Synthesis of Benzothiazole Derivatives Using Molecular Iodine as a Soft Catalyst

By

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In The Name of Allah, The Most Gracious,

The Most Merciful

Dedication

I dedicate this thesis to my

beloved Parents

Acknowledgments

I am very thankful to ***Almighty Allah,*** Who blessed me with the power, patience and courage to complete this research work.

I express my deep sense of cordial gratitude to my highly experienced and gracious Supervisor ***Dr. Muhammad Arfan,*** whose intellectual stimulation, illustrious advice, encouraging attitude and suggestions enabled me to write this thesis.

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Abstract

The present research work entitled, **"Synthesis of Benzothiazole Derivatives Using Molecular Iodine as a Soft Catalyst"** describes the synthesis of benzothiazole derivatives starting from very low cost reactants. Simple route was designed in which substituted aldehydes reacted with 2-amino thiophenol. In this synthetic scheme, iodine was used as soft Lewis catalyst and the reaction was performed at room temperature and progress was monitored by TLC. Reaction was completed in very short time (3- 5 minutes). Benzoyl and Boc protection of the aldehydes was also carried out to avoid the side reaction and maximize the yield. Benzoyl protection scheme was found to be more compatible in our reaction conditions. Good to moderate yields were obtained. Melting point of all the compounds was taken and characterization was done by FT-IR and GC-MS techniques. FT-IR showed the bands for C=N that provided first indication of successful synthesis of benzothiazole molecule. Molecular ion peaks in GC-MS also supported the synthesis of required derivatives.

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Abbreviations and Symbols

Boc	*tert*-Butyloxycarbonyl
Bz	Benzoyl
CNS	Central nervous system
CAN	Cerium ammonium nitrate
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DPPH	Diphenyl picryl hydrazyl
DMP	Dess-Martin periodinane
DMSO	Dimethyl sulfoxide
Equiv	Equivalent
EtOH	Ethanol
FT-IR	Fourier Transform Infra-Red
GC-MS	Gas Chromatography Mass-Spectrometery
g	Gram
LP	Lipid peroxidation
MIC	Minimum inhibitory concentration
m. p	Melting points
MeOH	Methanol
o	Ortho
PIFA	bis (trifluoroacetate)
P	Para
SPC	Sulfonated Porous Carbon

TLC	Thin layer chromatography
T3P	Propylphosphonic anhydride
UV-Vis	Ultraviolet- visible

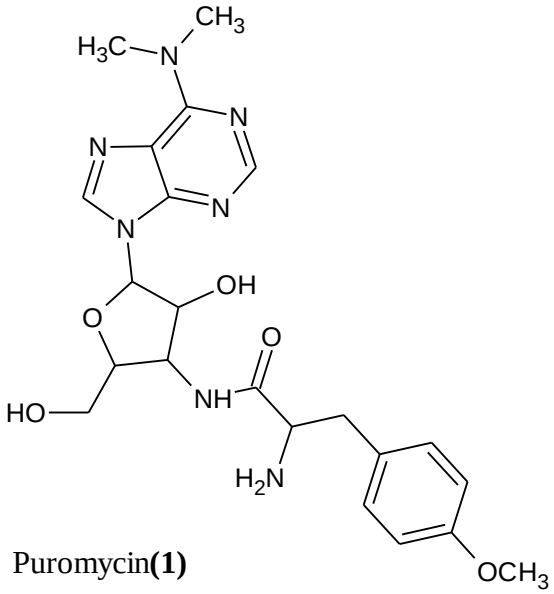
CHAPTER # 1

Introduction

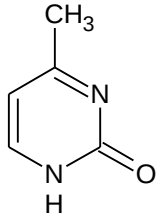
Introduction

Heterocyclic compounds are one of the most important topics in the literature, scientific researches and experiments from the last few decades. Heterocyclic compounds constitute almost 65 % of Organic Chemistry[1].

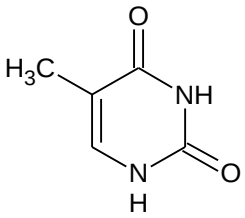
Heterocyclic compounds are widely distributed in nature. Most of them play fundamental role in biological processes occurring in living systems such as nuclear bases, adenine, guanine, thymine and cytosine play important role in process of replication. Few pyrimidines and purines are used as antibiotics e.g. Puromycin[2].



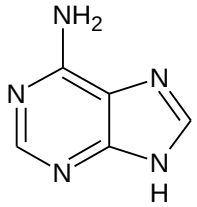
Puromycin**(1)**



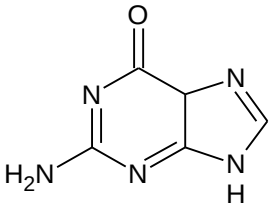
Cytosine**(2)**



Thymine**(3)**

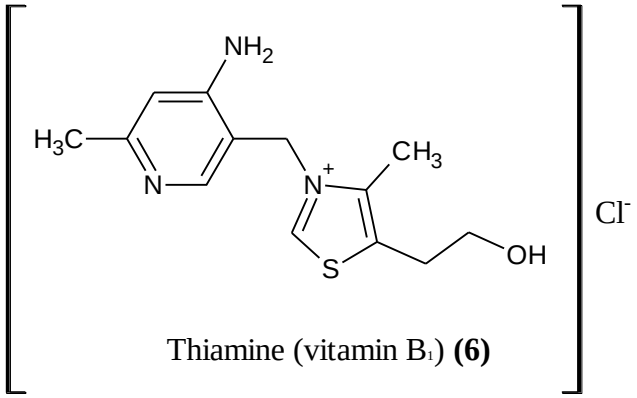


Adenine**(4)**



Guanine**(5)**

Chlorophyll and heme, which are derivatives of porphyrin ring system are the components required for the photosynthesis and for oxygen transport in higher plants and animals. Essential diet ingredients such as thiamine (vitamin B_1), riboflavin (vitamin B_2), pyridoxol (vitamin B_6), nicotinamide (vitamin B_3) and ascorbic acid (vitamin C) are heterocyclic compounds[3].



Thiamine (vitamin B_1) **(6)**

A large number of natural products contain heterocycles. Heterocyclic compounds are crucial for life. They play a fundamental role in the metabolism of all living cells. A wide range of heterocyclic compounds including synthetic and natural are pharmacologically active and are in clinical use. Heterocyclic compounds also play important role as key intermediates in Organic synthesis [4-6], probably this is because heterocyclic compounds have stable ring system that remain intact in multi-step synthetic procedures and cleaved when required to reveal other functional groups e.g. 4-chloro 5(4*H*)-oxazolones are useful intermediates in organic synthesis[7].

Among all benzo-heterocycles, benzothiazole is of considerable importance especially in the field of pharmaceutical chemistry because of its pharmacological activities.

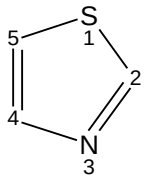
1.1 Benzothiazole:

Benzothiazole belongs to the family of bicyclic heterocyclic compounds having benzene nucleus fused with five-membered ring comprising nitrogen and sulfur atom. Benzothiazoles are present in a range of marine or terrestrial natural compounds that have useful biological activities[8].

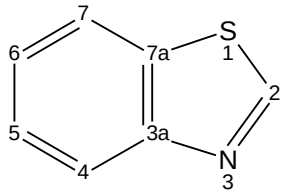
1.1.1 Nomenclature:

The ring system in which benzene ring is fused to the thiazole ring at 4, 5 position; two rings together constitute the basic nucleus 1, 3-benzothiazle. Benzothiazole ring is completely planar[9].

The various positions on the benzothiazole ring are numbered in the manner indicated, with the sulfur having priority over nitrogen as shown compound **(7).**



Thiazole **(7)**



Benzothiazole **(8)**

1.1.2 Importance of Benzothiazoles:

Benzothiazoles are very important class of hetrocyclic compounds because of their diverse biological activities. They play very important role in the development of pharmaceutical drugs that have potential for anticancer[10-13], antimicrobial [14], antioxidant[15], fungicidal[16], anti-diabetic[17], anti-allergic[18], antibacterial[19], anti-inflammatory[20], antiviral[21], antheltminitic[22], antitubercular[23], antimalarial[24], anticonvulsant[25] activities e.g. 2-(4-aminophenyl) benzothiazole derivatives were extensively studied for their anticancer activity[26].

1.2 Methods of Synthesis Benzothiazoles:

Hoffman first time synthesized benzothiazole during the synthesis of disulfhydryl derivative of thiocarbanilide. Hoffman also prepared benzothiazole by the reaction of sodium hydrosulphide with mustard oil. He also synthesized 2- anilinobenzothiazole[27].

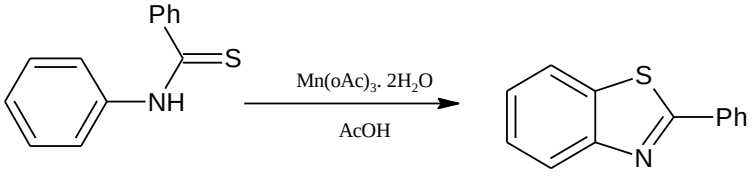
Jenkins *et al.* in **1960** described the synthesis of benzothiazole by treating 2-aminobenzenethiol or 2-aminophenol with the related *ortho*-esters in 75 – 85 % yield[28].

Yalcin *et al.* in **1992** reported the one step synthetic procedure of benzothiazoles by the reaction of carboxylic acids with appropriate N-substituted anilines on heating. They used several dehydrating agents[29]. Peter Stanetty and Barbara Krumpak in **1996** reported series of benzothiazole derivatives synthesized by directed lithiation of 2,2-dimethyl-*N*- (3-halophenyl) propanethioamides or *N*-(3-halophenyl)-*tert*-butylthionocarbamates[30].

Bradshaw *et al.* in **1996** designed the synthetic route for synthesis of new series of 2-(4-aminophenyl) benzothiazoles substituted in the phenyl ring and benzothiazole moiety[31].

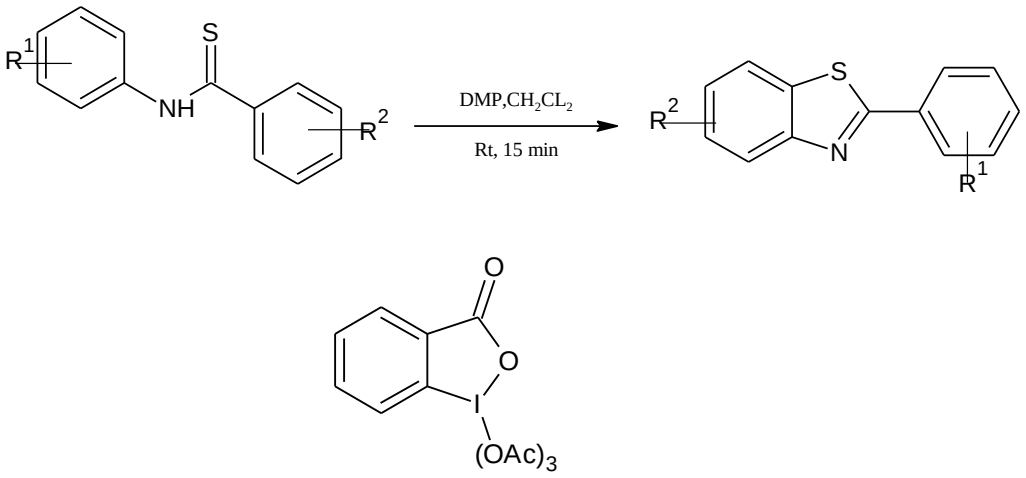
Kashiyama *et al.* in **1999** reported the conversion of 2-(4-aminophenyl) benzothiazoles and their *N*-acetylated forms to *C*- and *N*-hydroxylated derivatives and investigated the role of metabolic oxidation[26].

M. Xue-Jun *et al*. in **2005** used the manganese triacetate for the synthesis of 2-substituted benzothiazoles in radical cyclization procedure of thioformanilides. Reaction was completed in 6 minutes[32].



Scheme 1.1 Synthesis of 2-Substituted Benzothiazoles from Thioformanilides.

D. Subhas *et al*. in **2006** reported a new methodology for the synthesis of benzothiazoles from thioformanilides, in presence of Dess-Martin periodinane **(9)** and CH_2Cl_2. Benzothiazoles were obtained in good to excellent yield in very short time[33].

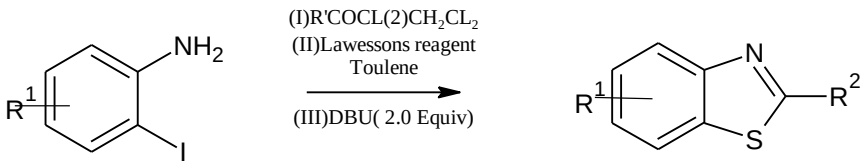


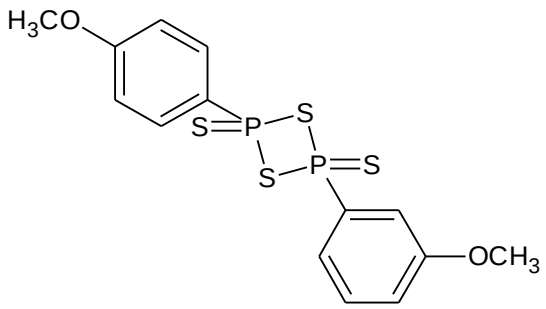
Desmartin periodinane **(9)**

Scheme 1.2 Synthesis of 2-Substituted Benzothiazoles using

Dess-Martin Periodinane Catalyst.

D. Qiuping *et al*. in **2009** presented the cascade synthesis of benzothiazoles by using 2-iodoanilines and acid chloride. They used Lawesson's reagent **(10)**, reaction scheme consist of three steps. In 1st step, reaction of 2-iodoanilines with acid chloride occured then synthesized benzamides transformed into benzothioamides. In 2nd step, Lawesson's reagent would support the reaction and finally intermolecular cyclization of benzothioamides occurs. Product was obtained in good yield, 66- 95 % [34].

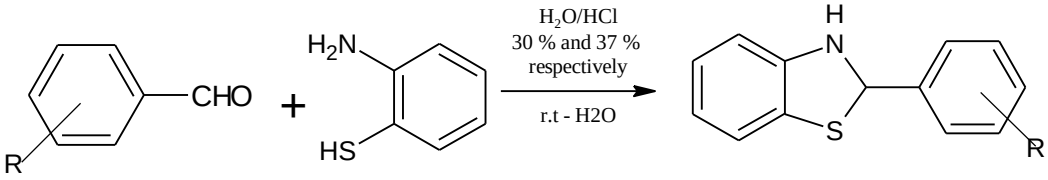




Lewsson's Reagent **(10)**

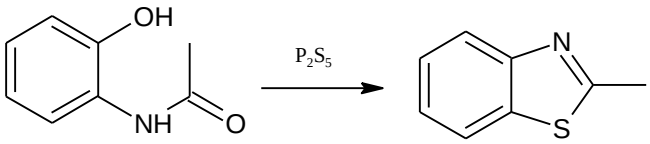
Scheme 1.3 Synthesis of Benzothiazoles by Using 2-Iodoanilines and Acid chloride.

G. Hong *et al*. in **2009** described the synthesis of substituted benzothiazoles by the reaction of aldehydes and 2-aminothiohenol, H_2O_2/HCl system in ethanol was used. Good to excellent yield was obtained[35].



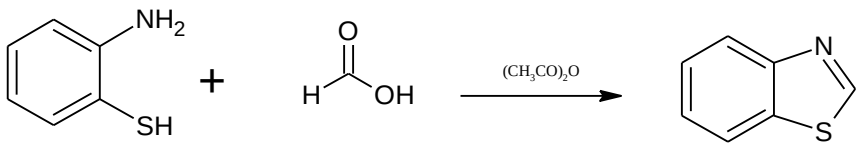
Scheme 1.4 Synthesis of Benzothiazoles by Using Aldehydes and 2-Aminothiohenol

H. Shivraj *et al*. in **2010** reported the synthetic method for benzothiazole in which phosphorus pentasulfide reacted with *o*-acylaminophenoles and yielded 2-substituded benzothiazole[36].



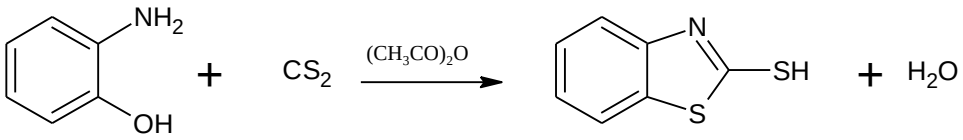
Scheme 1.5 Synthesis of 2-Substituted Benzothiazole Using Phosphorus Pentasulfide.

H. Shivraj e*t al*. in **2010** presented a synthetic route for 2-substituted benzothiazole. According to which *o*-aminothiophenols reacted with formic acid in the presence of acetic anhydride to produce benzothiazole[36].



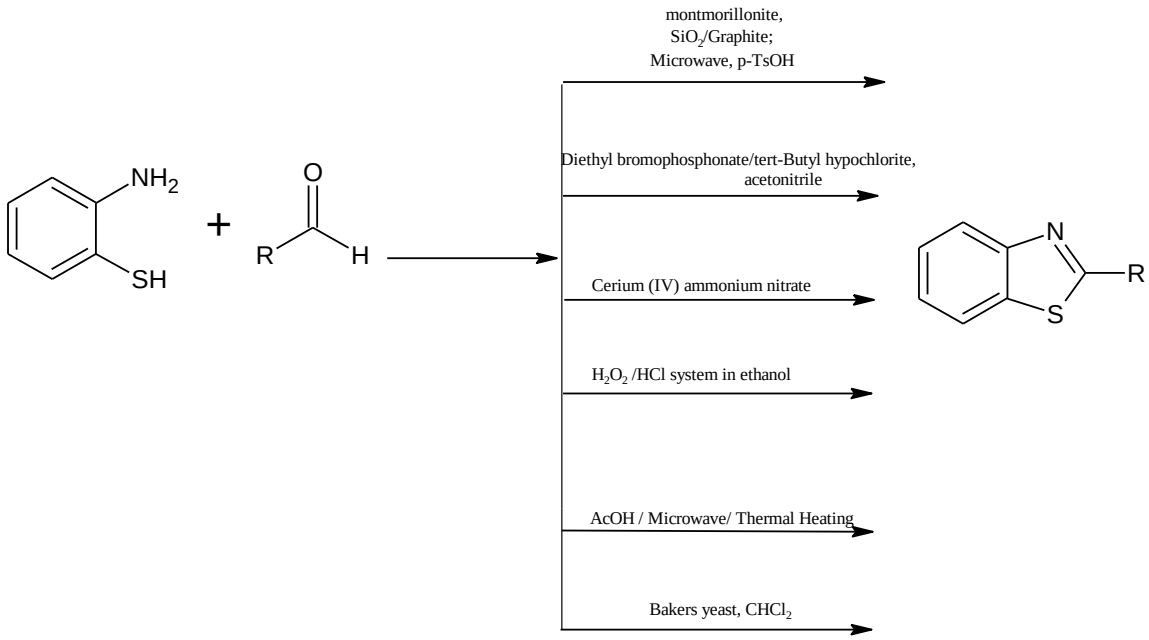
Scheme 1.6 Synthesis of Benzothiazole by Using Acetic anhydride.

