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Short communication

Synthesis and antiinflammatory activity of heterocyclic indole derivatives

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Abstract

Chalcones of indole **1–5** and their corresponding products; pyrazolines **6–10** and azo compounds **11–15** were synthesised and evaluated for their antiinflammatory activity against carrageenan induced oedema in albino rats at a dose of 50 mg kg^{-1} oral. The structure of compounds was confirmed by IR, ^{1}H-NMR and mass spectral data. All the compounds of this series showed promising antiinflammatory activity. The most active compound of this series is 3-[1-acetyl-5-(*p*-hydroxyphenyl)-2-pyrazolin-3-yl]indole (**7**) was found to be most potent, which has shown higher percent of inhibition of oedema, lower ulcerogenic liability and acute toxicity than the standard drug phenylbutazone.
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Keywords: Chalcones; Pyrazolines; Azo derivatives; Synthesis; Albino rates; Antiinflammatory activity; Ulcerogenic activity; Acute toxicity

1. Introduction

Indomethacin [1] and tenidap [2] are NSAIDs, and have been shown to exert its antiinflammatory effects. Indole, the potent basic pharmacodynamic nucleus has been reported to possess a wide variety of biological properties viz., antiinflammatory [3–5], anticonvulsant [6], cardiovascular [7], antibacterial [8]. Furthermore, substitution of heterocyclic moiety at 3-position markedly influenced the antiinflammatory activity [9]. Besides these, pyrazoline [10] and azo derivatives [11] have also been reported to possess antiinflammatory activity. Encouraged by these observations we synthesised newer heterocyclic indole derivatives in the hope of obtaining better antiinflammatory agents.

2. Chemistry

The synthetic route of compounds is outlined in Fig. 1. The starting compound 3-acetylindole on refluxing with various aromatic aldehydes in the presence of 2% NaOH solution for 10–12 h yielded 3-chalconylindoles **1–5,** these chalcones on cyclisation with hydrazine hydrate in the presence of glacial acetic acid resulted into corresponding 3-[1-acetyl-5-(substitutedphenyl)-2-pyrazolin-3-yl]indoles **6–10.** Diazotisation of compounds **6–10** with aniline yielded 3-[1-acetyl-5-(substitutedphenyl)-4-phenylazo-2-pyrazolin-3-yl]indoles i.e. compounds **11–15,** respectively.

3. Results

3.1. Antiinflammatory activity

All the newly synthesised compounds (**1–15**) were evaluated for their antiinflammatory activity against carrageenan induced rat's paw oedema at 50 mg kg^{-1} p.o., which exhibited antiinflammatory activity ranging from 14% to 47%. The results of all the compounds are depicted in Table 1. Chalcones (**1–5**), the first stage compounds have elicited moderate antiinflammatory activity of varying degree (15–20%). Cyclisation of these chalcones into pyrazolines (**6–10**) showed potent antiinflammatory activity (28–47%). Moreover, the compound **7** exhibited most potent activity (47% inhibition of oedema at 50 mg kg^{-1} dose). Being the most potent compound, it was further studied in detail to establish a dose–response relationship (25, 50 and 100 mg kg^{-1} p.o.) and was also compared with standard drug phenylbutazone and indomethacin. From the data it was observed that the potent compound was found to be more potent than phenylbutazone and exhibited lower protection than indomethacin. Fig. 2 showed bar diagram of compound **7** and phenylbutazone at three dose levels. Azo compounds (**11–15**), third stage compounds, showed moderate (14–26%) antiinflammatory activity.

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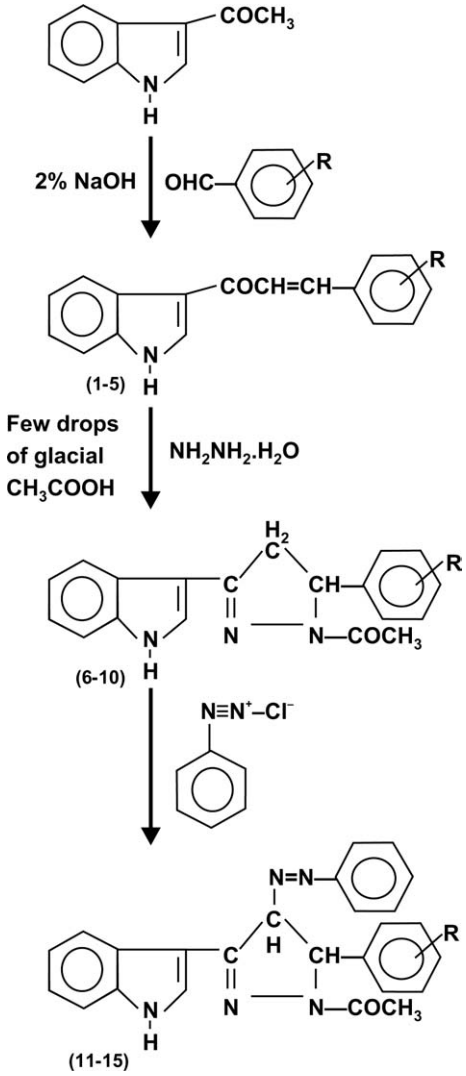

