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Synthesis Of Heterocyclic Nitrogen Containing Compounds Including In Silico Toxicity And Structural Activity Relationship

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Abstract: In silico toxicology tools, steps to generate prediction models, and categories of prediction models. The purpose of this study is to provide a comprehensive overview of existing modeling methods and algorithms for toxicity prediction (element D above), with a particular (but not exclusive) emphasis on computational tools that can implement these methods (element E), and expert systems that deploy the prediction models (element F). Due to the nature of this expanding field, this study cannot provide an exhaustive overview of all the seven in silico components mentioned above. Prediction of Toxicity-associated properties of new chemicals is a big challenge. In admetSAR, probabilistic, regression as well as qualitative classification models were implemented for 'Human Ether-a-go-go-Related Gene Inhibition', 'AMES Toxicity', Carcinogenecity', 'Fish Toxicity', 'Tetrahymena Pyriformis Toxicity', 'Honey Bee Toxicity'.Among all the synthesized Pyrimidine derivatives (P1 to P5) , Pyrimidine derivatives P4 and P5 shows lesser toxicity.

Keywords: Toxicity, Antifungal activity, Antibacterial activity, Heterocyclic compounds.

1. INTRODUCTION:

When a new pharmaceutical lead compound is discovered, extensive and costly efforts are usually made to prepare a series of analogues so that better activity can be found. The metabolism of the drug is an important object of study in the medicinal chemistry and considerable efforts needs to be spent on detailed analysis of bioconversions, a new drug series undergoes. Modern analytical methods such as Mass spectrophotometery permit the identification of minute quantities of metabolites. The intellectual goal of the medicinal chemistry is to determine the mode of action (MOA) of drugs at the molecular level. The objective of medicinal chemistry is the design and production of compounds that can be used in medicine for the prevention, treatment and cure of humans or animal diseases.[1]

Five and six-membered heterocyclic nitrogen containing systems such as pyrazoles, imidazoles, triazoles, thiozolidines, pyrazolidines, piperidines, oxane pyrimidines, pyridines, thianes far are the most important in the ongoing search for more efficacious drugs in the fields of antibacterials, antifungals, antituberculars, anti-inflammatory, diuretics,

antirheumatics, and antihistaminics. Nitrogen-containing heterocyclic compounds have received considerable attention due to their wide range of pharmacological activity. Pyrimidine and their derivatives are considered as highly important class for medicinal drugs as well. As pyrimidine is a basic nucleus in DNA & RNA, it has been found to be associated with diverse biological activities. Pyridine, a heterocyclic nucleus, has played a pivotal role in the development of different medicinal agents. Current studies have demonstrated that pyridine congeners are associated with different biological activities, such as pesticidal, fungicidal and antibacterial activity. Pyrimidines and pyridines have contributed to the diverse library of compounds demonstrating selective affinity to the 5-HT7 receptor. Pyrimidines are six-member heterocyclic rings, containing two nitrogen atoms on the 1, 3 positions, as depicted as (fig 1.1).

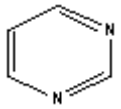


Fig.1.1

Pyrimidines are present among the three isomeric diazines. Several pyrimidines mainly cytosine (I), uracil (II) and thymine (III) have been isolated from the nucleic acid hydrolysis as shown in Fig 1.2. The nucleic acid are essential constituent of all cell and thus of all living matter cytosine is found to be present in both types of nucleic acids i.e. ribonucleic acid (RNA) and deoxyribonucleic acid (DNA) [2].

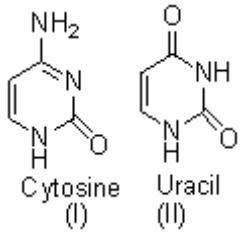


Fig.1.2

In addition to this, Pyrimidines ring is also found in Vitamin B_1, Barbituric acid (IV) and its several derivatives e.g. Veranal (V) which are used as Hypnotics (fig.1.3)[3].

