ARTICLE

Synthesis and Anti-inflammatory Activity of Newer Indolyl Pyrazolines and Indolyl Isoxazolines

Nancy[1], Sakshi Chaudhary[2], Deepak Kumar[2] and Archana[1,✉]

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ABSTRACT

Various 5-substituted aryl-3-(2′-carboxy-5′-methoxyindolyl)-2-pyrazolines **(9-15)** and 5-substituted aryl-3-(2′-carboxy-5′-methoxyindolyl)isoxazolines **(16-22)** have been synthesized by the cyclization of compounds 1-(2′-carboxyl-5′-methoxyindolyl-3-arylidenyl chalcones **(2-8)** by treating them with hydrazine hydrate/glacial acetic acid and hydroxylamine hydrochloride/2% NaOH, respectively and TLC checked for their purity. Structure of all these newly synthesized compounds was characterized by elemental (C, H, N) analysis and IR and ^{1}H NMR spectroscopy. All the synthesized compounds were tested for their anti-inflammatory and ulcerogenic activities and acute toxicity and found to possess varying degrees of these activities. Compound **15** is 5-(3″-methoxy-4″-hydroxyphenyl)-3-(2′-carboxy-5′-methoxyindolyl)-2-pyrazoline found to be the most potent compound of the series, more potent than the standard drug phenylbutazone.

KEYWORDS

Indoles, Pyrazolines, Isoxazolines, Ulcerogenic activity, Anti-inflammatory activity.

INTRODUCTION

Indole, an aromatic heterocyclic compound, is the parent molecule of several drugs have an extensive use throughout medical and veterinary practice. Moreover, literature survey reveals indole to be a valuable moiety of bioactive compounds showing anti-inflammatory [1-6], anticancer [7-11], anticonvulsant [12-14], antiviral [15-18], antibacterial [19,20], antimicrobial [21], antimalarial [22,23] properties. Pyrazolines [24-27] and isoxazolines [28-31] are also a known class of anti-inflammatory agents, as reported in the literature. Hence, it was thought worthwhile to fix pyrazoline and isoxazoline moieties at the 3rd position of the indole nucleus to enhance the anti-inflammatory activity.

Current therapy for the inflammatory disease is reported to cause severe adverse effects like gastrointestinal ulcer, cardiovascular, renal abnormalities, *etc.* Therefore, there is a massive need to explore new anti-inflammatory agents with good potentiality and lesser toxicity. The development of a safer anti-inflammatory agent remains to be a subject of great interest for biological chemists. The current project is therefore aimed at synthesizing such compounds.

Author affiliations:

[1]Medicinal Chemistry Laboratory, Department of Chemistry, Meerut College, Meerut-250001, India
[2]Department of Chemistry, D.N. College, Meerut-250002, India

✉To whom correspondence to be addressed:

E-mail: archanachemistrymcm@gmail.com

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EXPERIMENTAL

Melting points of all the synthesized compounds of the series were determined in open capillary tubes and are uncorrected. The purity with homogeneity of the synthesized compounds was checked by thin-layer chromatography (TLC) using silica gel-G plates. CHN analysis for carbon, hydrogen and nitrogen was performed on Carlo Erba-1108, Heraeus. Study (C, H, N) were within ± 0.04% of the theoretical values. The IR and ^{1}H NMR spectra were recorded on the Backman Acculab-10 spectrophotometer (KBr) and Brucker 400-FT (in $CDCl_3$) instrument, respectively.

