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Synthesis and antibacterial activity of some new triazole derivatives

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Abstract

The present communication deals with synthesis of some new triazole derivaties, their characterization and antibacterial activity against some medically important bacteria. The antibacterial activity was studied against E. coli (ATCC 25922), P. aeruginosa (ATCC 27853), S. aureus (ATCC 25923), B. cereus (ATCC 11778), A. fecalis (ATCC 8750), K. pneumoniae (NCIM 2719). The antibacterial activity in two solvents (1,4-Dioxan and DMF) was evaluated using Agar Ditch method. A differential effect of the compounds was found in the bacterial strains investigated and the solvents used, again suggesting that the antibacterial activity is dependent on the molecular structure of the compound, solvent used and the bacterial strains under consideration. In the present work, B. cereus appeared to be most susceptible bacteria while P. aeruginosa was the most resistant bacterial strain.

Key words: antibacterial activity, triazole compounds, polar and non polar solvents

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INTRODUCTION

Modern drug discovery relies on the interface of chemical and biological diversity through high throughput screening. Generation of true molecular diversity requires molecular scaffolds that are low molecular weight and are easily modified to create a variety of chemically diverse, biological active pharmacophores. The most spectacular advances in the medicinal chemistry have been made in the last few years, where the heterocyclic compounds played an important role in regulating biological activities.

The azole moiety is an important and frequent insecticide, agrochemical structural feature of many biologically active compounds such as cytochrome P450 enzyme inhibitors[1] and peptide analog inhibitor[2]. Various 1,2,4-triazole and 4,5-dihydro-1H-1,2,4-triazol-4-ones have been

found to be associated with diverse pharmacological activities. For eg. Antifungal for the treatment of superficial and systematic infections[3], diuretic[4], antiinflammatory[5], natriuratic[6] and plan growth regulators[7].

In view of the potential biological activity of 1,2,4-triazole, it was of interest to us to synthesize some new derivatives of this family of heterocyclic ring. The synthesized compounds along with their starting compounds were tested for antibacterial activity against E. coli, P.aero, S. aureus, B. cereus, A. fecalis and K. pneu. The antibacterial activity was done using Agar Ditch method. The antibacterial activity was evaluated in two solvents viz. 1,4-Dioxan and N,N-Dimethylformamide

Considering the aforesaid, in the present work we report, synthesis of some new triazole derivatives, their structural determination by spectral analysis and their antimicrobial analysis.

MATERIALS AND METHODS

Experimental

Synthesis of 4-Amino-5-(4-Methoxy Phenyl)-4H-1,2,4-triazole-3-thiol (E)
A methanolic solution of 4- methoxy benzoic acid (A) is refluxed for 12 h in presence of H_2SO_4 to yield ester (B). The resulting product is treated with hydrazine hydrate to get acid hydrazide (C). The hydrazide (C) (0.02 mole) is treated with alcoholic solution of KOH (0.03 mole) and carbon disulphide for 5 h at room temperature with constant stirring. The potassium salt, also known as dithiocarbazate (D) was filtered and washed with ether. In dithiocarbazate (0.02 mole), hydrazine hydrate(0.04 mole) was added drop wise and the mixture was refluxed for 8 hours in oil bath. It was poured in water, acidified and resulting solid was filtered, washed with water and purified by KOH treatment to give E.[(8)]

Synthesis of 4({[3-Mercapto-5-(4-Methoxy Phenyl)-4H-1,2,4-triazole-4yl] imino} methyl)Phenol (1)
Equimolar of E and different aldehydes were taken in methanol. The mixture was heated in water bath for about 10 h. The solution was poured in ice cold water and the resulting solid was filtered, washed and recrystallized from ethanol.

Melting points were determined on an electro thermal capillary melting point apparatus and were uncorrected. All the compounds were checked for their homogeneity by TLC using silica as stationary phase checked. The physical constants of all the synthesized compounds are given in Table 1. IR spectra were recorded by KBr (cm^-) pellet method on Shimadzu FTIR 8400 , ^1H NMR spectra were recorded on a Bruker spectrometer with TMS as internal standard (chemical shift in δ ppm).

