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Biological screening of some new 2-substituted benzoxazole-5-carbonyl-3,5- dimethyl pyrazole and 2-substitued benzoxazol-5-carbonyl-3-methyl pyrazalones

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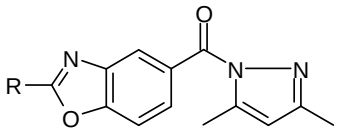
Abstract: In the present study, antifungal and antibacterial activities of some new substituted benzoxazoles were evaluated. Type-I and Type II compounds showed moderate anti bacterial activity. In type II, Compound IIa (R=H) showed comparatively more activity among all the compounds. Compounds of Type III were found to posses mild to moderate activity against the bacteria employed. The most active compound of the series was IIIb among all the compounds. The presence of substituents especially methyl, chloro and bromo groups increased the activity. Type-I exhibited good antifungal activity against *A. niger*, *A. flavus*. Compounds of the type-II showed moderate activity against the test organisms *A. niger*, *A. flavus*. In type III, compounds IIIa (R = H, Ar = C_6H_5), IIIb (R = H, Ar = 2-OH-C_6H_4), IIIc (R = H, Ar = 4-OCH_3-C_6H_5) and IIIg (R = CH_3, Ar = 2-OH-C_6H_5) exhibited good antifungal activity against *A. niger* and *A. flavus*. Significance of the above results are discussed in this communication.
Key words: Benzoxazoles, antibacterial activity, antifungal activity.

Introduction:

Benzoxazole (1) (m.p. 27-30^{o}C; b.p. 182^{o}C), is a planar molecule with conjugated π electrons sextets in the cyclic system. The chemical properties are 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 azolium species are significantly activated towards nucleophillic attack. Benzoxazoles have been extensively studied for their antibacterial and antifungal activity[1,2], anticancer activity[3] and also as new non-nucleoside topoisomerase I poisons [4] and HIV-1 reverse transcriptase inhibitors[5,6]. Benzoxazoles have been reported to show a broad spectrum of biological activities. Notable among these are antihistaminic[10], antifungal[11], Cyclooxygenase Inhibiting[12], antitumor[13], antiulcer[14], anticonvulsant[15], hypoglycemic[16], antiinflammatory[17,18] and antitubercular activity[19]. Pyrazole-containing compounds have received considerable attention owing to their diverse chemotherapeutic potentials including versatile antineoplastic activities. The azole moiety is an important and frequent insecticidal, agrochemical structural feature of many biologically active compounds such as cytochrome P450 enzyme inhibitors and peptide analog inhibitors. Recently, much attention has been focused on 1*H*-1,2,4-triazole derivatives for their broad-spectrum activities, such as fungicidal, herbicidal, anticonvulsant and plant growth regulatory activities. 2-Substituted benzoxazoles have been found to be biologically versatile compounds which posses a broad spectrum of biological activities. In addition, these derivatives have gained wide acceptance in clinical practice. The biological profile of substituted benzoxazoles is very extensive. Fused benzoxazoles are biologically interesting molecules and chemistry and biological

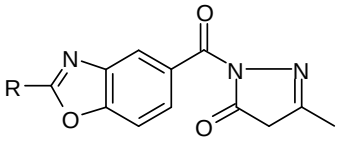
activity has received considerable interest. The manifold biological applications of 2-substituted benzoxazole and their heterocyclic condensed derivatives have promoted us to target the synthesis of some new 2-substituted benzoxazoles (both substituted and fused) to evaluate their biological activity.

i. (3,5-Dimethyl-1H-pyrazol-1-yl)(2-substituted-1,3-benzoxazolyl)- methanones (I a-c)



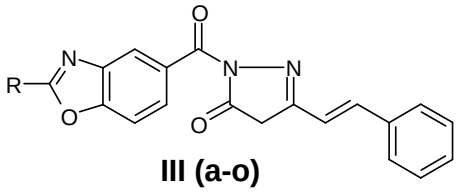
I (a-c)

ii. 5-Methyl-2-[(2-substituted-1,3-benzoxazol-5-yl)-carbonyl]-2,4-dihydro-3H-pyrazol-3-ones (II a-c)



II (a-c)

iii. 1-(2-Substituted-benzo[d]oxazole-5-carbonyl)-3-styryl-1H-pyrazol-5-(H)-ones (III a-l)



III (a-o)

Material and Methods:

These compounds have been screened for the biological properties by adopting standard protocols available in the literature.

Anti bacterial activity by Cup-plate method: The anti bacterial activity of synthesized compounds was evaluated against two gram positive bacteria viz.,- *Bacillus subtilis* and *Staphylococcus aureus* and two gram negative bacteria viz.,- *Escherichia coli* and *Proteus vulgaris* by using cup plate method. Ampicillin sodium was employed as standard drug to compare the results. The test organisms were subcultured using nutrient agar medium. The tubes containing sterilized medium were inoculated with respective bacterial strain. After incubation at 37 ^{0}C ±1 ^{0}C for 24 hours, they were stored in refrigerator. The stock culture was maintained. Bacteria inoculum was prepared by transferring a loopful of stock culture to nutrient broth (100 ml) in conical flasks (250 ml). The flasks were incubated at 37 ^{0}C ±1 ^{0}C for 48 hours before the experimentation.

Solution of the tested compounds was prepared by dissolving 10 mg in dimethyl formamide. A reference standard for both gram positive and gram negative bacteria was made by dissolving accurately weighed quantity of ampicillin sodium in sterile distilled water. Then 0.1 ml of the test solution was added to the respective cups asceptically and labeled accordingly. After incubation of the plates at surrounding each of the cups 37 ^{0}C ±1 ^{0}C for 24 hours, the diameter of zone of inhibition surrounding each of the cups was measured with the help of scale. All the experiments were carried out in triplicate.

