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One pot synthesis of 1–(3–methyl–4*H*–benzo [1,4]thiazin–2–yl) ethanone and its antimicrobial properties

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Abstract

A novel 1,4–benzothiazine derivative, 1–(3–methyl–4*H*–benzo[1,4]thiazin–2–yl) ethanone (ATPAC) is synthesized from 2–aminothiophenol and acetylacetone and is characterized by elemental analysis, ^{1}H NMR, IR spectroscopy and electronic spectroscopy. Antimicrobial property of the title compound was determined by MIC using *E. coli*, *V. cholerae* and *C. albicans*.

Keywords: 1,4–benzothiazine, ATPAC, Antimicrobial,

1. INTRODUCTION

Heterocyclic thiazine derivatives are important because they are biological constituents of many biomolecules and drugs [1]. It has been noticed that structural modifications in the thiazine and its derivatives results in valuable medicinal properties that should be further explored through structure activity relationship (SAR) methods for the development of highly potent compounds against multi–drug resistant microorganisms and other diseases. Thus, the research to explore different avenues of chemical modifications of thiazine and its available derivatives to obtain novel active compounds should be continued [2, 3]. They also act as multidentate ligands for different metals due to the presence of nitrogen and sulfur atoms and are thus used extensively in coordination chemistry to obtain new frameworks with potential bioactivity [4]. Several heterocyclic compounds in the developmental phase have the potential to be part of new drugs and also play an important role in modern drug discovery [5]. A large number of thiazine ring containing drugs with versatile type of applications are being used clinically while their chemosensing properties are not explored.

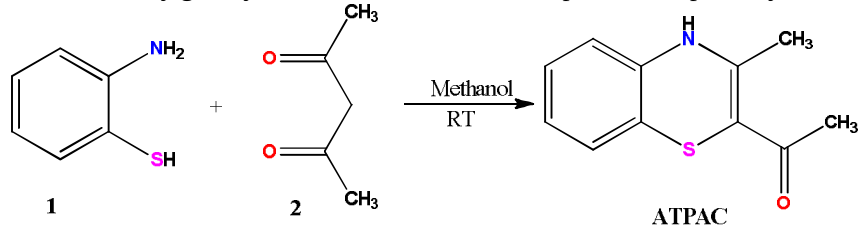
2. EXPERIMENTAL

Synthesis of ATPAC [1–(3–methyl-4H–benzo[1,4]thiazin–2–yl)ethanone]

2–aminothiophenol and acetylacetone were taken in 1:1 stoichiometric ratio and are separately dissolved in methanol. The two solutions mixed together, stirred for 10 minutes and kept aside for two days. Orange red crystals obtained were filtered, washed with ethanol and stored in desiccator.

3. RESULTS AND DISCUSSIONS

A novel 1,4–benzothiazine derivative, [1–(3–methyl–4H–benzo[1,4]thiazin–2–yl)ethanone] is synthesized from the reaction between 2–aminothiophenol and acetylacetone (Scheme 1). Formation of ATPAC in different reaction conditions were explored (Table 1). The reaction was studied: (a) without solvent at room temperature by intimate mixing in a mortar; (b) in ethanol (i) RT, (ii) with heating; (c) in ethanol–acetic acid (i) RT, (ii) with heating; (d) in methanol (i) RT, (ii) with heating (e) in methanol–acetic acid (i) RT, (ii) with heating. The maximum yield was compared and the optimum reaction condition was fixed according to the reaction temperature, time, solvents etc. Under all conditions 1,4–benzothiazine was formed exclusively and the best yield was obtained under RT methanol conditions. Fairly good yields were obtained, with separation of pure crystalline product.

