

Synthesis And Characterization Of Some Novel Indole Carboxamide Derivative And Its Anti-Inflammatory & Analgesic Evaluation

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Abstract

An indole carboxamide derivative is a structure that has an indole ring system, which is made up of a benzene ring and a pyrrole ring, with a carboxamide group ($-CONH_2$ or a variation of it) attached to one of the ring positions, usually at the 3-position (3-carboxamides) or 2-position (2-carboxamides) derivatives of indole-carbohydrazides indole-2-carbohydrazides (1a-b) and carboxaldehydes (2a-d) was reacted to produce indole carbohydrazide derivatives (4a-h) and indole carboxamide derivatives (5a-h), respectively. Formaldehyde was then added to the mixture. Using spectral data, the structures of every freshly synthesized molecule were verified. These substances have all undergone screening for analgesic and anti-inflammatory properties. The percentage inhibition of for anti-inflammatory potential was 73.02% and for analgesic activity resulted in a pain alleviation rate of 63.18% after a period of sixty minutes of use.

Keywords: Indole, synthesis, biological evaluation, activity, characterization

INTRODUCTION

There are a great number of compounds that have biological significance that are constructed using heterocycles of nitrogen, sulfur, and oxygen atoms as their primary building components [1]. This is because of the several biodynamic properties that they possess, which include antiviral, anti-hepatitis B virus, antioxidant, antituberculosis, and cyclooxygenase-2 inhibitory activities [2, 3]. Chemists have shown a significant amount of interest in the heterocyclic-containing quinoline ring system due to the fact that it possesses exceptional biological activity. We have reported from our laboratory that many indolo [2, 3-c] isoquinolines exhibit fungicidal and bactericidal characteristics [4, 5]. We have demonstrated these qualities [6]. These include cytotoxic and antiproliferative properties, spermicidal, bactericidal, bacteriostatic, smooth muscle relaxant, analgesic, anti-inflammatory, tranquilizing, sedative, and antireserpine properties [7, 8].

A tissue's response to an infection, an irritant, or an alien material is inflammation. Although it is a component of the host's defenses, high concentrations can cause acute inflammatory diseases. Tissue factors or mechanisms linked to inflammatory responses include the production of prostaglandins, histamine, and bradykinin [9]. Although they are not necessarily related, inflammation is actually a sequence of events rather than a single occurrence [10, 11].

Given that the aforementioned results have been obtained, and as part of our ongoing study on indoles, we report the synthesis and antibacterial activity of numerous indole carbohydrazide derivatives (4a-h) and indole carboxamide derivatives (5a-h). Starting with indole carbohydrazide derivatives 3a-h, we have added the nitrogen from the NH_2 group of these derivatives into the oxazine nitrogen of the quinolino-oxazine

system (Synthetic Scheme I). These derivatives have structures that contain both indole and quinolinoxazine components [12-14].

MATERIAL AND METHODS

Chemicals and instruments:

