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Synthesis and Antitubercular Activities of Azetidinone and Thiazolidinone Derivatives from 5-Chloro-3-Methylbenzofuran

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Abstract: 1-(5-Chloro-3-methyl-1-benzofuran-2'-yl)ethone hydrazone **3** was prepared by the condensation of 5-chloro-3-methyl-2-acetylbenzofuran **2** with hydrazinehydrate.The compound **3** was treated with different aromatic aldehydes in boiling ethanol gave benzaldehyde[1-(5'-chloro-3-methyl-1-benzofuran-2'-yl)ethylidine]hydrazones **3a-d**. Compounds **3a-d** underwent cyclisation with chloroacetylchloride and mercaptoacetic acid to furnished benzofuranyl azetidinone and thiazolidinone derivaties **4a-d** and **5a-d** respectively. The structure of all compounds have been characterized by elemental analysis and spectral studies. The synthesized compounds were screened for their antimicrobial, antitubercular and anticonvulsant activities.

Key words: 5-Cholo-3-methylbenzofuran, Azetidinones, Thiazolidinones, Antimicrobial, antitubercular and anticonvulsant activitives.

Introduction

Synthetic benzofuran and its analogues has attracted due to their biological activities and their potential applications as pharmacological agents. Most of the benzofuran derivatives possess antimicrobial, sedative and hypnotic, antitumer, anti-inflammatory, fungicidal and anticonvulsant activities[1-4].

Thiazolidinones and azetidinones have attracted considerable attention as they endowed with wide range of pharmaceutical properties[5-8]. Due to such an investigation and interest in the above suggestions and in continuation of our previous research work in the synthesis of biologically active heterocycles containing halogen substituted benzofuran[9]. This approach seems to be useful in view of the fact that it may combine the physiological action of the group with the well known biological activity of the compounds containing azetidinone and thiazolidinone and benzofuran groups.

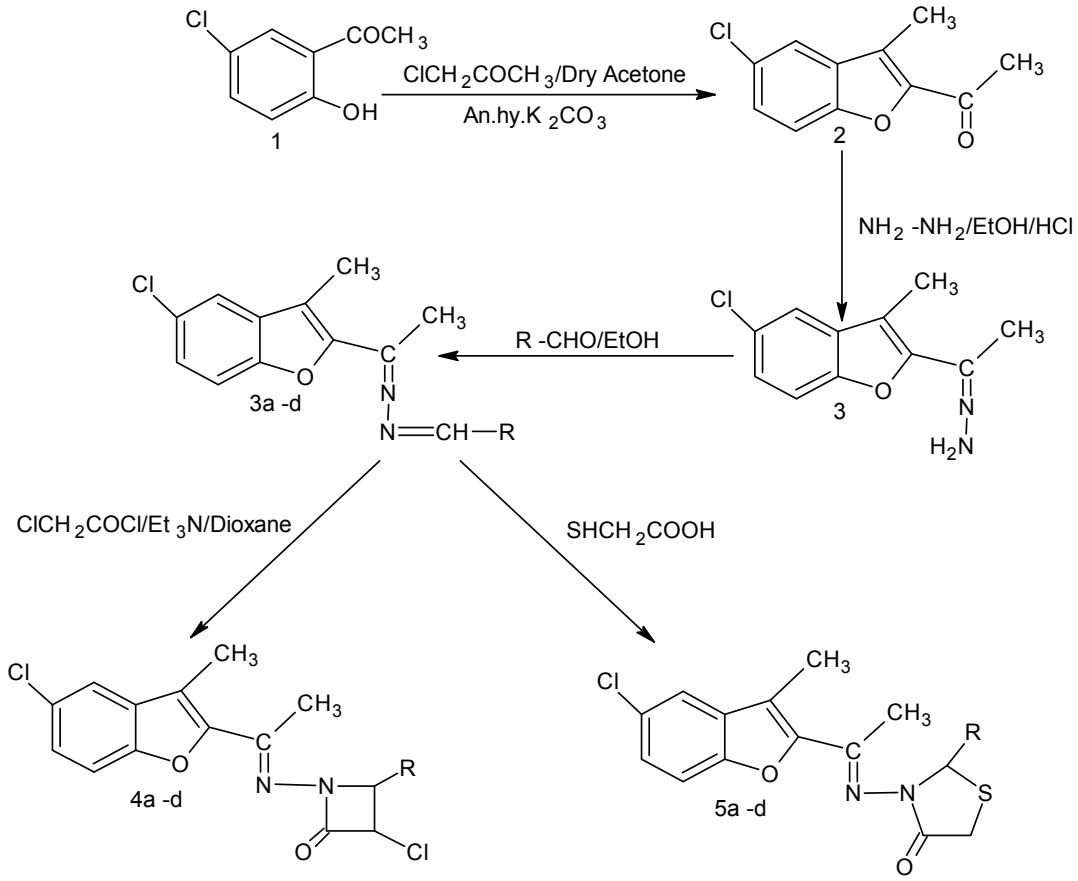
5-Chloro-3-methyl-2-acetylbenzofuran **2** was required in the present work has been obtained by a single step method by the reaction of 5-chloro-2-hydroxy acetophenone **1** with chloroacetone in anhydrous acetone in presence of basic catalyst anhydrous potassium carbonate, the acetyl group of benzofuran at 2 position has extensive utilities in the synthetic chemistry. The identity of the product **2** was already reported in the earlier work.

