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Research Article

Synthesis of Some 1, 3 - Benzothiazine-4-ones as Potential Antitubercular Agent

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Abstract: 1, 3-benzothiazin-4-ones moieties are a class of compounds that could be formed through Schiff base adducts and are known to exhibit anti-tubercular activity. 1, 3-benzothiazin-4-ones derivatives were synthesized through Schiff base adduct that were formed using environmental friendly solvents such as water and ethanol and the evaluation of their antibacterial and antifungal activities were investigated. The Schiff bases derivatives in this work were synthesized by condensation reaction between aromatic amines and aromatic carbonyl compounds at reflux temperature while the resulting Schiff bases derivatives were then coupled with thiosalicylic acid to obtain new interesting heterocyclic system (1, 3-benzothiazin-4-ones derivative).The progress of the reaction was monitored by Thin Layer Chromatography. The compounds synthesized were characterized by determining their corresponding uncorrected melting points and structural elucidation carried out by spectroscopic methods (UV, IR, H^1 NMR) and elemental analysis. The Schiff bases and the 1,3-benzothiazin-4-ones were screened for antibacterial and antifungal activities using agar well diffusion method at various concentration of 2.5, 5, 10, 15 and 20 mg/mL against clinical isolates of *Escherichia coli (E. coli), Pseudomonas aeruginosa (P. aeruginosa), Bacillus subtilus (B. subtilus), Klebsillia (K. pneumonea), Staphylococcus aureus (S. aureus),Candida albican (C. albican).*Results obtained showed good yield as well as good antimicrobial activity when compared to regular antibiotics such as Ciprofloxacin and Ketocozole which could just set the stage for anti- tubercular studies to be undertaken on the compounds synthesized**.**

Keywords: (1, 3-benzothiazin-4-ones derivative), (UV, IR, and H1 NMR), Chromatography.

INTRODUCTION

Tuberculosis (TB) is a chronic infectious disease caused by *Mycobacterium tuberculosis* (MTB) and it has been a serious problem to mankind, its treatment has become a major challenge. Death caused by TB in most developing countries is attributed to the emergence of Multi-drug resistant (MDR) strains of *Mycobacterium tuberculosis* and extensively drug resistant tuberculosis (XDR-TB) (Basu *et al.,* 2007).

Word Health Organisation (WHO) estimated that approximately one third of the world's population is infected with MTB and also reported that HIV and TB co-infection results to death within a few months of clinical symptoms (Anderson *et al.,* 2015 and Dony *et al.*, 2004).

First-line drug (FLD) and second-line drug (SLD) are drugs of choice for treatment of TB. FLD includes Ethambutol (ETB) -**1**-, Isoniazid (INH) -**2**-, and Pyrazinamide (PZA) -**3**-. SLD are used to treat TB diseases that are resistance to FLD and examples are Fluoroquinolones (FQs) -**4**-, *P*-aminosalicyclic acid (PAS) -**5**-, Ethionamide (ETH) -**6**-, Cycloserine (CS) -**7**- (Zhang *et al.,* 1992 and Marion *et al.,* 2011, Mohammed *et al.,* 2015).

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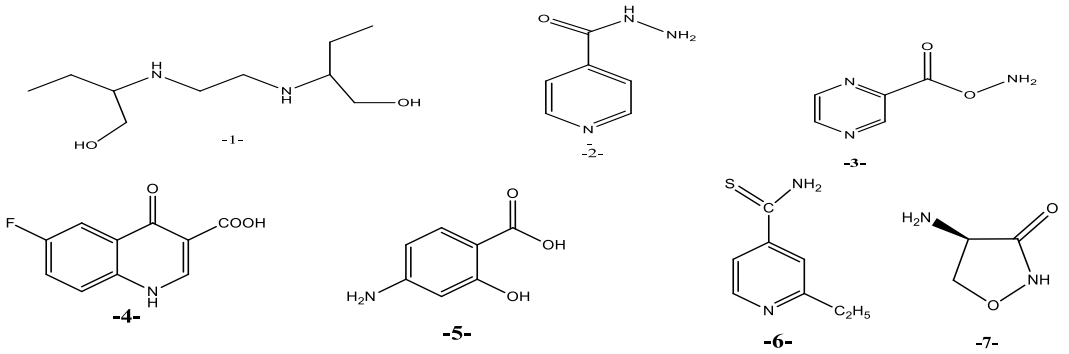


Fig.1. Structure of FLD and SLD anti-TB Agents

Mycobacterium tuberculosis that are resistance to treatment with FLD is referred to as Multi-drug ressistance tuberculosis (MDR-TB) and those resistance to SLD and any other combination drugs are called extensive drug resistance tuberculosis (XDR-TB). Current Drugs of choice for MDR-TB and XDR-TB are Linezolid -**7**-, Sutezolid -**7a**-, Bedaquiline -**8**- and Delamanid -**9**-.