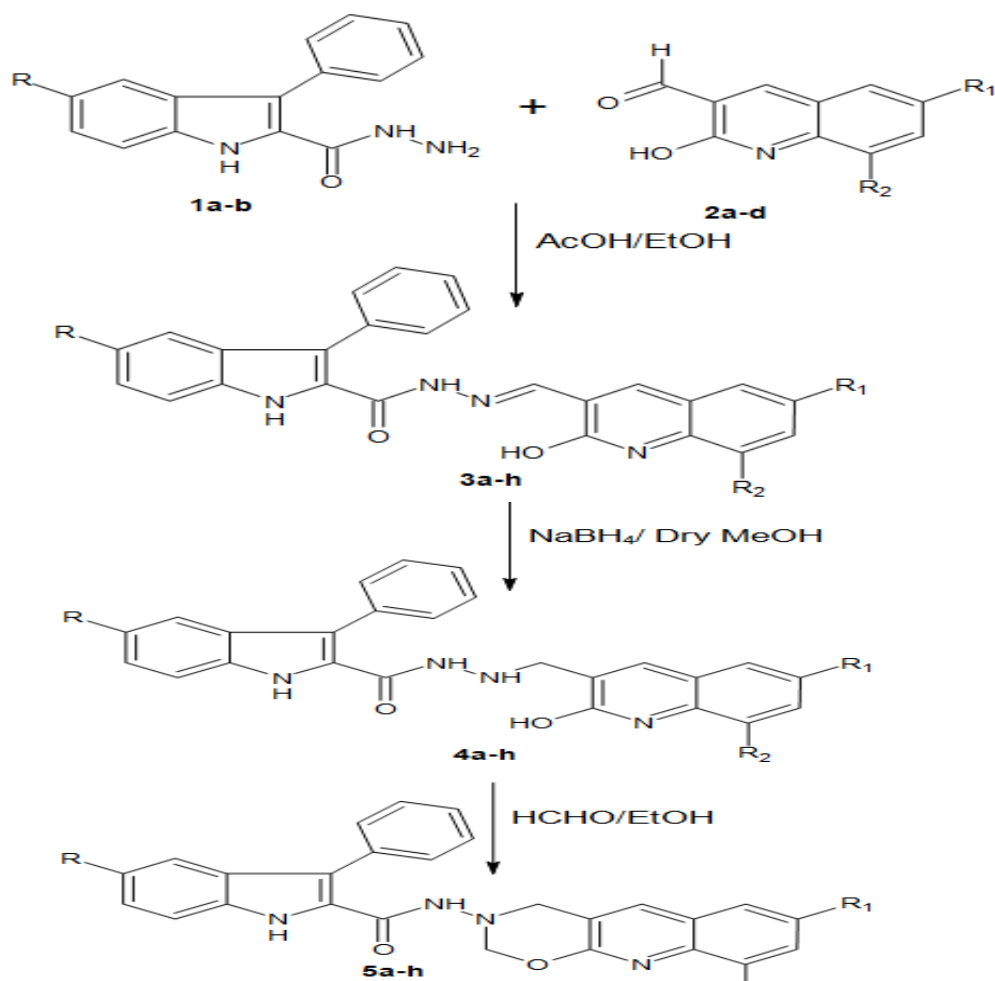
Open capillary tubes measured melting points. Mass spectra, ^1H NMR spectra, and IR spectra were taken. Iodine vapors were utilized as a visualization agent, and compounds were analyzed via TLC on silica gel 60GF254 plates to confirm their purity. The Flash EA1112 series elemental analyzer was employed for the elemental analysis. The described procedure was employed to synthesize the precursor materials, which were derivatives of indole carbohydrazides (3a-h). The synthesis component of this study, along with its antibacterial efficacy, has already been detailed.

Procedure for synthesis of indole carbohydrazides derivatives (step I) (3a-h): substituted -quinolines (2a-d) and carboxyhydrazides (1a-b) were mixed with 20 milliliters of ethanol and a catalytic quantity of glacial acetic acid, followed by refluxing for eight hours in a water bath. Filtered, rinsed with minimum alcohol, dried, and crystallized from dioxane, the particles were cleaned [15, 16].

Procedure for synthesis of indole carbohydrazides derivatives (step II) (4a-h): Upon the addition of sodium borohydride to a solution of molecules (3a-h) in 10 ml of methanol, the mixture was stirred for 30 minutes at ambient temperature. After adding the reaction mixture to ice-cold water, the isolated residue was filtered, washed, dried, and crystallized from dioxane to get 4a-h in an acceptable yield [17, 18].

Procedure for synthesis of indole carbohydrazides derivatives (step III) (5a-h)

Formalin (37%, 1 ml) and compound (4a-h) were refluxed in ten milliliters of ethanol for five hours. After adding the reaction mixture to ice-cold water, the residue was filtered, washed, dried, and recrystallized from dioxane to produce 5a-h. The compounds 5a, 5b, 5e, and 5h were recrystallized from dioxane, while 5c, 5d, 5f, and 5g were from benzene [19, 20].