They also synthesized 2-mercaptobenzothiazole as given in below.



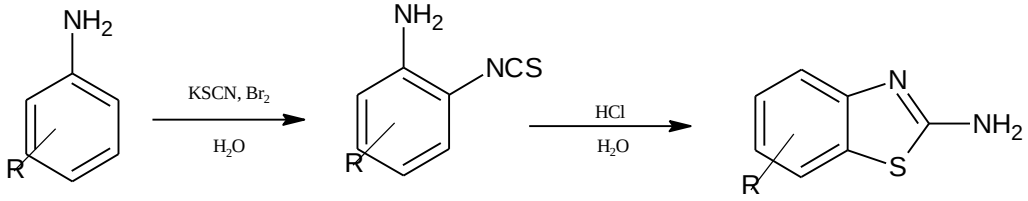
Scheme 1.7 Synthesis of 2-Mercaptobenzothiazole by Using Acetic anhydride.

Sukhbir *et al*. in **2011** presented that *ortho*-aminophenol is a versatile starting material for synthesis of different kinds of heterocyclic rings. They described 2-substituted benzothiazole could easily be synthesized by applying condensation with aldehydes and substituted aromatic acids in presence of different catalyst[37].



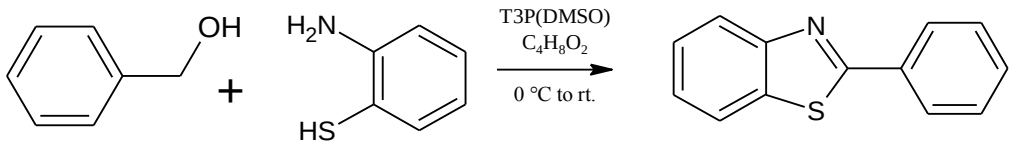
Scheme 1.8 Synthesis of 2-Substituted Benzothiazole Using Different Catalysts.

Different substituted anilines when treated with KSCN in presence of glacial acetic acid, yielded 2-substituted benzothiazoles[37].



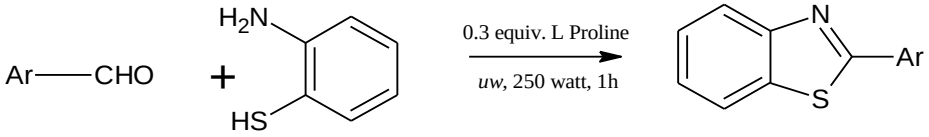
Scheme 1.9 Synthesis of 2-Substituted Benzothiazole from Anilines.

Raghavendra *et al.* in **2011** reported benzothiazole's synthesis by using propylphosphonic anhydride (T3P) as acatalyst along with DMSO and ethylacetate as solvent. Condensation reaction of alcohols and 2-aminothiophenol was performed at 0 ^{o}C. Benzothiazoles were obtained in good yields[38].



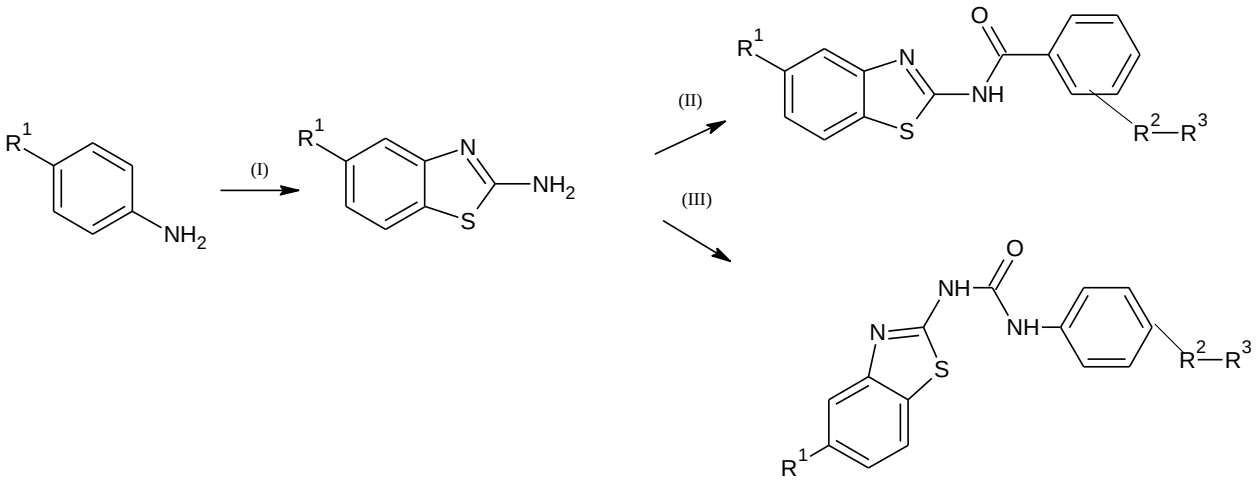
Scheme 1.10 Synthesis of 2-Substituted Benzothiazole from Alcohols and 2-Aminothiophenol

L. Adam *et al*. in **2012** described the synthesis of 2-arylbenzothiazoles by using *L*-proline, by the reaction of 2-aminothiahenol with aryl aldehydes. Reaction was performed under microwave irradiation, no solvent was used. Aldehydes gave good yield as compared to aromatic and aliphatic acids. However under microwave carboxylic acids also gave good yield[39].



Scheme 1.11 Synthesis of 2-Aryl Benzothiazole by Using by using *L*-Proline.

C. Rosanna *et al*. in **2012** reported the synthesis of arylamide and arylurea benzothiazole derivatives. 2-substituted benzothiazoles (amide derivatives) were obtained by the reaction of 2-amino-6-substituted benzothiazoles with different aryl chlorides. Aryl urea derivatives were obtained by reacting amino-6-substituted benzothiazoles with aryl-isocyanates. Reaction was performed at room temperature. Their *in-vitro* anticancer activity was also evaluated against 60 human cancer cell lines[40].



R_1 = OCH_3, OCF_3; R_2 = F, OCH_3, CN, F, $NHCOCH_3$; R_3 = H, F

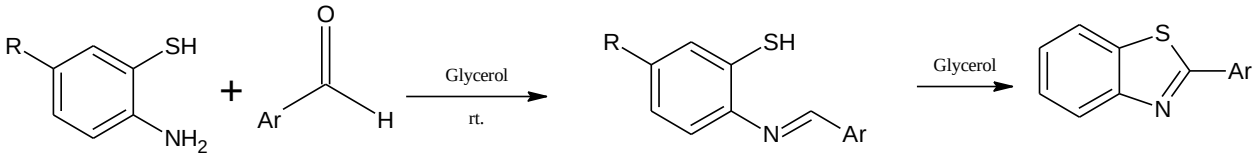
(I) KSCN, CH_3COOH, Br_2

(II) Aryl chloride, pyridine and NaH, DMF, N_2

(III) Aryl- isocyanate, CH_2Cl_2

Scheme 1.12 Synthesis of Arylamide and Arylurea benzothiazole.

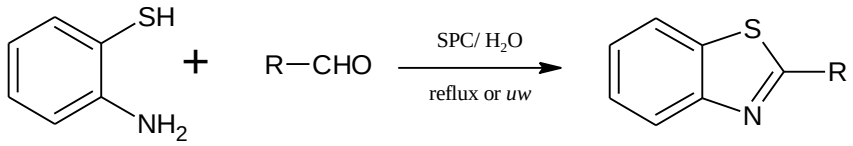
S. Kamal *et al*. in **2012** described the synthesis of 2-arylbenzothiazoles by the condensation reaction of 2-aminothiophenols and aromatic aldehydes using glycerol as a solvent. No catalyst was used. Solvent effect was checked by using H_2O, acetone and $CHCl_3$, under the same reaction conditions. Electron withdrawing and donating groups also gave the similar yield in the (scheme 1.13) described[41].



R = H, Cl, OCH_3

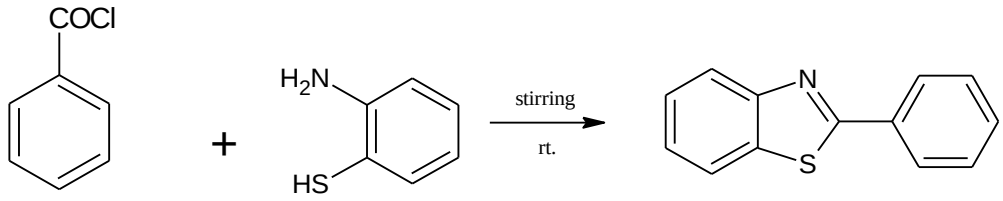
Scheme 1.13 Synthesis of 2-Substituted Benzothiazole from Aromatic Aldehydes.

S. Arash *et al*. in **2012** reported very efficient method for the preparation of benzothiazole derivatives. Reaction was performed in water through sulfonated porous carbon (SPC) as a heterogeneous catalyst. 2-Aminothiophenol was reacted with aldehydes under reflux and microwave irradiation conditions[42].



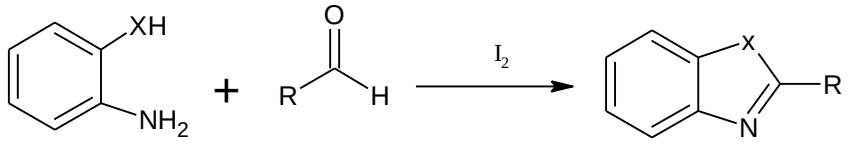
Scheme 1.14 Synthesis of 2-Substituted Benzothiazole Using Sulfonated Porous Carbon (SPC) as a Heterogeneous Catalyst.

G. Nagararaju *et al*. in **2015** proposed reaction mechanism in which *o*-amino thiophenol was reacted with benzoyl chloride in chloroform at room temperature. Almost 45-46 % yields were obtained[43].



Scheme 1.15 Synthesis of Benzothiazole from Benzoyl Chloride.

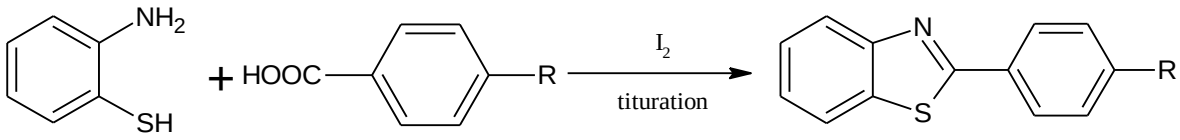
M. Matloubi *et al*. in **2006** reported the reaction of 2-aminothiophenol and 2-aminophenol with various aldehydes to synthesize 2-substituted-benzothiazoles and benzoxazoles. They employed the molecular iodine as a catalyst in presence and absence of microwave irradiation and solvent free conditions. Benzothiazole and benzoxazoles were obtained in good yield. In presence and absence of microwave yield was obtained in similar range 65-95%, but without microwave reaction time was increased up to 20 minutes[44].



X = O, S R= Aryl 65-95 %

Scheme 1.16 Synthesis of 2-Substituted Benzothiazoles and Benzoxazoles.

S. Gupta *et al*. in **2007** described the synthesis of benzothiazoles by the reaction of 2-aminothiophenol and benzoic acid by using molecular iodine as an efficient catalyst. Benzothiazoles were obtained in short time period of 10 minutes, yield was not mentioned, no additional solvent were used in this method[45].

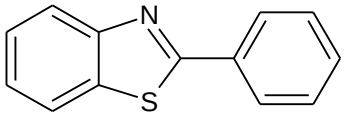


Scheme 1.17 Synthesis of Benzothiazoles from 2-Aminothiophenol and Benzoic acid.

1.3 Biological Activities

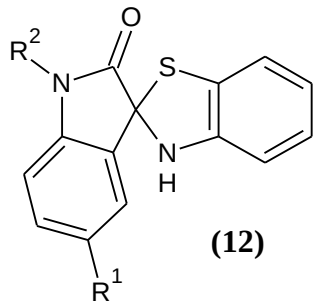
1.3.1 Antioxidant Activities:

G. Nagararaju *et al*. in **2015** synthesized 2-substituted benzothiazole **(11)** and their screening was done for *in-vitro* antioxidant activity through five methods, namely nitric oxide, diphenyl picryl hydrazyl (DPPH), hydroxyl radical scavenging activity, lipid peroxidation and their reductive ability. Ascorbic acid was taken as reference. These compounds showed significant antioxidant activity[43].



2-Phenyl benzothiazole **(11)**

K. Nilgun *et al*. in **2010** synthesized H-spiro[1,3-benzothiazole-2,30-indol]-20(10H)-ones **(12)** and evaluated for their antioxidant activities by finding their reducing power ability, diphenyl picryl hydrazine scavenging activity, trolox equivalent antioxidant capacity and Fe^{+3}/ ascorbate system induced inhibition of lipid peroxidation (LP). Compounds having methyl group at R_1 and R_2 positions found to be more antioxidant. These compounds showed good antioxidant activity[46].



(12)

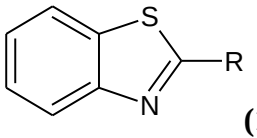
$R_{1=}$ CH_3, Cl, NO_2, CF_3O, Br $R_{2=}$ H, CH_3

1.3.2 Antibacterial Activities:

K. Ravindra *et al*. in **2014** prepared 1, 2, 3-triazole tagged amino bis(benzothiazole) derivatives and checked their minimum inhibitory concentrations (MIC) against *Bacillus subtilis, Staphylococcus aureus, Escherichia coli* , *Pseudomonas aeruginosa* and *Klebsiella pneumonia*. Compounds **(14)** and **(15)** showed good activity against all bacterial strains[47].

T. Ivan *et al*. in **2015** synthesized Oxazole and benzothiazole moieties **(16)** and tested for antibacterial activity against *Escherichia coli, Staphylococcus aureus* and *Pseudomonas aerugenosa*. They used nutrient agar medium. Benzothiazole derivatives showed moderate to good antibacterial activities[48].

C. Mohit *et al*.in **2016** prepared 2-substituted benzothiazole **(13)** analogues and evaluated against various bacterial strains that include *Escherichia coli, Staphylococcus aureus, Salmonella enterica* and *Salmonella bongori* and *Bacillus subtilis*. Benzothiazole with electron donating groups such as methyl, hydroxyl, methoxy groups in the benzene ring showed weak or no activity[49].

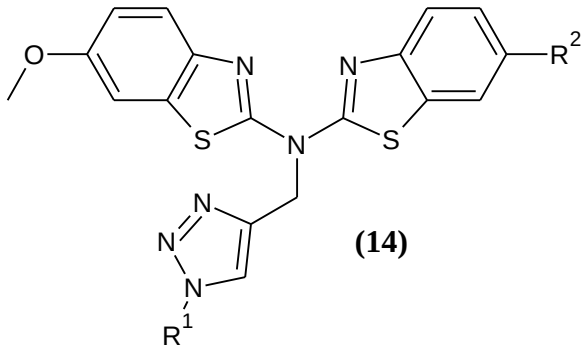


(13)

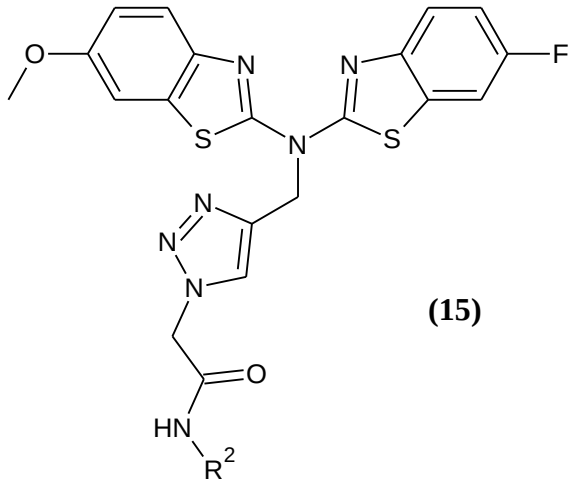
R = C_6H_5CHO, ClC_6H_4CHO, C_8H_8O, FC_6H_4CHO, BrC_6H_4CHO, $C_5H_4O_2$, C_9H_7NO, $C_{10}H_7CHO$, $HOC_6H_3(OCH_3)CHO$, C_5H_4OS, C_6H_5NO, $C_7H_6O_2$.

1.3.3 Antifungal Activities:

K. Ravindra *et al*. in **2014** screened the compounds for their *in-vitro* antifungal activity against the *Candida rugosa*, *Candida albicans*, *Rhizopus oryzae*, *Aspergillus niger* and *Saccharomyces cerevisiae* through Agar Well Diffusion Method. Compounds **(14)** and **(15)** showed good activity against all fungal strains[47].

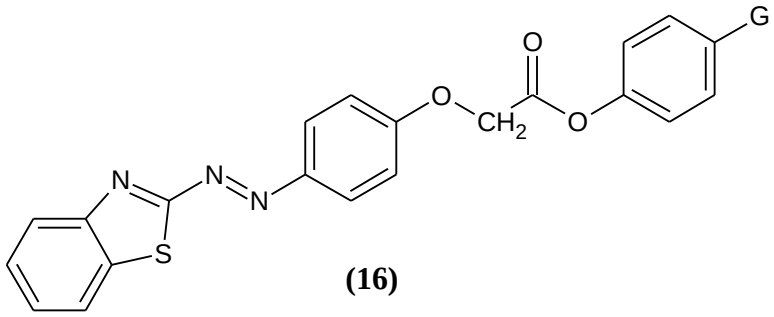


(14)



(15)

T. Ivan *et al*. in **2015** also evaluated the compound **(16)** for antifungal activity against the fungal strains namely *Aspergillus niger* and *Candida albicans*. They used Sabouraud's dextrose agar medium. These benzothiazole derivatives showed good to moderate antifungal activities[48].

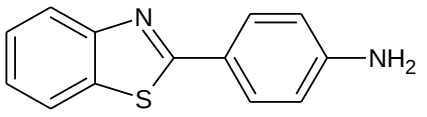


(16)

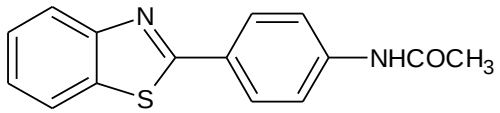
G= CN, NO_2, $OsCH_3$

1.3.4 Anti-Cancer Activities:

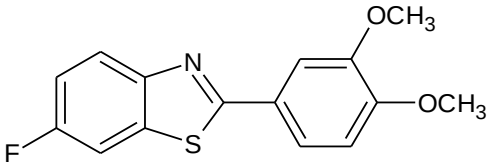
A. Kamal *et al.* in **2010** screened benzothiazole conjugates **(17-20)** against cancer cell lines that include leukemia, lung cancer, colon cancer, CNS cancer, melanoma, ovarian cancer, renal cancer, prostate cancer and breast cancer. 48 hours drug exposure was applied and a sulforhodamine B(SRB) protein assay was used to estimate cell proliferation, benzothiazole derivatives showed good to excellent anti-cancer activity[50].



