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RESEARCH ARTICLE

SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF FORMAMIDINE DISULFIDE SCHIFF BASES AND THEIR CORRESPONDING 1,3-OXAZEPINES

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Phthalic anhydride.

ABSTRACT

Formamidine disulfide was synthesized by oxidizing thiourea in the presence of potassium permanganate. It was then reacted with various aldehydes to give formamidine disulfide Schiff bases. Each Schiff base was then condensed with maleic anhydride and phthalic anhydride to yield corresponding 1,3-oxazepine derivatives respectively. The phthalic anhydride derivative of benzaldehyde Schiff base was not synthesized as a result of low yield. The antimicrobial activities of the schiff bases were better than the oxazepines. Those of the maleic anhydride oxazepine derivatives were better than those of the phthalic anhydride oxazepine derivatives. This shows that the imine group (-C=N-) is responsible for antimicrobial activity in schiff bases. More so, the best schiff base is the 3-nitro benzaldehyde derivative that is; 1,1'{disulfanediylbis[carbonimioylnitrilo (Z)methylylidene]}bis(3-nitrobenzene), for all the organisms used at the lowest concentration (@25mn/dl). At 200mg/dl, which is the highest concentration used, all the compounds synthesized show a level of activity. In between these two extreme concentrations antimicrobial activity of these analogues against *E.coli* began to show a trend.

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INTRODUCTION

Schiff bases are condensation products of primary amines with carbonyl compounds and they were first reported by Schiff [Cimerman *et al*., 2000] in 1864. The common structural feature of these compounds is the azomethine group with a general formula RHC=N-R1, where R and R1 are alkyl, aryl, cyclo alkyl or heterocyclic groups which may be variously substituted. The electrophilic carbon atoms of aldehydes and ketones can be targets of nucleophilic attack by amines. Schiff bases have been widely reported to have biological properties such as antibacterial, antifungal (Sari *et al*., 2003 and Verma *et al*., 2004) and herbicidal and plant growth regulatory properties (Shayma *et al*., 2011). The seven (7) membered heterocyclic ring system 1,3-oxazepine has been reported in many literatures (Al-Rubaay, A.K., 2008 and Toshio *et al*., 1977). 1,3-oxazepine derivatives also show biological activities against different types of bacteria, in addition to their uses as inhibitors of some enzymes (Tomma *et al*., 2009). In this work formamidine disulfide Schiff basess are synthesized and condensed with maleic and phthalic anhydrides to yield their corresponding 1,3-oxazepine derivatives.

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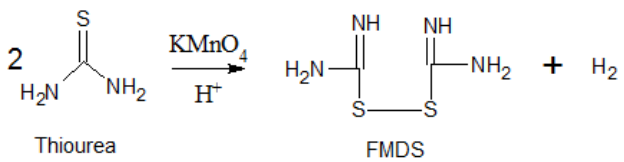
Experimentation

Melting points were determined on Gallen Kamp melting point apparatus and were uncorrected. The FTIR spectra were recorded with Shimadzu FTIR 8400 spectrophotometer. The GC-MS spectra were recorded on GCMS-QP2010 PLUS SHIMADZU, JAPAN

Synthesis of formamidine disulfide

Prepared acidified $KMnO_4$ was slowly added into the conical flask containing a solution of thiourea until a purple color was obtained. After about 30-45 minutes $NaHCO_3$ and distilled water were added until the solution turned a red litmus paper blue.

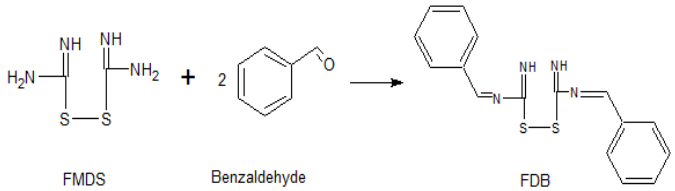


Thiourea (1) FMDS (2)

Scheme (1): Oxidation of thiourea

Synthesis of 1,1'{disulfanediyl bis [carbon imidoyl nitrilo (z) methylylidene]}dibenzene

Two grams of formamidine disulfide (2) was dissolved in 5ml dilute methanol. 10ml of benzaldehyde (30) was then added into the solution in a conical flask and warm on a water bath for about 15minutes with continuous stirring. On cooling, crystals formed, filtered off, allowed to dry and melting point determined.

