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SYNTHESIS, CHARACTERIZATION AND ANTI BACTERIAL ACTIVITY OF NOVEL 2-MERCAPTOBENZOXAZOLE DERIVATIVES

Narender Boggula*, Ridhika M Patel, Akhil Rapolu, Pramod Kumar Bandari, Krishna Mohan Chinnala

Nalla Narasimha Reddy Education Society's Group of Institutions, School of Pharmacy
Hyderabad, Telangana, India

Abstract

*Benzoxazole and its derivatives are important class of bioactive molecules, their importance is due to their versatile application in the field of drugs and pharmaceuticals as well as in chemical systems. It finds use in research as a starting material for the synthesis of larger, usually bioactive structures. A new series of Benzoxazol-2-ylthio-N'-(4-substituted) acetohydrazide derivatives (**IV a-k**), were obtained by synthesising new schiff's bases derived from benzoxolyl-2-mercaptoacetohydrazide derivatives by treating with various aryl/hetero aryl aldehydes. Their chemical structures have been confirmed by ^{1}H-NMR, ^{13}C-NMR, FT-IR and Mass spectral data. The synthesised derivatives **(IV a-k)** were screened for their in-vitro anti bacterial activities by agar diffusion method. Among the synthesized derivatives **IVb, IVe, IVk, IVi** showed significant antibacterial activity.*

Key Words: *Benzoxazole, heterocyclic compounds, aryl/hetero aryl aldehydes, schiff's bases, anti bacterial activity.*

Corresponding Author:

Narender Boggula,

Asst. Professor, School of Pharmacy,
Nalla Narasimha Reddy Education Society's Group of Institutions,
Chowdariguda, Korremula, Ghatkesar,
Ranga Reddy, Telangana, INDIA-500088.
E-Mail: narender.b987@gmail.com
Mobile: +91 966 655 2211

QR code

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INTRODUCTION:

Heterocyclic compounds are those which have a cyclic structure with two or more different kinds of atoms in the ring. The study of heterocycles is an evergreen field in organic chemistry. Heterocyclic chemistry has been progressing owing to their natural occurrence, specific chemical reactivity and broad spectrum utility.

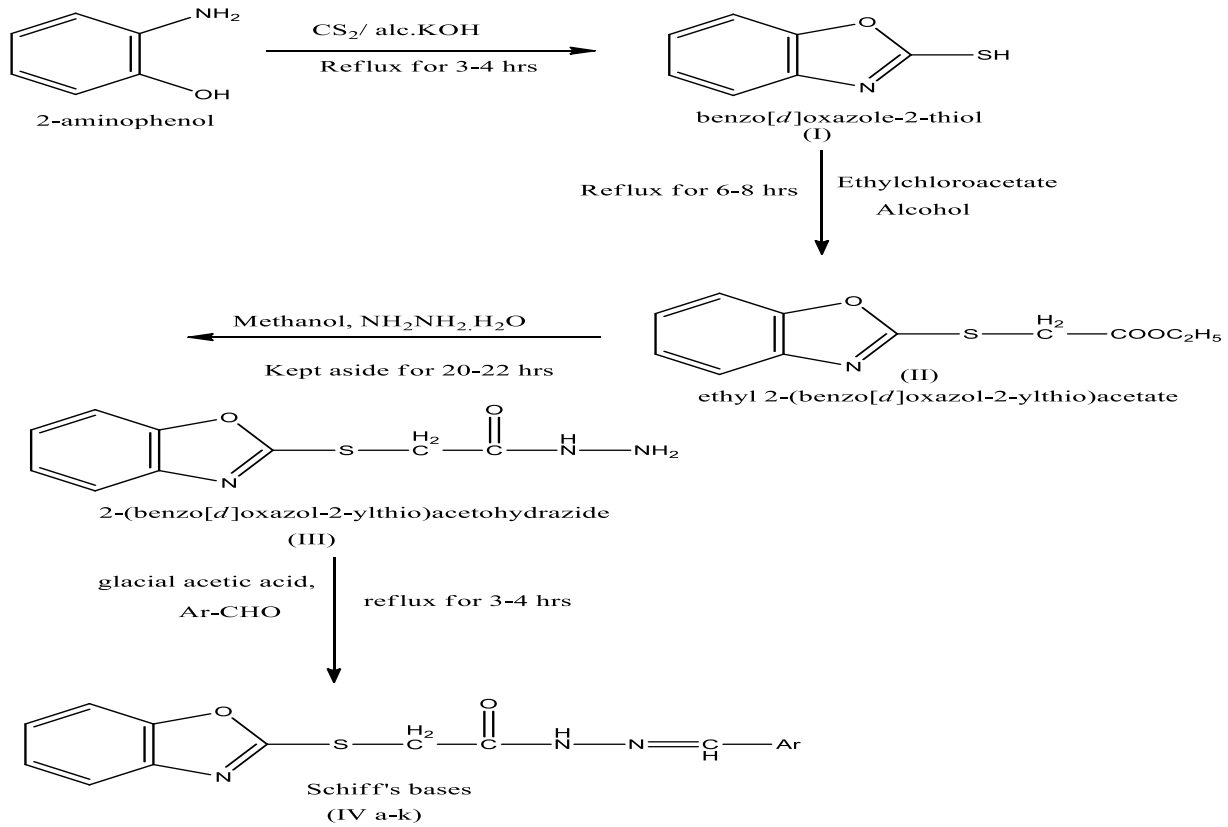
The heterocyclic compounds are very widely distributed in nature and are essential to living organisms. They play a vital role in the metabolism of all the living cells. Among large number of heterocycles found in nature, nitrogen heterocycles are the most abundant specially those containing oxygen or sulphur due to their wide distribution in nucleic acid illustration and their involvement in almost every physiological process of plants and animals.

