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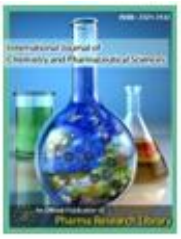

Research Article Open Access

Synthesis, Characterization of New Mercaptobenzoxazole Fused Mannich Bases for Anti-inflammatory and Antibacterial Activity

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A B S T R A C T

Mercaptobenzoxazole is a heteroaromatic chemical compound from the class of Benzoxazoles. A new series of Mercaptobenzoxazole compounds were synthesized from 2-Amino phenol, Carbon disulfide and in presence of ethanoic KOH when undergo mannich reaction i.e. reacted with secondary amines and furfuraldehyde in presence of ethanol eliminates the water molecule and gives mannich bases containing 2-Mercaptobenzoxazole. All the synthesized compounds were characterized by IR, ^{1}H NMR and MASS Spectroscopic methods and the synthesized compounds reaction i.e. reacted with secondary amines and furfuraldehyde in presence of ethanol eliminates the water molecule and gives mannich bases containing 2- Mercaptobenzoxazole. All the synthesized compounds were characterized by IR,^{1}H NMR and MASS Spectroscopic methods and the synthesized compounds were evaluated for Anti-bacterial activity against gram negative E. coli and anti-inflammatory activity.

Keywords: Mercaptobenzoxazole, Mannich Base, Furfuraldehyde, IR, ^{1}H NMR, Mass Spectroscopy, Antibacterial activity, Anti-inflammatory activity

A R T I C L E I N F O

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1. Introduction

Mercaptobenzoxazole: Benzoxazole nucleus has been reported various type of biological activities such as antidepressant, antifungal, analgesic, anti-inflammatory, anticancer and antimicrobial. 2-Mercaptobenzoxazol is a heteroaromatic chemical compound from the class of benzoxazoles. 2-mercaptobenzoxazole is for the synthesis of 2-mercapto-6-chlorobenzoxazole, from which the herbicide fenoxaprop-P-ethyl is recovered and anion-active as collectors in the flotation uses of sulfidic ores.

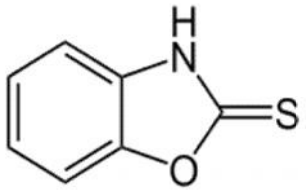


Figure 1: Mercaptobenzoxazole

2. Materials and Methods

Synthesis of 2-Mercaptobenzoxazole:

Equimolar mixture of 10.91 gms(0.1M) aminophenol and (0.1M) of KOH of Carbon disulfide and 100ml of 95ml ethanol was taken in a 500ml RBF and the mixture was reflux for 3hrs. Then 1.5gms of charcoal was added and the mixture was heated at 60-70°c for 10mins. Then 100ml of water was added and acidify with acetic acid with good stirring. Solid was separated for filtration and final solid was stored in the refrigerator. The product was crystallized with ethanoic KOH.MP180-185

Synthesis of *N*-{[(2,3-dihydro-1,3-benzoxazol-2-yl) sulfanyl] (furan-3-yl)methyl}-*N*-ethylethanamine

Equimolar mixture of furfuraldehyde (0.1mol, 10.6ml), Diethylamine (0.1mol, 8.7ml) and 2-mercaptobenzoxazole (0.1mol, 13.5gm) was dissolved in ethanol, the reaction mixture was refluxed for 5hrs, and the reaction mixture was cooled and poured into ice cold water. The precipitate was collected by filtration. The precipitate was dried and recrystallized from absolute ethanol.

Synthesis of 1-[(1, 3-benzoxazol-2-yl) sulfanyl]-1- (furan-2-yl)-N-N-dimethylmethanamine

Equimolar mixture of furfuraldehyde (0.1mol, 10.6ml), Dimethylamine(0.1mol, 8.7ml) and 2-mercaptobenzoxazole (0.1mol, 13.5gm) was dissolved in ethanol, the reaction mixture was refluxed for 5hrs, and the reaction mixture was cooled and poured into ice cold water. The precipitate was collected by filtration. The precipitate was dried and recrystallized from absolute ethanol.

