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SCENARIO OF SYNTHESIS AND BIOLOGICAL ACTIVITIES OF ARYL/ HETEROARYL-AZO-PYRIMIDINE DERIVATIVES: A REVIEW

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ABSTRACT:
Azo-heterocyclic compounds correlated with many biological activities. N-heterocyclic based azo-Pyrimidine compounds have been reported in different journals. This was challenging job for researcher for creating the distinct synthetic methods of pyrimidine azo compounds by use the common laboratory reagents and apparatus. Eventually, azo-imine(-N=N-) group in heterocyclic azo compounds is importantly responsible for various types of biological activities in different aspect. Therefore, I have been collected all the pyrimidine azo compound from literature and also rummage around their activities such as anti-bacterial, anti-fungal, anti-HIV, anti-cancer and little-bit mushroom tyrosine inhibition effect together for creating a unit frame. Mainly, azo pyrimidine possesses many high electronegative nitrogen atoms which regulate and reflect their extraordinary activities within the biological molecules.

KEYWORDS: Azo-pyrimidine; azo-imine; anti-bacterial; anti-fungal; anti-cancer activity.

INTRODUCTION:

Pyrimidine is the six-member heterocycles with two nitrogen atoms in it that have present into three nucleic acids (Cytosine, Thymine and Uracil) which are the main component of DNA and RNA. Thus natural derivatives of pyrimidine have important pharmacological and potent physicochemical properties[i,ii]. Pyrimidine and its derivatives are extremely observed as significant bioactive compounds in medicinal chemistry[iii,iv] due to their having unique clinical applications. Synthesis of pyrimidine drugs has been demandingly explored in recent years. The synthetic pyrimidine derivatives are highly research motivated for showing their diverse biological activities such as: cytotoxicity[v-vii],antifungal[viii,ix],antibacterial[x-xii], antiviral[xiii-xv], antimicrobial[xvi-xviii]. Besides the biological role of pyrimidine derivatives it have been developed and used as chemotherapeutic agents[xix-xxi]. It have been search as wide clinical application as various resistant agents: infective[xxii,xxiii], anti-insecticidal[xxiv-xxv], anti-hypoglycemic, hyperglycemic[xxvi-xxviii], hypolipidemic and hyperlipidemic[xxix-xxxi]. In addition it extends their usefulness activity as diureaticproperties[xxxii,xxxiii]. Some pyrimidine derivatives are highly potent drugs against anti-HIV[xxxiv-xxxvi] and cancer detection[xxxvii] and also remarkable

as anticancer agents[xxxviii-xl]. Also metal pyrimidine derivatives complexes have numerous biological activities[xli]. Heterocyclic azo compounds are well recognizes for their used in medicine purposes as anticancer and antibacterial[xlii,xliii], antifungal[xliv,xlv], antitumor[xlvi] and anti-tuberculosis[xlvii]. The connection of –N=N- bond in between aryl/heteroaryl substituted-amine and pyrimidine derivatives leads to enhancing the biological activities of simple pyrimidine derivatives. Also N-heterocycle i.e building unit of nucleic acid, pyrimidine, present in synthesized azo compounds that may influence several physiological activities towards different microorganism. Bioactivity of pyrimidine azo compounds relating in enormous anti-bacterial, anti-cancer, anti-HIV and anti-fungal activities that are reported in literature. Thus the azo pyrimidine compounds are one of the important classes in chemistry, so several studies are needed and their metal complexes which are reported in journal literature.

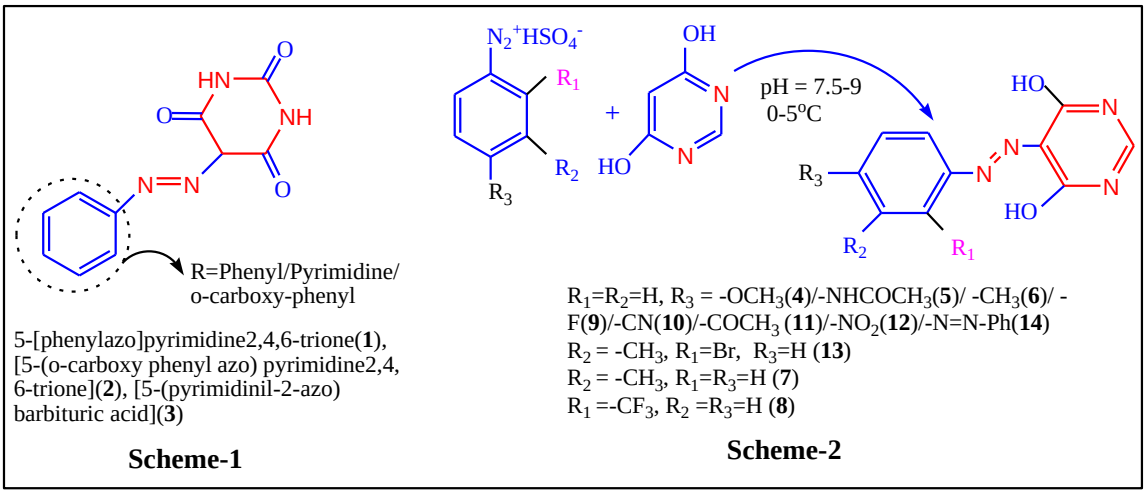
SYNTHESIS OF PYRIMIDINE BASED AZO COMPOUNDS (1-72):