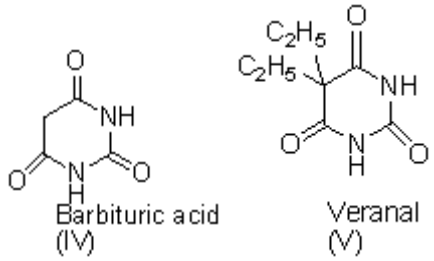


Fig.1.3

Numerous reports have appeared in the literature, that highlight chemistry and uses of pyrimidines, and their derivatives like Sulfamerazines, and Sulfamethazines. These agents are inhibitors of folic acid biosynthesis in microorganism. Pyridine is a ubiquitous chemical compound. The aromatic, monocyclic azine is utilized as a reagent or as a polar aprotic solvent. It is salient in a number of biological systems and industrial applications. Naturally occurring pyridines include the nicotinamides, a component of the vitamin B group. Pyridines are precursors to various pharmaceuticals, adhesives, agrichemicals, and synthetic pigments.A pyrimidine has many properties in common with pyridine, as the number of nitrogen atoms in the ring increases, the ring pi electrons become less energetic and electrophillic aromatic substitution gets more difficult while nucleophillic aromatic substitution gets easier [4].

1.1 Synthesis of pyrimidine: Several approaches are available for synthesis of pyrimidines and are as follows:

1.1.1 Synthesis from enamines, triethyl orthoformate: A $ZnCl_2$-catalyzed three-component coupling reaction allows the synthesis of various 4,5-disubstituted pyrimidine derivatives in a single step from functionalized enamines, triethyl orthoformate, and ammonium acetate. The procedure can be successfully applied in efficient synthesis of mono- and disubstituted pyrimidine derivatives, using methyl ketone derivatives instead of enamines (as shown in figure 4) [5].

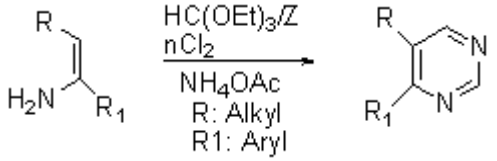


Fig.1.4

1.1.2. Synthesis from N-vinyl/aryl amides:

The direct condensation of cyanic acid derivatives with N-/aryl amides affords the corresponding C4-heteroatom substituted pyrimidines (as shown in fig 1.5) [6].

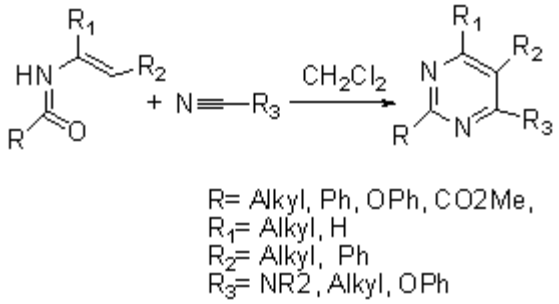


Fig. 1.5

1.1.3. Synthesis of pyrimidine from β-formyl enamides:

A novel and efficient synthesis of pyrimidine from β-formyl enamide involves samarium chloride, catalyzed cyclisation of β-formyl enamides, using urea as source of ammonia under microwave irradiation (as shown in fig.1.6) [7].

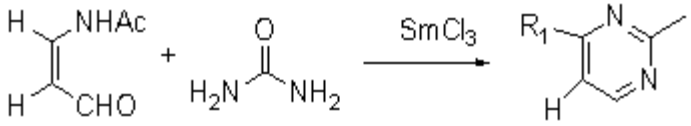


Fig.1. 6

1.1.4. Synthesis from activation of amide with 2-chloropyridine:

A single-step conversion of various N-vinyl and N-aryl amides to the corresponding pyrimidine and quinazoline derivatives, involves amide activation with 2-chloropyridine and trifluoromethanesulfonic anhydride followed by nitrile addition into the reactive intermediate and cycloisomerization (as shown in fig.1.7) [8].