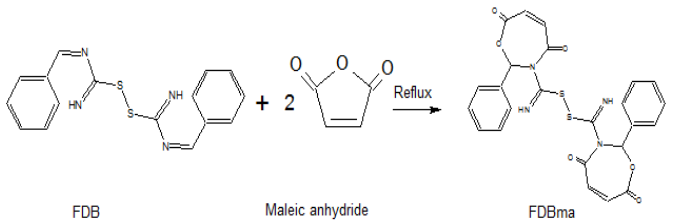


FMDS (3) Benzaldehyde (4) FDB (5)

Scheme (2): Reaction FMDS and benzaldehyde to yield FDB FMDS; formamidine disulfide, FDB; 1, 1'{disulfanediylbis [carbonimidoy l nitrilo (Z)methylylidene]}dibenzene. Other derivatives were prepared by the same method (see table)

Synthesis of 3 - (n - n - 4, 7 - dioxo - 2 - phenyl - 2, 3, 4, 7 - tetrahydro- 1, 3 - oxazepine - 3 carboximidoyl disulfanyl carboximidoyl) - 2 - phenyl -2, 3, 4, 7 - tetrahydro -1, 3 - oxazepine-4, 7-dione

A mixture of the prepared Schiff base, FDB (5) (0.027M) and Maleic anhydride (0.00726M) were dissolved in 20ml dry toluene and the mixture was refluxed for about 3hrs. Excess solvent was distilled and the precipitate obtained was filtered after cooling, recrystallized in ethanol and melting point was determined.



FDB (6) Maleic anhydride (7) FDBma (8)

Scheme (3): Reaction of FDB with Maleic anhydride to yield FDBma

FDB:1,1'{disulfanediylbis[carbonimidoylnitrilo(Z)methylylidene]}dibenzene

FDBma:3-(N-N-4,7-dioxo-2-phenyl-2,3,4,7-tetrahydro-1,3-oxazepine-3-carboximidoyldi sulfanylcarboximidoyl)-2-phenyl-2,3, 4,7- tetrahydro-1, 3-oxazepine-4,7-dione

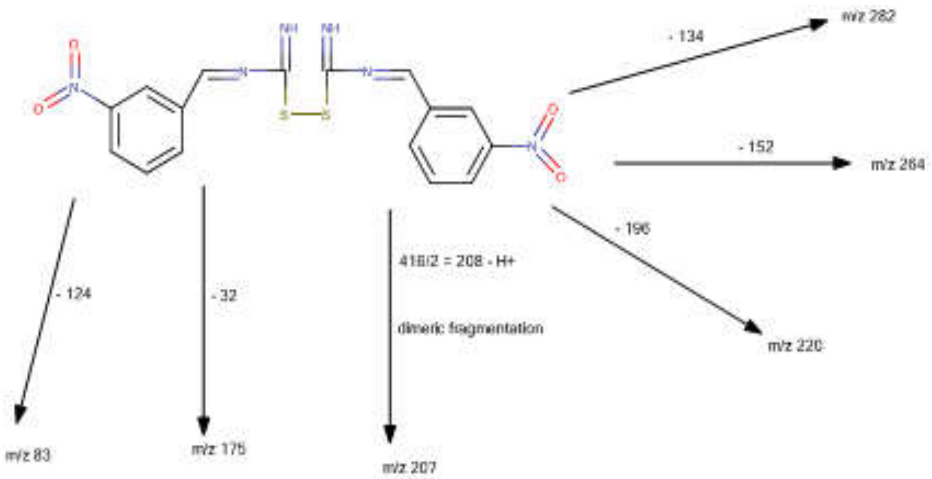
Phthalic anhydride was then used instead of maleic anhydride to prepare more 1,3-oxazepine derivatives using the same method of preparation.

