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Synthesis, Physical Characterization and Antibacterial Activity of Some Derivatives of 2-Amino Benzothiazoles

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Abstract

Some novel Schiff bases and thiazolidinones are synthesized from 6-methoxy 2-amino benzothiazole and their characterization was done using IR, NMR and mass spectral data. The antimicrobial screening of these synthesized compounds were done in two polar solvents DMF and DMSO. A differential effect of the compounds in a particular solvent (DMF / DMSO) inhibited different strain to a different level. This suggests that anti-microbial activity depends on molecular structure of the compound, solvent used and the strain under consideration.

Keywords: ***2-amino benzothiazoles; Schiff bases; Thiazolidinones; Antimicrobial activity***

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Introduction

Benzothiazoles are heterocyclic bicyclic ring containing nitrogen and sulfur hetero atoms. These moieties are of paramount interest in medicinal chemistry due to their biological a: lications [1-3]. The benzothiazole motif is building block of pharmaceutics and is widely found in bioorganic and medicinal chemistry with a: lication in drug discovery. Apart from biological interest, the compounds containing benzothiazole ring have a: lications as corrosion inhibitor, biological imaging, etc [4-8].

Due to its potent significant biological and industrial a:lications, in the present work, some compounds containing benzothiazole ring have been synthesized. These synthesized compounds are Schiff bases and thiazolidinones. Schiff bases are versatile ligands furnishing imine N and other donor sites, which are responsible for a wide range of biological and chemical a:lications [9-12].

Some of the biological activities are antifungal, antibacterial, anti-diuretic, anti-inflammatory, antitumor [13-18] etc.

Further, some of these compounds have other a: lications such as plant growth regulators [19], corrosion inhibitor [20], perfumery [21], dye manufacture [22], intermediate for various synthesis [23-25]. Thus, development of a new chemotherapeutic Schiff bases is now attracting the attention of medicinal chemist.

Thiazolidinones are always being an attraction point for researchers because of its efficiency towards various pharmacological usages. Some of their derivatives have been long used as precursors for the synthesis of biologically active molecules [26]. Various 5-methyl 4-thiazolidinone derivatives are known to exhibit biological activities such as antimicrobial

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[27, 28], anticonvulsant [29], anti-cancer [30], antiviral [31, 32], insecticidal and herbicidal activity [33], anti-HIV and anti-tubercular [34], anti-inflammatory [35] etc.

Thus, in the present work, some new Schiff bases and thiazolidinones are synthesized from 6-methoxy-2-amino benzothiazole and their structure characterization was done by IR, NMR and mass spectral data. The antibacterial activities of these synthesized compounds were evaluated against some gram positive and gram negative bacterial and fungal strains in two solvents: dimethylformamide (DMF) and dimethylsulfoxide (DMSO).

Experimental

Synthesis

[A] Synthesis of 6-methoxy 2-amino benzothiazole: A solution of p-methoxy aniline (1 mole) in chlorobenzene was prepared in a three-necked, round-bottom flask fitted with a stirrer, reflux condenser, thermometer, and droing funnel. Over a period of 5 minutes, 0.55 mole of concentrated sulfuric acid was added drop wise. 1.1 moles of sodium thiocyanate was added to this mixture and solution was heated for 3 hours at 100°C in an oil bath. The solution, which now contained the thiourea, was cooled to 30°C. 1.34 moles of sulfuryl chloride was added to this solution over a period of 15 minutes. Care was taken not to increase the temperature greater than 50°C. The mixture was kept at 50°C for 2 hours and solution was filtered. The solid residue was then dissolved in hot water, and concentrated ammonium hydroxide was added. The precipitated 6- methoxy 2-aminobenzothiazole was filtered and was washed with water. The crude product was isolated and crystallized from absolute ethanol.

[B] Synthesis of 4-[(Z)-[(6-methoxy-1,3-benzothiazole-2-yl)imino]methyl] phenol: Equi molar mixture of 6-methoxy 2-amino benzothiazole and 4-hydroxy benzaldehyde was taken in ethanol using catalytic amount of glacial acetic acid and the reaction mixture was refluxed for 10 hrs. The product was isolated and crystallized from absolute ethanol.

Similarly other Schiff bases were obtained.

Thiazolidinones

[A] Synthesis of 6-methoxy 2-amino benzothiazole: As above

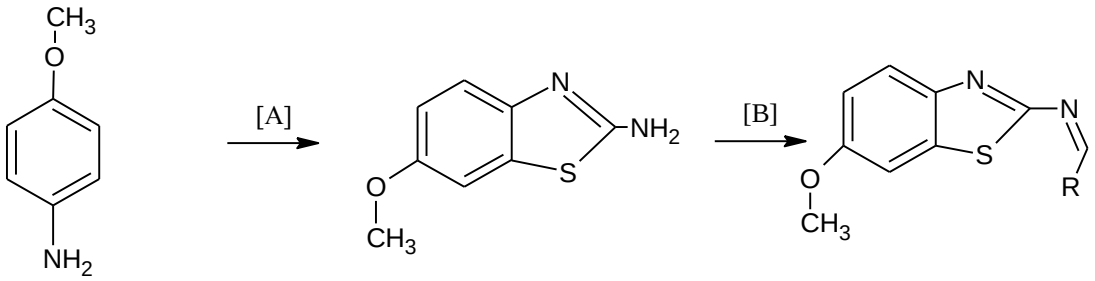
[B] Synthesis of 4-[(Z)-[(6-methoxy-1,3-benzothiazole-2-yl)imino] methyl] phenol: As above

[C] Synthesis of 2-(4-hydroxyphenyl)-3-(6-methoxy-1,3-benzothiazol-2-yl)-5-methyl-1,3-thiazolidin-4-one: Equimolar mixture of 4-[(Z)-[(6-methoxy-1,3-benzothiazole-2-yl)imino] methyl] phenol and thioglycolic acid was heated at 120°C for 10-12 hrs. The reaction mixture was cooled and treated with 10% sodium bicarbonate solution. The solid product was thus separated, filtered and washed with water and was crystallized from absolute ethanol. Similarly other thiazolidinone derivatives were synthesized. The reaction Schemes of these compounds are given in **FIG. 1**. All the synthesized Schiff bases and thiazolidinone compounds were recrystalized and purity of compounds was checked by TLC. Their structure confirmation was done by IR, NMR and Mass spectra data.