Antibacterial activity

The bacterial strains studied are identified strains and were obtained from National Chemical Laboratory (NCL), Pune, India. The investigated microorganisms belonged to both Gram positive and Gram negative category. The bacterial strains investigated are *E. coli* (ATCC 25922), *P. aeruginosa* (ATCC 27853), *S. aureus* (ATCC 25923), *B. cereus* (ATCC 11778), *A.*

fecalis (ATCC 8750), *K. pneumoniae* (NCIM 2719). Antibacterial activity was done by Agar-ditch method [9]

A loop full of the given test strain was inoculated in 10ml of N-broth and was incubated for 24h in an incubator at 37 ^{o}C in order to activate bacterial strain. Inoculation of the test strain was done by the Pour-plate technique. 0.2ml of the activated strain was inoculated into the media when it reached 40-45 ^{o}C temperatures. The media was allowed to solidify. After solidification of the media, ditch was made in the plates with the help of cup-borer (0.85 cm) and then the synthetic compound (dissolved in DMF/1,4-dioxan) was inoculated into the well. Synthetic compounds were soluble in DMF and 1,4-Dioxan and therefore the antibacterial activity is studied using these solvents. The controls were maintained (for each bacterial strain and each solvent), where 0.1ml of the pure solvent was inoculated into the well. The inhibition zone formed by these compounds against the particular test bacterial strain determined the antibacterial activities of the synthetic compounds. The mean value obtained for three individual replicates was used to calculate the zone of growth inhibition of each sample.

IR and NMR spectral data confirmed the molecular structure of the synthesizedncompounds. The IR and NMR analysis data are given below:

E*: 4-amino-5-(4-methoxyphenyl)-4H-1,2,4-triazole-3-thiol*
IR(cm^{-})1099 (S-H), 1508 (C=C), 1612(C=N), 3012 (Ar-H), 3334 (N-H); NMR(δ ppm) 10.26 (1H-CH), 11.49 (1H-SH), 3.79 (-OCH_3),7.40-7.82 (8H-Ar-H)

1*:4-({[3-mercapto-5-(4-methoxyphenyl)-4H-1,2,4-triazol-4-yl]imino}methyl*
IR(cm^{-})1088 (S-H), 1560 (C=C), 1608(C=N), 3008(Ar-H); NMR(δ ppm) 10.11 (1H-CH), 11.49 (1H-SH), 3.79 (-OCH_3),7.40-7.82 (8H-Ar-H)

2*: 4[{4-Methoxy benzylidene}amino]-5-(4-methoxy phenyl)-4H-1,2,4-triazole-3-thiol*
IR(cm^{-})1077 (S-H), 1556 (C=C), 1608(C=N), 3008(Ar-H); NMR(δ ppm) 10.13 (1H-CH), 11.45 (1H-SH), 3.84(-OCH_3),7.36-7.86 (8H-Ar-H)

3*: 4-[(4-fluorobenzylidene)amino]-5-(4-methoxyphenyl)-4H-1,2,4-triazole-3-thiol*
IR(cm^{-}) 1086 (S-H), 1545 (C=C), 1609(C=N), 3010(Ar-H); NMR(δ ppm)10.19 (1H-CH), 11.41 (1H-SH), 3.85 (-OCH_3),7.44-7.89 (8H-Ar-H)

4*: 5-({[3-mercapto-5-(4-methoxyphenyl)-4H-1,2,4-triazol-4-yl]imino}methyl)-2-methoxyphenol*
IR(cm^{-})1069 (S-H), 1476 (C=C), 1612(C=N), 3084 (Ar-H); NMR(δ ppm)10.10 (1H-CH), 11.39 (1H-SH), 3.85(6H-2OCH_3),7.40-7.90 (7H-Ar-H)