Synthesis of 2-{[(furan-2-yl) (morpholin-4-yl) methyl] sulfanyl}-1,3-benzoxazole

Equimolar mixture of furfuraldehyde (0.1mol, 10.6ml), morpholine (0.1mol, 8.7ml) and 2-mercaptobenzoxazole (0.1mol, 13.5gm) was dissolved in ethanol, the reaction mixture was refluxed for 5hrs, and the reaction mixture was cooled and poured into ice cold water. The precipitate was collected by filtration. The precipitate was dried and recrystallized from absolute ethanol.

Synthesis of 2{[(furan-2-yl) (1*H*-indol-1-yl) methyl] sulfanyl}-1, 3-benzoxazole:

Equimolar mixture of furfuraldehyde (0.1mol, 10.6ml), Indole (0.1mol, 8.7ml) and 2-mercaptobenzoxazole (0.1mol, 13.5gm) was dissolved in ethanol, the reaction mixture was refluxed for 5hrs, and the reaction mixture was cooled and poured into ice cold water. The precipitate was collected by filtration. The precipitate was dried and recrystallized from absolute ethanol.

Synthesis of 2{[furan-2-yl) (piperazin-1-yl) methyl] sufanyl}1, 3 benzoxazole

Equimolar mixture of furfuraldehyde (0.1mol,10.6ml), piperidine (0.1mol,8.7ml) and 2-mercaptobenzoxazole (0.1mol,13.5gm) was dissolved in ethanol, the reaction mixture was refluxed for 5hrs, the reaction mixture was cooled and poured into ice cold water. The precipitate was collected by filtration. The precipitate was dried and recrystallized from absolute ethanol. 150^{C}

Synthesis 2-{[(2,3-dihydro-1*H*-benzimidazol-1-yl)(furan-3-yl)methyl]sulfanyl}-2,3-dihydro-1,3-benzoxazole

Equimolar mixture of furfuraldehyde (0.1mol, 10.6ml), Benzimidazole (0.1mol, 8.7ml) and 2-mercaptobenzoxazole (0.1mol, 13.5gm) was dissolved in ethanol, the reaction mixture was refluxed for 5hrs, and the reaction mixture was cooled and poured into ice cold water. The precipitate was collected by filtration. The precipitate was dried and recrystallized from absolute ethanol $120^{oC.}$

Synthesis of *N*-{[(2,3-dihydro-1,3-benzoxazol-2-yl) sulfanyl] (furan-3-yl)methyl}-*N*-ethylethanamine

Equimolar mixture of furfuraldehyde (0.1mol, 10.6ml), Diphenylamine (0.1mol, 8.7ml) 2-mercaptobenzoxazole (0.1mol, 13.5gm) was dissolved in ethanol, the reaction mixture was refluxed for 5hrs, and the reaction mixture was cooled and poured into ice cold water. The precipitate was collected by filtration. The precipitate was dried and recrystallized from absolute ethanol $120^{oC.}$

Synthesis of N-{[(1,3-benzoxazol-2-yl) sulfanyl] (furan-2-yl) methyl}-N-cyclohexamine

Equimolar mixture of furfuraldehyde (0.1mol, 10.6ml), dicyclohexylamine (0.1mol, 8.7ml) 2-mercaptobenzoxazole (0.1mol, 13.5gm) was dissolved in ethanol, the reaction mixture was refluxed for 5hrs, and the reaction mixture was cooled and poured into ice cold water. The precipitate was collected by filtration. The precipitate was dried and recrystallized from absolute ethanol $120^{oC.}$

Synthesis of 4-chloro-*N*-{[(2,3-dihydro-1,3-benzoxazol-2-yl) sulfanyl](furan-3-yl)methyl}aniline

