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Design, Synthesis, Characterization and Biological Evaluation Of 6-Methoxy-2-aminobenzothioate Derivatives Against Certain Bacterial Strains

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Abstract

The current work reports the synthesized and biological evaluation of 6-methoxy-2-amino benzothiazole (A1), which was prepared via reaction p-Ansidine with ammonium thiocyanate followed by the oxidative ring closure of the resultant thiourea with a catalytic amount of bromine, in the alkaline medium. The resulting compound (A1) underwent condensation reactions with various kinds of aldehydes to produce Hydrazones (A3a-e). 6-methoxy2-hydrazinobenzothiazole (A2) was prepared through the reaction of the compound (A1) with 99.9 % hydrazine hydrate in the presence of concentrated HCl and ethylene glycol solution. After that, the compound (A2) was reacted with ethyl acetoacetate in alcohol to yield corresponding pyrazole-6-methoxybenzothiazole (A4). Moreover, the compound (A2) was reacted with 4- substituted aromatic aldehydes in absolute ethanol to create Hydrazones (A5a-d). Synthesized compounds were investigated as anti-bacterial activity against five microorganisms: (Gram-positive: *Bacillus subtilis & Staphylococcus aurea),* (Gram-negative: *Pseudomonas aeruginous Escherichia coli and Enterobacter*)

Keywords: 6-methoxy-2-amino-benzothiazole, anisidine, anti-bacterial, Schiff base**,** heterocycles

Introduction

2-Aminobenzothiazole is an aromatic organic compound with a molecular formula $C_7H_6N_2S$, a phenyl ring fused thiazole ring structure. [1].Several 2-Aminobenzothiazole derivatives play a significant role in the medicinal and pharmaceutical chemistry fields because of its synthetic utility and a wide spectrum of biological activities. [2-3].

Recently, the number of organic researches has been expanded rapidly for preparation heterocyclic ring system containing of sulfur and nitrogen.

They showed different synthetic derivatives of 2-Aminobenzothiazole and their derivatives have different biological activities and pharmacological like anti-bacterial anti-viral [4], anti-microbial[5], fungicidal activities[6], anti-cancer activity[7], anti-ulcer[8], anti-histaminic[9], anti-inflammatory activity[10], analgesic[11], anti-conversant, anti-diabetic[12], anthelmintic [13], anti-biotic[14], anti-helminthic[15], anti-tumor[16], anti-tubercular[17], antidepressant[18], anti-HIV agents [19], Anti-malarial [20]and diuretic[21]., anti-pyretic properties [22]anti-proliferative [23]. Schiff's bases system an essential kind of compounds in chemistry, pharmaceutical and medicinal [24] with some biological applications which involve anti-bacterial [25], anti-tumor, anti-fungal [26], anti-inflammatory, anti-malarial [27] anti-cancer, ant tubercular [28], and herbicidal [29], activities.

The nucleus of 2-aminobenzothiazole is current in compounds aimed to evaluating new compounds that possess biological activities. This work including synthesis of 5-methoxy -2-aminobenzothiazole, via treatment of *p*-Methoxy aniline with ammonium thiocyanate in G.A.A in presence of Br_2. and aqueous ammonia as a base under ice conditions, scheme (1).

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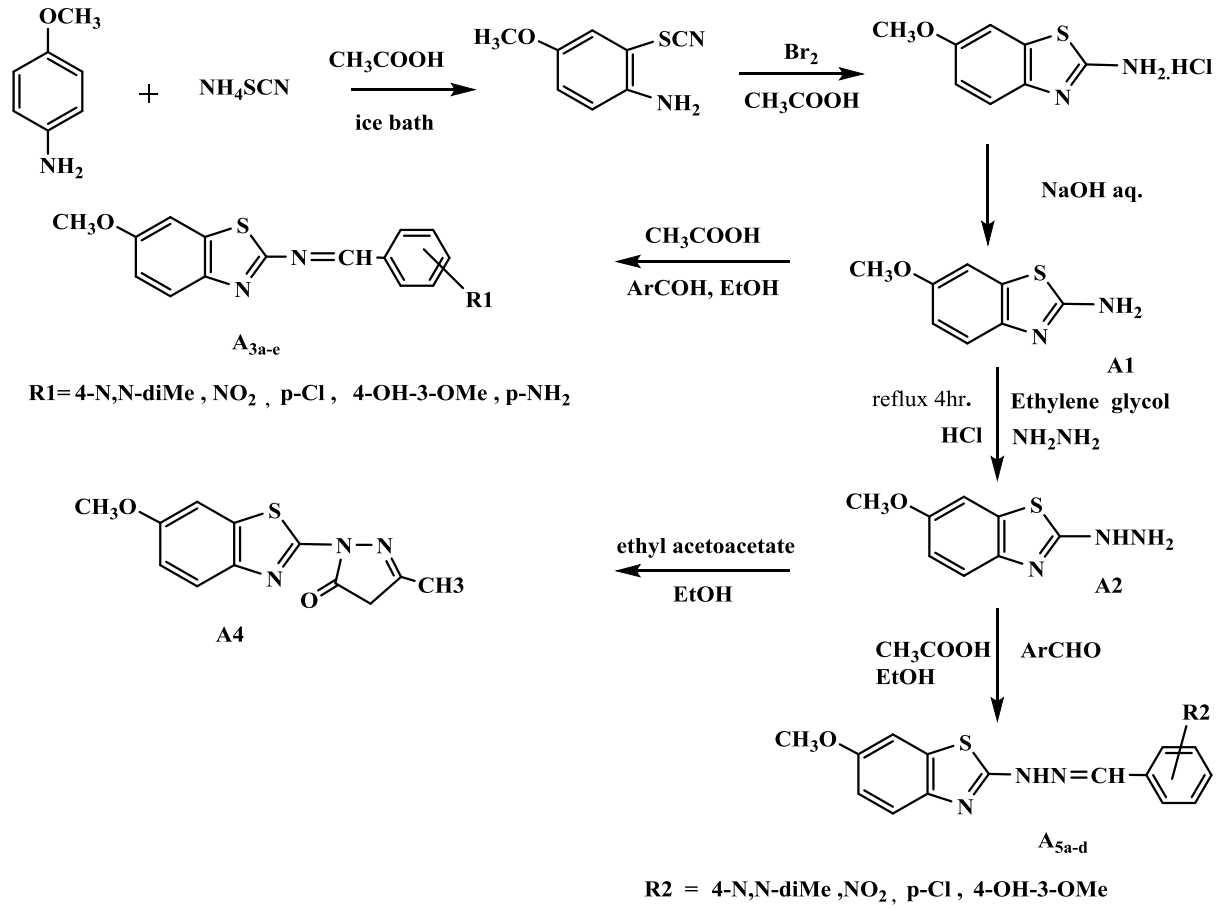

SCHEME -1

Experimental

Material and Methods

The melting points were established by V.-Scientific Melting Point apparatus in open capillary tubes and were uncorrected. 1H-NMR spectra were recorded on 500 MHz spectrometer Bruker using (DMSO), FTIR-8400 Prestige-211 Shimadzu spectrophotometer shows different levels of vibration for molecules by using KBr disk. Elemental analyses were performed using Perkin-Elmer Series 2400.

