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Synthesis and Pharmacological Screenings of Some N^1-Substitued Phenyl-N^3-(2′-substituted indole-3′-methine) Thioureas†

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Various N^1-substituted phenyl-N^3-(2′-substituted indole-3′-methine) thioureas were synthesised from respective 2-substituted indole-3-carboxaldehyde and 4-substituted phenylthioureas. The compounds were screened for thier various pharmacological properties, *viz.*, analgesic, anti-inflammatory, oxytocic and anthelmentic activities.

INTRODUCTION

Indole and its derivatives have occupied a unique place in the chemistry of nitrogen heterocyclic compounds because of their wide spectrum of biological activities. In continuation of our research[1–4] for pharmacologically potent indole derivatives, we report here the synthesis of some new N^1-substituted phenyl-N^3-(2′-substituted indole-3′-methine) thioureas and their pharmacological activities.

2-Substituted indole-3-carboxaldehydes (**Ia, b**) obtained by the Vilsmier-Haack formylation reaction conditions in $POCl_3$ and DMF, were reacted with 4-substituted phenyl-N^3-(2′-substituted indole-3′-methine) thioureas (**III a–f**). The formation of these compounds was confirmed by their IR spectral data. In the spectra, these compounds displayed absorption bands 3450–3400 cm^{-1} due to ν(NH), 1620 cm^{-1}due to ν(C=N) and 1300 cm^{-1} due to ν(C=S) functional groups, respectively.

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. The IR spectra were recorded in nujol on a Hitachi 270–50 IR spectrophotometer.

Preparation of N^1-Substituted Phenyl-N^3-(2′-substituted indole-3′-methine) thioureas (IIIa-f)

A mixture of 2-substituted indole-3-carboxaldehyde[5] (**Ia, b**) (0.001 mole) and substituted aryl thioureas (**IIa–c**) (0.001 mole) was refluxed in anhydrous ethanol on water bath for 3 h. The reaction mixture was cooled and decomposed in ice

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TABLE-1
PHYSICAL DATA OF THE COMPOUNDS SYNTHESISED

Comp. No.	Substituents		m.p. (°C)	Yield (%)	Nature	Mol. formula	Elemental analysis %, Found (Calc.)		
	R	R^1					C	H	N
IIIa	H	OCH_3	198–200	61.60	grey crystals	$C_{17}H_{15}N_3SO$	66.01 (66.06)	4.85 (4.89)	13.59 (13.65)
IIIb	H	CH_3	172–173	54.40	orange crystals	$C_{17}H_{15}N_3S$	69.62 (69.65)	5.11 (5.17)	4.33 (4.37)
IIIc	H	Cl	152–154	40.10	light orange crystals	$C_{16}H_{12}N_3SCl$	61.34 (61.38)	3.83 (3.90)	13.41 (13.46)
IIId	Ph	OCH_3	191–193	82.30	grey crystals	$C_{23}H_{19}N_3SO$	71.68 (71.73)	4.93 (4.98)	10.90 (10.96)
IIIe	Ph	CH_3	163–164	91.40	colourless crystals	$C_{23}H_{19}N_3S$	74.79 (74.86)	5.14 (5.18)	11.38 (11.43)
IIIf	Ph	Cl	111–112	60.70	colourless crystals	$C_{22}H_{16}N_3SCl$	67.86 (67.92)	4.11 (4.17)	10.79 (10.86)

