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Synthesis and Biological Evaluation of Some New 1-Pheyl, 3-ethoxycarbonyl, 5-hydroxy Indole Derivatives as a Potential Antimicrobial Agents

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Synthesis and Biological Evaluation of Some New 1-Pheyl,3-ethoxycarbonyl,5-hydroxy Indole Derivatives as a Potential Antimicrobial Agents

Basavaraj M. Kalshetty [α], Ramesh S. Gani [σ] & M.B.Kalashetti [ρ]

Abstract - The derivatives of Indole show biological activities including herbicidal. The newly synthesized compounds 1-phenylethyl,2-methyl,3-ethoxy carbonyl,5-methoxycarbonyl ,2-methoxy Indole (Compound 2) were prepared by treating 1-phenyl,3-ethoxycarbonyl,5-hydroxy,2-methyl Indole (Compound 1) successively with methyl bromo- acetate and refluxing with K2CO3 / KI in the presence of dry acetone. Newly synthesized compound 2 refluxed with hydrazine hydrate in alcoholic media forming 1-Phenylethyl,3-ethoxy carbonyl,2-methyl Indole,5-yl oxy acetic acid hydrizide (Compound 3). This drug which on separately reacting with carbon disulphide, phenyl iso-thiocynide, acetylacetone, triethylorthoformate gave condensed bridge head heterocyclic's such as 1-Phenyl ethyl,2-methyl,3-ethoxy cabonyl,5(5'-mercapto,1'-3'-4'-oxadiazol,2'-yl)-methoxy Indole (Compound 4), 1-Phenylethyl,3-ethoxycarbonyl,2-methyl,5-yl (methoxy carbothisemi cabazide) (Compound 5), 1-Phenyl,2-methyl,3-ethoxycarbonyl,5(2,5, dimethyl Pyrrole,1-yl) amino carbonyl methoxy Indole (Compound 8) and 1-Phenyl,3-ethoxycarbonyl,2-methyl,5-(1',3',4'-oxadiazole,2'-yl-methoxy Indole (Compound 9) respectively. Compound 6 and Compound 7 were also synthesized heterocycles of the Indole derivatives. The structures of the compounds were established with the help of the elemental analysis and spectral date (IR, NMR and Mass). Compounds were screened for their antimicrobial potential.

Keywords : biological evaluation, Indole derivatives, potential and microbial agents.

I. Introduction

Newly synthesized derivatives of Triazole, Coumarin and Indole show diverse types of Biological activities such as analgesic & anti-inflmmatory[1],anti-tumaor[2], anti-mycobecterial[3], anti-cancer[4], anti-convulsant[5], diuretic[6], anti-microbial[7] and anti-diabatic[8]. The literature survey reveals that the heterocyclic compounds of Indole may enhance the biological activity [14]. Keeping in view of these reports, in the present investigation, it was planned to synthesis various bisheterocycles interesting in Indole moiety is linked to Oxidiazole, Pyrrole and Triazole. The 1,3,4-oxidiazoles have been shown to possess muscle relaxant, tranquilizing and anti-tubercular[15]. In the light of biological activities shown by Oxadiazole [16] the continuation of our work on Chemo-selectivity of Indole dicarboxylates towards hydrazine hydrates [17] and bridged heterocycles as various Schemes.

1-Phenyethyl ,3-ethoxy carbonyl,2-methyl Indole,5-yl oxy acetic acid hydrizide (Compound 3) have been found to show anti-bacterial[9], anti-microbial[10,11], anti-flammatory[12] and anti-convulsant[13] activities. Hence the derivatives of compound in Scheme 1, Scheme 2, Scheme 3 and derivatives of compound 2 in Scheme 4 have been found to possess varying Pharmacological activities.

Hence, we started to link oxadiazoles, Pyrrole, Triazoles to C-5 position of biological active Indole moiety leading to the synthesis of hitherto unknown title compounds with view to study their pharmacological profile. In the present investigation the required starting material 1-Phenylethyl,3-ethoxycarbonyl,5-hydroxy,2-methyl Indole (Compound 1) was prepared by adopting the Nenitzescue method 18 where as by reacting Ethyl,3-Phenylethyl aminocrotanate (Compound B) with p-benzoquinone (Compound A) as reported in scheme 01. Thus formed compound 1 was allowed to react with methyl bromo acetate in the presence of anhydrous KOH, produced Indole dicarboxylates (Compound 2). This compound 2 was refluxed with hydrazine hydrate in the presence of ethanol, produced Indole monocarbohydrazine (Compound 3) was observed that the C-3 ethoxy carbonyl group in the ester of compound 2 did not react with hydrazine hydrate under the above reaction conditions and dicarbohydrazide was not produced, the observed resistant of C-3 ethoxycarbonyl of the diester (Compound 2) to wards nucleophilic attack of hydrazine hydrate may be attributed to the canonical form of the diester (Scheme 04). Where in C-3 ethoxycarbonyl group has less double bond character.

The monocarbohydrazide (Compound 3) was further reacted separately with alcoholic KOH and disulphide (Scheme 01), with alcoholic PhNCS (Scheme 02(, with Acetylacetone in the presence of glacial acetic acid (Scheme 03) and Triethylorthoformate in boiling alcohol (Scheme 03) to afford respectively. 1-Phenyl ethyl,2-methyl,3-ethoxycabonyl,5(5'-mercapto,1'-3'-4'-oxadiazol,2'-yl)-methoxy Indole **(Compound 4)** (Scheme 01), 1-Phenylethyl,3-ethoxycarbonyl,2-methyl,5-yl (meth oxy carbothisemi cabazide) **(Compound 5)** (Scheme

