes (excluding pregnant rats) weighing 180-250 g. The synthesized compounds were administered orally at a dose level of 20 mg/kg. The paw volume was measured using the mercury displacement technique with the help of plethysmograph immediately before and 30 min, 1, 2, 3 and 4h after carrageenan (1%, 0.1 ml) injection. The percent inhibition of edema was calculated and indomethacin was used as reference standard (20 mg/kg) (table-1).

Analgesic activity test. Analgesic activity was performed by means of tail-flick method using analgesiometer[25, 26] . The Wister albino mice (25-30 g) of either sex (excluding pregnant mice) selected by random sampling technique. Diclofenac sodium 20 mg/kg was administered as a reference standard for comparison and test compounds at a dose level of 20 mg/kg were administered orally. The reaction time was recorded at 30, 60, 90 and 120 min after treatment, cut off time was 10 sec. The percent analgesia was calculated (table-2).

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