One of the main objectives of organic and medicinal chemistry is the design, synthesis and production of molecules having value as human therapeutic agents. During the past decade, combinatorial chemistry has provided access to chemical libraries based on privileged structures, with heterocyclic structures receiving special attention as they belong to a class of compounds with proven utility in medicinal chemistry. Biologically active benzoxazole derivatives have been known for long time, since they are the isosteres of naturally occurring cyclic nucleotides and they may easily interact with the biopolymers of the organisms.

Benzoxazoles and its derivatives are important class of bioactive molecules, their importance is due to their versatile application in the field of drugs and pharmaceuticals as well as in chemical systems. Benzoxazole finds use in research as a starting material for the synthesis of larger, usually bioactive structures5. The benzoxazoles are a large chemical family used as antimicrobial agents against a wide spectrum of microorganisms. The high therapeutic activity of the related drugs has encouraged the medicinal chemists to synthesize a large number of novel chemotherapeutic agents. The incorporation of the benzoxazole nucleus is an important synthetic strategy in drug discovery. This class of molecules have broadened the scope in remedying various dispositions in clinical medicine.

MATERIALS AND METHODS:

Scheme:

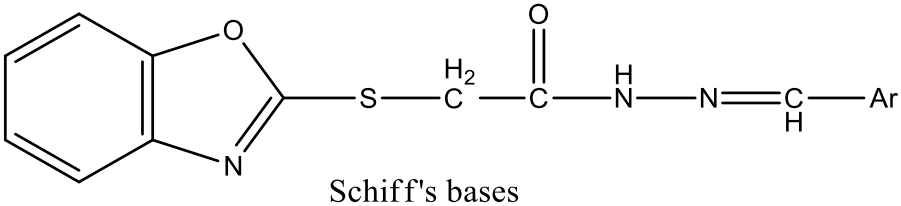


Step 1: Preparation of benzo[*d*]oxazole-2-thiol (I)
10.91g of 2-aminophenol, 6.19ml of carbon di-sulphide, 5.65g of potassium hydroxide, and 15 ml of water were taken in a 250ml RBF and refluxed in 100 ml of 95% ethanol for 3 to 4 hours. Later charcoal was added cautiously, refluxed for 10 minutes and filtered. The filtrate was heated up to 70-80^{0}C and 100ml warm water was added, 5% glacial acetic acid was added and stirred vigorously. The product was obtained as crystals and placed in refrigerator for 3 hrs, for further crystallization. The product was filtered and dried. The dried product was recrystallized with ethanol.

Step 2: Preparation of ethyl-2-(benzo[*d*]oxazol-2-ylthio) acetate (II)
Equimolar quantities of benzo[*d*]oxazole-2-thiol **(I)** and ethylchloroacetate were refluxed in ethanol for 6-8 hrs. The reaction mixture was poured in to ice cold and stirred vigorously. The precipitate obtained was filtered, washed with water and dried. The product was recrystallised with ethanol.

Step 3: Preparation of 2-(benzo[*d*]oxazol-2-ylthio) acetatohydrazide (III)
Equimolar quantities of ethyl-2-(benzo[*d*]oxazol-2-ylthio) acetate **(II)** and 99% hydrazine hydrate were dissolved in methanol and kept aside for 20-22 hrs. The precipitate obtained was filtered, washed with cold alcohol and dried.

Step 4: General preparation of Schiff's bases (IV a-k)
An appropriate aromatic aldehyde and 2-(benzo[*d*]oxazol-2-ylthio) acetatohydrazide **(III)** were dissolved in methanol, 1-2 drops glacial acetic acid was added and refluxed for 5-6 hrs. The mixture was kept in refrigerator overnight. The product obtained was filtered, dried and purified by recrystallization from ethanol.

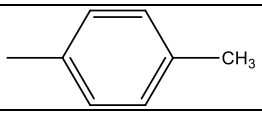
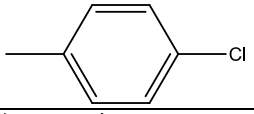
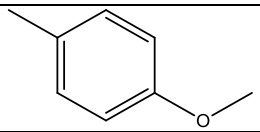
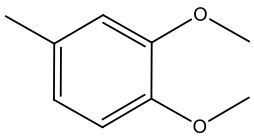


Schiff's bases

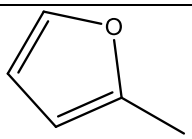
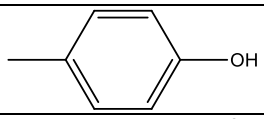
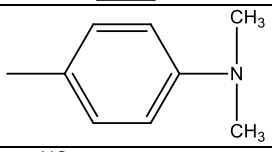
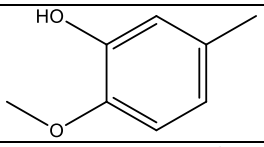
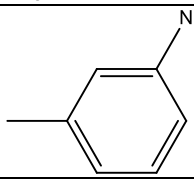
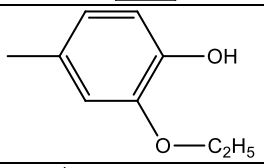
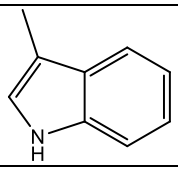
(IV a-k)

