The Synthesis and Antimicrobial Activity of Indolethiacarbamide derivatives

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Abstract:
Indoles and their derivatives are found to possess pronounced biological activates compounds in which the Indole ring is fused with other heterocyclic ring have also been found to possess remarkable biological properties. Many such derivatives are known in literature containing various, heterocyclic compounds fused with Indole. In recent review synthesis and antimicrobial activity of hetero-cyclic analogues of the Indolthiacarbamide are described. The Indole-thiacarbamide ring represents an important pharmacophore in drug, notable clinical examples. Keeping on view, the importance of Indole and its derivatives. A good number of these compounds are found to be biologically active.

KEYWORDS: Indolthiacarbamide, Vilsmeier Haack formylation, antifungal, antibacterial activity.

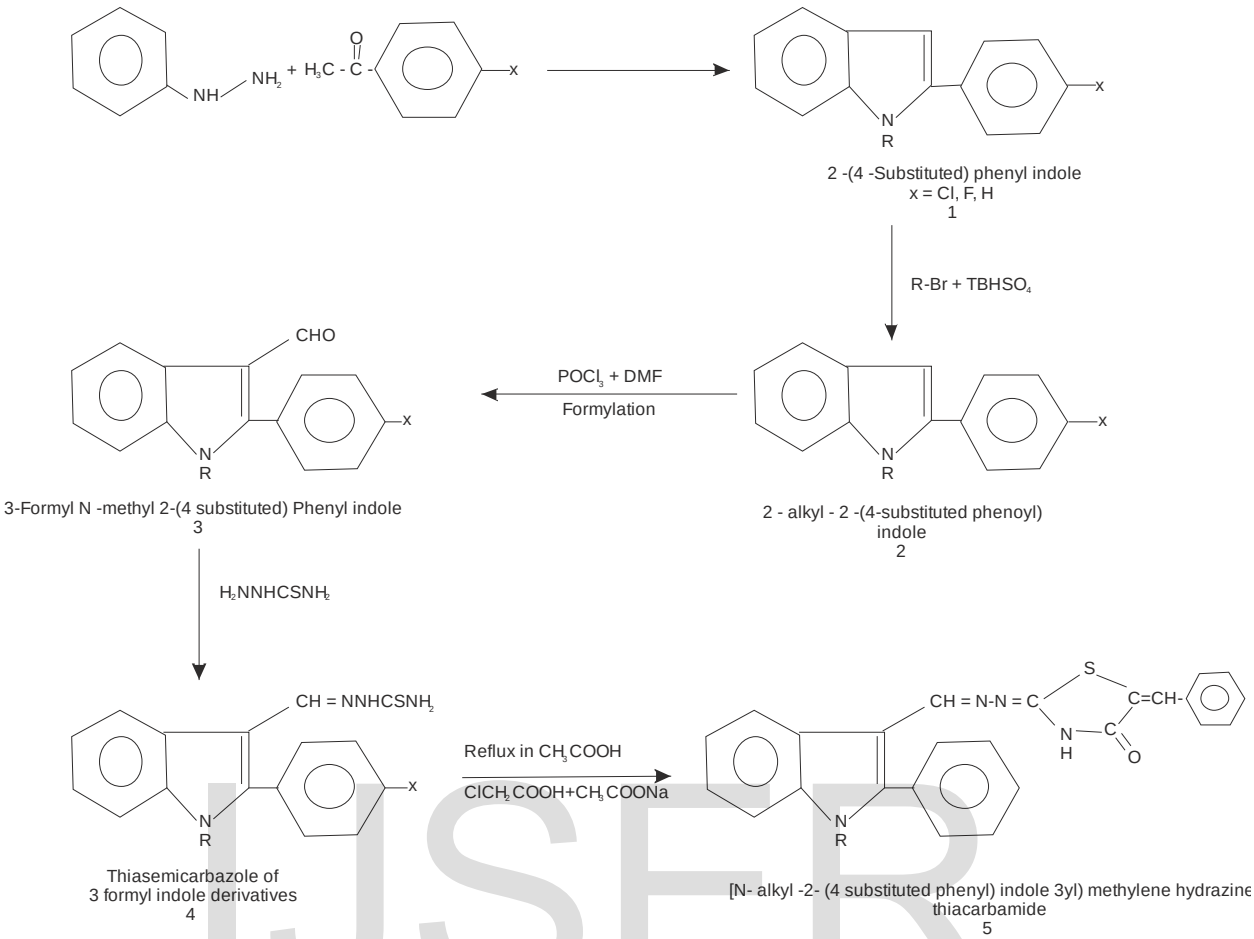
Introduction:

