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Research Article

ANTI FUNGAL AND ANTI OXIDANT ACTIVITIES OF NOVEL 2-MERCAPTOBENZOXAZOLE DERIVATIVES

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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 oxidant and anti fungal activities. Among the synthesized derivatives **IVb, IVe, IVj** showed significant anti fungal activity. The derivatives were also evaluated for their anti oxidant activity by DPPH free radical scavenging activity. All the synthesized compounds have shown free radical scavenging activity.

Keywords: Benzoxazole, Schiff's bases, anti fungal activity, anti oxidant activity, DPPH method.

INTRODUCTION

Organic compounds containing a ring made up of heteroatoms in addition to carbon atoms are called heterocyclic compounds. Heteroatoms include oxygen, nitrogen, sulfur and less frequently phosphorous, boron and silicon. Heterocyclic compounds by far are the largest classical divisions of organic chemistry and are immense importance biologically and industrially. The majority of pharmaceuticals and biologically active agrochemicals are heterocyclic, while countless additives and modifiers used in industrial application ranging for cosmetics, reprography, information storage and plastics are heterocyclic in nature. The diversity of types of heterocyclic compounds is very great, since they can differ in the number of ring atoms and by the nature, number and positions of the heteroatoms, by the presence or absence of substituents or condensed rings, and by the saturated, unsaturated or aromatic nature of the heterocyclic ring.

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.

The heterocyclic ring comprises of very core of the active moiety or the pharmacophore. Several benzofused hetero, bicyclic ring systems as indole, benzothiazole, benzimidazole, benzoxazole, have been studied and found to be possessing interesting pharmacological activities. One striking structural feature inherent to heterocyclic's, which continue to be exploited is their ability to be manifest substituent around a core scaffold. 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.

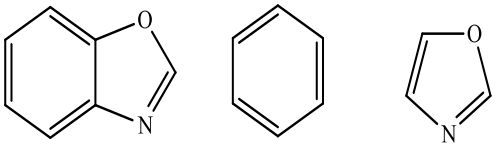
Benzoxazoles and its derivatives are important class of bioactive molecules, their importance is due to their versatile application in the field of drugs and pharmaceuticals as well as in chemical systems. Benzoxazole finds use in research as a starting material for the synthesis of larger, usually bioactive structures. It is found within the chemical structures of drugs such as flunoxaprofen and zoxazolamine.

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. This heterocyclic system has different activities as it can act as bacteriostatic or bactericidal, as well as fungicide and it is present in numerous anti viral drugs.

Literature survey revealed that benzoxazoles possess most remarkable and a wide range of biological activities. The substituted benzoxazoles have been shown to exhibit antitumor, anti histaminic, anti parasitic, herbicidal, anti allergic, anthelmintic, COX-2 inhibitory, anti fungal, anti bacterial, anti cancer, anti tubercular, anti convulsant, diarrhoea-predominant irritable bowel syndrome, hypoglycaemic, HIV-1 reverse transcriptase inhibitor & insecticidal activities. It has also been shown to have binding affinity to Aβ42 fibrils. Recent observations suggest that substituted benzoxazoles and related heterocycles, possesses potential activity with lower toxicities in the chemotherapeutic approach in man. The resistance of some pathogens to standard antibiotic therapies is quickly becoming a major public health problem all over the world. There is a real need for the discovery of new antimicrobial agents, possibly acting through the mechanisms, which are distinct from those of well-known classes of anti microbial agents to which many clinically relevant pathogens may be now resistant.

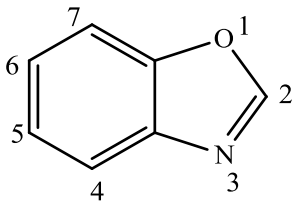
Discovering new drugs is an expensive and challenging process. Any new drug should not only produce the desired response to the disease but should do so with minimal side effects and be superior to the existing drugs in the market. One of the key steps in the drug design process is to identify the chemical compounds that display the desired and reproducible behaviour against the disease in a biological experiment.