Synthetic Scheme 1: Synthesis of indole carbohydrazides derivatives

Biological Activity Evaluation:

Evaluation of Anti-inflammatory activity:

Carrageenan-induced hind paw swelling in rats was used to test how well the anti-inflammatory worked. Albino male and female rats weighing 150-200 g were split into six groups. The first group was given Tween-80, 1% as a control. The second group was given oral indomethacin at a dose of 25 mg/kg body weight. Other animals were given 25 mg/kg body weight of chemicals that were made in a lab and were swallowed. A mark was placed slightly below the tibio-tarsal junction on both hind paws to ensure consistent paw volume. This approach allowed the paw to be immersed in the plethysmograph's mercury column to the mark each time. Each animal got 0.1 ml of 1% (w/v) carrageenan injected into the plantar tissue of its left hind paw 30 minutes after treatment to make it swell up. On both legs, the normal paw volume was found. The non-inflamed paw was compared to the right. Plethysmography measured initial paw volume 30 seconds after injection. The non-inflamed paw was compared to its proportionate growth. Four hours after carrageenan injection, control, standard, and treatment groups were compared for paw volume increases. The percent paw volume increase from the original measurement was also determined. Control animals were compared to those given normal treatment and synthetic indole and thiazole derivatives for paw volume increase [21-24]. The following method was used to figure out the % inhibition of paw volume:

$$\% \text{ inhibition} = (1 - V_t/V_c) \times 100$$

Where,

V_t and V_c are mean relative changes in the paw volume of the test and control respectively.

All of the new indole derivatives were tested to see how well they reduced inflammation compared to the usual drug indomethacin and a control group. Table 1 shows the anti-inflammatory test results for all the drugs that were tried.

Evaluation of Analgesic activity:

The analgesiometer used the tail flick method to measure the analgesic action. Six white mice, each weighing 25 to 30 grams, of each gender were put into groups at random. Orally given to the animals in the control group was Tween-80 (1%). The second group got 25 mg/kg of oral analgin. In other groups, 25 mg of indole derivatives were given by mouth for every kilogram of body weight. We timed the reactions at 0, 30, 60, and 90 minutes after the drug was given [25-27]. The following method was used to figure out tail flicking protection:

$$\% \text{ Protection} = (1 - W_c/W_t) \times 100$$

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

A 1% Tween-80 solution was used as a control, and all the new indole derivatives were tested to see how well they worked as pain relievers compared to the standard medicine, analgin. Table 2 below summarizes the analgesic test results for each investigated drug.

RESULTS AND DISCUSSION:

Our method was used to make the Schiff bases 3a-h. Compounds 3a-h made a lot of indole carbohydrazide derivatives 4a-h when they reacted with sodium borohydride in pure methanol at room temperature. This compound 4a had infrared absorption bands at 1682, 1723, 3062, 3188, 3361, and 3381 cm⁻¹. Its C=O and NH functions were visible. In compound 4a's ¹H NMR spectrum, seven different patterns were found: at 3.50, 5.68, 10.41, 10.62, 11.05, and 6.90-7.89 μ. In the third place of the quinoline molecule, there were thirteen aromatic protons, two methylene groups, four NH groups, and two methylene groups. The molecular ion peak M in chemical 4a's mass spectrum showed how heavy it was. There were fragment ions at m/z 414, 416, 283, 285, 255, 257, 225, 227 and 190 (14%), which were the molecular ions of compound 4a. This compound lost CO, 2-methylindole, an extra CO, a N₂H₂, and a chloride radical. Compounds 4a-h reacts with formalin in ethanol that is being boiled down to make compound 4a. This is shown by m/z 442 and 444 from compound 3a. We got a good yield of 5a-h -3-phenyl-1H-indole-2-carboxamides by replacing 2H with quinolin. The C-O-C, C=O, and NH/NH functional groups are shown by absorption lines at 1180, 1670, 3261, and 3308 cm⁻¹ in 5a's infrared

spectrum. There were two different signals at 4.25 and 4.68 in the ^1H NMR spectrum of 5a. These came from the two methylene protons in the oxazine moiety. There were thirteen aromatic protons in the range of 7.01 to 7.89. Indole NH and amide group protons are the same as singlets at 9.95 and 11.05 eV. Its molecular weight is shown by the main peak of 5a's mass spectrum, which is between 454 and 456. This is also its greatest signal. There are more fragment ions at m/z 425, 427, 255, 257, 225, 227, and 190 coming from the molecular ion. This is because the CHO radical ($\text{C}_{10}\text{H}_8\text{N}_0$) is released, followed by a chloride radical. The results make it very clear that chemical 5a comes from chemical 4a.