5*:4-[(4-chlorobenzylidene)amino]-5-(4-methoxyphenyl)-4H-1,2,4-triazol*
IR(cm^{-})1134 (S-H), 1508 (C=C), 1612(C=N), 3099(Ar-H); NMR(δ ppm)10.11 (1H-CH), 11.43 (1H-SH), 3.86 (-OCH_3),7.00-7.85(8H-Ar-H)

6*: 4-{[4-(dimethylamino)benzylidene]amino}-5-(4-methoxyphenyl)-4H-1,2,4-triazole-3-thiol*
IR(cm^{-})1097 (S-H), 1509 (C=C), 1613(C=N), 3012 (Ar-H); NMR(δ ppm)10.28 (1H-CH), 10.99 (1H-SH), 3.80 (-OCH_3),7.20-7.90 (8H-Ar-H)

7*: 5-(4-methoxyphenyl)-4-[(3-nitrobenzylidene)amino]-4H-1,2,4-triazole-3-thiol*
IR(cm^-)1074 (S-H), 1510(C=C), 1610(C=N), 3039 (Ar-H); NMR(δ ppm)10.41 (1H-CH), 10.88(1H-SH), 3.66 (-OCH_3),7.10-7.69 (8H-Ar-H)

8*: 4-[(2-chlorobenzylidene)amino]-5-(4-methoxyphenyl)-4H-1,2,4-triazole-3-thiol*
IR(cm^-) 1079(S-H), 1506 (C=C), 1612(C=N), 3010 (Ar-H); NMR(δ ppm)10.27 (1H-CH), 11.26 (1H-SH), 3.71 (-OCH_3),7.09-7.81 (8H-AH)

9*:2-({[3-mercapto-5-(4-methoxyphenyl)-4H-1,2,4-triazolyl]imino}methyl)phenol*
IR(cm^-)1112 (S-H), 1508 (C=C), 1608(C=N), 3006 (Ar-H); NMR(δ ppm)10.40 (1H-CH), 11.39 (1H-SH), 3.81 (-OCH_3),7.11-7.66 (8H-Ar-H)