Benzoxazole (1) is a bicyclic heterocyclic compound consisting of benzene (2) and oxazole (3).



(1) (2) (3)

Benzoxazoles can be considered as structural isosteres of naturally occurring nucleic bases adenine and guanine, which allow them to interact easily with polymers of living systems. It also finds use in research as a starting material for the synthesis of larger, usually bioactive structures. Benzoxazole (4) is an aromatic organic compound having benzene fused oxazole ring structure.



(4)

Benzaxozole is a planar molecule with conjugated π electrons sextets in the cyclic system. It is aromatic in character. The lone pair of electrons on nitrogen, which is coplanar with the heterocyclic ring, and therefore not involved in delocalization, confers weakly basic properties. Associated with the aromaticity is a degree of stability, but when these are quarternized the resulting azollium species are significantly activated towards nucleophillic attack.

MATERIALS AND METHODS

The present investigation is to build up benzoxazole derivatives attached with various substituted aromatic moieties and to screen their biological activities. So here, we synthesized various compounds mentioned in the table no. 1 and collected their physical, chemical and analytical data. Their chemical structures have been confirmed by ^{1}H-NMR, ^{13}C-NMR, FT-IR and Mass spectral data and identified the potent compounds, if any for their specific activity and for future exploitation.

Scheme

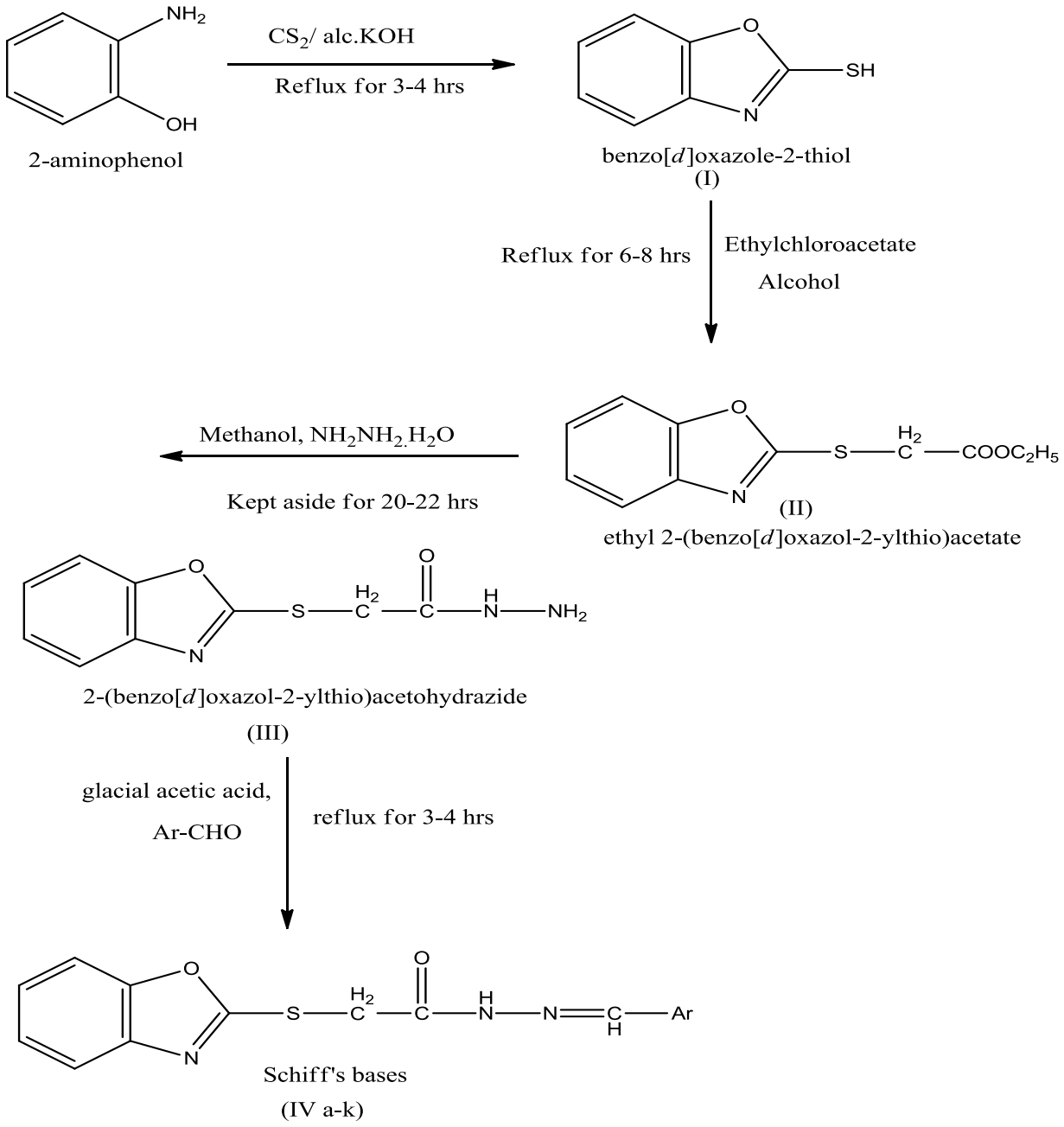
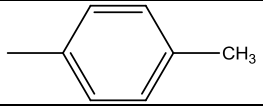
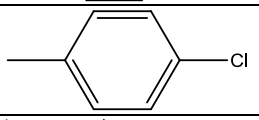
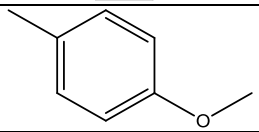
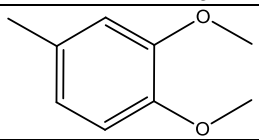
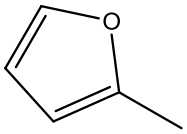
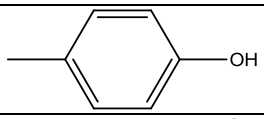
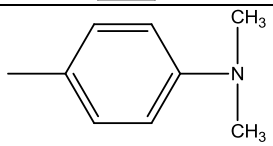
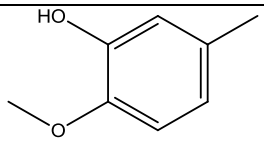
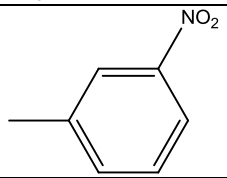
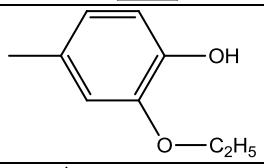
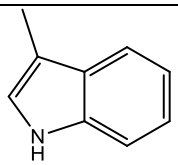


Table 1: Physical data of the 2-mercaptobenzoxazole Schiff's bases (IV a-k)

Code	Ar	Mol. Formula	Mol. Weight	%Yield	M.P. (^{0}C)
IV a		$C_{17}H_{15}N_3O_2S$	325	86	158-160
IV b		$C_{16}H_{12}N_3O_2SCl$	345.80	88	220-224
IV c		$C_{17}H_{15}N_3O_3S$	341.38	72	169-171
IV d		$C_{18}H_{17}N_3O_4S$	371.41	58	198-200
IV e		$C_{14}H_{11}N_3O_3S$	301.32	89	186-189
IV f		$C_{16}H_{13}N_3O_3S$	327.36	82	208-210
IV g		$C_{18}H_{17}N_3O_2S$	339.41	66	176-178
IV h		$C_{17}H_{15}N_3O_4S$	357.38	78	205-208
IV i		$C_{16}H_{12}N_4O_4S$	356	69	217-220
IV j		$C_{18}H_{17}N_3O_4S$	371.09	78	160-162
IV k		$C_{18}H_{16}N_4O_2S$	352.4	76	210-212