Synthesis of 3-acetyl-2-carboxy-5-methoxyindole (1): Acetyl chloride (50 mL) was added to 5-methoxyindole-2-carboxylic acid (20 g) dropwise with constant stirring at 0-5 ºC. The reaction mixture was further stirred for 10 h using a magnetic stirrer and kept overnight. It was distilled off to remove excess acetyl chloride. The residue thus obtained was washed using petroleum ether 40-60 ºC several times and then poured onto ice. The solid thus obtained was filtered using a filtration pump and recrystallized from the appropriate solvent. IR (KBr, ν_{max}, cm^{-1}): 3220 (NH of indole), 2780 (OCH_3), 3600 (COOH), 1690 (CO). ^{1}H NMR ($CDCl_3$) δ: 8.70 (brs, 1H, NH of indole, D_2O exchangeable), 7.00-7.35 (m, 3H, Ar-H), 2.46 (s, 3H, $COCH_3$), 9.10 (s, 1H, COOH), 3.18 (s, 3H, OCH_3).

Synthesis of 1-(2′-carboxyl-5′-methoxyindolyl-3-arylidenyl chalcones (2-8): A solution of 3-acetyl-2-carboxy-5-methoxyindole (**1**) in methanol (50 mL) containing 2% NaOH was refluxed with various aromatic aldehydes (0.01 mol) for 10-12 h. The resulting mixture was concentrated, cooled and poured onto ice. The solid thus obtained was filtered followed by washing with petroleum ether (40-60 ºC). The obtained solid after washing was recrystallized from appropriate solvent. IR (KBr, ν_{max}, cm^{-1}): 3210 (NH of indole), 2770 (OCH_3), 3590 (COOH), 1680 (CO), 1630 (CH=CH), 1570 (C-C of aromatic ring), ^{1}H NMR ($CDCl_3$) δ: 8.75 (brs, 1H, NH of indole, D_2O exchangeable), 7.00-7.70 8.90 (m, 8H, Ar-H), 2.42 (s, 3H, $COCH_3$), 9.15 (s, 1H, COOH), 3.20 (s, 3H, OCH_3), 6.65 (d, 1H, -COCH=), 8.39 (d, 1H, =CH-Ar).

Synthesis of 5-substituted aryl-3-(2′-carboxy-5′-methoxyindolyl)-2-pyrazolines (9-15): To a solution of 1-(2′-carboxyl-5′-methoxyindolyl-3-arylidenyl chalcones (**2-8**) (0.02 mol) in methanol and hydrazine hydrate (99%) (0.04 mol), few drops of glacial acetic acid were added. The reaction mixture thus formed was refluxed for 15 h. The excess solvent was distilled off and then the separated solid was filtered. After filtration, the solid was washed with petroleum ether and recrystallized from appropriate solvent to yield compound (**Scheme-I**). IR (KBr, ν_{max}, cm^{-1}): 3225 (NH of indole), 2790 (OCH_3), 3595 (COOH), 1560 (C-C of aromatic ring), 1490 (N-N), 1580 (C=N). ^{1}H NMR ($CDCl_3$) δ: 8.65 (brs, 1H, NH of indole, D_2O exchangeable), 7.10-7.90 (m, 8H, Ar-H), 9.05 (s, 1H, COOH), 3.25 (s, 3H, OCH_3), 7.10 (d, 2H of pyrazoline), 8.40 (t, 1H, -CH-Ar).

Synthesis of 5-substitutedaryl-3-(2′-carboxy-5′-methoxyindolyl)isoxazolines (16-22): To a solution of 1-(2′-carboxyl-5′-methoxyindolyl-3-arylidenyl chalcones (0.02 mol) (**2-8**) in methanol (50 mL), hydroxylamine hydrochloride (0.02 mol) was added. The reaction mixture thus formed was refluxed for 10 h in the presence of 2% NaOH solution. The reaction mixture was concentrated by distilled off the excess solution and then poured onto ice. TLC monitored the completion of the reaction. The solid thus obtained was filtered, washed with distilled water and recrystallized from appropriate solvent (**Scheme-I**). IR (KBr, ν_{max}, cm^{-1}): 3235 (NH of indole), 2780 (OCH_3), 3605 (COOH), 1675 (CO) 1230 (-C-O-N-), 1560 (C=N), 1570 (C-C of aromatic ring). ^{1}H NMR ($CDCl_3$) δ: 8.60 (brs, 1H, NH of indole, D_2O exchangeable), 6.90-7.70 (m, 8H, Ar-H), 2.60 (m, 2H, CH_2 of isoxazoline), 3.35 (m, 1H, CH-Ar), 9.12 (s, 1H, COOH), 3.22 (s, 3H, OCH_3).