Ion exchange of Zeolite erionite

Antimicrobial activity: The antibacterial and antifungal activities of all the synthesized compounds were studied in DMSO and DMF using Agar well diffusion method. The solvent DMSO and DMF were also purified before use by standard method [36].

Schiff bases:



Thiazolidinone derivatives:

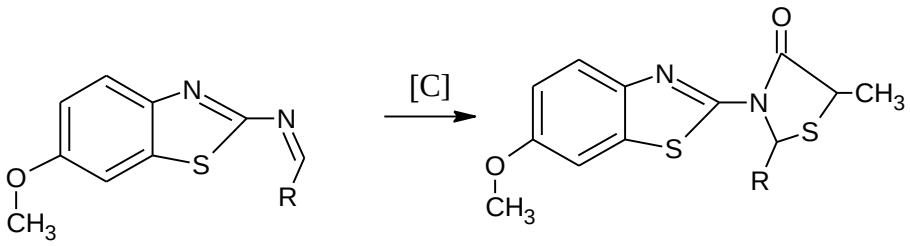


FIG.1. **Reaction Scheme for the Synthesis of Schiff bases and Thiazolidinone derivatives**

Preparation of the test compound: The synthesized compounds were dissolved in DMF and DMSO at concentration of 2 mg/100 µl.

Test microorganisms: The synthesized Schiff bases and Thiazolidinone were tested for its antibacterial activity against two Gram positive *Bacillus cereus* (ATCC 11778) and *Micrococcus flavus* (ATCC 10240), two Gram negative bacteria viz. *Escherichia coli* (ATCC 25922) and *Proteus mirabilis* (NCIM 2241) and two fungus *Cryptococcus luteolus* (ATCC 32044) and *Candida tropicalis* (ATCC 4563). Microorganisms were obtained from National Chemical Laboratory (NCL), Pune, India. Microorganisms were maintained at 4°C on nutrient agar slants.

Results and Discussion

TABLE 1 shows some physical properties of the synthesized Schiff bases

TABLE 1**. Physical constants of Schiff Bases**

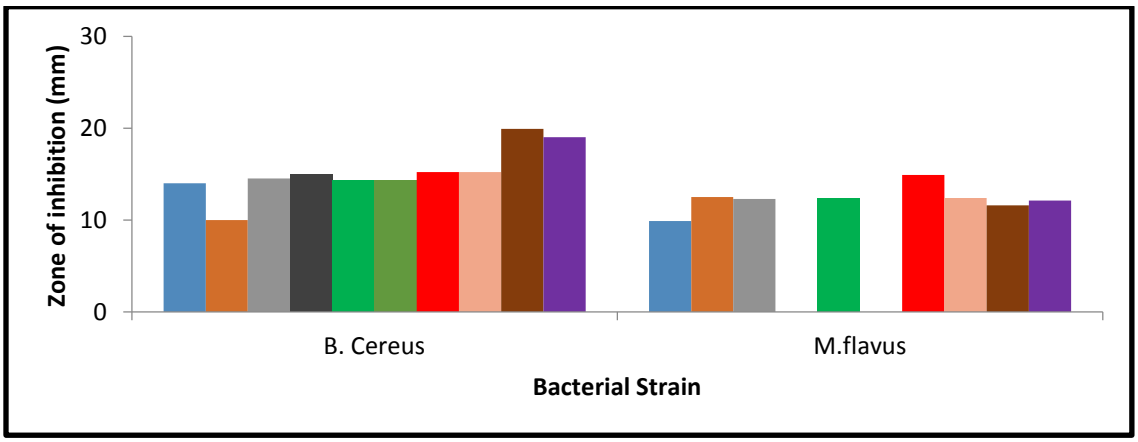
Sr. No.	Compound Code	Mol. Formula	R	Mol.Wt (g)	M.P. ^{0}C	Yield %	R_f^*
1	AKBS-1	$C_{15}H_{12}N_2O_2S$	4-OH-C_6H_4	284.33	248	68	0.53
2	AKBS -2	$C_{15}H_{12}N_2O_2S$	2-OH-C_6H_4	284.33	112	65	0.51
3	AKBS -3	$C_{15}H_{11}N_2O$ SCl	4-Cl-C_6H_4	302.77	140	57	0.47
4	AKBS -4	$C_{15}H_{11}N_2OSCl$	3-Cl-C_6H_4	302.77	185	60	0.49
5	AKBS -5	$C_{15}H_{11}N_3O_3S$	3-NO_2-C_6H_4	313.33	180	68	0.52
6	AKBS -6	$C_{15}H_{12}N_3O_3S$	2-NO_2-C_6H_4	313.33	156	54	0.50
7	AKBS -7	$C_{17}H_{14}N_2OS$	-CH=CH-C_6H_4	294.37	102	42	0.58
8	AKBS -8	$C_{15}H_{11}N_2OSF$	4-F-C_6H_4	286.32	172	49	0.46

