



Research Article

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Synthesis and antimicrobial screening of some 1,3- thiazines

Farooque Haider Zulfequar Haider

Department of Chemistry, Vidnyan Mahavidyalaya, Malkapur, Dist –Buldana, M S, India

ABSTRACT

Synthesis and antimicrobial screening with spectral analysis of some 1,3 - thiazines have been carried out in two series, first series starting material is 2- hydroxyacetophenone and we got 4-(2-hydroxy phenyl)-5-benzoyl-6-phenyl or 4-alkoxy phenyl or 4-dimethyl amino phenyl -2-imino -6-H-2,3- dihydro 1,3- thiazine(4a,4a',4a'',4a'''). Second series starting material is 2-hydroxy- 5- methyl acetophenone we got 4-(2-hydroxy -5-methyl phenyl)-5-benzoyl-6-phenyl-2-imino-6 H- 2,3 dihydro-1,3-thiazine and respected derivatives as written above (4b,4b',4b'',4b''') from thiourea. All these compounds have been analyzed by melting point, IR, ¹H NMR. All the synthesized compounds are tested for their antimicrobial activities.

Keywords: 1, 3 -thiazine, Thiourea, Antimicrobial screening.

INTRODUCTION

Thiazine is a six membered heterocyclic which contains two hetero atoms (N and S) placed in the heterocyclic ring at 1,3 positions. Thiazines are very useful units in field of medicinal and pharmaceutical chemistry and have been reported to exhibit variety of biological activities[1].

A large group of dyes has phenothiazine structure including methylene blue thiazine are used for dyes, tranquilizer and insecticide; thiazine can help reduce somewhat extra water weight you may be holding on to your stomach. Thiazine is fairly basic diuretics supplement it reduces water and increase vascularity, so it also use as anabolic agent in medicine[2]. The 1,3-thiazine nucleus is active core of cephalosporin which are among the widely used β -lactam antibiotics[3]. The ability of thiazine to exhibit antitubercular, antibacterial in which inactivate HIV in biological fluid and used as cannabinoid receptor agonist[4].

Sawant et al synthesized 1,3-thiazines and carried out antimicrobial screening which reveals that the compounds with methoxy substituent with negative sigma (-0.04) and negative pi (-0.27) values are good antimicrobials showing low minimum inhibitory concentration based on observation hydroxyl group with more negative sigma (-0.061) and pi (-0.37) values was selected to synthesized and observed that the set of these compounds were found better antimicrobial than initial set of compounds[5].

The potential use of chlorpromazine derivatives of this phenothiazine as antimicrobial, increasing activity of antibiotics to which bacteria are susceptible and reverse resistance of *Staphylococcus aureus* and corynebacteria to penicillin strongly supports that phenothiazine can be exploited for the management of bacterial infections[6].

Chalcones undergo a variety of chemical reactions and are found useful in synthesis of variety of hetero cyclic compounds like Pyrimidine and Thiazole derivatives are synthesized through the reaction of Chalcones with urea and thiourea in the presence of alkaline media in refluxing ethanol[7]. F.K.Mohammed et al synthesize new chromene base heterocyclic like thiazine from 2-Amino-5-hydroxy-4-phenyl-7-methyl-4H[1-chromeno-3-carbonitrile which may show a good biological activity[8]. In light of these biological activities it appeared of interest to synthesize 1, 3 thiazine derivatives.

EXPERIMENTAL SECTION

1,3- thiazines are synthesized in two series first by using 2-hydroxy acetophenone as starting material, second by using 2-hydroxy 5-methyl acetophenone as starting material by Literature method. All the melting point of synthesized compounds was determined by using open capillary method and are uncorrected. IR spectra of synthesized compounds were recorded on Bruker spectrophotometer using ATR method. NMR spectra of synthesized compounds were recorded on Bruker advance II 400 NMR spectrophotometer at Punjab University Chandigarh. The purity of all synthesized compounds were checked on thin layer chromatography on silica gel-G column. The antimicrobial activities were carried out at Zoology department Vidyan Mahavidyalaya, Malkapur.

1) Synthesis of 2-benzoyloxy acetophenone (1a)

2-hydroxy acetophenone (0.01 mole) and benzoyl chloride (0.01 mole) were taken in stoppered conical flask 50 ml 10% NaOH solution added reaction mixture shaken vigorously for one hour. The product filtered and washed with water crystallized with ethanol. m.p. 78°C, yield 78%.