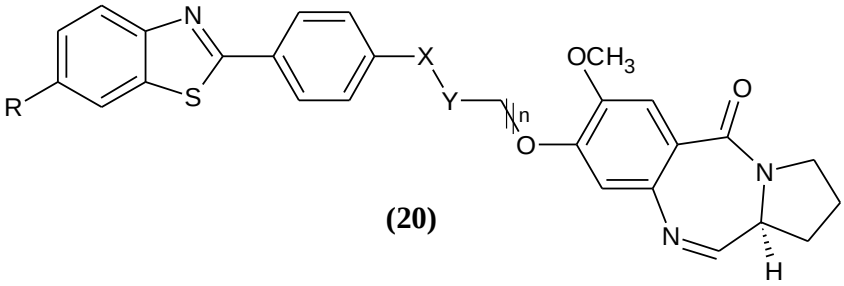
(17)



(18)



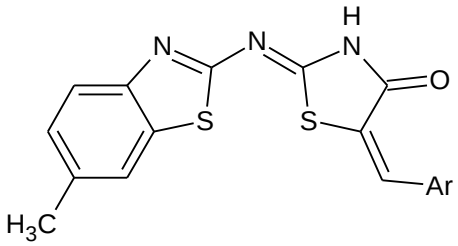
(19)



(20)

X= NH, O, Y= CH_2, CO, R= H, F; n = 3, 4

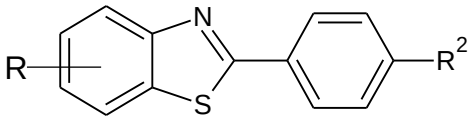
D. Havrylyuk et al. in **2010** described the synthesis of benzothiazole substituted 4-thiazolidinones **(21)** and screened these benzothiazoles against 60 cancer cell lines by using the single concentration of 10^{-5} M. Cell culture was exposed to drug for 48 hours and protein assay used to check cell growth was sulforhodamine (B). 5-Arylidene-3-(benzothiazol-2-ylamino)-2-thioxo-4-thiazolidones showed good activity against renal cancer cell line RXF 393 while 5-arylidene-2-(6-methylbenzothiazol-2-ylimino)-4-thiazolidinones were highly active against CNS cancer SF-295[51].



(21)

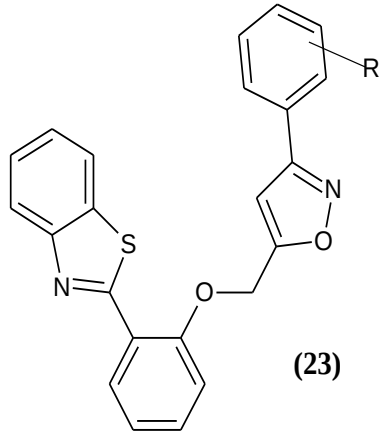
Ar = 4-NEt_2- C_6H_4, 4-OMe- C_6H_4, 4-Cl- C_6H_4, 2-(NH_2COCH_2O)-5-Cl-CH_3, 2-(4-OMe-$C_6H_4NHCOCH_2O$-5-Cl-C_6H_3

A. Bhuva *et al*. in **2010** described that benzothiazole derivatives **(22)** containing mono fluoro or mono bromo groups showed good results against MCF-7 cell line. *In vitro* cancer activity was increased with the increase in dose. Compound [5, 6-difluoro-2-(4-methoxyphenyl)-1, 3-benzothiazole] was least active[52].

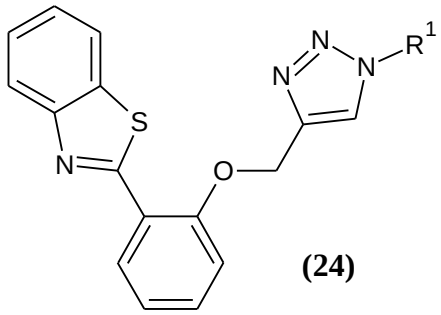


(22)

M. Kumbhare *et al*. in **2012** synthesized phenyl benzothiazole derivatives **(23, 24)** that exhibited positive result for MCF-7 cell line and colo-205 cell line. Flow cytometry (FACS) screening exhibited that benzothiazole possess the ability to cause apoptosis[53].



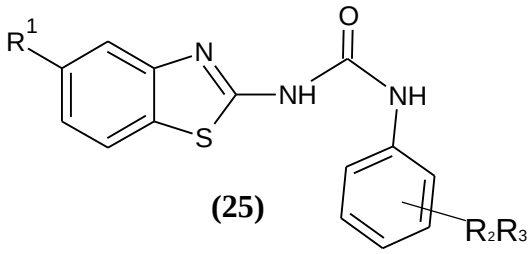
(23)



(24)

N. Malleshappa *et al*. in **2012** reported that benzothiazole derivative, 7-chloro-N-(2, 6 dichlorophenyl) benzo[d]thiazol-2-amine showed good results against lung cancer HOP-92[54].

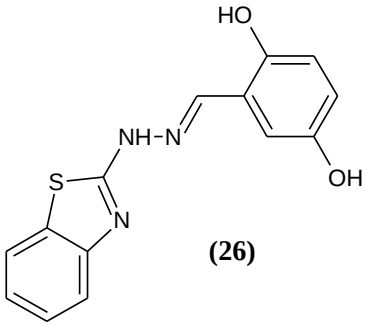
R. Caputo *et al*. in **2012** reported benzothiazole derivatives **(25)** substituted with amide and urea functional group and tested against human cancer cell lines. Urea linked benzothiazoles having electron withdrawing substituent at the *para* position were active against cancer[40].



(25)

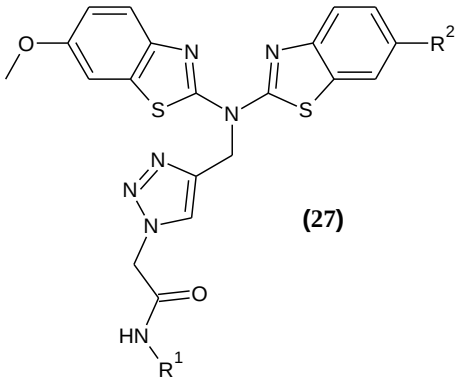
R_1 = OCH_3, OCF_3; R_2 = F, OCH_3, CN, F, $NHCOCH_3$; R_3 = H, F

B. Lindgren *et al.* in **2014** reported the synthesis and biological activity of (E)-2-benzothiazole **(26)** against breast (MDA-MB-435), leukemia (HL-60) and colon (HCT-8) cell lines. Synthesized compounds exhibited good activity against all three cell lines[55].



(26)

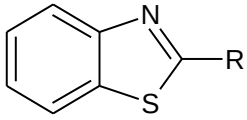
M. Kumbhare *et al*. in **2014** reported benzothiazole derivatives **(27)** containing fluoro triazole, showed good anti- cancerous activity against U937[THP-1][47].



(27)

R^1= 4- FC_6H_4 R^2 = CH_2-4-$OCF_3C_6H_4$

Moustafa *et al*. in **2015** synthesize benzothiazole and pyrimido[2, 1-b]benzothiazole derivatives and tested their biological activity was evaluated against 60 cancer cell lines at single dose of (10 µM). Cancer cell lines include leukemia, non-small cell lung, colon, central nervous system (CNS), melanoma, ovarian, renal, prostate and breast cancer cells[56]. O. Leong *et al*. in **2016** synthesized benzothiazole derivative, their cytotoxicity was analyzed against human epithelioid cervix carcinoma (HeLa) and human breast carcinoma cell line (MCF-7). It was revealed that MCF-7 cells were more biologically active toward all compounds **(28).** Many anticancer drugs that include doxorubicin, mitoxantrone and cisplatin were efficient against MCF-7 and HeLa cells by causing apoptosis, these drugs may also act by following the same apoptosis mechanism[57].



(28)

R = C_9H_7NO, $C_{10}H_7CHO$, $HOC_6H_3(OCH_3)CHO$, C_5H_4OS, C_6H_5NO, $C_7H_6O_2$.

1.4 Aims and Motivations:

It has been observed that scientists have proposed wide range of methodologies for synthesis of 2-substituted benzothiazole nucleus and its derivatives by using different type of reactants, reagents and catalysts to improve the selectivity, purity and yield of the products under environment friendly conditions starting from acetic anhydride[37], carboxylic acids coupling with thiophenols, aromatic nitriles and anilines[38]. Also different type of catalysts were used to synthesize 2-substituted benzothiazole such as bromine, sulphuric acid, benzene, phenyl iodine (III) bis(trifluoroacetate) (PIFA), cerium ammonium nitrate (CAN) catalyst[58]. Due to extensive pharmacological activities of benzothiazole molecule there is still need to synthesize such derivatives that show better results as a pharmaceutical drug under mild reaction conditions and from low cost reagents.

In our present research work we plan to synthesize such benzothiazole derivatives that contain aromatic substituents, under mild conditions by using molecular iodine as a catalyst. Moreover, implement different protection schemes where ever required to check the effect of our catalyst that which protection scheme will give the good yield and more economical under the given conditions. Also we wanted to observe that either these protection schemes are compatible, or not with iodine.

CHAPTER # 2

Experimental

Experimental

2.1 Instrumentation

All compounds were weighed through electronics analytical balance (ATY224). Melting points of all the compounds were determined from melting point apparatus (SMP10), which were uncorrected. Spots on TLC plates were monitored using UV lamp. Rotary evaporator (R-210) was used to remove excesses solvent during protection step. FT-IR spectra were recorded on Bruker ATR FTIR.

Instrument GC-MS was of PerkinElmerclarus600c MS.

Column: Elite-5, inner diameter: 0.25 mm.

Column flow: 1mL/minute.

Carrier gas: Helium.

Oven program: initial temperature 40 ^{o}C hold for 1 minute then with the rate of 10 ^{o}C/ minute and increased upto to 300 ^{o}C and hold for 1 minute, total run time was 28 minutes.

2.2 Reagents

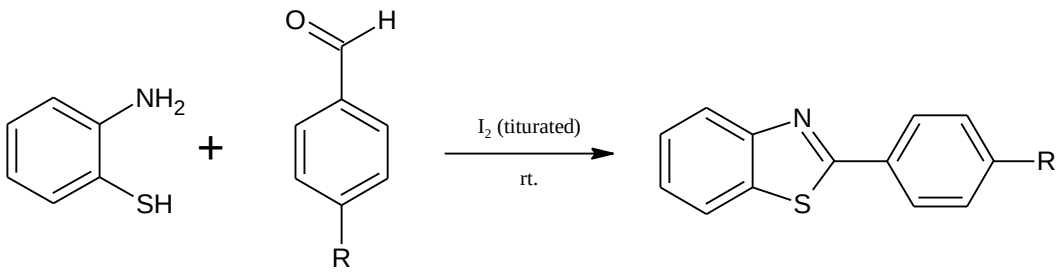
p-Amino benzaldehyde, *p*-methoxy benzaldehyde, furaldehyde, *p*-chloro benzaldehyde, *o*-chloro benzaldehyde, *o*-hydroxy benzaldehyde, benzaldehyde, thiophene carbanaldehyde, NaOH, $Na_2S_2O_3$, benzoyl chloride, $KHSO_4$, HCl, iodine, Boc (di-tertiary butyldicarbonate), Na_2SO_4, were purchased from Sigma Aldrich, Merck and Fluka.

2.3 General Method for the Synthesis of Benzothiazole Derivatives:

Benzothiazoles were synthesized by treating aromatic aldehydes with 2-aminothiophenol. Aromatic aldehyde (4.13 mmol, 1 equiv.) was taken in flask then iodine (1.33 mmol, 0.5 equiv.) was added as a catalyst and grinded for 3-5 minutes with aldehyde. Afterward 2-aminothiophenol (4.13 mmol, 1 equiv.) was added in three portions, immediate reaction

was occurred with release of heat. Reaction progress was monitored by TLC; spots were visualized under UV lamp. Reaction conditions were optimized as follows. Aldehyde was used 1 equiv. against 2-aminothiophenol, 0.5 equiv., 0.75 equiv. and 1 equiv., iodine was used 0.3 equiv., 0.5 equiv. and 0.75 equiv. Reaction was performed for 5-10 minutes. Best yield was obtained for (1 equiv.) aldehyde, (1 equiv.) 2-aminothiophenol and (0.5 equiv.) iodine for five minutes and with some reactants 0.3 equiv. iodine was used. After reaction, crude product was washed with 10 % $Na_2S_2O_7$ to remove iodine and filtered. Then crude product was purified by recrystallization. Methanol, ethanol, chloroform and water were used as recrystallizing solvents. After the selection of the suitable solvent, samples were recrystallized by placing in the flask. First of all sample was dissolved in minimum amount of hot solvent, then added more solvent and heated until all the sample was dissolved then placed for recrystallization and filtered. Yield was calculated by using formula eq (1).

$$\% \text{ Yield} = \text{Actual yield} / \text{Theoretical yield} \times 100 \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (1)$$

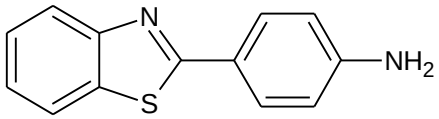


Scheme 2.1 General Reaction for Benzothiazole's Synthesis.

2.4 Synthesis of 2-substituted Benzothiazole Derivatives:

Single step method was developed for the synthesis of benzothiazoles, also Boc and benzoyl protections have been carried out.

2.4.1 Synthesis of 2-Amino Benzothiazole:



(27)

p-Amino benzaldehyde (500 mg, 4.13 mmol, 1 equiv.) was taken in mortar and grinded with iodine (160 mg, 1.33 mmol , 0.3 equiv.) for 5 minutes, then 2-aminothiophenol (4.13mmol,1 equiv.) was added in three portions and recrystallized from (70:30) EtOH:H_2O. Bright yellow crystalline precipitates were obtained in 0.4 g. Yield = 48 %, R_f value in 1% methanol: chloroform system (0.5), **m.p.** 179-180 ^oC. **FT-IR (**ν_{max}, cm^{-1}): 1603(C=N), 1476(C=C), 1427(C-C). **GC-MS**: m/z= 211, 105, 109.

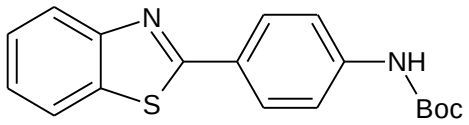
2.4.2 Synthesis of 2-(4-Boc aminophenyl) Benzothiazole:

This reaction was done in two steps, 1st step involve Boc protection of *p*-amino benzaldehyde and in 2nd step Boc *p*-amino benzaldehyde was reacted with 2-aminothiophenol as follows:

2.4.2.1 Boc Protection of *p*-Amino Benzaldehyde:

The solution of aldehyde (500 mg, 4.13 mmol) in 8.28 mL dioxane, 4.19 mL of water and 4.19 mL of 1M solution of NaOH was stirred and cooled in ice bath. $(Boc)_2O$ (900 mg, 4.54 mmol) was added to solution and stirred for 1 hour at room temperature the solution was concentrated under reduced pressure, cooled in ice bath, afterward ethyl acetate (2.76 mL) was added and acidified with dilute solution of $KHSO_4$ to pH 2-3. The aqueous layer was extracted with ethyl acetate and washed with H_2O, brine and dried over $MgSO_4$, solvent was removed under reduced pressure to afford *p*-aminobenzaldehyde[59]. **m.p.** 140-142 ^oC, **FT-IR(**ν_{max}, cm^{-1}): 1656(C=O), 1587(Boc, C=O), 1368($OC(CH_3)_3$).

2.4.2.2 Boc *p*-Amino Benzaldehyde Reaction with 2-Aminothiophenol:



(28)

After protection Boc *p*-amino benzaldehyde (500 mg, 2.1 mmol, 1 equiv.) was taken in mortar and grinded with iodine (70 mg, 0.6 mmol, 0.3 equiv.) for 5 minutes, then added 2-aminothiophenol (2.1 mmol, 1 equiv.) in three portions. Crude product was recrystallized from (70:30) EtOH:H_2O. Light yellow precipitates were obtained on filtration in 0.51 g. Yield = 69 %, R_f value in 1% methanol: chloroform system (0.4), **m.p.** 175-176 ^oC. **FT-IR (**ν_{max}, cm^{-1}): 3300(NH), 1700(C=O), 1604(C=N), 1476(Ar, C=C), 1427(C-C), 1368($OC(CH_3)_3$. **GC-MS:** m/z= 325 $[M+H]^+$, 211, 109, 53.

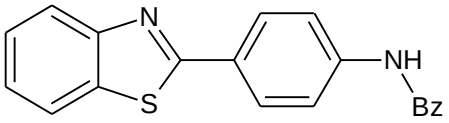
2.4.3 Synthesis of 2-(4-Bz Aminophenyl) Benzothiazole:

This reaction was done in two steps, 1st step involve benzoyl protection of *p*-amino benzaldehyde and in 2nd step benzoyl *p*-amino benzaldehyde was reacted with 2-aminothiophenol as follows:

2.4.3.1 Benzoyl Protection of *p*-Amino Benzaldehyde:

Dissolve (500 mg, 4.13 mmol) of aldehyde in 2 mL of 10 % NaOH solution contained in a conical flask. After that stirred for half hour then added 0.68 mL benzoyl chloride in three portions and again stirred for half hour. Then reaction mixture was transferred to a beaker added few grams of ice and then added concentrated HCl slowly with stirring until pH 3 is maintained. Resulting product washed was with 4 mL CCl_4, filtered and dried[59]. **m.p.** 150-153 ^oC, **FT-IR (**ν_{max}, cm^{-1}): 1676(C=O), 1452, 1417(Ar C=C), 1323 (C-N).

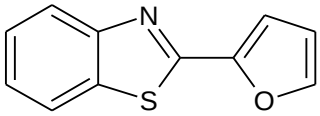
2.4.3.2 Benzoyl *p*-Amino Benzaldehyde Reaction with 2-Aminothiophenol:



(29)

Benzoyl *p*-amino benzaldehyde (500 mg, 2.2 mmol, 1 equiv.) was taken in mortar and grinded with iodine (70 mg, 0.6 mmol, 0.3 equiv.) for 5 minutes, then added 2-aminothiophenol (2.2 mmol, 1 equiv.) in three portions. Then product was recrystallized from (60:40) MeOH:H_2O. Yellow solid product was obtained on filtration in 0.62 g. Yield = 85 %, R_f value in 1% methanol: chloroform system (0.6), **m.p.** 179-180 ^oC. **FT-IR (**ν_{max}, cm^{-1}): 3300(N-H), 1700(C=O), 1605(C=N), 1474(Ar C=C), 1427(1427), 1313(C-N). **GC-MS:** m/z= 254, 239 and 211.