9	AKBS -9	$C_{19}H_{14}N_2OS$	1-naphthalene	318.39	164	56	0.54
10	AKBS-10	$C_{23}H_{16}N_2OS$	9-anthracene	368.45	140	70	0.59

Characterization of zeolite/polymer composites

Schiff Bases: FIG. 2 shows the zone of inhibition against the Gram positive bacteria in DMF and DMSO. It is observed in DMF that against *B. cereus*, AKBS-9 exhibited maximum inhibition whereas AKBS-1, AKBS-3, AKBS-4, AKBS-5, AKBS-6, AKBS-7, AKBS-8 and AKBS-10 exhibited moderate inhibition. Minimum inhibition is observed by AKBS-2. Against *M. flavus*, AKBS-7 exhibited maximum inhibition followed by AKBS-1, AKBS-2, AKBS-3, AKBS- 5, AKBS- 8 and AKBS-10. AKBS-9 exhibited minimum inhibition. AKBS-4 and AKBS-6 could not affect this bacterium. In case of DMSO, for *B. cereus* AKBS-2 and AKBS-3 exhibited maximum and minimum inhibition. Against *M. flavus*, AKBS-3 exhibited maximum inhibition as compared to other compounds.

(A)



(B)

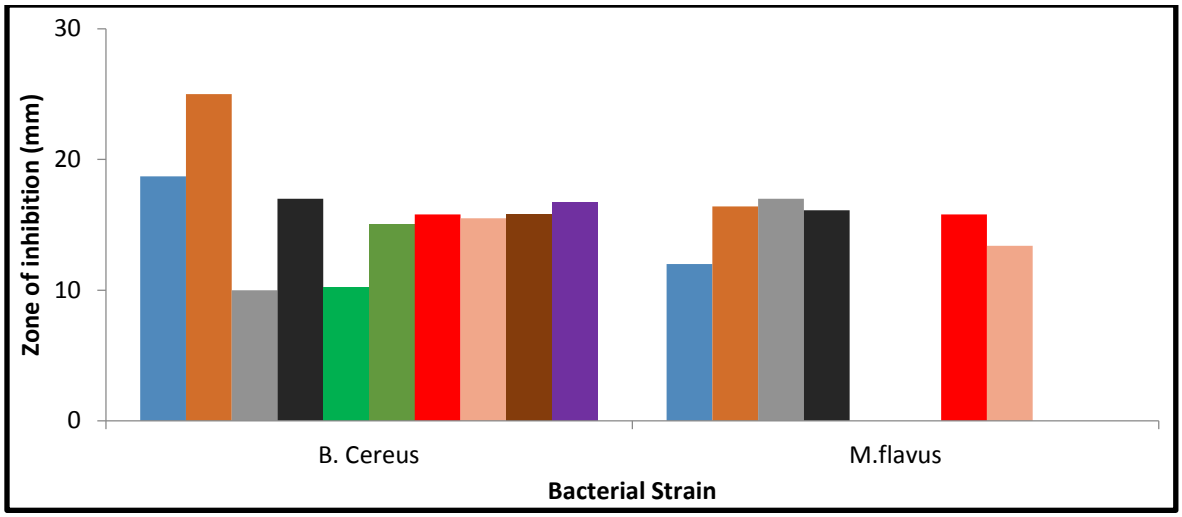


FIG. 2. **Zone of inhibition of Schiff bases against Gram positive bacteria in (A) DMF and (B) DMSO. ■: AKBS-1, ■: AKBS-2, ■: AKBS-3, ■: AKBS-4, ■: AKBS-5, ■: AKBS-6, ■: AKBS-7, ■: AKBS-8, ■: AKBS-9, ■: AKBS-10.**

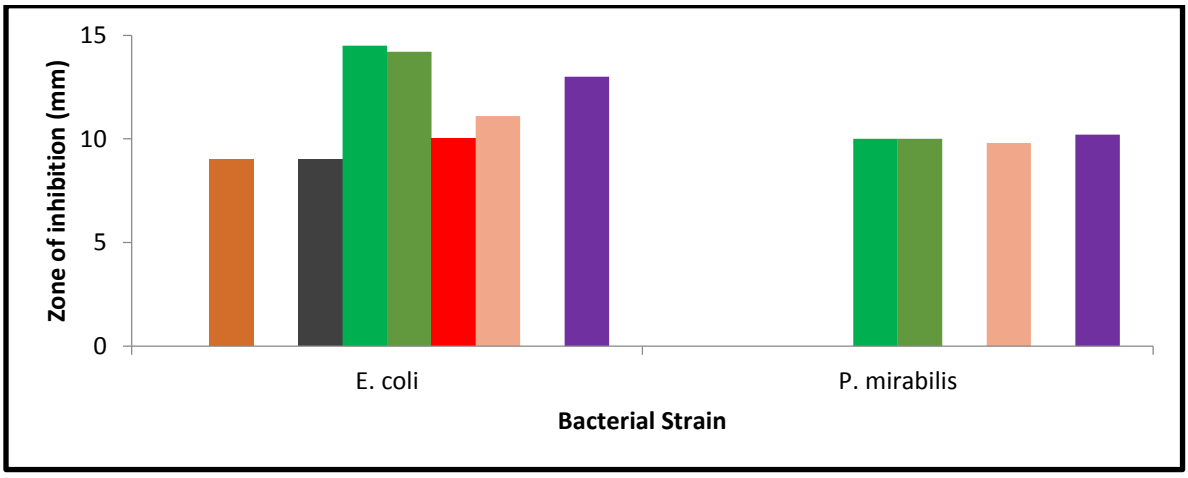
Thus, inhibition depends on solvent, strain and structure of compound. AKBS-9 contains naphthalene substitution whereas AKBS-2 contains 2-hydroxy substitution. Thus, in DMF, for *B. cereus*, naphthalene substitution is most effective whereas 2-hydroxy substitution is least effective. Against *M. flavus*, phenyl acrylic substitution (as in AKBS-7) is most effective. The substitutions, 2-hydroxy (as in AKBS-2) and 4-chloro (as in AKBS-3) are not effective at all.