Synthetic Procedures

Synthesis of 6-methoxy-2-aminobenzothiazole (A1) [30]

A solution of *p*- methoxy aniline (0.085 mol, 10.6 g) in glacial acetic acid (40 ml) was added to ammonium thiocyanate (0.308 mol) was dissolved in glacial acetic acid (75 ml). Then the mixture was cooled to 0 ^{o}C and Bromine (6.5 ml) dissolved in (30 ml) glacial acetic acid was added drop wise during 30 minutes with constant stirring. The temperature falls between (0 ^{o}C &10 ^{o}C). Then the mixture was stirred below 25 ^{o}C for 8hrs. The contents solution was allowed to stay overnight in the freezer. Hot water (20 ml) was added to the obtained precipitate. Then the reaction mixture was heated to (85-90 ^{o}C) and filtered. The brown precipitate was treated with glacial acetic acid (15ml) heated to 90 ^{o}C in a conical flask and filtered. Then the cooled filtrate was neutralized with ammonium hydroxide to pH (6.0-7.0). A light brown crystals was collected, treated with charcoal and washed with ice water to giving bright brown crystals of compound (A1) ,(9.2 g. 85 %), m. p 165-167 ^{o}C . $C_8H_8N_2OS$, FT.IR (KBr) ν max (cm^{-1}): (3390, 3259) (N-H), 1460 (aromatic C=C), 1325(aromatic C-N), 1245(C-S) ;^{1}HNMR (DMSO-d_6, 500 MHz.) (δ , ppm): 7.10(s, 2H, NH_2), 3.60 (s, 3H, OCH3),7.50-7.70 (m, 3H, Ar-H).

Synthesis of 2-Hydrazino-6-methoxybenzothiazole (A2) [31]

A concentrated solution of HCl (1ml) was added drop wise to hydrazine hydrate (1ml,99.9 % - ,0.2mol.) at (0-10)℃ ,then (25ml) of ethylene glycol, to the solution compound(A2) (0.01mol, 1.80g) was added in shares .After the addition was completed. It was stirring for 15min. It was heated on the steam bath for 6 hours, cooled and then poured into (100 ml) of ice distilled water. The formed crystals was separated and dried in a vacuum then was recrystallized by ethanol. The solid (1.31 g ,70 %), m.p.: (224–225) ^{o}C ; $C_8H_9N_3OS$, (FT-IR (KBr) ν max (cm^{-1}) : 3340 (NH-NH),3145 (Ar-H); 1635 (N=CH);^{1}HNMR (DMSO-d_6, 500 MHz) (δ,ppm) 6.70 -7.80 (m, 3H, Ar-H), 9.41 (s,1H, NH), 3.10 (s, 3H, C-OCH3), 4.80(s, 2H, NH_2), 9.8 (s, 1H, -NH-).

Synthesis of 2-(4- Substituted benzylidene) amino-6-methoxybenzothiazole (A3a-e) [32]

A mixture of 6-methoxy-2-aminebenzothiazol (A2) (0.01mol,1.80g) and para substituted benzaldehydes (0.01mol) were dissolved in alcohol (20 ml) with drops of glacial acetic acid & then heated with stirring on water bath at temperature 80°C for 4hrs. and then the mixture was cooled to room temperature and poured into ice and stirred with magnetic stirrer for 1hrs.The formed precipitate was separated and then recrystallization by using warm 10 % aqueous ethanol.

2-(4- N, N`-Di methyl amino benzylidene) amino -6-methoxybenzothiazole (A3a)

It is orange solid (1.4g, 81 %); Anal. Calcd. for $C_{17}H_{17}N_3OS$, m.p:50-52 ^{o} C; FT.IR (KBr) ν max (cm^{-1}) :3261(NH),3078 (Ar-C-H),1645(N=CH);1620 (C=C); ^{1}HNMR (DMSO-d_6, 500MHz.) (δ,ppm) 3.30 (s,3H, OCH_3), 2.80 ($N(CH_3)2$) (s, 6H, CH_3), 7.20 (s,1H, N=CH) ,(6.30 - 7.90) (m , Ar-H).

2-((4-nitrobenzylidene) amino-6-methoxybenzothiazole (A3b)

It is yellow solid (1.39 g, 83 %); Anal. Calcd. for $C_{15}H_{11}N_3O_3S$,m.p: 170-173 ^{o} C; FT-IR(K Br) ν max cm^{-1} :3250 (NH), 3070(Ar-H), 1642 (N=CH); 1624 (C=C);^{1}HNMR (DMSO-d_6 , 500 MHz.) (δ, ppm) 3.5 (s, 3H, OCH_3), 8.04 (s, 1H, N=CH), (7.38 - 7.10) (m , Ar-H).

2-((4-chlorobenzylidene) amino-6-methoxybenzothiazole (A3c)

It is white solid (1.4 g, 78 %) Anal. Calcd. for $C_{15}H_{11}ClN_2OS$; m.p.: 198-200 ^{o} C; FT.IR (K Br) ν max cm^{-1}:3261(NH),3073 (Ar-H) 1645 (N=CH); 1627 (C=C),^{1}HNMR(DMSO-d_6 ,500 MHz.) (δ,ppm) 3.5 (s,3H, OCH_3), 7.46 - 7.10 (m , Ar-H) 8.04 (s, 1H, N=CH).

2-((3-hydroxy-4-methoxybenzylidene) amino-6-methoxy benzothiazole (A3d)

It is Pale yellow solid (1.38 g, 81 %) Anal. Calcd. for $C_{16}H_{15}N_3O_3S$; m.p: (100-102) ^{o}C; FT-IR (K Br)ν max (cm^{-1}) : 3430 (NH),3054 (Ar-H),1623(C=C) 1641 (N=CH; ^{1}HNMR (DMSO-d_6 ,500 MHz.), (δ,ppm) 3.45 (s, 3H, OCH_3), (7.65-7.23) (m,Ar-H)10.24 (s,H,OH), 8.10 (s, 1H, N=CH).