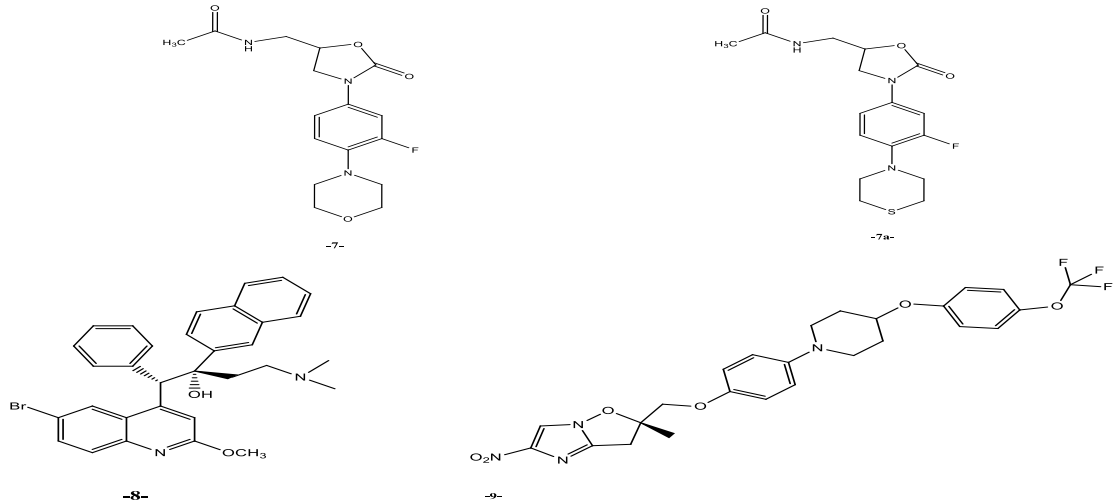


Fig. 2: Structure of MDR-TB and XDR-TB drugs

1,3 - benzothiazine-4-one is a bicyclic structure which contains thiazine-4-one combined with an aromatic benzene ring as shown below.

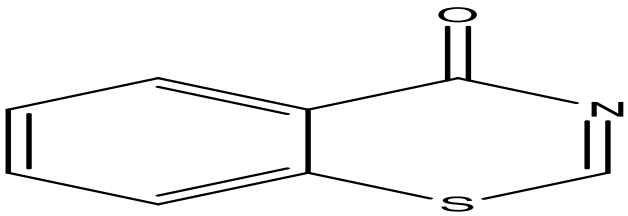


Fig. 3: Typical structure of 1, 3 -Benzothiazine-4-ones

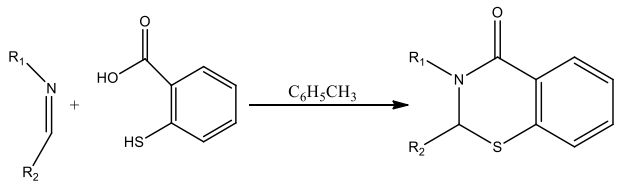
1, 3-benzothiazine-4-one core structure have been reported to possess a broad spectrum of biological activities such as antiproliferative (Kamel *et al.,* 2010), antibacterial (Gao *et al.,* 2013), anti-inflammatory (Zarghi *et al.,* 2009) and antiviral activity mainly against HIV virus (Mizuhara *et al.,* 2012). Literature search showed that the structure and modification attracts great interest in medicinal and pharmaceutical chemistry. For example 3-amino-7-chloro-9-(20-methylphenyl)-1,9-dihydropyrazolo-[4,3-b]benzothiazine-4,4- dioxide and 2,4-diamino-8-chloro-10H-phenyl-pyrimido-[5,4-b]benzothiazine -5,5-dioxide were investigated and found to inhibit β -hematin formation, haemoglobin hydrolysis and *in vivo* for antimalarial activity in rodent *Plasmodium berghei* (Barazarte *et al.,* 2008).