In DMSO, against *B. cereus* AKBS-2 containing 2-hydroxy substitution is most effective whereas 4-chloro (as in AKBS-3) is least effective. The compounds AKBS-1 and AKBS-4 also contain hydroxyl and chloro substitutions but at different positions. However, these compounds are found to be less effective. Thus, the position of substitution also plays an important role in inhibition. AKBS-8 exhibited minimum inhibition. AKBS-5, AKBS-6, AKBS-9 and AKBS-10 did not exhibit inhibition against this bacterium. Thus, in this case, 4-chloro substitution is more effective.

Comparison of zone of inhibition in DMF and DMSO shows that inhibition is more in DMSO. Thus, for these compounds and for these two Gram positive bacteria, DMSO is good solvent. However, *M. flavus* is most resistant in DMSO than in DMF.

FIG. 3 shows the zone of inhibition against Gram negative bacteria in DMF and DMSO. It is observed in DMF against *E. coli*, AKBS-5 exhibited maximum inhibition whereas AKBS-2 and AKBS-4 exhibited equal minimum inhibition. AKBS-1, AKBS-3 and AKBS-9 had no effect on this bacterial strain. AKBS-5 contains 3-nitro substitution whereas AKBS-2 and AKBS-4 contain 2-hydroxy and 3-chloro substitutions respectively. Thus, 3-nitro substitution is most effective. Against *P. mirabilis*, AKBS-10 containing anthracene substitution exhibited maximum activity while AKBS-8 (having 4-fluoro substitution) exhibited minimum activity. AKBS-5 and AKBS-6 also showed some inhibition of same magnitude. Other compounds could not inhibit this bacterium. Thus, it is again proved that the presence of halogen substitution decreases the inhibition. In DMSO, against *E. coli*, AKBS-2 containing 2-hydroxy substitution, exhibited maximum inhibition. AKBS-1, AKBS-4, AKBS-8 and AKBS-9 exhibited moderate inhibition. Minimum inhibition is observed by AKBS-3. Other compounds had no effect. Thus, again 2-hydroxy substitution is most effective whereas 4-chloro substitution had least effect. Against *P. mirabilis*, all compounds showed inhibition and AKBS-1 and AKBS-2 showed equal maximum inhibition. AKBS-3 exhibited minimum inhibition. Again, halogen substitution decreases and hydroxyl substitution increases the inhibition.

(A)



(B)

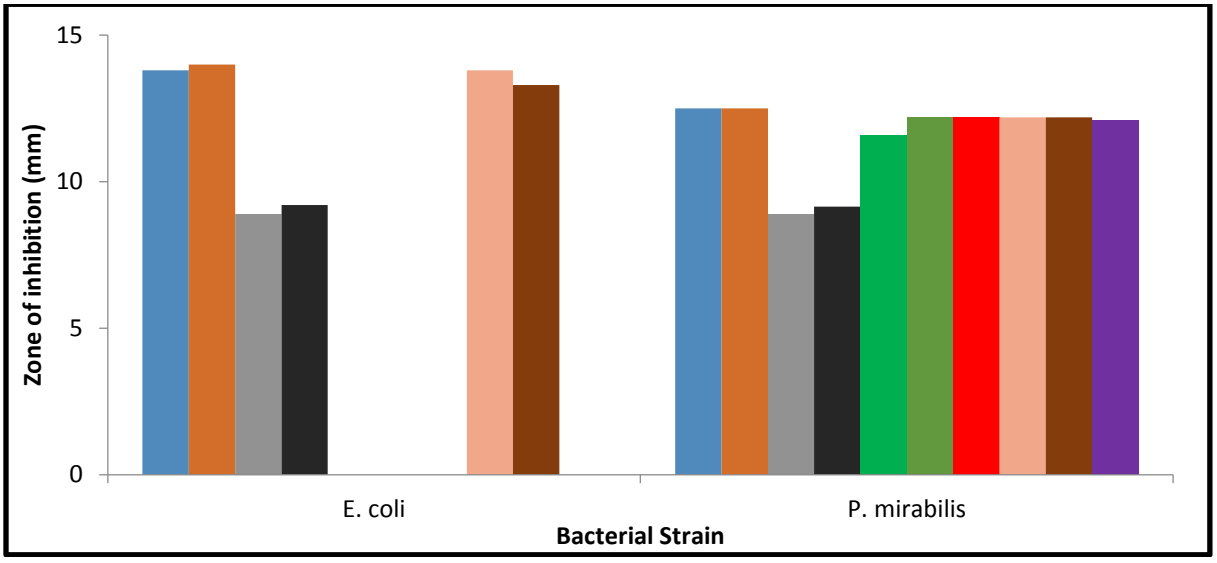
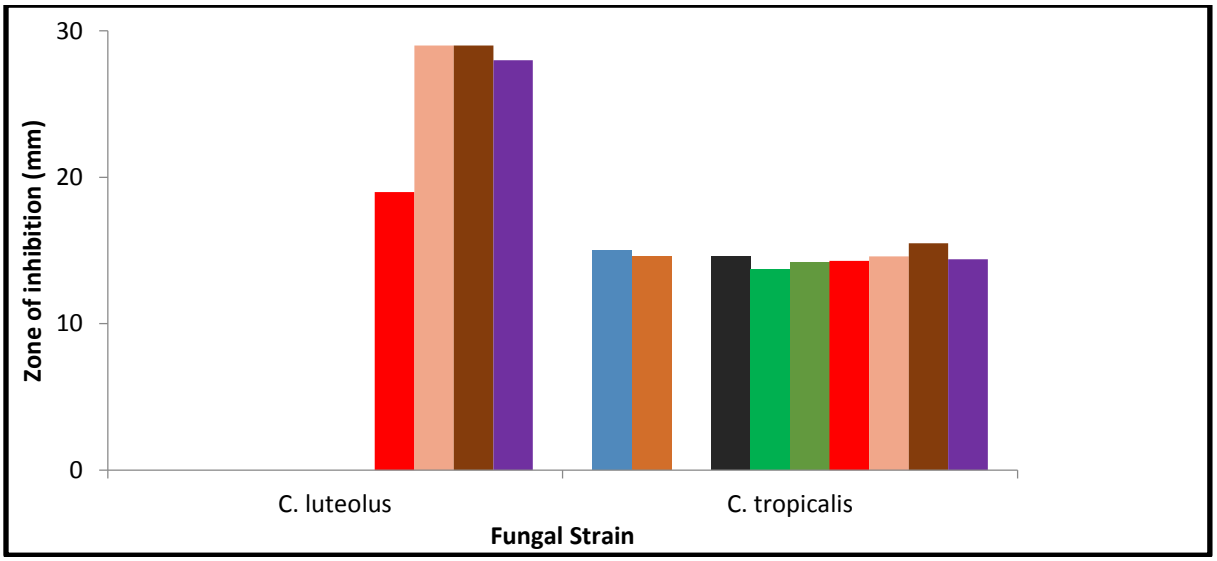


