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Design and synthesis of some novel thiophen analogues of indole as a potent antimicrobial and antioxidant agents

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ABSTRACT

This work reports an efficient synthesis of novel indole chalcones **(3a-d)** bearing thiophen ring by claisen-schimidt condensation and screening them for antimicrobial and *in-vitro* antioxidant (Free radical scavenging, total antioxidant capacity and ferric reducing antioxidant power) activities. Among the synthesized compounds **(3b)** and **(3c)** have shown promising antimicrobial activity and remaining compounds shown moderate activity. In all the test systems compounds **(3b)** and **(3c)** have exhibited excellent antioxidant activity. The structures of the synthesized compounds are assigned on the basis of elemental analysis, IR, 1H NMR, and mass spectral data.

KEYWORDS

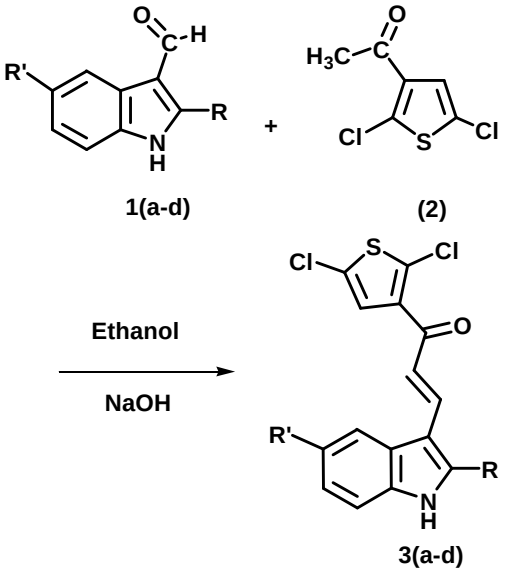
Indole-3-corboxaldehyde;
2,5-Dicholro-3-acetylthiophen;
Claisen-schimidt condensation;
Antimicrobial activity;
Antioxidant activity.

INTRODUCTION

Due to the rapid bacterial resistance to antibacterial agents, it is vital to discover novel scaffold for the design and synthesis of the new antibacterial agents to help in the battle against pathogenic microorganisms. With the increasing reports on insinuation of free radicals and reactive oxygen species in a variety of diseases and pathophysiological events including inflammation, cancer, myocardial infraction, arthritis and neurodegenerative disorders[1-3]. Much research has been carried out with the aim to discover the potent antioxidant agents.

Indole analogues constitute an important class of therapeutic agents in medicinal chemistry including anticancer[4], antioxidant[5], antirheumatoidal and anti-HIV[6,7] and also play a vital role in the immune system[8-10]. Many indole derivatives are considered as the most potent scavengers of free radicals[11], they directly scavenge toxic free radicals, such as hydroxyl radical, peroxynitrite anion and hypochlorous acid, reducing macromolecular damage in all organs[8]. Chalcones represent an essential group of natural as well as synthetic products and some of them possess wide range of Pharmacological activity such as antibacterial, antifungal antitumour, anticancer, antitubercular, anti-inflammatory[12], antioxidant[13], antimalarial[14] and antileishmanial[15]. Some chalcones demonstrated the ability to block voltage-dependent potassium channels[16]. They are also intermediates in the biosynthesis of flavonoids, which are substances widespread in plants and with an array of biological activities.

In continuation of our research on biologically potent molecules[17-20] and the pharmacological results exhibited by indole and chalcones have prompted us for the synthesis of some novel indole chalcones (Scheme 1) bearing a thiophen ring with a view to achieve enhanced antimicrobial and antioxidant activities.