Kaneko *et al.,*, 2002 in their work investigated a new series of 10H-pyrazino[2,3-b][1,4]benzothiazine derivatives then synthesized *N*-[1-(10*H*-pyrazino [2,3-*b*] [1,4] benzothiazin-8-ylmethyl)-piperidin-4-yl]-*N*',*N*'-dimethylsulfamide which was found to be potent oral inhibitor of neutrophil migration in a murin interleukin-1 induced paw inflammation model.

Whereas Hori *et al.,* 1973 reported the synthesis of 1,3-benzothiazine-4-one derivatives *via* condensation of *α*-aminothiophenole (α-ATP) and ketonic compound to produce dehydrobenzothiazole which further undergo intermolecular cyclization in the presence of sulfonyl chloride to afford 1,4-benzothiazine derivatives **.** Then Barange *et al.,,* 2007 also carried out a similar reaction between α-ATP and α-halocarbonyl system to afford benzothiazine derivatives.

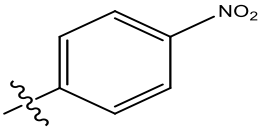
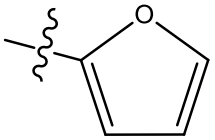
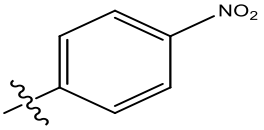
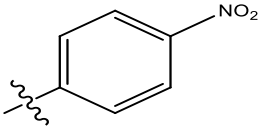
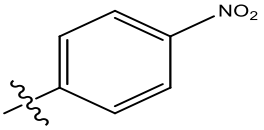
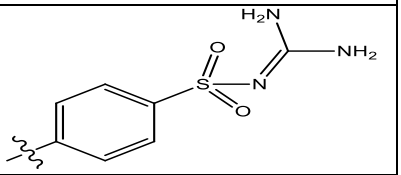
MATERIALS AND METHODS:

Evaluation of compounds: Structures were confirmed by ^{1}H-NMR using JOEL Lambda 400 spectrometer and an internal standard of TMS was used, while purity was determined by Thin Layer Chromatography (TLC) (E. Merck Kieselgel 60 F254). Melting point (uncorrected) was determined using Gallenkamp melting point machine. General synthesis of 1,3 -Benzothiazin-4-ones were achieved by the condensation reaction of aromatic amines and aromatic carbonyl compounds at 60 ^{0}C in ethanol to produce a Schiff base intermediate which were then coupled with thiosalicylic acid in toluene at reflux temperature to produce 1,3-Benzothiazin-4-ones and its derivatives.



Scheme 1: Reaction scheme for synthesizing 1, 3 -benzothiazine-4-one derivatives

Table 1: Showing various substituents used in the reaction.

Compound	R_1	R_2
AB-001. 2-(furan-2-yl)-3-(4-nitrophenyl)-2H-benzo[e][1,3]thiazin-4(3H)-one		
AB-002 2-methyl-2,3-bis(4-nitrophenyl)-2H-benzo[e][1,3]thiazin-4(3H)-one		
AB-003 N-(diaminomethylene)-4-(2-methyl-4-oxo-2-phenyl-2H-benzo[e][1,3]thiazin-3(4H)-yl)benzenesulfonamide		

Synthesis of 2-(furan-2-yl)-3-(4-nitrophenyl)-2H-benzo[e][1,3]thiazin-4(3H)-one (compound AB-001)

N-(furan-2-ylmethylene)-4-nitroaniline (2.16 g, 0. 01 mol.) in anhydrous toluene (15 ml), was added thiosalicylic acid (1.54 g, 0.01 mol. The reaction was stirred and heated at reflux temperature for 6 hr. TLC was used to monitor the reaction hourly. The reaction was then allowed to cool to room temperature and then left to stand overnight and solvent was removed *in vacuo.* 10 % sodium hydrogen carbonate solution (10 ml) was thereafter added and allowed to stand overnight. The resultant brown precipitate formed was filtered and dried in a desiccator over silica gel. The crude product was then recrystallized from ethanol and dried over silica gel in a desiccator to provide compound AB-001.

