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DESIGN, SYNTHESIS AND BIOLOGICAL ACTIVITY OF 1, 4-BENZOXAZINONE DERIVATIVES AS ANTI-MICROBIAL AGENTS

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ABSTRACT

Column chromatography is used to separate the components. Analytical and spectral data (IR, 1H NMR, and Mass) are used to identify and describe all novel compounds. Synthesized chemicals are tested for their ability to kill bacteria and fungi. The synthesised benzoxazinone derivatives were evaluated and found to be moderately to weakly antimicrobial. The antibacterial activity of the fused or combined moieties was found to be moderate to weak against Gram (+ve) and Gram (-ve) bacteria in screening experiments. Various biological activities have been attributed to the substituted benzoxazinone derivatives.

Keywords: *benzoxazinone, derivatives, spectral data.*

INTRODUCTION

The subject of drugs is as old as disease. Illness has been man's heritage from the beginning of his existence, along with globalization many new diseases are arising in the world and the search for remedies combat it is perhaps equally old. The sincere attempt by man to control and cure diseases has led to search of new drugs or suitable derivatives of existing drugs. The earlier sources of drugs were from plant, animal and mineral sources, but due to the lack of potential action and definitive cure and sometimes more toxicity, the discovery of new drugs that are more potential and less toxic is essential. The synthesis of derivatives has been an important part and is aimed at modifying the action of drugs, particularly to reduce the side effects and to potentiate the drug action. Today more than 60% drugs used in practice are synthesized derivatives and day-by-day the scope of synthetic medicinal chemistry is broadening. Drugs are chemicals that prevent disease or assist in restoring health to the diseased individuals as such they play an indispensable role in modern medicine. Medicinal chemistry is the branch of science that provides these drugs either through discovery or through design. In the last century, the classical drugs were primarily discovered either by alteration of natural substances or entirely by chemical synthesis. In the recent years, an ever-increasing understanding of pathophysiology of diseases has increasingly led to novel opportunities to design, synthesis and evaluation of candidate drug molecules.[1]

During the later decades of 20th century traditional dividing lines between biological, chemical and physical sciences were erased and in the present millennium, new borderline investigation such as ,molecular biology, molecular pharmacology, biomedicine, bio metallic chemistry, cellular biology, genetics, bioinformatics and others have begun to capture the interest of medicinal scientist. With the race to discover novel drug molecules, the drug discovery program has become a multidisciplinary approach. Thus, the activity of medicinal chemist essentially encompass biological (understanding of the enzymology and pharmacology) and physicochemical aspects (understanding of thermodynamic quantum mechanics, spectroscopy, crystallography etc.,) these aspects have acquired increasingly mechanistic underpinnings with the development and quantification of the enzyme/receptor concept and the availability of receptor-based assays. Lead discovery and lead optimization are the two important concepts of drug design in medicinal chemistry and the process of lead structure identification and refinement, now manifest further sophistication in accordance with developments in structural and molecular biology and the combinatorial chemical synthesis and automated screening techniques like high throughout screening.[1]

BIOLOGICAL ACTIVITY METHODS

ANTIBACTERIAL ACTIVITY

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The compounds synthesized during the present investigation were screened for their antibacterial activity. The antibacterial activity of the compounds was assessed by cup and plate method. The antibacterial tests were conducted on six common microorganisms which are the representative types of gram

The results of screening were included in the below table-1.

Gram positive bacteria	Gram negative bacteria
Bacillus subtilis	Pseudomonas aeruginosa
Staphylococcus aureus	Escherichia coli
Staphylococcus epidermdisis	Klebsiella pneumoniae

Preparation of nutrient agar media:

The nutrient agar media was prepared by using the following ingredients.

Peptone (Bacteriological): 20 g.

Beef extract (Bacteriological): 5 g.

Sodium chloride (Bacteriological): 5 g.

Agar (Bacteriological): 20 g.

Distilled water up to: 1000 ml.