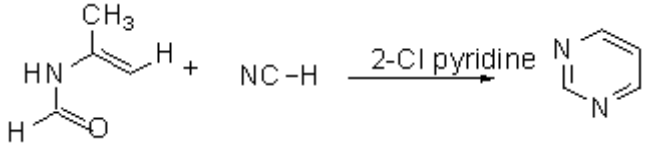


Fig.1.7

2. IN SILICO TOXICITY:

The process of new drug development requires a great deal of time and resources. The theoretical studies have a fundamental role to minimize these factors because they show indications of potential drug applications. Several authors mention that it is not enough for a compound to present high biological activity and low toxicity to be tested as a drug; it is also necessary to meet the ADME pharmacokinetics parameters (absorption, distribution,

metabolism and excretion), which determine the access and the concentration of the compound in the therapeutic target and its subsequent elimination by the organism. Many drug candidates can be discarded for presenting unfavorable pharmacokinetics. The ADME parameters can be verified by in silico studies based on calculated physico-chemical standards. These standards emphasize lipophilicity, water solubility, molecule size and flexibility.

Prior analysis of these parameters drastically reduces the necessary time for the pharmacokinetic study in the clinical phase. Many studies relating physico-chemical standards with ADME parameters were performed in the 90s. The most widespread study was from the pioneer. *Lipinski et al.*, which presented a relationship between pharmacokinetics and physico-chemical parameters. Acute toxicity is defined as the unwanted effect (s) that occurs either immediately or at a short time interval after a single or multiple administration of such substance within 24 hours. The unwanted (or adverse) effect is any effect that produces functional impairments in organs and/or biochemical lesions, which could alter the functioning of the organism in general or individual organs.Studies of acute toxicity however tends to establish the dose-dependent unwanted (or adverse) effect(s), which may take place and this includes all information that is important in the assessment of acute toxicity including mortality. The assessment of the lethal dose (LD50)(the dose that kills 50% of test animals population) has now been used as a major parameter in measuring acute toxicity and also as an initial procedure for general screening of chemical and pharmacological agents for toxicity. Apart from mortality, other biological effects and the time of onset, duration and degree of recovery on survived animals, are also important in acute toxicity evaluation. Acute toxicity study solely gives information about LD_{50}, therapeutic index and the degree of safety of a pharmacological agent. The toxicity assessment of pharmacological agents is a very important procedure that is usually carried-out before they are allowed to enter the market for sale. Conversely, different methods have been developed and adopted for acute toxicity testing. However, most of these methods have their short-comings and is now important to develop a better method, which may require the use of fewer animals if possible. The aim of this paper is to introduce a new method for testing acute toxicity, which if adopted, should produce more accurate and reproducible results using few animals.

Toxicity is a measure of any undesirable or adverse effect of chemicals. Specific types of these adverse effects are called toxicity endpoints, such as carcinogenicity or genotoxicity, and can be quantitative (e.g., LD_{50}: lethal dose to 50% of tested individuals) or qualitative, such as binary (e.g., toxic or non-toxic) or ordinary (e.g., low, moderate, or high toxicity) Toxicity tests aim to identify harmful effects caused by substances on humans, animals, plants, or the environment through acute-exposure (single dose) or multiple-exposure (multiple doses). Several factors determine the toxicity of chemicals, such as route of exposure (e.g., oral, dermal, inhalation), dose (amount of the chemical), frequency of exposure (e.g., single versus multiple exposure), duration of exposure (e.g., 96 h), ADME properties (absorption, distribution, metabolism, and excretion/elimination), biological properties (e.g., age, gender), and chemical properties.

Animal models have been used for a long time for toxicity testing. However, *in vitro* toxicity tests became plausible due to the advances in high throughput screening. *In silico* toxicology (computational toxicology) is one type of toxicity assessment that uses computational resources (i.e., methods, algorithms, software, data, etc.) to organize, analyze, model, simulate, visualize, or predict toxicity of chemicals. It is intertwined with *in silico* pharmacology, which uses information from computational tools to analyze beneficial or adverse effects of drugs for therapeutic purposes.

Computational methods aim to complement *in vitro* and *in vivo* toxicity tests to potentially minimize the need for animal testing, reduce the cost and time of toxicity tests, and improve toxicity prediction and safety assessment. In addition, computational methods have a unique advantage of being able to estimate chemicals for toxicity even before they are synthesized. *In silico* toxicology encompasses a wide variety of computational tools [9].

