Indian Journal of Advances in Chemical Science

Article

Synthesis of 1-acetyl- 5-Substitutedaryl-3- [5-(5'-Methoxy-3-Indomethyl)-2-Amino-1, 3, 4-Oxadiazol-2-N-yl] - 2-Pyrazoline Derivatives as Potent Anti-inflammatory Agent

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ABSTRACT

When 5-(5-methoxy-3-indomethyl)- -1,3,4-oxadiazol- 2-amino substituted chalcones (5a-5e) undergo cyclisation in presence of 99% hydrazine hydrate and few drops of glacial acetic acid and refluxed for 12 h, a novel series of 1-acetyl- 5-substitutedaryl-3- [5-(5'-methoxy-3-indomethyl)-2-amino-1,3,4-oxadiazol-2-N-yl]- 2-pyrazoline can be synthesized. These compounds were characterized by IR, ^{1}HNMR spectroscopy and screened for their promising anti-inflammatory activity.

Key words: Oxadiazol, Indole, Chalcones, Pyrazoline, anti-inflammatory activity.

1. INTRODUCTION

Heterocyclic compounds have paid enormously to the society in the form of large number of drugs for the treatment of various ailments and have occupied a prominent place in medicinal chemistry due to their varied biological activities [1-5].

Indole is an aromatic heterocyclic composite which has its heterobicyclic configuration as a six-membered ring fused to a five-membered pyrrole ring. "Indole" is the name given to all indole derivatives which have an indole ring system [6,7]. Indoles are obtained from coal pitch or a variety of plants and produced by the bacterial decay of tryptophan in the in-testine. It has been synthesized by one of the oldest method that known as fischer indole synthesis. Indoles are one of the most important nitrogen containing heterocyclic compounds. The indole nucleus is important moiety found in a large number of natural or synthetic alkaloids [8,9]. One of the naturally occurring indole is tryptamine. Indole has also known as benzypyrrole, is an aromatic organic compound composed of benzyl and a pyrrole ring. The aromatic properties of indole originate from the mobilization of its 10 π electrons throughout the indole structure. In this context, a large number of indole moieties have been investigated in the development of new efficient bioactive molecules with diverse pharmacological properties, such as antimicrobial, antiviral, anticancer, anti-inflammatory, inhibitors, and antioxidant [10-32]. In general, indoles substituted at 2nd or 3rd position [33-35] are known to exhibit certain bioactivity. Indole core is widely distributed in the nature [36] and is present in many important alkaloids, namely, auxins [37] and tryptophan [38]. The indole moiety is related to the neurotransmitter serotonin implicated for brain function and cognition as the endogenous receptor agonist [39]. Indole alkaloids, vallesiachotamine, and iso-vallesiachotamine isolated from the fruits of Anthocephalus cadamba (Family: *Rubiaceae*) are found to exhibit potent anticancer activity [40] and indole alkaloids from marine natural products show numerous biological activity, including cytotoxic, antiviral, antimicrobial, antiparasitic, anti-inflammatory, antiserotonin, Ca^{2+}, calmodulin-antagonistic activity, and antitopoisomerase-I activity, along with *in vivo* activity [41,42].

Furthermore, various derivatives of 1, 3, 4-oxadiazole [43,44] and pyrazolines [45,46] of different heterocyclic nuclei are well known to exhibit potent anti-inflammatory activity. These findings prompted us to synthesize a new series of 1-acetyl-5-substituted aryl-3-[5'-(3''-indolylmethyl-5''-methoxy)-2'-amino-1',3',4'-oxadiazol-2'-N-yl]-2-pyrazolines. By incorporation 1, 3, 4- thiadiazolyl and pyrazolinyl moieties at 3- position of indole nucleus with a hope to develop anti-inflammatory agent with lesser side effects. The structure of all newly synthesized compounds was characterized by elemental analysis and spectral studies.