2-((1-(3-aminophenyl) ethylidene) amino -6-methoxybenzothiazole (A3e)

It is white solid (1.4 g , 78 %), Anal. Calcd. for $C_{16}H_{15}N_3OS$; m.p. 88-90 oC; FT.IR (K Br)ν max (cm^{-1}) :3276 (NH),3054 (Ar-H), 1648 (N=CH); 1643 (C=C;1HNMR (DMSO-d_6, 500 MHz.) (δ, ppm): 3.53 (s, 3H, OCH_3), 8.04 (s,1H, N=CH), (7.65- 7.23) (m , Ar-H).

Synthesis of 2-(benzothiazol-2-ylthio) -5-methyl-2,5-dihydro-1H-pyrazol-3-ol (A4)

A mixture of 2-hydrazino-6-methoxy benzothiazole (A2), (1.80 g, 0.04mol) and acetoethyl acetate (0.52 g ,0.04mol) were dissolved in (15 ml) of alcohol& then it was stirring at temperature 25° C for 15min. The solution was reflexed on a steam bath for 7h.then concentrated to a light red precipitates which was recrystallized from ethanol, The yield (1.36 *g* ,77 %), $C_{12}H_{11}N_3O_2S$, m. p.= 158-160 ^{o} C.; (FT.IR (K Br) ν max ,cm^{-1}:3065 (Ar-H); 1645 (C=O), 1595 (C=C);1HNMR (500 MHz, DMSO-d6) (δ, ppm.), 3.70 (s,3H, OCH_3), (7.40-8.60) (m, Ar-H), 3.50 (s, 2H, $-CH_2$), 2.80 (s, 3H, $-CH_3$), 11.30 (s,1H,-OH tautomer) .

Synthesis of 2-(4-substituted benzylidene) hydrazineyl) -6-methoxybenzo[d]thiazole (A5a-d)

6-methoxy-2-Hydrazinobenzothiazole (A4**)**, (0.01 mole,1.95g) was mixed with various benzaldehydes (0.01 mol) in methanol (25ml) ,acidified with 2-5 drops of (G.A.A) glacial acetic acid and reflexed on a steam bath for 3hrous.Then the resulted solution was poured onto water ice and was kept over-night at 25^{o} C. The resulting that separated was filtered, and then washed with cool water, dried and recrystallization from pure ethanol.

2-(2-(4 -N, N- Dimethylbenzylidene) hydrazineyl) -6-methoxybenzo[d]thiazole (A5a)

It is orange solid (1.29 g 85 %); m.p.:247-249 ^{o} C; FT-IR (KBr) ν max, (cm^{-1}): 3295 (NH), 3089 (Ar-H), 1645 (N=CH); ^{1}HNMR (DMSO-d_6, 500 MHz.) (δ, ppm.), 3.40 (s,3H, OCH_3), 2.50 (s,6H, $-N(CH_3)_2$), (7.10 -7.20), (m , Ar-H), 7.50 (s, 1H, N=CH), 12.20 (s, 1H, NH**)**.

2-[2-(4-Nitrobenzylidene)hydrazineyl]-6-methoxybenzo[d]thiazole (A5b)

It is yellow solid (1.35g, 85 %) Anal. Calcd. for $C_{15}H_{12}N_4O_3S$; m.p.: (253-256) ^{o} C; FT-IR (KBr) ν max (cm^{-1}):3287 (NH),3075 (Ar-H) , 1655

(N=CH);[1]HNMR (DMSO-d_6 , 500 MHz) (δ, ppm.), 3.36 (s,3H, OCH_3), (7.80 -7.10) (m , Ar-H), 8.20 (s, 1H, N=CH) , 9.80 (s, 1H, NH**).**

2-(2-(4-chlorobenzylidene) hydrazineyl)-6-methoxy-benzo[d]thiazole (A5c)

It is white solid (1.37g ,75 %),Anal. Calcd. for $C_{15}H_{12}ClN_3OS$; m.p.:(229-231) ^{o} C; FT-IR (KBr) ν max, (cm^{-1}) : 3290(NH),3055 (Ar-H) , 1642 (N=CH); 1HNMR (DMSO-d_6, 500 MHz.) (δ, ppm.), 3.45 (s,3H, OCH_3), 7.86 -7.15 (m , Ar-H), 8.12 (s, 1H, N=CH).

2-(2-(3-hydroxy-4-methoxybenzylidene) hydrazineyl)-6-methoxybenzo[d]thiazole (A5d)

It is light solid (1.38g, 78 %) Anal. Calcd. for $C_{16}H_{15}N_3O_3S$; m.p.:234-236 ^{o} C; FT.IR (KBr) ν max (cm^{-1}): 3283 (NH),3065 (Ar-H), 1645 (N=CH); [1]HNMR (500 MHz., DMSO-d_6) (δ, ppm.), 3.56 (s, 3H, OCH_3), (7.92 -7.10)(m , Ar-H), 8.10 (s, 1H, N=CH **)**.

Results & Discussion [33].

The compounds (A3a-e) were prepared by direct reaction between 6-methoxy-2-aminebenzothiazol (A2) and substituted benzaldehydes in an alcohol medium in the presence of glacial acetic acid.

FT-IR spectra of the prepared compounds showed diagnostic bands in the range of (250-3430) cm^{-1}, (3054-078) cm^{-1}, (1641-1648) cm^{-1}, (1621-1643) cm^{-1} belong to (-NH), (Ar-H), (-N=CH-), (C=C) respectively.

[1]HNMR spectra of compounds (A3a-e) showed signals at δ= (3.30-3.53) ppm, δ= (7.2- 8.1) ppm and δ= (6.3-7.9) – (7.23- 7.65) ppm due to (-OCH_3), (-N=CH-) and (Ar-H) respectively.

[1]HNMR spectra of compounds (A3a) and (A3d) showed signals at δ= 2.8 ppm and δ= 10.24 ppm belong to (-$N(CH_3)_2$) and (OH) groups respectively.

The compounds (A5a-d) were prepared from the reaction of synthesized compound (A_2) with substituted benzaldehyde. The structure of synthesis compounds were confirmed by the melting point, FT-IR and [1]HNMR. FTIR spectra of prepared compounds showed a characteristic bands in the region between 1642 cm^{-1} and 1655 cm^{-1} that is belong to the stretching vibration of (C=N), and disappeared of two absorption bands at 3295, 3283 cm^{-1} belong to (asym. & sym.) stretching of (-$NH-NH_2$) group.

[1]HNMR spectra of compounds (A5a-d) showed signals at δ= 3.36-3.56 ppm (s) due to (-OCH_3) protons, δ = (7.10 -7.90) ppm (m) belong to (Ar-H), δ = 8.10 - 8.18 ppm (s) for (-N=CH-), and δ= 9.65-9.80 ppm (s) due to NNH proton.

Antibacterial activity [34].