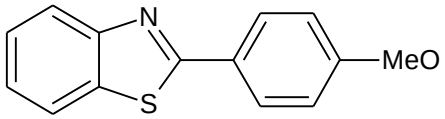
2.4.4 Synthesis of 2-(Furan-2-yl) Benzothiazole:



(30)

Five membered furaldehyde (500 mg, 5.2 mmol, 1 equiv.) was taken in mortar and grinded with iodine (190 mg, 1.5 mmol, 0.3 equiv.) for 5 minutes, then added 2-aminothiophenol (5.2 mmol, 1 equiv.) in three portions, immediate reaction took place. After that recrystallized was done from (70:30) EtOH:H_2O. Product was obtained in 0.98 g. Yield = 92 %, R_f value in 1% methanol: chloroform system (0.6) **FT-IR (**ν_{max}, cm^{-1}): 3371, 1605(C=N), 1472(Ar C=C), 1306(C-N). **GC-MS** m/z: 205[M^+], 174, 149, 136.

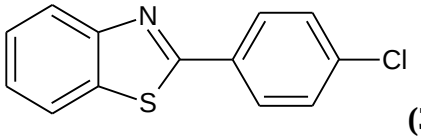
2.4.5 Synthesis of 2-(4-Methoxyphenyl) Benzothiazole:



(31)

Another aromatic aldehydes *p*- methoxy benzaldehyde (500 mg, 4.16 mmol, 1 equiv.) was then grinded in mortar with iodine (260 mg, 2.08 mmol, 0.5 equiv.) for 5 minutes after that 2-aminothiophenol (4.16 mmol, 1 equiv.) was added in three portions. Product was recrystallized from chloroform. Yellow semi solid product was obtained on filtration in 0.71 g. Yield = 81 %, R_f value in 1% methanol: chloroform system (0.8) **m.p.** 123-124 ^oC. **FT-IR** (ν_{max}, cm^{-1})*:* 3371, 1605(C=N), 1472(Ar C=C), 1306(C-N). **GC-MS** m/z: 149,105.

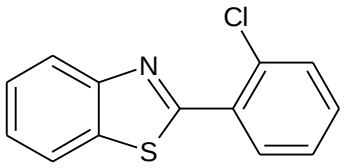
2.4.6 Synthesis of 2-(4-Chlorophenyl) Benzothiazole:



(32)

p- Chloro benzaldehyde (500 mg, 3.5mmol, 1 equiv.) was taken in mortar and grinded with iodine (220 mg, 1.75 mmol, 0.5 equiv.) for 5 minutes, then added 2-aminothiophenol (3.5mmol,1 equiv.) in three portions, immediate reaction took place then crude product was recrystallized from (70:30) EtOH:H_2O. On filtration bright yellow precipitates were obtained 0.8 g. Yield = 92 %, R_f value in 1% methanol: chloroform system (0.7) **m. p.** 129-130 ^oC. **FT-IR (**ν_{max}, cm^{-1})*:* 3371, 1605(C=N), 1472(Ar C=C), 1306 (C-N). **GC-MS** m/z: 245[M^+], 149,105.

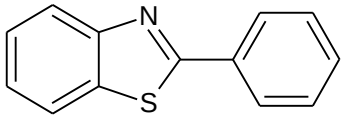
2.4.7 Synthesis of 2-(2-Chlorophenyl) benzothiazole:



(33)

o-Chloro benzaldehyde (500 mg, 3.5mmol, 1 equiv.) was taken in mortar and grinded with iodine (220 mg, 1.75 mmol, 0.5 equiv.) for 5 minutes, then added 2-aminothiophenol (3.5mmol, 1 equiv.) in three portions after that crude product was recrystallized from (70:30) EtOH:H_2O. Yellow crystalline solid was obtained on filtration in 0.72 g. Yield = 83 %, R_f value in 1% methanol: chloroform system (0.6) **m.p.** 127-128 ^oC. **FT-IR (**ν_{max}, cm^{-1}) 1605(C=N), 1472(Ar C=C), 1306(C-N). **GC-MS** m/z: 248 [M+H+2H] $^+$.

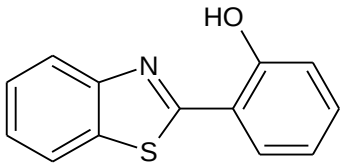
2.4.8 Synthesis of 2-(Phenyl) Benzothiazole:



(34)

2-(Phenyl) benzothiazole was synthesized by grinding benzaldehyde (500 mg, 4.7 mmol, 1 equiv.) with iodine (290 mg, 2.3 mmol, 0.5 equiv.) for 5 minutes, then added 2-aminothiophenol (4.7 mmol, 1 equiv.) in three portions, immediate reaction completion occurred. Crude product was then recrystallized from (70:30) EtOH:H_2O. On filtration Yellow solid precipitates were obtained in 0.93 g. Yield = 93 %, R_f value in 1% methanol: chloroform system (0.8) **m.p.** 111-112 ^oC. **FT-IR** (ν_{max}, cm^{-1}) 3371, 3100, 1605(C=N), 1472(Ar C=C), 1306(C-N). **GC-MS** m/z: 211[M^+], 212[M+ H] $^+$, 186, 134, 105, 109

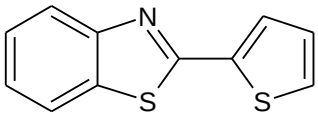
2.4.9 Synthesis of 2-(2-Hydroxy phenyl) Benzothiazole:



(35)

The reactant *o*-hydroxy benzaldehyde (500 mg, 4.09 mmol, 1 equiv.) was taken in mortar and grinded with iodine (250 mg, 2.04 mmol, 0.5 equiv.) for 5 minutes, then added 2-aminothiophenol (4.09 mmol, 1 equiv.) in three portions. Product was recrystallized from (70:30) EtOH:H_2O. Yellow semi solid product was obtained on filtration in 0.74 g. yield = 80 %, R_f value in 1% methanol: chloroform system (0.8), **m.p.** 129-130 ^oC . **FT-IR** (ν_{max}, cm^{-1}) 3365, 1604(C=N), 1473(C=C), 1444(Ar C-C), 1307(C-N). **GC-MS** m/z: 227 $[M^+]$, 228 $[M+H]^+$.

2.4.10 Synthesis of 2-(Thiphene-2- yl) Benzothiazole:



(36)

Thiophene carbanaldehyde (500 mg, 4.4 mmol, 1 equiv.) was taken in mortar and grinded with iodine (270 mg, 2.2 mmol, 0.3 equiv.) for 5 minutes, then added 2-aminothiophenol (4.4 mmol, 1 equiv.) in three portions, immediately reaction occurred. After reaction completion product was recrystallized from (70:30) EtOH:H_2O. Yellow semi solid product was obtained on filtration in 0.82 g. Yield = 85 %, R_f value in 1% methanol: chloroform system (0.5), **FT-IR** (ν_{max}, cm^{-1}) 1604(C=N), 1497(Ar C=C). **GC-MS** m/z: 217 $[M^+]$, 218 $[M+H]^+$, 175, 109.

Table 2.1 Physical Data of Synthesized Compounds 27-36:

Sr.No.	Compounds	Solvent for recrystallization	Physical appearance	M.P. ^{o}C	Yield %
1	2-(4-Aminophenyl) Benzothiazole **(27)**	70 % (EtOH:H_2O)	Bright yellow crystals	179-180	48
2	2-(4-Boc aminophenyl) Benzothiazole **(28)**	70 % (EtOH:H_2O)	Light yellow powder	175-176	69
3	2-(4-Benzoyl aminophenyl) Benzothiazole **(29)**	60%(MeOH:H_2O)	Yellow solid	185-186	85
4	2-(4-Methoxy phenyl) Benzothiazole **(31)**	Chloroform	Yellow solid	123-124	81
5	2-Phenyl Benzothiazole **(34)**	70 % (EtOH:H_2O)	Yellow solid	111-112	93
6	2-(4-Chloro phenyl) Benzothiazole **(32)**	70 % (EtOH:H_2O)	Bright yellow solid	129-130	92
7	2-(2-Chloro phenyl) Benzothiazole **(33)**	70 % (EtOH:H_2O)	Yellow solid	127-128	83
8	2-(Furan-2yl) Benzothiazole **(30)**	-------	Brown semi solid	-----	92
9	2-(Thiphene-2-yl) Benzothiazole **(36)**	**-----**	Yellow semi solid	-----	85
10	2-(2-Hydroxy phenyl) Benzothiazole **(35)**	70 % (EtOH:H_2O)	Yellow solid	129-130	80

CHAPTER # 3

RESULTS AND DISCUSSION

CHAPTER 3

RESULTS AND DISCUSSION

This chapter deals with the discussion about synthetic strategies for the synthesis of 2-substituted benzothizoles of aromatic aldehydes by reacting with 2-amino thiophenol. Molecular iodine has been used as a soft Lewis acid catalyst. In case of *p*-amino benzaldehyde first Boc and benzoyl protections have been carried out. Because amino group is reactive and provide second reactive site other than C=O that lower the yield. Yield of unprotected, Boc and benzoyl protected *p*-amino benzothiazoles have been compared. All the compounds were characterized by melting point, FT-IR and GC-MS data.

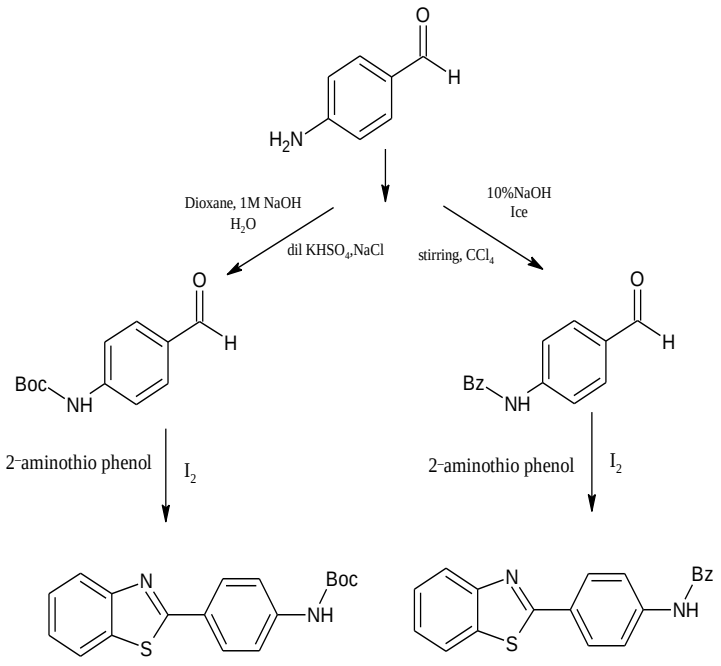
In FT-IR band at 1605 cm^{-1} indicated the synthesis of benzothiazole. GC-MS was performed to check the purity of the sample; also molecular ion peaks support the successful synthesis of benzothiazole.

3.1 Boc Protection of *p*-Amino Benzaldehyde:

Boc protection of *p*-amino benzaldehyde had been carried out and their successful protection was confirmed by FT-IR and melting point. In FT- IR spectrum characteristic band for NH_2 was absent that also indicated the Boc protection. The band at 1656 cm^{-1} was due to C=O of Boc group and 1518 cm^{-1} and 1368 cm^{-1} bands were observed due to aromatic moiety and $OC(CH_3)_3$, that provided the indication in the favor that protection was done successfully. For further confirmation melting point of the compound was measured, that was observed in the range 140-142 ^oC. In case of Boc low yield was observed. Boc is such a protecting group that is acid sensitive so conclusion is made that probably Boc was deprotected during the reaction as we used iodine as a catalyst, due to that reason side reactions may occurred, that decreased the yield.

3.2 Benzoyl Protection of *p*-Amino Benzaldehyde:

Benzoyl protection of *p*-amino benzaldehyde was also carried out so that we could compare the yields of unprotected, Boc and benzoyl protected aldehyde's benzothiazoles under our optimized reaction conditions. Benzoyl protection was performed to avoid the any side reaction that may occur at NH_2 functionality. FT-IR spectrum of the benzoyl *p*-amino benzaldehyde showed band at 1656 cm^{-1} that was due to C=O group and 1587 bands was observed because of aromatic C=C stretching. Melting point was observed in the range 150-152 ^oC that confirmed the benzoyl protection. Better yield was observed in case of benzoyl protection, that was due to the reason, benzoyl group was not acid sensitive as our reaction was performed under acidic conditions and this fact proved that benzoyl protection under acidic condition is better than Boc. This protection scheme consists on simple mild acidic conditions.



Protecting groups: Boc, Bz

3.1 General Scheme of Benzoyl and Boc Protection of Benzothiazoles

Table 3.1 Comparison of Yields of Benzothiazoles from Boc and Benzoyl Protected *p*-Amino benzaldehyde.

Sr. No.	Benzothiazoles	Yield (%)
1	2-(4- aminophenyl) Benzothiazole **(27)**	48
2	2-(4-*N*-Boc aminophenyl) Benzothiazole **(28)**	69
3	2-(4-*N*-Bz aminophenyl) Benzothiazole **(29)**	85

3.3 FT-IR and GC-MS of Benzothiazole:

GC-MS and FT-IR analysis have been carried out to confirm the synthesis of benzothiazole derivatives.

3.3.1 Synthesis of 2-(4-Aminophenyl) Benzothiazole:

2-(4-Aminophenyl) benzothiazole was synthesized by the reaction of *p*-amino benzaldehyde and 2- amino thiophenol at room temperature in very short time under solvent free conditions. Melting point was observed in range 179-180 ^{o}C that gave indication of benzothiazole synthesis as this melting point was different from the reactant. FT-IR spectrum of the compound is given in Fig. 3.1.1. In this spectrum band at 1603 cm^{-1} indicated the presence of C=N while 1476 showed the band due to aromatic C=C. Also band near 1700 cm^{-1} for C=O was absent that indicated the formation of C=N. In GC-MS spectrum, peaks at m/z 211 appeared by the loss of NH_2, C_7H_4NS have been lost from molecular ion peak to give fragment of m/z 92. Peak at 109 have been appeared by the loss of C_7H_5N from the fragment of m/z 211. All these peaks provided the confirmation of the synthesis of benzothiazole moiety. Fragmentation pattern is given below in Fig. 3.1.1.

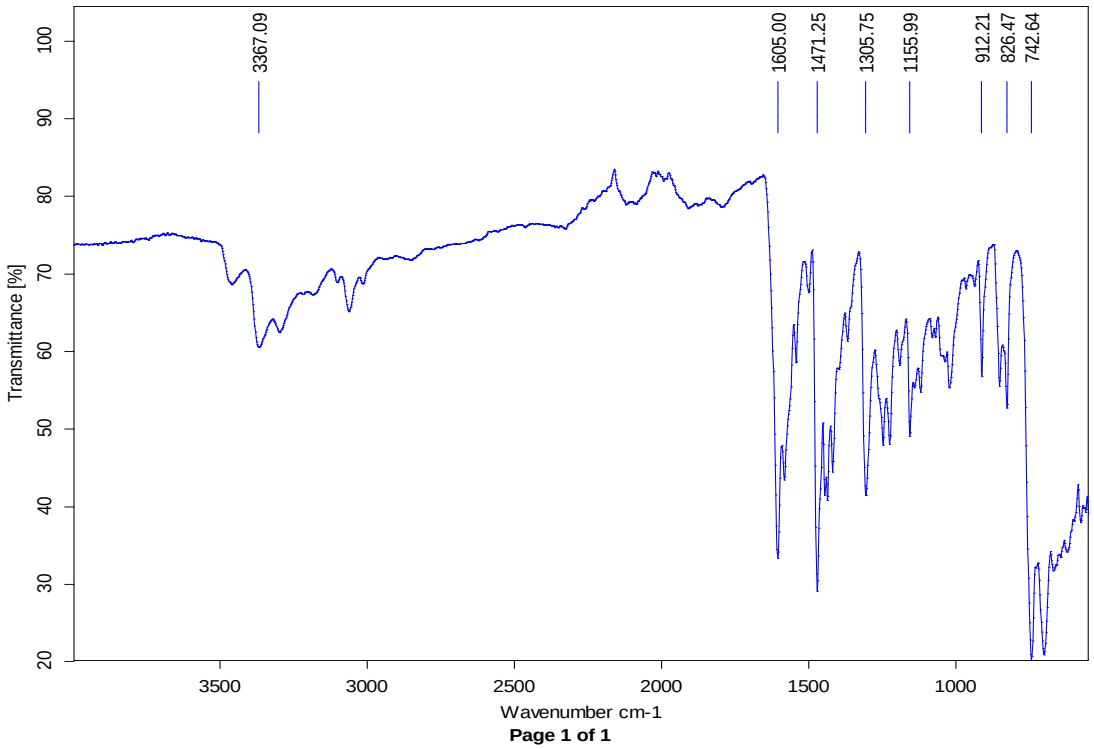


Fig. 3.1.1 FT-IR Spectrum of 2-(4-Aminophenyl) benzothiazole

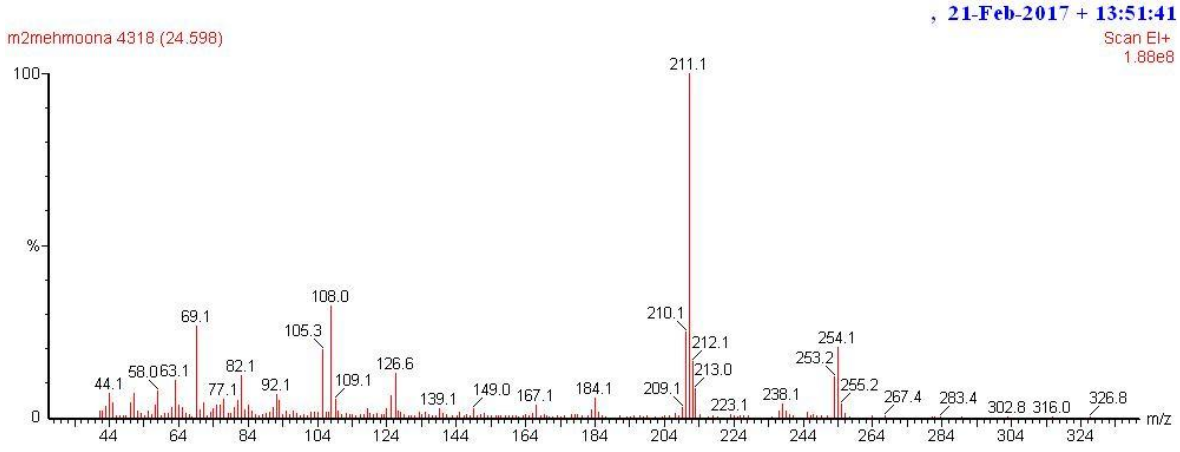


Fig. 3.2.1 GC-MS Spectrum of 2-(4-Aminophenyl) Benzothiazole

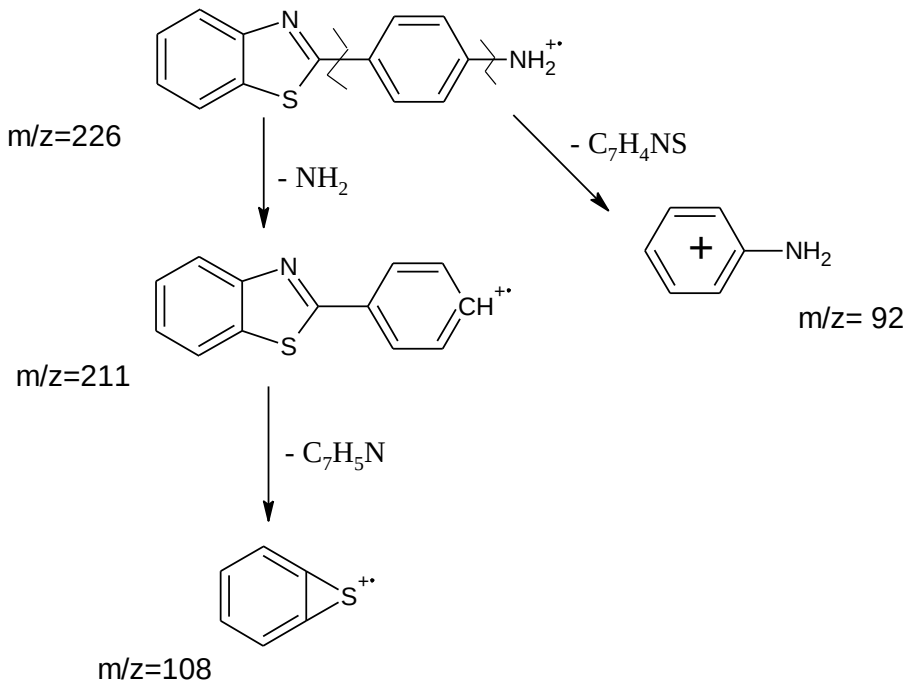


Fig. 3.3.1 Fragmentation Pattern of 2-Amino Benzothiazole

3.3.2. Synthesis of 2-(4-Boc-*N*-Aminophenyl) Benzothiazole:

This reaction was done in two steps, 1st step involved Boc protection of *p*-amino benzaldehyde and in 2nd step Boc *p*-amino benzaldehyde was reacted with 2-aminothiophenol as follows:

3.3.2.1. Boc Protection of *p*-Amino Benzaldehyde:

First we performed Boc protection of *p*-amino benzaldehyde. Its melting point was observed in the range 140-142 ^{o}C that indicated the Boc protection as melting point was observed in different range than the unprotected aldehyde. Fig. 3.1.2 shows the FT-IR spectrum of the Boc *p*-amino benzaldehyde in which 1656 cm^{-1} band is due to C=O of Boc group, aromatic bands were observed at

1587 cm^{-1} and band for $OC(CH_3)_3$ observed at 1368 cm^{-1} that showed successful synthesis of benzothiazole occurred.

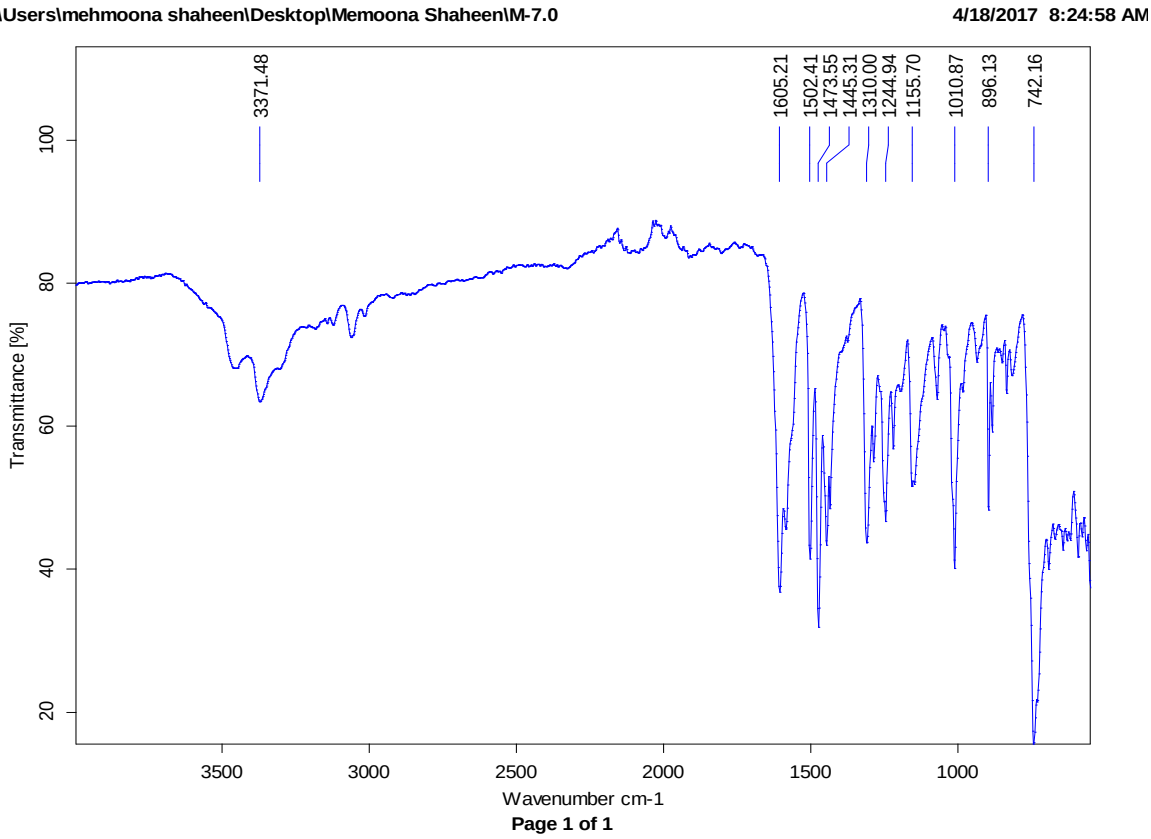


Fig. 3.1.2 FT-IR Spectrum of Boc Protected *p*-Amino Benzaldehyde

3.3.2.2. Boc Protected Benzothiazole:

Protected aldehyde was reacted with 2-amino thiophenol in presence of soft catalyst, iodine reaction was performed at room temperature and melting point was observed 175-176 ^oC. In FT-IR spectrum band at 1700cm^{-1} is for C=O of Boc group. FT-IR band at 1604 cm^{-1} indicated the C=N formation while 1476 and 1427 cm^{-1} are due to aromatic ring. Also band near 1368cm^{-1} is observed for $OC(CH_3)_3$ which showed that successful protection is carried out. FT-IR spectrum of the compound is given in Fig. 3.1.3. In case of Boc *p*-aminobenzaldehyde yield was comparatively high as compared to unprotected aldehyde but still was not very good, which may be due to the reason that Boc

group is acid sensitive and may be partially deprotected. In GC-MS spectrum loss of $H^{\bullet}$ from molecular ion gave peak at m/z = 325 confirmed the synthesis of 2-(4-Boc aminophenyl) benzothiazole, other peaks were observed at 211 m/z by the loss of NH-Boc group and at 253 m/z by the loss of C_4H_8O fragment from the moleculer ion peak. Peak at 109 m/z was also observed by the loss of C_7H_5N that further confirmed the synthesis. Fragmentation pattern for the compound is given below in Fig. 3.1.2.

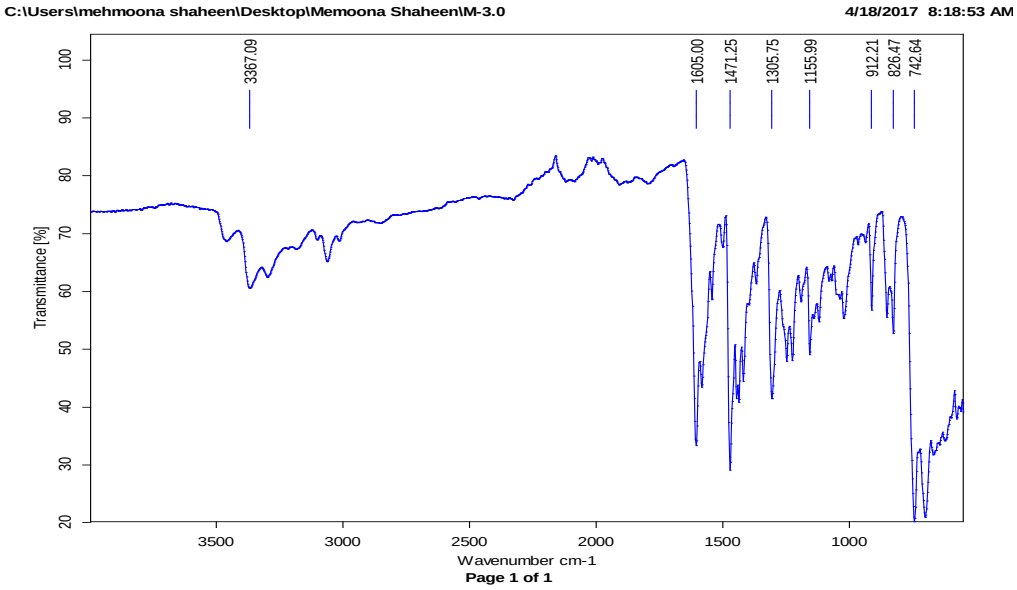


Fig. 3.1.3 FT-IR Spectrum of 2-(4-Boc aminophenyl) Benzothiazole

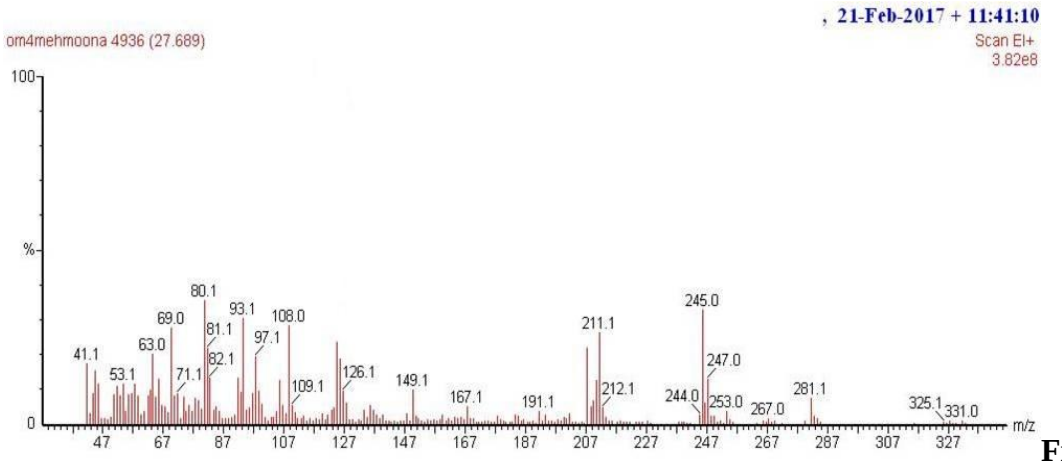


Fig 3.2.2

Fig. 3.2.2 GC-MS Spectrum of 2-(4-Boc aminophenyl) Benzothiazole

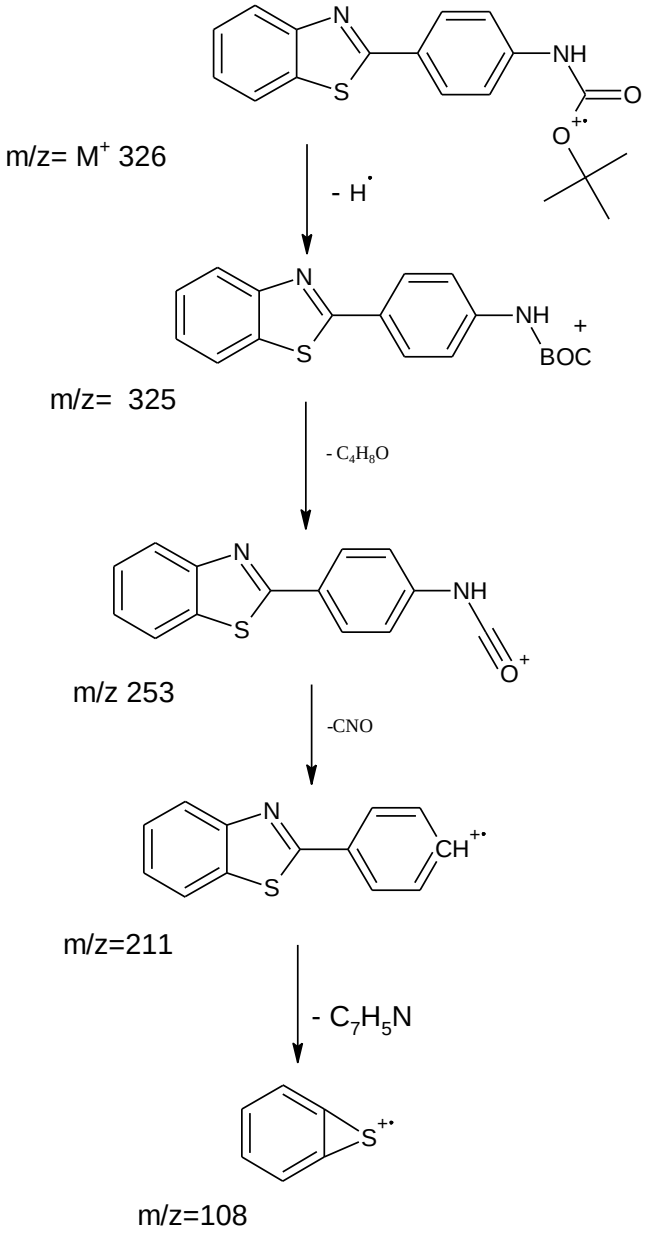


Fig. 3.3.2 Fragmentation Pattern of 2-(4-Boc aminophenyl) Benzothiazole

3.3.3. Synthesis of 2-(4-Bz aminophenyl) Benzothiazole:

This reaction was done in two steps, 1st step involved benzoyl protection of *p*-amino benzaldehyde and in 2nd step benzoyl *p*-amino benzaldehyde was reacted with 2-aminothiophenol as follows:

3.3.3.1. Benzoyl Protection of *P*-Amino benzaldehyde:

Melting point was observed in the range 150-153 ^{o}C that indicated the benzoyl protection. Fig. 3.1.4 shows the FT-IR spectrum of the benzoyl *p*-amino benzaldehyde in which 1676 cm^{-1} band is due to C=O of benzoyl group and 1452 and 1417 cm^{-1} aromatic bands also at 1323 cm^{-1} is for C-N that indicate toward the synthesis of benzoyl protected *p*-amino benzaldehyde.

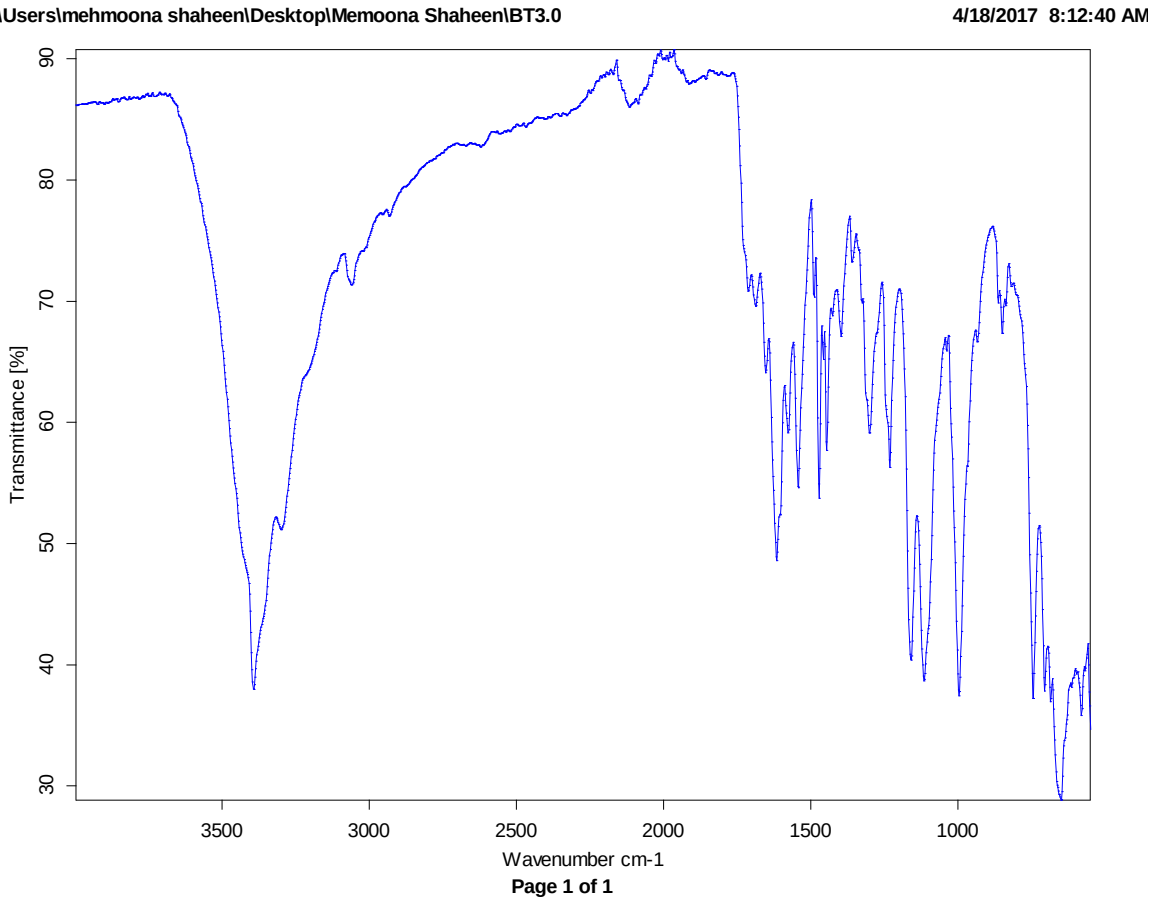


Fig. 3.1.4 FT- IR Spectrum of Benzoyl Protected *p*-Amino benzaldehyde

3.3.3.2. Benzoyl Protected Benzothiazole:

Reaction was performed at room temperature, under solvent free condition. Iodine was used as soft Lewis catalyst. Melting point of the compound was observed at 185-186 ^{o}C that gave indication of successful reaction. In FT-IR spectrum prominent peak is observed at 1605 cm^{-1} for C=N and 1313 cm^{-1} for C-N that gave the indication of benzothiazole synthesis. In this case yield was high as compared to unprotected and Boc protected *p*-amino benzaldehyde which was because of the reason that benzoyl group is not acid sensitive that is used as catalyst during the reaction. In GC-MS spectrum Fig. 3.2.3., peak at m/z 254 was observed by the loss of phenyl group from the molecular ion peak. Peak at 211 was observed by the loss of NCO that confirmed the synthesis of benzothiazole moiety. Fragmentation pattern is given below in Fig 3.1.3.