3. METHODOLOGY FOR TOXICITY ESTIMATION:

In present study, software named 'admetSAR' was implemented for estimation of toxicities of designed compounds. This software is a comprehensive tool for assessment of chemical ADMET properties. The admetSAR is freely accessible at http://lmmd.ecust.edu.cn/admetsar1. In total, the admetSAR database includes more than 210000 annotated measurements of 95629 unique compounds. These unique compounds belong to FDA approved and experimental drugs, pesticides, environmental agents, and industrial chemicals. It includes the data fields of each compound with three types of informstion: the general information (IUPAC name, formula, CASRN, common name, DrugBank ID, SMILES), the physicochemical properties (include MW, Log P, the number of hydrogen bond acceptors and donors, and TopoPSA), and the ADMET associated profiles. Software admetSAR provides more than 45 kinds of ADMET-associated properties. In this present study, Toxicity was estimated through two methods: (i) Qualitative Prediction & Probability and (ii) Predicted Activity through model. Qualitative Prediction & Probability based methods was implemented for 'Human Ether-a-go-go-Related Gene Inhibition', 'AMES Toxicity', Carcinogenecity', 'Fish Toxicity', 'Tetrahymena Pyriformis Toxicity', 'Honey Bee Toxicity', 'Biodegradation', and 'Acute Oral Toxicity. Predicted Activity through model based method was implemented for 'Rat Acute Toxicity', 'Fish Toxicity' and 'Tetrahymena Pyriformis Toxicity'.

Input for software:

AdmetSAR consider chemical structure input as SMILES and process it through pre-inbuilt QSAR models for estimation of toxicity associated parameters.

Calculation of Physicochemical Property:

The software inbuilt models require molecular physicochemical properties for computationally filtering of toxicity potentials. Software 'admetSAR' calculates five classic physicochemical properties, namely the number of hydrogen bond acceptors and donors, LogP, topological polar surface area (TopoPSA), and molecular weight (MW) for calculation of toxicity values through various models.

4. COMPUTATIONAL MODELS USED FOR TOXICITY CALCULATION:

Prediction of Toxicity-associated properties of new chemicals is a big challenge. In admetSAR, probabilistic, regression as well as qualitative classification models were implemented for 'Human Ether-a-go-go-Related Gene Inhibition', 'AMES Toxicity', Carcinogenecity', 'Fish Toxicity', 'Tetrahymena Pyriformis Toxicity', 'Honey Bee Toxicity', 'Biodegradation', and 'Acute Oral Toxicity. admetSAR implements validated QSAR models based on Support vector machine (SVM) based classification and regression methods. For prediction of toxicity parameters, structure of compounds was used in SMILES format.

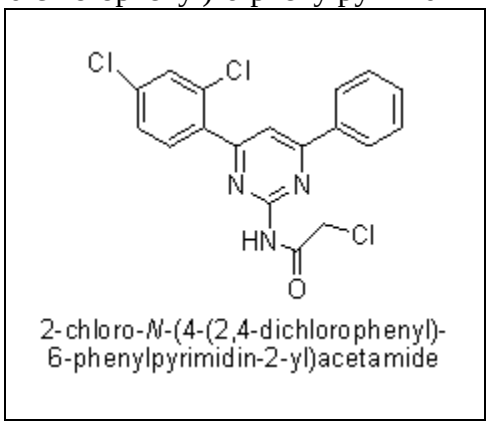
Toxicity screening was performed for: Drug Induced Toxicity, Genomic Toxicity, Aquatic & Terrestrial Toxicity, Reproductive Toxicity, Environmental Factor. These toxicity values were adapted from literature support [10]. (PubMed ID: 23092397). The new design molecules also tested for their possible toxicity against following parameters:

- Human Ether-a-go-go-Related Gene Inhibition: The Human Ether-a-go-go-related Gene (hERG) Potassium Channel represents an Unusual Target for Protease-mediated

Damage. This is responsible for cardiac arrhythmias and sudden death (PubMed ID: 16787254).