RESULTS AND DISCUSSION

Formamidine disulfide Schiff bases are prepared by condensation of formamidine disulfide with aromatic aldehydes to give the azomethine/imine compounds (scheme 1) and identified by melting point (see Table 1), FTIR and GC-MS. The reaction is followed by disappearance of (C=O) absorption band at (1690-1720) cm^{-1} with the appearance of (C=N) absorption band at (1645-1649) cm^{-1} (see Table 2). Derivatives of oxazepine are prepared by reaction of maleic anhydride with Schiff bases derivatives (Scheme 3). It was noted disappearance of the azomethine (C=N) absorption band and appearance of the (C=O) absorption band at (1670-1730) cm^{-1}. The compounds of oxazepine derivatives are identified by m.p. (see Table 1), and other important FTIR absorptions of compounds are shown in Table 2. The summary of the mass spectra fragmentation pattern of two Schiff bases (FDN and FDT) and two 1,3-oxazepines (FDNma and FDNpa) are summarized as (9), (10) and (11), (12) respectively. Thus;

The minimum inhibitory concentration (MIC) of the Schiff bases and 1,3-oxazepines is summarized in Tables (1) to (3) while the minimum bactericidal concentration is summarized in Tables (4) to (9)

Generally, the antimicrobial activity reveals that the Schiff bases exhibited superior Minimum Bactericidal Concentration (MBC) activity against the three organisms (*E. coli*, *Staph. aureus*, and *A. niger)* used compared to the 7-membered ring compounds.



(9)

Table 1. Antimicrobial activity; MIC

Organism: *Escherichia coli*

	Zones Of Inhibition in mm					
Serial No.	**Comp/Conc.(mg/dl)**	**200**	**100**	**50**	**25**	**Standard**
1.	FDB	20	16	13	9.5	20
2.	FDN	27	25	20	15.5	20
3.	FDD	11	0	0	0	21
4.	FDT	12.5	9	0	0	21
5.	FDP	17.5	15	12	0	21.5
6.	FDBma	30	26	12	0	20
7.	FDMma	17	16	9.5	0	20
8.	FDNma	20	17.5	14	10.5	20
9.	FDDma	30	24.5	15	0	17
10.	FDTma	17	13.5	0	0	17
11.	FDPma	22	19	12.5	0	16
12.	FDMpa	16	12.5	11	0	16
13.	FDNpa	24.5	20	13	0	18
14.	FDDpa	25	20	14	0	17
15.	FDTpa	17.5	12	0	0	18
16.	FDPpa	26	23.5	16.5	0	16

Table 2. Antimicrobial activity; MIC

Organism: *Staphylococcus aureus*

	Zones Of Inhibition in mm					
Serial No.	**Comp/Conc. mg/dl**	**200**	**100**	**50**	**25**	**Standard**
1.	FDB	14.5	12	9	0	20.5
2.	FDN	25.5	24.5	18	13	20
3.	FDD	10.5	0	0	0	20
4.	FDT	10	0	0	0	21.5
5.	FDP	16	13	9.5	0	20
6.	FDBma	20.5	13	9.5	0	20
7.	FDMma	14	11.5	0	0	23
8.	FDNma	17	13	10	0	21
9.	FDDma	16	12	0	0	17
10.	FDTma	13.5	10	0	0	17
11.	FDPma	17.5	13	0	0	16
12.	FDMpa	13	10.5	0	0	22
13.	FDNpa	21	12.5	0	0	16
14.	FDDpa	21	12.5	0	0	16
15.	FDTpa	10	0	0	0	18
16.	FDPpa	17.5	13	0	0	16