1. 5-(Phenyl/Pyrimidinil/o-Carboxyphenyl)-azo-pyrimidine-2,4,6-trione(1-3):

Synthesis of some pyrimidine / barbituric acid based azo compounds(**1-3**) (**Scheme-1**) and their metal complexes produced about in usual and conventional methods. These azo compounds are prepared, firstly diazotized salt by diazotization of 2-aminopyrimidine / anthranilic acid / aniline in presence of freshly prepared HNO_2 medium then diazotized salt was coupling with alkaline solution of barbituric acid to form azo compound. Cu(II), Ni(II) and Co(II)-metal ions form metal-complexes(**A**$_{1\text{-}3}$, **B**$_{1\text{-}3}$, &**C**$_{1\text{-}3}$) by the reaction of ethanolic solution of azo ligands(**1-3**) stirring in microwave within few seconds[xlviii].

2. Synthesis of 5-aryl-azo-4,6-dihydroxy-pyrimidine(4-14):

The author reported the synthesis of some 5-aryl-azo-4,6-dihydroxypyrimidine compounds(**4-14**), firstly diazotization process carried out by dissolving substituted aromatic amine in the mixture of glacial acetic acid and propionic acid which react with nitrosyl sulfate at low temperature. Then diazotized salt solutions are mixed with the alkaline solution (dil.NaOH) of 4,6-dihydroxypyrimidine at low temperature and produced crude azo-pyrimidine derivatives. After that pure solid 5-aryl-azo-4,6-dihydroxy-pyrimidines are obtained by addition of 10% HCl solution(pH=3-4) into the crude product[xlix]. (**Scheme-2**)



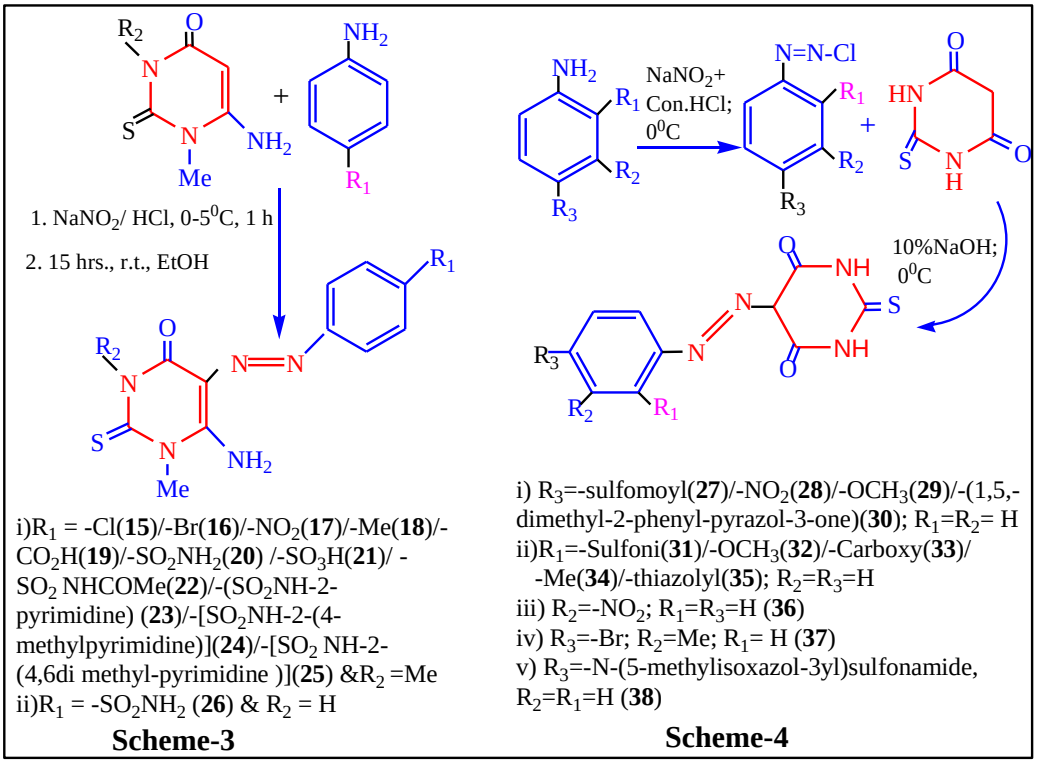
3. Synthesis of 6-amino-5-(aryldiazenyl)-N^1,N^3-di-methyl-2-thioxo-pyrimidin-4-one(15-26):