- AMES toxicity: The Ames test (Salmonella typhimurium reverse mutation assay) is a bacterial short-term test for identification of carcinogens using mutagenicity in bacteria as an endpoint (J.G. Hengstler, F. Oesch, in Encyclopedia of Genetics, 2001).
- Carcinogenesis: Test for causing cancer due to the molecule
- Fish toxicity
- Tetrahymena toxicity
- Honey Bee toxicity
- Biodegradation
- Acute oral toxicity
- Rat acute toxicity : The complete table about toxicity screening of (P1-P5) is available as following. The Pyrimidine derivatives can be further estimated for their utility for further study.

2-chloro-*N*-(4-(2,4-dichlorophenyl)-6-phenylpyrimidin-2-yl)acetamide(P1):

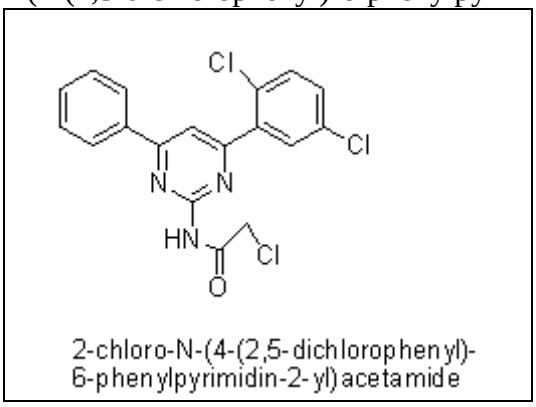


P1: Toxicity (Qualitative Prediction & Probability)		
Human Ether-a-go-go-Related Gene Inhibition	Weak inhibitor	0.9459
	Non-inhibitor	0.8279
AMES Toxicity	Non AMES toxic	0.8097
Carcinogens	Non-carcinogens	0.8768
Fish Toxicity	High FHMT	0.8322
Tetrahymena Pyriformis Toxicity	High TPT	0.9678
Honey Bee Toxicity	Low HBT	0.9275
Biodegradation	Not ready biodegradable	1.0000
Acute Oral Toxicity	III	0.7335

Carcinogenicity (Three-class)	Non-required	0.6821

Toxicity (Predicted Activity through model)		
Rat Acute Toxicity	1.8187	LD50, mol/kg
Fish Toxicity	1.1423	pLC50, mg/L
Tetrahymena Pyriformis Toxicity	1.1746	pIGC50, ug/L

2-chloro-*N*-(4-(2,5-dichlorophenyl)-6-phenylpyrimidin-2-yl)acetamide (P2):

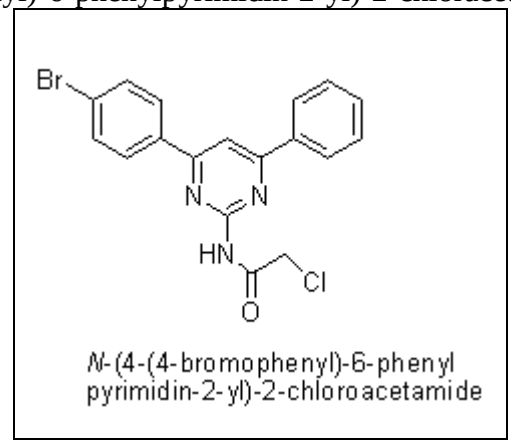


P2: Toxicity (Qualitative Prediction & Probability)		
Human Ether-a-go-go-Related Gene Inhibition	Weak inhibitor	0.9459
	Non-inhibitor	0.8279
AMES Toxicity	Non AMES toxic	0.8097
Carcinogens	Non-carcinogens	0.8768
Fish Toxicity	High FHMT	0.8322
Tetrahymena Pyriformis Toxicity	High TPT	0.9678
Honey Bee Toxicity	Low HBT	0.9275
Biodegradation	Not ready biodegradable	1.0000
Acute Oral Toxicity	III	0.7335
Carcinogenicity (Three-class)	Non-required	0.6821

Toxicity (Predicted Activity through model)		
Rat Acute Toxicity	1.8187	LD50, mol/kg
Fish Toxicity	1.1423	pLC50, mg/L