Pharmacology

Anti-inflammatory activity: The method of Winter *et al.* [32] was used for performing paw edema inhibition test on albino rats. Rats were transferred to individual cages. After 30 min, 0.2 mL of 1% carrageenan suspension in a 0.9% NaCl solution was injected subcutaneously into the plantar aponeurosis of the hind paw water plethysmometer socrel measured the paw volume and then was measured again after 3 h. The mean increase of paw volume at each time interval was compared with that of the control group at the identical time intervals and the percent inhibition values were calculated using the given formula:

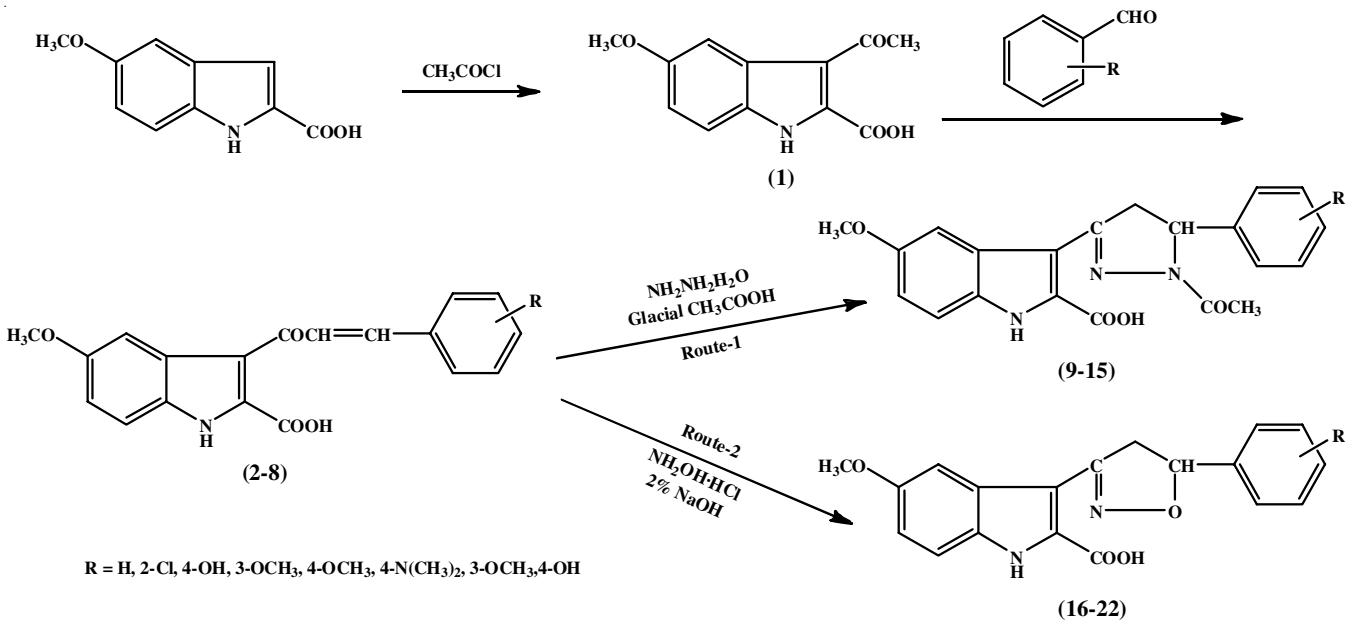
$$\text{Anti-inflammatory activity } (\%) = 1 - \left(\frac{V_t}{V_c}\right) \times 100$$

where V_t and V_c are tested and control groups, respectively.

