Available online on 30.08.2019 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

Open Access Research Article

Synthesis and Biological Evaluation of 1-(6-chlorobenzo [d]thiazol-2-yl)-2-(disubstituted methylene) hydrazine derivatives

Neetesh Kumar Sharma*, Dr. Raghvendra Singh Bhadauria

[1] Associate Professor (Pharmaceutical Chemistry), Adesh Institute of Pharmacy and Biomedical Sciences, Adesh University, Bhatinda, Punjab, India

[2] Principal at Shrinathji Institute of Pharmacy, Nathdwara, Rajasthan, India

ABSTRACT

Synthesis of a series of various 1-(6-chlorobenzo[d]thiazol-2-yl)-2-(disubstitutedmethylene)hydrazine derivatives (7a-7e)have been done. Synthesis of a series of intermediates (3 and 5) have been also done, 6-Chloro-2-amine-1,3-benzothiazole (3), 2-hydrazino-6-chloro-1, 3-benzothiazole (5) and final product (7a-7e), 1-(6-chlorobenzo[d]thiazol-2-yl)-2-(diphenylmethylene) hydrazine (7a), 1-(6-chlorobenzo [d]thiazol-2-yl)-2-(propan-2-ylidene) hydrazine (7b), (E)-2-(butan-2-ylidene)-1-(6-chlorobenzo[d]thiazol-2-yl)hydrazine (7c), (Z)-1-(6-chlorobenzo[d]thiazol-2-yl)-2-(cyclohexylmethylene) hydrazine (7d), 2-(6-chlorobenzo[d]thiazol-2-yl)-1-(7,7- dimethylbicyclo [2,2,1] heptan-2-ylidene)hydrazine (7e). Spectral analysis of all intermediates and final products has been done by IR and NMR. After spectral analysis, antibacterial activity has been screened against *S. aurius* and *E. coli* bacterias.

Article Info: Received 30 June 2019; Review Completed 13 Aug 2019; Accepted 21 Aug 2019; Available online 30 Aug 2019

Cite this article as:

Sharma NK, Bhadauria RS, Synthesis and Biological Evaluation of 1-(6-chlorobenzo [d]thiazol-2-yl)-2-(disubstituted methylene) hydrazine derivatives, Journal of Drug Delivery and Therapeutics. 2019; 9(4-A):561-572

http://dx.doi.org/10.22270/jddt.v9i4-A.3515

***Address for Correspondence:**

Neetesh Kumar Sharma, Associate Professor (Pharmaceutical Chemistry), Adesh Institute of Pharmacy and Biomedical Sciences, Adesh University, Bhatinda, Punjab, India

1. INTRODUCTION

Antimicrobial agents are those which treat infection by suppressing or destroying the causative microorganisms such as bacteria, mycobacteria, fungi, protozoa or viruses without significant effect on host tissues.[1] The use of antimicrobial agents in food animals for growth promotion that belong to classes of antimicrobial agents used in humans should be terminated[2].

Some benzothiazole derivatives (drugs) are clinically used such as Riluzole, Thioflavin, Pittsdurgh compound B, Ethoxzolamine, Pramipexole, Dimazole, Flutemetol and Dithiazanine Iodide.

There are no treatments available for infections caused by many of the antibiotic-resistant bacteria, and resistance to commonly used antibiotics is steadily increasing[3].

Tigecyclin is the first antibiotic approved in a new class called glycylcyclines and is indicated for the treatment of complicated intra-abdominal infections and complicated skin and skin structure infections in adults[4].

Ceftobiprole is resistant to staphylococcal β-lactamase. It is used in adults for the treatment of complicated skin and skin structure infection[5].

Benzothiazole ring containing compounds which are involved in research targeted for new compounds that having good biological activities such as antitumor[6], antimicrobial[7], anti-inflammatory, anti-tubercular, anti-HIV[8], anti-malarial[9], anti-convulsant[10], anthelmintic, anti-oxidants and analgesic.

In addition benzothiazole ring is present in various natural compounds that are biologically active.

A series of various derivatives of final products 1-(6-chlorobenzo[d]thiazol-2-yl)-2-(diphenylmethylene) hydrazine (7a), 1-(6-chlorobenzo [d]thiazol-2-yl)-2-(propan-2-ylidene) hydrazine (7b), (E)-2-(butan-2-ylidene)-1-(6-chlorobenzo[d]thiazol-2-yl)hydrazine (7c), (Z)-1-(6-chlorobenzo[d]thiazol-2-yl)-2-(cyclohexylmethylene) hydrazine (7d), 2-(6-chlorobenzo[d]thiazol-2-yl)-1-(7,7-dimethylbicyclo [2,2,1] heptan-2-ylidene)hydrazine (7e) has been synthesized by placing 2-Hydrazino amino benzothiazole and ketone compound (6a-e) in equimolar conc. in a RBF. Ethanol (20 ml) was added in the mixture and the reaction mixture was refluxed for 10-15 hrs. All the compounds synthesized have been characterized by spectral data and antibacterial activity has been done against Gram+ve *S. aurius* and Gram-ve *E. coli* bacterias by standard procedure using broth dilution method and minimum inhibitory concentration was determined by visual comparison with the negative control tubes.

2. EXPERIMENTAL

2.1 Synthesis of 2-amine -6-chloro-1,3-benzothiazole (3)

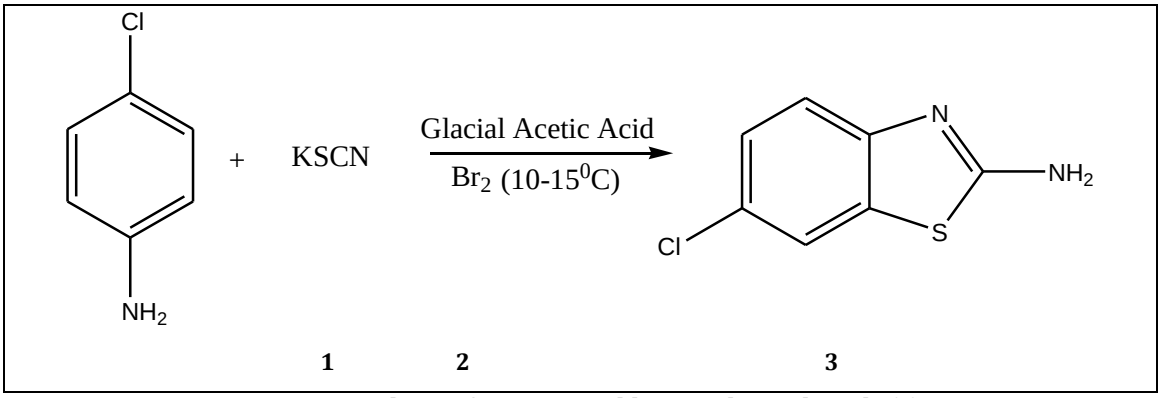


Figure 1: Synthesis of 2-amine -6-chloro-1,3-benzothiazole (3)

Procedure[11]

Triturate the mixture of p-chloroaniline (20g,0.156 moles) and potassium thiocyanate (18.19g, 0.187 moles) in motor pastle for 10-15 min. Add cold acetic acid (50ml) in to mortar and transfer this mixture in RBF, stirred the mixture at 10-15^{0}C then add cold acetic bromine mixture (10ml acetic acid and bromine) in 2-3 hr. After completion of bromine addition stirred the mixture for 10-15 minute. The reaction was monitored by TLC. Remove the RBF and keep overnight in to freeze.

Work up

In the overnight reaction mixture add 10ml H_2O and 5ml acetic acid. Heat the reaction mixture till cease of pungent smell of acetic acid. Cool this mixture and filter, the solid was removed and liquid was collected. The liquid was neutralize with ammonia dropwise at 5-10^{0}C. The precipitated solid was collected by filtration. The white solid was collected as pure product.