RESULTS AND DISCUSSION:

Table 1: Physical data of the 2-mercaptobenzoxazole Schiff's bases (IV a-k)

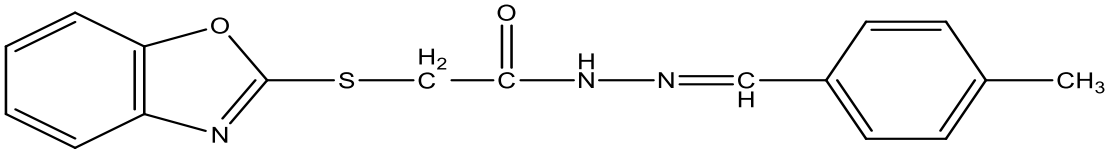
CODE	Ar	Mol. Formula	Mol. Weight	%Yield	M.P (^{0}C)
IVa		$C_{17}H_{15}N_3O_2S$	325	86	158-160
IVb		$C_{16}H_{12}N_3O_2SCl$	345.80	88	220-224
IVc		$C_{17}H_{15}N_3O_3S$	341.38	72	169-171
IVd		$C_{18}H_{17}N_3O_4S$	371.41	58	198-200

Continue……

IVe		$C_{14}H_{11}N_3O_3S$	301.32	89	186-189
IVf		$C_{16}H_{13}N_3O_3S$	327.36	82	208-210
IVg		$C_{18}H_{17}N_3O_2S$	339.41	66	176-178
IVh		$C_{17}H_{15}N_3O_4S$	357.38	78	205-208
IVi		$C_{16}H_{12}N_4O_4S$	356	69	217-220
IVj		$C_{18}H_{17}N_3O_4S$	371.09	78	160-162
IVk		$C_{18}H_{16}N_4O_2S$	352.4	76	210-212

Characterization Data:

2-(benzo[d]oxazol-2-ylthio)-N′-(4-methylbenzylidene)acetohydrazide (IVa):



Mol. Formula : $C_{17}H_{15}N_3O_2S$

Mol. Weight : 325

Solubility : Freely soluble in Methanol & Alcohol

TLC solvent : n-Hexane: Ethyl acetate (3:7)

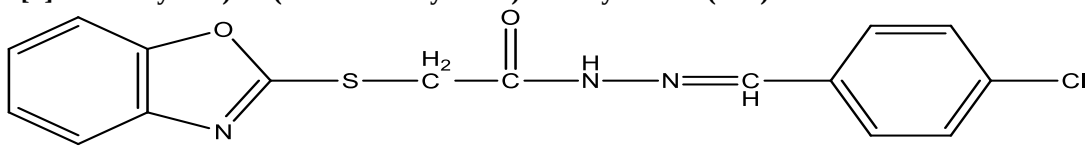
IR, Cm^{-1} (KBr) : 3424.51 (N-H, str.), 3029.80 (Ar-H, str.), 1736.85 (C=O, str. amide), 1621.71 (C=N), 1567.68 (N-H, out of plane), 1174.81 (C-S).

^{1}H-NMR, δ ppm : 8.1 (s, 1H, N=CH), 8.0(s, 1H, NH-N), 7.5 to 7.1 (m, 8H, Ar-H), 3.85 (s, 2H, S-CH_2), 2.35 (s, 3H, methyl).

^{13}C-NMR, δ ppm : 173.24(C=O), 165.31 (Benzoxazole C=N), 161.04-114.18

(Aromatic carbons), 143.208(C=N), 55.364, 40.9 (S-CH_2).
24.3 (Methyl)
Mass : m/z = 324 (M^{-1})

2-(benzo[d]oxazol-2-ylthio)-N′-(4-chlorobenzylidene) acetohydrazide (IVb):



Mol. Formula : $C_{16}H_{12}N_3O_2SCl$

Mol. Weight : 345.80

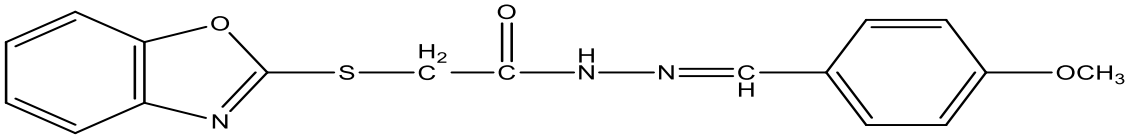
Solubility : Freely soluble in Methanol & Alcohol

TLC solvent : n-Hexane: Ethyl acetate (3:7)

IR, Cm^{-1} (KBr) : 3424.92 (N-H, str.), 3048.19 (Ar-H, str.), 1872.17 (C=O, str. amide), 1624.32 (C=N), 1592.04 (N-H, out of plane), 1168.01 (C-S).