2) Synthesis of 2-benzoyloxy-5-methyl acetophenone. (1b)

2-hydroxy -5-methyl acetophenone (0.01 mole) and benzoyl chloride (0.01 mole) were taken in stoppered conical flask 50 ml 10% NaOH solution added reaction mixture shaken vigorously for one hour. The product filtered and washed with water crystallized with ethanol. m.p. 74°C, yield 75%.

3) Synthesis of 1-(2-hydroxyphenyl)-3-phenyl-1,3-propandione. (diketone) (2a)

Compound 1a (0.01) mole were dissolved in 35 ml pyridine and heated in oil bath at 60°C and pulverized KOH (0.015 mole) added and stirred well, mixture allowed to stand for two hrs then decomposed with dilute hydrochloric acid yellow diketone separates by BVT crystallize with ethanol. m.p. 124°C, Yield 70%

4) Synthesis of 1-(2-hydroxyphenyl-5-methyl)-3-phenyl-1,3-propandione. (diketone) (2b)

Compound 1b (0.01 mole) were dissolved in 35 ml pyridine and heated in oil bath at 60°C and pulverized KOH (0.015 mole) added and stirred well, mixture allowed to stand for two hrs then decomposed with dilute hydrochloric acid yellow diketone separates by BVT crystallize with ethanol. m.p. 90°C, Yield 70%

5) Synthesis of 3- benzoyl flavanone. (3a)

Compound 2a (0.02 mole) and benzaldehyde (0.02 mole) were dissolved in 25 ml ethanol and 0.5 ml piperidine added, reaction mixture refluxed for 1hr then cooled at room temperature white shiny needle of product separates out filtered and crystallized with ethanol. m.p. 155°C Yield 68% .

6) Synthesis of 3- benzoyl 6-methyl flavanone. (3b)

Compound 2b (0.02 mole) and benzaldehyde (0.02 mole) were dissolved in 25 ml ethanol and 0.5 ml piperidine added, reaction mixture refluxed for 1hr then cooled at room temperature white shiny needle of product separates out filtered and crystallized with ethanol. m.p. 149 °C Yield 65% .

7) Synthesis of 3- benzoyl 4' methoxy flavanone. (3a')

Compound 2a (0.02 mole) anisaldehyde (0.02 moles) were dissolved in 25 ml ethanol and 0.5 ml piperidine added and processed as previous in 3a. m.p. 143°C, Yield 65%

8) Synthesis of 3- benzoyl-6-methyl- 4'-methoxy flavanone. (3b')

Compound 2b 0.02 mole anisaldehyde 0.02 moles were dissolved in 25 ml ethanol and 0.5 ml piperidine added and processed as previous in 3a. m.p. 140 °C. Yield 62%

9) Synthesis of 3- benzoyl 3',4'- dimethoxy flavanone. (3a'')

Compound 2a 0.02 mole 3,4-dimethoxy benzaldehyde 0.02 moles were dissolved in 25 ml ethanol and 0.5 ml piperidine added and processed as previous in 3a. m.p. 142°C Yield 62%

10) Synthesis of 3- benzoyl-6-methyl 3',4'- dimethoxy flavanone. (3b'')

Compound 2b 0.02 mole 3,4-dimethoxy benzaldehyde 0.02 moles were dissolved in 25 ml ethanol and 0.5 ml piperidine added and processed as previous in 3a. m.p. 156°C Yield 60%

11) Synthesis of 3- benzoyl 4'- dimethyl amino flavanone. (3a''')

Compound 2a (0.02 mole) , 4-dimethylamino benzaldehyde (0.02 moles) were dissolved in 25 ml ethanol and 0.5 ml piperidine added and processed as previous in 3a. mp. 165°C Yield 62%

12) Synthesis of 3- benzoyl-6-methyl 4'- dimethylamino flavanone. (3b''')

Compound 2b (0.02 mole), 4-dimethylamino benzaldehyde (0.02 mole) were dissolved in 25 ml ethanol and 0.5 ml piperidine added and processed as previous in 3a. m.p. 160°C Yield 60%

13) Synthesis of 4-(2-hydroxy phenyl)-5-benzoyl -6-phenyl-2-imino-6-H-2,3-dihydro-1,3-thiazine. (4a)

Compound 3a (0.01 mole) and thiourea (0.01 mole) were dissolved in 25 ml dry pyridine and refluxed for 4 hrs, after heating cooled at room temperature and poured on 150 ml ice cold water then acidified by dilute HCl yellowish compound 4a separates out crystallized with methanol m.p. 196°C yield 60%

IR(ATR) (cm⁻¹): 3736 (-OH Phenolic str.), 3615 (NH str.), 1757 (N-C=N str.), 1670 (ArCO str.), 1022 (C-S str.).