Weighed quantities of peptone, beef extract were dissolved in distilled water by gentle warming, and then the specified amount of agar was dissolved by heating on boiling water bath. Then the pH of the above solution is adjusted by adding sodium chloride and the volume of final solution is made up to 1000 ml with distilled water. Then the above prepared nutrient agar media is sterilized by autoclave at 121 oC for 20 minutes at 15 lbs/in2 pressure.

Preparation of test solution:

20 mg of the test compound was dissolved in 20 ml of DMF, from this stock solution, 1 ml of solution was taken and further diluted to required concentration with DMF. These sample solution were made in suitably labeled sterilized test tubes.

Preparation of standard solution:

The standard drug used for the comparison are Penicillin and Streptomycin, the solutions were prepared from sterile water soluble.

Method of testing:

The above prepared nutrient agar media is cooled to 45 oC with gentle shaking to bring about uniform cooling. To this 0.5–0.6 ml of 18-24 h old culture was injected aseptically and mixed well by gentle shaking. This was poured onto the petri dishes and was allowed to set for 1 h.

Thereafter the cups were made by punching into the set agar with a sterile cork borer and scooping out the punched part of the agar. The diameter of each cup was 6 mm. To these cups 50 µl of the test compound was put, which was prepared in DMF. After adding the drug solution, it was allowed to diffuse for about 45 minutes, at room temperature. Then the plates were incubated at 37 oC for 24 h in an incubator.

The minimum inhibitory concentration (MIC) is taken as a parameter of antibacterial activity.

Standard: Penicillin, Streptomycin.

Note: 20 µg/ml and above poor activity, 14-20 µg/ml moderate activity and 4-13 µg/ml significant activity.

ANTIFUNGAL ACTIVITY

ANTIFUNGAL ACTIVITY:

Procedure:

The anti-fungal activity of all compounds was determined on potato dextrose agar medium against Rhizopus oryzae, Aspergillus niger, Aspergillus flavus Candida albicans, and

Table No-2: Antibacterial activity of synthesized compounds (3A-F)

Compound Code	Minimum Inhibitory Concentration (µg/ml)					
	Gram Positive Organism			Gram Negative Organism		
	B.Subtilis	S.aureus	S.epidermis	E.coli	P.aeroginosa	K.pneumoniae
3_A	23.15	150	17.10	75	150	18.0
3_B	18.60	75	22.50	14.55	13.0	75
3_C	24.75	4.65	75	75	17.75	16.75
3_D	24.50	14.25	1.16	75	75	29.35
3_E	75	30.15	75	150	150	75
3_F	21.60	75	85	13.50	75	150
Penicillin	1.526	6.25	3.125	7.81	12.50	6.25
Streptomycin	6.25	1.56	1.56	3.125	3.125	3.125

Saccharomyces cerevisiae organisms using Amphotericin-B as a standard and DMF was used as control. The sterile molten potato dextrose medium was cooled to 45 oC and inoculated with test organisms and mixed the contents thoroughly and poured into the sterile petri dishes under aseptic conditions. All the inoculated petri dishes were incubated at 28 oC for 4 days and the extent diameter of inhibition was measured as the zone of inhibition in millimeters and the results were shown in Table No-3.

Preparation of sub-culture:

Peeled potato: 200-300 gm

Dextrose: 5 gm

Distilled water up to: 1000 ml

Peeled potato were cut into pieces and boiled for 30 min to get extract. The extract is filtered through muslin cloth. The dextrose was added to the filtrate and final volume is adjusted to 1000 ml with distilled water. Then it was sterilized by autoclave at 121 oC for 20 min.

Note: Two days before testing the culture is prepared by inoculating the fungus from master culture into potato dextrose medium and incubated for 48 h at room temperature

Preparation of fungal medium:

The potato dextrose medium is prepared by dissolving.