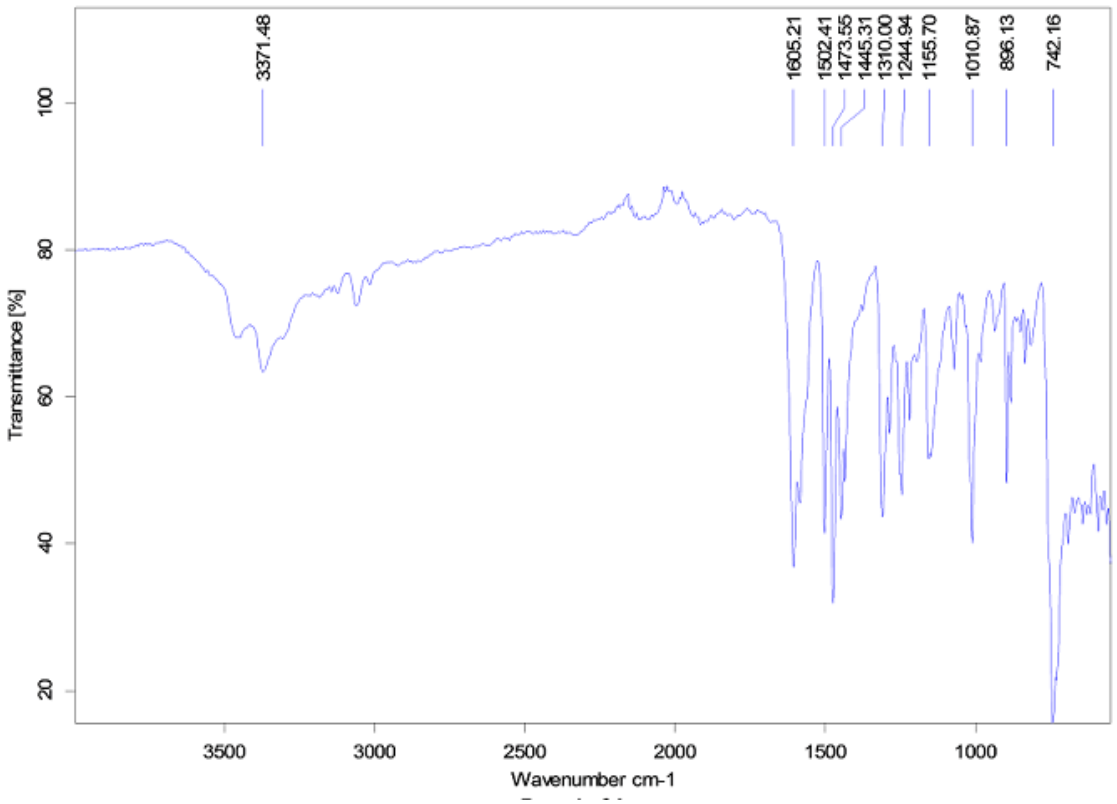


Fig. 3.1.5 FT-IR Spectrum of 2-(4-Benzoylaminophenyl) Benzothiazole

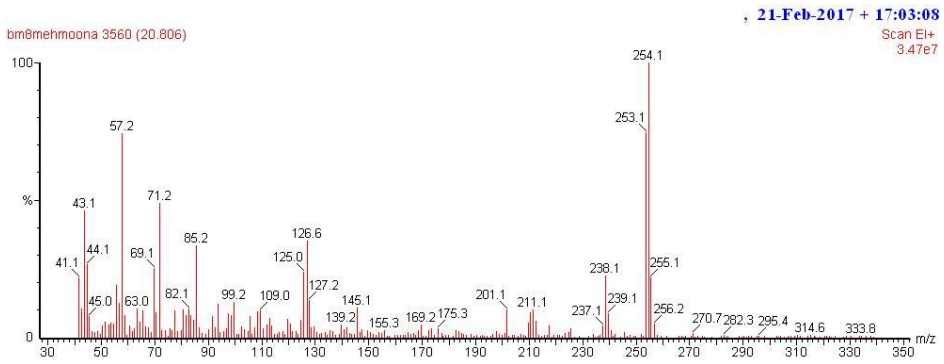


Fig. 3.2.3 GC-MS Spectrum of 2-(4-benzoylaminophenyl) Benzothiazole

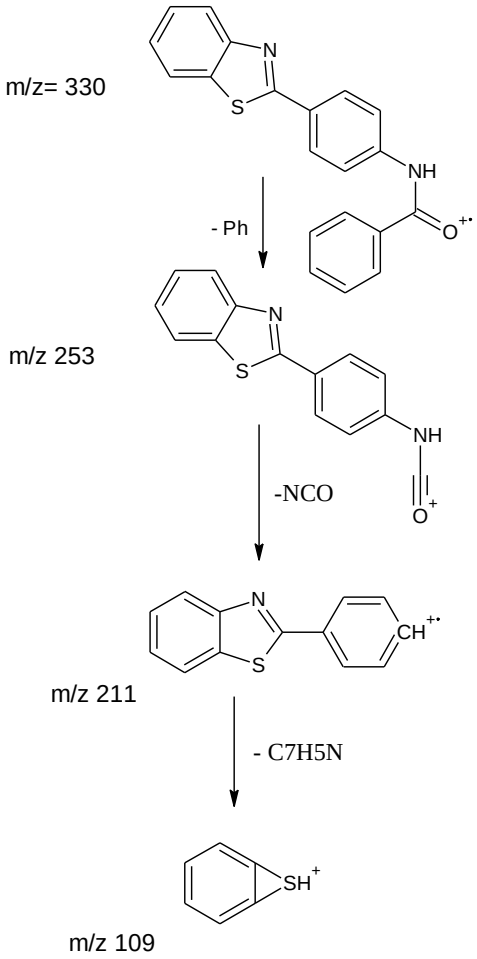


Fig. 3.3.3 Fragmentation Pattern of 2-(4-Bz aminophenyl) Benzothiazole

3.3.4. Synthesis of 2-(Furan-2-yl) Benzothiazole:

In FT-IR spectrum of 2-(furan-2-yl) benzothiazole (Fig. 3.1.6), bands at 1605 cm^{-1} and 1306 cm^{-1} indicated the presence of C=N and C-N moieties respectively. At 1472 cm^{-1} FT-IR band was observed for C=C of aromatic moiety. Disappearance of band at 1700 cm^{-1} for C=O also indicated the synthesis of benzothiazole. In mass spectrum molecular ion peak was observed at m/z = 205$[M]^+$ that confirmed the synthesis of benzothiazole. Other fragments were observed by the loss of CH_3O from molecular ion peak at m/z 174. Also m/z 136 was observed for benzothiazole nucleus. All these peaks provided sufficient evidence for the synthesis of benzothizole molecule. Expected fragmentation pattern is given below in Fig. 3.1.4.

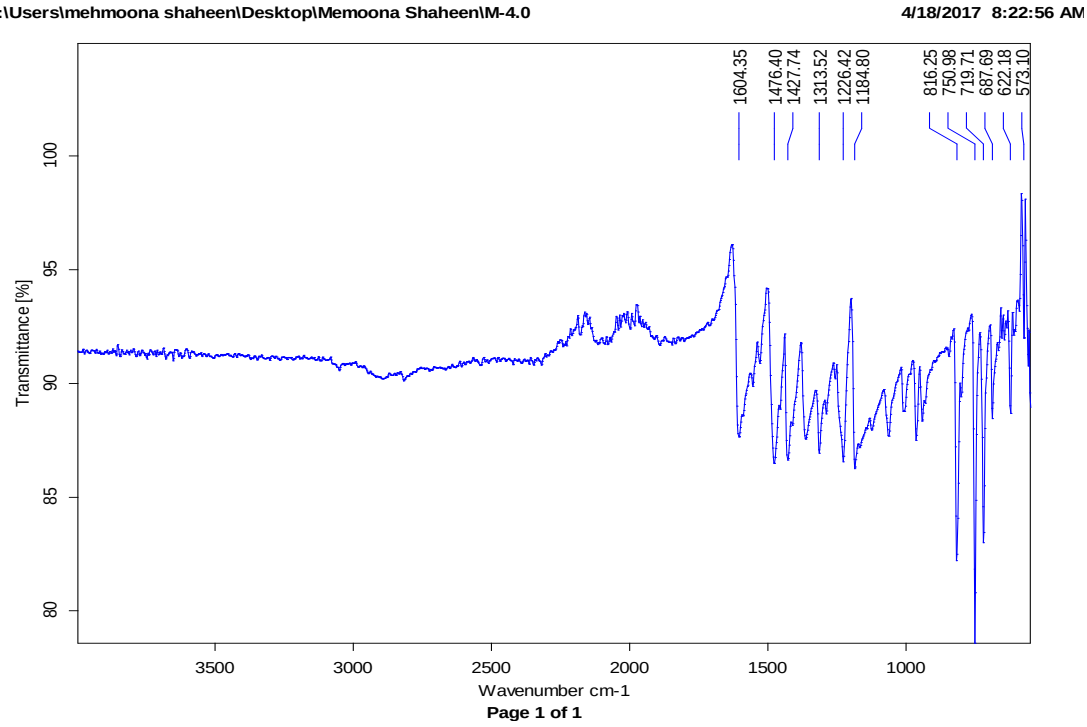


Fig. 3.1.6 FT-IR Spectrum of 2-(Furan-2-yl) Benzothiazole

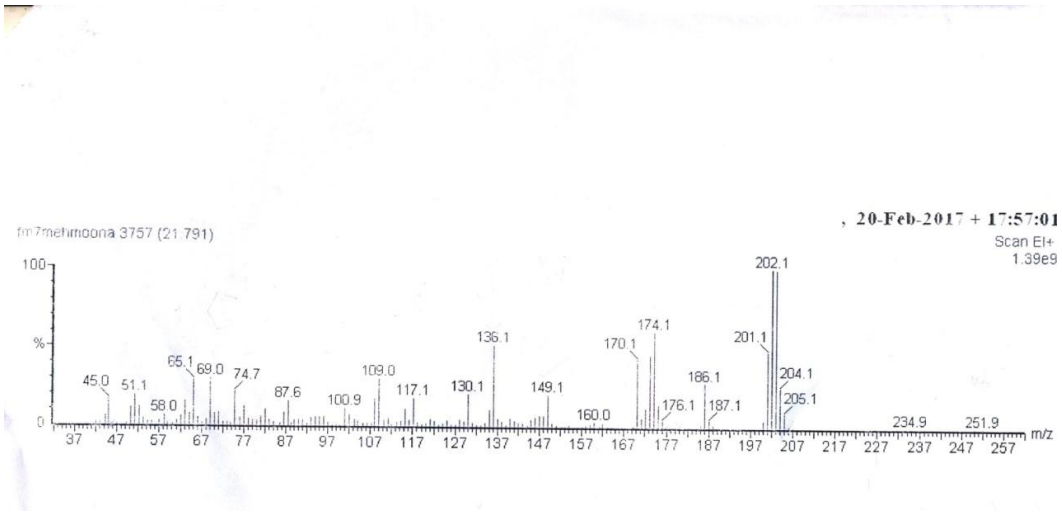


Fig. 3.2.4 GC-MS Spectrum of 2-(Furan-2-yl) Benzothiazole

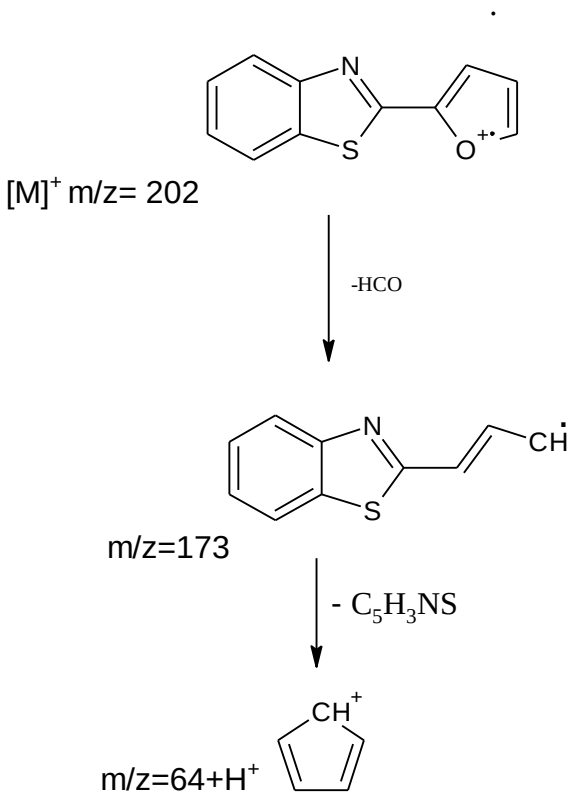


Fig. 3.3.4 Fragmentation Pattern of 2-(Furan-2-yl) Benzothiazole

3.3.5. Synthesis of 2-(4-Chlorophenyl) Benzothiazole:

For 2-(4-chlorophenyl) benzothiazole melting point was observed 129-130 ^{o}C. FT-IR spectrum of the compound is given in Fig. 3.1.7. In which a band at 1584 cm^{-1} indicated the presence of C=N and at 1306 cm^{-1} was for C-N that showed the synthesis of 2-(4-chlorophenyl) benzothiazole. FT-IR band at 1472 cm^{-1} was due to aromatic C=C. Disappearance of C=O band at 1700 cm^{-1} also indicated the synthesis of benzothiazole. Yield was high in case of 4-Cl as compared to 2-Cl substituent. It is may be due to reason that *para* position cause less hindrance as compare to *ortho* position and gave good yield. In mass spectrum molecular ion peak at m/z 245[M]$^{+}$ confirmed the synthesis of 2-(4-chlorophenyl) benzothiazole**.** Other peaks were observed at m/z 108 and m/z 65 that confirmed the synthesis of 2-(4-chlorophenyl) benzothiazole. Fragmentation pattern is given below in Fig. 3.1.6.

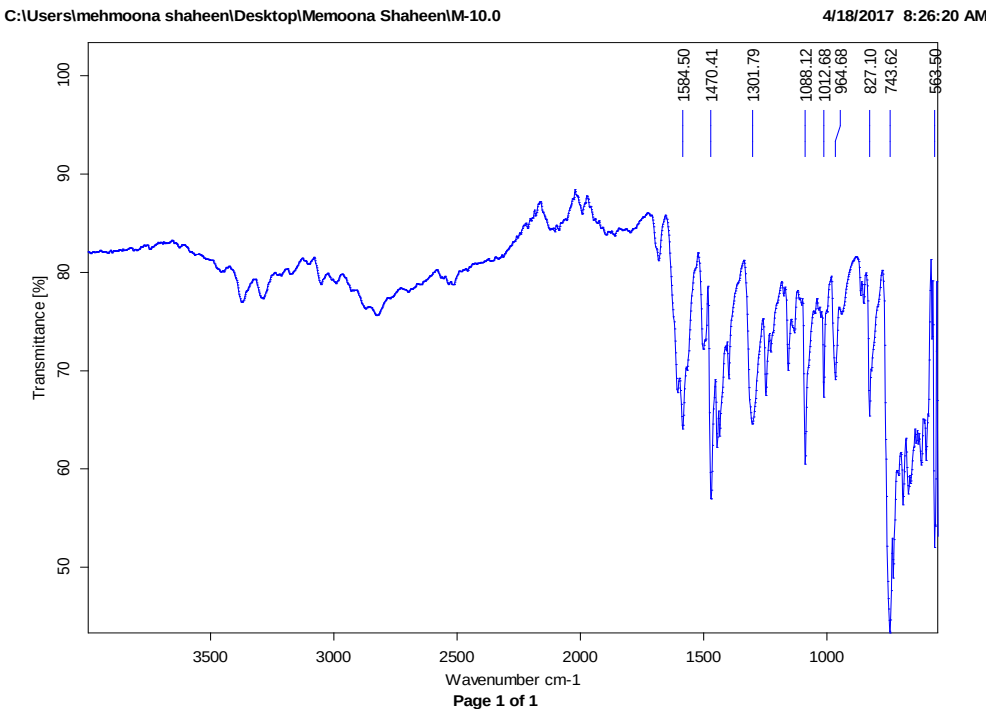


Fig. 3.1.7 FT-IR Spectrum of 2-(4-Chlorophenyl) Benzothiazole

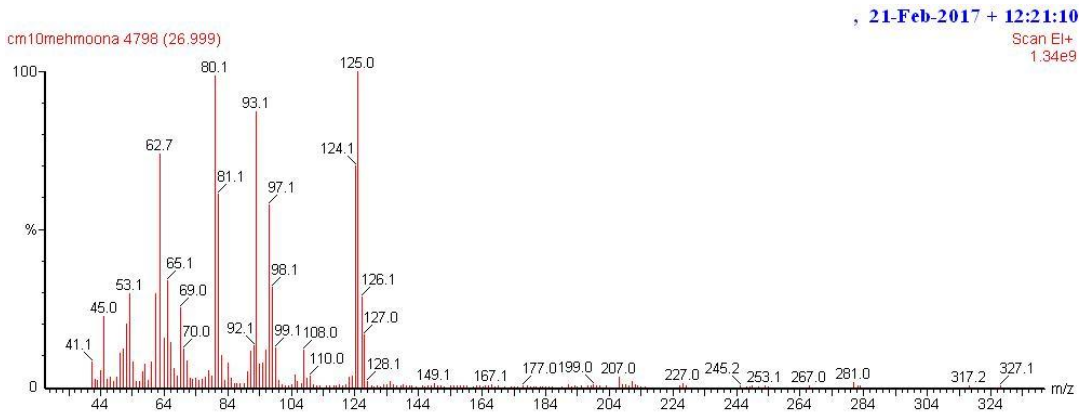


Fig. 3.2.5 GC-MS Spectrum of 2-(4-Chlorophenyl) Benzothiazole

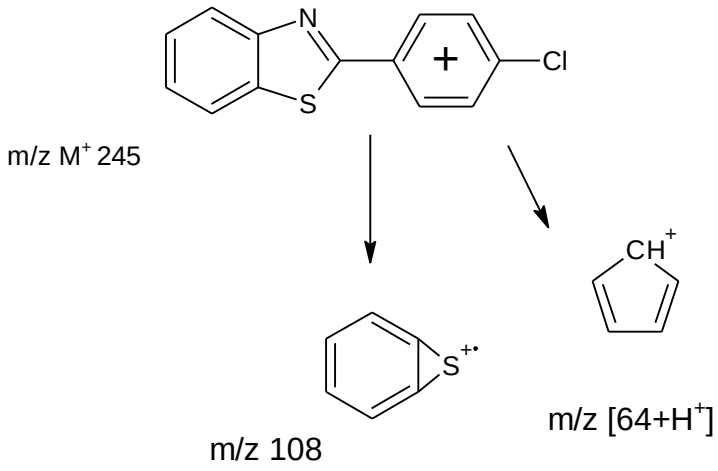


Fig. 3.3.5 Fragmentation Pattern of 2-(4-Chlorophenyl) Benzothiazole

3.3.6. Synthesis of 2-(2-Chlorophenyl) Benzothiazole:

Melting point was observed at 127-128 ^{o}C for 2-(2-chlorophenyl) benzothiazole. The band at 1605 cm^{-1} gave indication of C=N, another band at 1306 cm^{-1} for C-N provided further evidence in the favor of synthesis of 2-(2-chlorophenyl) benzothiazole. 1472 cm^{-1} band was observed due to aromatic C=C, showed in FT-IR spectrum Fig. 3.1.8. In GC-MS spectrum m/z 248 $[M+H+2H]^{+}$ gave confirmation of the 2-(2-chlorophenyl) benzothiazole

another peak was observed at 99 for the fragment C_5H_4Cl and at 108 for C_6H_4S. All these peaks confirmed the reaction. Expected fragmentation pattern is given below in Fig. 3.3.6.