Evaluation of Anti-inflammatory activity:

A standard of 1% Tween-80 was used to see how the new indole derivatives compared to indomethacin in terms of their ability to reduce inflammation. Indole compounds 4a, 4b, 4d, 5a, 5b, and 5d are better at reducing inflammation than indomethacin, as shown in Table 1. Compared to indomethacin, chemicals 4c, 4e, 4f, 5c, 5e, and 5f were much better at reducing inflammation. Other chemicals (4g, 4h, 5g, and 5h) are not as effective as indomethacin. Indomethacin, a commonly used medicine, worked 73.02 percent of the time to reduce inflammation, but 1% Tween-80 didn't.

Table 1: % inhibition for evaluation of Anti-inflammatory activity of indole derivatives

Group	Dose (mg/kg b.w)	Mean values \pm SE				% inhibition
		0 min	30 min	60 min	90 min	
Control	1 ml	0.234 \pm 0.020	0.230 \pm 0.024	0.220 \pm 0.026	0.210 \pm 0.017	
Indomethacin	25	0.190 \pm 0.010	0.160 \pm 0.010	0.060 \pm 0.006	0.059 \pm 0.010	72.99
4a	25	0.160 \pm 0.010	0.140 \pm 0.010	0.090 \pm 0.010	0.080 \pm 0.015	61.00
4b	25	0.170 \pm 0.020	0.124 \pm 0.020	0.080 \pm 0.015	0.045 \pm 0.010	66.10
4c	25	0.210 \pm 0.010	0.180 \pm 0.022	0.125 \pm 0.020	0.125 \pm 0.022	44.70
4d	25	0.170 \pm 0.015	0.160 \pm 0.020	0.100 \pm 0.010	0.110 \pm 0.015	58.60
4e	25	0.210 \pm 0.030	0.160 \pm 0.020	0.120 \pm 0.022	0.120 \pm 0.0110	47.21
4f	25	0.210 \pm 0.020	0.139 \pm 0.020	0.120 \pm 0.010	0.110 \pm 0.020	46.20
4g	25	0.290 \pm 0.020	0.220 \pm 0.020	0.220 \pm 0.022	0.190 \pm 0.020	13.40
4h	25	0.210 \pm 0.010	0.180 \pm 0.020	0.150 \pm 0.020	0.150 \pm 0.030	32.20
5a	25	0.220 \pm 0.020	0.165 \pm 0.010	0.150 \pm 0.020	0.120 \pm 0.030	47.11
5b	25	0.211 \pm 0.050	0.160 \pm 0.020	0.110 \pm 0.030	0.120 \pm 0.0150	50.69
5c	25	0.210 \pm 0.010	0.170 \pm 0.030	0.160 \pm 0.020	0.150 \pm 0.010	31.10
5d	25	0.180 \pm 0.020	0.130 \pm 0.020	0.100 \pm 0.020	0.050 \pm 0.010	60.11
5e	25	0.192 \pm 0.0120	0.150 \pm 0.020	0.120 \pm 0.030	0.150 \pm 0.030	46.10
5f	25	0.180 \pm 0.020	0.170 \pm 0.020	0.130 \pm 0.010	0.140 \pm 0.030	44.30

5g	25	0.180 ±0.030	0.190 ±0.020	0.150 ±0.030	0.140 ±0.030	34.15
5h	25	0.290 ±0.010	0.170 ±0.020	0.140 ±0.010	0.130 ±0.030	31.99

Each group has six animals, with 1% serving as a control. Tween-80 Significance levels were *P<0.05, **P<0.01, and ***P<0.001 compared to the respective control (ANOVA followed by Dunnet's test). The values represent ± SE (n = 6).