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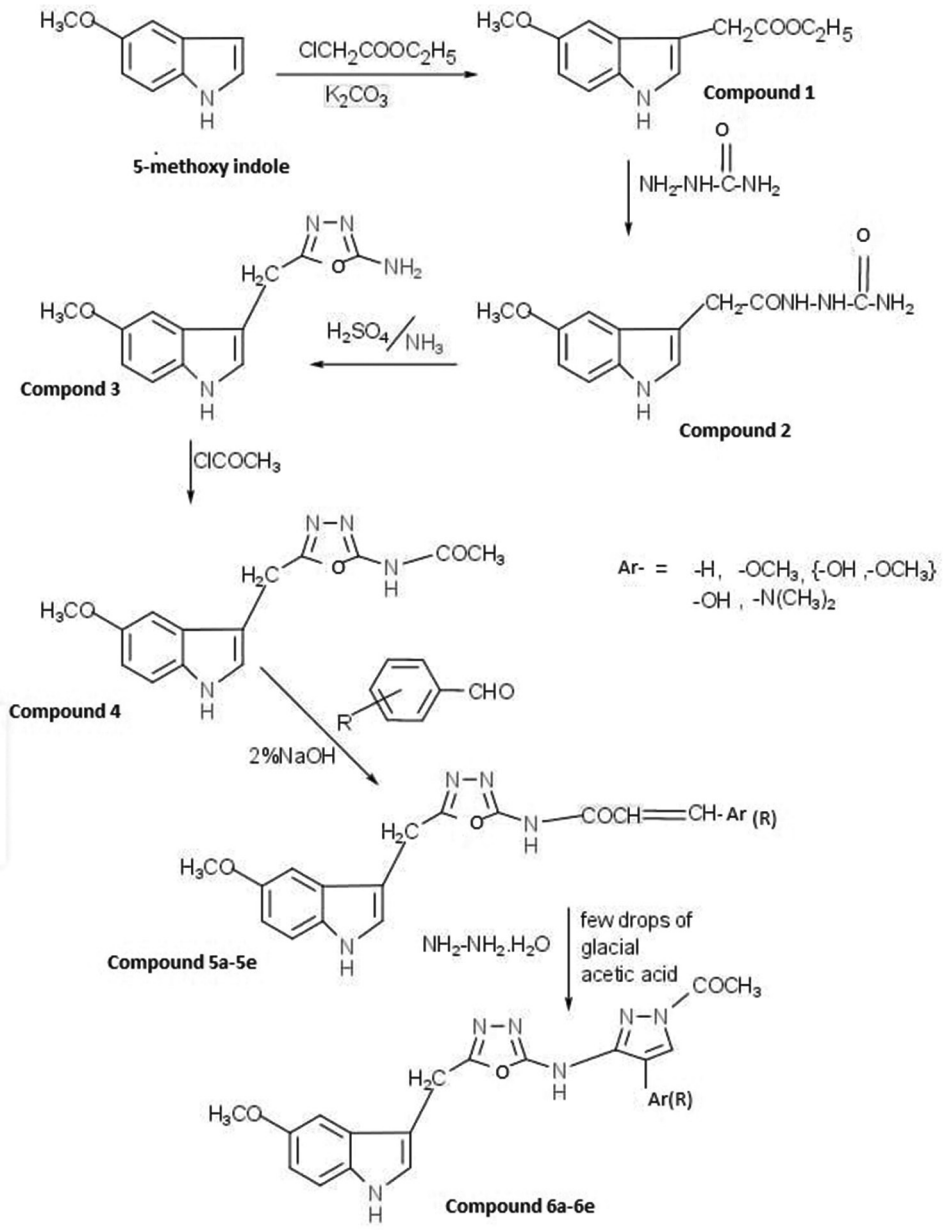
ISSN NO: 2320-0898 (p); 2320-0928 (e)
DOI: 10.22607/IJACS.2023.1102012

Received: 20th March 2023;
Revised: 11th April 2023;
Accepted: 23th April 2023.



Scheme of work

2. EXPERIMENTAL SECTION

2.1. Materials

Solvents are carried of S.D fine chem. and E. Merck grade, were purified and dried by conventional method [31]. All other chemicals of S.D. Fine Chem and E. Merck grade have checked for their purity before use.

The homogeneity and purity of the compounds were checked over thin layer chromatography coated with silica Gel–G (thickness 0.5 mm) developing solvent acetone/DMF (3:1) non-saturated chamber at room temp (20±1°C).

The melting points of the synthesized compounds were determined by capillary method and were uncorrected. The IR spectra (in KBr) were recorded on JASCO FTIR spectrophotometer. ^{1}NMR spectra (DMSO/$CDCl_3$) were taken on VRO–300 MHZ spectrophotometer and chemical shift expressed as ppm and TMS was used as internal standard. ε- bromoalkoxy phthalimides have been prepared by reported methods [32].