Peeled potato: 200-300 gm

Dextrose : 5 gm

Agar: 20 gm

Distilled water up to: 1000 ml

Peeled potato were cut into pieces and boiled for 30 min to get the extract. The extract is filtered through muslin cloth. The dextrose and agar were added to the filtrate and the final volume is adjusted to 1000 ml with distilled water. Then it was sterilized by autoclave at 121 oC for 20 min.

Preparation of test solution:

10 mg of the compound was dissolved in 10 ml of DMF, from this stock solution further required concentration solutions were prepared by dilution using DMF.

Preparation of standard anti-fungal solution:

Amphotericin-B was used as standard anti-fungal for comparison and solution were prepared by using sterile water, so that the concentrations of the solution were 100 µg/ml.

Method of testing:

The method of testing for fungicidal activity is the same as that of antibacterial testing. DMF was used as a solvent control.

Table No-3 Antifungal activity of synthesized compounds (3_{A-F})

	Zone of Inhibition(mm)				
Compound (100 µg/ml)	**R. oryzae**	**A.niger**	**A.flavis**	**C.albicans**	**S.cerevisiae**
3_A	24	15	-	-	16
3_B	17	16	12	14	22
3_C	16	14	18	12	12
3_D	15	14	12	12	10
3_E	28	16	14	-	-
3_F	14	-	21	15	16
Amphotericin-B	24	25	24	23.5	22

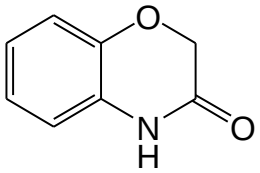
Standard: Amphotericin-B

Note:- '-' denotes no activity, 10–14 mm poor activity, 15–17 mm moderate activity, 18-25 mm significant activity.

RESULTS AND DISCUSSION

SPECTRAL DATA

Compound (1)



2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one

1H NMR Spectra (CDCl3, δ ppm):

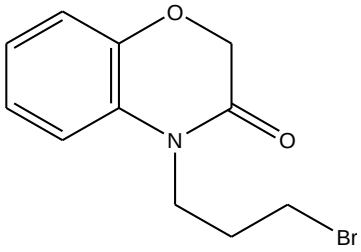
Value in δ ppm	Nature of segments	No of protons	Type of proton
8.98	Singlet	1H	1H of NH
6.8-7.2	Multiplet	4H	4H of Ar-H
4.64	Singlet	2H	2H of CH_2

MASS Spectra (m/z):

Molecular weight of the compound is 149; the molecular ion peak appeared at 150 as M+1.

Type of Vibration	Group frequency in Wave number (cm^{-1})
NH stretching	3133
Ar-CH=CH Stretching	2982 and 2902
C=O Absorption band	1709

Compound 2



4-(3-Bromo-propyl)-4*H*-benzo[1,4]oxazin-3-one

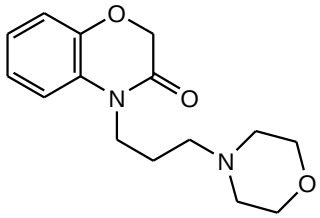
1H NMR Spectra (CDCl3, δ ppm):

Value in δ ppm	Nature of segments	No of protons	Type of proton
7.01-7.07	Multiplet	4H	4H of Ar-H
4.60	Singlet	2H	CH_2
4.09	triplet	2H	2H of CH_2
2.25	Pentet	2H	2H of CH_2
3.40	Triplet	2H	2H of CH_2

MASS Spectra (m/z):

Molecular weight of the compound is 269; the molecular ion peak appeared at 270 as M+1.