Yield : 84.78%

Melting point : 58-60^{0}C

TLC : Silica gel G; Hexane: Ethyl acetate (1:1)

R_f = 0.534

IR (**Spectrum 1**) : 3838, 3617, 2360, 1779, 1652, 1617, 1532, 1436, 1387, 1274 Cm^{-1}

2.2 Synthesis of 2-hydrazino-6-chloro-1, 3-benzothiazole (5)

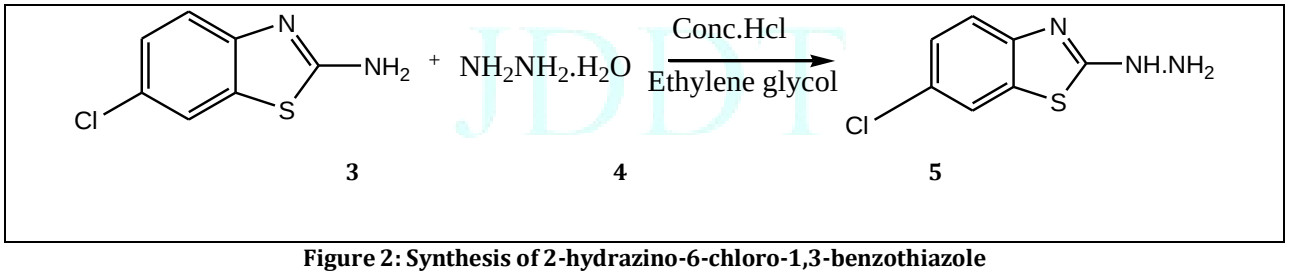


Figure 2: Synthesis of 2-hydrazino-6-chloro-1,3-benzothiazole

Procedure[12]

The obtained compound of 3 (5.00 gm,0.0264 moles) was dissolved in ethylene glycol (20 ml) and Conc. HCl (10 ml) was added drop by drop in this mixture, now cold hydrazine hydrate(10 ml) was added in this mixture. The reaction mixture was refluxed for 15 hr.

Work up:

Cool the mixture and pour this reaction mixture in to crushed ice. The precipitate was obtained and the precipitated compound was filtered under vacuum.

Yield : 82.63%

Melting point : 55-58^{0}C

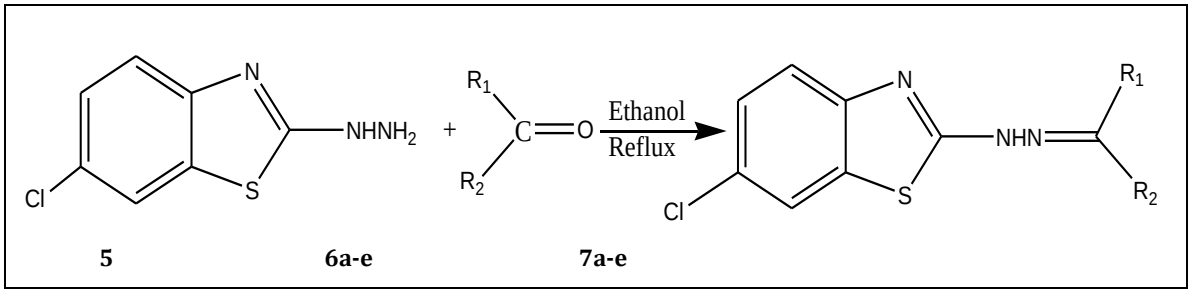
TLC : Silica gel G; Hexane: Ethyl acetate (1:1)

R_f = 0.567

IR (**Spectrum 2**) : 3734, 3674, 2954, 2411, 1759, 1716, 1651, 1557, 1521, 1497 Cm^{-1}

2.3 Synthesis of final products (7a-e)

General scheme



5 **6a-e** **7a-e**

Figure 3: General synthetic scheme for final product

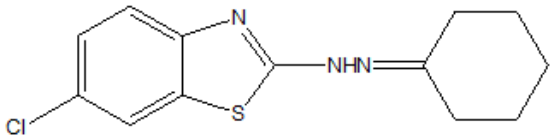
Procedure:[13]

The obtained compound 2-Hydrazino amino benzothiazole (compound 5) and ketone compound (6a-e) was taken in equimolar conc. in a RBF. Ethanol (20 ml) was added in the mixture and the reaction mixture was refluxed for 10-15 hrs. The reaction was monitored by TLC.

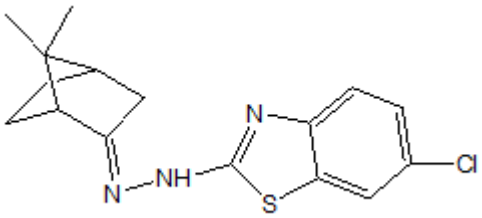
Work up:

Cool the mixture, the precipitate was collected. The product was purified by column chromatography (Ethylacetate: hexane) to give the final product.

Sr. No.	Compound	Name	R_1	R_2
1	7a	1-(6-chlorobenzo[d]thiazol-2-yl)-2-(diphenylmethylene) hydrazine	$-C_6H_5$	$-C_6H_5$
2	7b	1-(6-chlorobenzo [d]thiazol-2-yl)-2-(propan-2-ylidene) hydrazine	$-CH_3$	$-CH_3$
3	7c	(E)-2-(butan-2-ylidene)-1-(6-chlorobenzo[d]thiazol-2-yl)hydrazine	$-CH_3$	$-C_2H_5$

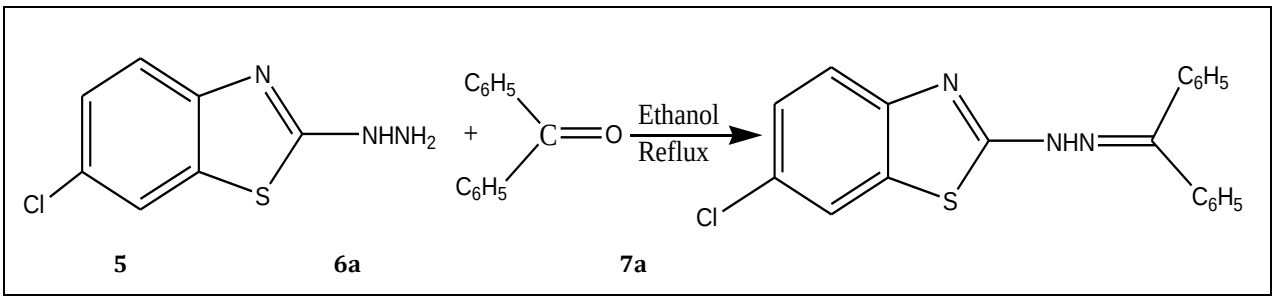


(Z)-1-(6-chlorobenzo[d]thiazol-2-yl)-2-(cyclohexylmethylene) hydrazine (7d).



2-(6-chlorobenzo[d]thiazol-2-yl)-1-(7, 7- dimethylbicyclo [2.2.1] heptan-2-ylidene)hydrazine (7e).

2.3.1. Synthesis of 1-(6-chlorobenzo[d]thiazol-2-yl)-2-(diphenylmethylene) hydrazine (7a):



5 **6a** **7a**

Figure 4: Synthesis of 1-(6-chlorobenzo[d]thiazol-2-yl)-2-(diphenylmethylene) hydrazine

Procedure[13]

The obtained compound 2-Hydrazino amino-6-chloro-1,3-benzothiazole (compound 5) (0.5gm,0.0024moles) and benzophenone (compound 6a) (0.43gm,0.0024moles) was taken in a RBF. Ethanol (20 ml) was added in the mixture and the reaction mixture was refluxed for 10-15 hrs. The reaction was monitored by TLC. Cool the mixture, the precipitate was collected. The product was purified by column chromatography.