Synthesis of the 6-amino-5-(aryldiazenyl)-N^1,N^3-dimethyl-2-thioxo-pyrimidin-4-one compounds(**15-25**) are happened by the coupling reaction of diazotized salt and pyrimidine derivatives in ethanol (6-amino-N^1,N^3-dimethyl-2-thioxo-pyrimidin-4-one(i)) and the reaction mixture kept for 15h at 0°-5°C temperature. Whereas diazotization reaction occurred by the reaction of 4-substituted aniline with the $NaNO_2$ and dil.HCl at 0-5°C. Another azo

compound(**26**) was synthesized by reaction of 6-amino-N^1-methyl-2-thioxo-pyrimidin-4-one(ii) with diazotized product of 4-sulfonylactamido-aniline in the presence of suitable reagents mention previously. Platinum metal complexes(**$D_{15,19,20,21}$**) has been synthesized by refluxing the methanolic solution of above ligands(**15,19,20,21**) and $PtCl_2$ in 1:1 molar ratio. Again ruthenium metal complex(**E_{15}**) is synthesized by stirring the MeOH solution of $RuCl_3.3H_2O$ and ligand(**15**) in 1:1 molar ratio[l].(**Scheme-3**)

4. Synthesis of 5-(2/3/4-substitutedphenyldiazenyl)-2-thiooxo-dihy-dropyrimidine-4,6 (1H,3H)dione(27-38):

Diazotization of 2,3,4-substituted phenylamine has been done by simple reaction of substituted aniline, $NaNO_2$ and Con.HCl under cold temperature condition. Then pure and pyrimidine characteristic compound of 5-(2/3/4-substitutedphenyldiazenyl)-2-thiooxodi-hydropyrimidine-4,6-(1H,3H)dione are established.[li](**Scheme-4**)



i)R_1 = -Cl(**15**)/-Br(**16**)/-NO_2(**17**)/-Me(**18**)/-CO_2H(**19**)/-SO_2NH_2(**20**) /-SO_3H(**21**)/ -SO_2 NHCOMe(**22**)/-(SO_2NH-2-pyrimidine) (**23**)/-[SO_2NH-2-(4-methylpyrimidine)](**24**)/-[SO_2 NH-2-(4,6di methyl-pyrimidine)](**25**) &R_2 =Me
ii)R_1 = -SO_2NH_2 (**26**) & R_2 = H

Scheme-3

i) R_3=-sulfomoyl(**27**)/-NO_2(**28**)/-OCH_3(**29**)/-(1,5,-dimethyl-2-phenyl-pyrazol-3-one)(**30**); R_1=R_2= H
ii)R_1=-Sulfoni(**31**)/-OCH_3(**32**)/-Carboxy(**33**)/ -Me(**34**)/-thiazolyl(**35**); R_2=R_3=H
iii) R_2=-NO_2; R_1=R_3=H (**36**)
iv) R_3=-Br; R_2=Me; R_1= H (**37**)
v) R_3=-N-(5-methylisoxazol-3yl)sulfonamide, R_2=R_1=H (**38**)

Scheme-4

5. Synthesis of 5-[(3,4-Dimethoxy/Dichloro-phenyl)-hydrazono]-pyrimidine-2,4,6-trione (39,40) and 5-[(3,4-Dimethoxy/Dichlorophenyl)-hydrazono]-2-thioxo-dihydro-pyrimidi-ne-4,6-dione(41,42):

Oxo pyrimidine based azo compounds(**39-42**) is distinctly synthesized by the chemical reaction of aniline with the aqueous solution of $NaNO_2$ and HCl (10%). Then the diazonium salt is mixed with constant stirring with the diethyl malonate in presence of 50% aqueous ethanolic solution of sodium acetate. After that products of 2-[3,4-dimethoxy/dicholoro-phenyl)-hydrazono]maloic acid, diethyl ester and sodium ethoxide solution mixture are poured into urea / thiourea solution where the resulted mixture are heated under reflux condition for 4hrs. Ultimately oxo-pyrimidine-azo compounds are formed by addition of water and HCl solution.[lii-liv](**39-42**)(**Scheme-5**)