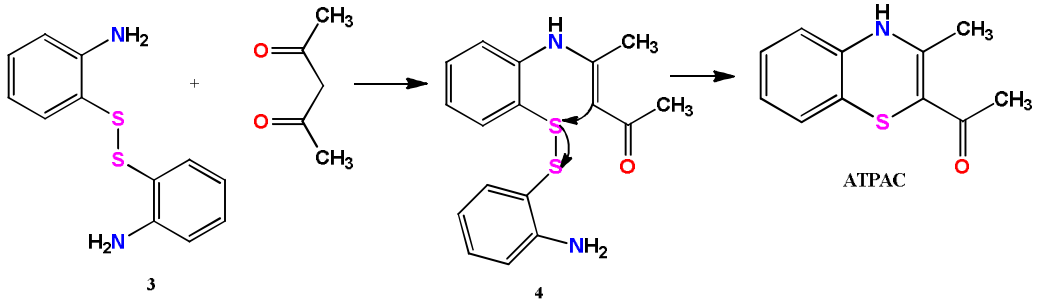


Scheme 1: Formation of ATPAC

Table 1: Reaction conditions and the corresponding yields of ATPAC

Solvents	Reaction conditions		Yield (%)
	Temperature	Time	
Without solvent	RT	2 days	95
Methanol	RT	2 days	**98**
	150 °C	5 hours	95
Ethanol	RT	2 days	70
	150 °C	5 hours	65
Ethanol + Acetic acid	RT	2 days	75
	150 °C	5 hours	80
Methanol + Acetic acid	RT	2 days	85
	150 °C	5 hours	85

The new ring system was obtained *via* oxidative cyclization by reacting a mixture of acetylacetone (**1**) and 2–mercapto aniline (**2**) in methanol at room temperature. Since the 2–mercapto aniline (**2**) readily oxidize to bis(*o*–aminophenyl)disulfide (**3**) under these reaction conditions, the reaction is considered to proceed via an intermediate (**4**), which is readily cyclized by the scission of the sulfur–sulfur bond upon the attack by the nucleophilic enaminone system. The possible mechanism is proposed in Scheme 2.



Scheme 2: Mechanism of oxidative cyclization

The result of elemental analysis and physical properties of ATPAC are given in Table 2. The percentages of C, H, N and S showed close agreement with the molecular formula $C_{11}H_{11}NSO$.

Table 2: Physical and analytical data of ATPAC

Compound	Colour	M. P. (°C)	Elemental percentage Calc. (found)				
			C	H	N	S	O
ATPAC	Orange Red	242	64.077 (64.390)	5.340 (4.890)	6.796 (6.950)	15.530 (15.290)	8.257 (8.480)

IR Spectrum of ATPAC

The benzothiazine, ATPAC exhibit a characteristic peak in the region 3443 cm^{-1}. This shift to a lower frequency suggests the possibility of a strong –NH…O intermolecular hydrogen bond. The IR band observed at 1798 cm^{-1} in ATPAC may be due to carbonyl group. IR spectra of the compound ATPAC is given in Figure 1.