Equimolar mixture of furfuraldehyde (0.1mol, 10.6ml), chloroaniline (0.1mol, 8.7ml) and 2-mercaptobenzoxazole (0.1mol, 13.5gm) was dissolved in ethanol, the reaction mixture was refluxed for 5hrs, and the reaction mixture was cooled and poured into ice cold water. The precipitate was collected by filtration. The precipitate was dried and recrystallized from absolute ethanol $120^{oC.}$

Synthesis of 4-bromo -*N*-{[(2,3-dihydro-1,3-benzoxazol-2-yl)sulfanyl](furan-3-yl) methyl}aniline

Equimolar mixture of furfuraldehyde (0.1mol, 10.6ml), Bromoaniline (0.1mol, 8.7ml) and 2-mercaptobenzoxazole (0.1mol, 13.5gm) was dissolved in ethanol, the reaction mixture was refluxed for 5hrs, and the reaction mixture was cooled and poured into ice cold water. The precipitate was

collected by filtration. The precipitate was dried and recrystallized from absolute ethanol 120°C.

3. Results and Discussion

Antibacterial activity: The antibiotic potency can be determined using the Cup plate method and *Staphylococcus aureus* (Gram positive) and *Eeshricia coli* (Gram negative) as test organisms. Initially, the prepared nutrient agar medium was sterilized by autoclaving method at 15 lbs pressure and 121°C for 25 min. Agar media was cooled to room temperature and the organism was inoculated to the media. 15 ml of media was transferred to a petri plates aseptically. Synthesized Compounds were dissolved in water and diluted to get 10mg/ml of concentration, whereas, streptomycin is used as standard drug at a concentration of 10µg/ml. The cultured plates were incubated at 37°C for 24 hrs. The zone of inhibition produced by test compounds and Mercaptobenzoxazole were recorded in mm [10].

***In-vivo* Anti-Inflammatory activity:**

Anti-inflammatory activity of the newly synthesized Mercaptobenzoxazole derivatives was evaluated by carrageenan induced paw edema assay in rats [11]. Synthesized test compounds with dose level 20 mg/kg and 50 mg/kg were administered and compared with that of standard drug Celecoxib (20mg/kg). The paw volumes were measured using the mercury displacement technique with the help of plethysmograph immediately before and 1h after carrageenan injection. The percent inhibition of paw edema was calculated from percent inhibition formula,

$$\%\text{inhibition (I)} = 100[1-(a-x)/(b-y)]$$

Where,

x = mean paw volume of rats before the administration of carrageenan and test compounds or reference compound (test group)

a = mean paw volume of rats after the administration of carrageenan in the test group (drug treated)

b = is the mean paw volume of rats after the administration of carrageenan in the control group

y = mean paw volume of rats before the administration of carrageenan in the control group.

Anti-inflammatory Activity: Anti-inflammatory activity of synthesized Mercaptobenzoxazole derivatives were evaluated by carrageenan induced paw edema bioassay in rats with Celecoxib (20mg/kg) as reference standard. Percentage inhibitions of the molecules are tabulated in Table2. % inhibition of paw edema with test compounds dose of 20 mg/kg is ranged between 17 and 37, whereas, with 50 mg/kg dose, it is between 59.9% and 83.5%. The results indicated that all the compounds reported significantly higher (two-tailed, paired *t* test; P<.0001) anti-inflammatory at dose of 50 mg/kg when compared to that of 20 mg/kg dose (Figure 2). However, the anti-inflammatory effect of compound 8 (50 mg/kg) and celecoxib (20 mg/kg) was found to be similar (82.6% vs. 84.6%; P = 0.105). The higher anti-inflammatory activity of compound 7 and compound 8 could be due to its higher hydrophobic as well as thiosubstitution.