The compound 1-(5'-chloro-3'-methyl-1'-benzofuran-2'-yl)ethanone hydrazone **3** was prepared by the reaction of 5-chloro-3-methyl-2-acetylbenzofuran **2** with hydrazine hydrate in boiling ethanol in presence of catalytic quantity of hydrochloric acid in acceptable yield. The structure of compound **3** was confirmed by IR, ^{1}HNMR and mass spectral analysis. The IR spectrum of compound **3** revealed a strong absorption bands in the region 3375-3232cm^{-1} due to the presence of the primary amino functional group as anti-symmetric and symmetric streching, an absorption band at 2923 and 2854cm^{-1} due to C-Hstr of methyl group and appearance of an strong absorption band at

1606cm^{-1} due to C=N. ^{1}HNMR spectrum exhibits a singlet at δ 2.20 and 2.40 ppm for two methyl groups, another singlet at δ 5.50 ppm due to two protons of amino group and aromatic protons shows a multiplet at δ 7.2-7.8 ppm. It also revealed its mass spectrum at m/z 222(M^+ , 33%) and m/z 224(M^{+2},100%) is its isotopic peak, which is in agreement with molecular formula compound **3**.

The reaction of 1-(5-chloro-3-methyl-1-benzofuran-2-yl) etanone hydrazone **3** with different aromatic aldehydes in equimolar quantities in ethanolic solution was heated under reflux for 30 min. resulted in the formation of yellow colored benzofuran ethylidine hydrazone analogues of Schiff's bases **3a-d**.

The IR spectrum of compound **3b** showed a characteristic absorption band at 3600cm^{-1} due to OH stretching, an absorption band at 2920cm^{-1} due to –C-H stretching of methyl group, another absorption band at 1610cm^{-1} due to C=N, the appearance of absorption bands at 1571, 1442, 1363cm^{-1} due to C=C stretching and another absorption band at 750cm^{-1} due to C-Cl stretching. The ^{1}HNMR spectrum of compound **3b** showed a singlets at δ 2.5 and δ 2.6 due to six protons of two methyl group, a multiplet at δ 6.6– 6.9 due to aromatic protons, a singlet at δ 8.7 due to -N=CH proton and another singlet appeared at δ 11.9 due to OH proton. The structure of compound **3b** was further supported by its mass spectrum. The mass spectrum of compound **3b** showed a molecular ion peak at m/z 326 (M^+ 90%) which corresponds to the molecular weight of the compound **3b,** m/z 328 (M^{+2} 30%) is its isotopic peak



Where R

a	C_6H_5
b	$C_6H_4OH(p)$
c	$C_6H_4Cl(p)$
d	$C_6H_4OCH_3(p)$

Scheme -1

The compound **3a-d** which upon treatment with chloroacetyl chloride in solvent dioxane in presence of triethylamine was stirred for about 3 hrs. gave a product which were identified as 3-chloro-1-{[1-(5-chloro-3-methyl-1-benzofuran-2-yl) ethylidine] amino}-4-substituted phenyl azetidine-2-ones **4a-d**.