Yield : 83.67%

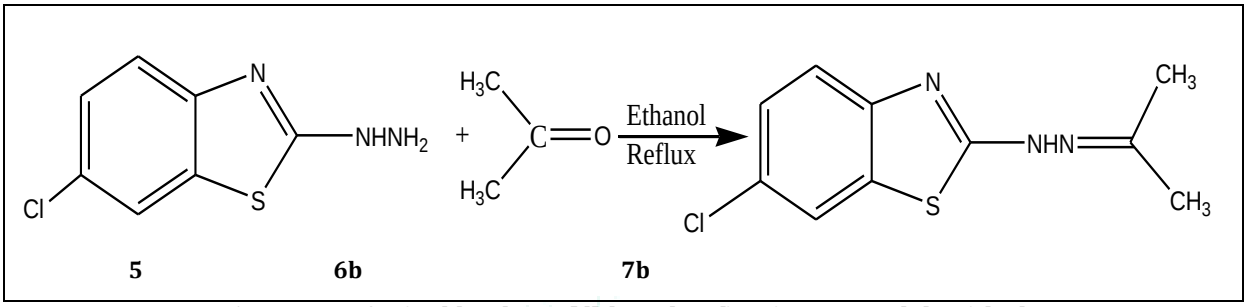
Melting point : 55-57^{0}C

TLC : Silica gel G; Hexane: Ethyl acetate (7:3)

R_f = 0.514

IR (**Spectrum 3**): 3800, 3701, 3648, 2398, 1828, 1771, 1716, 1636, 1557 Cm^{-1}

2.3.2 Synthesis of 1-(6-chlorobenzo[d]thiazol-2-yl)-2-(propan-2-ylidene)hydrazine (7b) :



5 **6b** **7b**

Figure 5: Syntesis of 1-(6-chlorobenzo[d]thiazol-2-yl)-2-(propan-2-ylidene) hydrazine

Procedure[13]

The obtained compound 2-Hydrazino amino-6-chloro-1,3-benzothiazole (compound 5) (0.5gm, 0.0024moles) and acetone (compound 6b) (0.176ml, 0.0024moles) was taken in a RBF. Ethanol (20 ml) was added in the mixture and the reaction mixture was refluxed for 10-15 hrs. The reaction was monitored by TLC. Cool the mixture, the precipitate was collected. The product was purified by column chromatography.

Yield : 79.83%

Melting point : 57-60^{0}C

TLC : Silica gel G; Hexane: Ethyl acetate (7:3)

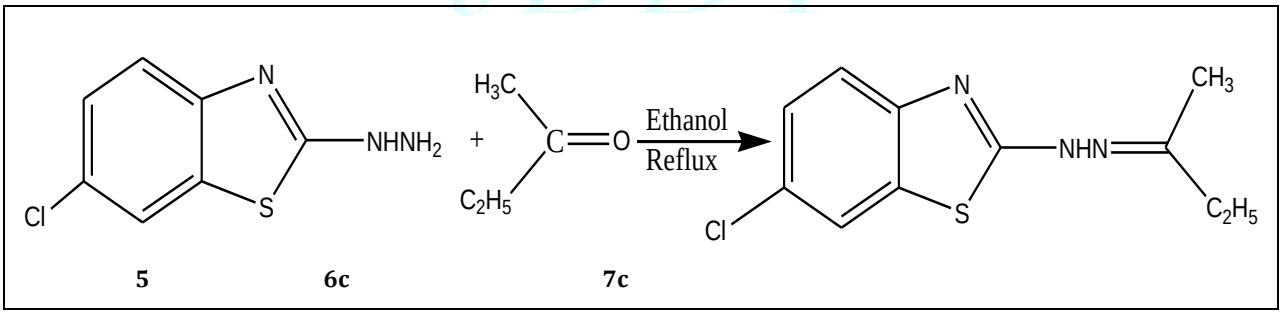
R_f = 0.587

IR (**Spectrum 4**): 3819, 3749, 3648, 2935, 2359, 1670, 1615, 1596, 1418, 1338, 1263 Cm^{-1}

^{1}**H NMR (Spectrum 5**): δ ppm 7.22-7.59 (m, 3H, Ar-H), 1.99-2.05 (s, 6H, CH_3*2)

^{13}**C NMR (Spectrum 6) :** δ ppm. 169.29, 151.01, 127.21, 126.37, 120.88, 119.33, 77.42, 77.00, 76.58, 25.10, 21.51, 17.03

2.3.3 Synthesis of (E)-2-(butan-2-ylidene)-1-(6-chlorobenzo[d]thiazol-2-yl) hydrazine (7c):



5 **6c** **7c**

Figure 6: Synthesis of (E)-2-(butan-2-ylidene)-1-(6-chlorobenzo[d]thiazol-2-yl) hydrazine

Procedure[13]

The obtained compound 2-Hydrazino amino-6-chloro-1,3-benzothiazole (compound 5) (0.5gm,0.0024moles) and Ethyl methyl ketone 6c (0.215ml,0.0024moles) was taken in a RBF. Ethanol (20 ml) was added in the mixture and the reaction mixture was refluxed for 10-15 hrs. The reaction was monitored by TLC. Cool the mixture, the precipitate was collected. The product was purified by column chromatography.

Yield : 84.97%

Melting point: 55-60^{0}C

TLC : Silica gel G; Hexane: Ethyl acetate (7:3)

R_f = 0.535

IR (**Spectrum 7**): 3766, 3674, 2927, 2397, 1800, 1733, 1683, 1661, 1541, 1456, 1396 Cm^{-1}

2.3.4 Synthesis of (Z)-1-(6-chlorobenzo[d]thiazol-2-yl)-2-(cyclohexylmethylene) hydrazine (7d):

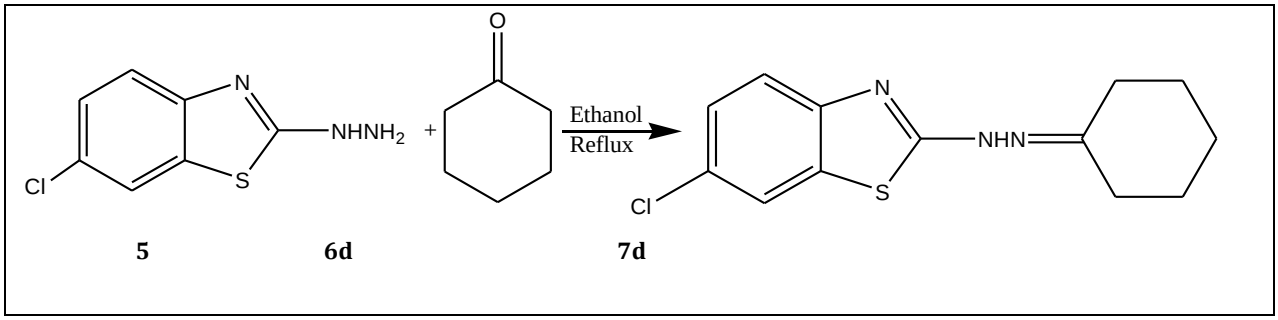


Figure 7: Synthesis of (Z)-1-(6-chlorobenzo[d]thiazole-2-yl)-2-(cyclohexylmethylene) hydrazine

Procedure[13]

The obtained compound 2-Hydrazino amino-6-chloro-1,3-benzothiazole (compound 5) (0.5gm,0.0024moles) and Cyclohexanone (compound 6d) (0.248ml,0.0024moles) was taken in a RBF. Ethanol (20 ml) was added in the mixture and the reaction mixture was refluxed for 10-15 hrs. The reaction was monitored by TLC. Cool the mixture, the precipitate was collected. The product was purified by column chromatography.

