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SYNTHESIS OF THE HETEROCYCLIC HYDROXAMIC ACID DERIVATIVES FOR PDF INHIBITORS AS A ANTIBIOTICS

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Key words:

PDF, THF, 1,3,4-oxadiazole, 1,3,4-triazole,hydrazine hydrate

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ABSTRACT: Peptide deformylase (PDF) is a mononuclear metal ion protein that is responsible for removing the N-formyl group of nascent proteins found in bacteria and chloroplasts in order for them to become mature proteins. From literature it was found that heterocyclic derivatives containing hydroxamic acid and hydroxyl amine exhibit good antibacterial and PDF inhibitory activity. Heterocycles bearing nitrogen, sulphur, oxygen and thiazole moieties constitute the core structure of a number of biologically interesting compounds. Recently 1,3,4 oxadiazole and 1,3,4 – triazole derivatives received significant attention owing to their diverse range of biological properties particularly being antifungal, antitubercular, antibacterial, antiviral, anticancer and antioxidant. Ethyl-cyano- acetate when treated with sodium hydrate and THF give acetate derivatives, which on further treatment with hydrazine hydrate and various reagent afforded heterocyclic hydroxylamine derivatives.

INTRODUCTION: Current research mainly focuses on target specific therapy. In this context many target have been identified of which PDF is one such potential target. From literature it was found Peptide deformylase (PDF) is a prokaryotic metalloenzyme that is essential for bacterial growth but is not required by mammalian cells. Thus, it represents a selective and promising target for the development of new antibacterial agents.[1] Using structural and mechanistic information together with high throughput screening, several types of potent PDF inhibitors have been identified. PDF inhibitors identified to date share a common structural feature of a "chelator + peptidomimetic" scaffold.[2-5] Although compounds with many different chelators inhibit the cell free enzyme, only compounds containing hydroxamic acid or N-formyl hydroxylamine exhibit appreciable antibacterial activity.

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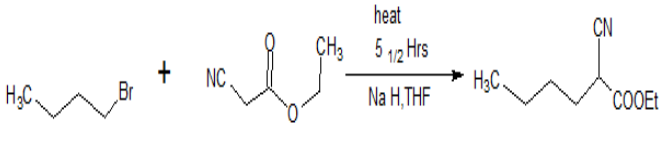
Several lead inhibitors have demonstrated in vivo efficacy and an excellent safety profile. From literature it was also found that heterocyclic derivatives containing hydroxamic acid and hydroxyl amine exhibit good antibacterial and PDF inhibitory activity. PDF inhibitor synthesis have shown to posses potent antibacterial activity structural features have been used in the present work for designing novel antibacterial compounds. The SAR of various PDFIs synthesized revealed some specific characters essential for antibacterial activity.[6]

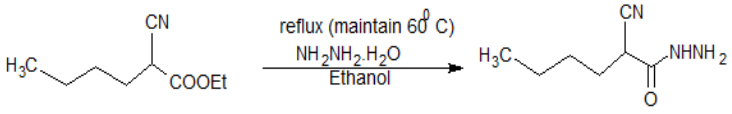
General Scheme for Synthesis of Heterocyclic Derivatives:

Step 1: Alkylation of Ethyl-2- Cyanoacetate : [7]



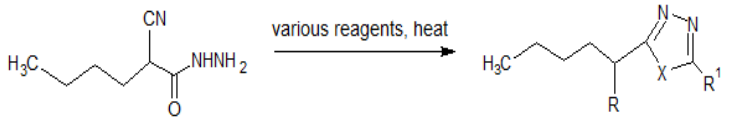
n-Butyl bromide ethyl-2 cyanoacetate 2- cyano- ethyl hexanoate

Step 2: Formation of Hydrazide: [8]



2-cyano- ethyl hexanoate 2-cyanohexane hydrazide

Step 3: formation of heterocyclic derivative: [9-11]