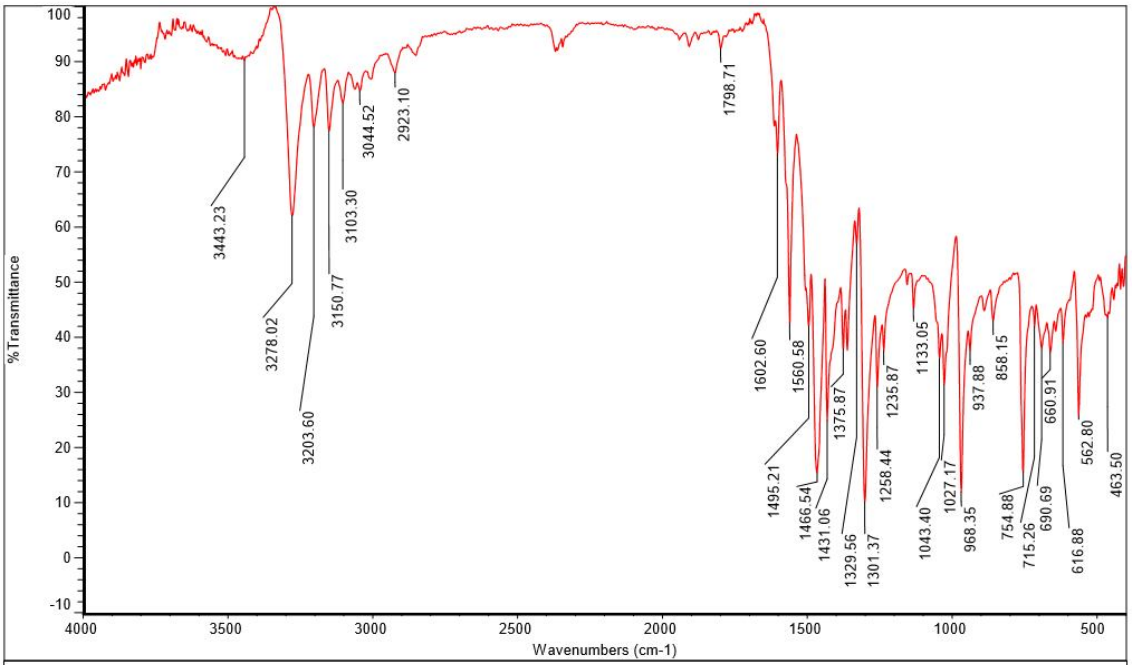


Fig. 1: IR Spectrum of ATPAC

^{1}H NMR Spectrum of ATPAC

In the ^{1}H NMR spectra of ATPAC, we have a signal at 11.100 ppm, which corresponds to the N–H proton frequency. Signals in the range 8.866–9.177 ppm with relative intensities in the rato 1:2:1 represent 4 aromatic protons in the benzene ring. We have another signal at around 4.452 ppm. It is given by methyl protons attached to C=O. Signal at 4.413 ppm also shows the presence of methyl protons, but attached to Nitrogen. The shift in the NMR frequency of two types of methyl protons is due to the presence of electronegative oxygen and nitrogen atoms in the vicinity of methyl protons. There is a sharp signal at around 5.6 ppm which is of DMSO. ^{1}H NMR results agree well with the assigned structure of ATPAC. ^{1}H NMR spectrum of ATPAC is shown in Figure 2.

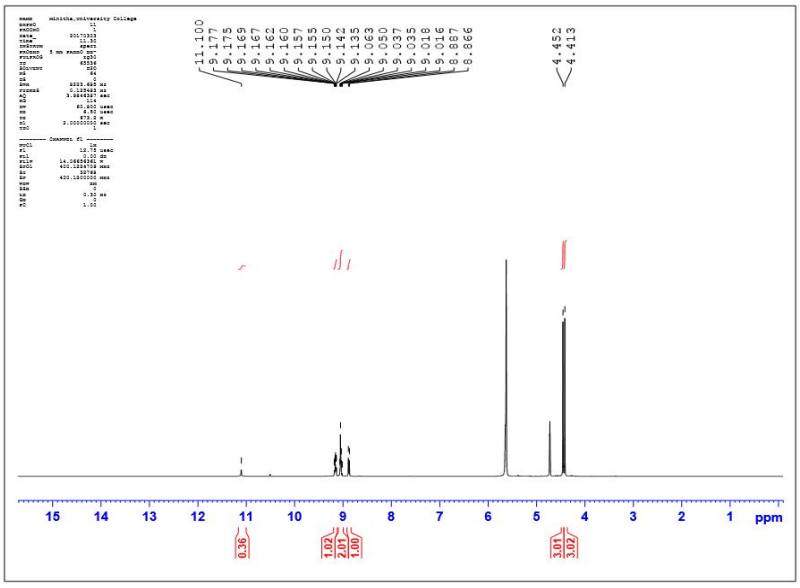


Fig. 2: ^{1}H NMR Spectrum of ATPAC

Electronic spectrum of ATPAC

Electronic spectrum of ATPAC was recorded in acetonitrile (Figure 3). The spectrum of ATPAC shows a relatively weak band at 298 nm, assigned to n→π* transition of the thiazine and carbonyl group. In addition, one strong band also appeared at 220 nm assignable to π→π* transitions, respectively.