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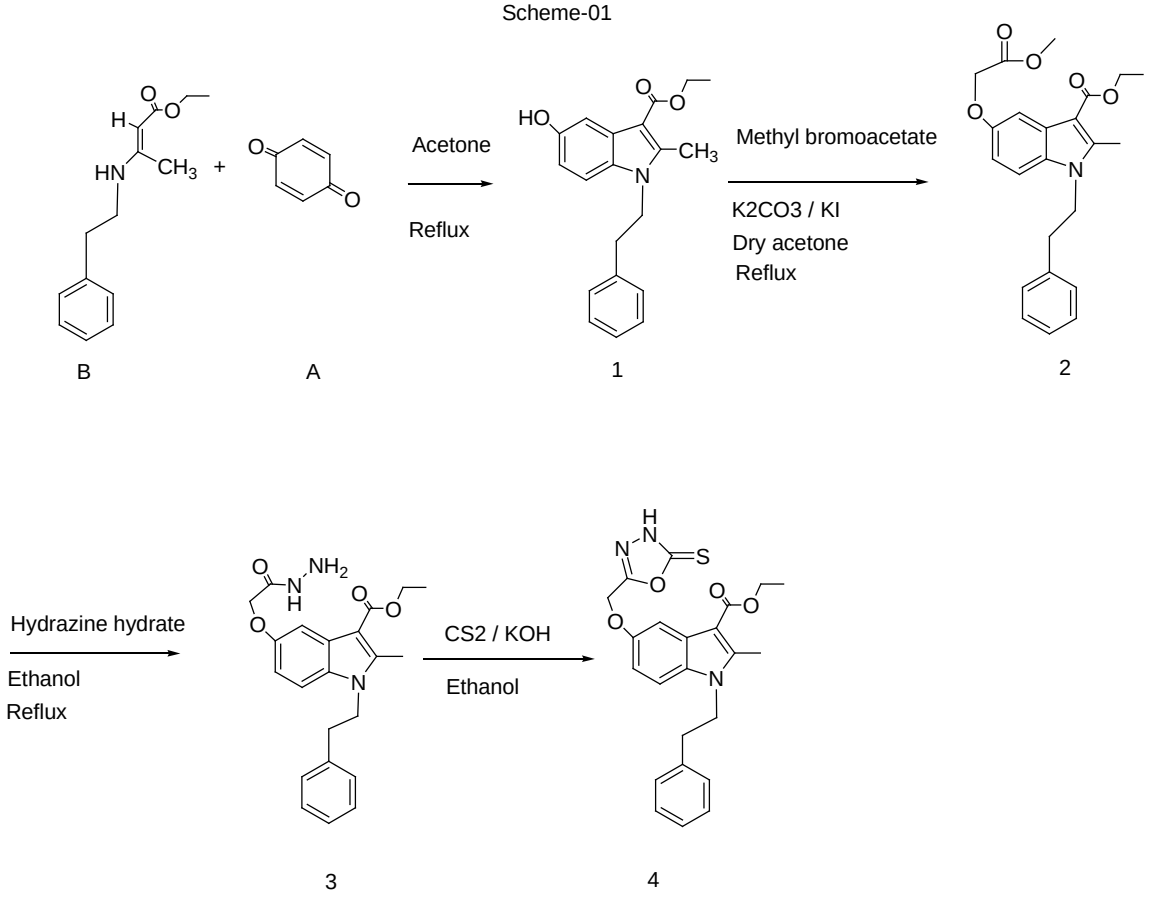
02), 1-Phenyl,2-methyl,3-ethoxycarbonyl,5 (2,5, dimethyl Pyrrole,1-yl) amino carbonyl methoxy Indole **(Compound 8)** and 1-Phenyl,3-ethoxycarbonyl,2-methyl,5-(1',3',4'-oxadiazole,2'-yl-methoxy Indole **(Compound 9)** 0f Scheme 03.

In the compound 5 the thiosemicarbazide was oxidiatevely cyclised to the desired 1-Phenyl,3-ethoxy carbonyl,2-methyl,5(5'-analino,1',3',4',-Oxadiazole,2'-yl, 1-methylethoxy Indole **(Compound 6)** Scheme 02. This compound 5 specifically reacting with Iodine and KI in 4% sodium hydroxide solution forming 1-Phenylethyl,3-ethoxycarbonyl,2-methyl,5(4'-phenyl,5'-mercapto,1',2',4' -Triazole,3-yl) methoxy Indole **(Compound 7).** The structures of these newly synthesized compounds were confirmed by their spectral and analytical data tested for their anti- bacterial activities by Cup Plate method. Analgesic activity by aceti acid induced writhing response, hot plate reaction time and tail immersion method and anti- inflammatory activity by Carrageenan induced Paw edema method.