Synthesis of 2-Mercaptobenzoxazole:

FT IR data :C=C 1655 $cm^{-1,}$ -C-C 753 $cm^{-1,}$ =C-H 3195 $cm^{-1,}$ -C=N1208 $cm^{-1,}$ -C=S1106 $cm^{-1,}$-C-01279 $cm^{-1,}$ =N-H 3195 cm^{-1} , H^1NMR :Ar-**H** 7.0978, -N-**H** 1.8133, Mass :152 (M+1)

Synthesis of 2-{[(furan-2-yl) (morpholin-4-yl) methyl] sulfanyl}-1,3-benzoxazole: C=C 1619$cm^{-1,}$ -C-C 591 $cm^{-1,}$ =C-H 3040 $cm^{-1,}$ -C=N1040 $cm^{-1,}$ -C=S1153 $cm^{-1,}$-C-0 1015 $cm^{-1,}$ =N-H 3382 cm^{-1} , H^1NMR : Ar-**H** 7.3373, -N-**H** 1.8348, C-**H** 2.4674, **H**C=C**H** 7.8795, =C$\mathbf{H_2}$-1.6517, Mass :339 (M+23) ,135^0 C

Synthesis of 2{[furan-2-yl) (piperazin-1-yl) methyl] sufanyl} 1, 3 benzoxazole: C=C 1619$cm^{-1,}$ -C-C 591 $cm^{-1,}$ =C-H 3040 $cm^{-1,}$ -C=N1040 $cm^{-1,}$ -C=S1153 $cm^{-1,}$-C-0 1015 $cm^{-1,}$ =N-H 3382 cm^{-1} , H^1NMR : Ar-**H** 7.3373, -N-**H** 1.8348, C-**H** 2.4674, **H**C=C**H** 7.8795, =C$\mathbf{H_2}$-1.6517, Mass :339 (M+23) ,135^0 C

Synthesis of *N*-{[(2, 3-dihydro-1,3-benzoxazol-2-yl) sulfanyl] (furan-3-yl) methyl}-*N*-ethylethanamine H^1NMR: 170^{0}C: Ar-**H** 7.0959, -N-**H** 3.2016, C-**H** 0.0316, **H**C=C**H** 7.3119, 125 C,Mass 415(M+18).