2-cyanohexane hydrazide Heterocyclic derivatives

R- CN, NHOH

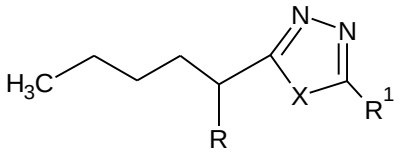
R_1 –SH, NH_2

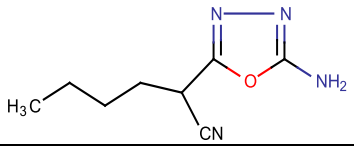
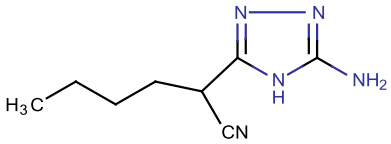
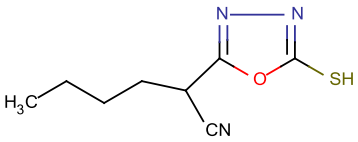
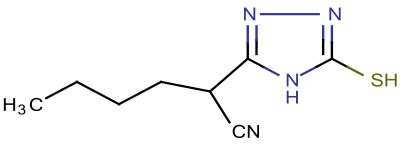
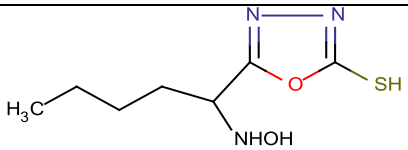
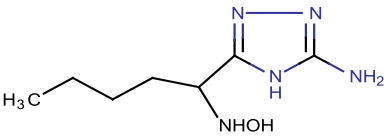
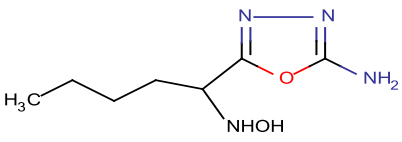
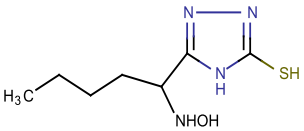
X- O, N

Series of synthesized compounds:

General structure:

TABLE 1: SERIES OF SYNTHESIZED COMPOUNDS



Sr. No.	Synthesized compounds	Sr. No.	Synthesized compounds
1		5	
2		6	
3		7	
4		8	

MATERIAL AND METHOD:

General: Starting material and solvent used for each reaction were procured from S D Fine, molychem, Fischer Scientific and Merck specialties are of synthetic grade. All the reactions were monitored using thin layer chromatography on pre-coated TLC plates (silica gel 60-120#) using various solvent systems. The structures of the synthesized compounds were characterized by IR, NMR. Infrared spectroscopy was carried out using potassium bromide (KBr) pellet method on the SHIMADZU IR affinity-1. Nuclear magnetic resonance spectroscopy was done by using dimethylsulfoxide (DMSO) and $CDCL_3$ (chloroform) as solvent and recording spectra ^{1}HNMR on 400 & ^{13}C NMR on 400 Ft/NMR MHz analyzer respectively.

Step 1 for the alkylation of ethyl-2-cyano acetate: 2 gm (0.03 moles) of sodium hydride and 20 ml of THF was taken in the dry Round bottom flask, the suspension cooled to 0^0 C. To the above suspension slowly added ethyl-2-cyano acetate 20 ml (0.15 moles) in THF 20 ml, after 15 min. Butyl bromide 20 ml (0.05 moles) was added drop wise via syringe to the solution. The resulting mixture was allow to stirred at 0^0 C for 15 min. and then it was reflux at 100^0C for $5^{1/2}$ Hrs. The whole reaction was monitored by using TLC, and it was observed under UV chamber or iodine chamber. The mixture was then quenched with 30ml H_2O and diluted with Et_2O. The aqueous layer was removed and organic layer was wash twice with brine solution. Then combine the aqueous layers were then extracted 2-3 times with Et_2O. The combine extract were pass through the $MgSO_4$ and the solvent were removed by distillation method. Yield light brown color oily liquid was obtained.[7]