Some of the synthesized compounds A1, A2,A3a, A4, (A5a,b) were tested against various strains of bacteria: gram positive bacteria, *Pseudomonas aeruginos*, *staphylococcus*, *aureus*, and gram negative bacteria, *Bacillus subtilis*, *Eterobactern* and *Escherichia*, *coli* by cup plate agar diffusion method [34]. The microbial cultures was incubated at (37^o C for 8 hur.) and diluted with 0.8% sterile saline. The concentration of solution for used drugs in DMF, were kept at 100µg/mL. Ampicillin as standard, streptomycin as a reference drug, and D.M.F. as a negative control were used. The biological activity was measured by measuring the inhibition diameter of growth of bacteria around the disk in use, Table (1).

TABLE (1):Evaluation of antimicrobial screening activity of compounds(A_1,A_2,A_3a,A_4,$A_{5a,b}$)

Code Comp. A	Antimicrobial activity,(inhibition zone in mm)				
	Bacillus subtilis (-)	*Eterobactern (-)*	*E. coli(-)*	*Pseudomonas aeruginos (+)*	*Staphylococcus aurea (+)*
1	20	18	17	19	18
2	25	23	16	16	21
3a	24	30	13	15	19
4	23	14	12	13	19
5a	25	15	11	10	11
5b	17	21	32	29	15
streptomycin	25	25	13	12	16
ampicillin	21	21	20	20	20
control	0.0	0.0	0.0	0.0	0.0

From the results, it is also clear that the compounds examined showed variable toxicity against types of bacteria. Some of the prepared compounds showed high inhibition activity against bacteria. This difference in toxicity may be due to various (structures and functional groups) attached to the primary nucleus. Also, It is cleared from the result presented in table (2) that NMe_2 phenyl substituted N, N`-Dimethyl, Nitro group $-NO_2$, Cl and methoxy.

group and (– OCH_3, OH) groups in the primary nucleus, the anti-bacterial activity was increased.

C.H.N.S Analysis

The (C.H.N.S) measurements of compounds that prepared (A_1, A_2, A_{3C}, A_4, A_{5b}) are mention to correct suggested structure of this research compounds, as in table (2).

TABLE (2): (C.H.N.S), Elemental Analysis

No. sample A	Molecular formula (M.Wt)	% C		% H		% N		% S	
		Cal. %	Found%	Cal. %	Found%	Cal. %	Found%	Cal. %	Found%
1	$C_8H_8N_2OS$ (180)	53.71	53.360	4.41	4.810	15.91	15.56	17.57	16.98
2	$C_8H_9N_3OS$ (195)	53.45	54.467	4.56	4.420	23.87	24.05	17.07	16.72
3c	$C_{15}H_{11}ClN_2OS$ (302)	57.32	57.531	3.47	3.762	8.54	8.05	10.05	9.85
4	$C_{12}H_{11}N_3O_2S$ (261)	66.84	67.06	4.98	5.120	19.53	18.93	14.44	15. 08
5b	$C_{15}H_{12}N_4O_3S$ (328)	54.07	54.741	3.52	3.441	17.53	17.36	9.42	9.11

Conclusion

All of 6-methoxy-2-aminobenzothiazole derivatives containing Schiff bases prepared in this work were characterized and validated using ^{1}HNMR spectroscopy and FT-IR spectroscopy.

The Schiff bases obtained 6-methoxy-2-hydrazino-benzothiazole showed difference in the anti-microbial activity, based on the structure of the substituents.

FIGURE (1) : FTIR Spectrum of compound (A1)

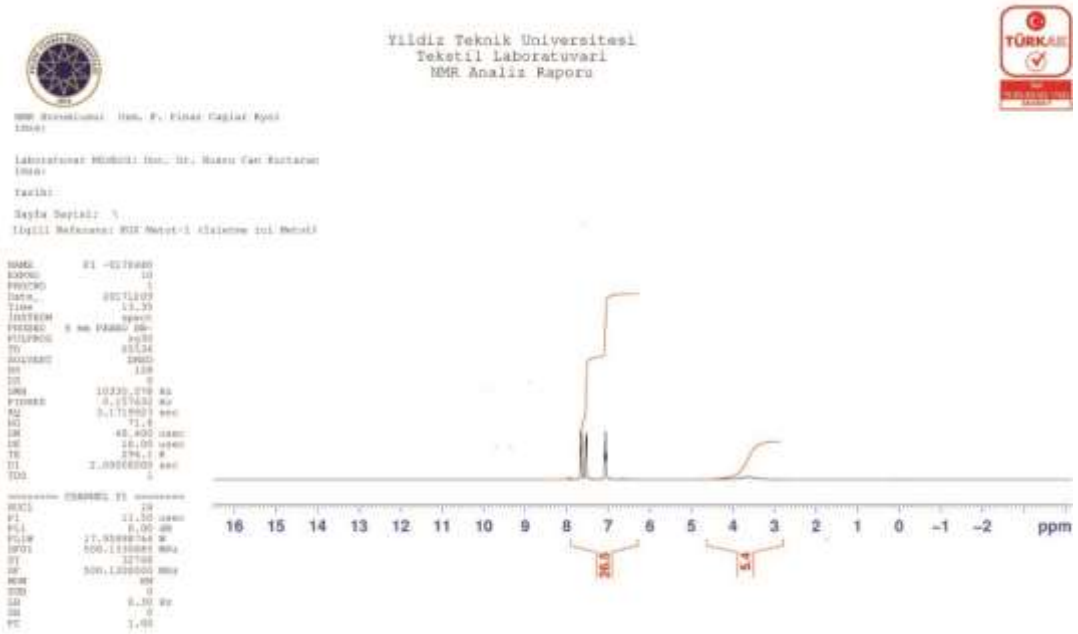

FIGURE (2): ^{1}HNMR Spectrum of compound (A1)