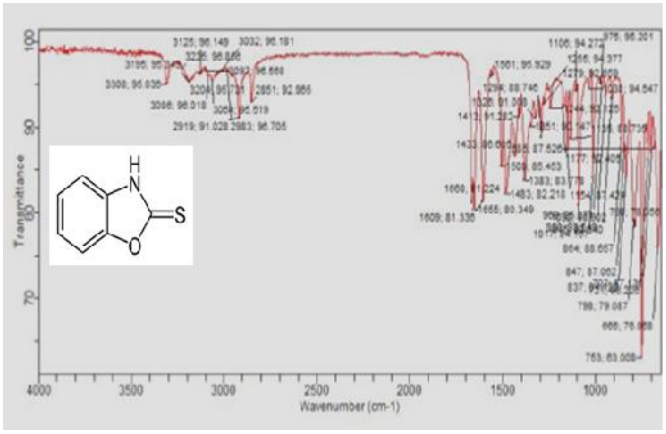


Figure 1: FT-IR Spectra of 2-Mercaptobenzoxazole

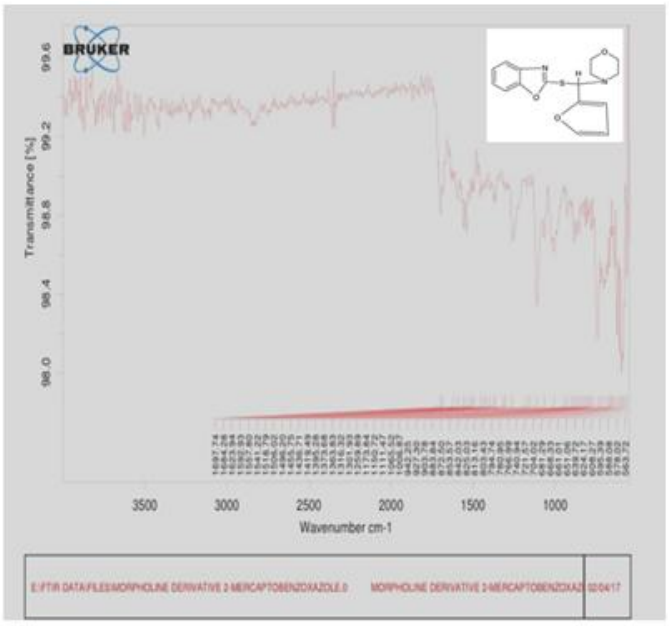


Figure 2: FT-IR Spectra of 2-{[(furan-2-yl) (morphlin-4-yl) methyl] sulfanyl}-1,3-benzoxazole

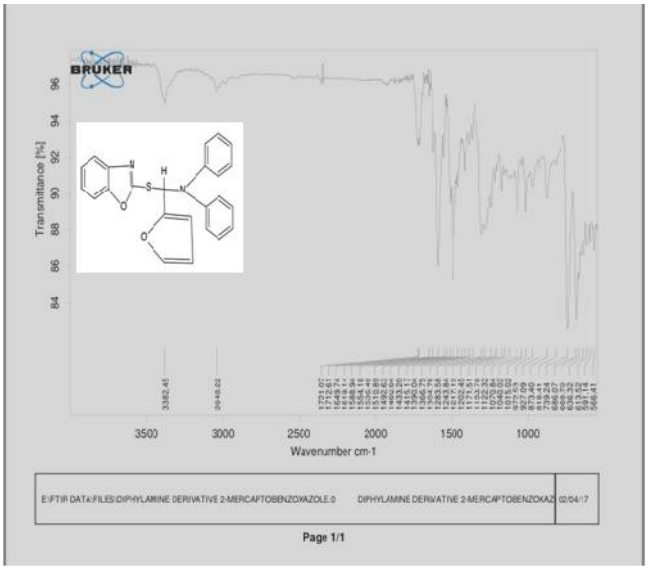


Figure 3: FT-IR Spectra of N-{[(1,3-benzoxazol-2-yl) sulfanyl] (furan-2-yl) methyl}-N-phenylaniline