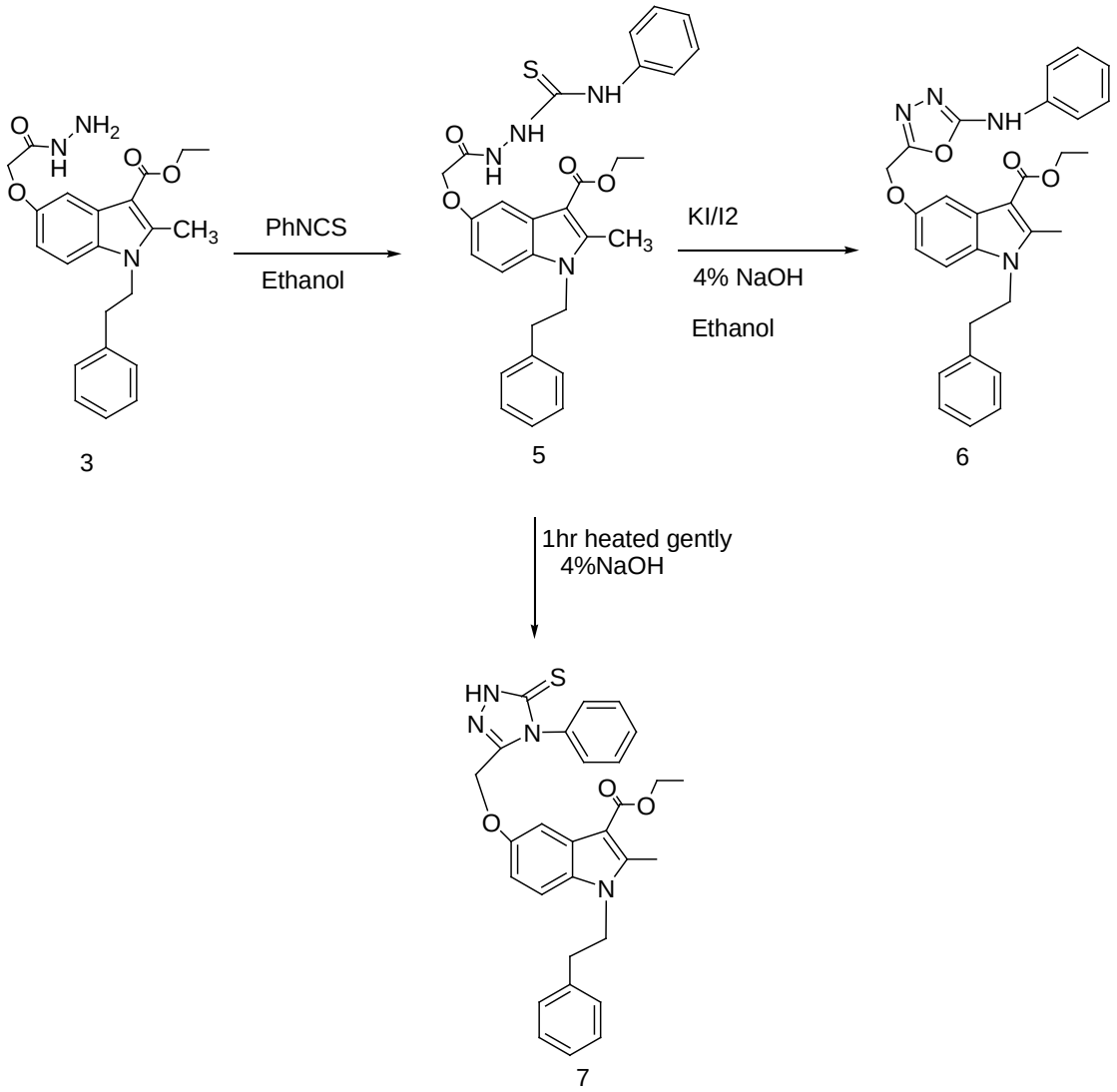
Scheme-01



B A 1 2

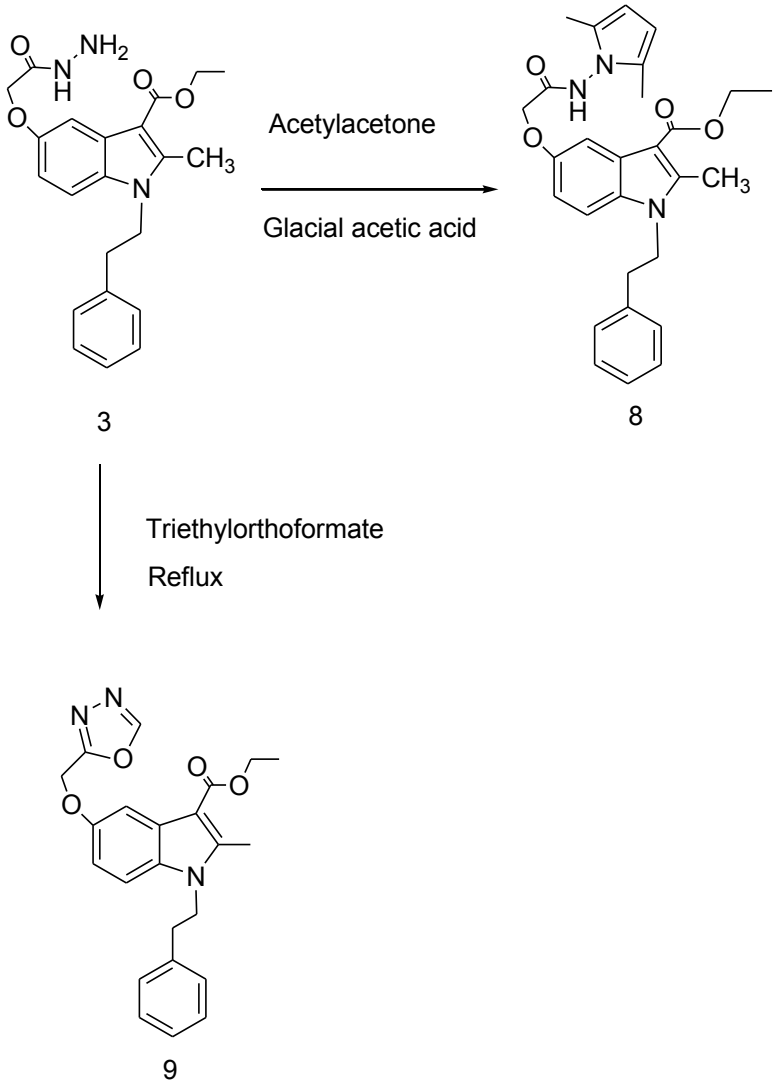
3 4

Scheme-02



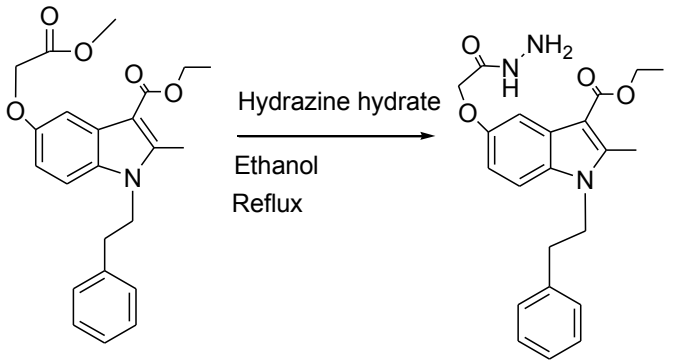
3 5 6 7

Scheme-03



3 8 9

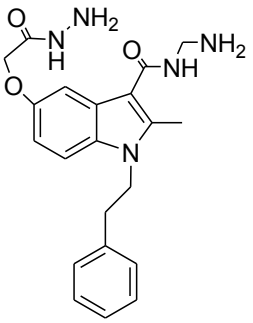
Scheme-04



2

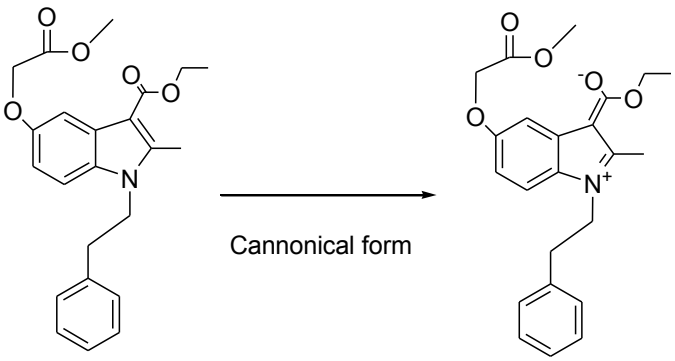
3

Monocarbohydrazide



C

Dicarbohydrazide



2

D

Nucleophilic substitution reaction does not take place at C-3 carbonyl group

II. Results and Discussion

All the synthesized compounds were screened for analgesic and anti-inflammatory activity in rats and mice, Wister rats (230-250g) ND Swise mice (25-30g) were used. The animals were kept in 26°C±2°C with the relative humidity of 44-56% continuously for 12 hours in light / dark cycle. They were fedded with standard diet and water. An approval for the experimental protocol was obtained and the procedure was carried at H.S.K College of Pharmacy, Bagalkot, Karnataka State, India. The rats had been fasted for 18-24 hours, were used for the experiments. The test compounds were suspended in 0.5% Sodium carboxymethyl cellulose (Na-CMC) and administered at the doses of 3 and 10 mg/kg of the body weight (bw), diclofence and pentazocine were administered as reference standard srugs for anti-inflammatory and analgesic respectively; at a dose of 10mg / kg body weight. The control group received 0.5% Na-CMC in distilled water,