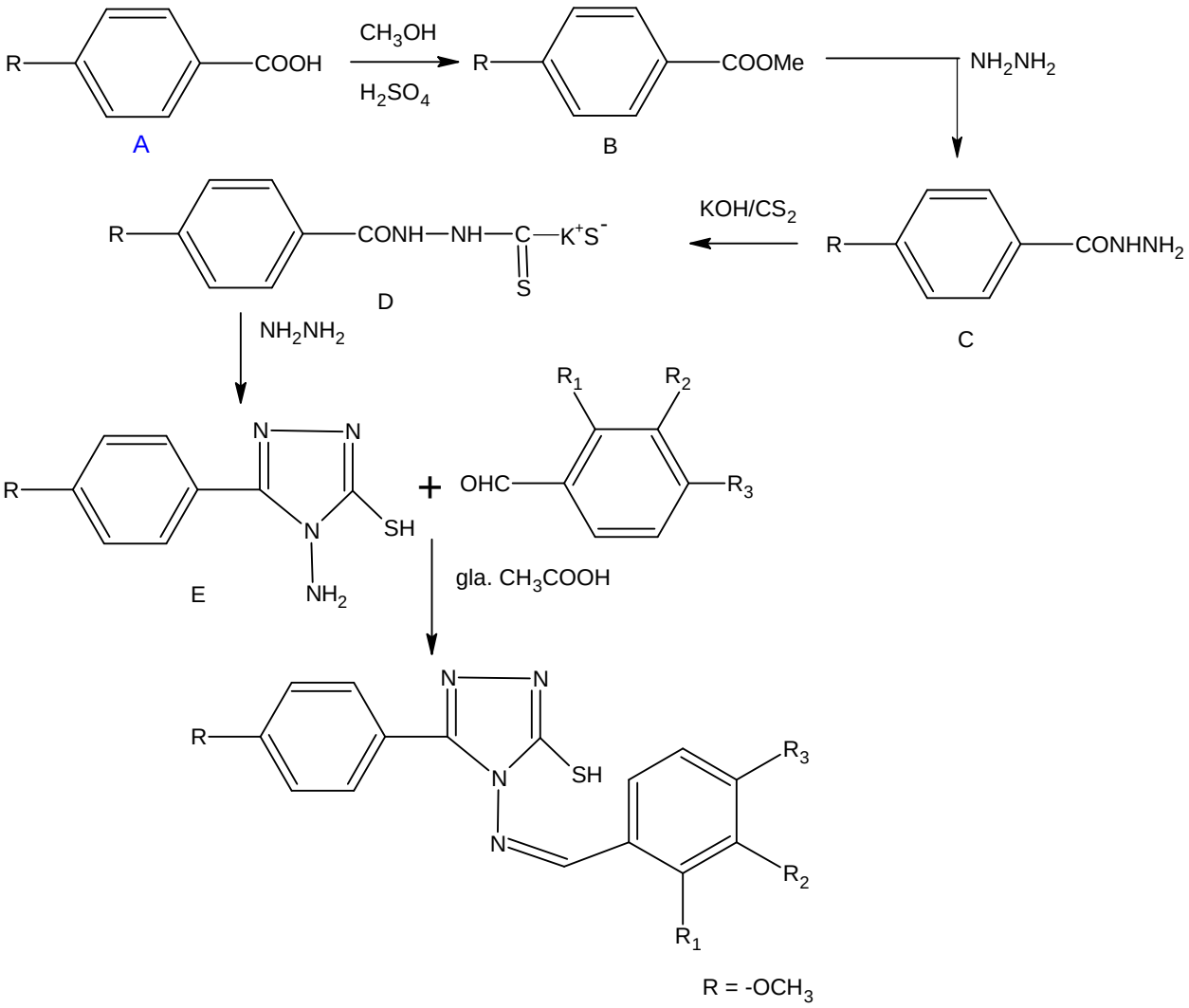
10: *5-(4-methoxyphenyl)-4-{[(1E)-phenylmethylene]amino}-4H-1,2,4-triazole-3-thiol*
IR(cm^-)1101 (S-H), 1530 (C=C), 1616(C=N), 3010 (Ar-H); NMR(δ ppm)10.31 (1H-CH), 11.42 (1H-SH), 3.70 (-OCH_3),7.0-7.67(8H-Ar-H)

Table 1: Physical data of triazole derivatives

Sr. No.	**Ar Aldehydes**	**Code.**	**M.Wt. (g)**	**M.F.**	**Rf* Value**	**M.P. ºC**	**Yield %**
1.	Acid	A	152	$C_8H_8O_3$		220	
2.	Ester	B	166	$C_9H_{10}O_3$	0.66	219	81
3.	Hydrazide	C	166	$C_8H_{10}O_2N_2$	0.74	210	76
4.	Salt	D	280	$C_9H_9O_2N_2KS_2$	0.75	208	85
5.	1,2,4-triazole	E	222	$C_9H_{10}ON_4S$	0.72	215	65
6.	4-Hydroxy	1	326	$C_{16}H_{14}O_2N_4S$	0.60	227	72
7.	4-methoxy	2	340	$C_{17}H_{16}O_2N_4S$	0.83	215	82
8.	4-fluoro	3	328	$C_{16}H_{13}ON_4SF$	0.81	222	79
9.	Vanilline	4	356	$C_{17}H_{16}O_3N_4S$	0.77	232	69
10.	4-chloro	5	344	$C_{16}H_{13}ON_4SCl$	0.86	207	72
11.	4-N-Ndimethyl	6	353	$C_{18}H_{19}ON_5S$	0.74	244	74
12.	3-NO_2	7	355	$C_{16}H_{13}N_5O_3S$	0.88	230	68
13.	2-chloro	8	344	$C_{16}H_{13}ON_4SCl$	0.84	238	79
14.	2-Hydroxy	9	326	$C_{16}H_{14}O_2N_4S$	0.88	223	81
15.	Benzaldehyde	10	310	$C_{16}H_{14}ON_4S$	0.75	241	76

* Benzene : Acetone = 9 : 1 for A,C,D,E,2 ; 9.5 : 0.5 for B,1,3,…..10.

