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Pharmacological Activities of 6-substituted-3-(5-chloro-3-phenyl-*1H*-indole-2yl)-3, 4-dihydro-4-substituted-4-substituted-phenacyl-*2H*-1, 3-benzoxazin-2-ones

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Abstract: ***In the present investigation, a series of new 4-substituted-2-[(E)-(4"substituted-phenyl)-oxoprop-1-enyl]-phenyl-5'chloro-3'-phenyl-1'H-indol-2'yl-carbamates (6a-f) and 6-substituted-3-(5'-chloro-3'-phenyl-1'H-indole-2'yl)-3, 4-dihydro-4-substituted-phenacyl-2H-1, 3-benzoxazin-2-ones (7a-f) were screened for their pharmacological activities like anti-inflammatory and analgesic activities.***

Keywords: Indoles; Chalcones; Benzoxazin-2-ones; Antimicrobial activity

1. Introduction

Heterocycles bearing nitrogen, sulphur and oxygen atoms in their structure constitute the core structure of a number of biologically interesting compounds. Indole derivatives have been shown to possess antibacterial, antifungal and anti HIV activities (1). There have also been several reports on the anticancer properties (2), antiviral (3), antihepatitis-B virus (HBV) (4**)**, anthelmintic effects (5), spermicidal activities (6), antituberculosis activity (7) and cyclooxygenase-2 inhibitors (8) of compounds bearing this ring system. 1, 3-Benzoxazines (9, 10**)** exhibit a wide range of biological activity, such as bactericidal, fungicidal, antitumour and antituberculosis, therefore, the synthesis of these compounds has attracted great interest.

In light of above findings and in continuation of our research work on indoles (11-14), we hereby report the synthesis and antimicrobial activities of 6-substituted-3-(5'-chloro-3'-phenyl-*1'H*-indole-2'yl)-3, 4-dihydro-4-substituted-phenacyl-*2H*-1, 3-benzoxazin-2-ones (**7a-f)** by making use of 5-chloro-3-phenyl-*1H*-indole-2-carboxyazide **(2)** and *(E)*-1-(4"-substituted-phenyl)-3-(2'-hydroxy-5'-substituted phenyl) prop-2-en-1-ones **(5a-f).** 5-chloro-3-phenyl-*1H*-indole-2-carboxyazide **(2)** was prepared by the reaction of 5-chloro-3-phenyl-*1H*-indole-2-carbohydrazide **(1)** with nitrous acid in 1, 4-dioxane **(Scheme-1)**.

2. Materials and Methods

2.1. Synthesis

The synthesis and antimicrobial activities of a open chain 4-substituted-2-[(*E*)-(4"substituted-phenyl)-oxoprop-1-enyl]-phenyl-5'chloro-3'-phenyl-*1'H*-indol-2'yl-carbamates **(6a-f)** and 6-substituted-3-(5'-chloro-3'-phenyl-*1'H*-indole-2'yl)-3, 4-dihydro-4-substituted-phenacyl-*2H*-1, 3-benzoxazin-2-ones (**7a-f)** were already published (14)**.** We hereby report the pharmacological activities of **(6a-f)** and (**7a-f).**

2.2. Pharmacological activities

2.2.1 Antinflammatory activity by paw-edema method (17)

Anti-inflammatory activity was evaluated by carrageen an induced rat hind paw oedema method. Albino rats of either sex weighing between 150-200 g were divided into groups of six animals each. The first group served as the control and received vehicle only (Tween-80, 1%), second group of animals were administered with standard drug Indomethacin 25 mg/kg body weight, orally. The animals of the other groups were treated with synthesized compounds at a dose of 25 mg/kg body weight, orally. A mark was made on both the hind paws just below the tibio-tarsal junction so that every time the paw could be dipped in the mercury column of plethysmo graph upto the mark to ensure constant paw volume. The normal paw volume was measured for both the legs, after 30 min. of above treatment an inflammation was induced in the left hind paw by injecting 0.1 ml of carrageen an (1%, w/v) in the planter tissue of the paw of all animals. The right paw served as a reference to non-inflammed paw for comparison. The initial paw volume was measured plethysmo graphically within 30 sec. of the injection. The relative increase in the paw served as a reference to non-inflammed paw for comparison. The relative increase in the paw volume was measured in control, standard and treated group, for 4 hr after carrageen an injection. The percent increase in paw volume over the initial reading was also calculated. This increase in paw volume in animals treated with standard drug and the synthesized indole and thiazole derivatives were compared with the increase in paw volume of control animals. Thus, percent inhibition of paw volume was calculated using the formula,

% inhibition = (1-Vt / Vc) x 100.