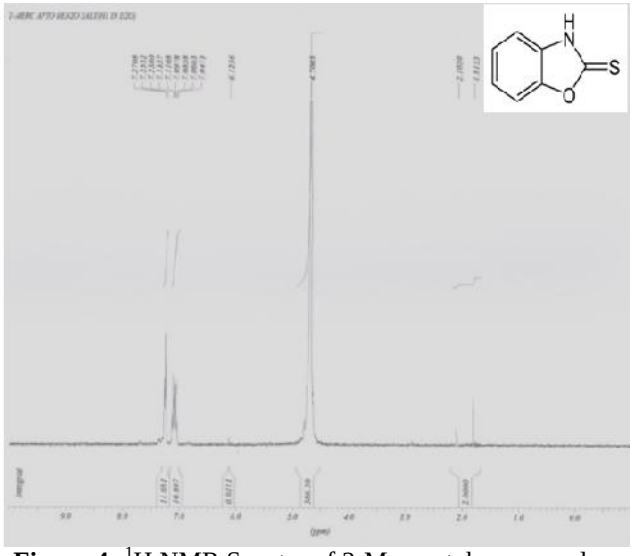


Figure 4: ^{1}H NMR Spectra of 2-Mercaptobenzoxazole

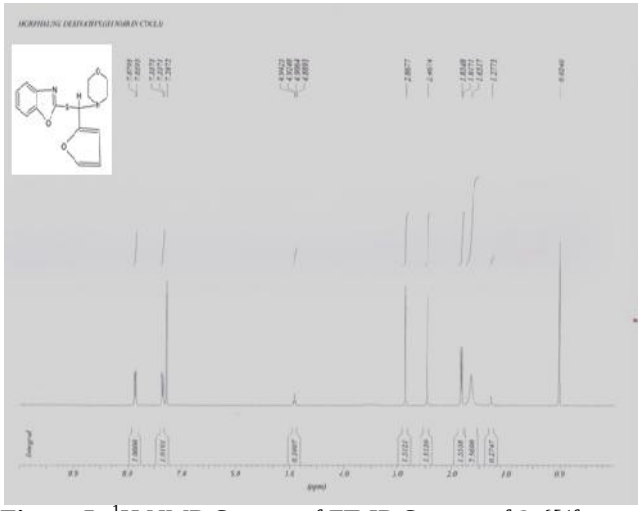


Figure 5: ^{1}H NMR Spectra of FT-IR Spectra of 2-{[(furan-2-yl) (morphlin-4-yl) methyl] sulfanyl}-1, 3-benzoxazole

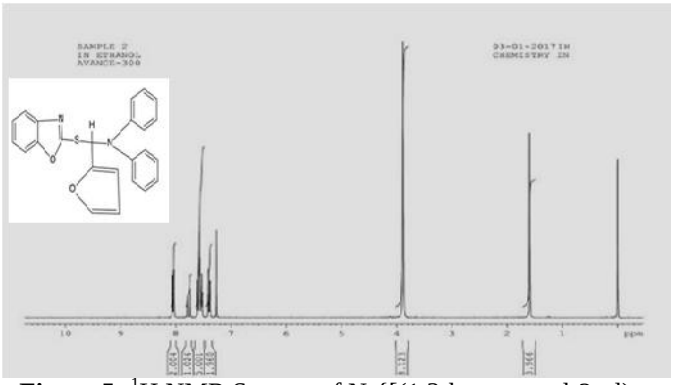


Figure 5: ^{1}H NMR Spectra of N-{[(1,3-benzoxazol-2-yl) sulfanyl] (furan-2-yl) methyl}-N-phenylaniline

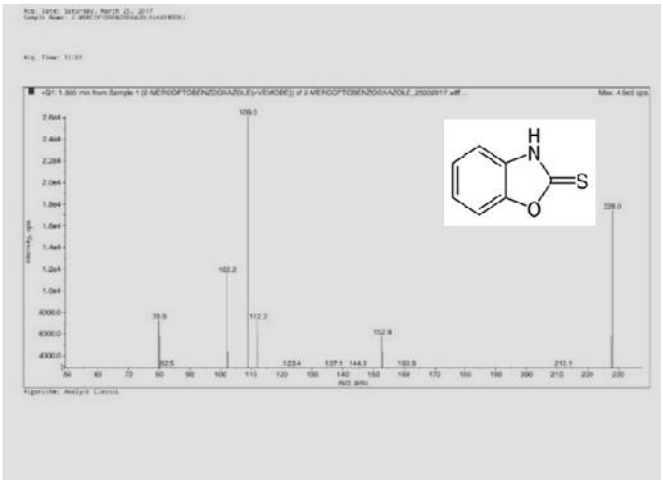


Figure 6: Mass Spectra of 2-Mercaptobenzoxazole

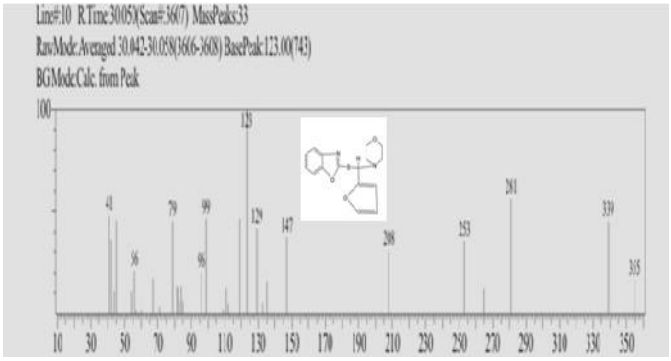


Figure 7: Mass Spectra of FT-IR Spectra of 2-{[(furan-2-yl) (morphlin-4-yl) methyl] sulfanyl}-1,3-benzoxazole