Compound



4-(3-Morpholin-4-yl-propyl)-4*H*-benzo[1,4]oxazin-3-one

^{1}H NMR Spectra ($CDCl_3$, δ ppm):

Value in δ ppm	Nature of segments	No of protons	Type of proton
6.99-7.09	Multiplet	4H	4H of Ar-H
4.60	Singlet	2H	CH_2
4.00	triplet	2H	2H of CH_2
1.89	Pentet	2H	2H of CH_2
2.48	Triplet	6H	CH_2,
3.72	Triplet	4H	CH_2(morpholine) CH_2(morpholine)

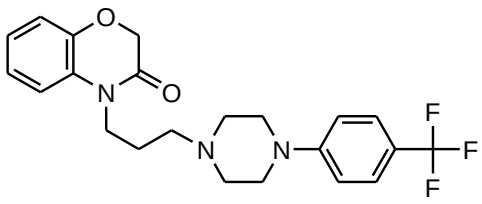
MASS Spectra (m/z):

Molecular weight of the compound is **276**; the molecular ion peak appeared at **277** as **M+1**.

IR Spectra (cm^{-1}):

Type of Vibration	Group frequency in Wave number (cm^{-1})
=CH stretch	2922
=CH bend	823
CH_2 strech	2851
Alkane CH_2 strech	2816
C=O stretch	1606

Compound 3B



4-{3-[4-(4-Trifluoromethyl-phenyl)-piperazin-1-yl]-propyl}-4*H*-benzo[1,4]oxazin-3-one

^{1}H NMR Spectra (DMSO, δ ppm):

Value in δ ppm	Nature of segments	No of protons	Type of proton
6.90-7.48	Multiplet	8H	8H of Ar-H
4.60	Singlet	2H	CH_2
4.00	Triplet	2H	2H of CH_2
1.92	Pentet	2H	2H of CH_2
3.28	Triplet	4H	CH_2
2.62	Triplet	4H	CH_2
2.50	Triplet	2H	CH_2

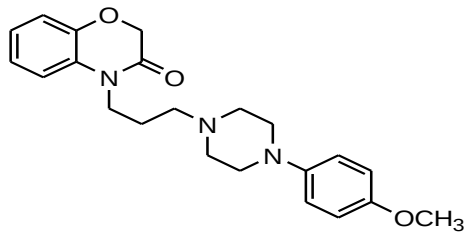
MASS Spectra (m/z):

Molecular weight of the compound is 419; the molecular ion peak appeared at 420 as M+1

IR Spectra (cm^{-1}):

Type of Vibration	Group frequency in Wave number (cm^{-1})
=CH stretch	2922
=CH bend	823
CH_2 strech	2851
Alkane CH_2 strech	2816
C=O stretch	1606

Compound 3C



4-{3-[4-(4-Methoxy-phenyl)-piperazin-1-yl]-propyl}-4*H*-benzo[1,4]oxazin-3-one

^{1}H NMR Spectra ($CDCl_3$, δ ppm):

Value in δ ppm	Nature of segments	No of protons	Type of proton
6.83-7.11	Multiplet	8H	8H of Ar-H
4.60	Singlet	2H	CH_2
4.00	triplet	2H	2H of CH_2
1.92	Pentet	2H	2H of CH_2
3.11	Triplet	4H	CH_2
2.62	Triplet	4H	CH_2
2.49	Triplet	2H	CH_2
3.77	singlet	3H	CH_3

MASS Spectra (m/z):

Molecular weight of the compound is 381; the molecular ion peak appeared at 382 as M+1.

IR Spectra (cm-1):

TYPE OF VIBRATION	GROUP FREQUENCY IN WAVE NUMBER(cm^{-1})
C=O stretch	1606
=CH stretch	2957
=CH bend	860
Alkane CH_2 strech	2817

BIOLOGICAL EVALUATION

From the literature survey, it reveals that novel benzoxazinones have been reported for number of pharmacological activities and some molecules have shown significant activities and some compounds shows moderate and good activities. All the synthesized compounds **(3_{A-F})** were screened them for their anti-bacterial and anti-fungal activities and the results are as follows:

ANTIMICROBIAL STUDIES

ANTIBACTERIAL ACTIVITY:

All the synthesized compounds were screened for antibacterial activity studies against Bacillus subtilis, Staphylococcus aureus, Staphylococcus epidermidis, Escherichia coli, Pseudomonas aeruginosa and Klebsiella pnenmoniae by cup-plate technique on nutrient agar media, Penicillin and Streptomycin used as standard against Gram positive and Gram-negative bacteria.