Fig. 1.

3.2. Ulcerogenic activity

Compound **7** was also tested for ulcerogenic activity and found to be less ulcerogenic liability as compared to phenylbutazone (UD_{50} of compound **7** = 199.9 mg kg^{-1} i.p. and UD_{50} of phenylbutazone = 66.6 mg kg^{-1} i.p.).

3.3. Acute toxicity

All the compounds showed ALD_{50} > 800 mg kg^{-1} p.o., suggesting a good safety margin. However, the most potent compound **7** showed approximate lethal dose (ALD_{50}) > 2000 mg kg^{-1} p.o. (maximum dose tested).

4. Discussion

An insight into the antiinflammatory activity with respect to chemical structure revealed that compounds having chalcone, pyrazoline or azo moiety at 3-position of the indole nucleus exhibited significant antiinflammatory activity. All the chalcones (**1–5**) exhibited varying degree of antiinflammatory activity (15–20%). Compound **1,** in which phenyl ring was substituted with methoxy at *meta* and hydroxy at *para* position has shown maximum activity (20%), when phenyl ring was substituted with dimethylamino group at *para* position i.e. compound **4** showed lesser degree of inhibition of oedema (15%). The cyclisation of chalcones into their corresponding pyrazolines **6–10,** in general, exhibited greater degree of inhibition of oedema as compared to their parent compounds **1–5.** The compound **7,** which was substituted with hydroxy group at *para* position has shown maximum antiinflammatory activity (47%). On the other hand when phenyl ring was substituted with dimethylamino group at *para* position i.e. **9** showed lower degree of antiinflammatory activity (28%). Hence it may be concluded that all the five pyrazolines (**6–11**) possessed more potent antiinflammatory activity than their corresponding chalcones (**1–5**). Azo derivatives (**11–15**) exhibited better activity than chalcones but found to possess less percentage inhibition of oedema than the corresponding pyrazolines. Therefore, it may be concluded by the mentioned data of antiinflammatory activity that all the five pyrazolines (**6–11**) possessed more potent antiinflammatory activity than their corresponding chalcones (**1–5**). Azo derivatives (**11–15**) exhibited better activity than chalcones but found to possess less % inhibition of oedema than their corresponding pyrazolines.

5. Experimental protocols

5.1. Chemistry

Melting points were taken in open capillary tubes and are uncorrected. The purity of the compounds was confirmed by thin layer chromatography using silica gel-G and spots were located by iodine. IR spectra were recorded on Perkin Elmer 881 spectrophotometer in KBr (ν_{max} in cm^{-1}). ^{1}H-NMR spectra were recorded on Bruker DPX-300 MHz spectrometer and mass spectra were determined on JEOL-JMS-D-300 spectrometer. Analytical data of C, H, N were within ±0.4% of theoretical values.

5.1.1. 3-Chalconylindoles (*1–5*)

To a solution of 3-acetylindole (0.01 mol) in methanol (dry, 50 ml), different aromatic aldehydes (0.01 mol) were added in the presence of 2% NaOH solution (5 ml). The reaction mixtures were stirred for 10–12 h at room temperature. The solvent was distilled off and crude product poured into ice water. The compound thus obtained was washed with water and recrystallised from suitable solvents. Physical and analytical data of compounds **1–5** are given in Table 1. Compound **2:** IR (KBr) (cm^{-1}): 3160 (NH), 3020 (aromatic C–H), 1710 (C=O), 1630 (–CH=CH–), 1550 (C⎓C of aromatic ring). ^{1}H-NMR ($CDCl_3$) δ; (ppm): 5.82 (1H, d, –COC*H*=), 6.86 (1H, d, =C*H*–Ar), 7.11–7.89 (9H, m, Ar–*H*), 8.60 (1H, ss, N*H* of indole, exchangeable with D_2O), 9.00 (1H, s, Ar–O*H,* exchangeable with D_2O). MS: $[M]^+$ *m/z* 263.