Table 3. Antimicrobial activity; MIC

Organism: *Aspergillus niger*

	Zones Of Inhibition in mm					
Serial No.	**Comp/Conc. g/dl**	**200**	**100**	**50**	**25**	**Standard**
1.	FDB	18	15	11.5	0	20
2.	FDN	27.5	25	20.5	17	20
3.	FDD	15.5	10.5	0	0	20
4.	FDT	10	0	0	0	21
5.	FDP	11	0	0	0	21
6.	FDBma	18	11.5	0	0	16
7.	FDMma	15.5	13	10.5	0	23
8.	FDNma	18.5	14.5	11	0	21
9.	FDDma	18.5	14	0	0	16.5
10.	FDTma	19.5	16	13	0	17
11.	FDPma	16.5	12	0	0	17
12.	FDMpa	17	15	12	0	22
13.	FDNpa	25.5	20	10.5	0	16.5
14.	FDTpa	11.5	0	0	0	18
15.	FDPpa	14	10.5	0	0	16.5
16.	FDDpa	16.5	13	0	0	16.5

Table 4. Antimicrobial Activity; MBC of FDB and FDBma

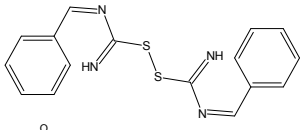
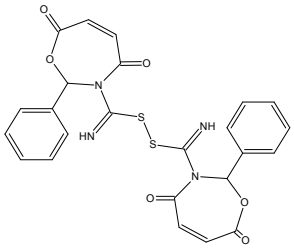
NAME	STRUCTURE	GRADE (1,2,3 OR 4) E.c	S.a	A.n	COMMENT
FDB		1	2	2	Effective
FDBma		2	3	3	Fairly Effective

Table 5. Antimicrobial Activity; MBC of FDM, FDMma and FDMpa

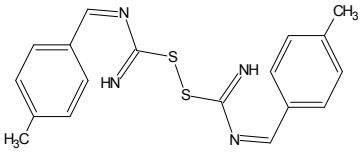
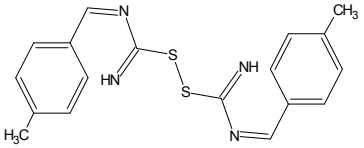
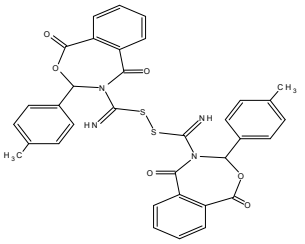
NAME	STRUCTURE	GRADE (1,2,3 OR 4) E.c	S.a	A.n	Comment
FDM		-	-	-	-
FDMma		2	3	2	Effective
FDMpa		2	3	2	Effective

Table 6. Antimicrobial Activity: MBC of FDD, FDDma and FDDpa

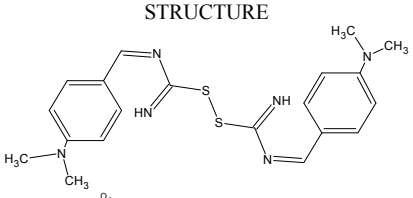
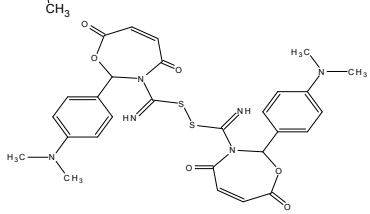
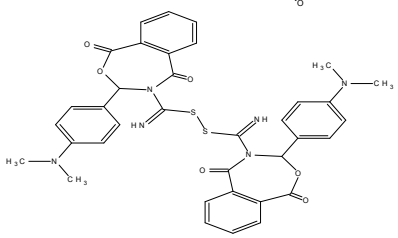
NAME	STRUCTURE	GRADE (1,2,3 OR 4) E.c	S.a	A.n	Comment
FDD		4	4	3	Poorly Effective
FDDma		2	3	3	Fairly Effective
FDDpa		2	3	3	Fairly Effective

Table 7. Antimicrobial Activity: MBC of FDN, FDNma and FDNpa

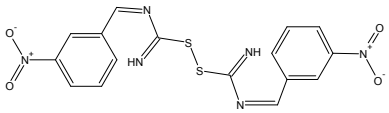
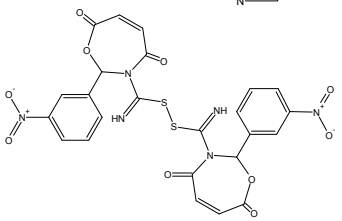
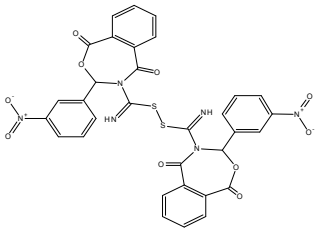
NAME	STRUCTURE	GRADE (1,2,3 OR 4) E.c	S.a	A.n	Comment
FDN		1	1	1	Very Effective
FDNma		1	2	2	Effective
FDNpa		2	3	2	Effective