¹H NMR (CDCl₃): δ 2.2 (s, 1H, NH), δ 4.46 (d, 1H, CH), δ 5.1 (d, 1H, CH), δ 6.56 (s, 1H, -OH), δ 6.68 – 7.89 (m, 14 H, Ar-H).

14) Synthesis of 4-(2-hydroxy-5-methyl phenyl)-5-benzoyl-6-phenyl-2-imino-6-H-2,3-dihydro-1,3-thiazine. (4b)

Compound 3b 0.01 mole and thiourea 0.01 mole were dissolved in 25 ml dry pyridine and refluxed for 4 hrs, after heating cooled at room temperature and poured on 150 ml ice cold water then acidified by dilute HCl yellowish compound 4a separates out crystallized with methanol m.p. 192°C, yield 63%

15) Synthesis of 4-(2-hydroxy phenyl)-5-benzoyl -6 (4-methoxyphenyl)-2-imino-6-H-2,3-dihydro-1,3-thiazine. (4a')

Compound 3a' (0.01 mole) and thiourea (0.01 mole) were dissolved in 25 ml dry pyridine and refluxed for 4 hrs, after heating cooled at room temperature and poured on 150 ml ice cold water then acidified by dilute HCl yellowish compound 4a separates out crystallized with methanol m.p. 186°C, yield 60%

IR (ATR) (cm⁻¹): 3736 (-OH Phenolic str.), 3615 (-NH str.), 1756 (N-C=N str.), 1688 (C=O str.), 1249 (Ar-O-C str.), 1026 (C-S str).

¹H NMR (CDCl₃): δ 2.12 (s, 1H, NH), δ 3.73 (s, 3 H, ArOCH₃), δ 4.51 (d, 1H, CH), δ 5.3 (d, 1H, CH), δ 6.3 (s, 1H, -OH), δ 6.65 – 7.89 (m, 13 H, Ar-H).

16) Synthesis of 4-(2-hydroxy-5-methyl phenyl)-5-benzoyl-6 -(4-methoxyphenyl)-2-imino-6-H-2,3-dihydro-1,3-thiazine. (4b')

Compound 3b' (0.01 mole) and thiourea (0.01 mole) were dissolved in 25 ml dry pyridine and refluxed for 4 hrs, after heating cooled at room temperature and poured on 150 ml ice cold water then acidified by dilute HCl yellowish compound 4a separates out crystallized with methanol m.p. 187°C yield 63%

17) Synthesis of 4-(2-hydroxy phenyl)-5-benzoyl -6 (3,4-dimethoxyphenyl)-2-imino-6-H-2,3-dihydro-1,3-thiazine. (4a'')

Compound 3a'' (0.01 mole) and thiourea (0.01 mole) were dissolved in 25 ml dry pyridine and refluxed for 4 hrs, after heating cooled at room temperature and poured on 150 ml ice cold water then acidified by dilute HCl yellowish compound 4a separates out crystallized with methanol m.p. 182°C yield 60%

IR (ATR) (cm⁻¹): 3736 (-OH Phenolic str.), 3615 (-NH str.), 1756 (N-C=N str.), 1690 (C=O str.), 1213 (Ar-O-C str.), 1024 (C-S str).

¹H NMR (CDCl₃): δ 2.2 (s, 1H, NH), δ 3.72 (s, 6 H, ArOCH₃), δ 4.5 (d, 1H, CH), δ 5.2 (d, 1H, CH), δ 6.0 (s, 1H, -OH Phenolic), δ 6.46 – 7.90 (m, 12 H, Ar-H).