The mass spectrum of newly synthesized compounds was good agreement with their molecular ion peaks. The characterization data of new compounds were given in **Table 1**. The synthesized compounds were evaluated in vitro for anti-bacterial activity against Escherichia Coli and Sacillus Cirraflagellous by Cup Plate method. The results were summarized in **Table 2**.

a) Anti-bacterial and Anti-fungal activity

The compounds 1 – 9 were screened for their in vitro anti-fungal potential activity by Cup Plate method[20] against Aspergillus fumigates (A F), human pathogenic yeast [Candida alb cans (OA)], Griseofulvin used as a standard. the compounds were tested, the anti-fungal activity results indicated that the some of the Indole derivatives possessed a broad spectrum of activity against the reference drugs, the compound which have no anti-fungal activity are not included in **Table 2**.

The compounds were tested at 1 mg / ml concentration in DMSO by Tube Dilution Technque[21]. The drug dilution were made serially, the test was performed at 28-29oC and Minimum Inhibitory Concentration (MIC) in mg / ml was recorded by Visual observations after 24-60 hours incubation. The suitable controls and standard drugs were set under identical conditions. Hence, the synthesized compounds have shown varying degree of anti-fungal activity against Candida albicans (human pathogenic yeast) although they have shown their major potential against Aspergillus fumigates (AF). However, the anti-fungal activity of the compounds 1 to 9 was screened and was found broad spectrum of activity against the reference drugs.

i. *Anti-inflammatory activity*

The anti-inflammatory activity of the test compounds was evaluated as described by winter et al [22] and Diwan et al [23] .One hour after administration of the test compounds. Rates in all groups were challenged with carrageenan (1% prepared in 0.4% NaCl) in the sub planter region of the right hind paw. The paw volume was measured at different intervals of time (0.5, 1, 2, 3, and 5h) using a digital plethysmometer (UGO Basil.Italy) and a zero hour reading, before administration of the carrageenan was taken. The percentage inhibition of the paw volume for each test group was calculated using following equation;

Percentage of inhibition (%)= [1-volume in ml]

(test compound) / Volume in ml (control)]x 100

The results in Table 3 and **Table 4** showed that some of the synthesized compounds have significant anti-inflammatory activity among these compounds. The compounds 1, 3, 6 showed significant anti-inflammatory activities at third and fifth hour, where as these were found to be non-significant at the 30 min. similarly, the other compounds showed more or less significant activity at the third and fifth hour were non-significant at the first hour.

ii. *Analgesic Activity*

The Eddy and Leimback hot plate test [24] was carried out in mice for evaluating analgesic activity. Albino mice of either sex were divided in to 12 groups, containing six animals each. Animals were administered with control (0.4% NaCl), test compoundes (3 and 10mgkg^{-1}) and pentazocine (10mgkg^{-1}) as an aqueous suspension of 1% sodium carboxy methyl cellulose .One hour after administration of compoundes , mice were kept on hot plate pre heated to 50°C for 15 seconds . The time taken to lick the hind paw was recorded at 60, 120, and 180min.increasein the reaction time (time interval taken by the animal to lick paw) was considered as proportional to analgesic activity as shown in **Table 5.**

Table 1 : Characterization of synthesized New compounds

Compound	Substituent	m.p. (^{0}C)	Yield(%)	Nature (solvent)	Molecular formula	Elemental analysis for Calcd) %		
						C	H	N
Compound 01	1-Phenylethyl	177-178	71	Brown granules (Ethanol)	$C_{20}H_{21}NO_3$	74.2 74.12	6.55 6.51	4.33 4.31
Compound 02	1-phenylethyl		66	Pale yellow (Ethanol)	$C_{23}H_{25}NO_5$	69.86 69.78	6.37 6.31	3.54 3.52
Compound 03	1-phenylethyl		61	Colorless needle (Ethanol)	$C_{22}H_{25}N_3O_4$	66.82 66.71	6.37 6.30	10.63 10.59
Compound 04	1-phenylethyl		69	yellow granules (Ethanol)	$C_{23}H_{23}N_3O_4S$	63.14 63.10	5.30 5.29	9.60 9.57
Compound 05	1-phenylethyl		82	Yellow flakes (Ethanol)	$C_{29}H_{30}N_4O4S$	65.64 65.61	5.70 5.66	10.56 10.51
Compound 06	1-phenylethyl		69	Pale yellow (Ethanol)	$C29H28N_4O_4$	70.15 70.09	5.68 5.61	11.28 11.17
Compound 07	1-phenylethyl		68	Pale yellow (Ethanol)	$C_{29}H_{28}N_4O_3S$	67.95 67.91	5.51 5.49	10.93 10.88
Compound 08	1-phenylethyl		71	Pale yellow (Ethanol)	$C_{28}H_{31}N_3O_4$	71.01 71.0	6.60 6.56	8.87 8.76
Compound 09	1-phenylethyl		68	Pale yellow (Ethanol)	$C_{23}H_{23}N_3O_4$	68.13 68.09	5.72 5.69	10.36 10.29

Table 2 : Antibacterial activity of compounds 3-11 were against B, cirroflagellosus and Escherichia coli. Antifungal activity of compounds 3-11 were against Candida albicans and Aspergillus.