Table 8. Antimicrobial Activity: MBC of FDP, FDPma and FDPpa

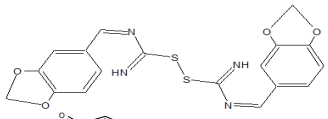
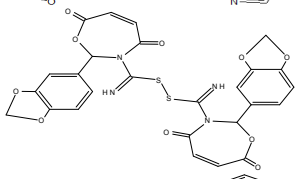
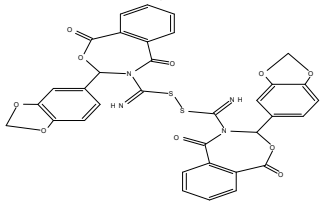
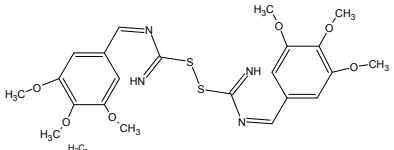
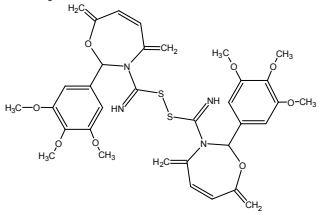
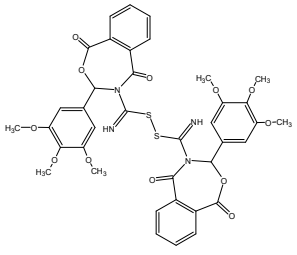
NAME	STRUCTURE	GRADE (1,2,3 OR 4) E.c	S.a	A.n	Comment
FDP		2	2	4	Effective
FDPma		2	3	3	Fairly Effective
FDPpa		2	3	3	Fairly Effective

Table 9. Antimicrobial Activity; MBC of FDT, FDTma and FDTpa

NAME	STRUCTURE	GRADE (1,2,3 OR 4) Ec	S.a	A.n	Comment
FDT		3	4	4	Poorly Effective
FDTma		3	3	2	Fairly Effective
FDTpa		3	4	4	Poorly Effective

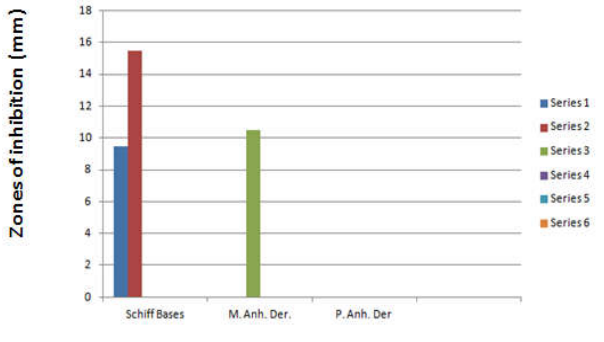


Figure (1): Histogram plot of zones of inhibition in 'mm' against Schiff bases and 1,3-oxazepine derivatives @25mg/dl {*E.coli*}

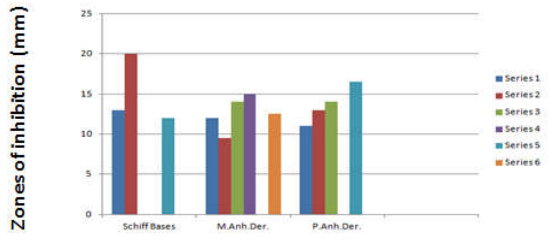


Figure (2): Histogram plot of zones of inhibition in 'mm' against Schiff bases and 1,3-oxazepine derivatives @50mg/dl {*E.coli*}