The data in the **Table No-1** indicate that,

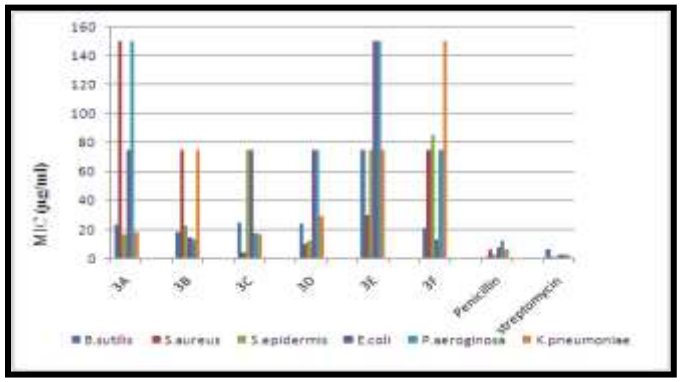
- Compound **3_C** show significant activity and compound **3_D** shows moderate activity against staphylococcus aureus.
- Compound **3_D** also shows moderate activity against staphylococcus epidermidis.
- Compound **3_B** shows moderate activity against Escherichia coli.
- Compound **3_B** and Compounds **3_C** shows moderate activity against Pseudomonas aeruginosa.
- Compound **3_A** and Compounds **3_C** shows moderate activity against Klebsiella pneumoniae.

And rest of the compounds were found to exhibit poor activity when compared to the standard Penicillin and Streptomycin.

Table No-4 SPECTRAL DATA OF THE SYNTHESISED COMPOUNDS

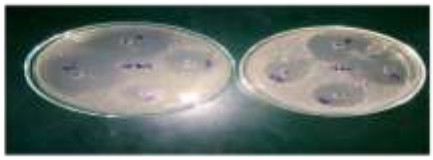
C.NO	IUPAC Name	MOLECULAR FORMULA	MOL. WT	^{1}H NMR in $CDCL_3$+DMSO (JCAMP), δ, J(Hz)	MS (m/z)	IR (KBr disc in cm^{-1})
I	4H-Benzo[1,4]oxazin-3-one	$C_8H_7NO_2$	149	8.98(s.1H,NH),4.64(s, 2H, CH_2), 6.80-7.20(m, 4H, Ar-H)	150 (M+H)	3133 NH-Strech 2982 =CH strech 2856 CH_2 strech 1606 C=0strech 888 =CH bend
II	4-(3-Bromo-propyl)-4H-benzo[1,4]oxazin-3-one	$C_{11}H_{12}O_2NBr$	269	2.25(p, 2H, CH_2), 4.60(s, 2H, CH_2), 3.40(t, 2H, CH_2), 4.09(t, J=7.554, 2H, CH_2), 7.01-7.07(m, 4H, Ar-H).	270 (M+H)	----------
3A	4-(3-Morpholin-4-yl-propyl)-4H-benzo[1,4]oxazin-3-one	$C_{15}H_{20}O_3N_2$	276	6.99-7.09(m, 4H, Ar-H), 4.60(s, 2H, CH_2), 4.00(t, J=7.365, 2H, CH_2),1.89(p, 2H, CH_2),2.48(6H,CH_2), 3.72(d,4H,CH_2(Morpholine))	277 (M+H)	2922 =CH strech 2851 CH_2 strech 2816 alkane CH_2 str 1606 C=O stretch 823 =CH bend
3B	4-{3-[4-(4-Trifluoromethyl-phenyl)-piperazin-1-yl]-propyl}-4H-benzo[1,4]oxazin-3-one	$C_{22}H_{24}O_2N_3F_3$	419	6.90-7.48(m,8H,Ar-H), 4.60(s, 2H, CH_2), 4.00(t, J=7.176, 2H, CH_2), 3.28(d,4H,CH2) ,2.62(d,4H,CH_2) ,2.50(t, J=6.987, 2H, CH_2),1.92(p, 2H, CH_2)	420 (M+H)	2923 =CH stretch 2856 CH_2 strech 1683 C=0strech
3C	4-{3-[4-(4-Methoxy-phenyl)-piperazin-1-yl]-propyl}-4H-benzo[1,4]oxazin-3-one	$C_{22}H_{27}O_3N_3$	381	6.83-7.11(m,8H,Ar-H), 4.60(s, 2H, CH_2), 4.00(t, J=7.554, 2H, CH_2), 3.11 (d,4H,CH2),3.77(s,3H,CH_3),1.91(p, 2H, CH_2), 2.49(t, J=6.798, 2H, CH_2), 2.62(d,4H,CH_2)	382 (M+H)	1606 C=O stretch 2817 alkane CH_2 str 2957 =CH stretch 860 =CH bend