2.2. Experimental Method

A. Synthesis of 5-methoxy -3-indole ethyl acetate (1): Ethyl chloroacetate (0.1 mole) and anhydrous $_{K2CO3}$ (5.0 g) were added to the solution of 5-methoxy indole (0.1 mole) in CH_3OH (60 mL). The reaction mixture was refluxed for 10 h, cooled and excess of solvent was removed. The solid thus obtained was filtered and washed with water and recrystallized from ethanol to get product.

Yield: 70%, M.P. 48°C, Color: Colorless solid shining crystals

Molecular formula: $C_{13}H_{15}O_3N$, Molecular weight = 233

Elemental analysis (Calculated %) C = 66.90 (66.95), H = 6.38 (6.43), N = 5.93 (6.0)

IR (KBr) (in Cm^{-1}) 3145 (N-H str), 3005(C-H str, Ar-H), 2925 (C-H aliphatic), 1735 (C=O str), and 1580 (C=C of aromatic ring).

^{1}H-NMR ($CDCl_3$) (δ-ppm): 7.65–7.40 (m, 5H, Ar-H), 8.20 (s, 1H, NH of indole, exchangeable with D_2O), 6.80 (s,2H, CH2 attached to

indole nucleus), 4.20 (q, 2H, J = 7Hz, -$COOCH_2$-CH_3), 1.40 (s,3H, J = 7Hz, -$COOCH_2$-CH_3), 3.85 (s,3H, Ar-OCH_3).

B. Synthesis of 1-(5'-methoxy-3'-acetylindolyl)-semicarbazide (2): A mixture of Compound (1) [0.075 mole] in 60 mL. C_2H_5OH and semicarbazide (0.075 mole) in CH_3OH (60 mL) was refluxed for 10 h sin presence of anhydrous NaOH. After removing the excess solvent under reduced pressure, gives solid compound on cooling in ice bath, which was filtered, dried and washed with water. The product was recrystallized from ethanol.

Yield: 65%, M.P. 282°C, Color: Colorless needle like crystals

Molecular formula: $C_{12}H_{14}N_4O_2$, Molecular weight = 246

Elemental analysis (Calculated %) C = 54.93 (54.96), H = 5.30 (5.34), n = 21.32 (21.37)

IR (KBr) (in Cm^{-1}) 3150 (NH str), 3032 (C-H str, Ar-H), 2922 (C-H aliphatic) 1700 (C=O str), 1600 (C=C of aromatic ring), 1220 (C-N), 1040 (N-N).

^{1}H-NMR ($CDCl_3$) (δ-ppm): 7.65–7.40 (m, 5H, Ar-H), 8.15 (s, 1H, NH of indole, exchangeable with D_2O), 6.90 (s, 2H, CH_2 attached to indole nucleus), 8.50 (m, 4H, $NHNHCONH_2$, exchangeable with D_2O), 3.50 (s, 3H, Ar-OCH_3)

C. Synthesis of 2-amino-5-(5'-methoxy-3'-indolylmethyl)-1,3,4-oxadiazole (Compound 3): A mixture of compound (2) (0.05 mole) and 20 mL. Conc. H_2SO_4 was kept overnight at room temperature and then add 300 mL ice cold water to it and shake the contents. The reaction mixture was neutralized with liquid ammonia. The solid thus obtained was washed with water and the product was recrystallized from methanol.

Yield: 65%, M.P. 221°C, Color: Colorless crystals

Molecular formula: $C_{12}H_{12}N_4O_2$, Molecular weight = 244

Elemental analysis (Calculated %) C = 58.93 (59.01), H = 4.85 (4.91), n = 22.90 (22.95)

IR (KBr) (in Cm^{-1}) 3355 (NH str), 3165 (N-H), 3025 (C-H str, Ar-H), 2915 (C-H aliphatic) 1550 (C=C of aromatic ring), 1210 (C-O-C), 1047 (N-N), 1610 (C=N, str).

^{1}H-NMR ($CDCl_3$) (δ-ppm): 8.20 (s, 1H, NH of indole, exchangeable with D_2O), 7.60–7.45 (m, 5H, Ar-H), 6.92 (s, 2H, CH_2 attached to indole nucleus), 5.76 (bs, 2H, NH_2, exchangeable with D_2O), 3.54 (3H, s, CH_3).