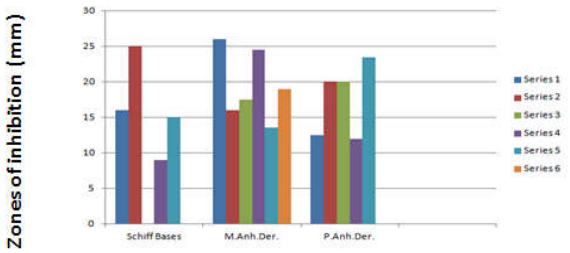


Figure (3): Histogram plot of zones of inhibition in 'mm' against Schiff bases and 1,3-oxazepine derivatives @100mg/dl {*E.coli*}

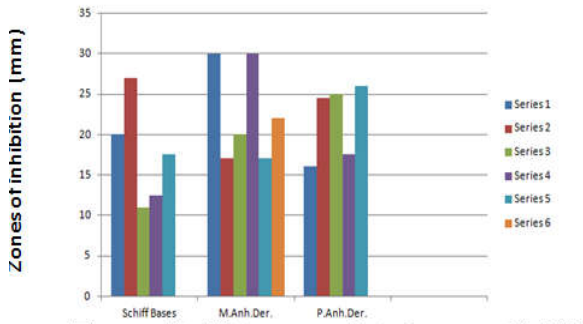


Figure (4): Histogram plot of zones of inhibition in 'mm' against Schiff bases and 1,3-oxazepine derivatives @200mg/dl {*E.coli*}

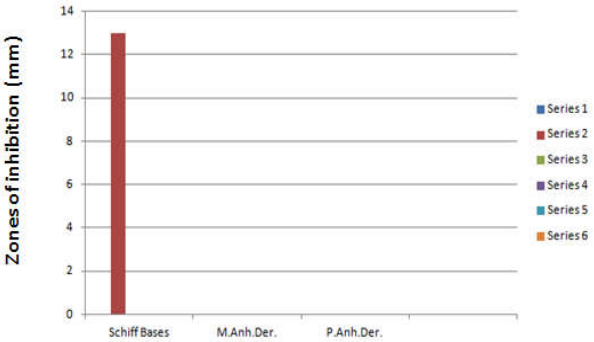


Figure (5): Histogram plot of zones of inhibition in 'mm' against Schiff bases and 1,3-oxazepine derivatives @25mg/dl {*S. aureus*}

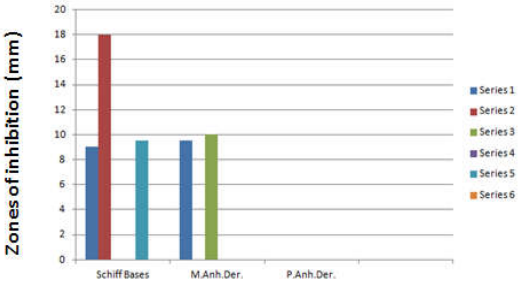


Figure (6): Histogram plot of zones of inhibition in 'mm' against Schiff bases and 1,3-oxazepine derivatives @50mg/dl {*S. aureus*}

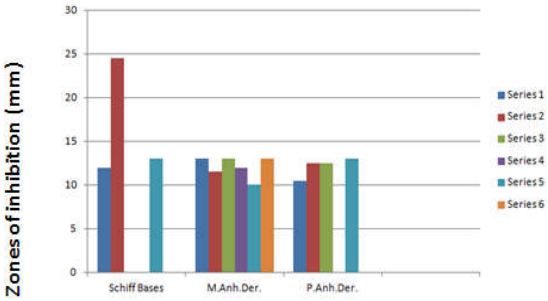


Figure (7): Histogram plot of zones of inhibition in 'mm' against Schiff bases and 1,3-oxazepine derivatives @100mg/dl {*S. aureus*}