Step 2 general procedure of hydrazide:
To the ethanolic (30ml) solution of the 2-cyano-ethyl hexanoate, (0.02 mole), hydrazine hydrate (0.04 mole) was taken in round bottom flask and heated at 60^0 C for 4 Hrs. Reaction was monitored by TLC. On cooling yellowish colored crystallized compound was filtered, dried.[8]

Step 3: synthesi of heterocyclic derivatives: [9-11]
Synthesis of the amino-oxadiazole derivative:
To the methanolic solution of (0.01 mole) 2-cyanohexane hydrazide, (0.01 mole) cynogen bromide was added. The reaction mixture was stirred at room temperature for 3 Hrs. The resulting mixture was neutralized with sodium bicarbonate solution. The solvent evaporated and dried the product. Recrystallization was done using ethanol.

Synthesis of the thio-oxadiazole derivative:
The mixture of 2-cynohexane hydrazide (0.01 mole), (0.04mole) KOH, 5 ml CS_2 and 10 ml ethanol was exposed in microwave at 6 watt for 10 min.After 10 min. the reaction mixture was cooled and acidifies with dil. HCL, precipitated product was filtered.

Formation of the amino- triazole derivative: A mixture of 0.01 mole 2-cyanohexane hydrazide and formamide (0.02mole) in ethylene glycol (50 ml) was reflux at 180^0C for 12 Hrs. the reaction mixture was poured into ice cold water. Water under rotary evaporator and dried the product. Reaction was monitored by TLC Recrystallize from ethanol.

Synthesis of Thio- triazole:
Mixture of 2-cyanohexane hydrazide(0.01 mole) 2.75 gm and potassium thiocyanate(0.02mole) 1.943 gm were reflux in water 100 ml containing 10 ml hydrochloric acid for 3 hours. White colour powder form which was again reflux for 3 hours with sodium hydroxide solution to obtained a gray colour powder compound.

The remaining four product are synthesize by the conversion of cyanide to hydroxylamine of first four previous synthesized compounds by the following general method: Mixture of 0.01 mole of cyano drivatives, 0.02 mole of water and 0.01 mole of HCL was taken in round bottom flask and reflux for 1hour. Cool and dry the compound in oven below 100℃. The resulting mixture in diethylether (30 mL) was taken at 0℃ , ethyl-chloroformate (1.3 g, 12mmol) and N-methylmorpholine (1.3 g, 13 mmol) were added and the mixture was stirred for 10 min. The solid was filtered of and the filtrate was added to freshly prepared hydroxylamine (0.5 g, 15 mmol) in methanol. The reaction mixture was stirred at room temperature for 15 min.

FIG.2: TABLE OF YIELD, MELING POIN, TLC (MOBILE PHASE RATIO), AND RF VALUE OF SYNTHESIZE COMPOUND

Compound no.	Yield%	Melting point ℃	TLC	
			Mobile phase	R f value
1	62%	138-140	E.A: hexane (0.7:0.3)	0.68
2	65.48%	191-195	E.A: hexane (0.7:0.3)	0.58
3	48.75%	190-197	Hexane: E.A: Methanol (1:1:1)	0.42
4	58.60%	150-160	Hexane : E.A (0.3: 1)	0.36
5	65%	140-150	E.A: hexane (0.7:0.3)	0.52
6	63%	110-120	E.A :Hexane(1:05)	0.48
7	57%	188-190	Hexane: E.A: Methanol (1:1:0.5)	0.46
8	60.33%	178-180	E.A: methanol (0.5:1:0.5)	0.58

Biological activity of synthesized drug:
The synthesized compounds were subjected to antibacterial and antioxidant activity. Antibacterial activity of all the synthesized heterocyclic and hydroxyl amine derivatives were screened against both gram positive and gram negative bacteria by cup plate method (agar well diffusion technique). Streptomycin was used as standard drug.