D. Synthesis of 2-acetylamino-5-(5'-methoxy-3'-indolylmethyl)-1,3,4-oxadiazole (Compound 4): To a solution of solution of Compound 3 (0.02 mole) in 50 mL dry chloroform, acetyl chloride (0.02 mole) was added drop wise at 0–5°C. Further, the reaction mixture was stirred with the help of magnetic stirrer for about 2 h at room temperature and then refluxed for 6 h on water bath. The excess of solvent was distilled off, contents were cooled and poured into crushed ice. The resulting mixture was filtered to afford solid product which was filtered, dried, and washed with petroleum ether. The product is recrystallized from ethyl alcohol-water.

Yield: 75%, M.P. 248°C, Color: White crystals

Molecular formula: $C_{14}H_{14}N_4O_3$, Molecular weight = 286

Elemental analysis (Calculated %) C = 58.69 (58.74), H = 4.82 (4.89), n = 19.50 (19.58)

IR (KBr) (in Cm^{-1}) 3170 (NH str), 3020 (C-H str, Ar-H), 2930 (C-H aliphatic), 1555 (C=C of aromatic ring), 1215 (C-O-C), 1700 (C=O), 1032 (N-N).

^{1}H-NMR ($CDCl_3$) (δ-ppm): 7.70–7.55 (m, 5H, Ar-H), 8.20 (s, 1H, NH of indole, exchangeable with D_2O), 6.90 (s, 2H, CH_2 attached to indole nucleus), 8.50 (bs, 2H, NHCO exchangeable with D_2O), 2.40 (3H, s, $COCH_3$), 2.62 (s,3H,OCH_3).

E. Synthesis of 5-(5'-methoxy-3'-indolylmethyl)-1,3,4-thiadiazolyl-2-amino(p-hydroxy-m-methoxyphenyl) chalcone(Compound (5c): To a solution of compound 4 (0.01 mole) in CH_3OH (50 mL), p-hydroxy-m –methoxybenzaldehyde (0.01 mole) was added in presence of 2% NaOH solution. The reaction mixture was heated under reflux for 12 h. Completion of reaction was monitored on TLC. The excess of solvent distilled off, and contents were cooled. The resulting product was filtered and washed with cold water and recrystallized with methanol-water.

Yield: 48%, M.P. 268°C, Color: White dull crystals

Molecular formula: $C_{22}H_{20}N_4O_5$, Molecular weight = 420

Elemental analysis (Calculated %) C = 62.72 (62.85), H = 4.64 (4.76), N = 13.79 (13.33)

IR (KBr) (in Cm^{-1}) 3560(O-H), 3135 (NH str), 3080 (C-H str, Ar-H), 2960 (C-H aliphatic), 1720 (C=O str), 1530 (C=C of aromatic ring), 1588 (C=N), 1047 (N-N) 1125 (C-O-C, str).

^{1}H-NMR ($CDCl_3$) (δ-ppm): 7.65–7.45 (m, 8H, Ar-H), 8.20 (s, 1H, NH of indole, exchangeable with D_2O), 6.95 (s, 2H, CH_2 attached to indole nucleus), 8.65 (bs, 2H, NHCO exchangeable with D_2O), 6.45 (d,1H,-COCH=), 9.20 (d, 1H, = CH-Ar), 3.48 (s, 3H, OCH_3), 11.20 (s,1H,OH,exchangeable with D_2O).

Various other 5-(5'-methoxy-3'-indolylmethyl)-1,3,4-oxadiazolyl-2-amino substituted chalcone 5a, 5b, 5d, and 5e were prepared with different aromatic aldehydes by the above mentioned method. Their physical and analytical data are given in Table 1.

F. Synthesis of 1-acetyl-5- (p-hydroxy-m-methoxyphenyl)-3-([5-methoxy-3'-indolylmethyl]-2-amino-1,3,4-thiadiazolyl-2-N-yl)-2-pyrazoline (Compound 6c): To a solution of compound 5c (0.02 mole) in 40 mL C2H5OH, hydrazine hydrate 99% (0.04 mole) and few drops of glacial acetic acid were added into it. Moreover, the reaction mixture was refluxed for 12 h. The excess of solvent was distilled off and cooled the contents. The separated solid was filtered, washed with water, and recrystallized with methanol-water.