Tetrahymena Pyriformis Toxicity	1.1746	pIGC50, ug/L

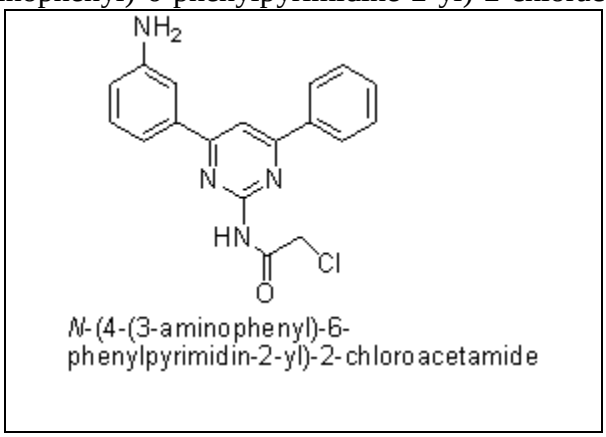
N-(4-(4-bromophenyl)-6-phenylpyrimidin-2-yl)-2-chloracetamide (P3):



P3: Toxicity (Qualitative Prediction & Probability)		
Human Ether-a-go-go-Related Gene Inhibition	Weak inhibitor	0.9449
	Non-inhibitor	0.8359
AMES Toxicity	Non AMES toxic	0.8024
Carcinogens	Non-carcinogens	0.8766
Fish Toxicity	High FHMT	0.8046
Tetrahymena Pyriformis Toxicity	High TPT	0.9934
Honey Bee Toxicity	Low HBT	0.8942
Biodegradation	Not ready biodegradable	1.0000
Acute Oral Toxicity	III	0.6906
Carcinogenicity (Three-class)	Non-required	0.5920

Toxicity (Predicted Activity through model)		
Rat Acute Toxicity	1.9770	LD50, mol/kg
Fish Toxicity	1.3860	pLC50, mg/L
Tetrahymena Pyriformis Toxicity	1.2935	pIGC50, ug/L

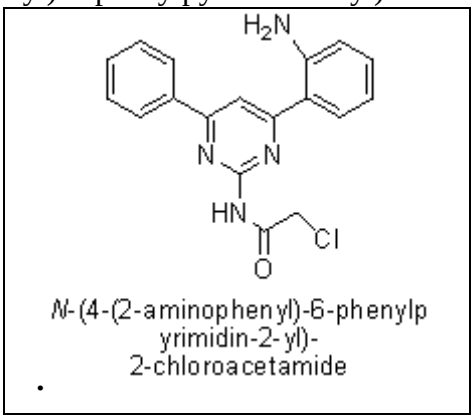
N-(4-(3-aminophenyl)-6-phenylpyrimidine-2-yl)-2-chloracetamide (P4):



P4: Toxicity (Qualitative Prediction & Probability)		
Human Ether-a-go-go-Related Gene Inhibition	Weak inhibitor	0.9861
	Non-inhibitor	0.7675
AMES Toxicity	Non AMES toxic	0.6509
Carcinogens	Non-carcinogens	0.8498
Fish Toxicity	High FHMT	0.5856
Tetrahymena Pyriformis Toxicity	High TPT	0.8870
Honey Bee Toxicity	Low HBT	0.8997
Biodegradation	Not ready biodegradable	1.0000
Acute Oral Toxicity	III	0.6434
Carcinogenicity (Three-class)	Non-required	0.5918

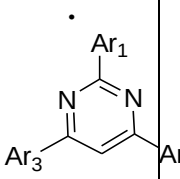
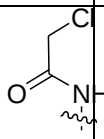
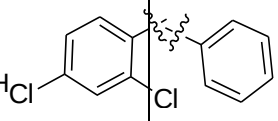
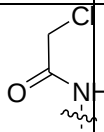
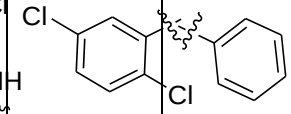
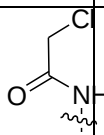
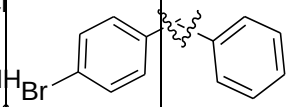
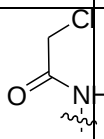
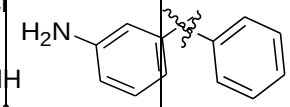
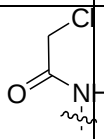
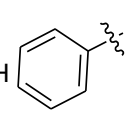
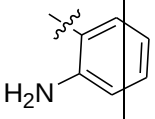
Toxicity (Predicted Activity through model)		
Rat Acute Toxicity	2.1034	LD50, mol/kg
Fish Toxicity	1.6855	pLC50, mg/L
Tetrahymena Pyriformis Toxicity	0.5689	pIGC50, ug/L