Anti fungal activity

All the compounds have been screened for anti fungal activity using cup-plate agar diffusion method by measuring the inhibition zone in mm. Griseofulvin (50 µg/mL) was used as a standard drug for antifungal activity. The compounds were screened for antifungal activity against *Aspergillus niger, Aspergilus tevatus, Pencillium notatum and Collitricum coffeanum* in Asthana hawkers medium. These sterilized media were cooled and added with fungal suspension in individual portions and poured into petri-dishes and allowed to solidify. A stainless steel cylinder of 8 mm diameter (pre-sterilized) was used to bore cavities. All synthesized compounds were placed in serially in the cavities with the help of micropipette and allowed to diffuse for 1.0 hr. DMSO was used as a solvent for all the compounds, and as a control. These plates were incubated at 28^0C for 48 hrs, for anti fungal activity. The zone of inhibition observed around the cups after respective incubation was measured.

Table 2: Composition for Asthana hawkers medium

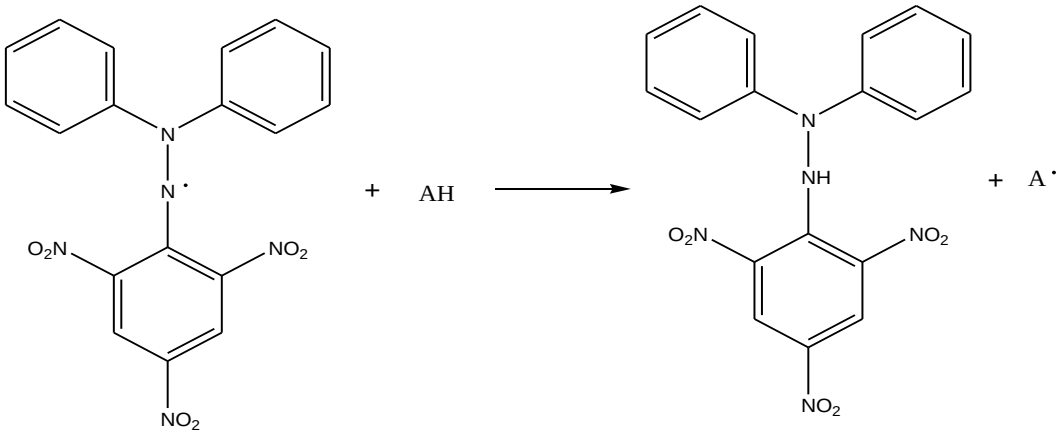
Sl. No.	Ingredients	Quantity
1.	Glucose	5g
2.	Potassium nitrate	3.5g
3.	KH_2PO_4	1.75g
4.	$MgSO_4.7H_2O$	0.75g
5.	Agar	15g
6.	Distilled water	1000ml

Anti oxidant activity

Anti oxidants react with DPPH and convert it to 1, 1-diphenyl-2-picryl hydrazine. The degree of decolourisation indicates the scavenging efficacy of added substance. The change in absorbance at 517 nm has been used as a measure of anti oxidant property.

Spectrophotometry–principle of the method

The spectrophotometric method for assessing the total antioxidant activity is based on the absorbance decrease monitoring of the DPPH· radical diphenyl-1-picrylhydrazyl) in the presence of anti oxidants. DPPH· is characterized as a stable free radical due to the delocalization of the spare electron over the molecule. Thus, the molecule cannot dimerise, as would happen with other free radicals. The delocalization gives rise to a deep violet colour characterized by an absorption band at about 520 nm. When a DPPH· solution is mixed with a substance which can donate a hydrogen atom, the reduced form is generated, accompanied by the loss of the violet colour.



1,1-Diphenyl-2-picrylhydrazyl

Reaction of DPPH free radical with an anti oxidant

DPPH preparation

1,1-Diphenyl-2-picrylhydrazyl (DPPH, 0.004gm) was dissolved in 100 ml of methanol to obtain 60 µM DPPH and measure it at 517 nm and this reading was used control reading.