Indole, as the important heterocyclic ring present in a large number of biologically active molecules of different pharmacological classes known to have herbicidal,[1-5] antitubercular[6-9], anticonvulsant,[10] analgesic,[11] antithyroid[12] and antiparkinson activity.[13] Indole derivatives also display a wide range of antibacterial[14-19] and antifungal[20-21] activities. Although the structure of indole was not correctly assigned until 1869 by Adolf von Baeyer, its derivatives have had a prominent role in commerce for centuries.[22] It is therefore considered to link the thiacarbamide moiety in search of better antimicrobial agents. Keeping these observations in view, we have undertaken a comprehensive program for developing better antimicrobial agents, and have synthesized [N-alkyl or aryl{2-(4-Substituted phenyl)indole 3-yl} methylene]hydrazine thiacarbamide and screened them for their antibacterial and antifungal activities.

Results And Discussion:

Synthesis

Phenyl hydrazine was heated with required p-substituted acetophenone. Resultant hydrazone was then heated with polysulphuric acid on an oil bath at 125^0-180^0c to give 2-(4-subtituted phenyl) indole **1.** Then **1** was treated with $TBHSO_4$and bromoethane in benzene,provide stirring vigorously to form N-alkyl- 2-(4-halophenyl) indole **2.**This N-alkyl-2-(4-chlorophenyl) indole **2** subjected to Vilsmeier-Haack formylation with $POCl_3$and *N,N*-dimethyl formamide to give N-ethyl 2-(4-chlorophenyl) indole-3-carboxaldehyde **3.** Then, N-alkyl-2-(4-substituted phenyl) indole-3-carboxaldehyde **3** and thiasemicarbazide in ethyl alcohol was refluxed for 2 hours to give [N-alkyl {2-(4-substituted phenyl) indole-3-thiasemicarbazone **4.** A mixture of compound [N-alkyl {2-(4-substituted phenyl) indole-3-thiasemicarbazone **4**,$ClCH_2COOH$ and CH_3COONa was refluxed in glacial acetic acid. 4-Fluorobanzaldehyde was then added and the mixture was further refluxed for additional 4-5 hours to form [N-alkyl-{2-(4-chlorophenyl) 3-yl}methylene]hydrazine thiacarbamide **5**.



SCHEME-1

The physical and analytical data of compounds (5a-5g) are given in (Table-1).

Table-1

Compounds	Molecular formula	Melting point(c^0)	Yield (%)
5a	$C_{27}H_{22}N_4SOCl$	242-245	70
5b	$C_{27}H_{21}N_4SOF$	230-235	65
5c	$C_{28}H_{24}N_4SO$	235-238	68
5d	$C_{27}H_{22}N_4SO$	250-255	55
5e	$C_{27}H_{21}N_4SOBr$	265-270	54
5f	$C_{32}H_{24}N_4SO$	248-250	70
5g	$C_{26}H_{20}N_4SO$	238-240	62

In the ^1H NMR spectrum of compound [N-Ethyl {2-(4-substitutedphenyl) 3-yl}methylene]hydrazine thiacarbamide a triplet at δ1.5 accounted for three protons of $-CH_3$group. A multiplet appeared in the region δ7.7-7.9ppm accounting for aromatic protons.A peak at δ 4.8 as a singlet was attributed to one proton of –N-H- group. The presence of of$-CH_2$ was confirmed by a quartet at δ 1.8 for two protons. A singlet at δ 2.5 was due to the presence of one proton of -CH-.

The IR spectrum of compound [N-alkyl-{2-(4-substitutedphenyl)3-yl} methylene] hydrazine thiacarbamide showed significant absorption band at 3020 Cm^{-1} which was characterized to Ar-H stretching vibrations. Strong C=C stretching bands was observed at 1640Cm^{-1} .Characteristic absorption bands at 1670-1690Cm^{-1}attribued to >C=O stretching vibrations. This downfield shift from the normal>C=O absorption (1720 cm^{-1}) is attributed to the presence of high degree of conjugation . Presence of C-Cl linkage was confirmed by the absorption band at 750 Cm^{-1}. An absorption band at 1450 Cm^{-1} was ascribed to -N-H stretching vibration. The band absorbed at 2920 Cm^{-1} was characteristics of C-H stretching vibrations.