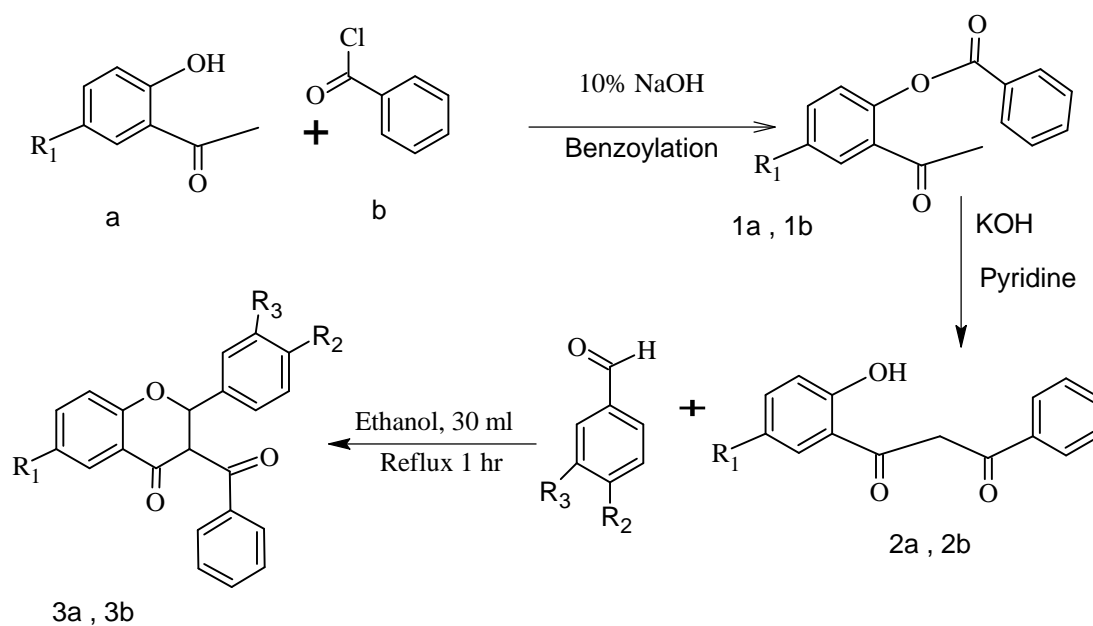
18) Synthesis of 4-(2-hydroxy-5-methyl phenyl)-5-benzoyl-6 -(3,4-dimethoxyphenyl)-2-imino-6-H-2,3-dihydro-1,3-thiazine. (4b'')

Compound 3b'' (0.02 mole) and thiourea (0.02 mole) were dissolved in 25 ml dry pyridine and refluxed for 4 hrs, after heating cooled at room temperature and poured on 150 ml ice cold water then acidified by dilute HCl yellowish compound 4a separates out crystallized with methanol m.p. 183°C, yield 63%

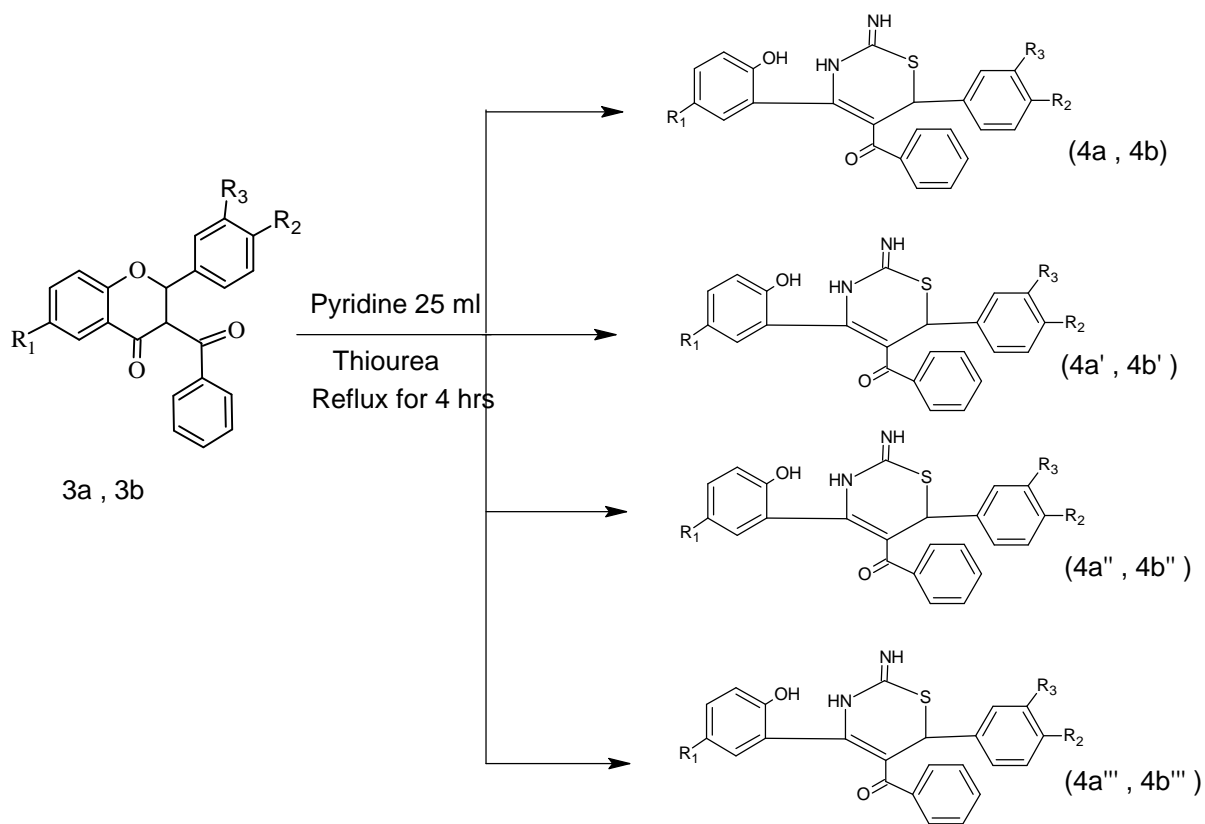
19) Synthesis of 4-(2-hydroxyphenyl)-5-benzoyl-6(4-dimethylphenyl)-2-imino-6-H-2,3-dihydro-1,3-thiazine. (4a''')