Yield : 83.34%

Melting point: 53-55^{0}C

TLC : Silica gel G; Hexane: Ethyl acetate (7:3)

R_f = 0.546

IR (**Spectrum 8**): 3734, 3674, 2945, 2360, 1697, 1623, 1558, 1521, 1362, 1288 Cm^{-1}

2.3.5 Synthesis of (E)-2-(6-chlorobenzo[d]thiazol-2-yl)-1-(7,7-dimethylbicyclo [2.2.1] heptan-2-ylidene) hydrazine (7e) :

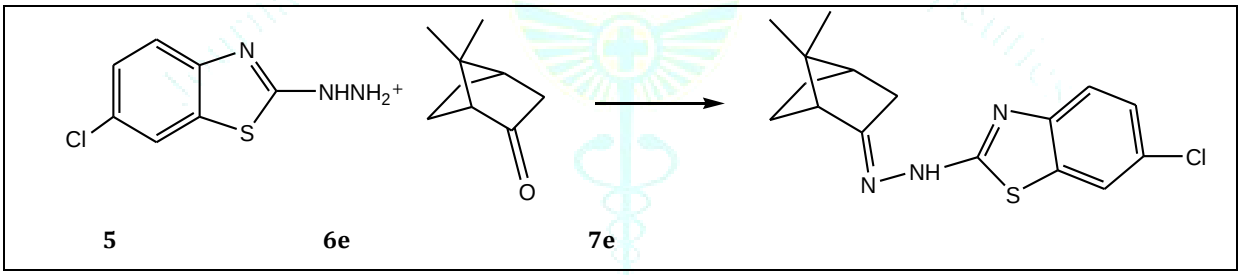


Figure 8: Synthesis of (E)-2-(6-chlorobenzo[d]thiazol-2-yl)-1-(7,7-dimethylbicyclo[2.2.1] heptanes-2-ylidene)hydrazine

Procedure[13]

The obtained compound 2-Hydrazino amino-6-chloro-1,3-benzothiazole (compound 5) (0.5gm,0.0024moles) and Camphor (compound 6e) (0.365gm,0.0024moles) was taken in a RBF. Ethanol (20 ml) was added in the mixture and the reaction mixture was refluxed for 10-15 hrs. The reaction was monitored by TLC. Cool the mixture, the precipitate was collected. The product was purified by column chromatography.

Yield : 82.87%

Melting point : 55-58^{0}C

TLC : Silica gel G; Hexane: Ethyl acetate (7:3)

R_f = 0.574

IR (**Spectrum 9**): 3766, 3724, 2955, 2821, 2384, 2017, 1967, 1901, 1799, 1766 Cm^{-1}

3. BIOLOGICAL SCREENING

Antimicrobial testing

Activity of antimicrobial agents may be demonstrated under suitable conditions by their inhibitory effect on microorganisms. The antimicrobial activity of the synthesized compounds (7a-7e) was carried out by standard procedure using broth dilution method and minimum inhibitory concentration was determined by visual comparison with the negative control tubes.

Detailed test procedure:

(i) Stock Solutions of test compounds and standard drug

Compounds were taken as test samples along with a standard Streptomycin sample. Weight taken in the range of 8-20 mg of each test compound and was dissolved in 1 ml of DMSO. For preparing stock solution of Streptomycin, 10 mg of Streptomycin was dissolved in 1 ml of water.

(ii) Test organism

The organisms employed in the *in vitro* testing of the compounds were *Escherichia coli* and *S. aureus*. All the cultures were maintained on nutrient broth agar (Microbiology grade, CDH Pvt. Ltd. New Delhi) medium by periodic sub culturing.

(iii) Preparation of Innoculum

Procedure for the preparation of innoculum for both the strains was same. The innoculum was prepared from a 24-hours old growth of organism on nutrient broth agar slant. To the agar slant, saline solution was added to obtain O.D

value of 0.1 on photoelectric optical colorimeter. 0.5ml of this solution was further diluted to 20ml with use of saline.

(iv) Preparation of Medium

1.3 gms of nutrient broth (Microbiology grade, CDH Pvt. Ltd. New Delhi.) was dissolved in 100 ml of sterile distilled water.

(v) Addition of drug, innoculum solution to medium

From diluted innoculum solution prepared, 100µl was added to separate test tube each containing 0.9ml of medium. 25 µl solution of test stock solution was added in four separate test tube containing 0.9ml of medium with 100 µl innoculum. The tests were carried out in duplicate. Apart from putting the controls of standard drug (Streptomycin), controls with dimethylsulphoxide (DMSO) were used. DMSO (positive control) is DMSO inoculated with organisms and dimethylsulphoxide (negative control) is plain DMSO. For incubation, test tubes were kept in incubator at 35°C for 24 hours.

(vi) Observations

At the end of incubation period, the results were interpreted by comparison with negative control. The lowest concentration of test compound which showed inhibitory effect on growth on visual distinction was taken as minimum inhibitory concentration (MIC) and visual turbidity was consider for MIC of the test molecules; standard drug and DMSO positive and negative control visual turbidity were recorded.

4. RESULT AND DISCUSSIONS

4.1 Characterization of the benzothiazole derivatives*:*

IR: The spectrum showed characteristic absorption band accordingly of the presence of functional group. The Ar-C-H stretching showed the absorption band in the range of 3010-3150 cm^{-1}. The –C=N stretching band appeared in the range of 1630-1660 cm^{-1}, -C=C- stretching peak comes in the range of 1400-1500 cm^{-1}, alkyl C-H stretching peak comes in the range of 2820-2860 cm^{-1}. N-H stretching band was appeared in the range of 3150-3300 cm^{-1}

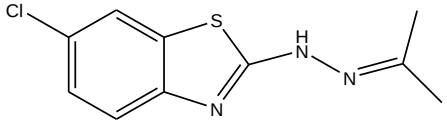
One representative molecule Compound **7b** was characterized ^{1}H NMR and ^{13}C NMR spectroscopy**.**

^{1}H NMR: The methyl protons appeared as a singlet at around δ 2.01-1.91. The aromatic protons appeared as multiple singlets between δ 7.22-7.59. Representative example is **7b.**

Sr. No.	No of proton	Predicted (δ in ppm)	Experimental (Spectrum 5)
1	$-CH_3$	2.0	2.01-1.91
3	Ar-H	7.56-8.17	7.22-7.59

Comparison of ^{1}H NMR values

^{13}C NMR: The ^{13}C NMR values for compound **7b** is listed and compared with the predicted values in the table below (Chembio office Chemdraw Ultra 8.0). Representative example is **7b** (Spectrum 6**)**



Structure of compound 7b

Sr. No.	No of carbon	Predicted	Experimental (Spectrum 6)
1	CH_3-C	16-22	17-25
2	Ar-C	121-151	119-151
3	ArC=N	169	169.9

Comparison of ^{13}C NMR values

4.2 Biological evaluation

The synthesized NCEs were subjected to antimicrobial evaluation against *Escherichia coli* and *S. aureus* microorganism using broth dilution method keeping appropriate positive and negative controls simultaneously.