Where, **Vt** and **Vc** are mean relative changes in the paw volume of the test and control respectively.

All the newly synthesized indole derivatives were screened for their anti-inflammatory activity as compared with standard drug indomethacin and 1% Tween-80 was used as a control. The results of anti-inflammatory testing of all the tested compounds are summarized in the following **Tables-1**.

2.2.2 Analgesic activity by Tail flick method (18)

Tail flick method was followed for the evaluation of analgesic activity using the instrument analgesiometer. Albino mice of either sex weighing between 25-30 g were randomly distributed into groups consisting of six animals in each group. The first group served as a control group and animals were administered with vehicle (Tween-80, 1%) orally. The second group was administered with standard drug analgin at a dose of 25 mg/kg body weight, orally. The animals of the other groups were treated with indole derivatives at a dose of 25 mg/kg body weight, orally. The reaction time was noted at 0, 30, 60 and 90 min. of time intervals after the drug administration. Percent protection against tail flicking was calculated using the formula:

% Protection = (1-Wc/Wt) x 100

Where Wc and Wt are the mean time for the tail flicking in the test and control groups, respectively.

All the newly synthesized indole derivatives were screened for their analgesic activity as compared with standard drug analgin and 1% Tween-80 was used as a control. The results of analgesic testing of all the tested compounds are summarized in the following **Tables-2**.

3. Results and Discussion

3.1 Pharmacological activities.

3.1.1 Antinflammatory activity

All the newly synthesized indole derivatives were screened for their anti-inflammatory activity as compared with standard drug indomethacin and 1% Tween-80 was used as a control.

From **Table-1** of the results of anti-inflammatory activity of indole derivatives, it is clear that the compounds **6a, 6b, 6c, 7a, 7b** and **7c** have exhibited good anti-inflammatory activity as compared with that of standard drug indomethacin. The compounds **6e, 6f, 7e** and **7f** showed moderate anti-inflammatory activity as compared with that of standard drug indomethacin. The remaining compounds **6d** and **7d** were less active when compared with that of standard drug indomethacin. Under these conditions, the standard drug indomethacin used exhibited 73.02 % anti-inflammatory activity and control 1% Tween-80 used as a control did not show any anti-inflammatory activity.

3.2.2 Analgesic activity

All the newly synthesized indole derivatives were screened for their analgesic activity as compared with standard drug analgin and 1% Tween-80 was used as a control.

From the **Table-2**, it is clearly that the compounds **6a, 6b, 6c, 7a, 7b** and **7c** exhibited good analgesic activity as compared with that of standard drug analgin. The compounds **6e, 6f, 7e** and **7f** showed moderate analgesic activity as compared with that of standard drug analgin. The remaining compounds **6d** and **7d** were less active when compared with that of standard drug. Under these conditions the standard drug analgin used exhibited 63.18% analgesia, after 60 min drug administration and 1% Tween-80 used as a control did not show any analgesic activity.

4. Conclusion

All the newly synthesized indole derivatives were screened for their anti-inflammatory activity as compared with standard drug indomethacin and 1% Tween-80 was used as a control. The results of anti-inflammatory and analgesic activities of indole derivatives, it is clear that the compounds **6a, 6b, 6c, 7a, 7b** and **7c** have exhibited good pharmacological activities as compared with that of standard drugs.

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Table 1: Anti-inflammatory activity of indole compounds.