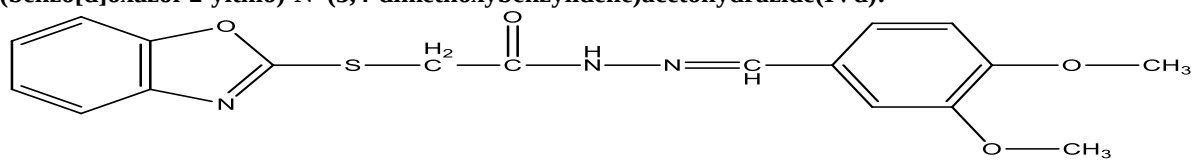
^{1}H-NMR, δ ppm : 8.1 (s, 1H, N=CH), 8.01(s, 1H, NH-N), 7.6 to 7.26 (m, 8H, Ar-H), 3.82 (s, 2H, S-CH_2).
^{13}C-NMR, δ ppm : 173(C=O), 165 (Benzoxazole C=N),150.04-110.18 (Aromatic carbons), 143.208(C=N), 40.09 (S-CH_2).
Mass : m/z = 346 (M^{+1})

2-(benzo[d]oxazol-2-ylthio)-N′-(4-methoxybenzylidene) acetohydrazide (IVc):



Mol. Formula : $C_{17}H_{15}N_3O_3S$
Mol. Weight : 341.38
Solubility : Freely soluble in Methanol & Alcohol
TLC solvent : n-Hexane: Ethyl acetate (3:7)
IR, Cm^{-1} (KBr) : 3454.85 (N-H, str.), 3037.34 (Ar-H, str.), 1731.76 (C=O, str. amide), 1618.95(C=N), 1601.59(N-H, out of plane), 1250.61 (C-O, str. ether), 1165.76 (C-S).
^{1}H-NMR, δ ppm : 8.61 (s, 1H, N=CH), 7.798(s, 1H, NH-N), 7.78 to 6.94(m, 8H, Ar-H), 3.85 (s, 2H, S-CH_2), 3.77 (s, 3H, methoxy).
^{13}C-NMR, δ ppm : 174.187(C=O), 161.970 (Benzoxazole, C=N),161.04-114.18 (Aromatic carbons), 143.208(C=N), 55.364 (Methoxy), 41.061(S- CH_2).
Mass : m/z = 340 (M^{-1})

2-(benzo[d]oxazol-2-ylthio)-N′-(3,4-dimethoxybenzylidene)acetohydrazide(IVd):



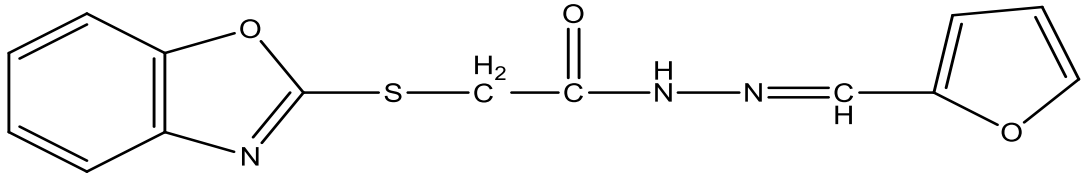
Mol. Formula : $C_{18}H_{17}N_3O_4S$

Mol. Weight : 371.41

Solubility : Freely soluble in Methanol & Alcohol

TLC solvent : n-Hexane: Ethyl acetate (3:7)
IR, Cm^{-1} (KBr) : 3423.76 (N-H, str.), 3073.54 (Ar-H, str.), 1729.98 (C=O, str. amide), 1623.18 (C=N), 1598.50 (N-H, out of plane), 1258.73 (C-O-C, ether), 1140.11 (C-S).
^{1}H-NMR, δ ppm : 8.1 (s, 1H, N=CH), 8.0(s, 1H, NH-N), 7.5 to 6.7(m, 7H, Ar-H), 3.85 (s, 2H, S-CH_2), 3.73 (s, 6H, methoxy).
^{13}C-NMR, δ ppm : 173.24(C=O), 165.31 (Benzoxazole C=N), 162.31-114.18 (7C, Ar-C), 143.208(C=N), 56.21 (Methoxy), 40.9 (S-CH_2).
Mass : m/z = 371

2-(benzo[d]oxazol-2-ylthio)-N′-(furan-2-methylene)acetohydrazide (IVe):



Mol. Formula : $C_{14}H_{11}N_3O_3S$

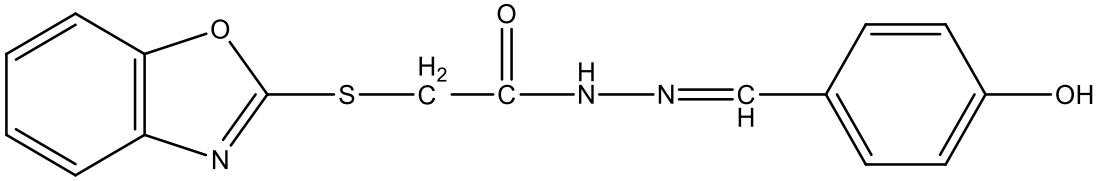
Mol. Weight : 301.32

Solubility : Freely soluble in Methanol & Alcohol

TLC solvent : n-Hexane: Ethyl acetate (3:7)

IR, Cm^{-1} (KBr) : 3434.6 (N-H, str.), 3109.65 (Ar-H, str.), 1770.33 (C=O, str. amide), 1644.02(C=N), 1147.44 (C-S).
^{1}H-NMR, δ ppm : 7.6 (s, 1H, N=CH), 7.37 (s, 1H, NH-N), 7.30 to 6.43(m, 7H, Ar-H), 3.83 (s, 2H, S-CH_2).
^{13}C-NMR, δ ppm : 173.24(C=O), 165.31 (Benzoxazole C=N), 161.04-109.5 (Aromatic carbons), 134.7(C=N), 40.9 (S-CH_2).
Mass : m/z = 300.9 (M^{-1})