Ulcerogenic activity: The ulcerogenic activity of newly synthesized compounds was performed by the method of Verma *et al.* [33]. Albino rats were made to fast for 24 h foregoing drug administration. All the animals were sacrificed 8 h after drug treatment and then their stomachs and small intestines were microscopically examined to assess the incidence of hyperemia, shedding of epithelium, petechial and frank hemorrhages and erosion or discrete ulceration with or without perforation. Presence of any one of these criteria was considered to be evidence of ulcerogenic activity.

Acute toxicity study: The approximate lethal dose (ALD_{50}) of compounds was determined in albino mice. The test compounds were given orally at different dose levels in groups of 10 animals. After 24 h of drug administration, percent mortality in each group was observed and from the obtained data, ALD_{50} was calculated by the method of Smith [34].

Animal ethics: The animals were housed under standard conditions and received a diet of commercial food pellets and water *ad libitum* during the captivity, but were entirely fasted during the experiment period. Each group was composed of 6–15 animals. The experiments were conducted with the recommendations in the Guide for the Care and Use of Laboratory Animals of the 393 Committee for the Purpose of Control and Supervision on Experiments on Animals (CPCSEA) 394 in India. All the animal studies were conducted in adherence to experimental guidelines and 395 procedures approved by the Institutional Animal Care and Use Committee (KSBT/IAEC/2020-39420/MCL-1/A4) of the Medicinal Chemistry Laboratory, Department of Chemistry, Meerut College, Meerut, India.



Scheme-I

RESULTS AND DISCUSSION

The physico-chemical parameters of the synthesized compounds are given in Table-1. The synthesized compounds **(1-22)** were also tested for their anti-inflammatory activity. The characteristic feature of the compounds of this series is the incorporation of two heterocyclic moieties that are pyrazoline and isoxazoline, at the third position of the indole nucleus to develop more potent anti-inflammatory agents with minimum or no side effects. An insight into the anti-inflammatory activity concerning chemical structure revealed that compounds having chalcone, pyrazoline or isoxazoline moiety at the 3rd position of the indole nucleus exhibited significant anti-inflammatory activity.

Compound **1**, 3-acetyl-2-carboxy-5-methoxyindole, was found to exhibit 20-60% inhibition of oedema induced by carrageenan when tested at the dosage of 50 mg/kg p.o. Screening of compounds, 1-(2′-carboxyl-5′-methoxyindolyl-3-arylidenyl chalcones (**2-8**) revealed that these compounds possess somewhat enhanced anti-inflammatory activity (ranging from 23.18 to 30.23%) in comparison to route-1 compounds when tested at the same dose.

Further cyclization of compounds (**2-8**) by the addition of hydrazine hydrate and glacial acetic acid into five-membered ring compounds (**9-15**) that is 5-substituted aryl-3-(2'-carboxy-5'-methoxyindolyl)-2-pyrazolines (route-1), showed high percentage protection ranging from 34.12 to 56.33%. Compound

TABLE-1
PHYSICAL AND ANALYTICAL DATA OF COMPOUNDS (**1-22**)