Visual turbidity of evaluated compounds as in following Table:

Table 1: Visual turbidity of evaluated compounds

Sr. No.	**Compounds**	Visual Turbidity (*E. Coli*)	Visual Turbidity (*S. Aureus*)
1.	**7a**	-	-
2.	**7b**	-	+
3.	**7c**	+	+
4.	**7d**	**-**	+
5.	**7e**	-	-
6.	Streptomycin	-	-
7	DMSO positive	**++**	**++**

- = No Turbidity (No bacterial growth), + = Turbidity (Bacterial growth)

Based on the visual turbidity, the MIC of the evaluated molecules is given in above **Table** the evaluation concentration was used single therefore, the exact MIC could not determined and results are represented in less than and more than format. To get more exact MIC of the tested molecules need to be evaluated at low concentration. The evaluation results of the single concentration is tabulated in **Table**

Table 2: Microbiological activity results of evaluated compounds

Sr. No.	**Compounds**	*E. coli* (µg/ml)	*S. aureus* (µg/ml)
1.	**7a**	<12.5	<12.5
2.	**7b**	<12.5	>12.5
3.	**7c**	>12.5	>12.5
4.	**7d**	<12.5	>12.5
5.	**7e**	<12.5	<12.5
6.	Streptomycin	<6.25	<6.25

4.3 Result of antibacterial testing

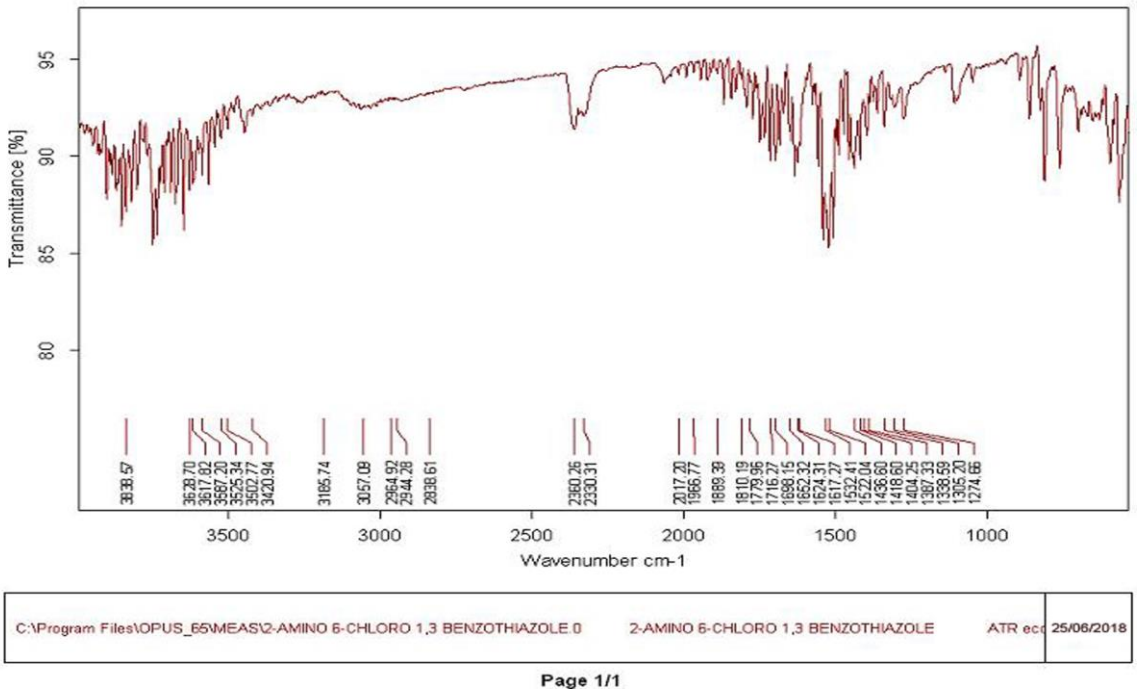
Most of the tested compounds had bacterial growth inhibition activity at tested concentration against both of microorganisms. Compounds 7a, 7b, 7d and 7e exhibited growth inhibition of *E.coli* while 7c didn't show activity. The

compound 7a and 7e showed the inhibition of *S. aureus* and 7b, 7c and 7d didn't show activity against *S. aureus* at tested concentration. Further testing for compounds 7a, 7b, 7d and 7e at lower concentrations has been done to compare their activity with streptomycin at its MIC to find exact MIC of the synthesized compounds. Compound 7c was inactive against both of microorganisms at the tested concentration and it was tested at higher concentration to get the exact MIC in comparison of streptomycin.

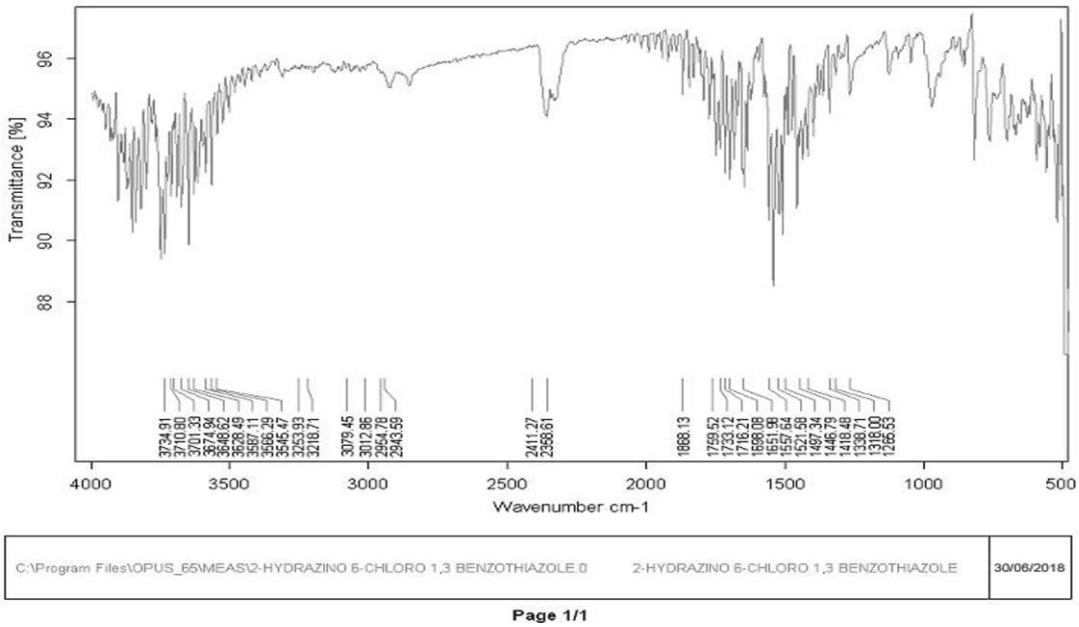
5. CONCLUSION

Thus, it can be concluded that designed benzothiazole derivatives were synthesized successfully and compound 7a-7e had antibacterial activity at tested concentration less than 1000µg per ml. and compound 7a exhibited activity at lower concentration less than 200µg per ml. Compound 7c didn't show activity at higher concentration upto 1000µg per ml. against both Gram +ve and Gram -ve microorganisms. So, synthesized benzothiazole derivatives can act as a lead for development of broad spectrum antibacterial agents.