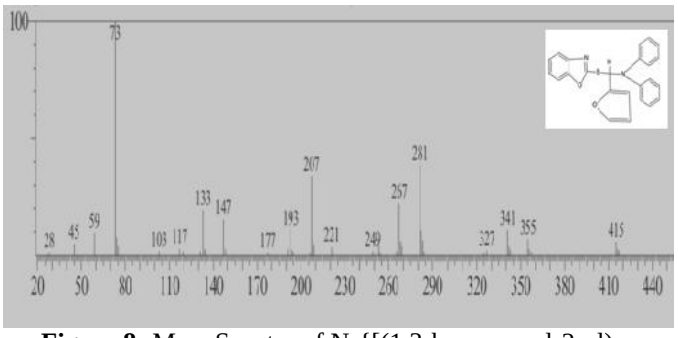
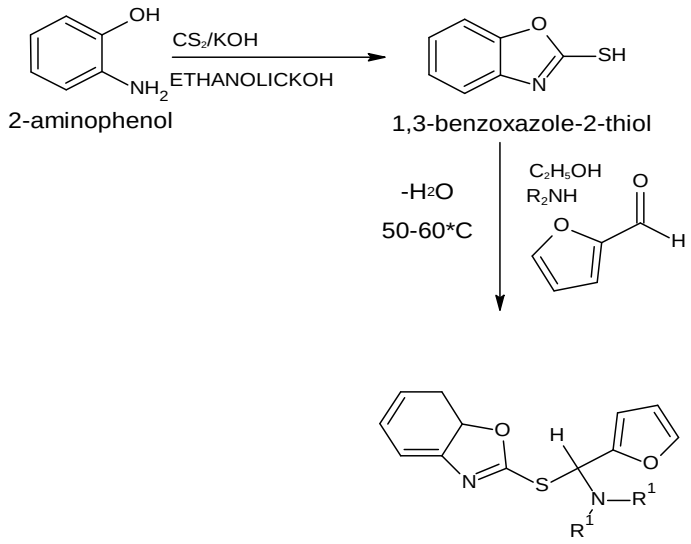


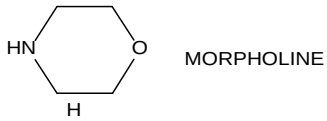
Figure 8: Mass Spectra of N-{[(1,3-benzoxazol-2-yl) sulfanyl] (furan-2-yl) methyl}-N-phenylaniline

Discussion

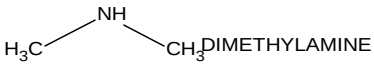
All the newly synthesized compounds were purified and separated using column chromatography. The compounds were dried for about 12 h under high vacuum. Synthesized compounds were characterized by using ^{1}H NMR, ^{13}C NMR and Mass spectrometric studies. The orientation of protons in the analysed compounds fully supported by the integration curves. Furthermore, all the mercaptobezoxazole derivatives demonstrated the characteristic chemical shifts for their nucleus. Additionally, synthesized mercaptobezoxazole derivatives were analyzed by mass spectra under ESI conditions and indicate no difference in the fragmentation pattern among the set of synthesized series. The synthesized mercaptobenzoxazole derivatives evaluated for their antibacterial and anti-inflammatory activities. Compound 8 and compound 7 have shown relatively higher antibacterial activity and higher when compared to streptomycin against *S. aureus* and *E. coli*, respectively. The higher anti-inflammatory activity of compound 7 and compound 8 could be due to its higher hydrophobic as well as thio substitution.