Table 1
Physical, analytical and biological data of compounds **1–15**

Compound number	R	M.P. (°C)	Yield (%)	Recrystallisation solvent	Molecular formula	Molecular weight [a]	Dose (mg kg^{-1} p.o.)	% Decrease in paw oedema (anti-inflammatory activity)	ALD_{50} (mg kg^{-1} p.o.)	UD_{50} (mg kg^{-1} i.p.)
1	*m*-OCH_3, *p*-OH	215	75	Methanol	$C_{18}H_{15}NO_3$	293	50	20 [b]	>800	–
2	*p*-OH	226	50	Ethanol/water	$C_{17}H_{13}NO_2$	263	50	18	>800	–
3	H	172	40	Ethanol	$C_{17}H_{13}NO$	247	50	16	>800	–
4	*p*-$N(CH_3)_2$	187	60	Methanol	$C_{19}H_{18}N_2O$	290	50	15	>800	–
5	*p*-OCH_3	146	55	Methanol/water	$C_{18}H_{15}NO_2$	277	50	18	>800	–
6	*m*-OCH_3, *p*-OH	173	50	Ethanol/water	$C_{20}H_9N_3O_3$	349	50	35	>800	–
							25	23		
7	*p*-OH	212	35	Ethanol	$C_{19}H_{17}N_3O_2$	319	50	47 [b]	>2000	199.9
							100	72		
8	H	178	30	Methanol	$C_{19}H_{17}N_3O$	303	50	38 [b]	>800	–
9	*p*-$N(CH_3)_2$	200	40	Ethanol/water	$C_{21}H_{22}N_4O$	346	50	28	>800	–
10	*p*-OCH_3	138	25	DMF/water	$C_{20}H_{19}N_3O_2$	333	50	32	>800	–
11	*m*-OCH_3, *p*-OH	198	40	Acetone	$C_{26}H_{23}N_5O_3$	453	50	23 [b]	>800	–
12	*p*-OH	224	25	Ethanol	$C_{25}H_{21}N_5O_2$	423	50	26 [b]	>800	–
13	H	146	30	Ethanol	$C_{25}H_{21}N_5O$	407	50	24	>800	–
14	*p*-$N(CH_3)_2$	165	45	DMF/water	$C_{27}H_{26}N_6O$	450	50	14	>800	–
15	*p*-OCH_3	140	20	Methanol	$C_{26}H_{23}N_5O_2$	437	50	19 [b]	>800	–
							25	15		
Phenylbutazone	–	–	–	–	–	–	50	39 [b]	–	66.6
							100	66		
Indomethacin	–	–	–	–	–	–	1.8	38	–	–
							3.6	49		
							5.4	63		

[a] C, H, N were found within ±0.4%.
[b] $P < 0.001$.

*5.1.2. 3-[1-Acetyl-5-(substitutedphenyl)-2′-pyrazolin-3-yl] indoles (**6–10**)*

To a solution of compounds **1–5** (0.01 mol) in absolute ethanol, hydrazine hydrate (99%, 0.02 mol) and few drops of glacial acetic acid were added. The reaction mixtures were refluxed for 6–8 h. The excess of solvent was distilled off and crude product poured into ice water. The separated solids were filtered and recrystallised from suitable solvents. Physical and analytical data of compounds **6–10** are given in Table 1. Compound **7:** IR (KBr) (cm^{-1}): 3150 (NH), 3010 (aromatic C–H), 2930(CH_2), 1730 (C=O of acetyl moiety of pyrazolin ring), 1680 (C=N), 1600 (C–N), 1570 (C⋯⋯C of aromatic ring), 1510 (N–N). ^{1}H-NMR ($CDCl_3$) δ; (ppm): 2.28 (3H, s, –COC*H*$_3$), 5.90 (2H, d, –C*H*$_2$ of pyrazoline ring), 6.55–7.96 (10H, m; 9H, Ar–*H* + 1H, C*H*Ar), 8.62 (1H, ss, N*H* of indole, exchangeable with D_2O), 9.02 (1H, s, Ar–O*H,* exchangeable with D_2O). MS: $[M]^+$ *m/z* 319.