Standard preparation

Ascorbic acid (0.01 g) was dissolved in 10 ml of absolute methanol and then it was further diluted to obtain 10µg/ml, 20µg/ml, 50µg/ml, 75µg/ml and 100µg/ml and it was measured in calorimeter at 517 nm.

Sample preparations

Sample (0.01 g) was dissolved in 10 ml of absolute methanol and then it was further diluted to obtain 10µg/ml, 25µg/ml, 50µg/ml, 75µg/ml and 100µg/ml.

Procedure

The scavenging effect of sample as well as vitamin C corresponding to the quenching intensity of 1,1-diphenyl-2-picrylhydrazyl (DPPH) as carried out. The sample solution of each tested (500 µl or 0.5 ml) was mixed with the same volume of DPPH solution and allowed to stand for 30 min at room temperature. The absorbance was the measured at 517 nm. The percentage scavenging effect was determined by comparing the absorbance of solution containing the test sample to that of control solution without the test sample taking the corresponding blanks. This was again measured after 1 hour. The result is tabulated as mean of the three readings for each sample. The vitamin C was used as positive control samples.

Calculation

$$\%\text{Inhibition} = \frac{A_c - A_s}{A_c} \times 100$$

Where,

A_c = Absorbance of control

A_s = Absorbance of sample

Control– DPPH in methanol

Sample- Sample solution in methanol and DPPH

To evaluate the scavenging effect of the sample in our study, DPPH inhibition was investigated and the results were evaluated as related against activities and control. The results of the free radical scavenging effect of sample and positive control (ascorbic acid) in DPPH – free radical system were determined.

RESULTS AND DISCUSSION

The newly synthesized compounds were assayed for anti fungal activity by zone of inhibition and anti oxidant activity by DPPH free radical scavenging method. The results were represented in the given tables and figures.

Table 3: Anti fungal activity by zone of inhibition

Compound code	Zone of inhibition (mm)			
	C. coffeanum	*A. niger*	*A. terreus*	*P. notatum*
IV a	7	6	5	6
IV b	11*	12	11	10
IV c	5	8	7	NA
IV d	7	NA	NA	6
IV e	9	14*	16*	13*
IV f	6	11	10	9
IV g	5	7	8	7
IV h	9	NA	6	NA
IV i	7	5	NA	7
IV j	NA	9	7	5
IV k	8	7	6	8
Griseofulvin (50 µg/ml)	14	18	20	15

NA = No activity, * = Significant activity

Concentration of test compound = 50 µg/ml.

Table 4: Percentage inhibition values for anti fungal activity

Compound code	% inhibition			
	C. coffeanum	*A. niger*	*A. terreus*	*P. notatum*
IV a	50	33.3	25	40
IV b	78.5*	66.6	55	66.6
IV c	35.7	44.4	35	NA
IV d	50	NA	NA	40
IV e	64.21	77.7*	80*	86.6*
IV f	42.8	61.1	50	60
IV g	35.7	38.8	40	46.6
IV h	64.2	NA	30	NA
IV i	50	27.7	NA	46.6
IV j	NA	50	35	33.3
IV k	57.1	38.8	30	53.3
Griseofulvin (50 µg/ml)	100	100	100	100

