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Synthesis and Characterization of Benzofuran Derivatives having Pyrimidine Moiety as Antimicrobial Agents

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ABSTRACT

A series of benzofuran Chalcones were synthesized by condensation of 2-acetyl-5-substituted benzofuran and pyrrole-2-carboxaldehyde in presence of base. These Chalcones further on reaction with urea and thiourea gives hydroxyl pyrimidines and thiopyrimidines having benzofuran scaffold. The structures of all synthesized compounds were established on the basis of analytical and spectral data. The synthesized compounds were screened for antimicrobial activity.

Keywords: Benzofuran Chalcones, Hydroxypyrimidines, Thiopyrimidines, Antimicrobial activity.

I. INTRODUCTION

Benzofurans are one of the heterocyclic compound types with strong biological properties. Benzofuran derivatives are pivotal biodynamic agents from both synthetic and natural sources.[1].Chalcones(1,3-diaryl-2-propen-1-ones) are an important class of plant secondary metabolites and possess a wide range of biological activities.[2] It has been reported that chalcone derivatives are able to directly scavenge a variety of reactive oxygen species (ROS) and possess strong antioxidant properties.[3] Recent evidence has suggested that chalcone derivatives have the capacity to inhibit Aβ fibril formation and exert neuro protection.[4] Interestingly, curcuminoids, a class of chalcone, have been shown to exhibit potent inhibitory effects on oxidative stress.[5] Therefore, introducing a chalcone pharmacophore into a hybrid molecule could impart it with neuro protective effects and the capacity to decrease oxidative stress [6].

Ailanthoidol, obtained by isolating from the Chinese herbal medicine Zanthoxylum ailanthoides, is a neol-ignan bearing a 2-arylbenzofuran ring. Studies show that neolignans have properties including antioxidant, antiviral, anticancer, antifungal, and immune suppressive activities [7]. Benzofuran-chalcone hybrids shows potential multifunctional agents against Alzheimer's disease.[8].Chalcones bearing benzofuran scaffolds shows anticancer [9] ,anti-Alzheimer's, Anti-Leishmanial [10],anti-cancer activity for human lung and breast [11],cytotoxic effect [12],antimicrobial [13] activity.

The role of pyrimidine entity is shown to attract essentiality in several biological processes, such as nucleoside antibiotics, multivitamin synthesis and functional activity maintenance of coenzymes [14]. Nevertheless, much

interest has been concentrated on the synthesis of pyrimidine possessing fungicidal, herbicidal, anti-depressant [15, 16], anti-infective [17], anti-convulsant [18], anti-viral [19], antiprotozoal [20], anti-hypertensive [21], anthelmintic [22], anti-tubercular [23], anticancer [24, 28] and anti-HIV [26] properties. The benzofuran having pyrimidine ring was screened in vitro anticancer activity using human lung cancer cell line A549 cells and human leukemia cell line K562 cells.[29].

In the present work, we have decided to synthesize some new chalcones containing benzofuran moiety; in addition, a novel series of fused pyrimidine with a potential to act as antibacterial and antifungal agents.

II. METHODS AND MATERIAL

Reagents and solvents were used as obtained from the supplier without further purification. All melting points reported are uncorrected and were determined on a Stuart electric melting point apparatus. TLC was performed on Merk TLC aluminium sheets silica gel. Column chromatography was performed on silica gel 90,200–300 mesh and then used for spectral analysis. IR spectra (in KBr, cm^{-1}) were recorded on Shimadzu spectrophotometer in the range of 400-4000 cm^{-1}. ^{1}H-NMR spectra were recorded on a Varian 300 MHz with deuterated solvent ($CDCl_3$). Tetramethylsilane (TMS) was used as an internal standard with chemical shifts δ in ppm. LC-MS were obtained using QP 2010 mass spectrometer using EIMS techniques at 70eV.

Experimental:

A) Typical experimental procedure for synthesis of (5-substituted benzofuran-2-yl)-3-(5-substituted-1H-pyrrol-2-yl)prop-2-en-1-one. (3a-d).

Flask was charged with mixture 2-acetyl 5-substituted benzofuran (I) (0.011 mole) and 5-substituted -1H-pyrrole-2-carbaldehyde (II) (0.011 mole). It was stirred in ethanol (25 mL) and then potassium hydroxide (50%) (10 ml) was added portion wise, keeping the temperature below the 10^0C throughout the Addition.