REACTION SCHEME



RESULTS AND CONCLUSIONS

The IR and NMR analysis of the synthesized compounds confirmed their molecular structures. The physical data of triazole derivatives are given in table 1. The antibacterial activity of triazole derivatives showed a differential activity against the bacterial strains investigated. The activity was also solvent dependent. The antibacterial activity of all the 15 compounds in both the solvents 1,4-Dioxan and DMF against *E. coli* and *P. aeruginosa* is shown in Fig.1. None of the compounds in either of the solvent could inhibit P. aeruginosa except compound number two. On the other hand, considerable activity was envisaged against E. coli. The compounds dissolved in 1,4-Dioxan showed better antibacterial activity than those dissolved in DMF. Of the 15 compounds, the starting compound A, B, C, D and E showed best antibacterial activity

against this Gram negative bacteria. In fact, the best activity was shown by the very starting compound A i.e. 4-methoxy benzoic acid and D its salt , dithiocarbazate. Both compounds (A and D) did not show similar antibacterial activity when extracted in DMF. The compound E which is 1,2,4 triazole showed slight activity in both the solvents. The rest 10 compounds did not show any antibacterial activity except compound number 2. In this the attachment is 4 methoxy This differential response of the compounds is because of the structural differences amongst them. In the present work total 15 compounds are present in which A to D are the starting compounds and E is synthesized and 10 side chains are attached to it (E). A is an acid, B is its ester, C is its hydrazide, Dis its salt known as dithiocarbazate. E is 1,2,4, triazole moiety to which different side chains are attached. 1 is 4-hydoxy, 2 is 4 methoxy, 3 is 4-fluoro, 4 is vanilline, 5 is 4-cloro, 6 is 4,N-Ndimethyl, 7 is 3-NO_2, 8 is 2-chloro, 9 is 2-hydroxy and 10 is benzaldehyde. It can be clearly seen that the group or the molecule that is attached to the central ligand play an important role in inhibiting the bacteria. The inhibition of bacterial growth depends on the solubility of the compounds in a particular solvent, its diffusion capacity and penetration into the bacterial cell wall.

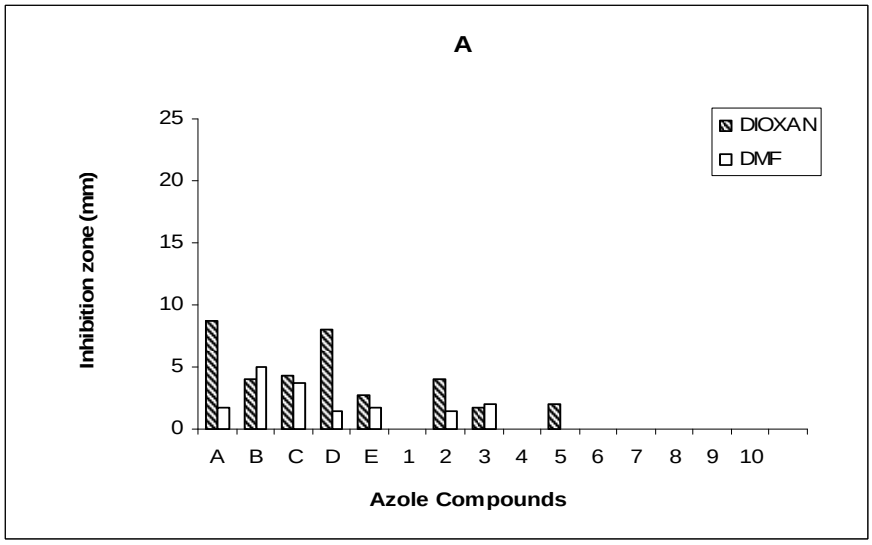
The antibacterial activity against two Gram positive bacteria *S. aureus* and *B. cereus* are shown in fig. 2. None of the compounds in either of the solvent could inhibit the Gram positive bacteria *S. aureus* except a very negligible activity was shown by the starting compounds A and D. An entire different trend was observed against B. cereus. A considerable activity was shown by some of the compounds when the solvent used was 1,4-Dioxan. Maximum activity was shown by compound D in both the solvents followed by compound A, though the activity was more with 1,4-Dioxan. Compounds 4 and 6 showed little activity while the other compound could not inhibit this bacterial strain.