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

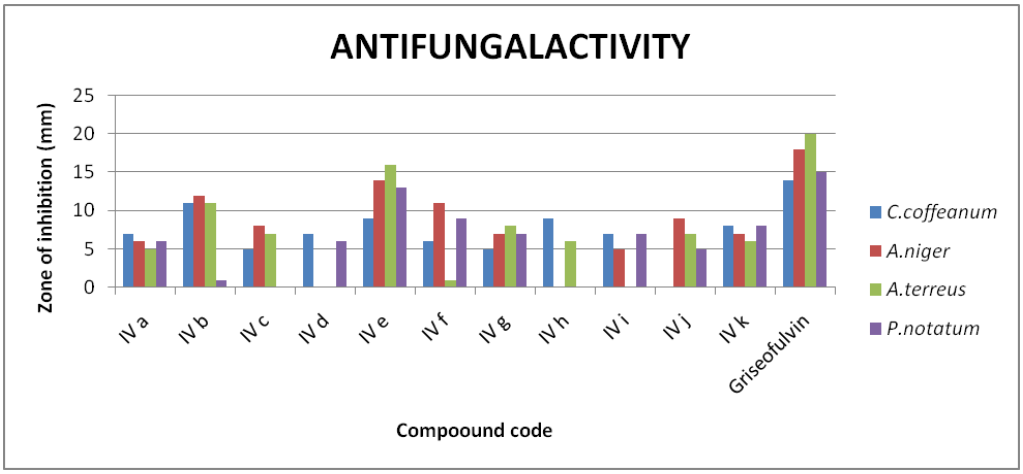


Fig. 1: Graphical representation of anti fungal activity by zone of inhibition

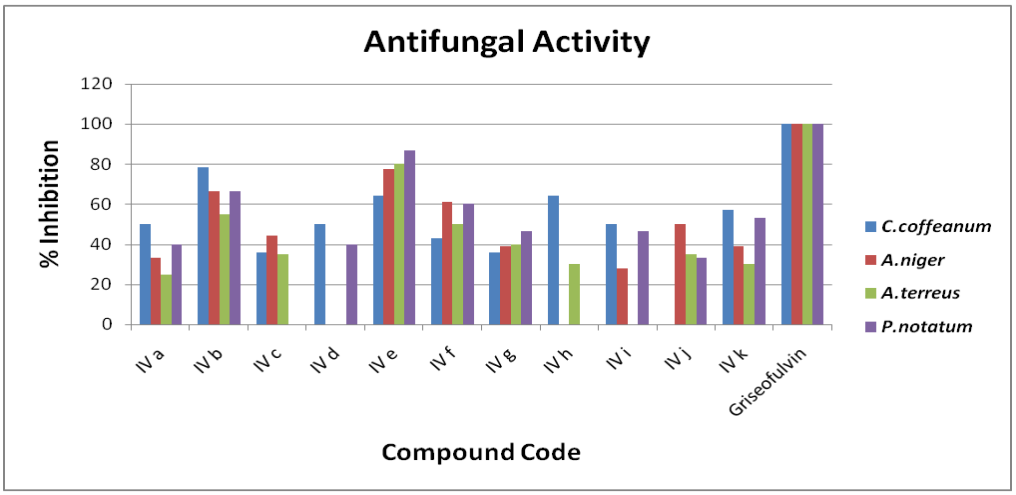


Fig. 2: Graphical representation of anti fungal activity by % inhibition

Table 5: Anti oxidant activity by DPPH free radical scavenging method

Compound code	IC_{50} (µg/ml) (Mean ± S.E.M)
IV a	74.52 ± 0.95
IV b	73.09 ± 0.55
IV c	73.12 ± 1.01
IV d	72.57 ± 2.09
IV e	73.52 ± 1.6
IV f	71.27 ± 0.86
IV g	72.4 ± 2.06
IV h	71.8 ± 1.97
IV i	73.37 ± 2.8
IV j	70.29 ± 0.38
IV k	72.83 ± 0.88
Ascorbic acid	67.8± 1.02