The mixture was kept for 36 hrs at room temp., after completion of reaction, reaction mixture was poured into crushed ice and the solid obtained was filtered under vacuum. It was washed firstly with sodium carbonate solution and then with water, dried and the product was recrystallized from ethanol to afford the pure product in 78-86 % yield (3a-d). Same procedure is extended for other compounds of this series.

B) Typical experimental procedure for synthesis of 4-(5-substituted-1H-pyrrol-2-yl)-6-(5-substituted benzofuran-2-yl)pyrimidin-2-ol (4a-d).

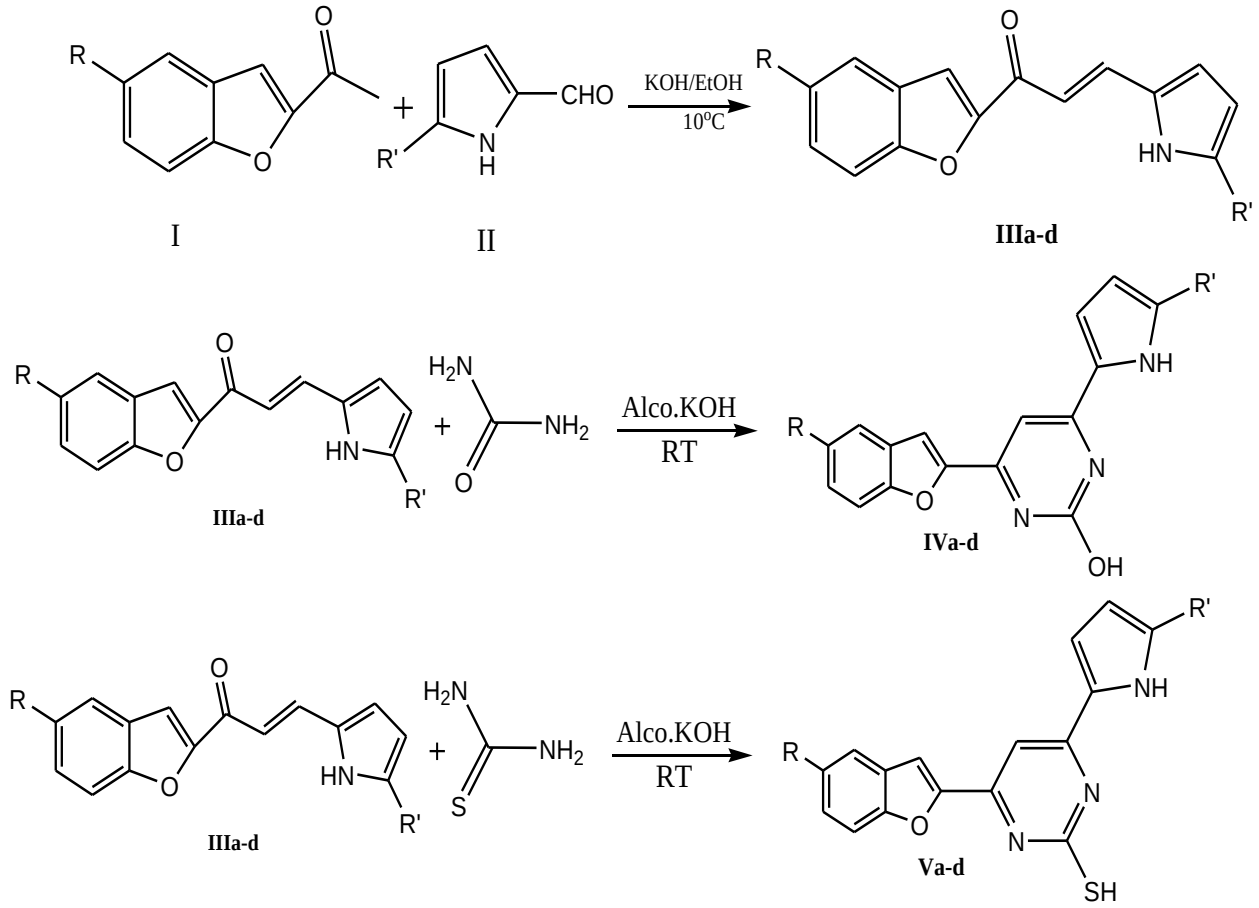
Benzofuran chalcones (2 mmol) (3a-d) were condensed with urea(2 mmol) in alcoholic KOH in a round bottom flask and the reaction mixture was continuously stirred for about 5-6 hr at room temperature.The progress of the reaction was monitoredby TLC and spots were observed by iodine vapor and/or UV light. After completion of reaction, the reaction mixture was cooled, poured into crushed ice with constant stirring and neutralized using 10% $NaHCO_3$.The precipitated product was filtered, dried and recrystallized using ethanol.(4a-d) Yield 71-74 %