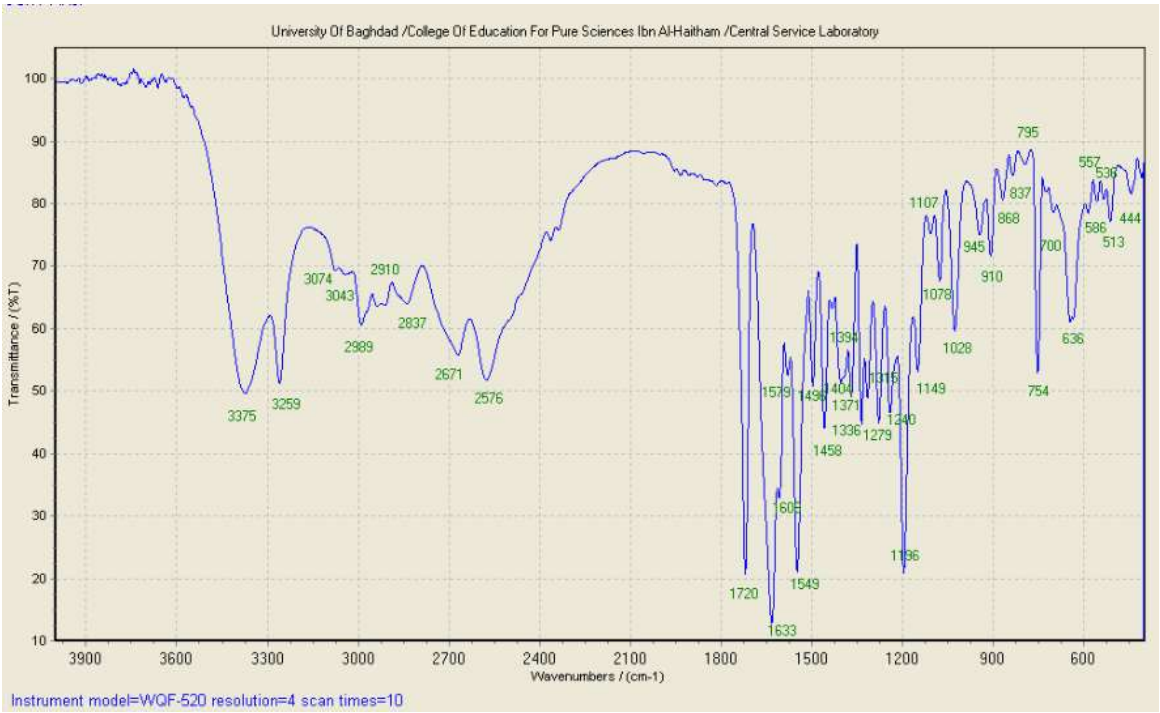

FIGURE (3): FTIR Spectrum of compound (A2)

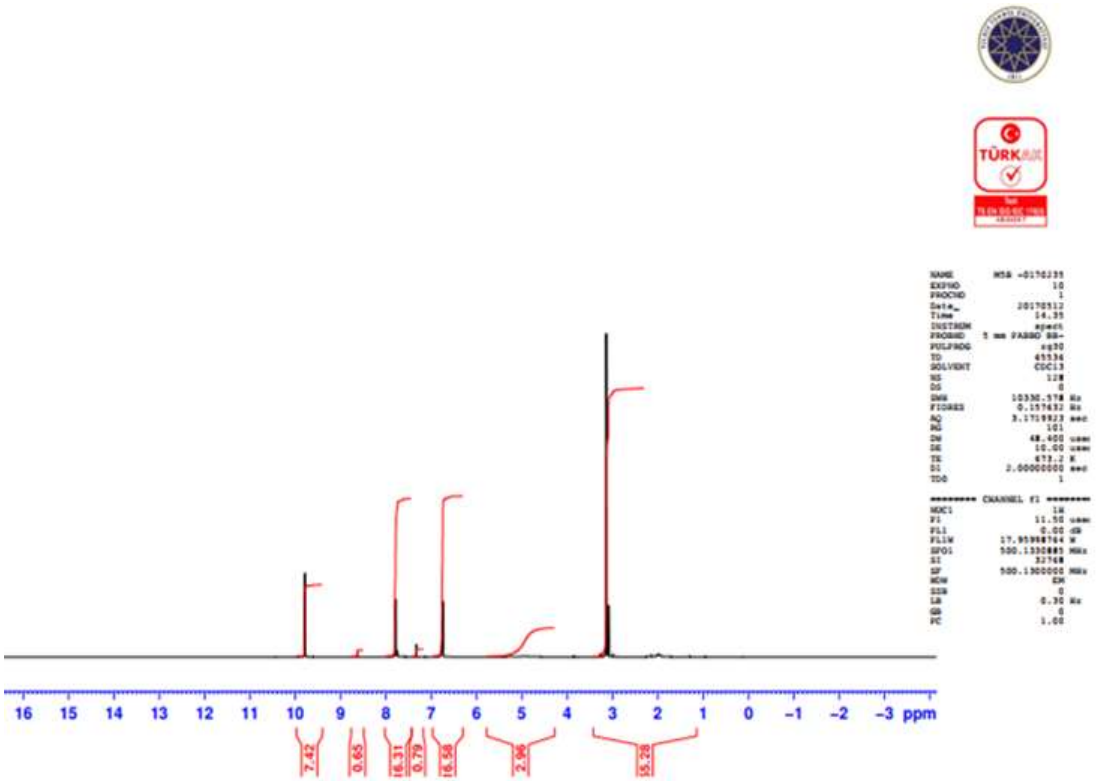

FIGURE (4): ^{1}HNMR Spectrum of compound (A2)

FIGURE (5): FTIR Spectrum of compound (A3a)

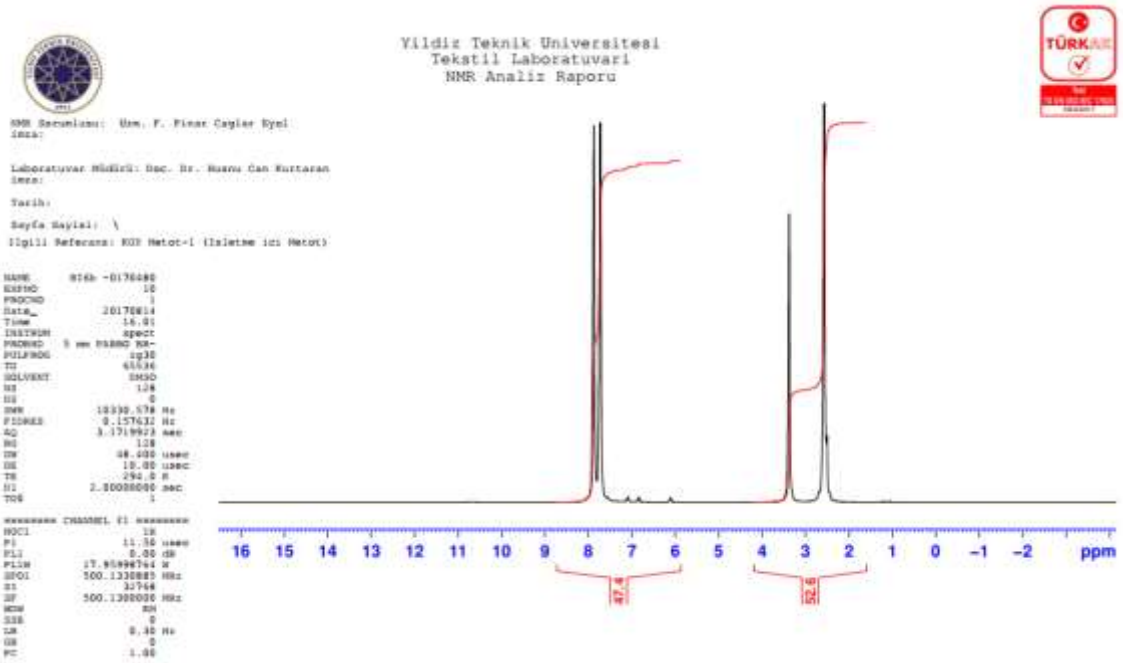

FIGURE (6) : ^{1}HNMR Spectrum of compound (A3a)