Anti fungal activity by Cup-plate method: All those compounds screened for antibacterial activity were also tested for their antifungal activity. The fungi employed for screening were: *Aspergillus niger, Aspergillus flavus, Fusarium oxysporum* and *Curvularia lunata*. The test organisms were sub-cultured using potato-dextrose-agar

medium. The tubes containing sterilized medium were inoculated with test fungi and after incubation at 37 ^{0}C for 48 hours, they were stored at 4 ^{0}C in refrigerator. Clotrimazole (10 µg) was employed as the standard drug.

Table 1: Antibacterial activity of the synthesized compounds

Type	Compd	R	Ar	Zone of inhibition (mm)			
				Gram positive		Gram negative	
				Bacillus subtilis	*Staphylococcus aureus*	*Escherichia coli*	*Proteus vulgaris*
I	Ia	H	--	10	9	9	9
	Ib	CH_3	--	9	8	9	9
	Ic	C_2H_5	--	9	8	9	8
II	IIa	H	--	9	10	8	8
	IIb	CH_3	--	9	8	8	6
	IIc	C_2H_5	--	8	8	6	6
III	IIIa	H	C_6H_5	6	8	6	6
	IIIb	H	2-OHC_6H_5	8	10	6	7
	IIIc	H	4-$OCH_3C_6H_4$	7	8	6	6
	IIId	H	4-ClC_6H_4	5	6	6	5
	IIIe	H	4-$N(CH_3)_2C_6H_4$	7	8	6	6
	IIIf	CH_3	C_6H_5	6	7	6	6
	IIIg	CH_3	2-OHC_6H_5	8	8	6	6
	IIIh	CH_3	4-$OCH_3C_6H_4$	7	7	5	6
	IIIi	CH_3	4-ClC_6H_4	5	6	5	6
	IIIj	CH_3	4-$N(CH_3)_2C_6H_4$	7	8	5	5
	IIIk	C_2H_5	C_6H_5	6	6	6	5
	IIIl	C_2H_5	2-OHC_6H_5	6	7	5	5
	IIIm	C_2H_5	4-$OCH_3C_6H_4$	6	7	6	6
	IIIn	C_2H_5	4-ClC_6H_4	5	6	5	6
	IIIo	C_2H_5	4-$N(CH_3)_2C_6H_4$	5	7	6	5
Standard			Ampicillin	19	18	18	15

Table 2: Antifungal activity of the synthesized compounds

Type	Compd	R	Ar	Zone of inhibition (mm)			
				Aspergillus niger	*Aspergillus flavus*	*Fusarium oxysporum*	*Curvularia lunata*
I	Ia	H	--	14	13	7	6
	Ib	CH_3	--	12	14	5	4
	Ic	C_2H_5	--	11	12	8	6
II	IIa	H	--	10	12	6	5
	IIb	CH_3	--	8	10	7	5
	IIc	C_2H_5	--	11	10	6	7
III	IIIa	H	C_6H_5	13	12	6	5
	IIIb	H	2-OHC_6H_5	11	11	5	4
	IIIc	H	4-$OCH_3C_6H_4$	13	12	7	3
	IIId	H	4-ClC_6H_4	11	10	8	5
	IIIe	H	4-$N(CH_3)_2C_6H_4$	10	9	5	4
	IIIf	CH_3	C_6H_5	7	10	6	4
	IIIg	CH_3	2-OHC_6H_5	11	10	5	6
	IIIh	CH_3	4-$OCH_3C_6H_4$	9	8	6	4
	IIIi	CH_3	4-ClC_6H_4	9	7	5	4
	IIIj	CH_3	4-$N(CH_3)_2C_6H_4$	8	7	4	4
	IIIk	C_2H_5	C_6H_5	10	7	4	5
	IIIl	C_2H_5	2-OHC_6H_5	9	6	5	4
	IIIm	C_2H_5	4-$OCH_3C_6H_4$	12	7	4	5
	IIIn	C_2H_5	4-ClC_6H_4	10	5	4	4
	IIIo	C_2H_5	4-$N(CH_3)_2C_6H_4$	7	5	5	4
Standard			Clotrimazole	18	19	21	14

Results and Discussion:

Among the type-I, all the compounds are active against the gram positive and gram negative bacteria. The results indicate that the compounds showed moderate anti bacterial activity. The data of antibacterial activity of compounds of type-II reveals that all the compounds showed moderate bacterial activity against gram (+) and gram (-) organisms employed. Compound **IIa (R=H)** showed comparatively more activity among all the compounds. The results of antibacterial activity of the type-III compounds presented in Table 1 shows that all the compounds were found to posses mild to moderate activity against the bacteria employed. The most active compound of the series was **IIIb** among all the compounds. The presence of substituents especially methyl, chloro and bromo groups increased the activity.

The results reveal that the test compounds of type-I exhibited good antifungal activity against *A. niger, A. flavus*, mild activity against *F. oxysporum* and *C. lunata*. Compounds of the type-II showed moderate activity against the test organisms *A. niger, A. flavus*, mild activity against the rest of the fungal organisms employed. All the compounds among type-III showed antifungal activity against the test organisms employed. Compound **IIIa** (R = H, Ar = C_6H_5), **IIIb** (R = H, Ar = 2-OH-C_6H_4), **IIIc** (R = H, Ar = 4-OCH_3-C_6H_5) and **IIIg** (R = CH_3, Ar = 2-OH-C_6H_5) exhibited good antifungal activity against *A. niger* and *A. flavus* where as they were mildly active against *F. oxysporum* and *C. lunata*. Rest of the compounds were moderately active against *A. niger, A. flavus* and showed mild activity against *F. oxysporum, C. lunata*.

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