2-(benzo[d]oxazol-2-ylthio)-N′-(4-hydroxybenzylidene)acetohydrazide (IVf):



Mol. Formula : $C_{16}H_{13}N_3O_3S$

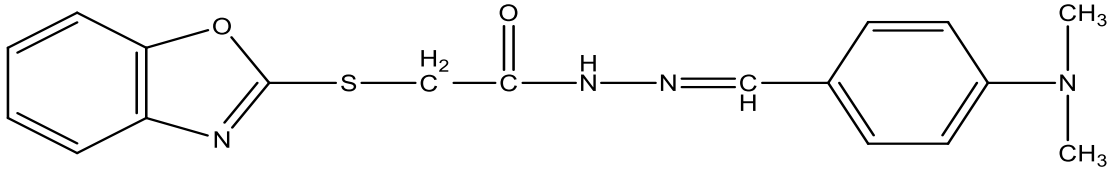
Mol. Weight : 327.36

Solubility : Freely soluble in Methanol & Alcohol

TLC solvent : n-Hexane: Ethyl acetate (3:7)

IR, Cm^{-1} (KBr) : 3043.65 (Ar-H, str.), 1715.38 (C=O, str. amide), 1689.99(C=N), 1623.78 (N-H, out of plane), 1147.59 (C-S).
^{1}H-NMR, δ ppm : 8.1 (s, 1H, N=CH), 8.0(s, 1H, NH-N), 7.5 to 6.8 (m, 8H, Ar-H), 5.0 (s, OH), 3.85 (s, 2H, S-CH_2).
^{13}C-NMR, δ ppm : 173.24(C=O), 165.31 (Benzoxazole C=N),160.08-116.0 (Ar-C), 143.208(C=N), 40.9 (S-CH_2).
Mass : m/z = 326.21(M^{-1})

2-(benzo[d]oxazol-2-ylthio)-N′-(4-(dimethylamino)benzylidene)acetohydrazide (IVg):



Mol. Formula : $C_{18}H_{17}N_3O_2S$

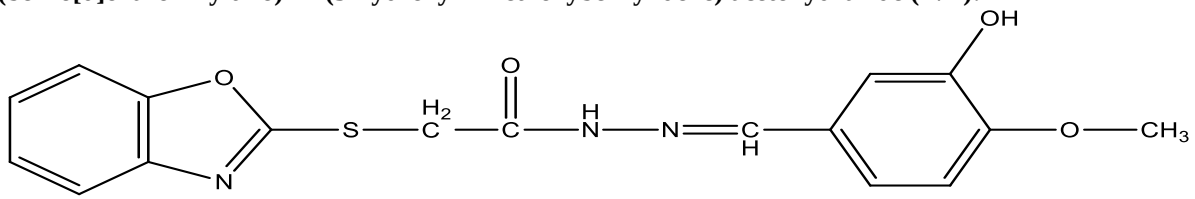
Mol. Weight : 339.41

Solubility : Freely soluble in Methanol & Alcohol

TLC solvent : n-Hexane: Ethyl acetate (3:7)

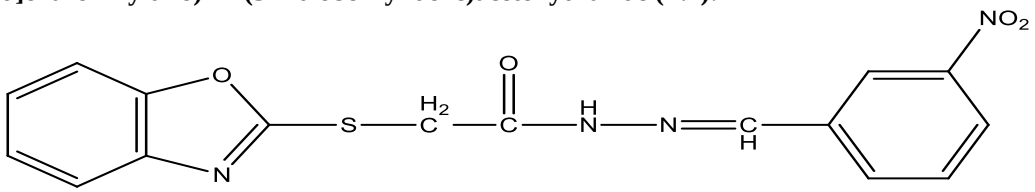
IR, Cm^{-1} (KBr) : 3082.40 (Ar-H, str.), 1891.11 (C=O, str. amide), 1602.15 (N-H, out of plane), 1165.76 (C-S).
^{1}H-NMR, δ ppm : 8.1 (s, 1H, N=CH), 8.0(s, 1H, NH-N), 7.5 to 6.6(m, 8H, Ar-H), 3.85 (s, 2H, S-CH_2), 2.85(s, 6H, N,N-dimethyl).
^{13}C-NMR, δ ppm : 173.24(C=O), 165.31 (Benzoxazole C=N), 158.33-114.18 (9C,Ar-C), 143.208(C=N), 38.47(N,N-dimethyl), 40.9 (S-CH_2)
Mass : m/z = 339.41 (M^{+1})

2-(benzo[d]oxazol-2-ylthio)-N′-(3-hydroxy-4-methoxybenzylidene) acetohydrazide (IVh):



Mol. Formula : $C_{17}H_{15}N_3O_4S$
Mol. Weight : 357.38
Solubility : Freely soluble in Methanol & Alcohol
TLC solvent : n-Hexane: Ethyl acetate (3:7)
IR, Cm^{-1} (KBr) : 3434.85 (N-H, str.), 3037.34 (Ar-CH, str.), 1731.76 (C=O, str. amide), 1618.95(C=N), 1165.76 (C-S).
^{1}H-NMR, δ ppm : 8.1 (s, 1H, N=CH), 8.0(s, 1H, NH-N), 7.5 to 6.6 (m, 7H, Ar-H), 5.0 (OH), 3.85 (s, 2H, S-CH_2), 3.73 (s, 3H, methoxy).
^{13}C-NMR, δ ppm : 173.24(C=O), 165.31 (Benzoxazole, C=N),153.07-115.8 (Ar-C), 143.208(C=N), 56.2 (Methoxy), 40.9 (S-CH_2).
Mass : m/z = 356.1 (M^{-1})