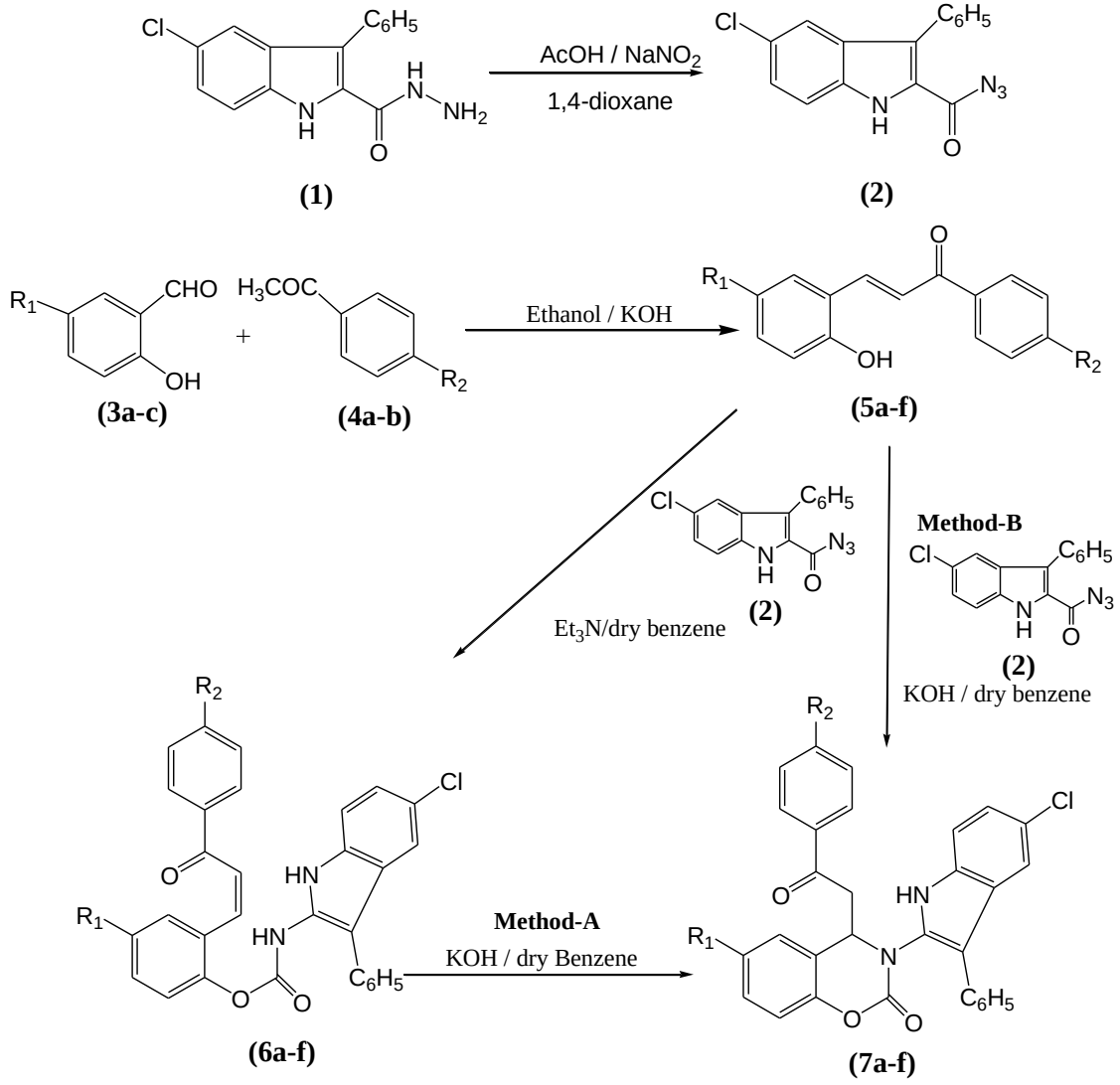
Group (Compound)	Dose mg/kg b.w	Mean values (± SE) of oedema volume at different intervals				% inhibition at 2hr
		0	30	60	90	
1 (Control)	1 ml	0.305 (±0.014)	0.295 (±0.024)	0.285 (±0.022)	0.275 (±0.019	-
2 (Indomethacin)	25	0.195** (±0.010)	0.145 (±0.012)	0.081*** (±0.009)	0.091 (±0.011)	71.57
6a	25	0.213 (±0.011)	0.154 (±0.013)	0.104*** (±0.009)	0.112 (±0.011)	63.35
6b	25	0.212** (±0.016)	0.122 (±0.016)	0.104 (±0.021)	0.164 (±0.019)	63.51
6c	25	0.195** (±0.015)	0.115 (±0.019)	0.091*** (±0.021)	0.101 (±0.015)	68.07
6d	25	0.295* (±0.011)	0.241* (±0.019)	0.261** (±0.011)	0.231 (±0.018)	8.42
6e	25	0.245* (±0.021)	0.191 (±0.021)	0.195 (±0.018)	0.211 (±0.014)	31.57
6f	25	0.195** (±0.010)	0.155 (±0.014)	0.134** (±0.009)	0.142 (±0.010)	52.98
7a	25	0.208 (±0.011)	0.161 (±0.013)	0.110*** (±0.009)	0.108 (±0.011)	62.35
7b	25	0.200* * (±0.016)	0.118 (±0.016)	0.111 (±0.021)	0.171 (±0.019)	65.51
7c	25	0.189** (±0.015)	0.119 (±0.019)	0.089*** (±0.021)	0.121 (±0.015)	67.17
7d	25	0.272* (±0.011)	0.232* (±0.019)	0.254** (±0.011)	0.211 (±0.018)	15.42
7e	25	0.241** (±0.011)	0.199 (±0.021)	0.192 (±0.018)	0.217 (±0.012)	32.63
7f	25	0.257** (±0.021)	0.189 (±0.012)	0.140** (±0.021)	0.168 (±0.017)	50.88