The IR spectrum of compound **4b s**howed a characteristic absorption band at 1741cm^{-1} due to –C=O stretching, an absorption band at 2921 cm^{-1} due to –C-H stretching of methyl group, another absorption band at 1610 cm^{-1} due to C=N stretching, the absorption bands at 1569 and 1442cm^{-1} due to C=C stretching and absorption band at 794cm^{-1} due to C-Cl stretching. The ^{1}HNMR spectrum of compound **4b** displayed a singlet at δ 2.5 and δ 2.6 due to methyl protons, doublets at δ 6.9 and δ 7.1 due to each proton of -CH-Ph and CH-Cl. The multiplet at δ 7.1-7.6 due to aromatic protons and a singlet at δ 11.9 due to OH proton. The mass spectrum of compound **4b** showed a molecular ion peak at m/z 402(M+, 10%) which corresponds to the molecular weight of the compound **4b.**

Similarly compound **3a-d** treated with thioglycolic acid, the reaction mixture was heated on the oil-bath at 115-120^{0}C for 12 hrs. the resulting mass treated with 10% sodium bicarbonate gave 3-{[(1E)-1-(5-chloro-3-methyl-1-benzofuran-2-yl) ethylidine] amino}-2-substituted phenyl-1,3-thiazolidin-4-one **5a-d** in 70-80% yield.

The IR spectrum of compound **5a s**howed a characteristic absorption band at 2923cm^{-1} due to –C-H stretching, 1737cm^{-1} due to –C=O stretching of thiazolidinone ring, another absorption band at 1591cm^{-1} due to C=N stretching, the absorption band at 1448cm^{-1} due to C=C stretching and another absorption band at 798cm^{-1} due to C-Cl stretching. The ^{1}HNMR spectrum of compound **5a** displayed a singlet at δ 2.3 and δ 2.5 due to methyl protons, another two singlets appeared at δ 4.9 due to one proton of CH-ph. and at δ 5.1 due to two protons of –CH_2 of thiazolidinone ring. A aromatic protons observed as multiplet in the region at δ 6.6-7.5 . The mass spectrum of compound **5a** showed a molecular ion peak at m/z 383 (M^+, 10%) which corresponds to the molecular weight of the compound **5a.**

Experimental

The melting points were determined by open capillaries and are uncorrected. The IR spectra in KBr(cm^{-1})were taken on FT-IR-8400S(SHIMADZU)Spectrophotometer, Karnataka College of Pharmacy, Department of Pharmaceutical Chemistyr, Bidar.The ^{1}HNMR spectra were carried out on Avance 300 MHZ NMR Spectrophotometer and were procured from IICT, Hyderbad, chemical shift are expressed in δppm by using TMS as a internal standard. Mass spectra of synthesized compounds were taken on a EI technique on Shimadzu QP 2010 PLUS Gc-MS mass spectrophotometer, IICT Hyderbad. The purity of all synthesized compounds were monitered by TLC on silica gel-G plates using suitable solvent system.

1-(5'-Chloro-3'-methyl-1'-benzofuran-2'-yl)ethanone hydrazone 3

A mixture of compound **2** (0.002 mole) and hydrazine hydrate (0.003 mole, 99%) was refluxed in absolute ethanol (30ml) on a steam bath for 6hrs. The product which separated on cooling was collected and crystallized from aqueous ethanol. Yield 68.53%, m.p. 120^{0}C. (Found C,59.00; H,4.94; N,12.50; $C_{11}H_{11}ClN_2O$ requires C, 59.33 ; H, 4.98; N, 12.58 %).

Substitutedbenzaldehyde[1-(5,-chloro-3'-methyl-1'-benzofuran-2'- ethylidine]hydrazones 3a-d

General procedure :

A suspension of compound **3** (0.02mole) in alcohol (20ml) was treated with appropriate amount of substituted aromatic aldehydes (0.02mole), the reaction mixture was heated under reflux for 30 min on water bath. The product which separated as solid on cooling to room temperature. The solid separated out and was filterd and dried to give the desired compounds **3a-d**.

3a : IR(KBr)cm^{-1} 2918(C-H), 1598(C=N), 1448(C=C), 796(C-Cl). ^{1}HNMR($CDCl_3$), δ(ppm) 2.5(s, 3H, CH_3), 2.6(s, 3H, CH_3), 7.2-7.6(m, 8H, Ar-H); MS: m/z 310(M^+ 10%).

3d:IR(KBr)cm^{-1} 2921(C-H), 1605(C=N), 1568, 1454(C=C), 796(C-Cl). ^{1}HNMR($CDCl_3$), δ(ppm) 1.6 (s, 3H, CH_3), 2.6(s, 3H, CH_3), 3.80(s, 3H, OCH_3), 7.0-7.9(m, 7H, Ar-H), 8.6(s, 1H, -N=CH); MS: m/z 340(M^+, 60%), 342(M^{+2}, 20%).