Compound/Code	Concentration ; 1mg/ml		Compound/Code	Concentration ; 1mg/ml	
	Zone of inhibition in mm after 48hr			Zone of inhibition in mm after 48hr	
	E.col	B.cirroflagellosus		Candida albicans	Aspergillus Niger
Compound 01	++	+	Compound 01	++	++
Compound 02	-	++	Compound 02	+	++
Compound 03	+	+	Compound 03	+	+
Compound 04	+++	+++	Compound 04	++	+++
Compound 05	++	++	Compound 05	++	+++
Compound 06	+	+	Compound 06	+	+
Compound 07	+++	++	Compound 07	+++	+++
Compound 08	++	++	Compound 08	++	+++
Compound 09	+++	+++	Compound 09	++	+++
Norfloxicin	+++	+++	Griseofulvin	+++	+++

Symbols: Zone diameter of growth inhibition (-) inactive; (<12mm); (+) = weakly active (12-16mm); (++) moderately active (16-21mm); (+++)=highly active (22-28mm)

Table 3 : In vivo anti-inflammatory activity of 1-Phenylethyl-2-methyl-3-ethoxycarbonyl-5-hydroxyindole derivatives

Treatment	½ hr		1hr		3hr		5hr	
	Paw-volume (ml)	%EI	Paw-volume (ml)	%EI	Paw-volume (ml)	%EI	Paw-volume (ml)	%EI
Normal	0.6625±0.01315	--	0.6225±0.06415	--	0.6675±0.01109	--	0.6675±0.01652	--
Control	1.2523±0.45213 [c]	--	1.2950±0.64300 [c]	--	1.3520±0.07325 [c]	--	1.1983±0.02314 [c]	--
Diclofenac (10mg/kg)	0.2263±0.0149***		0.2763±0.0239***		0.2838±0.0171***		0.2988±0.028***	
Compound-02 (3mg/kg)	0.2475±0.02414	80.23	0.3876±0.01724*	70.06	0.3975±0.01248	70.59	0.2925±0.00212	75.59
Compound-02 (10mg/kg)	0.2600±0.01475	79.23	0.3427±0.01318*	73.53	0.3575±0.01215*	73.55	0.3050±0.0102**	74.54
Compound-01 (3mg/kg)	0.2825±0.01047*	77.44	0.3612±0.011**	72.10	0.4075±0.02179	69.85	0.3755±0.01287	68.66
Compound-01 (10mg/kg)	0.2560±0.02911	79.55	0.3310±0.0130*	74.44	0.4108±0.02202	69.61	0.3955±0.02200	66.99

*All the values are expressed as Mean±SEM, Analysis of Variance (ANOVA) followed by Dunnett's test. *P<0.05; **P<0.01 and ***P<0.001*
as comparison of test groups to control group; [a]P<0.05; [b]P<0.01 and [c]P<0.001 as comparison of normal group to control group.

Table 4 : In vivo anti-inflammatory activity of 1-Phenylethyl-2-methyl-3-ethoxycarbonyl-5-hydroxyindole derivatives

Treatment	½ hr		1hr		3hr		5hr	
	Paw-volume (ml)	%EI	Paw-volume (ml)	%EI	Paw-volume (ml)	%EI	Paw-volume (ml)	%EI
Normal	0.6625±0.01315	--	0.6225±0.06415	--	0.6675±0.01109	--	0.6675±0.01652	--
Control	1.2523±0.45213 [c]	--	1.2950±0.64300 [c]	--	1.3520±0.07325 [c]	--	1.1983±0.02314 [c]	--
Diclofenac (10mg/kg)	0.2263±0.0149***		0.2763±0.0239***		0.2838±0.0171***		0.2988±0.0281***	
Compound-08 (3mg/kg)	0.4231±0.821*	66.21	0.3327±0.08315	74.30	0.3984±0.03352	70.53	0.3764±0.0321	68.58
Compound-08 (10mg/kg)	0.3981±0.0283	68.21	0.3527±0.04251	72.76	0000.4192±0.6035	68.99	0.3847±0.0172	67.89
Cmpound-04 (3mg/kg)	0.2561±0.0372	79.55	0.2738±0.01154*	78.85	0.3193±0.0362	76.38	0.29837±0.0172	75.10
Compound-08 (10mg/kg)	0.2451±0.0372	80.42	0.2392±0.03416*	81.52	0.3291±0.0364*	75.65	0.3150±0.3261**	73.71
Compound-04 Tracho-2 (3mg/kg)	0.3261±0.0364	73.96	0.35647±0.03212*	72.47	0.42918±0.0253	68.25	0.3982±0.0162	66.76
Compound-04 Tracho-2 (10mg/kg)	0.3012±0.0374*	75.94	0.4103±0.02718**	68.31	0.4343±0.0241	67.87	0.3873±0.02342	67.67

*All the values are expressed as Mean±SEM, Analysis of Variance (ANOVA) followed by Dunnett's test. *P<0.05; **P<0.01 and ***P<0.001*
as comparison of test groups to control group; [a]P<0.05; [b]P<0.01 and [c]P<0.001 as comparison of normal group to control group.

Table 5 : In vivo analgesic activity of 1-Phenylethyl-2-methyl-3-ethoxycarbonyl-5-hydroxyindole derivatives

Compound	Reaction Time (X ± SE) in seconds (difference in reaction time compared to basal value)			
	Basal	60 min	120 min	180 min
Control	4.60 ± 0.11	10.01 ± 1.20	9.550 ± 0.62	10.35 ± 1.24
Pentazocine (5mg/kg)	4.93 ± 0.23	11.21 ± 1.23 (6.28 ± 0.30	14.32 ±1.23*** (9.39± 0.20)	15.00 ±0.00*** (10.07± 1.53)
Compound-02 (3mg/kg)	4.29 ± 0.21	12.43 ± 0.62 (8.14± 1.05)	11.30 ± 0.48** (± 0.31) 7.01	12.22 ± 1.43 (7.91± 0.84)
Compound-02 (10mg/kg)	5.67 ± 0.41	14.12 ± 0.88 (8.45± 0.01)	13.60 ± 0.20*** (7.93± 0.19)	12.95 ± 0.22* (7.28± 0.77)
Compound-01 (3mg/kg)	6.30 ± 0.17	10.23 ± 0.62 (± 0.25) 3.93	11.30 ± 0.38** (5.00± 0.41)	12.37 ± 0.23 (6.07± 0.14)
Compound-01 (10mg/kg)	5.61 ± 0.29	11.22 ± 0.35 (5.61± 0.34)	12.24 ± 0.13** (6.63± 0.36)	13.15 ± 1.20* (7.54± 0.19)
Compound-08 (3mg/kg)	6.25 ± 0.54	09.21 ± 021 (2.96± 0.38)	11.35 ± 0.13** (5.1± 1.08)	12.12 ± 2.73* (5.87± 0.21)
Compound-08 (10mg/kg)	7.65 ± 0.35	10.01 ± 021* (2.36± 0.25)	13.31 ± 0.10*** (5.66± 0.27)	14.02 ± 1.03** (6.37± 0.24)
Compound-04 (3mg/kg)	6.17± 0.66	10.21 ± 0.21 (4.04± 0.25)	12.10 ± 0.18** (5.93± 0.41)	13.45 ± 0.33 (7.28± 0.14)
Compound-04 (10mg/kg)	6.63 ± 0.16	10.22 ± 0.21 (3.59± 0.34)	11.33 ± 0.31** (4.7± 0.36)	14.21 ± 2.13* (7.58± 0.19)
Compound-04 Tracho-2 (3mg/kg)	4.35 ± 0.98	09.28 ± 1.45 (4.93± 0.10)	12.65 ± 1.15 (8.3± 0.31)	14.32 ±1.43* (9.97± 1.60)
Compound-04 Tracho-2 (10mg/kg)	7.55 ± 0.87	10.61 ± 0.32* (3.06± 0.23)	14.78 ±0.33*** (7.23± 0.51)	15.00 ±0.00*** (7.45± 0.23)