Compd. No.	R	m.p. (°C)	Recrystallization solvent	Yield (%)	m.f.	Elemental analysis (%): Calcd. (found)		
						C	H	N
1	–	125	Methanol	65	$C_{12}H_{11}NO_4$	61.80 (61.77)	4.72 (4.39)	6.01 (5.99)
2	H	185	Ethanol	50	$C_{19}H_{15}NO_4$	71.02 (71.03)	4.67 (4.70)	4.36 (4.33)
3	2-Cl	245	Benzene	48	$C_{19}H_{14}NO_4Cl$	64.13 (64.10)	3.93 (3.90)	3.93 (3.96)
4	4-OH	200	Ethanol	55	$C_{19}H_{15}NO_5$	67.65 (67.67)	4.45 (4.48)	4.15 (4.12)
5	3-OCH_3	235	Pet. ether	58	$C_{20}H_{17}NO_5$	68.37 (68.40)	4.84 (4.81)	3.98 (4.00)
6	4-OCH_3	210	Ethanol	52	$C_{20}H_{17}NO_5$	68.37 (68.40)	4.84 (4.87)	3.98 (4.01)
7	4-$N(CH_3)_2$	225	DMF	50	$C_{21}H_{20}N_2O_4$	69.23 (69.20)	5.49 (5.51)	7.69 (7.72)
8	3-OCH_3, 4-OH	240	Methanol	52	$C_{20}H_{17}NO_6$	65.39 (65.42)	4.63 (4.60)	3.81 (3.78)
9	H	160	Ethanol	48	$C_{21}H_{19}N_3O_4$	66.84 (66.87)	5.03 (5.05)	11.14 (11.11)
10	2-Cl	175	Acetone/water	38	$C_{21}H_{18}N_3O_4Cl$	61.23 (61.20)	4.37 (4.40)	10.20 (10.17)
11	4-OH	170	Toluene	46	$C_{21}H_{19}N_3O_5$	64.12 (64.09)	4.83 (4.80)	10.68 (10.71)
12	3-OCH_3	190	Methanol	42	$C_{22}H_{21}N_3O_5$	64.86 (64.89)	5.15 (5.18)	10.31 (10.28)
13	4-OCH_3	185	Benzene	49	$C_{22}H_{21}N_3O_5$	64.86 (64.83)	5.15 (5.12)	10.31 (10.35)
14	4-$N(CH_3)_2$	180	Ethanol/water	44	$C_{23}H_{24}N_4O_4$	65.71 (65.69)	5.71 (5.98)	13.33 (13.30)
15	3-OCH_3, 4-OH	198	Methanol	40	$C_{22}H_{21}N_3O_6$	62.41 (62.38)	4.96 (4.99)	9.92 (9.89)
16	H	168	Acetone/water	48	$C_{19}H_{16}N_2O_4$	67.85 (67.82)	4.76 (4.79)	8.33 (8.30)
17	2-Cl	210	DMF/water	35	$C_{19}H_{15}N_2O_4Cl$	61.63 (61.59)	4.04 (4.07)	7.55 (7.58)
18	4-OH	178	Benzene	38	$C_{19}H_{16}N_2O_5$	64.77 (64.80)	4.54 (4.57)	7.95 (7.98)
19	3-OCH_3	186	Toluene/water	40	$C_{20}H_{18}N_2O_5$	65.57 (65.60)	4.91 (4.88)	7.65 (7.68)
20	4-OCH_3	168	Methanol	38	$C_{20}H_{18}N_2O_5$	65.57 (65.55)	4.91 (4.90)	7.65 (7.62)
21	4-$N(CH_3)_2$	200	Toluene	42	$C_{20}H_{21}N_3O_4$	66.49 (66.52)	5.54 (5.57)	11.08 (11.11)
22	3-OCH_3, 4-OH	172	Ethanol	36	$C_{20}H_{18}N_2O_6$	62.82 (62.79)	4.71 (4.68)	7.32 (7.29)

15 was found to be more potent 56.33% than the standard drug phenylbutazone, which was found to protect 38.90%. Due to the potent nature of compound **15** that is 5-(3′′-methoxy-4′′-hydroxyphenyl)-3-(2′-carboxy-5′-methoxyindolyl)-2-pyrazoline, it was analyzed in detail at three graded doses of 25, 50 and 100 mg/kg p.o. for its anti-inflammatory activity and was found to possess 30.25%, 56.33% and 58.82% inhibition of oedema, respectively.