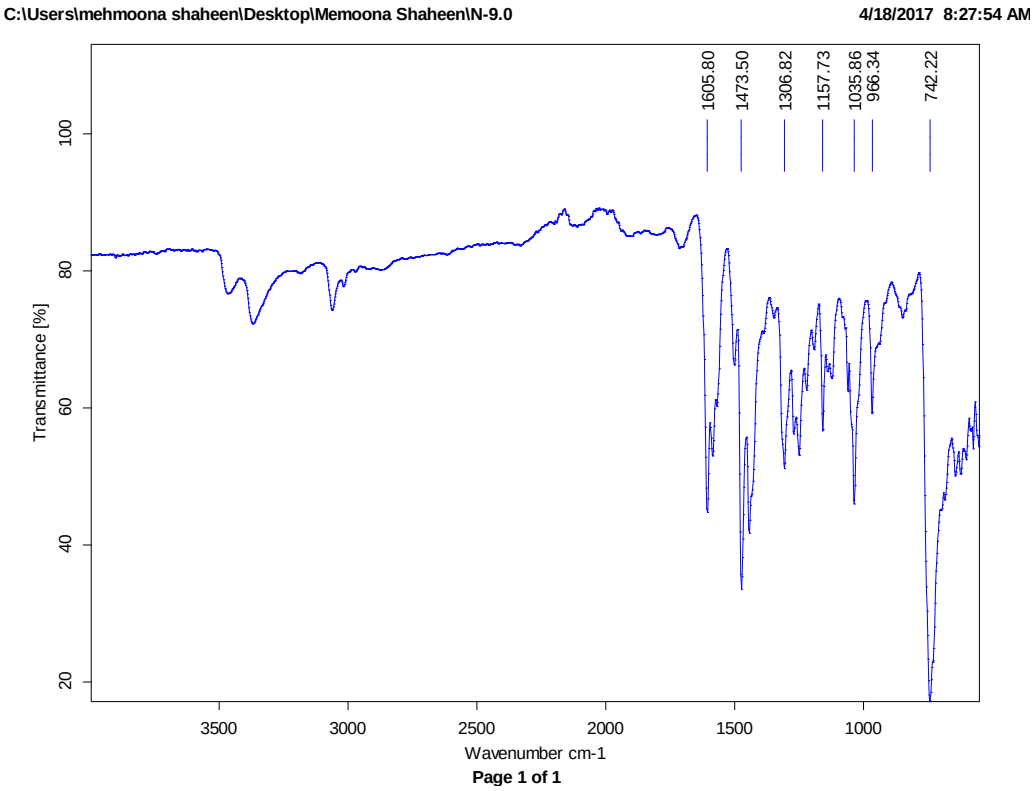


Fig. 3.1.8 FT-IR Spectrum of 2-(2-Chlorophenyl) Benzothiazole

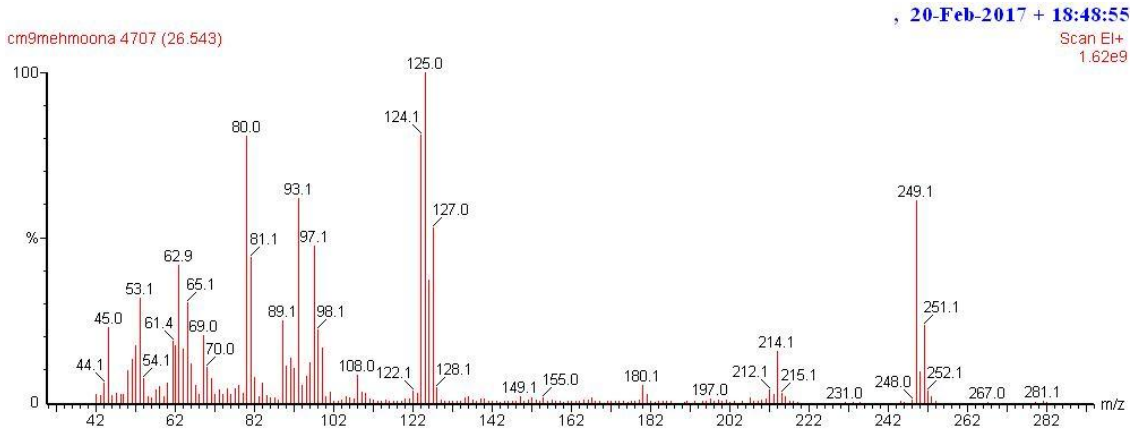


Fig. 3.2.6 GC-MS Spectrum of 2-(2-Chlorophenyl) Benzothiazole

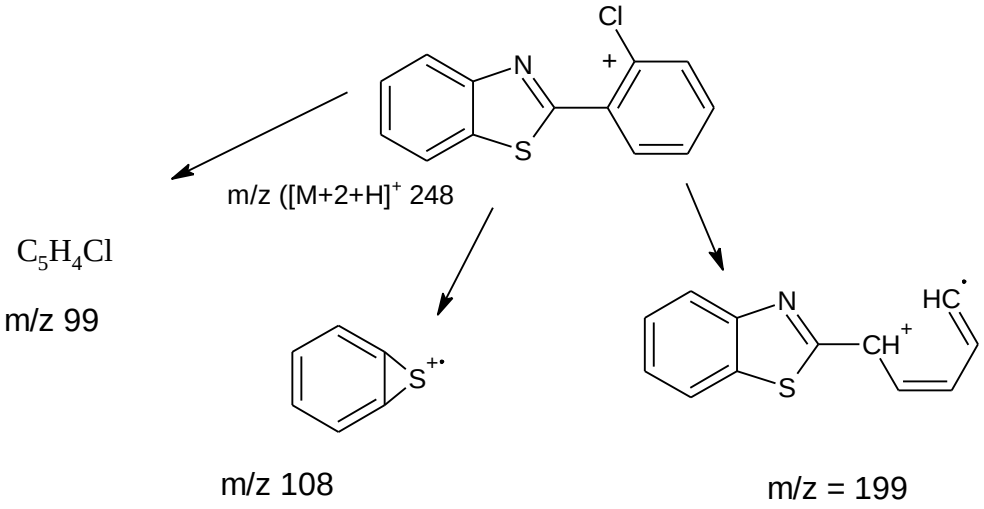


Fig. 3.3.6 Fragmentation Pattern of 2-(2-Chlorophenyl) Benzothiazole

3.3.7. Synthesis of 2-(Phenyl) Benzothiazole:

First indication was obtained by measuring melting point observed at 111-112 ^{o}C. In FT-IR spectrum, given in Fig. 3.1.9, appearance of FT-IR band at 1605 cm^{-1} was due to C=N other bands at 1472 cm^{-1} and 1306 cm^{-1} were observed for C=C and aromatic C-C respectively. In mass spectrum molecular ion peak at $[M]^{+}$ m/z 211 confirmed the synthesis of benzothiazole other prominent peaks were at m/z 186 by the loss of C_2H_2, m/z 134 by the loss of C_4H_3 and m/z 109 by the loss of CN, all these peaks further supported the synthesis of 2-(phenyl) benzothiazole. Fragmentation pattern is given below.

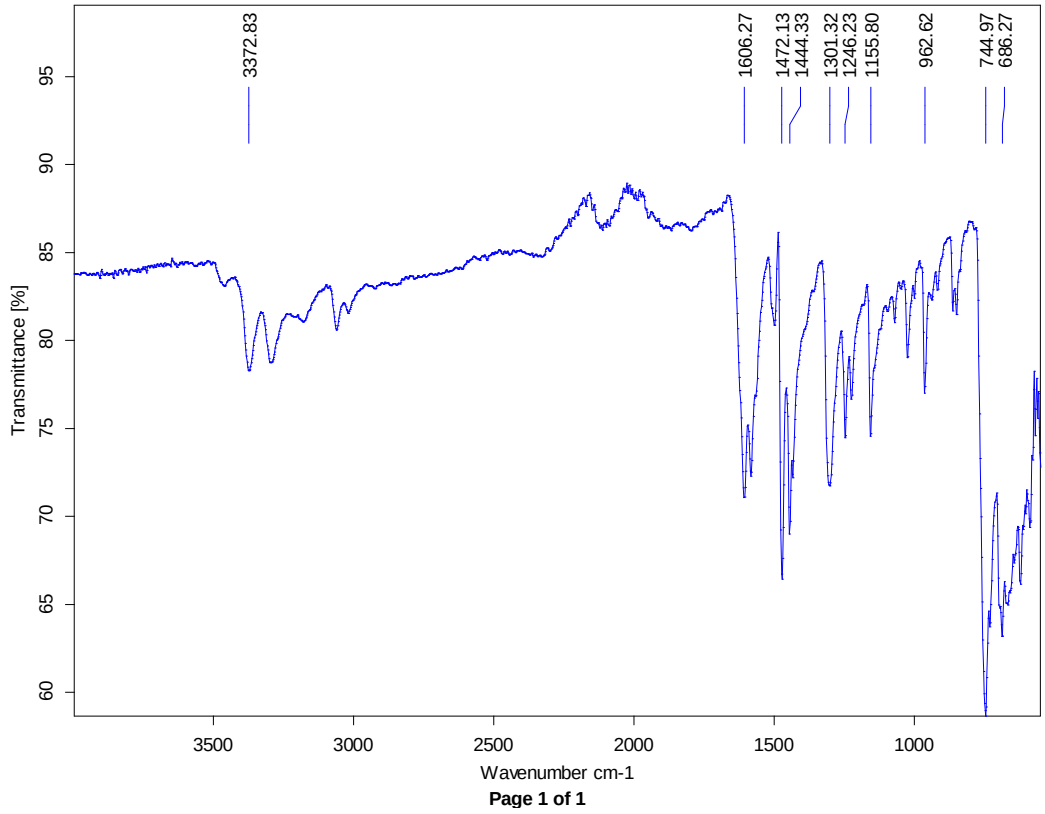


Fig. 3.1.9 FT-IR Spectrum of 2-Phenyl Benzothiazole

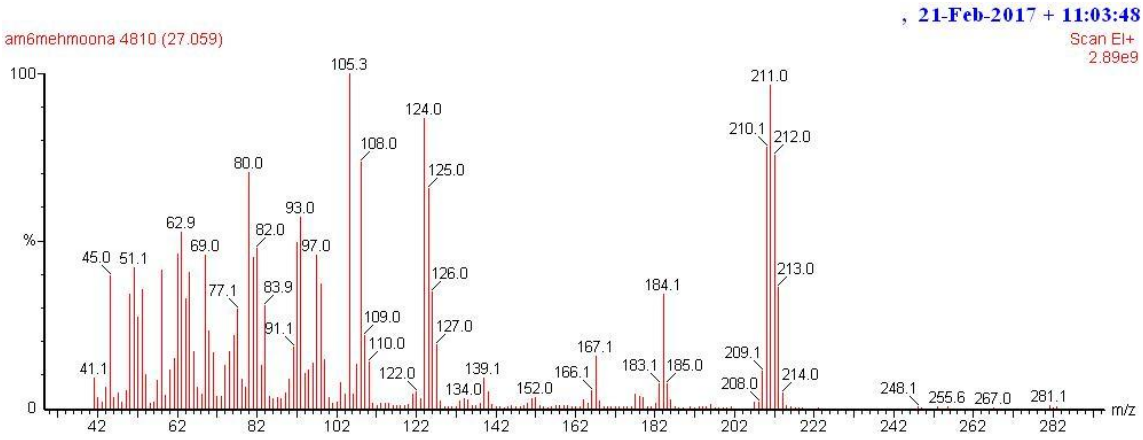


Fig. 3.2.7 GC-MS Spectrum of 2-Phenyl Benzothiazole

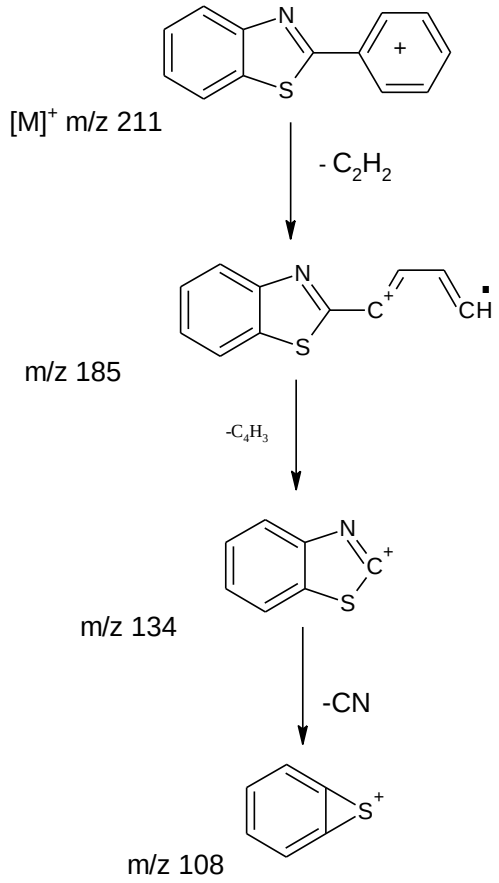


Fig. 3.3.7 Fragmentation Pattern of 2-Phenyl Benzothiazole

3.3.8. Synthesis of 2-(2-Hydroxy phenyl) Benzothiazole:

Melting point of 2-(2-hydroxy phenyl) benzothiazole is observed at 129-130 ^{o}C which give indication of reaction success moreover sharp melting point show that our product is pure. FT-IR spectrum of 2-(2-hydroxy phenyl) benzothiazole is given in Fig. 3.1.10 , a broad band at 3365 cm^{-1} was observed for OH, FT-IR band at 1604 cm^{-1} was due to C=N while 1473 cm^{-1} was due to C-C and 1444 cm^{-1} appeared due to aromatic C=C. In mass spectrum molecular ion peaks at m/z 227[M]$^{+}$ confirmed the synthesis of benzothiazole other prominent peaks were observed at 135 peak for benzothiazole nucleus and by the loss of CN from benzothiazole nucleus, gave peak at 109 also peak for C_6H_5O fragment was observed at m/z 93. The fragmentation pattern is given below in Fig. 3.3.8.