*Results expressed in mean ± SEM (n=6) Significance level *p<0.5, **p<0.01, *** p<0.001;*

III. Experimental

Melting points were determined in open capillary tubes and are uncorrected. IR spectra(cm-) recorded on Perkins-Elmer 881; 1HNMR spectra in $CdCl_3$ or TMS ON BRUKERS 400MHz NMR spectrometer (chemical shift in delta ppm); and mass spectra on a Auto spec E1 mass spectrometer. Elemental analysis was carried out on Heraeus CHN rapid analyzer.

a) Synthesis of Heterocyclic's

1. Ethyl,3-phenylethylaminocrotanate (Compound B):

Ethylacetoacetate was added drop wise to mixture of phenyl ethylamine and concentrated hydrochloric acid (2drops) with stirring at such a rate so that temperature remained at 40-45°C.The addition required one hour and stirring was continued for additional 2 hr at 40-45°C. The mixture was set aside overnight at room temperature, then extracted with ether. Ethereal solution was dried over anhydrous sodium sulfate and ether was evaporated to get β aminocrotanate as violet oil.(80-90% yield).IR (KBR): 1651(ester C=O) 3289cm (NH).

2. 1-Phenylethyl ,3-ethoxycarbonyl,5-hydroxy,2-methyl Indole (Compound 1) :

To a cooled solution of p-benzoquinone 1(.0.1mol)) in dry acetone (40ml) was added Ethyl-3-phenylethylaminocrotanate(Compound B) 0.1M with shaking. The reaction mixture was allowed to stand at room temperature for one hour and then it was heated for 1.5 hour on steam bath. Excess of solvent was removed under reduced pressure and the residue was recrystalized from suitable solvent (75-80% yield) ;Molecular formula **$C_{20}H_{21}NO_3$;**

IR (KBr): 1657(C3 ester C=0) and 3252cm- (C5-OH):

^{1}HNMR ($CdCl_3$)/TMS)δ 1.44(t 3 H,J=7.01 Hz of C_3–ester CH_3),2.43 (s, 3H, C_2-CH_3), 3.0(t 2H, J= 7.32Hz, of Ph-CH_2), 4.29(t, 2H,J=7.32Hz, N-CH_2), 4.44(q,2H, J=7.32Hz, , C_3-OCH_2) 5.36 (s, 1H, C_5-OH),6.82(dd, J_{1-3}=8.44,Hz, J_{2-4}=8.83Hz, Ar C_6-H), 7.28(d, J=2.7Hz, Ar C_7-H), 7.65(d, J=2.44Hz, Ar C4-H), 7.03(d, J=7.62, Ar 6'-H), 7.16&7.14(d,J=8.54Hz, Ar 4'& 8'-H), 7.25&7.23 (dd, J1-3=6.7Hz, J2-4=6.40Hz Ar 5' and 7' H);

^{13}CNMR(200MHz, $CDCl_3$) ;δ=11. 14. 35. 38. 40. 44. 58. 101. 105. 110. 111. 126. 126. 127. 128. 129. 138. 144. 152. 165.

MS (m/z relative intensity); 346(M^++23), (10), 324(M^+ +1), (100), 278(10),

3. 1-phenylethyl,2-methyl,3-ethoxycarbonyl,5-methoxycarbonyl, 2-methoxy Indole (Compound 2) :

To a solution of cooled solution of 5-hydroxyindole (0.03mole,) in dry acetone (500ml) were added methyl bromo acetate (0.06mole),anhydrous potassium carbonate(8gm) and potassium iodide (0.1gm). The reaction mixture was heated at reflux for 57hr. It was filtered and solvent was removed under reduced pressure. The residue was collected and crystallized from suitable solvent. Residue was purified by colum by using 10% ethyl acetate in hexane.mp 74-77°C, yield 63%. Molecular formula $C_{23}H_{25}NO_5$ IR (KBr); 1686(C_3- ester- C=0) 1731(C_5 –ester C=O) and absent (C_5-OH group was observed);

^{1}HNMR, delta 1..42 (t, 3H,J=7.32Hz, C_3-ester CH_3), 2.44(s,3H,C_2-CH_3),3.03(t, 2H J=7.32, Phenyl CH_2), 3.82(s, 3H, C-5-OCH3), 4.26(q, 2H,J= 7.32Hz, and C3-OCH_2),4.72(s,2H,C-5-OCH2),4.39,(t,J=7.32Hz,1NCH_2),-6.86(dd, J_{1-3}=8.85Hz, J_{2-4}=8.85Hz, 1H,Ar-C_6-H), 7.03(d, 1H,J=1.52Hz,Ar-C_7-H),7.63(d,1H,J=2.44HzAr-C_4H,)7.05 (dd,J_{13}=7.62Hz,&J_{24}=7.32Hz1Hof'6'Phenyl),7.19 & 7.21 (d,J=8.85Hz,2H of "4&"8 phenyl),7.27&7.24(dd,J1-3= 6.7Hz, J2-4,7.01Hz,2H of '5&'7 Phenyl), MS (m/z relative intensity); 438(M^++1), (100),392,(30), 324(10),