FIG. 3**. Zone of inhibition of Schiff bases against Gram negative bacteria in (A) DMF and (B) DMSO ■: AKBS-1, ■: AKBS-2, ■: AKBS-3, ■: AKBS-4, ■: AKBS-5, ■: AKBS-6, ■: AKBS-7, ■: AKBS-8, ■: AKBS-9, ■: AKBS-10.**

FIG. 4 shows the zone of inhibition against fungal strains in DMF and DMSO. It is observed in DMF that against *C. luteolus*, only four compounds AKBS-7 to AKBS-10 exhibited inhibition. AKBS-8 and AKBS-9 exhibited equally maximum inhibition, while AKBS-7 exhibited minimum inhibition. Other compounds had no effect on this fungal strain. Against *C. tropicalis*, only AKBS-3 is found to be ineffective and maximum inhibition is exhibited by AKBS-9. AKBS-5 exhibited minimum activity. Overall, inhibition is very less for this strain as compared to *C. luteolus.* In both the strains, AKBS-9 exhibited maximum inhibition in DMF suggesting thereby that naphthalene substitution is most effective.

(A)



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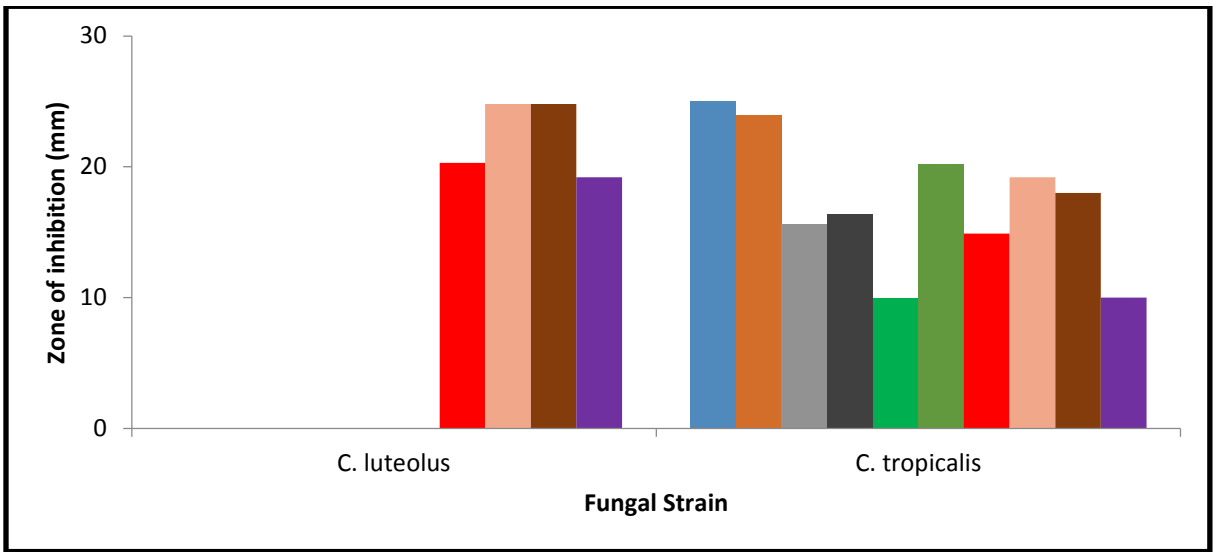