Bacterias used for antibacterial screening of synthesized compounds were *Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*. Inoculums for all bacteria were obtained from national chemical laboratory. All bacteria were maintained by sub culturing and were used whenever required in nutrient agar medium.[12-13]

Preparation of Inoculums:
The suspension of all organisms were prepared by inoculating one colony of the strain in 20 ml of Nutrient broth in a conical flask and incubated at 37°C for 24 hours to activate the strain.

Procedure for Cup-plate method:
About 20-25 ml of Nutrient agar medium was poured aseptically into the each sterilized Petri plates. The poured material was allowed to set without disturbing it, until it got solidified. A definite volume of suspension containing test organism cultures (inoculums) was streaked on the respective Petri plates (cooled at 40ºC). Thereafter the wells (10 mm diameter) were made by boring into the agar surface with a sterile cork borer and scooping out the punched part of the agar. Into these prepared wells the test compounds solution, standard drugs solution and H_2O (control) separately were added with the help of a micropipettes using sterile tip each time. After a period of pre-incubation diffusion, the plates were incubated at 37°C for 24 hours. The zones of inhibition were measured, as a parameter to assess antibacterial properties of the synthesized compounds[14].

Antioxidant activity screening:
From literature survey it was found that PDF inhibitors have antibacterial, anticancer, antioxidant, anti-tuberculosis.

Preparation of test material:
Experimental compounds were reconstituted in methanol to get different concentration (0-200 µg/ml) and used for assay.

Methodology:
The reaction mixture consisted of 1 ml of 0.1 mM DPPH in methanol and 0.5 ml of methanolic (80%) solution of experimental compounds at various concentrations (0-200 µg/ml). ascorbic acid used as positive control. The absorbance of the mixture at 517 nm was measured after 30 min of incubation period. The percentage of scavenging activity was determined by comparing the result of test materials with that standard antioxidant Ascorbic acid. The radical scavenging activity was expressed as the initiation percentage and monitored as per the equation:

$$\text{Inhibition (\%)} = [(\text{control- test}) \times 100]/\text{control.}$$

The result was expressed as % inhibition by comparing value of the compounds with standard used i.e. Ascorbic acid.[15]

RESULTS AND DISCUSSION:

TABLE 4.1 FT-IR OF ETHYL-2-CYANOHEXANOATE

Peak value	Groups
2985	C-H stretch of alkane
2264	C-N stretch of cyanide
1743	C=O stretch of ester
1028-1097	C-O-C stretch of ester
1448	C-H bending of alkane

TABLE 4.2: 1H NMR OF ETHYL-2 CYANOHEXANOATE AT 400 HZ

Functional Group	Splitting	No. of proton	Experimental value
CH_3	Singlet	3H	0.91-0.95
OCH_2	Quartet	2H	4.23-4.28
CH_2	Multiplet	6H	1.3 -1.8
CH	Triplet	1H	3.4

TABLE 4.4 FT-IR OF 2-CYANOHEXANE HYDRAZIDE

Peak value	Group
2929.87	C-H stretch of alkane
2260.57	C-N stretch of cyanide
3197-34	N-H stretch of amine
1685	C=O of carbonyl
1527	N-H of bending

TABLE: 4.5 ^{13}C NMR OF 2-CYANOHEXANE HYDRAZIDE

Functional Group	Splitting	Experimental value
NH-C=O	Singlet	164
CN	Singlet	115
CH	Doublet	62.46-62.55
CH_3	Quartet	13.65
3 CH_2	Triplet	21-28