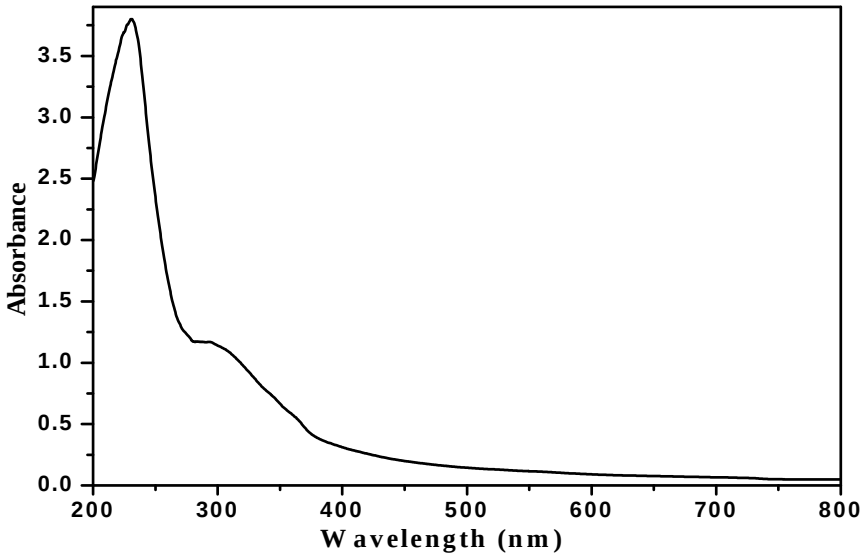


Fig. 3: Electronic spectrum of ATPAC

Antimicrobial properties

The synthesized compound ATPAC is screened for the antimicrobial activities against two bacteria and one fungus. The bacteria used for the study are *Escherichia coli* and *Vibrio cholerae*. The fungus used is *Candida albicans*. The test was performed using the disc diffusion agar technique. The minimum inhibitory concentration (MIC) is determined by different concentrations such as 100%, 75%, 50% and 25%. The activity was compared with known antibiotic Erythromycin. The results are tabulated in Table 3. Photographs showing antimicrobial activities are given below.

The antimicrobial activity results show that the synthesized ATPAC is active only against *V. cholera* and is inactive towards *E. Coli* and *C. Albicans*. The MIC value for *V. Cholerae* is 50%.

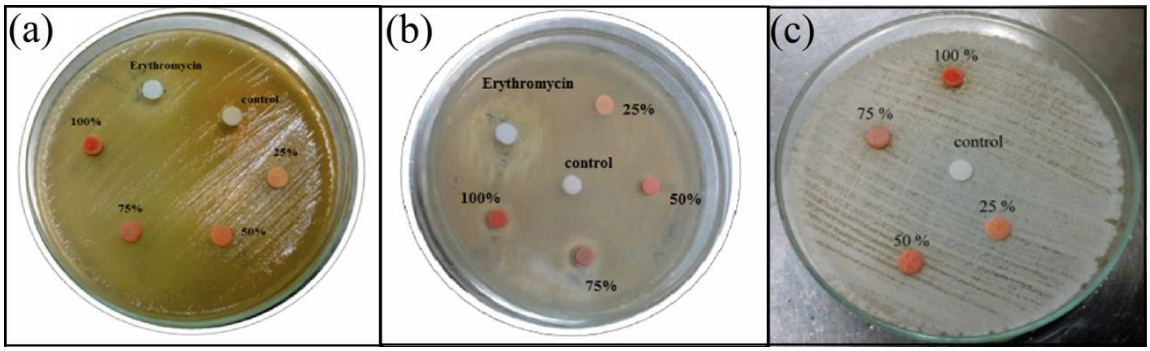


Fig. 4: Antimicrobial activity against (a) *E. Coli* (b) *V. Cholera* and (c) *C. Albicans*

Table 3: Antimicrobial activity of ATPAC

Organism	Zone of inhibition in mm					
	100%	**75%**	**50%**	**25%**	**Control**	**Erythromycin**
E. coli	NZ	NZ	NZ	NZ	NZ	12
V. cholerae	13	10	8	NZ	NZ	18
C. albicans	NZ	NZ	NZ	NZ	NZ	–

NZ: No Zone

4. CONCLUSIONS

An 1,4–benzothiazine derivative was synthesized from 2–aminothiophenol and acetylacetone by oxidative cyclization reaction. Different reaction conditions are chosen to optimize the best reaction condition which gives the maximum yield and it was observed that reaction carried out in methanol at room temperature produced an yield of 98%. The synthesized compound was characterized by means of elemental analysis, FT–IR, ^{1}H NMR and electronic spectroscopy. The compound is active against the bacteria *V. cholera* with MIC 50%. Thus, the acetylacetone based benzothiazine provided good antibacterial agent for *V. cholerae*.

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