Compound 3a''' (0.01 mole) and thiourea (0.01 mole) were dissolved in 25 ml dry pyridine and refluxed for 4 hrs, after heating cooled at room temperature and poured on 150 ml ice cold water then acidified by dilute HCl yellowish compound 4a separates out crystallized with methanol m.p. 172°C yield 60%

Reaction scheme 1



Reaction scheme 2



20) Synthesis of 4-(2-hydroxy-5-methyl phenyl)-5-benzoyl-6-(4-dimethylaminophenyl)-2-imino-6-H-2,3-dihydro-1,3-thiazine. (4b''')

Compound 3b'''' (0.02 mole) and thiourea 0.02 mole were dissolved in 25 ml dry pyridine and refluxed for 4 hrs, after heating cooled at room temperature and poured on 150 ml ice cold water then acidified by dilute HCl yellowish compound 4a separtes out crystallized with methanol m.p. 170°C yield 63%

IR (ATR) (cm⁻¹): 3737 (-OH Phenolic str.), 3615 (-NH str.), 3006(C-H str.) 1756 (N=C=N str.), 1688 (C=O str.), 1213 (Ar-O-C str), 1002 (C-S str.), 1155 (C-N str.).

¹H NMR (CDCl₃): δ 2.2 (s, 1H, NH), δ 2.35 (s, 3 H, ArCH₃), δ 2.86 (s, 6H, N(CH₃)₃) δ 4.47 (d, 1H, CH), δ 5.12 (d,1H, CH), δ 6.2 (s, 1H, -OH Phenolic), δ 6.47 – 7.99 (m, 12 H, Ar-H).

RESULT AND DISCUSSION

The compounds (4a-4a''') and (4b-4b''') were synthesized and screened for their antimicrobial activity against gram positive bacteria *S. aureus* and *S. subtilus* and gram negative bacteria *E.coli* and *P. aeruginosa*. DMSO was used as solvent controle using disc diffusion method. Zones of inhibition were measured in mm are as shown in table -2.

The presence of Phenolic group, Sulphur, Nitrogen the compounds shows antibacterial activity also, with increase in number of hetero atoms the antimicrobial activity increases in the same order for all tested gram positive and gram negative bacteria.

Table – 1, Characterization data of synthesize new compounds

Compound	R ₁	R ₂	R ₃	Molecular formula	M.P. °C	Yield (%)	Rf
4a	H	H	H	C ₂₃ H ₁₈ N ₂ O ₂ S	196	60	0.81
4a'	H	OCH ₃	H	C ₂₄ H ₂₀ N ₂ O ₃ S	186	60	0.82
4a''	H	OCH ₃	OCH ₃	C ₂₅ H ₂₂ N ₂ O ₄ S	182	60	0.80
4a'''	H	N(CH ₃) ₂	H	C ₂₅ H ₂₃ N ₃ O ₂ S	172	65	0.79
4b	CH ₃	H	H	C ₂₄ H ₂₀ N ₂ O ₂ S	192	63	0.83
4b'	CH ₃	OCH ₃	H	C ₂₅ H ₂₂ N ₂ O ₃ S	187	60	0.86
4b''	CH ₃	OCH ₃	OCH ₃	C ₂₆ H ₂₄ N ₂ O ₄ S	183	60	0.85
4b'''	CH ₃	N(CH ₃) ₂	H	C ₂₆ H ₂₅ N ₃ O ₂ S	170	65	0.75

Table – 2

Compounds	Zone of Inhibition (mm)			
	<i>S.aureus</i>	<i>S.subtilus</i>	<i>E.coli</i>	<i>P.aeruginosa</i>
4a	9	10	8	8
4a'	12	13	12	11
4a''	15	18	15	14
4a'''	18	20	17	17
4b	8	7	6	7
4b'	11	9	8	10
4b''	14	11	10	13
4b'''	16	12	11	15

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