TABLE-2
PHARMACOLOGICAL ACTIVITIES OF SYNTHESISED COMPOUNDS

Compd. No.	Analgesic activity		Antiinflammatory activity, % inhibition of hind paw volume	Oxytocic activity along with standard in %	Anthelmintic activity, time (min) taken for paralysis (P) and death (D)	
	Reaction time (sec) after 60 min	Raction time (sec) after 120 min			P	D
IIIa	5.15 (± 0.03)	6.65* (± 0.03)	0.77† (± 0.06)	85.71	182.50	252.50
IIIb	5.40 (± 0.09)	5.75* (± 0.08)	0.595† (± 0.04)	97.22	195.00	215.00
IIIc	5.38 (± 0.02)	8.20 (± 0.32)	0.35† (± 0.04)	122.58	99.33	123.00
IIId	8.57* (± 0.04)	6.13* (±0.20)	0.55†† (± 0.04)	91.52	—	—
IIIe	6.65* (± 0.56)	5.40* (± 0.02)	0.69†† (± 0.13)	88.80	405.00	465.00
IIIf	4. 65 (± 0.03)	6.23* (± 0.10)	0.47†† (± 0.02)	101.03	33.00	44.50
Standard§	5.86 (± 0.01)	5.95 (± 0.06)	0.23 (± 0.05)	100.00	48.00	66.00
Control	3.40 (± 0.07)	2.75 (± 0.07)	0.57 (± 0.06)	—	—	—

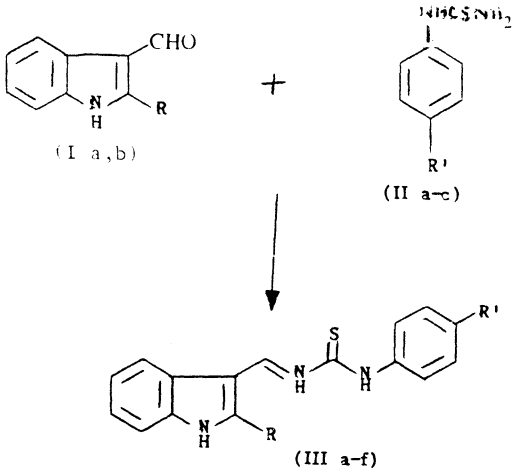
*P < 0.001, †P < 0.01, ††P < 0.5

§Standard for: Analgesic activity—Analgin
Antiinflammatory activity—Phenyl butazone
Oxytocic activity—Oxytocin
Anthelmentic activity—Piperazine citrate

cold water. The solid thus separated was filtered, washed with water and crystallized from benzene to get (**IIIa–f**) (Table -1).

Pharmacological Activities

Analgesic activity: Tail-flick method[6] was adopted for the evaluation of analgesic activity. The compounds were tested at a dose of 30 mg/kg body weight of Albino rats, using analgin as standard. Compounds (**IIIa–f**) exhibited promising activity as compared to that of standard analgin, during 60 and 120 min (Table-2).



	a	b	c	d	e	f
R	H	H	H	Ph	Ph	Ph
R′	OCH_3	CH_3	Cl	OCH_3	CH_3	Cl

Antiinflammatory activity: Antiinflammatory activity of compounds (**IIIa–f**) was evaluated according to the reported method[6] using formalin induced paw odema test in rats. The compounds were tested at a dose of 30 mg/kg body weight of rat using phenyl butazone as standard. The compound **IIIc** exhibited promising antiinflammatory activity, compound **IIIf** showed moderate activity, whereas other compounds were found to be inactive (Table-2).

Oxytocic activity: Compounds **IIIa-f** were tested for their *in vitro* oxytocic activity on an isolated *Albino rat* uterus according to literature method[7]. Oxytocin was used as standard and the compounds were tested at concentration of 10 μg/mL. The compound **IIIc** exhibited good oxytocic activity, whereas compounds **IIIa, IIIb, IIId** and **IIIe** inhibited the oxytocic activity when tested along with oxytocin and compound **IIIf** was inactive (Table-2).

Anthelmentic Activity: Anthelmentic activity of compounds (**IIIa–f**) was carried out against Pherituma postuma by following the reported procedure[8], using piperazine citrate suspension (2 mg/mL) as standard. Only the compound **IIIf** exihibited strong anthelmentic activity, where as all other compounds either moderately active or inactive (Table-2).

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