TABLE 4.6: FT-IR OF 2-(5-AMINO-1,3,4-OXADIZOL-2-YL) HEXANENITRILE

Peak value	Group
3421.72	N-H stretch of amine
2924.09	C-H stretch of alkane
2864	C-H stretch of alkane
2262-2364.73	C-N stretch of cyanide
1627	N-H bending
1458.18	C-H bending of alkane
1367	C-O-C of ether

TABLE 4.7: ^{1}H NMR OF 2-(5-AMINO-1,3,4-OXADIZOL-2-YL) HEXANENITRILE

Functional group	Splitting	No. of hydrogen	Experimental value
CH_3	Singlet	3	0.8-0.9
CH_2	Multiplet	6	1.33-1.96
CH	Triplet	1	3.3-3.8
NH_2	Singlet	2	7.0-7.5

TABLE 4.8: FT-IR OF 2-(5-THIO-1,3,4-OXADIZOL-2-YL) HEXANENITRIL

Peak value	Groups
2978.95	C-H stretch of alkane
1620.21	N-H bending
1006.84-1056.99	C-O-C stretch of ether
2881.85	C-H stretch of alkane
2214.38	CN stretch
1327-1361	C=N stretch
2716.85	SH stretch

TABLE 4.9: FT-IR OF 2-(5-AMINO-4*H*-1,2,4-TRIAZOL-3-YL)HEXANENITRILE

Peak value	Groups
3426.89	N-H stretch of amino
2925.17	C-H stretch of alkane
2863.81	C-H stretch of alkane
2214.38	CN stretch
1599.06	N-H bending
1364.70	C=N stretch

TABLE 4.10: FT-IR OF 2-(5-SULFANYL-4*H*-1,2,4-TRIAZOL-3-YL)HEXANENITRILE

Peak value	Groups
3426.89	N-H stretch of amino
2881.77	C-H stretch of alkane
2830.66	C-H stretch of alkane
2214.38	CN stretch
1599.06	N-H bending
1364.70	C=N stretch

TABLE 4.11: FT-IR OF 5-[1-(HYDROXYLAMINO)PENTYL]-1,3,4-OXADIAZOLE-2AMINE

Peak value	Groups
3062.96	NHOH
2883.58	C-H stretch of alkane
2823.79	C-H stretch of alkane
1599.06	N-H bending
1477.47	C-H bending of alkane
1364.70	C=N stretch
1159.22-1190.08	C-O-C stretch of ether