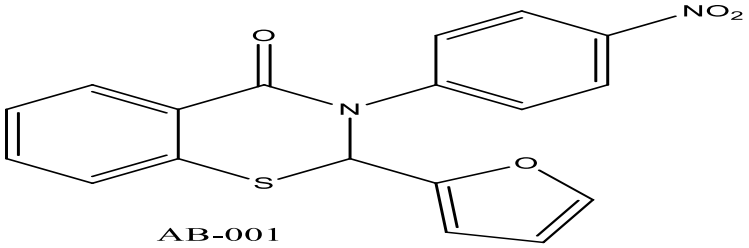
Synthesis of 2-methyl-2, 3-bis (4-nitrophenyl)-2H-benzo[e][1,3]thiazin-4(3H)-one (compound AB-002)

The procedure above was employed, but a mixture of 4-nitro-N-(1-(4-(nitrophenyl)ethylidene)aniline (2.85 g, 0.01 mol.) in anhydrous toluene was used and this provided compound AB-002.

Synthesis of N-(diaminomethylene)-4-(2-methyl-4-oxo-2-phenyl-2H-benzo[e][1,3]thiazin-3(4H)-yl)benzenesulfonamide (compound AB-003)

The same procedure as reported above was employed, but a mixture of N-(diaminomethylene)-4-(2-methyl-4-oxo-2-phenyl-2H-benzo[e][1,3]thiazin-3(4H)-yl)benzenesulfonamide (3.31 g, 0.01 mol.) in anhydrous toluene, was used to afford compound AB-003.

RESULTS

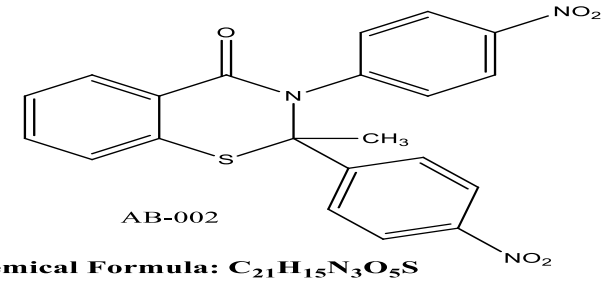


AB-001

Chemical Formula: $C_{18}H_{12}N_2O_4S$
Molecular Weight: 352.36

2-(furan-2-yl)-3-(4-nitrophenyl)-2H-benzo[e] [1,3]thiazin-4(3H)-one (AB-001)

Yield: 60 %. Colour: (Brown), R_f : 0.74 Hex : EtOAC (4 : 1)}, mp: 187-190 ^{0}C, UV(Methanol) λ_{max} : 320, 580, 600, 780. IR(KBr) $V_{max/cm-1}$: 687 (C-S), 853 (C=C-H), 1102 (C=C-O), 1307 (C=C), 1414 (C-N), 1507 asy., 1340sym (O=N=O),1660 (C=O), 3101 (C-H). ^{1}H NMR ($CDCl_3$, 400MHz) δ (ppm): 3.29 (s, CH), 5.72 (d, J=1.4 Hz, Ar-H), 6.51-6.70 (m, Ar-H), 7.32 - 7.43 (m, Ar-H), 7.55 (d, J=0.9 Hz, Ar-H), 8.28 (dd, J=8.7 Hz, 1.8, Ar-H), 9.54 (s, Ar-H). Calculated: C (61.35 %), H (3.43 %), N (7.95 %), O (18.16 %), S (9. 10%). Found: C (61.30 %), H (3.45 %), N (7.92 %), O (18.20 %), S (9.13 %).

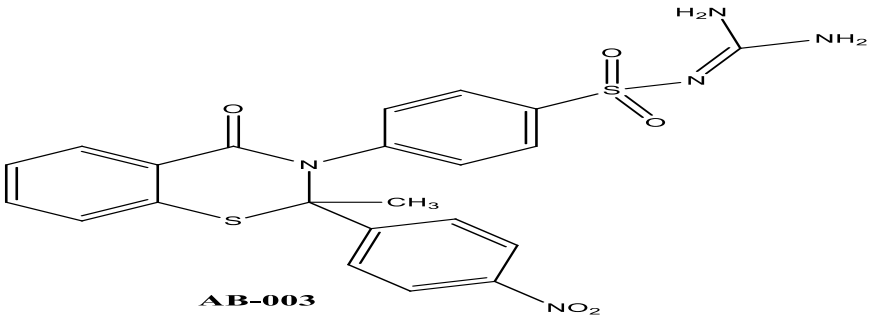


AB-002

Chemical Formula: $C_{21}H_{15}N_3O_5S$
Molecular Weight: 421.43

2-methyl-2, 3-bis(4-nitrophenyl)-2H-benzo[e] [1,3]thiazin-4(3H)-one (compound AB-002)

Yield: 85 % Colour (Brown), R_f : 0.68 {Hex : EtOAC (7:3)}, mp: 174-175 ^{0}C, UV(Methanol) λ_{max} : 320, 560, 620, 780. IR (KBr) $V_{max/cm-1}$: 3403 (-OH),1643 (C=O). ^{1}H NMR ($CDCl_3$, 400MHz) δ (ppm): 3.30 (s, CH_3), 5.64 (s, Ar-H), 6.49 – 6.52 (m, Ar-H), 7.33-7.43 (m, Ar-H). Calculated: C (59.85 %), H (3.59 %), N (9.97 %), O (18.98 %), S (7.61 %). Found: C (59.80 %), H (3.65 %), N (9.80 %), O (18.96 %), S (7.79 %).