4. 1-phenylethyl,3-ethoxycarbonyl,2-methylindole,5-yl, oxyaceticacid hydrazide (Compound 3) :

A mixture of 4(0.02mole) in ethanol (200ml) hydrazine hydrate (9ml 99%), and pyridine (1drops) was heated on a boiling water bath for 25hr and was concentrated to half volume and left overnight. The separated solid was filtered, washed with little ethanol and crystallized from suitable solvent mp116-117°C, Yield, 67%.Molecular formula $C_{22}H_{25}N_3O_4$, IR (KBr) 1673(C_3-easter C=O), 1633(C_5-amode C=O);3273, 3557cm^{-1} (NH/NH_2);

^{1}HNMR ($CDCl_3$/TMS); 1..33(t, 3H,J=7.01Hz, C_3-ester CH_3), 2.41(s,3H,C_2-CH_3),2.98(t,J=7.01, 2H, Phenyl CH_2), 4.23(q, 2H,J= 7.09Hz, C3-OCH_2) ,4.49 (s, 2H,C-5-OCH2),4.36,(t,J=7.01,1N-CH_2),-6.87(dd, J_{1-3}=8.85Hz, J_{2-4}=8.85Hz,1H,Ar-C_6-H), 7.09(d, 1H,J=1.52 Hz,Ar- C_7-H),7.48(d,1H,J=2.1Hz,,Ar-C_4-H,)7.05(dd,J_{13}=7.62Hz, & J_{2-4}=7.32Hz1Hof'6'-Phenyl),7.20&7.22(d, J=7.32Hz,2H of "4&"8 phenyl), 7.26&7.25(dd,J1-3=6.7Hz,J2-4,7.01 Hz, 2H of '5&'7 Phenyl), 9.38, (s 1H, Amide NH, Disappeared on D_2O exchange,) MS (m/z relative intensity); 396(M+1)(18), 350(M-45)(100),

5. 1-phenylethyl,2-methyl,3-ethoxycarbonyl,5(5'mercapto-1',3',4'-oxadiazol-2'-yl)-methoxyindole(Compound 4) :

A mixture of carbohydrazide (Compound 3) 0.0015M in absolute ethanol (20ml) KOH (0.003M) dissolved in water (3ml) and carbon disulfide (0.0045M) was heated under reflux until the evolution of H_2S ceased (20hr). The reaction mixture was cooled to room temperature and poured in to ice-cold water. It was then neutralized with dil. HCl. The precipitated solid was filtered washed with water and dried. The product was recrystalised from ethanol. Yield mp206-208°C, Yield, 78%. Molecular formula $C_{23}H_{23}N_3O_4S$ IR (KBr) 1655 (C_3-easter C=O),3084cm (NH);

^{1}HNMR ($CDCl_3$/TMS); δ1.34(t, 3H J=6.96.Hz,, C3-ester CH3), 2.43(s,3H, C_2-CH_3),2.98(t,2H, J=6.96 Hz,Phenyl-CH_2), 4.28(q,2H, J=7.32Hz,C3-OCH_2) 4.39 (t, 2H,J=7.32Hz,1N-CH_2),5.25(s,2H,C5-O-CH_2),6.94(dd,J_{1-3} =8.79Hz, J_{2-4}= 8.79, Ar,C_6-H), 7.1(d, 1H,J=1.52Hz,Ar-C_7-H), 7.57(d, 1H,J=2.44Hz,,Ar-C_4-H,),7.05(dd,J_{1-3}=7.62 Hz,&J_{2-4}=7.32Hz1Hof'6'-Phenyl),7.19&7.21(d,J=8.85Hz, 2H of "4&"8 phenyl), 7.27&7.24(dd,J1-3=6.7Hz, J2-4,7.01Hz,2H of '5&'7 Phenyl),14.68(s, amide NH disappeared on D_2O exchange),

^{13}CNMR(200MHz,$CDCl_3$);δ=11.14. 35. 38. 39. 40. 40. 44. 58. 60. 102. 105., 111., 121. 126. 128.,131.,138.,145.152.,159.164.178.02,MS (m/z relative intensity); 460(M+Na), (60),392,(M-45), (100),

6. 1-phenylethyl,3-ethoxycarbonyl,2-methyl,5-yl(methoxycarbothiosemicarbazide) (Compound 5) :

To a solution of carbohydrazide (Compound 3) 0.095M in ethanol (50ml) was added phenylisothiocynate (0,095M) with stirring. The mixture was heated under reflux for 12hr. The yellow solid that separated on cooling to room temp was filtered, and recrystalized from alcohol. Yield, 69%. Molecular formula $C_{29}H_{30}N_4O_4S$ IR (KBr), 3222, 3310 cm^{-1} secondary amide NH. 1693 cm^{-1} (C-5-ester C=O) and 1673cm^{-1}(C-3-ester C=O),

^{1}HNMR ($CDCl_3$/TMS); δ1.45(t, 3H,,J=7.0 Hz,3h, C-3-ester CH3), 2.48(s,3H, C_2-CH_3), 3.03(t,2H, J=6.96 Hz, Phenyl-CH_2), 4.39(t,2H, J=7.12Hz,1N-CH_2), 4.27(q, 2H, J=6.96Hz,C3-OCH_2), 7.78(d, J=2.19Hz, Ar-C_4-H), 6.96(dd,J_{1-3}=8.79Hz, J_{2-4}=8.79, Ar,C_6-H), 7.29(d, J=2.7 Hz, 1H, Ar-C_7-H), 7.2 to7.4 (m 10H , Aromatic H),

8.39, 9.1, 9.9(s 1H, Amide NH, Disappeared on D_2O exchange,) ; ^{13}CNMR(200MHz, $CDCl_3$);11,14,,25, 53,45,59,76,77,78,81,103,109,114,117,121,124,125,126, 126,127,128,129,129,132,137,145,148,165,171,188,MS(m/z relative intensity); 540(M+1), (100). 495(M-45) (60).