The antibacterial activity against Gram negative bacteria *A. fecalis* and *K. pneumoniae* are shown if figure 3. The antibacterial activity against *A. fecalis* is similar to that of *E. coli*; i.e. here also only starting compounds (A to E) showed considerable antibacterial activity and that too when the solvent used was non polar solvent 1,4-Dioxan. An entirely different trend was observed when the activity of these compounds was studied against *K. pneumoniae*. Here the compounds extracted in DMF proved better than those extracted in 1,4-Dioxan. The starting compounds (A to E), which showed antibacterial activity in 1,4-Dioxan against the other five bacterial strains, did not inhibit this bacteria at all but in DMF the same compounds showed considerable activity. Almost all the compounds (except compound number 2) in DMF inhibited *K. pneumoniae*. Compound number 7 and 8 in 1,4-Dioxan showed antibacterial activity.

Two hundred and fifty years ago there were few or no synthetic medicines; higher plants were the main source for the world's population. However, the imposing anthropogenic activities are forming an increasing threat to the natural habitat of medicinal plants. They are continuously under the threat of extinction. To overcome this alarming problem, the discovery of novel active compounds is a matter of urgency.

From the present work, it can be concluded; that it cannot be assumed that one solvent is better than the other. It is dependent on the molecular structure of the compound, the solvent used and the particular bacterial strain under consideration considered. Amongst the solvents used, 1,4-Dioxan appears to be better than DMF. This is in agreement with our earlier work[9] that non-

polar solvents may be beneficial in our attempt to search lead molecules for drug designing. *B. cereus* appeared to be most susceptible bacteria while *P. aeruginosa* was the most resistant bacterial strain. Except *K. pneumoniae*, none of the newly synthesized triazole compounds could inhibit any of the bacterial strains investigated. Hence, though triazole compounds are reported to show many pharmacological activities but these particular compounds did not show any antibacterial activity. Therefore, such screening of various organic compounds and identifying active agents is the need of the hour; because successful prediction of lead molecule and drug like properties at the onset of drug discovery will pay off later in drug development.