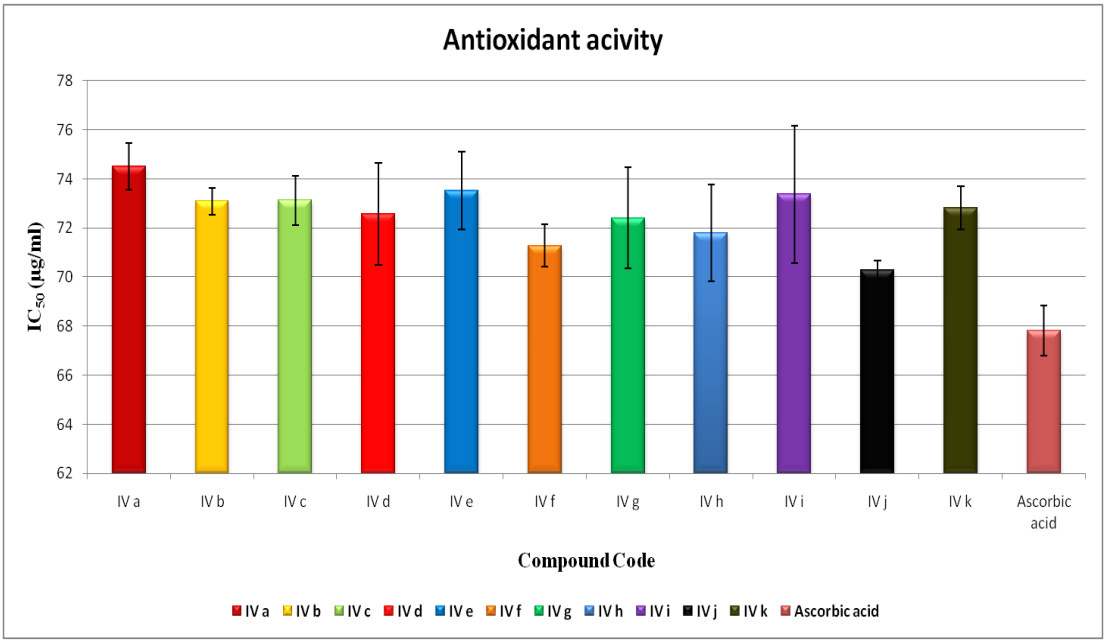


Fig. 3: Graphical representation of IC_{50} values for anti oxidant activity

All values were expressed as Mean ± S.E.M, N=3.
All groups were compared with standard (Ascorbic acid).
All compounds showed the Statistical significance - P<0.001

The *in vitro* anti fungal activity was performed against fungal strains including *Colleotrichum coffeanum, Aspergillus niger, Aspergillus terreus* and *Penicillium notatum*. Asthana-hawkers medium was used for this activity. Griseofulvin was used as standard reference. All the derivatives were taken at a concentration of 50µg/ml. The compound (**IVb)** was more effective against *Colleotrichum coffeanum.* Compounds (**IVe)** and **(IVj)** were effective against *Aspergillus niger.* Compound (**IVe)** was also more effective against *Aspergillus terreus* and *Penicillium notatum.* Some of the compounds did not show activity.

The *in vitro* anti oxidant activity of the synthesized benzoxazole Schiff's bases was evaluated using DPPH free radical scavenging assay. Ascorbic acid was used as standard. The results of anti oxidant screening were depicted in table. As from the table it could be seen that most of the compounds showed significant anti oxidant activity. The highest scavenger activity observed in compound **(IVf)** is probably due to the presence of hydroxy group in aldehydic moiety. In the series compounds (**IVf, IVh** and **IVj**) showed significant activity with IC_{50} values (70.29 ± 0.38, 71.8 ± 1.97

and 71.27 ± 0.86 respectively). Other compounds showed less activity.

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 biological activities. The compounds were screened for their anti fungal and anti oxidant activities. The work states that novel 2-mercaptobenzoxazole derivatives were responsible for anti oxidant and anti fungal activities these exhibit a maximum zone of inhibition. Further studies should be undertaking to elucidate the mechanism of action by which exert their anti oxidant and anti fungal activities.

From the above study, it is concluded that the novel 2-mercaptobenzoxazole derivatives may represent a new source of anti oxidant and anti fungal with stable, biologically active components that can establish a scientific base for the use of this in modern medicine. This knowledge about the medicinal compounds usage can also be extended to other fields like field of pharmacology. The above results establish the fact that benzoxazole derivatives could be a rich source for exploitation and to synthesize potent and more specific compounds based on QSAR studies.

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