C) Typical experimental procedure for synthesis of 4-(5-substituted-1H-pyrrol-2-yl)-6-(5 substituted benzofuran-2-yl)pyrimidine-2-thiol (5a-d).

Benzofuran chalcones (2 mmol) (3a-d) were condensed with thiourea (2 mmol) in alcoholic KOH in a round bottom flask and the reaction mixture was continuously stirred for about 5-6 hr at room temperature.The progress of the reaction was monitoredby TLC and spots were observed by iodine vapor and/or UV light. After

completion of reaction, the reaction mixture was cooled, poured into crushed ice with constant stirring and neutralized using 10% $NaHCO_3$.The precipitated product was filtered, dried and recrystallized using ethanol.(5a-d) Yield 68-71 %

Reaction Scheme:



Where R= -Cl and $-CH_3$ R'= -H and $-CH_3$

III.RESULTS AND DISCUSSION

Spectral discussion:

1) (5-chlorobenzofuran-2-yl)-3-(5-methyl-1H-pyrrol-2-yl)prop-2-en-1-one. (3b)

Yield 78 %, Yellow solid (EtOH) , M.P. 187°C;

IR (KBr, vcm^{-1}): 3067 cm^{-1} (-CH str. of. Ar), 1635 cm^{-1}(C=O str.in ketone), 1578 cm-^{1}(C=C str.) 1509 cm^{-1} (C=C str. in Ar), 1148 and 1178 cm^{-1} (C-O-C str) 832 cm^{-1}(-CH str.) 757 cm^{-1}(Ar-H-opb).

^{1}H NMR ($CDCl_3$ in δ ppm): 2.12 (s, 3H, 5-methyl protons on pyrrole ring) ,5.02(s, 1H, pyrrole N-H),6.86-7.02 (dd, 2H, Ar-protons of pyrrole), 6.31 (d,1H, Trans proton of alkene-CH=CH, J= 16.2 Hz),7.51 (d,1H, Trans proton of alkene-CH=CH-, J= 16.4 Hz) 7.26-7.42 (Complex multiplet , 3H, benzofuran protons), 7.49 (singlet, 1H, Aromatic proton of Furan ring)

Mass (m/z):285[M]$^+$

2) 4-(5-methylbenzofuran-2-yl)-6-(1H-pyrrol-2 yl)pyrimidin-2-ol (4c)

Yield 71 %, faint brown solid (EtOH) , M.P. 136°C;
IR (KBr, vcm^{-1}): 3467 cm^{-1} (-OH str.) ,1625 cm^{-1}(C=N str.in pyrimidine), 1518 cm^{-1} (C=C str. in Ar) ,1133 and 1158 cm^{-1} (C-O-C str.), 838 cm^{-1}(-CH str.),767 cm^{-1} (Ar-H-opb).
^{1}H NMR (CDCl$_3$ in δ ppm): 2.39(s, 3H, 5-methyl protons on benzofuran ring),7.31(d,1H,pyrrole N-H), 7.41-7.52 (dd,2H,pyrrole protons),8.86 (s, 1H, pyrimidine), 10.31 (s,1H,OH proton) , 7.38-7.58 (Complex multiplet , 3H, benzofuran protons), 7.52 (singlet, 1H, Aromatic proton of Furan ring).
Mass (m/z):291[M]$^+$