AB-003

Chemical Formula: $C_{22}H_{19}N_5O_5S_2$
Molecular Weight: 497.55

Synthesis of N-(diaminomethylene)-4-(2-methyl-4-oxo-2-phenyl-2H-benzo[e][1,3]thiazin-3(4H)-yl)benzenesulfonamide (compound AB-003)

Yield: 95 %, R_f : 0.76 {Hex: EtOAC (3:2)}, mp: 140-142 ^{0}C. UV $_{(MeOH)}$ λ_{max} : 320, 600, 780. IR (KBr) $V_{max/cm-1}$: 685 (C-S), 826 (C=C-H), 1307 (O=S=O), 1686 (C=O), 3220 (C-H), 3409 (N-H). ^{1}H NMR ($CDCl_3$, 400MHz) δ (ppm): 3.29 (d, J=5 Hz, Ar-H), 3.29(d, J=5, Ar-H). Calculated: C (53.11 %), H (3.85 %), N (14.08 %), O (16.08 %), S (12.89 %). Found: C (53.10 %), H (3.80 %), N (14.00 %), O (16.18 %), S (12.92 %).

Table 2: Zone of Inhibition of compounds at 20 mg/ml against standard isolates

Compound	E. Coli	P. aeruginesa	B. subtilus	K. pneumonia	S. aureus	C. albician
AB 001	30	-	-	-	-	-
AB 002	-	10	25	-	-	12
AB 003	-	-	-	-	40	18
Ciprofloxacin	28	20	20	-	-	-
Ketocozole	-	-	-	-	-	22
DMSO	-	-	-	-	-	-

Table 3: Minimum inhibitory concentration at 2.5 mg/ml

Compound	E. coli	P. aeruginosa	B. subtilis	K. pneumoniae	S. aureus	C. albican
AB 001	+	+	+	+	+	+
AB 002	+	+	+	+	+	+
AB 003	+	+	+	+	+	+
Ciprofloxacin	-	-	-	-	-	-
Ketoconazole	+	+	+	+	+	+

DISCUSSION

1,3-Benzothiazin-4-ones were synthesized by first forming a precursor intermediate of Schiff base through the condensation reaction of aromatic amines and aromatic carbonyl compounds, which then made to couple with thiosalicylic acid to form the bicyclic compounds known as benzothizin-4-ones. The results obtained showed that the benzothiazin-4-ones may have been formed when the electron rich thiol group in an anchimeric assistance type reaction attack the nitrogen centre of the imine intermediate of the Schiff base thereby forming the bicyclic thiazinone compound. The spectral data confirms the formation of the proposed structures in this work.

The UV data of the bicyclic compounds showed the disappearance of the conjugation in the Schiff bases that showed maximum absorption at 380 – 420 nm. The absorption was recorded at 300 nm showing an hypsochromic shift. Similarly the appearance of multiplet around the aromatic region in the ^{1}H-NMR data points towards the formation of the bicyclic aromatic rings.

Our synthesized 1,3-benzothizin-4-ones have similar bicyclic structures to fluoroquinones -4- and Bendaquinones -8- which are potent antitubercular agents. More so the comparative studies of the antimicrobial screening indicates that our compound AB001 has very good effect against E.coli which is comparative to Ciprofloxacin, while our AB 002 has comparative effect to Ciprofloxacin against P. aeruginosa and B. subtilis. AB 003 was very active against S. aureus which none of the standards were active against. This indicate that our AB 003 is more active against S. aureus type of infections over Ciprofloxacin and Ketocozole. On the other hand AB 002 and AB 003 were similar to Ketocozole against C. albican.

Therefore an inference maybe drawn that 1,3-Benzothiazin-4-ones could be very good antimicrobial agents and may just possess some antitubercular activity if similarity of structure to -4- and -8- are anything to go bye as it has always been the case in isosterism chemistry.

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