TABLE 4.12: FT-IR OF 5-[1-(HYDROXYLAMINO)PENTYL]-1,3,4-OXADIAZOLE-2-THIOL

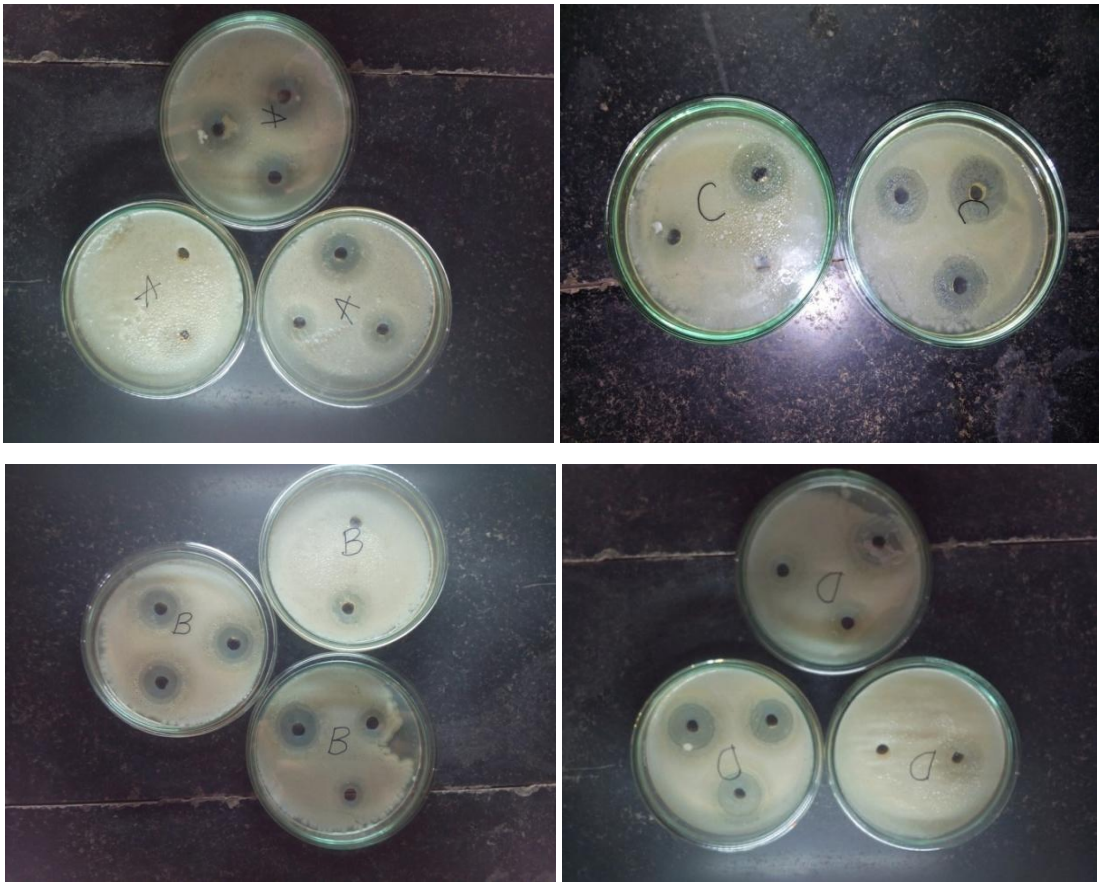
Peak value	Groups
3106.19	NHOH
2881.77	C-H stretch of alkane
2830.66	C-H stretch of alkane
2716.85	S-H stretch
1620.21	N-H bending
1477.47	C-H bending of alkane
1361.74	C=N stretch
1006.84-1166.93	C-O-C stretch of ether

Results of antibacterial screening:

In the following table, mean zone of inhibition is expressed in mm at concentration level of 200µg/ml of test compounds and standard drug.

TABLE 3: RESULTS OF ANTIBACTERIAL ACTIVITY

Compound number	Mean zone of inhibition (mm)			
	E.coli **(A)**	***B. subtilis*** **(B)**	***P. aeruginosa*** **(C)**	***S. aureus*** **(D)**
1	24	23	23	23
2	16	22	29	24
3	22	23	31	24
4	19	18	13	13
5	23	21	24	20
6	23	17	15	12
7	20	15	20	15
8	19	17	16	18
+ve control (streptomycin)	24	18	19	12
-ve control (water)	–	–	–	–



Results of Anti-oxidant activity:

The following table represents the % inhibition of synthesized compounds and standard drug ascorbic acid.

TABLE 4: % INHIBITION OF SYNTHESIZED COMPOUNDS AND STANDARD DRUG ASCORBIC ACID.

concentration	c1	c2	c3	c4	c5	std
0	0	0	0	0	0	0
10	10.45	0.69	0.083	3.72	9.81	39.75
20	29.04	2.37	1.48	15.74	12.64	92.86
40	38.88	14.84	4.24	20.6	14.11	95.25
60	39.77	19.94	4.32	20.62	31.83	95.3
80	48.28	22.1	5.94	27.09	43.06	95.38
100	52	40.73	9.047	31.06	47.45	95.46