Evaluation of Analgesic activity:

One percent Tween-80 was used as a control to evaluate the analgesic efficacy of all freshly synthesized indole derivatives. The results of this evaluation were compared to the effectiveness of the reference medicine, analgin. When looking at the standard pain reliever analgin, Table 2 clearly shows that compounds 4a-b, d, 5b, and d were much more effective at reducing pain. When looking at the common medicine analgin, the pain relief from compounds 4c, e, f, 5c, e, and f showed a fair level of effectiveness. In comparison to the typical drug, the activity of the other compounds, which were 4g-h, 5g-h, was significantly lower. Under these circumstances, the typical pain reliever, analgin, resulted in a pain alleviation rate of 63.18% after a period of sixty minutes of use. On the other hand, the control, 1% Tween-80, did not result in any pain relief at all.

Table 2: Assessment of Indole compounds analgesic properties

Group	Dose (mg/kg b.w)	Average ± SE reaction time				Percent analgesia
		0 sec	30 sec	60 sec	90 sec	
Control	1 ml	4.110 ±0.200	3.300 ±0.230	2.900 ±0.190	3.350 ±0.190	
Analgin	25	4.100 ±0.220	6.100 ±0.300	9.100 ±0.300	10.002 ±0.240	64.20
4a	25	3.800 ±0.200	6.001 ±0.310	8.100 ±0.300	9.100 ±0.110	60.11
4b	25	4.120 ±0.080	6.120 ±0.300	8.100 ±0.300	7.100 ±0.310	54.60
4c	25	4.230 ±0.250	4.320 ±0.240	4.100 ±0.280	4.120 ±0.110	16.60
4d	25	4.200 ±0.320)	4.800 ±0.320	7.100 ±0.230	7.250 ±0.210	47.17
4e	25	2.999 ±0.222	3.210 ±0.220	4.005 ±0.310)	4.100 ±0.210)	16.67
4f	25	3.560 ±0.356	2.999 ±0.360	5.590 ±0.354	4.560 ±0.320	20.90
4g	25	4.260 ±0.020	4.100 ±0.310	4.100 ±0.320	4.500 ±0.300	06.32
4h	25	4.120 ±0.302	4.120 ±0.300	4.920 ±0.310	4.120 ±0.390	14.80
5a	25	4.100 ±0.150	6.123 ±0.230	9.230 ±0.290	9.120 ±0.210	60.15
5b	25	4.120 ±0.080	6.152 ±0.358	8.485 ±0.420	7.520 ±0.300	55.77
5c	25	4.510 ±0.305	3.456 ±0.560	5.110 ±0.120	7.850 ±0.240	34.88
5d	25	4.100 ±0.310	6.100 ±0.300	6.100 ±0.320	7.100 ±0.120	46.50
5e	25	3.600 ±0.260	4.780 ±0.410	6.100 ±0.352	6.546 ±0.230	38.31

5f	25	4.125 ±0.352	6.220 ±0.356	6.258 ±0.362	4.990 ±0.360	36.80
5g	25	4.005 ±0.220	6.520 ±0.520	3.990 ±0.310)	4.560 ±0.310	20.15
5h	25	4.120 ±0.040	4.230 ±0.320	4.160 ±0.320	4.120 ±0.320	14.20

Each group contains six animals, with 1% serving as the control. Tween-80 In comparison to the corresponding control (ANOVA followed by Dunnett's test), significance levels $P < 0.05$, $*P < 0.01$, and $***P < 0.001$ were observed. Every value denotes \pm SE (n=6).

CONCLUSION

Using 1% Tween-80 as a point of reference, we compared the anti-inflammatory effects of novel indole derivatives to those of the conventional medication indomethacin. Compounds 4a-b, d, 5a-b, and d were discovered to have significantly more potent anti-inflammatory effects than the conventional medicine indomethacin. This was discovered among the indole derivative components. A comparison was made between the pain-relieving capabilities of each novel indole derivative and those of the conventional medicine analgin, with 1% Tween-80 serving as the control variable. Based on the information that is provided in Table 2, it can be shown that compounds 4a-b, d, 5a-b, d displayed a significant analgesic effect in comparison to the traditional medicine that is commonly referred to as analgin.

Declarations:

Consent for publication:

All the authors approved the manuscript for publication.

Competing interests:

All authors declare no competing interests.

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