N-4-(2-aminophenyl)-6-phenylpyimidine-2-yl)-2-chloracetamide (P5):



P5: Toxicity (Qualitative Prediction & Probability)		
Human Ether-a-go-go-Related Gene Inhibition	Weak inhibitor	0.9864
	Non-inhibitor	0.7266
AMES Toxicity	Non AMES toxic	0.6086
Carcinogens	Non-carcinogens	0.8529
Fish Toxicity	High FHMT	0.6570
Tetrahymena Pyriformis Toxicity	High TPT	0.8345
Honey Bee Toxicity	Low HBT	0.9253
Biodegradation	Not ready biodegradable	1.0000
Acute Oral Toxicity	III	0.5720
Carcinogenicity (Three-class)	Non-required	0.6607
Toxicity (Predicted Activity through model)		
Rat Acute Toxicity	2.1951	LD50, mol/kg
Fish Toxicity	1.5257	pLC50, mg/L
Tetrahymena Pyriformis Toxicity	0.7351	pIGC50, ug/L

1. Generalized Structure Activity Relationship:

	**Ar_1**	**Ar_2**	**Ar_3**	***Aspergillus niger*IC$_{50}$µg/ml**	***Penicillium chrysogenum* MIC µg/ml**	***Pseudomonas aeruginosa* IC$_{50}$ µg/ml**	***Staphylococcus aureus* IC$_{50}$ µg/ml**
P1				385.47	273.71	2.06	61.22
P2				385.47	273.71	2.06	61.22
P3				385.47	273.71	2.06	61.22
P4				311.02	141.00	1.13	61.22
P5				311.02	141.00	1.13	61.22

5. RESULT AND DISCUSSION:

Substituted Pyrimidine derivatives have received considerable attention during last two decades as they are endowed with variety of biological activities. As Pyrimidine derivatives are well established in literature as important biologically active heterocyclic compounds. These derivatives are the subject of many research studies due to their widespread potential biological activities. A considerable amount of research activity is directed towards a potent, more specific and less toxic compounds. We had planned to incorporate different substitutions on parent molecule in our synthesized series of Pyrimidine derivatives and evaluate them for different biological activities to search the potent compounds. Aim of the proposed research work was to synthesize novel Pyrimidine derivatives and evaluation of their biological activities (antibacterial and antifungal activity) and its Toxicity. The purpose of was to examine whether molecular modification might result in detection of new potential drugsin various biological activities. The Pyrimidine derivatives were derivatives prepared by the Clasein Schmidt condensation of acetophenone with various substitute benzaldehydes in the presence of methanol and NaOH, Initially the chalcone was prepared by the reaction (IS1-5). The cyclization of chalcone intermediate (IS1-30) to yield Intermediate Pyrimidine derivatives- second (S1-S5) was effected with guanidine nitrate.The reaction of intermediate with chloroacetyl chloride and benzene formation of substituted Pyrimidine derivatives. (**P1-5**).The chemical structures of the synthesized compounds were established by the