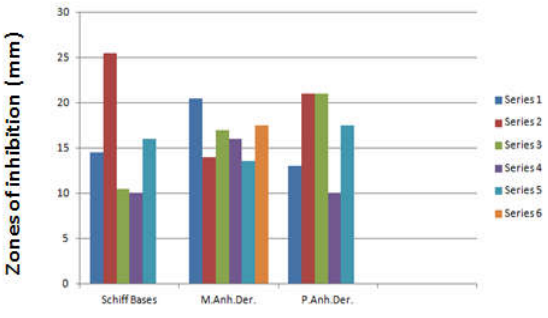


Figure (8): Histogram plot of zones of inhibition in 'mm' against Schiff bases and 1,3-oxazepine derivatives @200mg/dl {*S. aureus*}

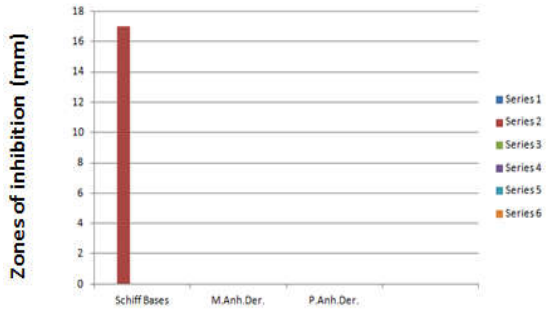


Figure (9): Histogram plot of zones of inhibition in 'mm' against Schiff bases and 1,3-oxazepine derivatives @25mg/dl {*A. niger*}

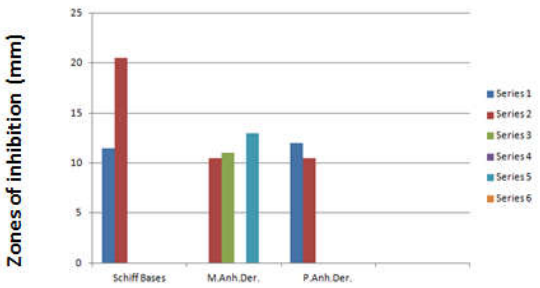


Figure (10): Histogram plot of zones of inhibition in 'mm' against Schiff bases and 1,3-oxazepine derivatives @50mg/dl {*A. niger*}

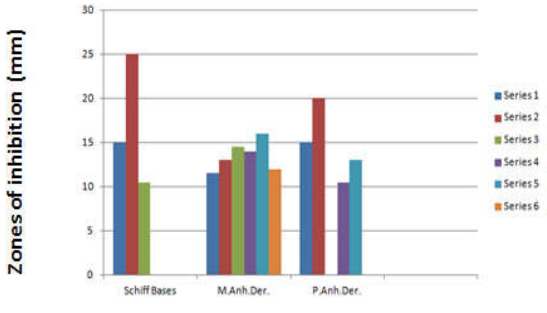


Figure (11): Histogram plot of zones of inhibition in 'mm' against Schiff bases and 1,3-oxazepine derivatives @100mg/dl {*A. niger*}

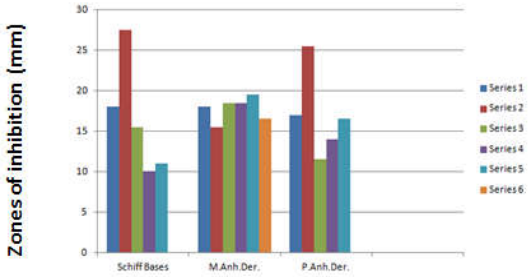


Figure (12): Histogram plot of zones of inhibition in 'mm' against Schiff bases and 1,3-oxazepine derivatives @200mg/dl {*A. niger*}

And the MBC activity against the gram negative organism, *E. coli* is better relative to activity against *Staph. aureus.* FDN (a Schiff base), consistently exhibited better antimicrobial activity compared to all the other synthetic compounds. Histogram plots of zones of inhibition against Schiff bases and 1,3-oxazepines at various concentrations (see Fig. 1 to 12) further explains the activity of the Schiff bases and the 7-membered ring compounds.

Conclusion

In this work, Schiff bases and 1,3-oxazepiness were synthesized, characterized by melting point, FTIR and mass fragmentation pattern. Although all the synthetic compounds exhibited some degree of antimicrobial activity (against *E.coli, S.aureus* and *A.niger*) FDN-a Schiff base, exhibited the best activity compared to the rest of the compounds.

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