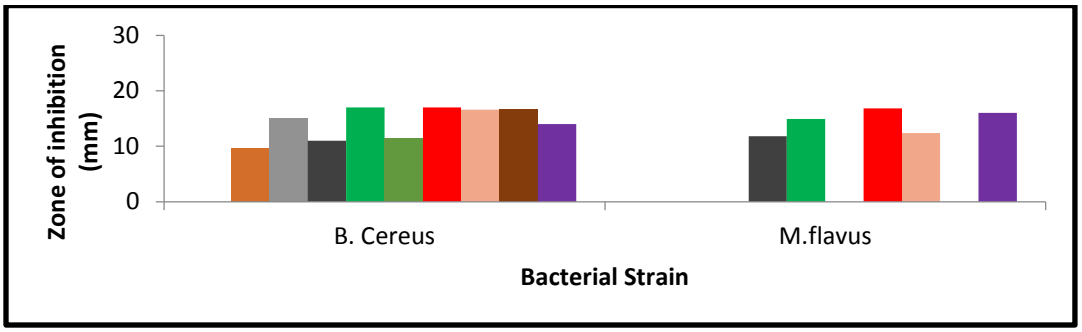
FIG. 4. **Zone of inhibition of Schiff bases against fungal strains in (A) DMF and (B) DMSO ■: AKBS-1, ■: AKBS-2, ■: AKBS-3, ■: AKBS-4, ■: AKBS-5, ■: AKBS-6, ■: AKBS-7, ■: AKBS-8, ■: AKBS-9, ■: AKBS-10.**

In DMSO, against *C. luteolus again* AKBS-8 and AKBS-9 containing 4-fluoro and naphthalene substitution respectively, exhibited maximum inhibition. Minimum effect is due to AKBS-10 containing anthracene substitution. Against *C. tropicalis*, all compounds exhibited inhibition. AKBS-1 containing p-hydroxy substitution had maximum inhibition. While AKBS-05 containing m-nitro substitution exhibited minimum activity. Thus, again hydroxy substitution is proved to be more active.

Thiazolidinone

FIG. 5 shows the zone of inhibition against Gram positive bacteria in DMF and DMSO. In DMF, against *B. cereus*, no inhibition was observed for ABT-1 whereas ABT-5 and ABT-7 exhibited maximum inhibition. Minimum inhibition is observed by ABT-2. Thus, 3-nitro (as in ABT-5) and phenyl acrylic (as in ABT-7) are more effective. Against *M. flavus*, ABT-7 and ABT-10 exhibited equal maximum inhibition. Moderate inhibition was observed by ABT-5 and ABT-8. ABT-4 showed minimum inhibition. Other compounds had no effect against this bacterial strain. So, phenyl acrylic and anthracene substitutions are more effective in this case.

(A)



(B)

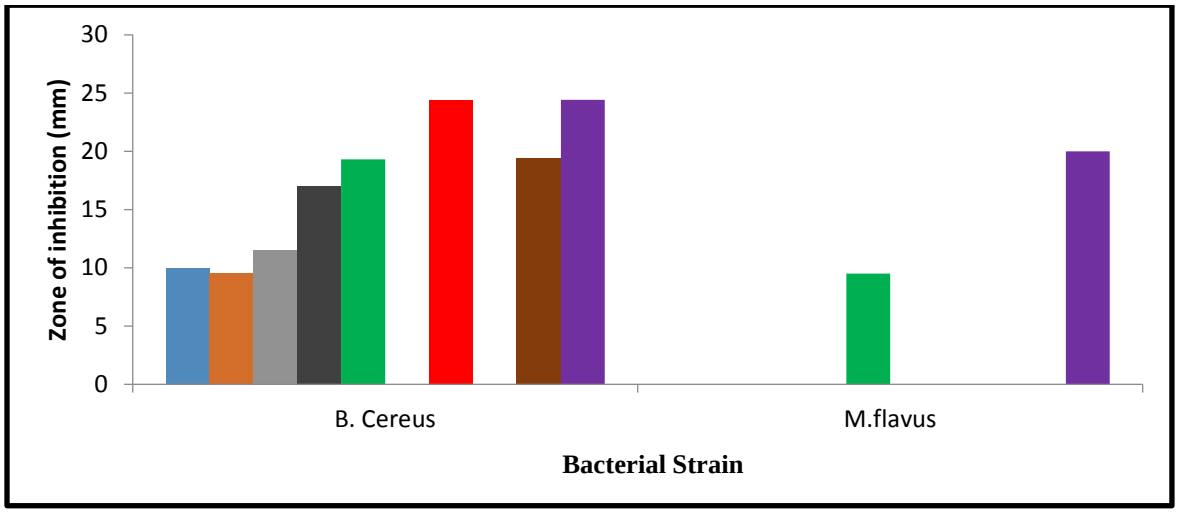


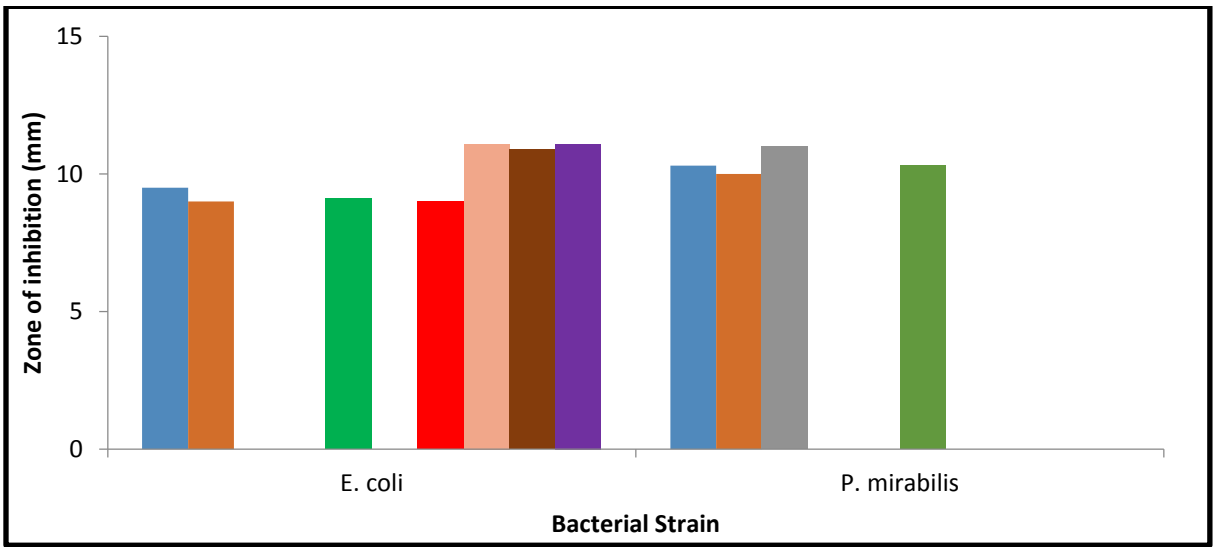
FIG. 5. **Zone of inhibition of Thiazolidinone derivatives against Gram positive bacteria in (A) DMF and (B) DMSO ■: ABT-1, ■: ABT -2, ■: ABT -3, ■: ABT -4, ■: ABT -5, ■: ABT -6, ■: ABT -7, ■: ABT -8, ■: ABT -9, ■: ABT -10.**