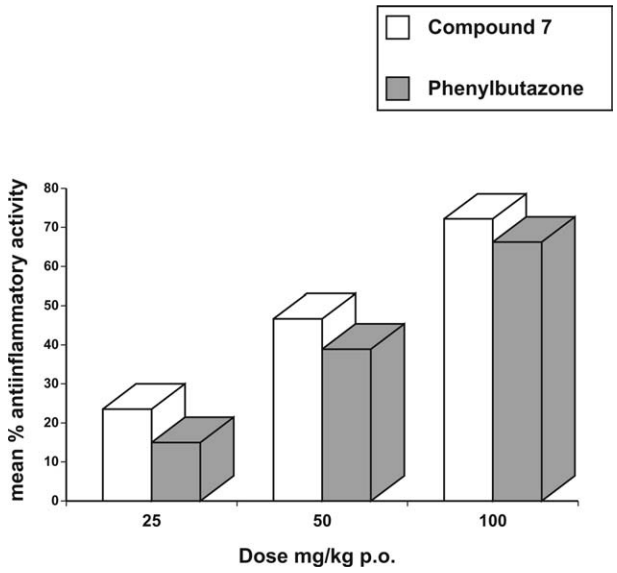

Fig. 2. Bar diagram showing mean % antiinflammatory activity of compound **7** and reference drug phenylbutazone at three graded doses.

*5.1.3. 3-[1-Acetyl-5-(substitutedphenyl)-4-phenylazo-2-pyrazolin-3-yl]indoles (**11–15**)*

To a solution of aniline (0.01 mol) in glacial acetic acid (5 ml) was added conc. HCl (3 ml) at 0–5 °C. A solution of sodium nitrite (1 g in 5 ml of water) was then added dropwise. The diazonium salt solution thus prepared was added to a solution of compounds **6–10** (0.01 mol) in methanol drop wise with stirring below 0 °C. The reaction mixtures were kept at room temperature for 2–3 days and then poured into cold water (200 ml). The resulting solids were washed with water and recrystallised from suitable solvents. Physical and analytical data of compounds **11–15** are given in Table 1. Compound **12:** IR (KBr) (cm^{-1}): 3150 (NH), 3020 (aromatic

C–H), 1710 (C=O), 1680 (C=N), 1600 (C–N), 1560 (C⋯⋯C of aromatic ring), 1500 (N–N), 1430 (N=N). ^{1}H-NMR ($CDCl_3$) δ; (ppm): 2.17 (3H, ss, –COC*H*$_3$), 5.92 (1H, d, –C*H*-N=N–Ar), 6.25–7.88 (15H, m; 14H, Ar–*H* + 1H, –C*H*–Ar), 8.62 (1H, ss, N*H* of indole, exchangeable with D_2O), 9.0 (1H, s, Ar–O*H,* exchangeable with D_2O). MS: $[M]^+$ *m/z* 423.

5.2. Pharmacology

5.2.1. Antiinflammatory activity

A freshly prepared suspension of carrageenan (1.0% in 0.9% saline) 0.05 ml, was injected under the planter aponeurosis of right paw of the rat by the method of Winter et al. [12]. The volume of foot was measured by micropipette method as described by Buttle et al. [13]. The percentage of antiinflammatory activity was calculated by the following formula: $\%\ Antiinflammatory\ activity = 1 - \frac{V_t}{V_c} \times 100$ where, V_t and V_c are volume of paw oedema in drug treated and control groups.

5.2.2. Ulcerogenic liability

The ulcerogenic liability was determined in albino rats following the method of Djahanjuiri [14]. The rats were fasted for 24 h to the administration. Water was allowed ad libitum to the animals. The test compounds and standard drug were given intraperitoneally. All rats were killed 8 h after dosing and the stomach, duodenum and jejunum were removed and examined to assess: shedding of epithelium; petechial and frank haemorrhage; and erosion or discrete ulceration with or without perforation. The presence of any one of these conditions was considered to be as an evidence for ulcerogenic activity.

5.2.3. Acute toxicity

Approximate lethal dose (ALD_{50}) for all the compounds was investigated in albino mice by the method of Smith [15].

5.2.4. Statistical analysis

All values are expressed as mean ± S.E.M. Statistical significance was determined using Student's '*t*' test.

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