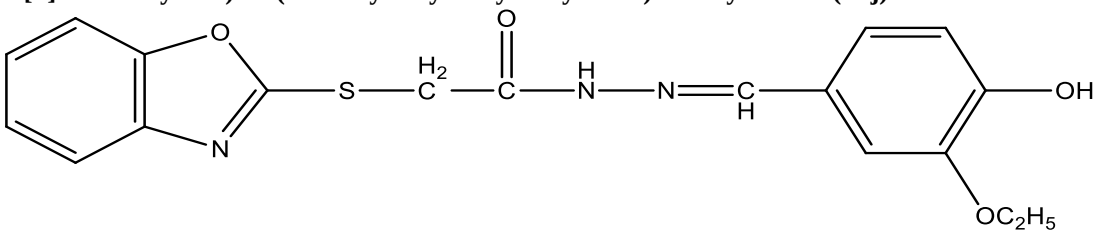
2-(benzo[d]oxazol-2-ylthio)-N′-(3-nitrobenzylidene)acetohydrazide (IVi):



Mol. Formula : $C_{16}H_{12}N_4O_4S$
Mol. Weight : 356
Solubility : Freely soluble in Methanol & Alcohol
TLC solvent : n-Hexane: Ethyl acetate (3:7)
IR, Cm^{-1} (KBr) : 3406.07 (N-H, str.), 3011.79 (Ar-CH, str.), 1622.47 (C=N), 1579.79 (N-H out of plane), 1184.38 (C-S).
^{1}H-NMR, δ ppm : 8.1 (s, 1H, N=CH), 8.0(s, 1H, NH-N), 8.6 to 7.6 (m, 9H, Ar-H), 3.85 (s, 2H, S-CH_2).

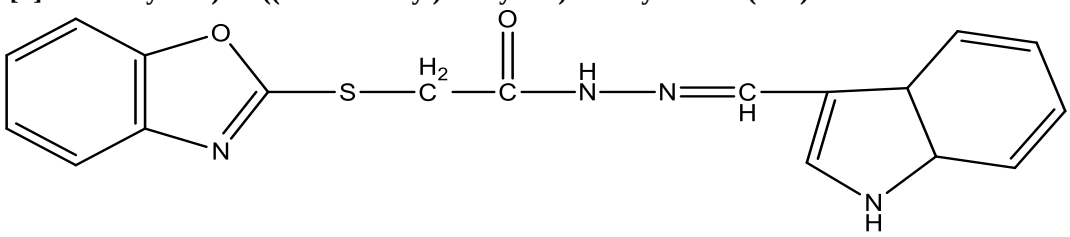
^{13}C-NMR, δ ppm : 173.24(C=O), 165.31 (Benzoxazole C=N),163.04-124.18 (Ar-C), 143.208(C=N), 40.9 (S-CH_2)**.**
Mass **:** m/z = 356 (M^{+1})

2-(benzo[d]oxazol-2-ylthio)-N′-(3-ethoxy-4-hydroxybenzylidene)acetohydrazide (IVj):



Mol. Formula **:** $C_{18}H_{17}N_3O_4S$
Mol. Weight **:** 371.09
Solubility **:** Freely soluble in methanol & alcohol
TLC solvent **:** n-Hexane: Ethyl acetate (3:7)
IR, Cm^{-1} (KBr) **:** 3434.85 (N-H, str.), 3037.34 (Ar-CH, str.), 1731.76 (C=O, str. amide), 1618.95(C=N), 1165.76 (C-S).
^{1}H-NMR, δ ppm **:** 8.1 (s, 1H, N=CH), 8.0(s, 1H, NH-N), 7.5 to 7.1 (m, 7H, Ar-H), 5.0 (OH), 3.85 (s, 2H, S-CH_2), 3.98, 1.33 (ethoxy protons).
^{13}C-NMR, δ ppm : 173.24(C=O), 165.31 (Benzoxazole C=N), 161.04-114.9 (Ar-C), 143.208(C=N), 65.0 (Ethoxy), 40.9 (S-CH_2)**.**
Mass **:** m/z = 371 (M^{+1})

2-(benzo[d]oxazol-2-ylthio)-N′-((1*H*-indol-3-yl)methylene)acetohydrazide (IVk):



Mol. Formula **:** $C_{18}H_{16}N_4O_2S$
Mol. Weight **:** 352.4
Solubility **:** Freely soluble in Methanol & Alcohol
TLC solvent **:** n-Hexane: Ethyl acetate (3:7)
IR, Cm^{-1} (KBr) **:** 3434.85 (N-H, str.), 3037.34 (Ar-CH, str.), 1731.76 (C=O, str. amide), 1618.95(C=N), 1165.76 (C-S).
^{1}H-NMR, δ ppm **:** 7.5 (s, 1H, N=CH), 7.0(s, 1H, NH-N), 7.5 to 7.1 (m, 9H, Ar-H), 3.85 (s, 2H, S-CH_2).
^{13}C-NMR, δ ppm : 173.24(C=O), 165.31 (Benzoxazole C=N),158.04-115.18 (Ar-C), 144.8(C=N), 40.9 (S-CH_2)**.**
Mass **:** m/z = 353.12 (M^{+1})