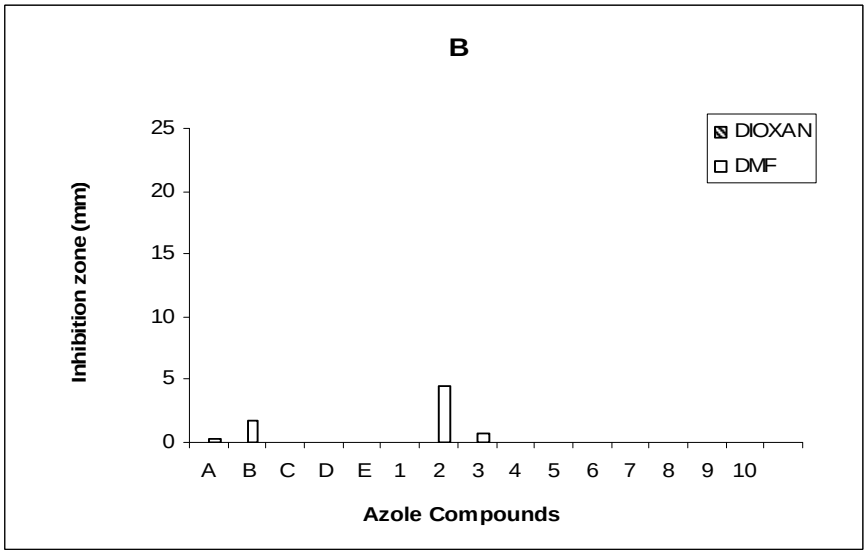
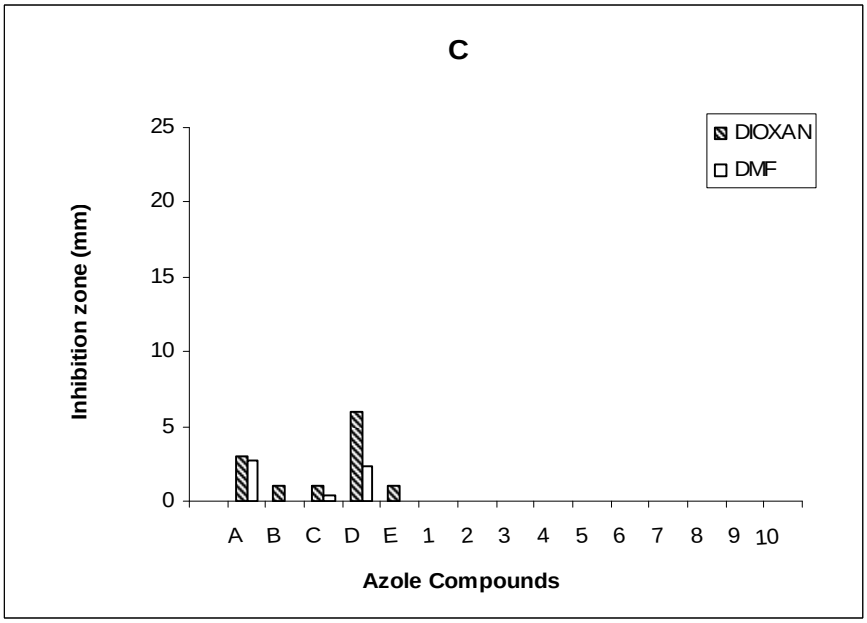


Fig-1: Antibacterial activity of some azole compounds against A (*E. coli*) and B (*P. aeruginosa*)