3-Chloro{[1-(5'-chloro-3'-methyl-1'-benzofuran-2'-yl)ethylidine]amino}-4-substituted phenyl azetidine-2-ones 4a-d

General procedure :

To a solution of appropriate amount of compound **3a-d** (0.01mole) in Dioxane (15ml), triethyl amine (0.02mole) was added. To this a solution a chloroacetyl chloride(0.02mole) was added in portion wise with vigorous shaking at room temperature for 20min and was heated under reflux for an 3hrs and content was kept at room temperature for 48hrs. The azetidinone compounds, which separated on dilution with ice cold water, was collected and dried to gave desired products **4a-d**.

4d : IR(KBr)cm^{-1} 2920(C-H), 1726(C=O), 1605(C=N), 1440, 1359(C=C), 798(C-Cl). ^{1}HNMR($CDCl_3$), δ(ppm) 2.5(s, 3H, CH_3), 2.6(s, 3H, CH_3), 3.80(s, 3H, OCH_3), 6.9(d, 1H, CH-Ph), 7.1(d,

1H, CH-Cl), 7.2-7.9(m, 7H, Ar-H), 8.6(s, 1H, -N=CH); MS: m/z 387(M^+), 389(M^{+2}).

3-{[(1E)-1-(5'-Chloro-3'-methyl-1'-benzofuran-2'-yl)ethylidine]amino}-2-substituted phenyl-1,3-thiazolidin-4-ones 5a-d

General procedure :

A mixture of substituted benzaldehyde[1-(5,-chloro-3'-methyl-1'-benzofuran-2'- ethylidine]hydrazone **3a-d** (0.01mole) and mercaptoacetic acid (0.01mole) was heated on a oil bath to maintain temperature between 115-120^{0}C for 10-12hrs. The resulting mass was treated with 10% sodium bicarbonate and thus solid obtained, filtered and dried to give compounds **5a-d**.

5b : IR(KBr)cm^{-1} 3596(OH), 2920(C-H), 1743(C=O), 1590(C=N), 1450, 1359(C=C), 798(C-Cl). MS: m/z 400(M^+,5%) .

5c : IR(KBr)cm^{-1} 2962(C-H), 1649(C=O), 1590(C=N), 1452, 1359(C=C), 798(C-Cl). MS: m/z 400(M^+), 402(M^{+2})

Table-1 Characteristics data of synthesized compounds (3a-d), 4a-d) and (5a-d)

Comp. No.	R	MP (^{0}C)	Yield (%)	Molecular Formula	S	Elemental Analysis Found (Calculated)%		
						C	H	N
3a	C_6H_5	260	67.26	$C_{18}H_{15}ClN_2O$	B	69.50 (69.57)	4.90 (4.86)	9.00 (9.01)
3b	C_6H_4OH(o)	164	63.83	$C_{18}H_{15}ClN_2O_2$	A	66.10 (66.16)	4.60 (4.63)	8.60 (8.57)
3c	C_6H_4Cl(p)	220	70.06	$C_{18}H_{15}Cl_2N_2O$	B	62.60 (62.62)	4.00 (4.09)	8.10 (8.11)
3d	$C_6H_4OCH_3$(p)	270	55.0	$C_{19}H_{17}ClN_2O_2$	B	66.90 (66.96)	5.03 (5.03)	8.25 (8.22)
4a	C_6H_5	274	90.69	$C_{20}H_{16}Cl_2N_2O_2$	B	62.05 (62.03)	4.20 (4.16)	7.25 (7.23)
4b	C_6H_4OH(o)	142	51.20	$C_{20}H_{16}Cl_2N_2O_3$	A	59.55 (59.57)	4.01 (4.00)	6.90 (6.95)
4c	C_6H_4Cl(p)	254	74.42	$C_{20}H_{15}Cl_3N_2O_2$	B	56.98 (56.96)	3.55 (3.59)	6.66 (6.64)
4d	$C_6H_4OCH_3$(p)	282	59.34	$C_{21}H_{18}Cl_2N_2O_3$	B	60.40 (60.44)	4.36 (4.35)	6.70 (6.71)
5a	C_6H_5	276	90.79	$C_{20}H_{17}ClN_2OS$	D	62.42 (62.41)	4.40 (4.45)	7.30 (7.28)
5b	C_6H_4OH(o)	278	85.31	$C_{20}H_{17}ClN_2O_3S$	D	59.90 (59.92)	4.20 (4.27)	6.90 (6.99)
5c	C_6H_4Cl(p)	274	82.37	$C_{20}H_{16}Cl_2N_2O_2S$	D	57.20 (57.29)	3.90 (3.85)	6.60 (6.68)
5d	$C_6H_4OCH_3$(p)	280	96.05	$C_{21}H_{19}ClN_2O_3S$	D	60.70 (60.79)	4.60 (4.62)	6.70 (6.75)