No. of animals for each group=6, Control= 1% Tween-80
Significance levels *P< 0.05, **P<0.01, ***P<0.001 compared with respective control (**ANOVA followed by Dunnet's test**). Each value represents ±SE (n=6).

Table 2: Analgesic activity of indole compounds.

Group (Compound)	Dose mg/kg b.w	Average (± SE) reaction time (sec.) Time after drug treatment (min.)				Percent analgesia at 60 min
		0	30	60	90	
1 (Control)	1 ml	3.245 (±0.219)	3.260 (±0.223)	3.271 (±0.230)	3.257 (±0.212)	-
2 (Analgin)	25	3.895** (±0.219)	5.278** (±0.223)	8.884** (±0.208)	9.057 (±0.218)	63.18
6a	25	3.545 (±0.211)	4.215 (±0.224)	6.184* (±0.198)	6.686 (±0.188)	47.10
6b	25	3.698 (±0.211)	4.315 (±0.224)	6.124* (±0.198)	6.721 (±0.188)	47.36
6c	25	3.745** (±0.214)	4.768 (±0.187)	7.841** (±0.188)	8.107 (±0.180)	58.28
6d	25	3.514 (±0.215)	3.687 (±0.200)	4.010 (±0.213)	4.347* (±0.218)	18.43
6e	25	3.235 (±0.219)	3.868 (±0.223)	5.009 (±0.2108)	5.957* (±0.2108)	34.69
6f	25	3.154 (±0.129)	4.128 (±0.223)	5.178* (±0.218)	5.271 (±0.198)	36.83
7a	25	3. 569 (±0.211)	4.229 (±0.224)	6.201* (±0.198)	6.659 (±0.188)	47.25
7b	25	3.655 (±0.211)	4.289 (±0.224)	6.104* (±0.198)	6.706 (±0.188)	46.41
7c	25	3.705** (±0.219)	4.882 (±0.197)	7.847** (±0.188)	8.547 (±0.200)	58.32
7d	25	3.215 (±0.221)	3.958 (±0.235)	3.871 (±0.241)	4.105* (±0.227)	15.50
7e	25	3. 524 (±0.169)	3. 826 (±0.199)	4.727 (±0.210)	3.257 (±0.205)	30.80
7f	25	3.205 (±0.209)	3.801 (±0.183)	4.714 (±0.118)	6.207* (±0.201)	30.61

No. of animals for each group=6, Control= 1% Tween-80
Significance levels *P< 0.05, **P<0.01, ***P<0.001 compared with respective control (**ANOVA followed by Dunnet's test**). Each value represents ±SE (n=6).



For Compounds (5a-f), (6a-f) and (7a-f)

	a	b	c	d	e	f
R_1 =	-H	-Br	-Cl	-H	-Br	-Cl
R_2=	-H	-H	-H	$-CH_3$	$-CH_3$	$-CH_3$

Scheme-1