Fig No.1 Antibacterial activity of synthesized compounds (3_{A-F})



7b

6b



ANTIFUNGAL ACTIVITY:

The antifungal activities of the test compounds were tested by agar diffusion method (cup-plate method) taking drug at a concentration of 150µg/50 µL against five fungal organisms. The area of Zone of Inhibition (ZOI) was taken as a parameter of antifungal activity. The ZOI of the compound was compared to that of the standard drug i.e. Amphotericin-B.

The compounds were screened at 150µg/50 µL showed different ZOI against five fungal organisms (Table 2). Among the compounds screened the maximum ZOI was observed against Saccharomyces cerevisiae, Aspergillus niger, Rhizopus oryzae, Candida albicans and C.rugosa.

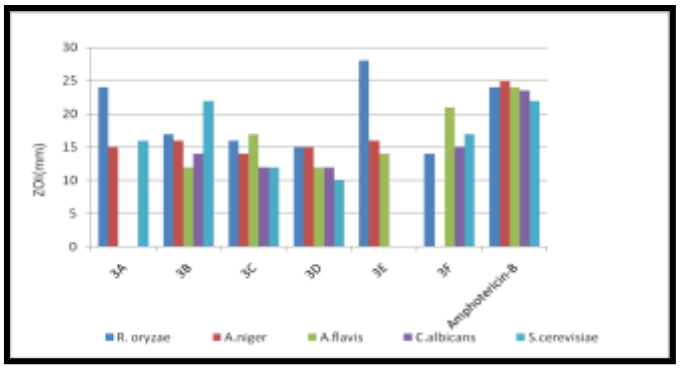
• 3A and 3E show significant activity and compounds 3B and 3C show moderate activity against Rhizopus oryzae

• compound 3D show moderate activity against Aspergillus niger and

• Compound 3F show significant activity and compound 3C show moderate activity against Aspergillus flavus and

• compound 3F show moderate activity against Candida albicans and

• Compound 3B show significant activity and compounds 3A and 3F show moderate activity against Saccharomyces cerevisiae and rest of the compounds were found to exhibit poor activity when compared to the standard Amphotericin-B.



CONCLUSION

The compounds are purified by coloumn chromatography. All new compounds are characterized by the analytical and spectral (IR, 1H NMR and Mass) data. The compounds synthesized are evaluated for antibacterial, antifungal activity

It is clearly concluded that the synthesized benzoxazinone derivatives were found to be moderate to weak antibacterial agents. When the two moieties are fused or combined and screened for antibacterial studies they showed moderate to weak antibacterial activity against Gram (+ve) and Gram (-ve) bacteria.

The substituted benzoxazinone derivatives are already known for different biological activity.

Further the detail structure activity relationship studies are required along with the molecular manipulation i.e. molecular modeling may give better drugs and further toxicological study is needed. Molecules prepared for the biological testing do not always turn out as potential new molecules, but may be intended to serve as models for evaluation of the hypothesis.

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