Anti Bacterial Activity

All the synthesized derivatives were characterized and screened for their anti bacterial activities by agar diffusion method. The standard cultures of gram-positive bacteria *Bacillus subtilis* and gram-negative bacteria *Enterobacter aerogenous, Proteus mirabitus, Klebsiella pneumonia, Salmonella paratyphi* and *Escherichia coli* species. All the glassware were cleaned by a suitable cleansing agent and sterilized at 121^{0}C and 15 lb/inch^2 for 15 minutes. A volume of 25 ml of sterile hot agar medium was poured in each plate and allowed to harden on a level surface. The compounds were screened for antibacterial activity against *Salmonella paratyphi, Enterobacter aeruginus, Proteus mirabitus, Klebsiela pneumonia, Escherichia coli* and *Bacillus subtilis* in nutrient agar medium. The agar plates were inoculated with 24 hrs test cultures by spreading uniformly with sterile cotton swabs. The plates were then allowed to dry in the inverted position in an incubator for 30 min. Afterwards they were removed and bores were made on the medium using sterile borer. A volume of 0.1 ml of test solution was added to respective bores. Streptomycin at a concentration of 50µg/ml was taken as standard reference. Only

DMSO was taken in a bore as control. The petriplates were kept in the refrigerator at 4^0C for 15 min for diffusion to take place. Afterwards they were incubated at 37^0C for 24 hrs and zones of inhibition were observed and measured using a scale. Each experiment was carried out in triplicate and the mean diameter of inhibition zone was recorded. The various anti bacterial results of synthesized compounds are shown in the Table no 2.

Table 2: Anti bacterial activity by zone of inhibition

Compound code	Zone of Inhibition(mm)					
	Gram –ve					Gram +ve
	S. paratyphi	*P. mirabitus*	*E. aerogenus*	*K. pneumoniae*	*E.coli*	*B. subtilis*
IV a	8	7	8	6	8	5
IV b	13	10	12	11*	8	9
IV c	6	7	5	5	6	NA
IV d	NA	5	NA	8	8	7
IV e	14*	9	17*	10	11	10*
IV f	12	5	11	4	6	8
IV g	NA	4	7	NA	9	6
IV h	5	9	8	9	8	4
IV i	11	12*	14	7	5	8
IV j	9	NA	7	6	7	5
IV k	6	6	8	5	12*	7
Streptomycin (50µg/ml)	18	15	20	14	15	13

NA = No activity. * = Significant activity, Concentration of test compound = 50µg/ml.

Table 3: Percentage Inhibition values for antibacterial activity

Compound code	% Inhibition					
	Gram –ve					Gram +ve
	S.paratyphi	*P.mirabilis*	*E.aerogenous*	*K.pneumoniae*	*E.coli*	*B.subtilus*
IV a	44.4	46.6	40	42.8	53.3	38.4
IV b	72.2	66.6	60	78.5*	53.3	69.2
IV c	33.3	46.6	25	35.7	40	NA
IV d	NA	33.3	NA	57.1	53.3	53.8
IV e	77.7*	60	85*	71.4	73.3	76.9*
IV f	66.6	33.3	55	50	33.3	61.5
IV g	NA	26.6	35	NA	50	46.1
IV h	27.7	60	40	64.2	53.3	50.7
IV i	38.8	80*	70	28.5	27.7	38.4
IV j	50	NA	35	42.8	46.6	61.5
IV k	33.3	40	40	35.7	80*	53.8
Streptomycin (50 µg/ml)	100	100	100	100	100	100

NA = No activity, * = Significant activity.
Concentration of test compound = 50 µg/ml.