7. 1-phenyl,3-ethoxycarbonyl,2-methyl,5(5'analino-1', 3',4'-oxadiazol-2'-yl-methoxyindole) (Compound 6) :

To a solution of thiosemicarbazide (Compound 5) 0.005M in ethanol (15ml) was added NaOH solution (1 ml, 4%) with cooling and shaking. Then a solution of iodine in KI (aq 5%) was added gradually to it with shaking till the colur of iodine persisted at room temp. The contents were heated at reflux on a water bath for 7 hr. The solvent was removed under reduced pressure and residue was recrysatlized from ethanol. Yield, 76%. IR (KBr)

1674cm^{-1} (C_3-easter C=O), 3222cm^{-1}(NH);

^{1}HNMR ($CDCl_3$/TMS); δ1.32(t,3H J=7.33.Hz,, C3-ester CH3), 2.41(s,3H, C_2-CH_3) 3.01(t, J=7.32 Hz, Phenyl-CH_2),4.34 (t,J =7.32Hz,1N- CH_2),4.26(q,,2H,C3-OCH_2), 6.6 to7.5 (m 13H , Aromatic H), 10.6,(s, 1H of phenyl NH , disappeared on D_2O exchange,) MS (m/z relative intensity); 503(M+NH3), (100),458,(M-45).(15).

8. 1-phenylethyl,3-ethoxycarbonyl,2-methyl,5(4'-phenyl,5' -mercapto-1',2',4'-trizole-3'-yl) methoxyindole (Com - pound 7) :

To the suspension of thiosemicarbazide (Compound 5) 0.0015 M in a sodium hydroxide solution (4%) (10ml) was heated gently under reflux for 1hr. The reaction mixture after cooling room temperature was poured in to crushed ice (20gm) and acidified carefully with dilute acetic acid. The precipitation thus obtained was filtered, washed with water, dried and recrystallised from suitable solvent. Yield, 78% Molecular formula $C_{29}H_{28}N_4O_4$;1HNMR ($CDCl_3$ / TMS); δ1.32(t, 3H J=6.2.Hz,C3-ester CH3), 2.48(s,3H, C_2-CH_3) 3.04(t, J=7.32Hz, Phenyl-CH_2),4.32(t, J=7.32Hz,1N-CH_2) 4.39(q, J=7.0Hz,C3-OCH_2), 6.6 to7.7 (m 8H , Aromatic H),MS (m/z relative intensity); 483(M+1) (100),438(M-45),(15).

9. 1-phenyl,2-methyl,3-ethoxycarbonyl 5(2,5 dimethyl pyrrole,1-yl) amino carbonyl 1-methoxy Indole (Compound 8) :

To a solution of (Compound 3) 0.0015M in absolute ethanol (10ml) were added acetyl acetone 0.0015M and glacial acetic acid (1ml). The reaction mixture was heated on a boiling water-bath for 3 hr. the reaction mixture was concentrated to half of its original volume and poured into ice-cold water (20ml) .The reaction the separated solid was collected by filtration. Washed with water .dried and recrystalised from ethanol. ,mp 147-148^{0}C Yield, 63%. Molecular formula $C_{28}H_{31}N_3O_4$;IR (KBr) 1619cm (C_3-easter C=O), 1692(C_5-amode C=O); 3298cm(NH);

^{1}HNMR ($CDCl_3$/TMS); δ1.42(t,3H J=7.32.Hz,,C_3-ester CH_3), 2.08(s,6H, pyrrole 2 CH_3) 2.49(s,3H, C_2-CH_3) 3.05(t, 2H,J=6.96 Hz, Phenyl-CH_2),4.32(t, 2H, J=6.96 Hz,1N-CH_2) 4.36(q, 2H,J=6.96Hz,C3-OCH_2), 5.80(s, 2H, Ar pyrrole- H), ,6.90(dd,$J_{1\text{-}3}$=8.79Hz, $J_{2\text{-}4}$=8.79, Ar,C_6-H), 7.24 (d, J=1.83Hz, 1H, Ar-C_7-H), 7.72(d, J=2.56,Hz, Ar-C_4-H),7.01(dd,$J_{1\text{-}3}$=7.62Hz,1H of 6'-Phenyl) 7.16&7.14 (d,J=8.85Hz, 2H of 4'&8' Phenyl group)7.26&7.23 (dd, of 5'&7'Phenyl; group), 8.98,(s,1H of Amide NH dis-appeared on D_2O exchange), ^{13}CNMR(200MHz, $CDCl_3$) ;δ=11. 11. 14. 25. 35. 45. 59. 76. 77, 63, 103. 104. 105. 110. 111. 126. 127. 127. 128. 128.131.137. 145, 146. 148, 152. 165. 167. MS (m/z relative intensity); 574(M+1), (100),

10. 1-phenyl,3-ethoxycarbonyl,2-methyl,5(1', 3', 4'-oxadi azol,2'-yl,methoxy Indole (Compound 9).

Triethyl orthoformate was added to indole carbohydrazide (Compound 3) 0.002M and heated at reflux for 10-12hr. The excess of triethyl orthoformate was removed under reduced pressure and the residue was triturated with pet ether the resulting solid was filtered and recrystalised from ethanol, Yield, 73%. Molecular formula $C_{23}H_{23}N_3O_4$ IR (KBr) 1657cm^{-1} (C_3-easter C=O),

^{1}HNMR ($CDCl_3$/TMS); δ1.28(t,3H J=6.72.Hz,, C3-ester CH3), 2.48(s,3H, C_2-CH_3),3.94 (t,2H, J=7.33Hz, Phenyl-CH_2),4.35(t,, 2H,J=7.32Hz,1N-CH_2),4.24 (q,,2H, J= 7.33Hz,C3-OCH_2), 6.6 to7.5 (m 13H, Aromatic H), MS (m/z relative intensity); 506(M+1), (100),

IV. Conclusions

1- phenylethyl-2-methyl-3-ethoxycarbonyl-5(5'-mercapto-1',3',4'-oxadiazol-2'-yl)-methoxyindole (**Compound 4)** and 1-phenyl-2-methyl-3-ethoxy carbonyl5(2,5 dimethyl pyrrole -1-yl) amino carbonyl methoxyindole (**Compound 8)** ,1-phenyl-3-ethoxy carbonyl-2-methyl-5(1',3',4'-oxadiazol-2'-yl-methoxyin dole (**Compound 9)** prepared as a part of our ongoing Structure Activity Relationship study showed good analgesic activity, These compounds also exhibited systematic as well as a topical anti-inflammatory, antifungal and antibacterial activity. The research and development of new 5-hydroxy Indole derivatives linked with Oxadiazole, Triazole and Pyrrole in conjugation with metal complex will provide the focus of future research in the development of new Indole effective drugs.

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