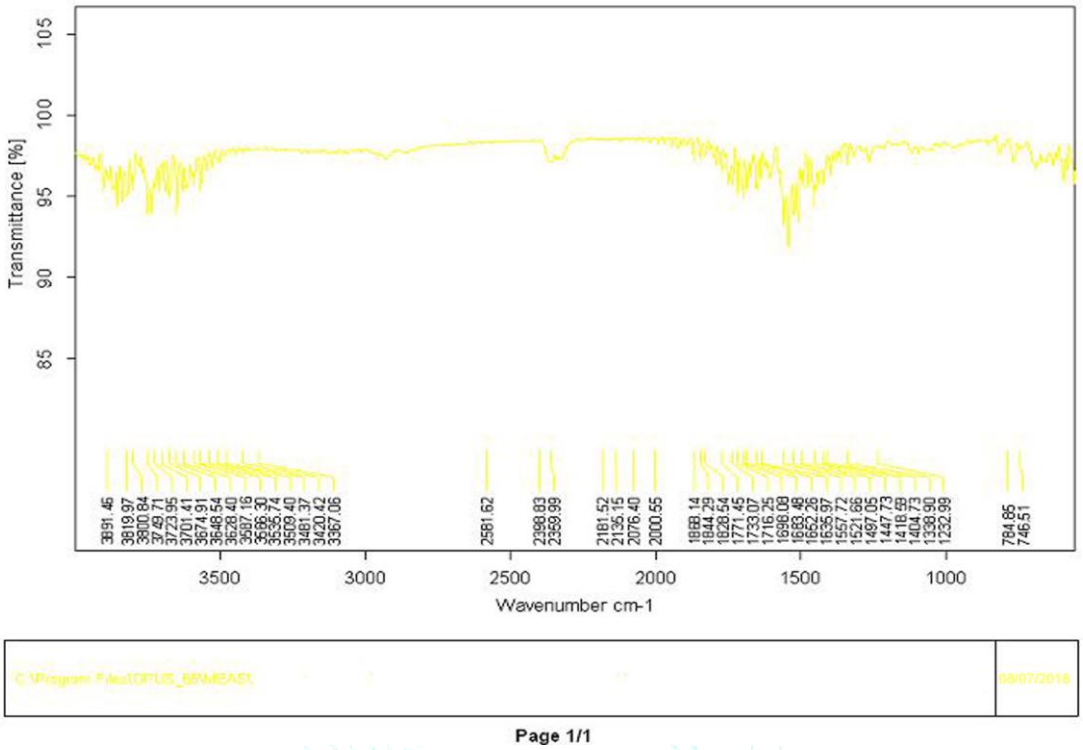
6. SPECTRAS



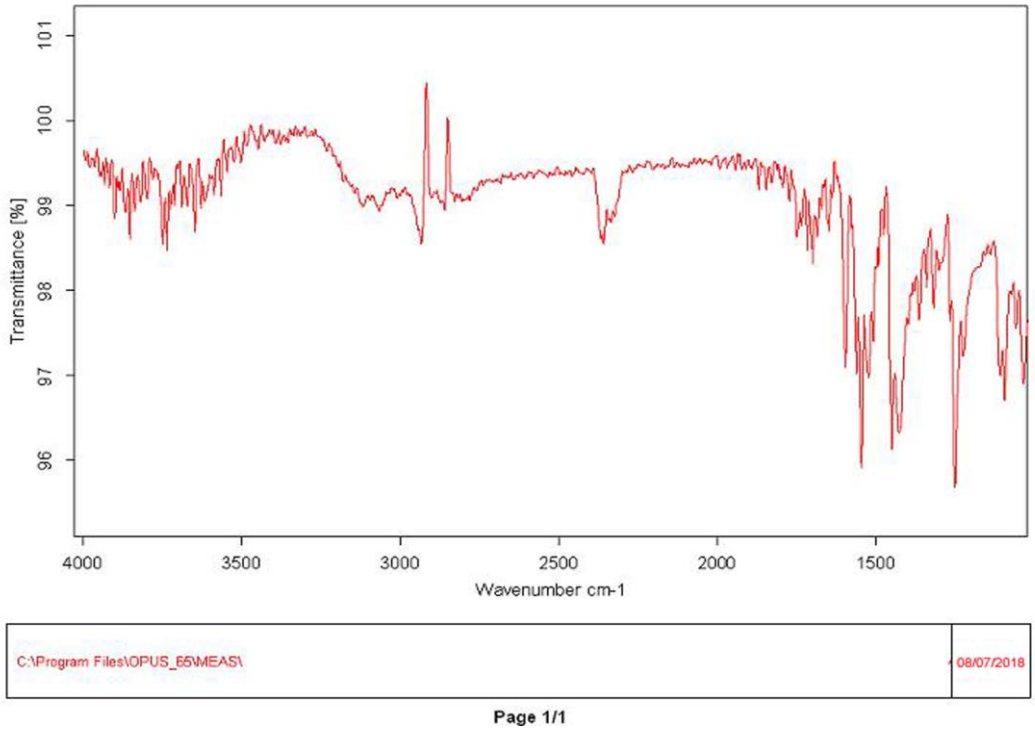
Spectrum 1: IR Spectra of 3



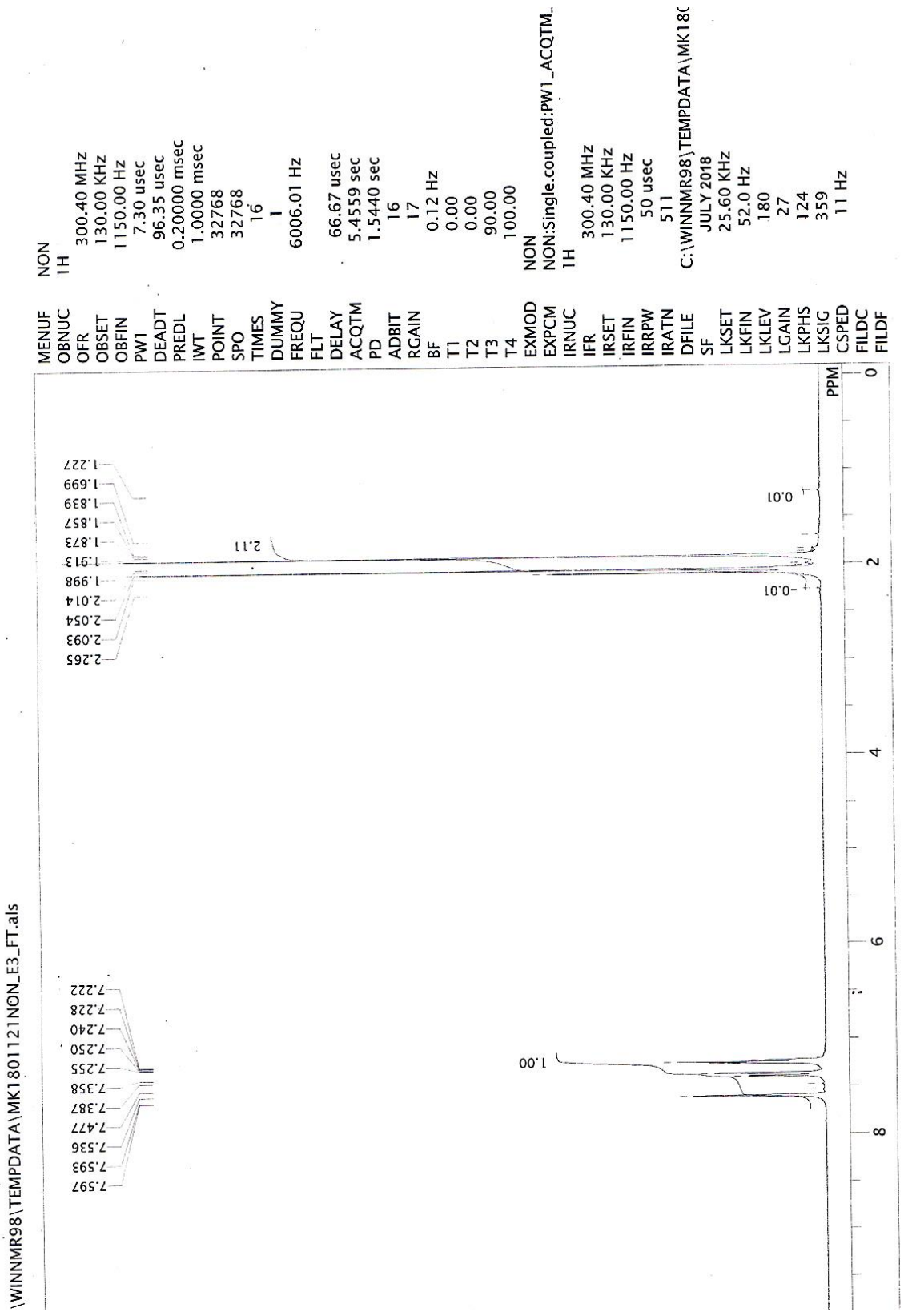
Spectrum 2: IR Spectra of 5



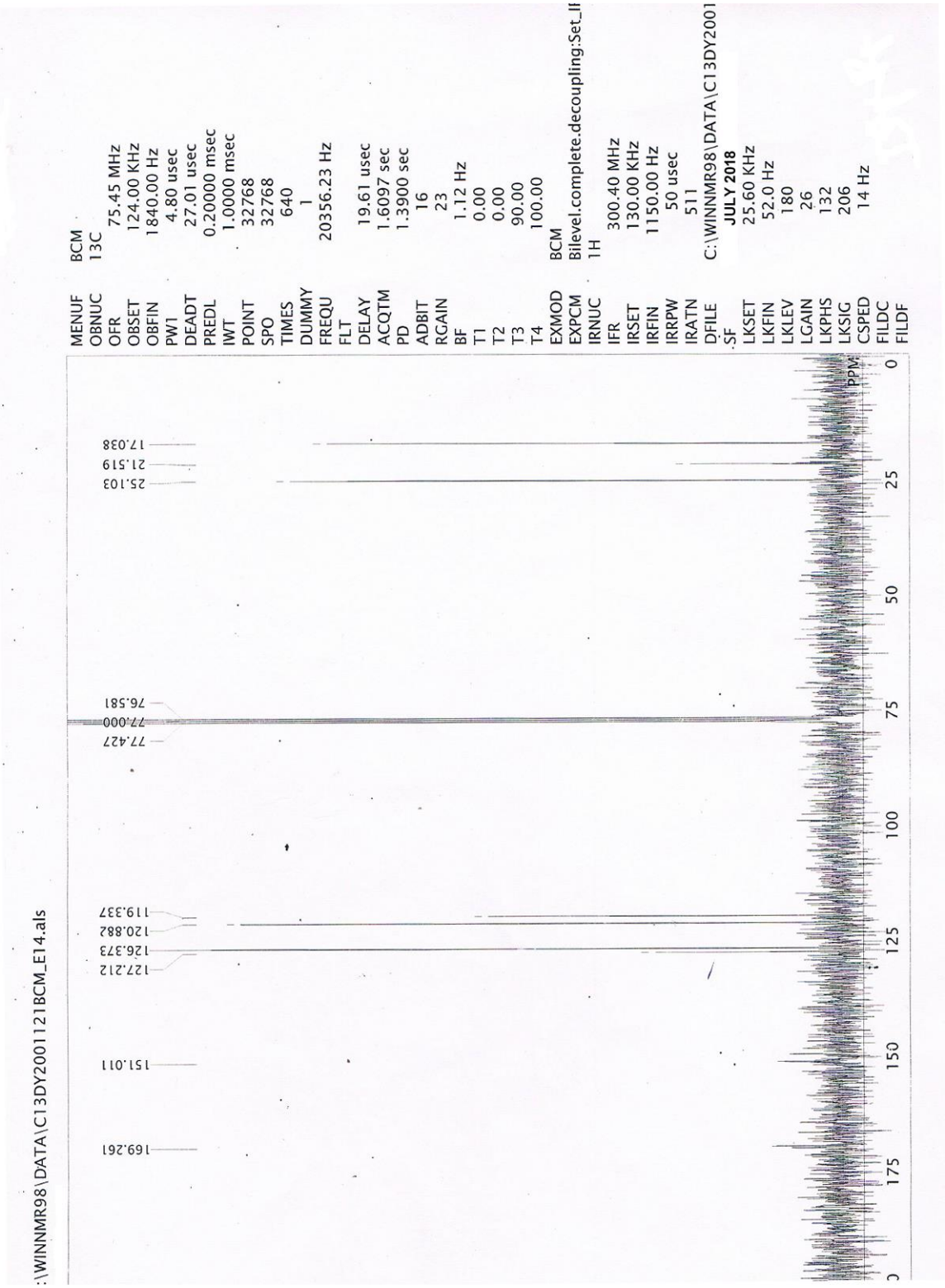
Spectrum 3: IR Spectra of 7a



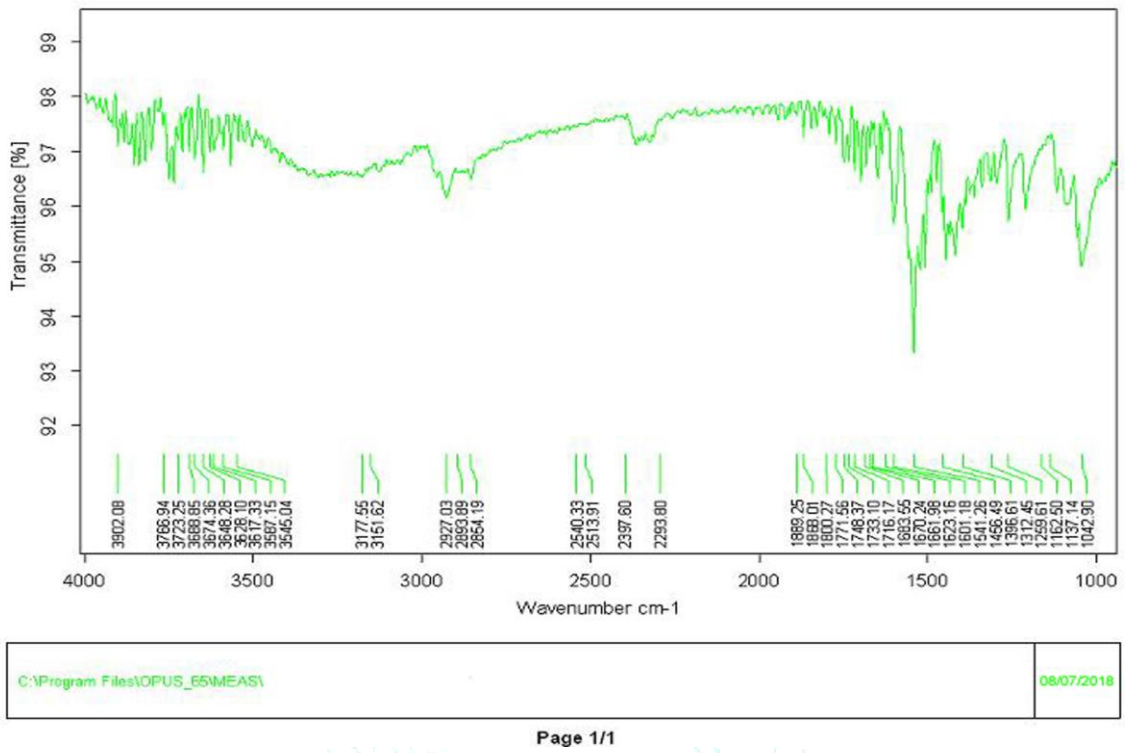
Spectrum 4: IR Spectra of 7b



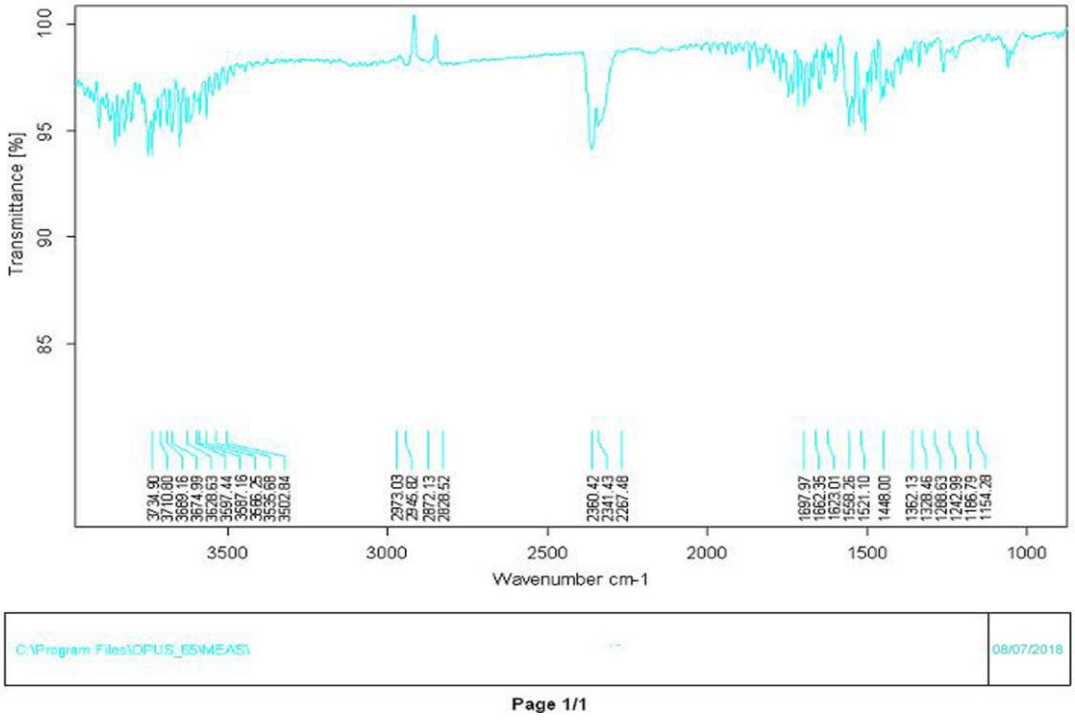
Spectrum 5: [1]HNMR of 7b



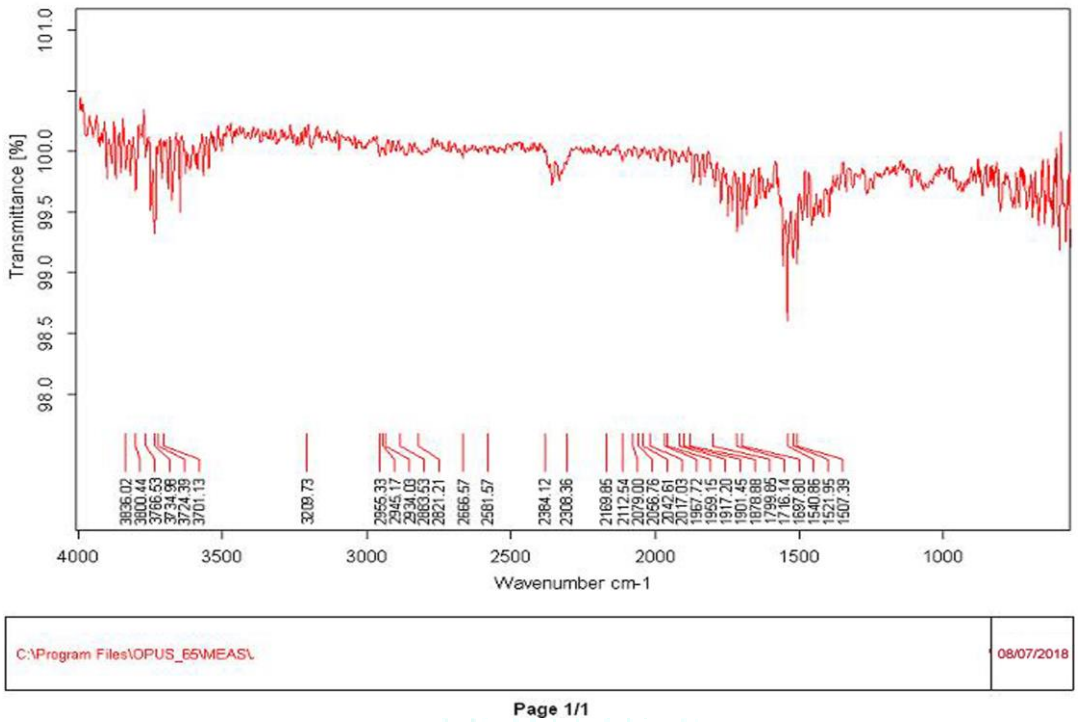
Spectrum 6: ^{13}C NMR of 7b



Spectrum 7: IR Spectra of 7c



Spectrum 8: IR Spectra of 7d



Spectrum 9: IR Spectra of 7e

REFERENCES

1. Souney F., Debellis R., Anthony Zimmerman, Infectious Diseases Comprehensive Pharmacy Review, Edited by Leon Shargel, Alan Mutnick, Paul Souney, and Larry Swanson. Published by Lippincott Williams and Wilkins, 2004, 5.
2. World Health Organization, The Medical Impact of the Use of Antimicrobials in Food Animals: Report and Proceedings of a WHO Meeting. Berlin, Germany, 1997.
3. Shlaes DM, Moellering, RC Jr. The United States Food and Drug Administration and the end of antibiotics. *Clin Infect Dis*, 2002, 34, 402-420.