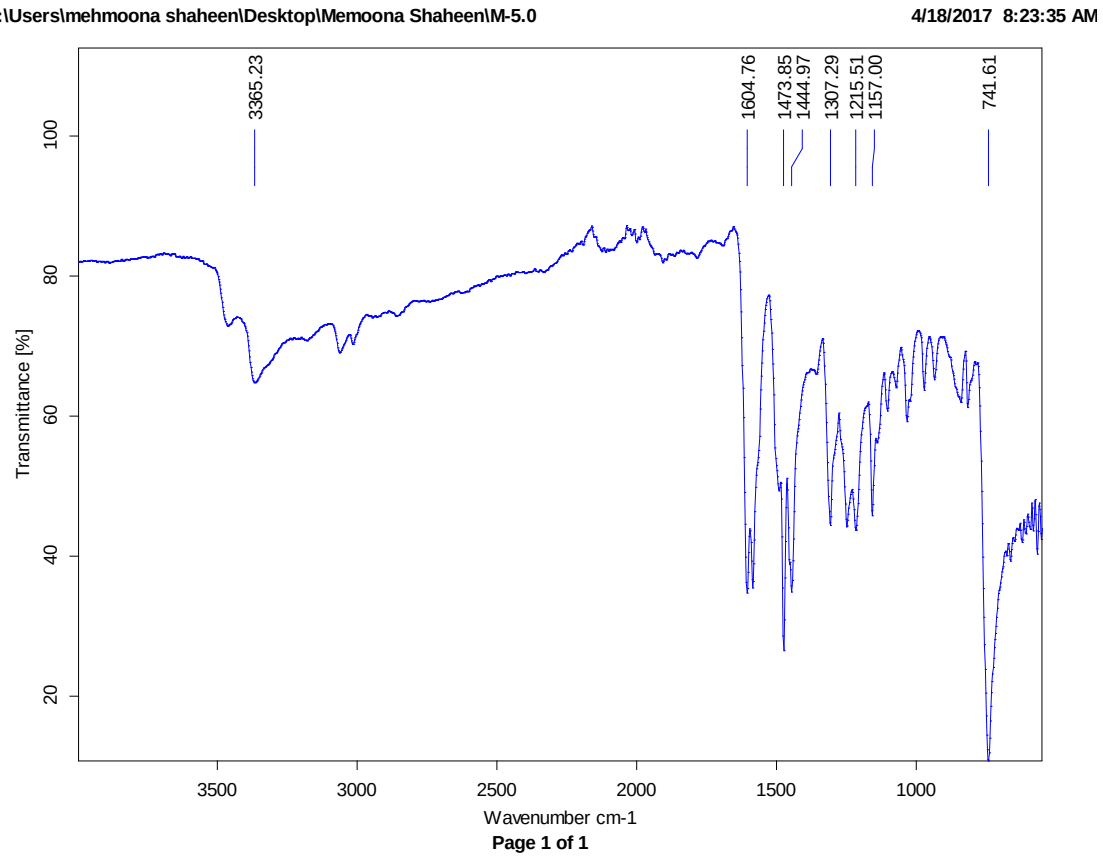


Fig. 3.1.10 FT-IR Spectrum of 2-(2-Hydroxy phenyl) Benzothiazole

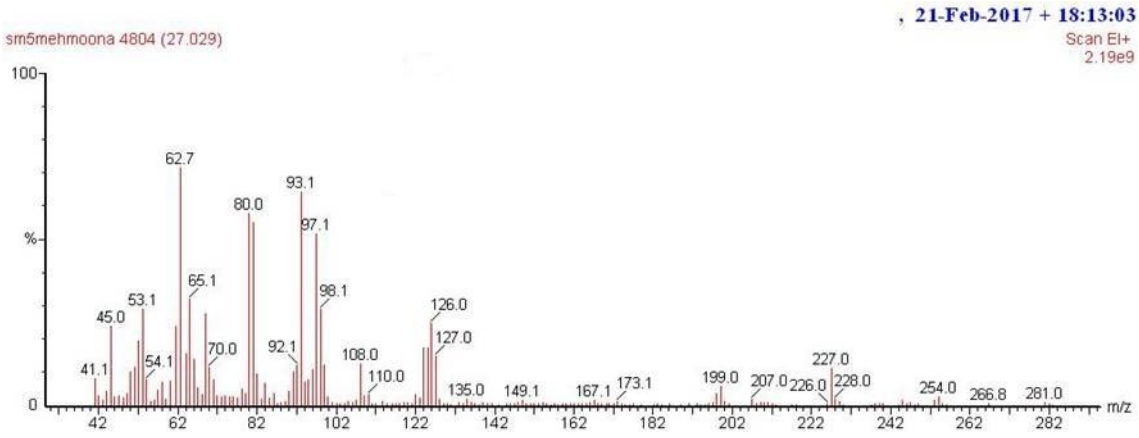


Fig. 3.2.8 GC-MS Spectrum of 2-(2-Hydroxy phenyl) Benzothiazole

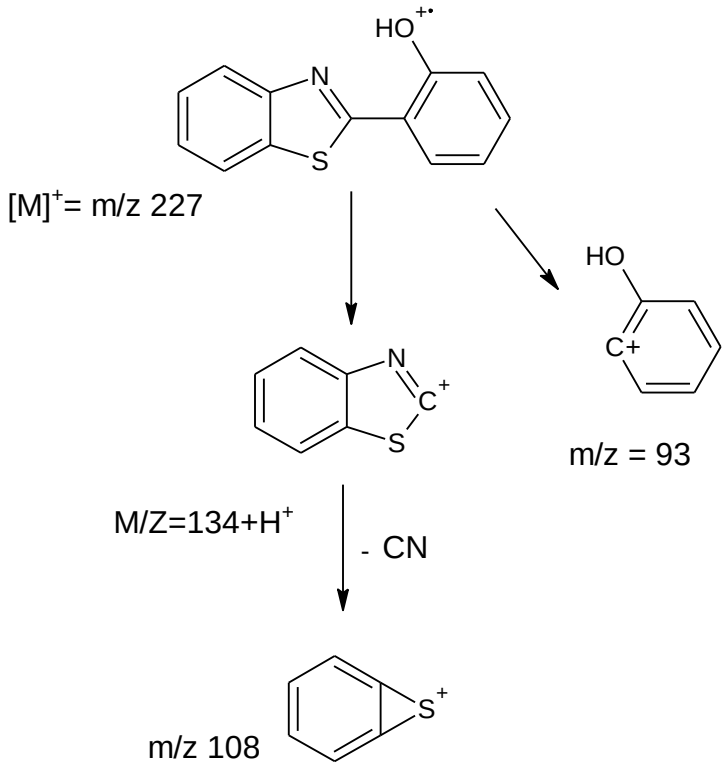


Fig. 3.3.8 Fragmentation Pattern of 2-(2-Hydroxy phenyl) Benzothiazole

3.3.9. Synthesis of 2-(Thiphene-2-yl) Benzothiazole:

In FT-IR spectrum of our synthesized compound, a band at 1604 cm^{-1} was due to C=N and band at 1497 cm^{-1} appeared because of C=C these bands indicated the synthesis of 2-(thiphene phenyl) benzothiazole. Absence of C=O FT-IR band near 1700 cm^{-1} also provided evidence in the favor of benzothiazole synthesis. In mass spectrum molecular ion peak at m/z $[M]^+$ 217confirmed the synthesis of 2-(thiphene phenyl) benzothiazole, other peaks were observed at 173 by the loss SCH and 109 by the loss of C_4H_2N further supported the synthesized product, fragmentation pattern is shown below in Fig. 3.3.9:

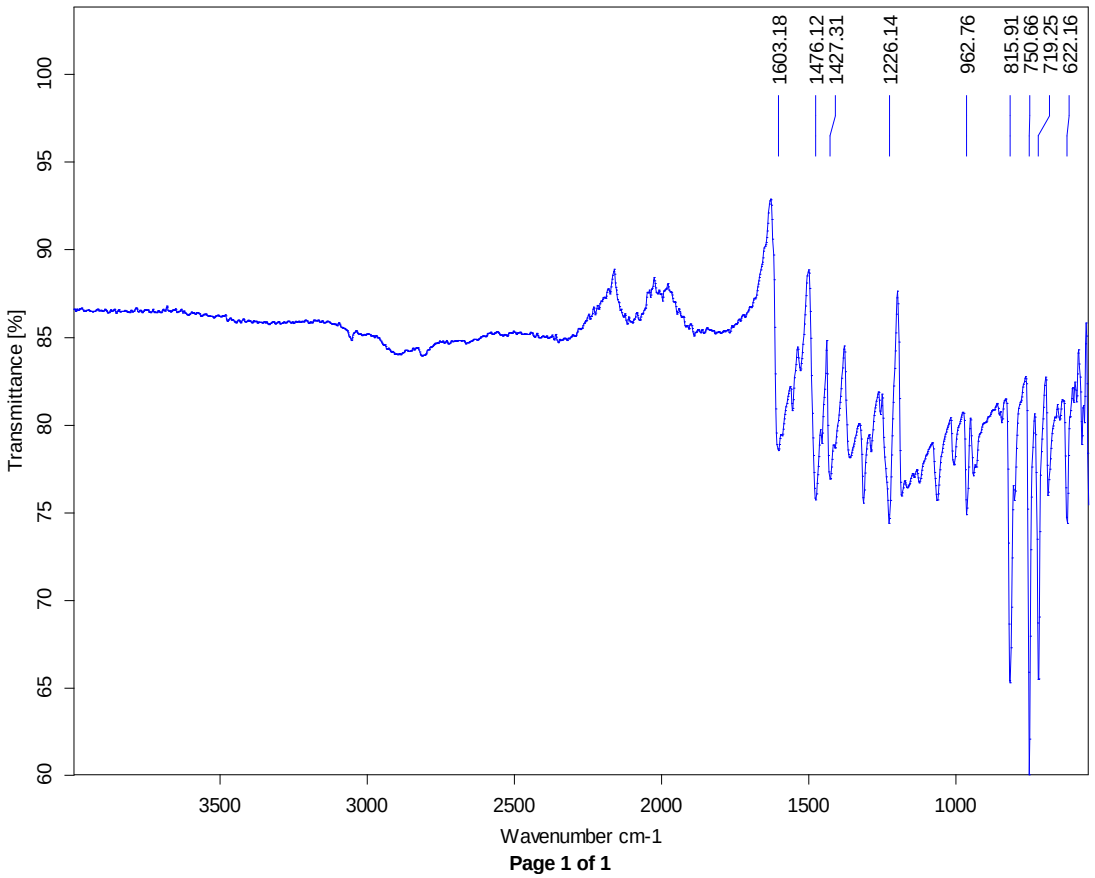


Fig. 3.1.11 FT-IR Spectrum of 2-(Thiphene phenyl) Benzothiazole

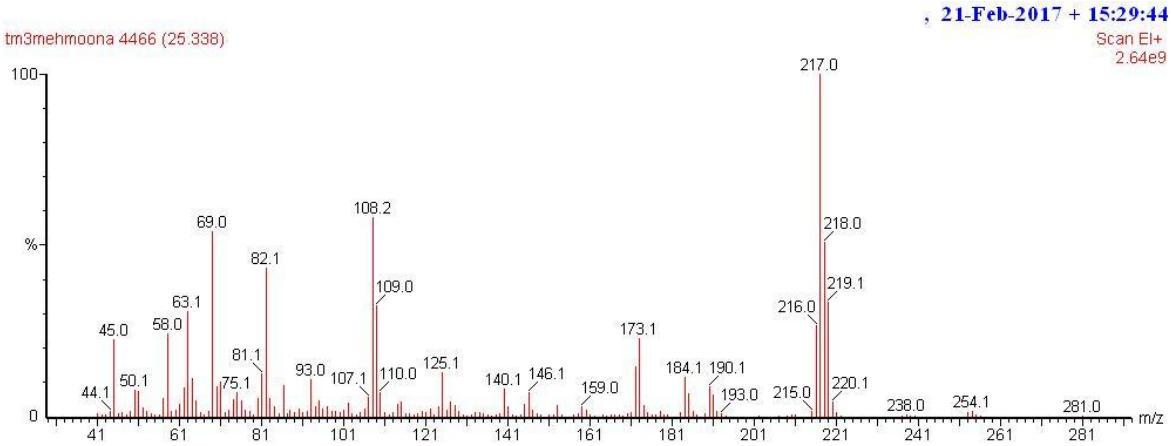


Fig. 3.2.9 GC-MS Spectrum of 2-(Thiphene phenyl) Benzothiazole

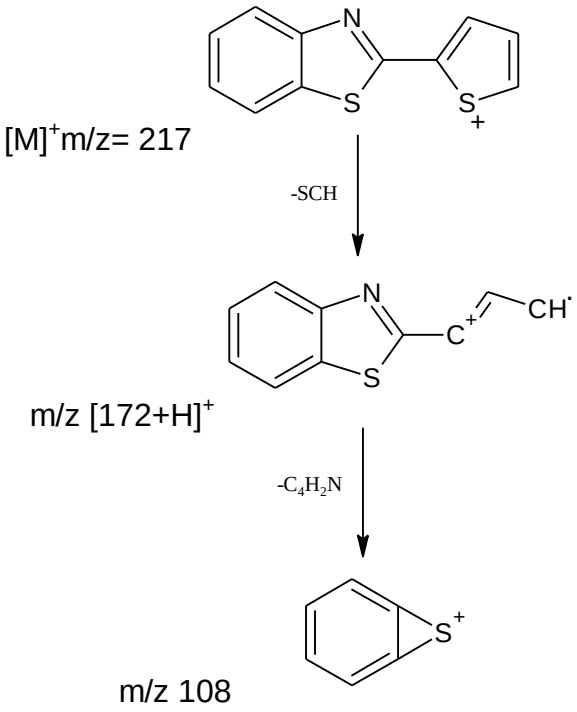


Fig. 3.3.9 Fragmentation Pattern of 2-(Thiphene phenyl) Benzothiazole

3.3.10. Synthesis of 2-(4-Methoxyphenyl) Benzothiazole:

In FT-IR spectrum shown in Fig. 3.1.12, a band at 1605 cm^{-1} was observed for C=N and at 1306 cm^{-1} for C-N that indicated synthesis of 2-(4-methoxyphenyl) benzothiazole, furthermore band for aromatic C=C was observed near 1472 cm^{-1}. In GC-MS a peak at m/z 149 was observed by the loss of fragment C_6H_7O, another peak at m/z 105 was observed by the loss of C_2H_2S, these peaks confirmed the synthesis of 2-(4-methoxyphenyl) benzothiazole. Fragmentation pattern is given below in Fig. 3.3.10.

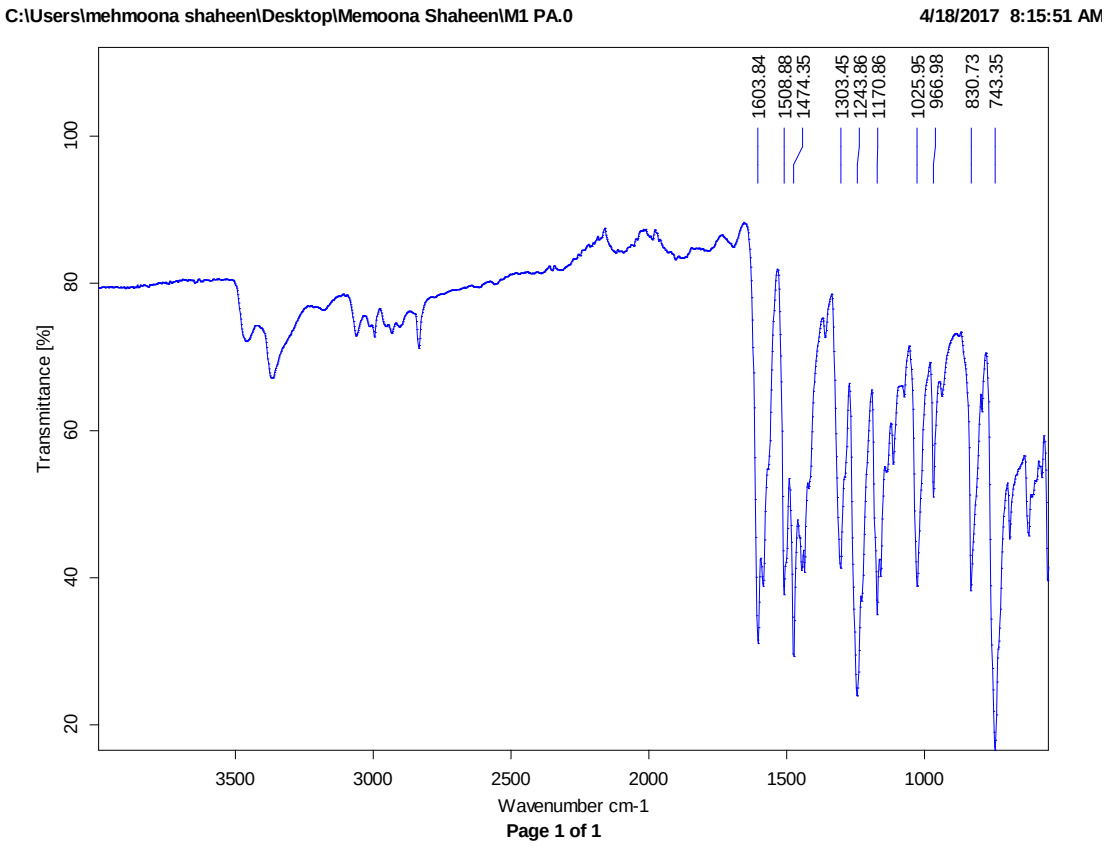


Fig. 3.1.12 FT-IR Spectrum of 2-(4-Methoxyphenyl) Benzothiazole

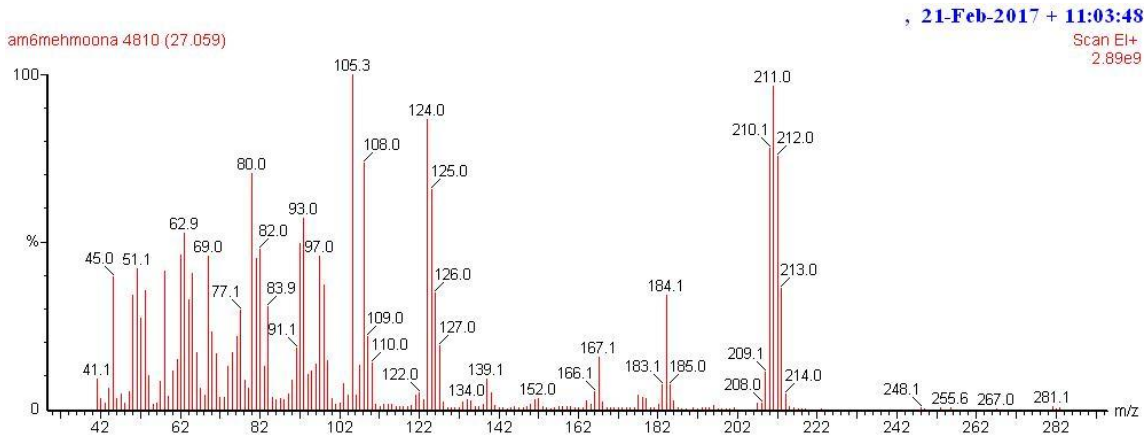


Fig. 3.2.10 GC-MS Spectrum of 2-(4-Methoxyphenyl) Benzothiazole

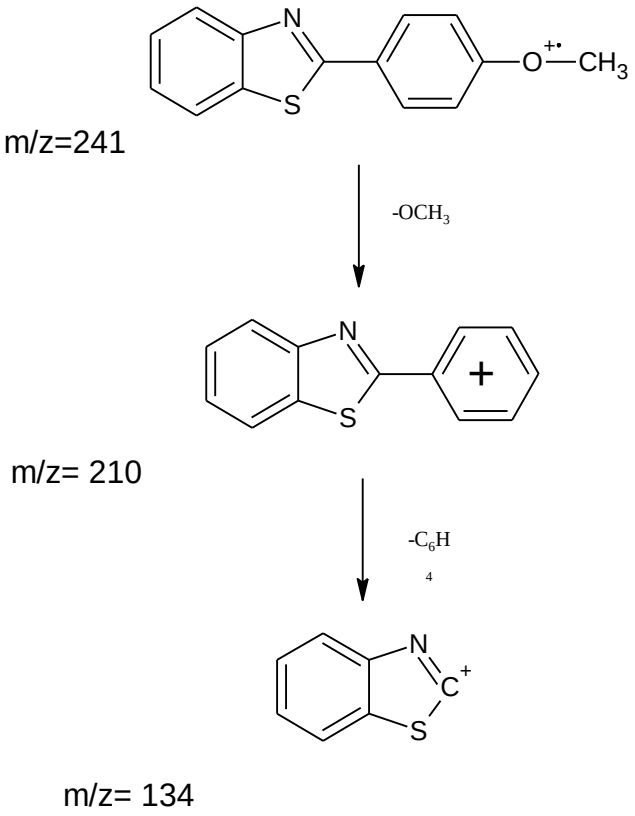


Fig. 3.3.10 Fragmentation Pattern of 2-(4-Methoxyphenyl) Benzothiazole

3.4 Conclusion and Future Prospects:

In this research work, a simple method for the synthesis of new benzothiazole derivatives starting from cheap reactants is described. Molecular iodine as a cheap and facile catalyst was used to catalyze the reaction; which was completed in very short time. Also Boc and benzoyl protection of *p*-amino benzaldehyde were performed with good yield. FT-IR data showed that band at 1605 cm^{-1} was appeared due to the C=N bond that indicated formation of benzothiazole moiety. GC-MS analysis showed the molecular ion peak, formation of benzothizole molecule was also confirmed from fragmentation patterns in MS.

The versatile synthetic applicability along with industrial and biological activity of these heterocyclic compounds will help the chemists to explore the array of biological potentials and industrial applications of these synthesized derivatives of benzothiazole.

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