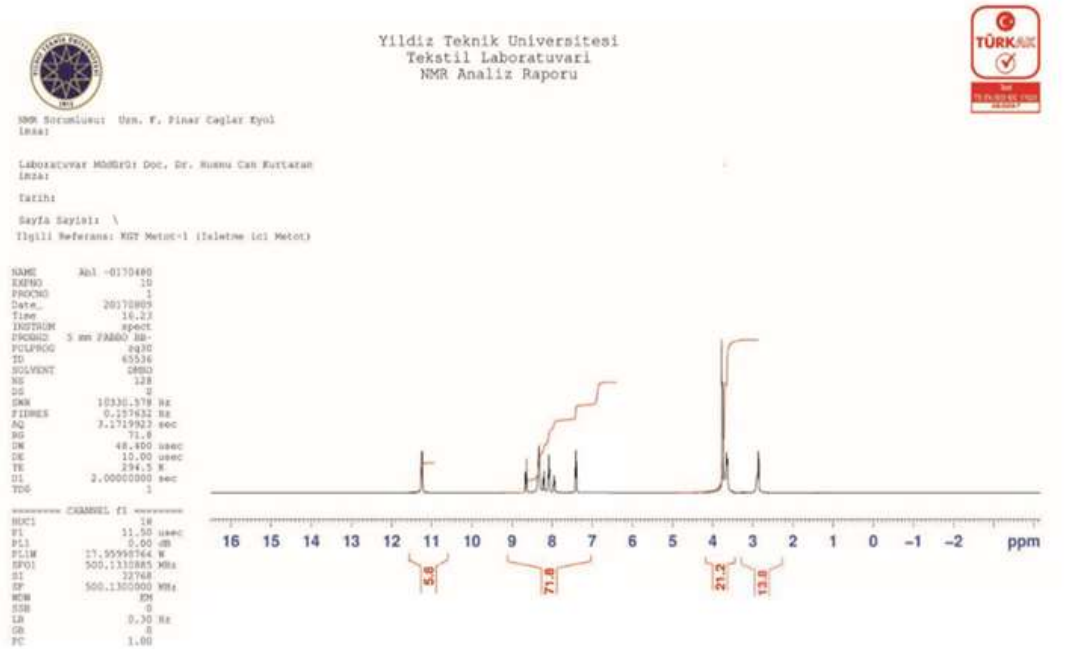

FIGURE (9): ^{1}HNMR Spectrum of compound (A4)

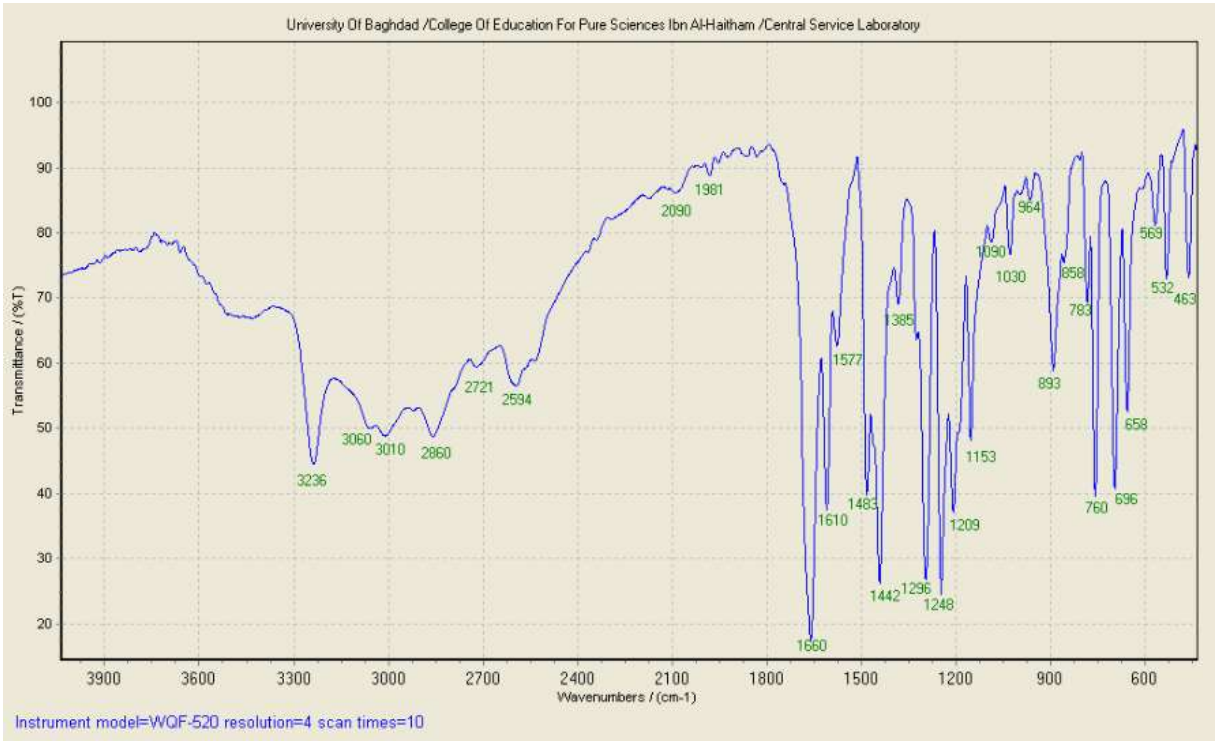

FIGURE (7): FTIR Spectrum of compound (A5a)