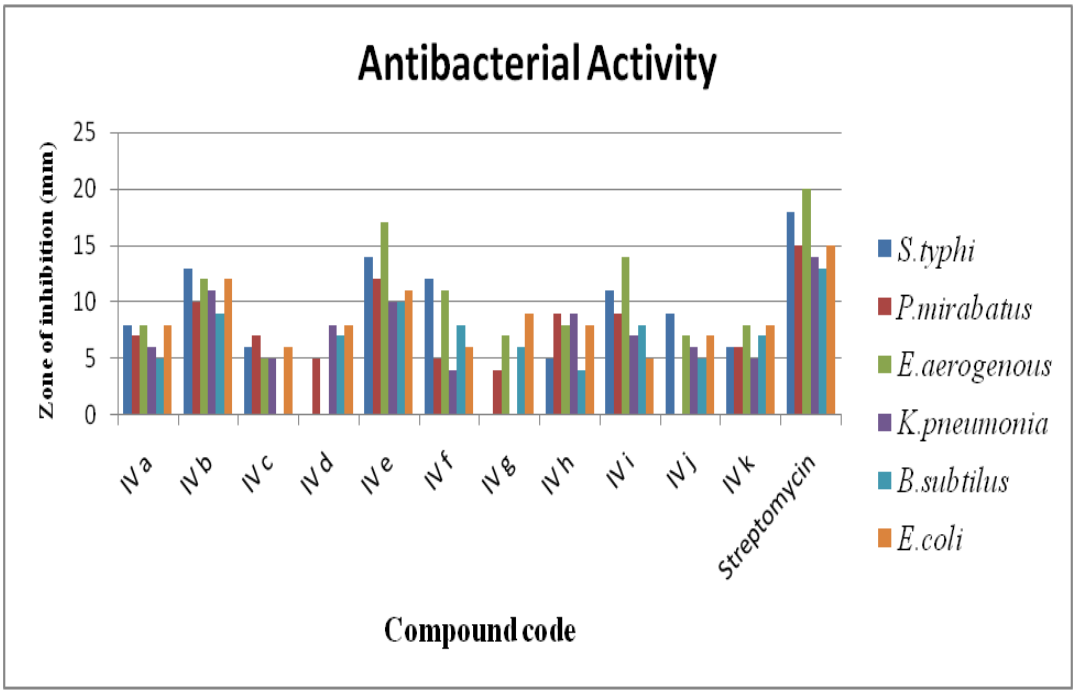


Fig 1: Graphical representation of anti bacterial activity by zone of inhibition

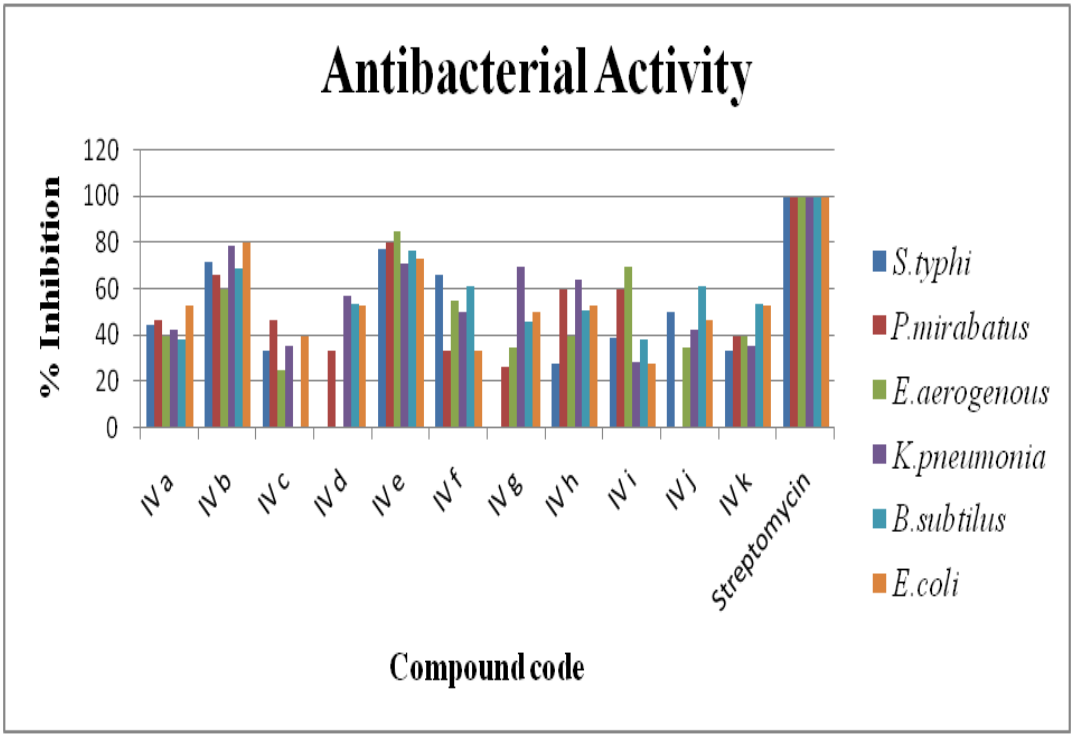


Fig 2: Graphical representation of anti bacterial activity by % inhibition

Fig 3: Anti bacterial activity for standard and control

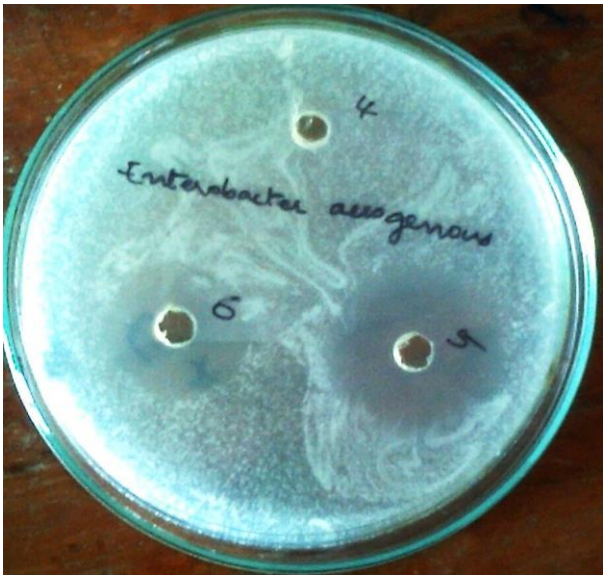


Fig 4: Anti bacterial activity of compounds IVd, IVe, IVf

CONCLUSION:

Introduction of benzoxazole moiety, in the synthesis and biological evaluation of novel 2-mercaptobenzoxazole derivatives, the synthesized products was characterized by IR, NMR, mass and evaluated for anti bacterial activity by agar diffusion method. The compounds were screened for their anti bacterial activity. Among all the compounds synthesized, the furan containing compound (**IVe)** and chlorine containing compound (**IVb)** were effective against *S. paratyphi.* The compound (**IVe)** was also effective against *E. aerogenous* and *B. subtilis.* The compound (**IVb)** was effective against *Klebsiella pneumonia* and the compound **(IVk)** was effective against *Escherichia coli.* The nitro group containing compound **(IVi)** was effective against *P. mirabilis.* The compound (**IVb)** was more effective against *Colleotrichum coffeanum.* Compounds (**IVe)** and (**IVj)** were effective against *Aspergillus niger.*

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