Yield: 50%, M.P. 290°C, Color: White needle crystals

Molecular Formula: $C_{24}H_{24}N_7O_5$, Molecular weight = 490

Elemental analysis (Calculated %) C = 61.28 (61.34), H = 5.46 (5.52), n = 19.96 (20.0)

IR (KBr) (in Cm^{-1}) 3520 (O-H), 3150 (NH str), 3070 (C-H str, Ar-H), 2945 (C-H aliphatic), 1710 (C=O str), 1590 (C=N), 1035 (N-N), 1120 (C-O-C).

^{1}H-NMR ($CDCl_3$) (δ-ppm): 7.60–7.15 (m, 8H, Ar-H), 8.15 (s, 1H, NH of indole, exchangeable with D_2O), 6.92 (s, 2H, CH_2 attached to indole nucleus), 5.75 (bs, 1H, NH, exchangeable with D_2O), 5.25 (d, 2H,CH_2 of pyrazoline ring), 6.55 (t, 1H, CH-Ar of pyrazoline ring), 2.52 (s, 3H, $COCH_3$), 11.15 (ss,1H,OH, exchangeable with D_2O).

Other 1-acetyl-5-substitutedaryl-3-([5-methoxy-3'-indolylmethyl]-2-amino-1,3,4-oxadiazol-2-N-yl)-2-pyrazolines 6a, 6b, 6c, and 6e were synthesized by the same method as given above. Their physical and analytical data are given in Table 2.

Table 1: Physical data of compounds 5a-5e.

S. No.	Substituted (R) aromatic aldehyde	Yield	Recrystallization solvent	M.P. (°C)	Molecular formula	Found (calculated) %		
						C	H	n
5a	H	60	Ethanol-water	231	$C_{21}H_{18}O_3N_4$	67.22 (67.37)	4.78 (4.81)	14.83 (14.97)
5b	p-OCH_3	65	DMF	245	$C_{22}H_{20}O_4N_4$	65.25 (65.34)	4.83 (4.95)	13.73 (13.86)
5c	m-OCH_3, p-OH	70	Methanol-water	268	$C_{22}H_{20}O_5N_4$	62.75 (62.85)	4.65 (4.76)	13.20 (13.33)
5d	p-OH	45	Acetic acid	272	$C_{21}H_{18}O_4N_4$	64.50 (64.61)	4.51 (4.61)	14.24 (14.35)
5e	p-N $(CH_3)_2$	60	Methanol-water	292	$C_{23}H_{23}O_3N_5$	66.05 (66.18)	5.40 (5.51)	16.80 (16.78)

Table 2: Physical data of compounds 6a-6e.

S. No.	Substituted (R) aromatic aldehyde	Yield	Recrystallization solvent	M.P. (°C)	Molecular formula	Found (Calculated) %		
						C	H	N
6a	H	55	Ethanol-water	215	$C_{23}H_{22}O_3N_6$	64.67 (64.18)	5.00 (5.11)	19.47 (19.53)
6b	p-OCH_3	65	Methanol-water	198	$C_{24}H_{24}O_4N_6$	60.43 (60.50)	4.90 (5.04)	17.58 (17.64)
6c	m-OCH_3, p-OH	50	Methanol-water	290	$C_{24}H_{24}O_5N_6$	60.43 (60.50)	4.90 (5.04)	17.58 (17.64)
6d	p-OH	65	Acetic acid	278	$C_{23}H_{22}O_4N_6$	61.81 (61.88)	4.87 (4.93)	18.75 (18.83)
6e	p-N $(CH_3)_2$	54	Methanol-water	245	$C_{25}H_{26}O_3N_7$	63.47 (63.55)	5.42 (5.50)	20.70 (20.76)

2.3. Biological Activity

2.3.1. Anti-inflammatory activity

Anti-inflammatory activity [47] of all newly synthesized derivatives was determined by the carrageenan-induced rat paw edema model. Albino rats (80–140 g) were divided into three groups as control, test and standard (six animals per group). Overnight fasted animals were used and during that period only tap water was given. In general, phenylbutazone was used as standard drug. Both test and standard drugs were suspended in 1% carboxymethyl cellulose (CMC) and administered orally through gastric gavage needle. One percentage of CMC was administered in control group. After 1 h of administrating the compound, we induced the carrageenan (1%) by the sub planner surface of the right hind paws of animals. The initial paw volume and also the paw volume after 3 and 6 h of administrating carrageenan were measured. Percent paw edema inhibition was calculated according to the formula given below-% anti-inflammatory activity = $(1- V_t/V_c) \times 100$

Where V_t and V_c are volume of edema in drug treated and control group, respectively.