4. Gupta K., Kaushal S., Chopra S. C., Tigecycline: A novel glycylcycline antibiotic, *Indian J Pharmacol*, 2006, 38(3), 217-219.
5. Noel G. J., Bush K., Bagchi P., Ianus J., Strauss R. S., "A randomized, double-blind trial comparing ceftobiprole medocaril with vancomycin plus ceftazidime plus ceftazidime for the treatment of patients with complicated skin and skin-structure infections". *Clin Infect Dis,* 2008, 46(5), 647–655.
6. Kumbhare RM, Kosurkar UB, Ramaiah MJ, Dadmal TL, Pushpavalli SN, Bhadra MP. Synthesis and biological evaluation of novel triazoles and isoxazoles linked 2-phenyl benzothiazole as potential anticancer agents. Bioorg Med Chem Lett, 2015 22(17), 5424-5427.
7. Prajapat P, Rathore KK, Gandhi D, Agarwal S, Hussain N, et al. A facile synthesis of biologically significant 2-(1,3-benzothiazol- 2-ylimino)-1,3-thiazolidin-4-one / 3-(1,3-benzothiazol-2-yl)-2- thioxoimidazolidin-4-on analogues from 1-(1,3-benzothiazol-2-yl) thiourea and their alphahydroxylamine derivatives. Iranian Journal of Organic Chemistry, 2016, 8(2), 1795-1801.