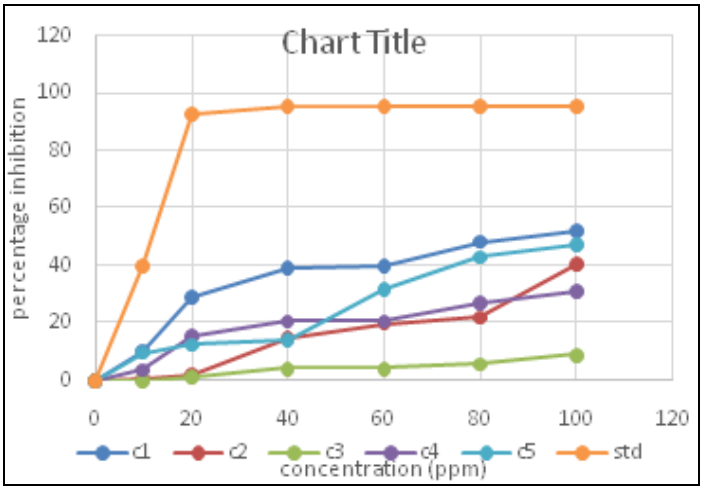


FIG. 5: % INHIBITION VS CONCENTRATIONS OF DRUGS AND STANDARD COMPOUND

DISCUSSION:

With a view to develop effective antimicrobial agents, a series of oxadiazole and triazole derivatives with a various substituent's were synthesized. The series was designed on the basis of many considerations from literature.

1. Search of novel antibiotics have mainly focused the vital targets of life cycle of bacteria like amino acyl- tRNA synthetase, fatty acid biosynthesis etc. of which PDF enzyme was focused and inhibitors of this enzyme show potent antibacterial activity.

2. PDFIs available were thoroughly studied and as per the literature, study of Peptide Deformylase Inhibitors (Actinonin) revealed certain SAR points that would exhibit potent antibacterial activity which are as follows.

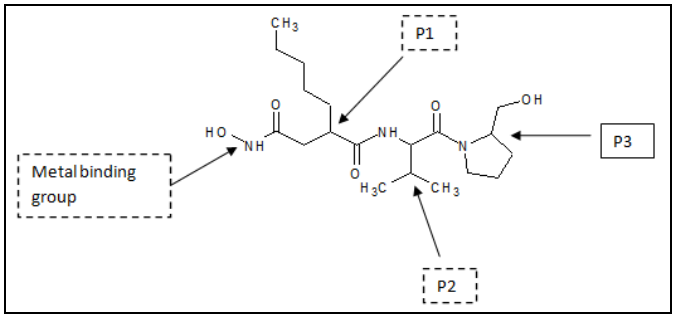


FIG .6: ACTINONIN

1. Presence of metal binding group eg. N-formyl hydroxyl amine, hydroxamic acid.

2. Methylene spacer essential for activity.

3. P1 side chain containing n-butyl group for optimal activity.

4. P2 side chain containing t-butyl group for optimal activity.

5. P3 side chain containing heterocyclic substitutes. pipridine, imidazole pyrazole,etc.[6]

Thus, taking the above points in to consideration the present work aimed at, synthesizing compounds with general structure (**Fig.7**) having promising antibacterial activity.

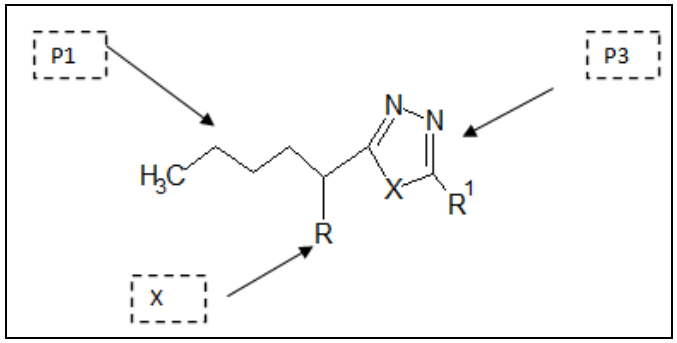


FIG.7: GENERAL STRUCTURE OF SYNTHESIZED COMPOUND.