3. RESULTS AND DISCUSSION

SAR study of indole nucleus has revealed that substitution at 3-position of indole nucleus markedly enhanced the anti-inflammatory activity. Furthermore, indole was substituted with oxadiazolyl moieties at its 3-position. These compounds further converted into different substituted chalcones and finally cyclized into their corresponding pyrazolines. It was noticed that the chalcones showed mild to moderate anti-inflammatory activity. The inflammation inhibiting property increased on cyclisation of chalcones 5a-5e into their corresponding pyrazolines 6a-6e. Moreover, it has been observed that when compound 6c was substituted at 5-position of pyrazoline ring with phenyl group having methoxy group at meta position and hydroxyl group at para position, they showed maximum percentage inhibition of rat's paw edema (49.0%). On the other hand, compound 6b substituted at 5-position of pyrazoline ring with phenyl ring having methoxy group at para position, which has shown substantive anti-inflammatory activity (43.6%).

Table 3: Anti-inflammatory activities of compounds (5a-5e) and (6a-6e).

Compounds	Dose mg/kg	Inhibition of paw edema after 3 h (%) 1	Inhibition of paw edema after 6 h (%) 2
5a	50	3.28±0.28	29.14
5b	50	2.48±0.23	41.62
5c	50	3.46±0.22	43.10
5d	50	1.62±0.27	35.16
5e	50	1.10±0.20	31.15
6a	50	3.45±0.28	34.4
6b	50	2.49±0.23	44.6
6c	50	3.86±0.22	31.2
			48.8
			70.30
6d	50	1.45±0.27	38.12
6e	50	1.63±0.20	33.10
Phenylbutazone			26.7
			46.8
			66.2

1: Dose for 1–7: 50 mg/kg b.wt; 2: Dose for phenylbutazone 50 mg/kg b.wt; mean ± SEM; n+6

Hence, it may be concluded that the substitution in chalcones (5a-5e) and pyrazolines (6a-6e) with phenyl group at meta position and hydroxyl group at para position show maximum anti-inflammatory activity, while the substitution in chalcones and pyrazolines with phenyl group possess minimum anti-inflammatory activity.

All newly synthesized compounds (5a-5e and 6a-6e) were screened for their anti-inflammatory activity at a dose at 50 mg/kg p.o. The results of study are shown in Table 3. Most of these congeners showed potent anti-inflammatory activity ranging from 24.3% to 49% and were found

statistically significant. All these compounds were compared with standard drug (Phenylbutazone), which provided with 45.6% inhibition of edema at the identical dose. Compound 6c exhibited most potent anti-inflammatory activity (47.6%) and exhibited higher inflammation inhibiting property in comparison to phenylbutazone at 50 mg/kg p.o., by considering their potentiality, compound 6c and standard drug were further tested for their anti-inflammatory activity at three grades doses, that is, 25, 50, and 100 mg/kg p. o. and results are given in Table 3.

3.1. Anti-Inflammatory Study

All newly synthesized compounds (5a-5e and 6a-6e) were screened for their anti-inflammatory activity at a dose at 50 mg/kg p.o. The results of study are shown in Table 3. Most of these congeners showed potent anti-inflammatory activity ranging from 24.3% to 49% and were found statistically significant. All these compounds were compared with standard drug (Phenylbutazone), which provided with 45.6% inhibition of edema at the identical dose. Compound 6c exhibited most potent anti-inflammatory activity (47.6%) and exhibited higher inflammation inhibiting property in comparison to phenylbutazone at 50 mg/kg p.o., by considering their potentiality, compound 6c and standard drug were further tested for their anti-inflammatory activity at three grades doses, that is, 25, 50, and 100 mg/kg p. o. and results are given in Table.

4. CONCLUSION

On the basis of above discussion, it was found that newly synthesized compounds (6c, 6b, 5c, and 5b) show high anti-inflammatory active while synthesized compound (5a, 5e, 6a) show low anti-inflammatory activity. This paper gives a new route map for synthesis of new drugs for human health and society.

5. ACKNOWLEDGMENT

The author wish to express their sincere thanks to Principal, Sahu Jain College, Najibabad, for providing necessary lab facilities and also thankful to Prof. R.N. Goyal Former Head and Dean, Faculty of Science, I.I.T., Roorkee for helping in spectral studies of compounds and Director, C.D.R.I. Lucknow for helping in biological evaluation of newly synthesized compounds.

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