8. Xu YS, Zeng CC, Jiao ZG, Hu LM, Zhong RG. Design, synthesis and anti-HIV integrase evaluation of 4-oxo-*4H*-quinolizine-3-carboxylic acid Dderivatives. Molecules, 2009, 14(2), 868-883.
9. Takasu K, Inoue H, Kim H, Suzuki M, Shishido T, et al. Rhodacyanine dyes as antimalarials. Preliminary evaluation of their activity and toxicity, J Med Chem, 2002, 45(5), 995-998.
10. Siddiqui N, Rana A, Khan SA, Haque SE, Alam MS, et al.Synthesis of 8-substituted-4-(2/4-substituted phenyl)-2H-[1,3,5]triazino[2,1-b] [1,3]benzothiazole-2-thiones and their anticonvulsant, anti-nociceptive, and toxicity evaluation in mice. J Enz Inhib Med Chem, 2009, 24(6), 1344-1350.
11. Soni B., Ranawat M.S., Sharma R., Bhandari A., *European Journal of Medicinal Chemistry*, 2010, 45(7), 2938-2942.
12. Al-Soud Y. A., Al-Sa'doni H. H., Saeed B., Jaber I. H., Beni-Khalid M. O., Al-Masoudi N. A., Kadir T. A., Colla P. L., Bernardetta B., Sanna T., Loddo R. Synthesis and *in vitro* antiproliferative activity of new benzothiazole derivatives, *ARKIVOC*, 2008, 15 , 225-238.
13. Yadav P., Chauhan D., Sharma N.K., Singhal S., *International Journal of Chemistry*, 2010, 2(2), 1209-1213.