	a	b	c	d
R	Ph	Ph	H	Ph
R'	CH_3	Cl	H	H

Scheme 1

RESULTS AND DISCUSSION

In the present investigation titled compounds **(3a-d)** are obtained by the claisen-schimidt condensation of 2,5-Dicholro-3-acetylthiophen with various 2,5- disubstituted indole-3-corboxaldehydes. The IR spectrum of compound **(3a)** showed a strong absorption at 3258cm^{-1} corresponding to indole NH, absorption at 2930cm^{-1} corresponds to C-H stretching, an absorption at 1717cm^{-1} corresponds to C=O stretching and absorption at 1590 cm^{-1} corresponds to the C=C stretching. The ^{1}H NMR spectrum of **(3a)** has exhibited a singlet at δ 11.2 (S, 1H, NH) integrating for a single proton due to deshielded Indole NH which is D_2O-exchangeable. A singlet at δ 2.0 (S, CH_3, 3H,) for methyl protons and a multiplet between δ 6.9 - 8.0 (m, Ar-H, 2H, -CH=CH-) integrating for eleven protons in the molecule. This spectrum has also exhibited the absence of aldehyde proton confirming the formation of product. In the Mass spectrum of compound **(3a)**, molecular ion peak is observed at m/z 412(100%) which is also the base peak, corresponding to molecular weight of the compound. These spectral data supports the formation of **(3a)**.

BIOLOGICAL ACTIVITIES

Antimicrobial activity

Newly synthesized compounds are tested for *invitro* antibacterial activity against *S.aureus*, and *B.subtilis* and antifungal activity against *A. Niger and A. flovous*, using DMF as solvent at 1000 μg/ml concentration by cup-plate method. The activity was compared with known drugs Gentamycin and Neomycine for antibacterial and Clotrimazole and Fluconozole for antifungal activity. The zone of inhibition after 24 hr of incubation at 37^{0}C, in case of antibacterial activity and 48 hr in case of antifungal activity was compared with that of standards (TABLE 3).

TABLE 1 : Physical data of synthesized compounds (3a-d).

Compd	Substituents		M.P (^{0}C)	Yield (%)
	R	R'		
3a	Ph	CH_3	244-246	77
3b	Ph	Cl	275-277	75
3c	H	H	220-223	67
3d	Ph	H	256-258	70

TABLE 2 : Spectral data of synthesized compounds (3a-d).

Compd No.	Substituents		IR (KBr) ν_{max} in cm^{-1}	^{1}H NMR (DMSO) in δ
	R	R^1		
3a	Ph	CH_3	3258(NH), 2930(C-H)	11.2 (s, 1H, Indole NH), 2.0 (s, 3H, CH_3)
			1717(C=O), 1590(C=C)	6.9-8.0(m, 11H, ArH, 2H, -CH=CH-)
3b	Ph	Cl	3309(NH), 2923(C-H)	11.6(s, 1H, Indole NH), 7.1-8.2(m, 11H,
			1725(C=O), 1581(C=C)	ArH, 2H, -CH=CH-),
3c	H	H	3211(NH), 2930(C-H)	11.0(s, 1H, Indole NH), 7.0-8.3(m, 8H,
			1717(C=O), 1595(C=C)	ArH, 2H, -CH=CH-)
3d	Ph	H	3298(NH), 2925(C-H)	10.9(s, 1H, Indole NH), 6.8-8.5(m, 12H,
			1695(C=O), 1598(C=C)	ArH, 2H, -CH=CH-)

All the compounds gave satisfactory analysis for C, H and N.

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TABLE 3 : Antimicrobial activity data of synthesized compounds (3a-d).

Compd. No.	Substituent's		Zone of inhibition in mm			
			Antibacterial activity		Antifungal activity	
	R	R'	S. aureus	B. subtilis	A. niger	A. flavous
			24 hrs	24 hrs	48 hrs	48 hrs
3a	Ph	CH_3	16	16	13	13
3b	Ph	Cl	17	18	17	15
3c	H	H	18	19	16	17
3d	Ph	H	15	16	14	14
Std. S_1	-	-	18	20	-	-
Std. S_2	-	-	19	18	-	-
Std. S_3	-	-	-	-	19	18
Std. S_4	-	-	-	-	17	19
Control DMF	-	-	-	-	-	-

S_1 - Neomycine; S_2 - Gentamycin; S_3 - Fluconozole; S_4 - Clotrimazole;

In active less than: 13 mm; weakly active: >13-15 mm; moderately active: >15-17 mm: Highly active: >17 mm.