determination of their physicochemical and spectroscopic data (FT-IR, ^{1}HNMR and Mass spectroscopy). The IR spectrum of chalcone derivative (IS1) showed the characteristics band at 1690 cm^{-1} which indicates the presence of a C=O group and characteristics band at 3106 and 1517 cm^{-1} presence of C-H and C=C group in aromatic ring respectively, 2986-2965 cm^{-1}, for CH_3 (IS1). The existence of Ar-NO_2 group in chalcone derivatives (IS8) stretches in the scale of 1314 cm^{-1} and characteristics bands at 2906 cm^{-1}, Ar-OCH_3, group in chalcone derivatives shows band at 1160 cm^{-1} to 1180 cm^{-1}. Intermediate Pyrimidine derivatives (S1-30) showed the characteristics band at 3105-1517 cm^{-1} for the presence of C-H and C=C group in aromatic ring respectively and characteristics bands at 3371, 1350 cm^{-1} for indicated the presence of C-NH_2, of pyrimidine and C-N sym of aromatic group.
Substituted Pyrimidine derivatives (P1-P30) showed appearance of IR stretching around 1648 cm^{-1} in the spectral data for the presence of C-H and C=C group in the aromatic ring repectively and characteristics band at 1688, 2928, 761, 1349 for presence of (NH-C=O), of Pyrimidine, C-H str, CH_2 ,C-Cl. The structure of the chalcone derivatives and its cyclized products were further confirmed by the ^{1}H-NMR. The ^{1}H-NMR of Chalcone derivatives showed two doublets at 7.59 ppm and 8.06 ppm indicating that the CH=CH group in the enone linkage is in a transformation. The ^{1}H-NMR spectrum of Pyrimidine derivatives Intermediate (S1-30) showed a sharp singlet at 7.86 ppm due to CH=CH group which confirmed the cyclization of the chalcone into a Pyrimidine derivatives showed the multiplet signals between 7.54-8.93 ppm in ^{1}HNMR spectra which is indicative of aromatic proton and also exhibited sharp singlet at 6.8 of C-H of Pyrimidine, 8.5 of NH, 3.66 of CH_2, respectively confirmed the conversion of the Pyrimidine to Pyrimidine acetamide derivatives. The appearance of IR strectching around 1545-1698 cm^{-1}, 2909-3452 cm^{-1}, 1548-1601 cm^{-1}.specified the existence of C=N group of Pyrimidne ring, C-H and C=C group respectively. The IR absorption band in the scale of 1108-1088 cm^{-1} corresponds to the C-Br stretching of 617 cm^{-1}.Further the existence of and halogen group in the Pyrimidine derivatives is indicated by the existence of Ar-Cl strectching vibrations 761-700 cm^{-1}.NH stretching of all the Pyrimidine derivatives shows at the range of (P1-30) of 3770-3335 cm^{-1}, C=O stretching of all the Pyrimidine derivatives shows at the range of 1706-1553 cm^{-1},The ^{1}HNMR spectrum (**P1-P5**) showed multiplet signals between 6.2-8.7 ppm of aromatic proton, the pyrimidine derivatives.All Pyrimidine derivatives, due to existence of CH_2 group showed doublet at 2.5 - 3.38 ppm, NH group at 13.29-9.13 ppm. All Pyrimidine derivatives having CH of Pyrimidine ring shows singlet at 7.7-6.8 and Pyrimidine derivatives having amino group **(P4** and **P5)** showed doublet at 6.8-4.37 ppm . 2,4-dichlorophenyl substituent shows excellent activity might be due to the attachment of chloro group at 2 and 4 position of phenyl group in Pyrimidine moiety. This result suggests that the introduction of halogen substituent increased hydrophobicity of the synthesized compound. Among all the synthesized Pyrimidine derivatives (**P1** to **P5**) , Pyrimidine derivatives **P4** and **P5** shows lesser toxicity**.**

6. CONCLUSION:

Purines and pyrimidines are simply fused pyrimidines which by themselves are active from biological point of view and for some naturally occurring substrates they are very essential components such as nucleic acids. Pyrimethamine and Trimethoprim are some of the diamino pyrimidines which are strong anti malarial medicines and along with sulphonamides they are used in combination for better outcomes. This is also an antibacteriostatic which is potent. The pyrimidine moiety containing chemotherapeutic includes one of the most important suphadiazine. On the other hand, for the treatment of tuberculosis the nitrogen containing a lot of heterocycles are used such as Pyrazinamide and Clofazimine, Isoniazid etc. The structural precedence is offered by these compounds which along with analogues of

pyrimidine as well as chalcone can end up in the generation of new therapeutics for tuberculosis. On the development of newer six member heterocyclic derivatives like pyrimidine and pyridine having antimycobacterial properties is the main focus of our research. The new and improved artificial applicability as well as action of these heterocycles biologically are considered helpful for the pharmacists to plan and put into practice better and improved ways to find out and discover new series of drugs.

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