In DMSO, against *B. cereus*, ABT-6 and ABT-8 had no effect. ABT-10 exhibited maximum inhibition which is followed by ABT-7. ABT-2 had minimum inhibition. Against *M. flavus*, ABT-10 exhibited maximum inhibition, while ABT-5 exhibited minimum inhibition. Other compound did not exhibit inhibition. Thus, in DMSO, against both Gram positive bacteria, anthracene substitution is most effective.

Comparison of zone of inhibition in DMF and DMSO shows that inhibition is more in DMSO. Thus, for these compounds against Gram positive bacteria, DMSO is good solvent. However, *M. flavus* is most resistant in DMSO than in DMF.

FIG. 6 shows the zone of inhibition against Gram negative bacteria in DMF and DMSO. It is observed that in DMF against *E. coli*, ABT-8 and ABT-10 exhibited equally maximum inhibition. ABT-3, ABT-4 and ABT-6 exhibited no inhibition and ABT-2 exhibited minimum inhibition. Thus, 4-fluoro (as in ABT-8) and anthracene (as in ABT-10) are good for inhibiting this strain. Against *P. mirabilis* ABT-3 exhibited maximum inhibition. ABT-1 and ABT-2 exhibited moderate inhibition. While ABT-6 exhibited minimum inhibition. Other compound had no effect. In this case, 4-chloro substitution is good for inhibition. In DMSO, for *E. coli*, only three compounds showed inhibition. ABT-4 exhibited maximum inhibition whereas ABT-6 exhibited minimum inhibition. Thus, 3-chloro substitution is effective. Against *P. mirabilis*, all compounds showed inhibition and ABT-10 containing anthracene substitution exhibited maximum inhibition.

(A)



(B)

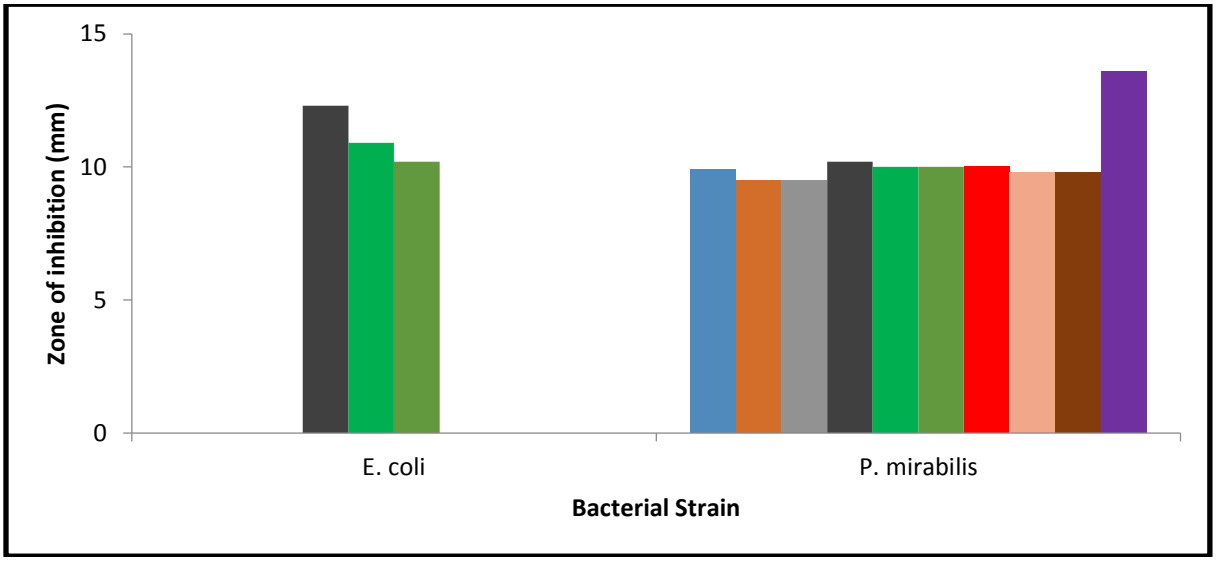
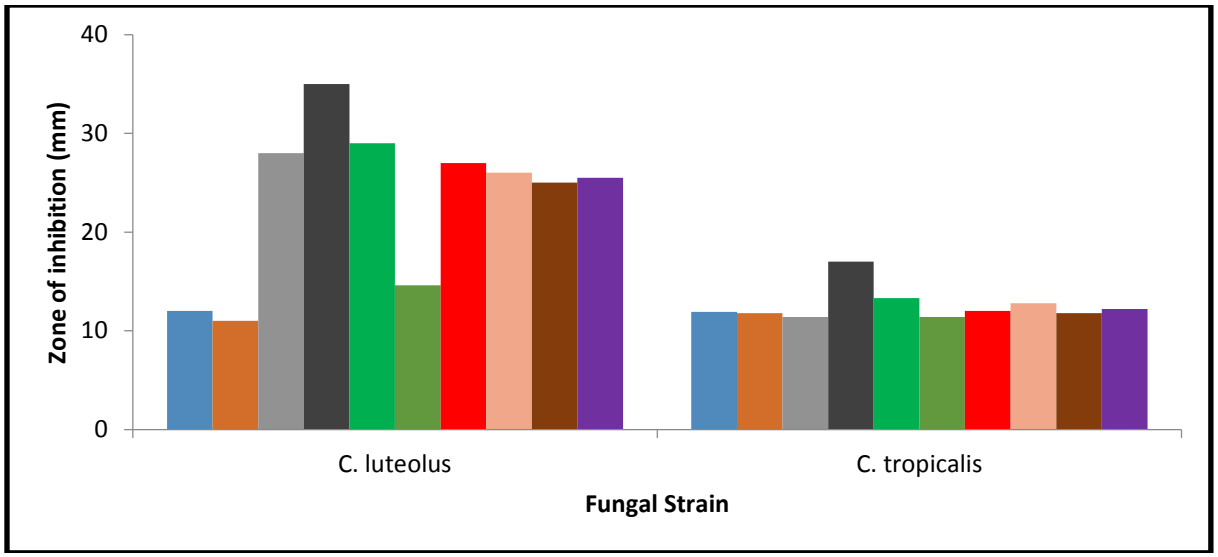