Antioxidant activity

(a) Free radical scavenging activity

The newly synthesized compounds were screened for free radical scavenging activity by DPPH method[21]. The samples were prepared at concentrations of 10, 50, and 100 µg / 100 µl and butylated hydroxy anisole (BHA) is taken as standard. Simple and chloro substituted indole derivatives **(3b)** and **(3c)** respectively have very good scavenging activity. The results are tabulated in TABLE 4.

(b) Total antioxidant capacity

Total antioxidant activity was performed to all the newly synthesized compounds[22]. Antioxidant capacities are expressed as equivalents of ascorbic acid. Among the tested compounds **(3b)** and **(3c)** have shown very good activity and remaining compounds have shown less activity. The results of total antioxidant activity are shown in TABLE 4

(c) Ferric reducing antioxidant activity

All the novel compounds were screened for ferric reducing antioxidant activity[23]. Butylated hydroxy anisole (BHA) was used as standard. In this case all the tested compounds have shown promising activity. The results are presented in TABLE 4

TABLE 4 : Antioxidant activity of synthesized compounds (3a-d).

Compd. No.	Free Radical Scavenging Activity (%)	Total Antioxidant Capacity Activity µg equivalent to Ascorbic Acid	Ferric Reducing Antioxidant Activity Absorbance at 700nm
3a	40	34	0.35
3b	66	52	0.40
3c	70	60	0.35
3d	46	30	0.30
BHA	86	76	0.45

EXPERIMENTAL

All the chemicals and reagents were purchased from MERCK, Himedia and Sd fine chemical companies and are used without further purification. Melting points of the synthesized compounds are determined in open capillaries and are uncorrected. Reactions are monitored by thin-layer chromatography (TLC) on silica gel 60 F_{254} aluminium sheets (MERCK). The mobile phase was chloroform and benzene (1:1) and detection was made using UV light and iodine. IR spectra were recorded in KBr on Perkin-Elmer and FTIR Spectrophotometer (ν_{max} in cm^{-1}). ^1H NMR spectra on BRUKER AVENE II 400 MHz NMR Spectrometer (Chemical shift in δ ppm down field from TMS as an internal reference). The Mass spectra are recorded on LC-MSD-Trap-SL instruments. The elemental analysis was determined on FLASH EA 1112 SERIES instrument. All the compounds gave C, H and N analysis within ±0.5% of the theoretical values.

Preparation of 2,5-disubtituted indole-3-corboxaldehydes (1a-d)

The starting compounds 2,5-disubstituted indole-3-corboxaldehydes **(1a-d)** were prepared according to literature method[24].

Preparation of (E)-1-(2,5-dichlorothiophen-3-yl)-3-(2,5-disubstituted-1H-indol-3-yl) prop-2-en-1-one (3a-d)

A mixture of appropriate 2, 5-disubstituted indole-3-corbaxaldehyde **(1a-c)** (0.01mol), 2,5-Dicholro-3-acetylthiophen **(2)** (0.01mol) in ethanol (15-20ml) were

taken, an aqueous solution of NaOH (10%, 2-3ml) and refluxed for 6-7 hrs. After completion (TLC), the reaction mixture was Cooled and poured into crushed ice with constant stirring. The solid mass thus obtained was filtered and washed with water and recrystallized from ethanol to get **(3a-d)**.

CONCLUSION

In conclusion, we have synthesized novel indole chalcones **(3a-d)** and evaluated these compounds for their antimicrobial and antioxidant activities. Compounds **(3b)** and **(3c)** emerged as promising antimicrobial agents by showing good activity against both antibacterial and antifungal screening. Most of them demonstrated a broad spectrum of antioxidant activities. The simple and chloro substituted indole derivatives **(3b)** and **(3c)** respectively were concluded as most potent derivatives in all the three cases.

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