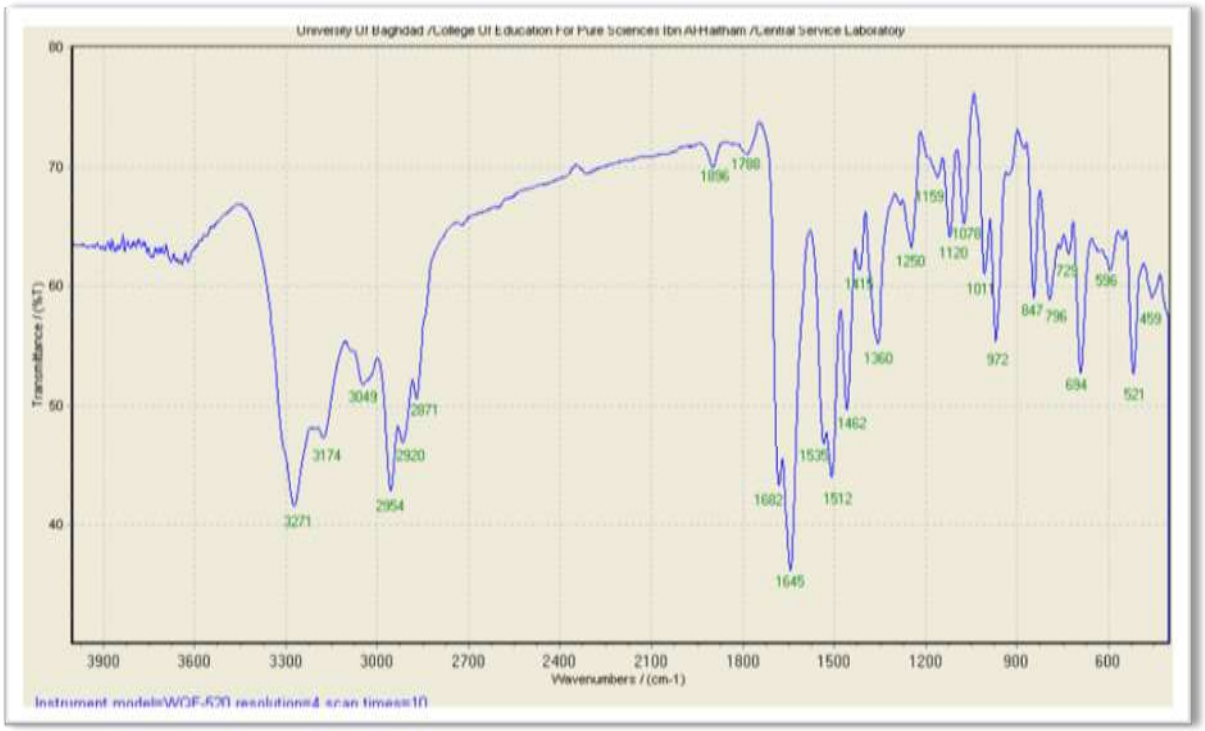

FIGURE (8): FTIR Spectrum of compound (A5b)

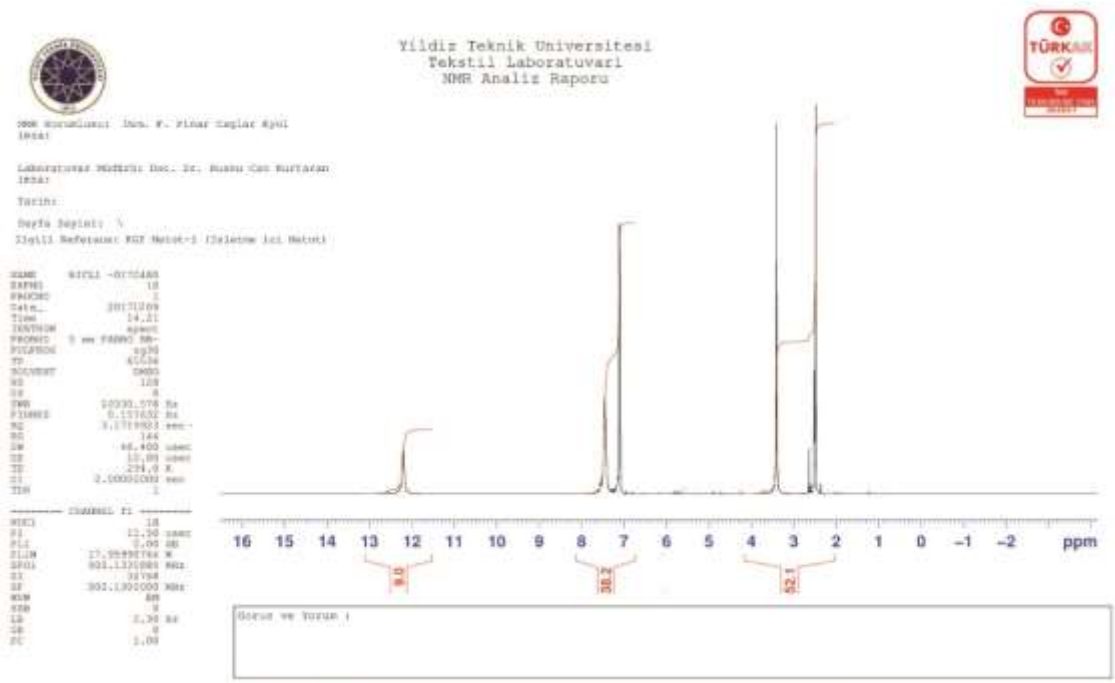

FIGURE (10): ^{1}HNMR Spectrum of compound (A5a)

References

1- Jordan, Alfonzo D., et al. Potential anxiolytic agents. Part 4: novel orally-active N5-substituted pyrido [1, 2-a] benzimidazoles with high GABA-A receptor affinity. *Bioorganic & medicinal chemistry letters*, **12** (17)2381-2386(2002).

2- J. K Malik , F. V. Manvi , B. K. Nanjwade1 , S. Singh1 , P. Purohit ,.Review of the 2-Amino Substituted Benzothiazoles: Different Methods of the Synthesis. *Der Pharmacia Letter*, **2** (1) 347-359(2010).

3- Alessia C., Ivana D., Marilena M., Antonio C., Françoise Van B., Antonio R., Filomena C., Carlo F. 2-Aminobenzothiazole derivatives: Search for new antifungal agents. *European Journal of Medicinal Chemistry*, **64**, 357-364(2013).

4- Thomas, Andrew P., et al. New nonpeptide angiotensin II receptor antagonists. 1. Synthesis, biological properties and structure-activity relationships of 2-alkylbenzimidazole derivatives. *Journal of medicinal chemistry*, **35** (5)877-885(1992).

5- Evers, David L., et al. Interactions among antiviral drugs acting late in the replication cycle of human cytomegalovirus. *Antiviral research*, **56** (1) 61-72(2002).

6- RAMLA, Mostafa M., et al. Synthesis and antitumor activity of 1-substituted-2-methyl-5-nitrobenzimidazoles. *Bioorganic & medicinal chemistry*, **14** (21)7324-7332(2006).

7- Mauro, V. A., et al. Synthesis of 2-Mercapto benzthiazole and 2-Mercaptobenzimidazole Derivatives Condensed with Carbohydrates as A potential Antimicrobial Agents". *J. Sulfur, Chem.*, **28**, 17(2007).