3) 4-(5-substituted-1H-pyrrol-2-yl)-6-(5 methylbenzofuran-2-yl)pyrimidine-2-thiol (5d).
Yield 68 %, brown solid (EtOH) , M.P. 168°C;
IR (KBr, vcm^{-1}): 2567 cm^{-1} (-SH str.), 1612 cm^{-1}(C=N str.in pyrimidine), 1522 cm^{-1} (C=C str. in Ar), 1386 cm^{-1} (C-H str.in –CH$_3$), 1121 and 1167 cm^{-1} (C-O-C str.) 828 cm^{-1}(-CH str.) 758 cm^{-1}(Ar-H-opb).
^{1}H NMR (CDCl$_3$ in δ ppm): 2.11 (s, 3H, 2-methyl protons on pyrrole ring), 2.22 (s, 3H, 5-methyl protons on benzofuran ring),7.11 (d,1H,pyrrole N-H), 7.52-7.72 (dd,2H,pyrrole protons), 8.74 (s, 1H, pyrimidine),10.37 (s,1H,SH proton),7.42-7.63 (Complex multiplet , 3H, benzofuran protons), 7.63 (singlet, 1H, Aromatic proton of Furan ring),
Mass (m/z):321[M]$^+$

Evaluation of anti-microbial activity;
All synthesized compounds were evaluated in-vitro for their antibacterial activity against gram positive bacteria Bacillus subtilis ,gram negative bacteria Escherichia coli and Pseudomonas aeruginosa.The antifungal activity against Alternaria alternate , Aspergillus niger and Candida albicans. Agar well diffusion technique was used for the determination of preliminary antibacterial and antifungal activities (37). Streptomycin and fluconazole were used as reference drugs for comparison. The tested compounds were dissolved in DMSO to get a concentration of 100% and 50%. The samples were loaded into wells of agar plates directly. Plates inoculated with the bacteria were incubated at 38 °C for 24 hr and the fungal culture was incubated at 25 °C for 72 hr.The results were recorded for each tested compound as average diameter of inhibition zones around the well in mm have been depicted in Tables-II and Table-III.

Experimental analysis
Synthesis of the various pyrimidine derivatives were achieved according to the reactions illustrated in the Scheme.
Chalcone intermediates were obtained by Aldol condensation of corresponding 2-acetyl -5 substituted benzofuran (I) with different pyrrole carbaldehydes (II) according to the reported procedure (30). The condensed heterocyclic compounds 4-(5-substituted-1H-pyrrol-2-yl)-6-(5-substituted benzofuran-2-yl) pyrimidin-2-ol (4a-d) and 4-(5-substituted-1H-pyrrol-2-yl)-6-(5 substituted benzofuran-2-yl)pyrimidine-2-thiol (5a-d) were synthesized by treating (2E)-(5-substituted benzofuran-2-yl)-3-(5-substituted-1H-pyrrol-2-yl)prop-2-en-1-one.(3a-d) with urea and thiourea respectively in ethanoic KOH. The structure of desired pyrimidine analogs (4a-d) and (5a-d) were confirmed using IR, NMR and Mass spectral data. The IR spectrum of compounds 4a-d exhibited a broad absorption band at 3454-3472 cm $^{-1}$which confirms the presence of hydroxyl group. Another peak in the region of 1607-1633 cm^{-1}which suggests presence of C=N stretching vibration. The ^{1}HNMR spectrum of compound 4a-d exhibited a broad singlet at δ 10.31-10.48 ppm due to

hydroxyl proton and multiplet between δ 7.21-7.59 ppm for aromatic protons. The mass spectrum of the compound 4c showed molecular ion peak at m/z 291.30 [M+] which corresponds to molecular weight of the compound. The physical and analytical data of the newly synthesized compounds (3a-d), (4a-d) and (5a-d) are tabulated in Table-1

Table-I Characterization data of synthesized compounds

Compound	R	R'	Yield %	Mol.Wt.
3a	Cl	H	78	$C_{15}H_{10}ClNO_2$
3b	Cl	CH_3	79	$C_{16}H_{12}ClNO_2$
3c	CH_3	H	86	$C_{16}H_{13}NO_2$
3d	CH_3	CH_3	74	$C_{17}H_{15}NO_2$
4a	Cl	H	73	$C_{16}H_{10}ClN_3O_2$
4b	Cl	CH_3	71	$C_{17}H_{12}ClN_3O_2$
4c	CH_3	H	74	$C_{17}H_{13}N_3O_2$
4d	CH_3	CH_3	72	$C_{18}H_{15}N_3O_2$
5a	Cl	H	69	$C_{16}H_{10}ClN_3OS$
5b	Cl	CH_3	71	$C_{17}H_{12}ClN_3OS$
5c	CH_3	H	68	$C_{18}H_{15}N_3OS$
5d	CH_3	CH_3	70	$C_{18}H_{15}N_3OS$

Table II. Anti-bacterial activity data of synthesized compounds.