FIG. 6. **Zone of inhibition of Thiazolidinone derivatives against Gram negative bacteria in (A) DMF and (B) DMSO**
■: ABT-1, ■: ABT -2, ■: ABT -3, ■: ABT -4, ■: ABT -5, ■: ABT -6, ■: ABT -7, ■: ABT -8, ■: ABT -9, ■: ABT -10.

(A)



(B)

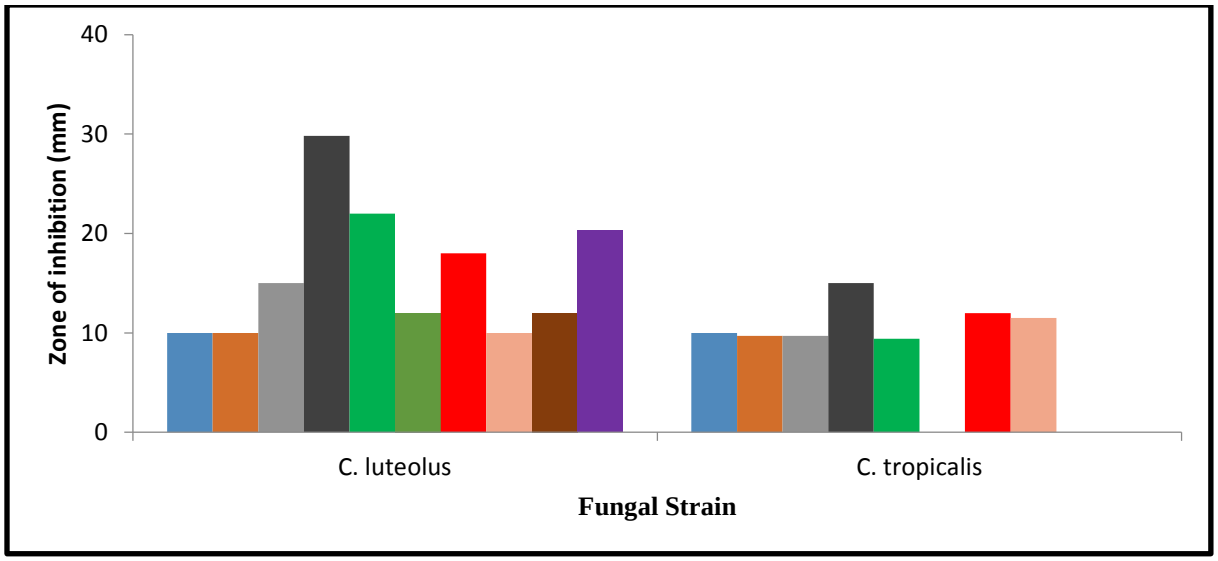


FIG. 7. Zone of inhibition of Thiazolidinone derivatives against fungal strains in (A) DMF and (B) DMSO
■: ABT-1, ■: ABT -2, ■: ABT -3, ■: ABT -4, ■: ABT -5, ■: ABT -6, ■: ABT -7, ■: ABT -8, ■: ABT -9, ■: ABT -10.

FIG. 7 shows the zone of inhibition against fungal strains in DMF and DMSO. It is observed in DMF that against *C. luteolus*, all compounds are found to be effective and ABT-4 exhibited maximum inhibition. Minimum inhibition is observed by ABT-2. Against *C. tropicalis* also, ABT-4 exhibited maximum inhibition. Other compounds showed almost same activity. Thus, in DMF, for these two bacteria strains 3-chloro substitution is found to be most effective. In case of DMSO again for *C. luteolus*, all compounds showed inhibition and ABT-4 exhibited maximum inhibition. Against *C. tropicalis* also, ABT-4 exhibited maximum inhibition. ABT-6, ABT-9 and ABT-10 exhibited no inhibition. Thus, ABT-4 which contains m-chloro substitution is most effective for both the fungal strains in both the solvents.

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