8- Willey, Cynthia, et al. Stages of change for adherence with medication regimens for chronic disease: development and validation of a measure. *Clinical therapeutics*, **22** (7)858-871(2000).

9- Shea, Tara A., et al. Identification of proton-pump inhibitor drugs that inhibit Trichomonas vaginalis uridine nucleoside ribohydrolase. *Bioorganic & medicinal chemistry letters*, **24**(4)1080-1084(2014).

10- MAHAJAN, S. S.; NANDRE, R. G. Studies in the synthesis of 2-mercapto-5-methoxybenzimidazole.**45B**, 1756(2006).

11- ORJALES, Aurelio, et al. New 2-piperazinylbenzimidazole derivatives as 5-HT3 antagonists. Synthesis and pharmacological evaluation. *Journal of medicinal chemistry*, **40**(4)586-593(1997).

12- Am.., Aj. Chovancova, B. h., & Varkonda b, Synthesis and pesticidal activity of acyl derivatives of 4-chloro-2-aminobenzothiazole and the products of their reduction, *Chem. Papers*. **5** (3)411-418(1991).

13- Bespalov, A. Ya, et al. Alkylation and Aminomethylation of 1, 3-Dihydro-2H-Benzimidazole-2-Thione. *Chemistry of Heterocyclic Compounds*, **50**(11)1547(2015).

14- Marco, M., Claudia, B. F. S., Rivara, S., Valentina, Z., Federica, V., Mirko, R., Elisabetta, B., Simona, B.Vigilio, B., Francesca, M., Mariannina, I., Pier, V. P. *Bioorg. Med. Chem.*, ***12***, 663(2004).

15- Ngaini, Zainab, et al. One-pot multicomponent synthesis of thiourea derivatives in cyclotriphosphazenes moieties. *Journal of Chemistry*, (2017).

16- 1558Ramla, Mostafa M., et al. Synthesis and antitumor activity of 1-substituted-2-methyl-5-nitrobenzimidazoles. *Bioorganic & medicinal chemistry*, **14**(21)7324-7332(2006).

17- Kumari S.; Sharma N. K. and Kumar N. *Der Chem. Sinica*, **1**, 36 (2010).

18- Bakhareva, E. V., et al. Synthesis and neurotropic properties of 2-(carboxymethylthio) derivatives of benzimidazole, benzothiazole and their ammonium salts. *Pharmaceutical chemistry journal*, **30**(2)89-91(1996).

19- VALGAS, Cleidson, et al. screening methods to determine antibacterial activity of natural products. *Brazilian journal of microbiology*, **38** (2)369-380(2007).

20- Priyanka Y., Deepa Ch., N. K Sharma , S. Singhal., 2-Substituted Hydrazino-6-Fluoro-1,3-Benzothiazole:Synthesis and characterization of new Novel antimicrobial Agents , *International Journal of Chem. Tech Research*, **2**(2)1209-1213(2010).

21- Ravi S. R., D. and D. Sudhakar,. Synthesis, characterization and biological evaluation of some novel 6-fluorobenzothiazole substituted thiazolidinones as anthelmintic activity *Der Pharma Chemica*, **6**(1)111-114(2014***).***

22- D. R . S . Reddy & R. L. Priyadarshini ,Synthesis, characterization and *in vivo* antiinflammatory activity of some novel 6-fluorobenzothiazole substituted pyarzole analogues *Der Pharma Chemica*, , **5**(4)207-212(2013)**.**

23- Saleh, M.Y., Synthesis and Antibacterial Evaluation of 2-(chloro/ethyl thio/seleno)-1, 8-naphthyridine-3-azetidine Derivatives. *Diyala Journal For Pure Science*, **13**(3-part 1)104-115(2017).

24- P.Venkatesh &.N.Pandeya, Kovai E., Kalapatti R., C. Saroj,. Synthesis, characterization and anti-inflammatory activity of some 2-amino benzothiazole derivatives, *International Journal of Chem* .Tech Research **1**(4)1354-1358(2009).

25- Poonam W., Avinash B., Vishwas I. Efficient Synthesis and Characterization of Novel 2-Aminobenzothiazole Derivatives, *International Journal for Pharmaceutical Research Scholars*, **5** (4)108-112(2016).

26- S D.Srivastava & JP.Sen .Synthesis and biological evaluation of 2-aminobenzo thiazole derivatives, *Indian Journal of Chemistry*, **47B**, 1583-1586(2008).

27- Wahid U. Malik P. K. Srivastava S. C. Mehra, Interaction of 2-aminobenzothiazoles with benzoyl and tert-butyl isothiocyanates, *J. Chem. Eng. Data*, **14** (1)110-110 (1969).

28- Rajinder K., Uday K., Amandeep K.& Puneet K. Synthesis, Spectral Studies and Biological Evaluation of Schiff Base Derivatives of Benzothiazole for Antimicrobial Activity, **3**(4) ,847(2012).

29- Shanthalakshmi K., Mahesh B. & Belagali S.,Synthesis of Benzothiazole Schiff's Bases and screening for the Antioxidant Activity ,*Journal of Chemical and Pharmaceutical Research*, , **8**(10) 240-243(2016).

30- Ahmood KH. J.Hamid M. S. layth W.A. Synthesis, characterization and evaluation biological activity of some new Ethyl-2-amino benzothiazole -6-carboxylate derivatives, *Eurasian Journal of Analytical Chemistry*, **13**(4) 269-279(2018).

31- Hamed M. , Hawraa K.S., Wea,H.Kadim, Sh. Hamed, Sh.,Synthesis and Characterization of Co(II),Ni(II),Cu(II) and Zn(II) Complexes with Benzothiazol-2-yl-(4-chloro-benzylidene)-amine. *Journal of Applied Chemistry*,**9**,(9)11-16(2016).

32- Jitender K M, F. V. Manvi1 , B. K. Nanjwade , Sanjiv S , Pankaj P,. Review of the 2-Amino Substituted Benzothiazoles: Different Methods of the Synthesis, *Der Pharmacia Letter*, **2** (1) 347-359(2010).

33- Abdellah M. Douniazad E. G. Boyer Jean P. F. Jean P. G. Didier S. Reactivity of 2-Aminothiazole and 2- or 6-Aminobenzothiazole Derivatives Towards the Triphenylbismuth Diacetate /Catalytic Copper Diacetate Phenylation System.**2004**, (7), 1509-1516(2004).

34- B. Moulder, W. Lewert, J.M. and R.M. Rippon, "Textbook of Microbiology", 19th edition, Sannders, W.B. Comp. Ltd., Philadelphia London, Toronto, (1969).