Compd.	Zone of inhibition (in mm)					
	B. subtilis		E. coli		P. aeruginosa	
	100 (mg)	50 (mg)	100 (mg)	50 (mg)	100 (mg)	50 (mg)
3a	20.02	9.84	18.21	9.21	11.20	5.20
3b	19.35	7.95	17.89	8.95	18.32	9.65
3c	17.21	8.36	12.30	6.15	15.20	7.51
3d	16.68	7.56	15.20	7.14	18.32	9.31
4a	15.89	7.65	9.51	4.24	15.24	7.89
4b	18.23	8.21	17.20	8.85	14.21	7.41
4c	22.37	11.0	18.36	9.32	17.89	9.21
4d	19.36	9.50	20.41	10.21	16.66	8.21
5a	20.47	10.20	18.62	9.21	17.30	9.21
5b	21.22	10.43	17.88	8.97	17.21	8.91
5c	18.14	9.21	19.21	9.98	18.21	9.34
5d	19.18	8.99	21.21	10.22	14.54	7.41
Penicillin	24.32		22.04		19.09	

Table-III Antifungal activity of synthesised compounds

Comp.	B. subtilis	E. coli	P. aeruginosa	A. niger	C. albicans
3a	-ve	+ve	-ve	+ve	-ve

3b	+ve	- ve	+ve	+ve	-ve
3c	-ve	+ve	+ve	+ve	+ve
3d	+ve	+ve	+ve	-ve	-ve
4a	+ve	+ve	+ve	-ve	+ve
4b	--	+ve	+ve	+ve	+ve
4c	+ve	+ve	+ve	-ve	+ve
4d	-ve	+ve	-ve	-ve	+ve
5a	+ve	+ve	-ve	+ve	+ve
5b	-ve	+ve	+ve	-ve	-ve
5c	+ve	-ve	-ve	+ve	+ve
5d	+ve	-ve	+ve	+ve	+ve
Griseoful- vin	+ve	+ve	+ve	+ve	+ve

Biological activity

Many of the literature data suggests that the structural parameters of synthesized compounds may have better impact on changing the efficacy of antimicrobial activity (31). A study shows that all the compounds displayed a varied degree of MIC (22.37 to 4.24 μg/mL) against all the tested bacterial strains. The compound 4c, 5a and 5b exhibited excellent antibacterial activity against bacterial strain Bacillus subtilis. The compound 5a,5c and 5b exhibit good antibacterial activity against E. coli. Compounds 3b,3c,3d and 5c showed excellent effect against P. aeruginosa. Nevertheless, the remaining compounds showed negligible antibacterial activity.

The antifungal effect of newly synthesized compounds also indicate that mmajority of thhe compounds exhibited antifungal activity against all tested pathogens. All the antifngal and antibacterial study shows that presence of benzofuran scaffold incorporated with thiol and phenolic group moiety enhances the antimicrobial activity

IV.CONCLUSION

In present work, biologically active derivatives of benzofuran that is 4-(5-substituted-1H-pyrrol-2-yl)-6-(5-substituted benzofuran-2-yl) pyrimidin-2-ol and -2 thiols were synthesized from benzofuran chalcones having high chemical reactivity and diverse synthetic and biological applications. From antimicrobial activity results, it is also found that, the presence of hydroxyl and thiol groups in the pyrimidine ring displayed promising antimicrobial activity. Henceforth it can serve as pyrimidines have engendered long considerable interest which makes new building blocks for synthesis and design of broad spectrum antimicrobial compounds and needs medicinal chemist to be continued interest in pyrimidine moiety in drug development against microbes. It will also ensure the development of reliable methods for the construction of important area of research in heterocyclic chemistry.

V. REFERENCES

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