scheme

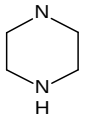




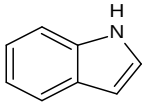
MORPHOLINE



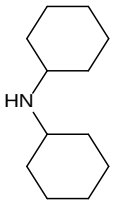
DIMETHYLAMINE



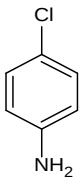
PIPERIDINE



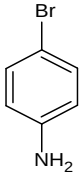
INDOLE



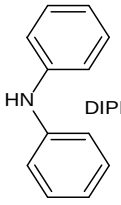
DICYCLOHEYLAMINE



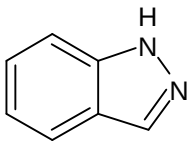
4-chloroaniline



4-bromoaniline



DIPHENYLAMINE



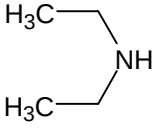


Table 1: IR Spectral data of synthesized compounds

Compound	**-C=C**	**-C-C**	**=C-H**	**-C=N**	**-C=S**	**-C-0**	**=N-H**
A	$1655cm^{-1}$	$753cm^{-1}$	$3195cm^{-1}$	$1208cm^{-1}$	$1106cm^{-1}$	$1279cm^{-1}$	$3195cm^{-1}$
B	$1619cm^{-1}$	$591cm^{-1}$	$3040cm^{-1}$	$1040cm^{-1}$	$1153cm^{-1}$	$1015cm^{-1}$	$3382cm^{-1}$
C	$1623cm^{-1}$	$588cm^{-1}$	$1065cm^{-1}$	$1259cm^{-1}$	$1173cm^{-1}$	$1259cm^{-1}$	$3391cm^{-1}$

Table 2: ^{1}H NMR Spectral Data of the Synthesized Compounds

Compounds	Ar-**H**	-N-**H**	C-**H**	**H**C=C**H**	=C**H**$_2$-	=C**H**$_2$-N**H**
A	7.0978	1.8133	-	-	-	-
B	7.3373	1.8348	2.4674	7.8795	1.6517	-
C	7.1960	1.2773	1.3966	7.5001	-	3.8123
D	7.0959	3.2016	0.0316	7.3119	-	-

Table 3: Mass spectral data of synthesized compounds

Compounds	Molecular mass	M^{+} ion
A	151	152 (M+1)
B	316	339 (M+23)
C	315	315
D	397	415 (M+18)

Table 4: Antibacterial activity of compounds

	concentration	Zone of inhibition
Standard	20	9
	40	11
	60	12
	80	13
Compound-1	20	9
	40	10
	60	11
	80	12
Compound-2	20	11
	40	11
	60	13
	80	14
Compound-3	20	9
	40	11
	60	12
	80	10
Compound-4	20	11
	40	9
	60	12
	80	10
Compound-5	20	9
	40	10
	60	11
	80	12
Compound-6	20	10
	40	13
	60	9
	80	11
Compound-7	20	10
	40	13
	60	11
	80	12

Compound-8	20	9
	40	11
	60	12
	80	13
Compound -9	20	11
	40	12
	60	9
	80	13
Compound -10	20	10
	40	13
	60	9
	80	11

Table 5: Anti-inflammatory Activity of Synthesized compounds (% inhibition of Paw Edema)

Compound	**% Inhibition of Paw Edema**	
	20mg/kg	**50 mg/kg**
1	**17**	**58**
2	**22.8**	**59.9**
3	22.2	59.7
4	21.3	60.4
5	21.8	61.5
6	25.5	59.4
7	29.5	68.9
8	17.3	60.8
9	37	83.5
10	33	78
Celecoxib (20 mg/kg)	84.6	

4. Conclusion

A series of new mannich bases with mercaptobenzoxazole derivatives were synthesized and evaluated for their antibacterial and anti-inflammatory activities. Compound 8 and compound 7 have shown relatively higher antibacterial activity and higher when compared to streptomycin against *S. aureus* and *E. coli*, respectively. The higher anti-inflammatory activity of compound 7 and compound 8 could be due to its higher hydrophobic as well as thio substitution. Similarly, compound 8 also reported highest activity among molecules tested at both dose levels and statistically. The results demonstrated that antibacterial and anti-inflammatory activity properties of new moleculare due to larger hydrophobic groups at amino substitution.

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