The IR and ^1H NMR data of [N-Ethyl {2-(4-substitutedphenyl) 3-yl}methylene]hydrazine thiacarbamide

are summarized in Table-2

Table-2

Compound	IR(KBr)ν_{max}(cm^{-1})	^{1}H NMR($CDCl_3$)δ(ppm)
5a	3020 (=CH),1640 (C=C),1710 (-C=O 750 (-C-Cl),1450 –N-H)	7.7-7.9 (m, 13H,Ar-H),1.8 (q,2H, CH_2-),1.5 (t,3H,-CH_3) 4.8 (s,1H,-NH)2.5(s,1H,=CH-)
5b	3045(=CH),1630(C=C),1722(-C=O),1220(-C-F),1420(-N-H)	7.8-7.9 (m,13H,Ar-H),2.1 (q,2H,CH_2-),1.7 (t, 3H,-CH_3), 2.8 (s, 1H, -CH) 4.3(s,1H,-NH)
5c	3040(=CH),1625(C=C),1715(-C=O) 2940 (-C-H), 1435(-N-H)	7.5-7.8 (m, 13H,Ar-H),2.5 (q, 2H, CH_2-),1.6 (t, 3H,-CH_3), 2.6 (s, 1H, -CH) 2.2 (s, 3H, -CH_3) 4.2(s,1H,-NH)
5d	3035(=CH),1620(C=C),1725(-C=O) 2945 (-C-H),1420(-N-H)	7.4-7.6(m,14H,Ar-H),2.6(q,2H,CH_2-),1.8(t, 3H, -CH_3), 2.9 (s, 1H, -CH) 4.6(s,1H,-NH)
5e	3030(=CH),1625(C=C),1720(-C=O) 2935 (-C-H),700 (C-Br), 1430(-N-H)	7.5-7.8(m,13H,Ar-H),2.2(q,2H,CH_2-),1.6(t, 3H, -CH_3),2.6(s, 1H, -CH) 4.5 (s,1H,-NH)
5f	3035(=CH),1635(C=C),1724(-C=O) 2945 (-C-H) 710(C-Br) 1425(-N-H)	7.4-7.7(m,18H,Ar-H),2.2(q,2H,CH_2-),,2.7(s, 1H, -CH) 4.5 (s,1H,-NH) 2.2(s,1H,CH_2-)
5g	3040(=CH),1645(C=C),1720(-C=O) 2935 (-C-H), 1420(-N-H)	7.47.8(m,13H,ArH),2.4(s,1H,CH)4.2(s,1H,-NH) 1.6 (s,1H,-CH_3)

Antimicrobial activity of synthesized compounds

The synthesized compounds (5a-5g) have shown inhibitory action against all the tested microorganisms used in the present investigation. The synthesized compounds 5a, 5b and 5d have, however, been found to be more effective than the antibiotic streptomycin against S.aureus and can thus serve better for its inhibition. The above said synthesized compounds possess more potential than streptomycin to combat the harmful effect of the bacteria S.aureus at a cheaper rate to the farmers in the fields.

Antifungal activity: The antifungal activity of all the synthesized compounds were carried out against the fungi, Aspergillus niger and aspergillus paracitica at 500 µg/ml concentration .the fungi were subcultured in Sabourad's Dextrose Agar medium .the fungal susceptibility testing was done by disc diffusion method using Griseofulvin (1000 unit/ml) as standard . The petridishes were incubated for 24hr. at 22 to 25°C. synthesized compounds (5a-5g) have shown inhibitory action against all the tested microorganisms used in the present investigation. The synthesized compounds 5a, 5b and 5d have, however, been found to be more effective than the antibiotic streptomycin against S. Aureus and can thus serve better for its inhibition. The synthesized compound 5d has, however been found to be more effective than the antifungal Griseofulvin against A.Paraciticus. S.Aureus and can thus serve better for its inhibition.

Table-3

S. No.	Bacteria	Bacteria	Fungi	Fungi
	B. megaterium	*S. aureus*	*A. niger*	*A.paraciticus*
5a	20	18	10	13
5b	18	17	8	16
5b	17	15	10	14
5d	16	14	10	10
5e	18	12	11	15
5f	14	19	9	12
5g	20	16	12	14

Keeping in mind the above discussed facts regarding antimicrobial activity of the synthesized compounds we may conclude that they can prove very beneficial to man to mankind in the era of 21st century.

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