Heterocyclic derivatives is very important for PDF inhibitory activity and hence retained as a major functional group as per the literature, substituted aliphatic chain , with hydroxylamine, so that some conclusion drawn at the end of work.

Synthesis were carried out by procedures reported in literature and compounds were confirm by IR, NMR etc. details of which have been discussed in result and experimental part.

All the compounds were screened for antibacterial activity at the concentration of 200 µg/ml. water was used as a solvent and streptomycin were used as standard drugs.

The antibacterial activity results show that all compounds showed comparable antibacterial activity. Following observation were made from results of antibacterial screening.

1. *Escherichia coli*: A compound 1 possessed highest activity against Escherichia coli and was found to be as active as streptomycin (standard drug).

2. *Bacillus subtilis*: A compounds 1,2,3,5 showed highest activity as compare to streptomycin while compound 4 showed same comparable activity as that of streptomycin.

3. *Pseudomonas aeruginosa:* A compounds 1, 2, 3, 5, 7 were found to be more active as compare to the standard drug streptomycin.

4. *Staphylococcus aureus*: All the synthesized compounds were found to exhibit better

activity against staphylococcus aureus as compare to standard drug.

From above studies it is clear that oxadiazole and Triazole ring containing hydroxyl amine and cyanide group can prove to be promising pharmacophore for antibacterial activity. These findings need to be confirming by further detail study. The compound 1 i.e. 2-(5-thio-1, 3, 4-oxadizol-2-yl) hexanenitrile has highest potent antibacterial inhibitory activity than that of standard in all four microorganisms. Where the compounds 2, 3 and 5 i.e. 2-(5-amino-1,3,4-oxadizol-2-yl) hexanenitrile, 5-[1-(hydroxylamino) pentyl]-1,3,4-oxadiazole-2-thiol,2-(5-amino - 4*H* - 1, 2, 4- triazol-3-yl) hexanenitrile respectively possess moderate activity on *Bacillus subtilis, Pseudomonas aeruginosa, Staphylococcus aureus.*

Solvent was used as negative control showed no inhibitory activity against any four microorganisms. And standard drug showed less inhibitory activity than that of all synthesized compounds against *Staphylococcus aureus*. Thus, the antibacterial screening showed that compound 1 exhibited best antibacterial activity followed by compound 3 and 5.

Antioxidant activity:

PDF inhibitors mentioned in literature are known to posse's antioxidant activity. Hence the synthetic compounds were also tested for antioxidant activity. Five compounds were screened for antioxidant activity at various concentrations from 10 to 100 µg/ml. Results shows comparable antioxidant activity as that of standard. As concentration increases percentage inhibition of the synthetic compounds also increases. Compound 1 shows good antioxidant activity than that of the other five compounds.

CONCLUSION: Bacterial infections are the major cause of morbidity and mortality throughout the world and still remain a prime area of research. Bacterial resistance towards the antibiotics has been the major concern since last few decades. With aim to develop novel antibacterial the need for synthesis of antibacterial compound is intensified. The main aim is to develop safe and affordable antibacterial agents which will hinder the spread of bacterial infections and treat them.[16-17]

The present work aimed at synthesizing novel antibacterial agents based on PDF inhibitory and antibacterial activity. Literature survey revealed that heterocyclic containing hydroxylamine derivatives play important role in reported PDF inhibitors and potent antibacterial agent. Based on this, a series of compounds containing different substituted Oxadiazole and Triazole derivatives containing hydroxylamine were successfully synthesized. The characterized compounds were taken for antibacterial as well as antioxidant activity was performed. The compounds were purified and characterized by physical constant, IR and NMR.

FUTURE SCOPE: Compounds can further taken for toxicity profile and specific PDF inhibitor activity as well as compounds possessing good antioxidant activity can be further taken for anticancer activity study.

The same work can be carried forward for specifically checking the mechanism by which the derivatives synthesized show antibacterial activity.

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