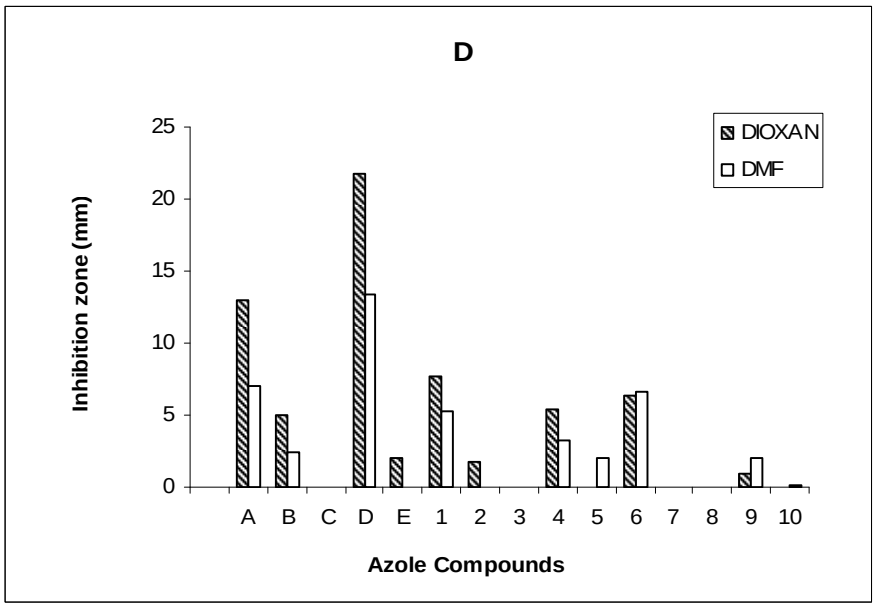
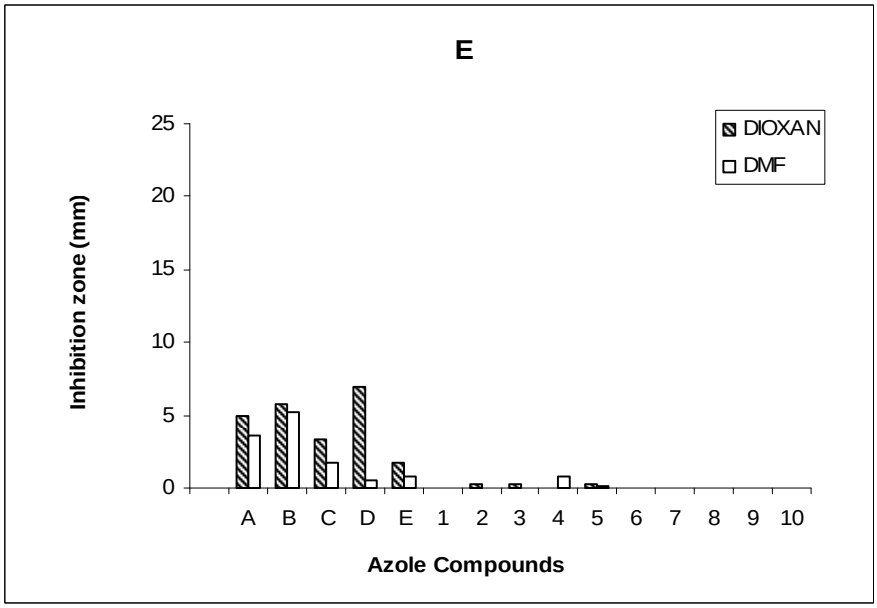


Fig-2: Antibacterial activity of some azole compounds against C (*S. aureus*) and D (*B. cereus*)



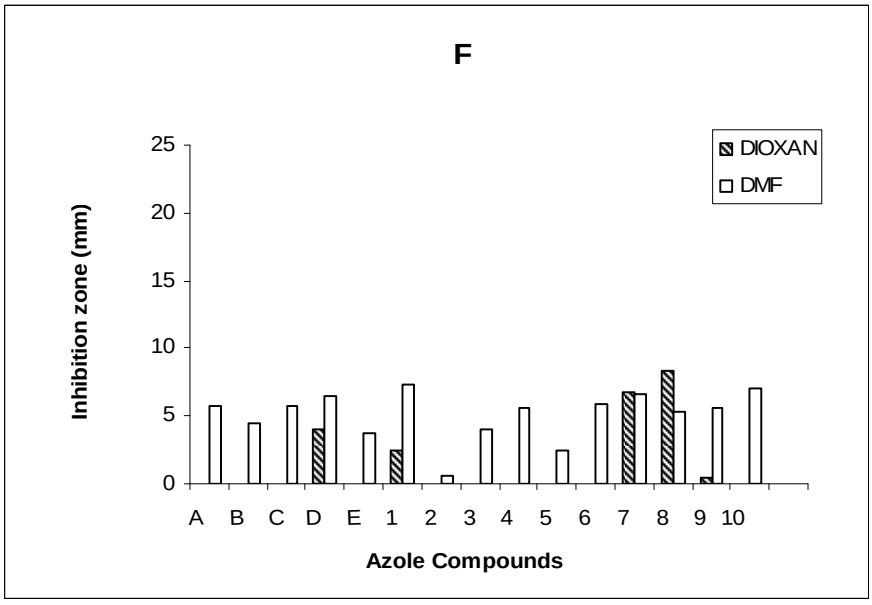


Fig-3: Antibacterial activity of some azole compounds against E *(A. fecalis)* and F *(K. pneumoniae)*

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