S= Solvent for crystallisation

Table-2, Results of antimicrobial activity of synthesized compounds

Compound No.	Zone of Inhibition in mm*			
	Antibacterial		Antifungal	
	S.aureus	*E.coli*	*A.niger*	*C.albicans*
3a	13	12	17	15
3b	15	16	17	15
3c	17	19	18	19
3d	16	14	18	22
4a	13	10	13	14
4b	15	14	15	16
4c	17	18	20	22
4d	18	16	18	21
5a	14	16	14	16
5b	17	16	15	15
5c	18	20	18	16
5d	19	18	20	17
Controle (DMF)	06	06	-06	06
Ciprofloxacin	22	20		
Griseofulvin	-	-	26	24

*Diameter of the well

Table-3, Antitubercular activities of some selected compounds

MINIUM INHIBITORY CONCENTRATION

$H_{37}Rv$			
Compound No.	**Concentration (μg/ml)**		
	25	**50**	**100**
Streptomycin (standard)	S	S	S
4b	S	S	S
4c	R	S	S
4d	R	R	S
5b	S	S	S
5c	R	R	S
5d	R	S	S

R=Resistant, S=Sensitive

Table-4, Anticonvulsant activity of test compounds against pentylenetetrazol induced convulsions

Compound	Convulsions (clonic) Present (+) Absent (-)	Time required for onset of convulsions (Sec.)	Duration of convulsions (sec.)	Death / Recovery (D) / (R)
Pentylenetetrazol	+ + + +	40 44 48 52	120 123 130 140	D D D D
Diazepam + Pentylenetetrazol	- - - -	Convulsions were not produced at all	- - - -	- - - -
4a + Pentylenetetrazol	+ + + +	30 24 32 40	130 127 150 165	D D D D
4c + Pentylenetetrazol	+ + + +	36 38 40 48	140 130 142 150	D D D R
4d + Pentylenetetrazol	+ + + +	34 38 41 47	130 128 140 154	D R D D
5a + Pentylenetetrazol	+ + + +	41 33 43 30	140 135 150 165	D D D R
5c + Pentylenetetrazol	+ + + +	40 42 44 46	145 140 150 160	R R D D
5d + Pentylenetetrazol	+ + + +	38 44 46 48	150 152 158 140	D R D D

Result and discussion

Antimicrobial activity

All representative compounds were screened for *in-vitro* antibacterial and antifungal activity against a bacterial strains such as *S.aureus* and *E.coli*, the fungi such as *A.niger* and *C.albicans*. The known antibiotics Ciprofloxacin and Griseofulvin are used for comparison. Dimethyl formamide was used as a control and method employed was Cup-plate diffusion method and zone of inhibition measured in mm.

Compounds **3c**, **3d**, **4c** and **5c** exhibited maximum activity in the range of (17-20mm) against both bacteria and remaining compound shows moderate to weak activity against *S.aureus* and *E.coli.* Compounds **3c**, **3d**, **4c** and **5d** were shown to be good fungicidal activity against *A.niger* and *C.albicans* where as compounds **3a**, **4b**, **4d**, **5b** and **5c** shown moderate activity against both fungi and remaining compounds of the series exhibited weak activity against both fungi.

Antitubercular activity

Some representative azetidinones and thiazolidinones derivatives **4b-d** and **5b-d** were evaluated for their antitubercular activity against Mycobacterium

H_{37}RVconcetration of 25µg/ml, 50 µg/ml and 100 µg/ml using streptomycin as a standard drug at the concentration of 7.5 µg/ml.
Compound **4b** and **5b** exhibited good antitubercular activity against Mycobacterium tuberculi H_{37}RV and remaining compounds shows weak activity (Table-3).

Anticonvulsant activity
Anticonvulsant activity of synthesized compounds **4a, 4c-d** and **5a**, **5b-d** were tested against pentylenetetrazol induced convulsions in the mice. The Diazepam was used as a standard drug.

None of the tested compounds abolished pentylene tetrazol induced convulsions in test animals, the standard drug Diazepam abolished the convulsions produced by pentylene tetrazole.

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