Furthermore, compounds **2-8** were cyclized *via* route-2 by the addition of hydroxylamine hydrochloride and 2% NaOH solution to give five-membered ring compounds (**16-22**) or 5-substituted aryl-3-(2′-carboxy-5′-methoxyindolyl)isoxazolines. These compounds also elicited good percentage protection ranging from 30.23% to 47.04%. Out of the seven compounds (**16-22**), the most active compound was **22**. This compound, due to its potential nature, was studied in detail at three graded doses and found to possess the same protection at a lower amount of 25 mg/kg p.o. and at a higher dose of 100 mg/kg i.p. (provides protection of 15.00% and 66.58% at a dose of 25 mg/kg p.o. and 100 mg/kg p.o., respectively) when compared with standard drug phenylbutazone at these dose levels. But the results of this compound showed more significant activity (47.01%) than common drug (38.90%) at a dose of 50 mg/kg p.o.

Compounds **1**-**22** showed varying degrees of hyperemia (30 to 90% of animals) but were associated with a low degree of ulcer production (10 to 30% of animals). Compounds **5**, **10**, **11**, **15**, **17**, **18**, **19** and **22** have shown a very low degree of ulcer production. In addition, all the compounds exhibited a high value of ALD_{50}, which is greater than 1000 mg/kg p.o., except compounds **15** and **22**, which showed ALD_{50} greater than 2000 mg/kg p.o., thereby suggesting a good safety margin. The pharmacological results are summarized in Table-2.

Conclusion

On comparing the entire data of these compounds, it may be concluded that the incorporation of five-membered ring at 3rd-position of indole nucleus was responsible for increasing anti-inflammatory activity. Pyrazolines were found to be more potent than the corresponding isoxazolines and presence of 3-methoxy-4-hydroxyphenyl ring in the molecular framework of 3-pyrazoline/isoxazoline substituted indole was found to enhance the anti-inflammatory activity.

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TABLE-2
PHARMACOLOGICAL DATA OF COMPOUND (**1-22**)

Compd. No.	Acute toxicity (ALD_{50} mg/kg p.o.)	Mean increase in paw volume ± S.E.	Dose (mg/kg p.o.)	% Decrease in oedeme (anti-inflammatory activity)	Ulcerogenic activity	
					% of animals with hypermia	% of animals with ulcer
1	1000	0.372 ± 0.003	50	20.66**	70*	30**
2	1000	0.301 ± 0.001	50	23.18***	50**	30**
3	1000	0.336 ± 0.003	50	26.98*	40**	20*
4	1000	0.406 ± 0.001	50	24.98**	60***	30***
5	1000	0.420 ± 0.001	50	28.41**	40**	10*
6	1000	0.365 ± 0.002	50	25.42*	60*	20**
7	1000	0.360 ± 0.003	50	27.71***	40*	20*
8	1000	0.355 ± 0.005	50	30.23**	30***	30***
9	1000	0.299 ± 0.001	50	35.10*	50***	20**
10	1000	0.210 ± 0.004	50	37.22**	60**	10*
11	1000	0.285 ± 0.003	50	34.45**	40*	10*
12	1000	0.277 ± 0.004	50	36.41***	70**	10**
13	1000	0.210 ± 0.002	50	34.12*	40*	20**
14	1000	0.235 ± 0.002	50	37.99**	60*	20***
15	2000	0.238 ± 0.001	25	30.25***	60**	10**
		0.322 ± 0.004	50	56.33**	90*	10*
		0.411 ± 0.002	100	58.82**	90**	10**
16	1000	0.343 ± 0.002	50	30.23*	60**	20**
17	1000	0.376 ± 0.001	50	34.46*	90*	10*
18	1000	0.378 ± 0.001	50	33.18**	30*	10**
19	1000	0.346 ± 0.003	50	35.41**	70**	10*
20	1000	0.385 ± 0.002	50	32.42*	40*	20*
21	1000	0.339 ± 0.001	50	37.41*	70**	20**
22	2000	0.342 ± 0.002	25	15.00*	50*	10***
		0.388 ± 0.002	50	47.01**	90*	10*
		0.401 ± 0.001	100	66.58*	90**	10**
Phenyl butazone		0.450 ± 0.015	25	15.00		
		0.310 ± 0.020	50	38.90		
		0.260 ± 0.011	100	66.58		

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

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