6. Synthesis of Pyrazolopyrimidine derivatives(43a,b-47a,b and 48b):

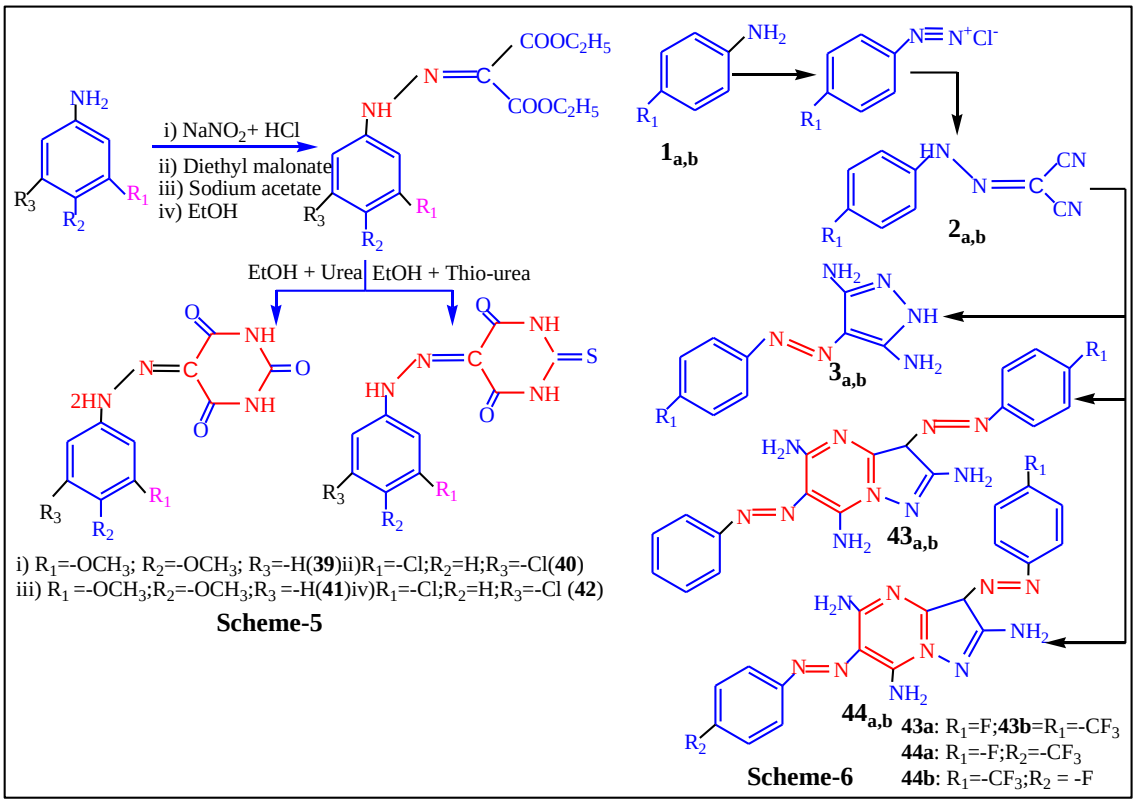
Various type of pyrazolo-pyrimidine derivatives are synthesized by the author in the following steps where using different reagents as well as changing reaction path.

Synthesis of 2-[(4-fluoro/trifluoro-methyl)arylazo]malononitrile(**2a,b**): Aqueous solution of $NaNO_2$ mixes with HCl solution of fluoro / trifluoromethyl aniline at low temperature to

produce diazonium salt. Then the diazonium salt is added to a mixture of malononitrile, sodium acetate and aqueous ethanol then a specific solid product of 2-arylazomalononitrile is obtained by purification.

Synthesis of 4-aryl-azo-3,5-diaminopyrazole(**3a,b**): The mixture of ethanolic solution of 2-aryl-azomalononitrile, hydrazine hydrate and pyridine is heated under reflux condition during 2hrs then solid product of 4-aryl-azo-3,5-diaminopyrazole is collected and purified.[lv]

Synthesis of 3,6-bis[(4-fluoro/trifluoro)phenylazo]-2,5,7-triamino-pyrazolo[1,5-a]pyrimidine (**43a,b**): Sonicated the mixture of ethanolic solution of 4-aryl-azo-3,5-diaminopyrazole, 2-arylazomalononitrile and pyridine at room temperature. After 1hr completion of reaction a symmetrical compound is comes and then purified(**43a,b**).



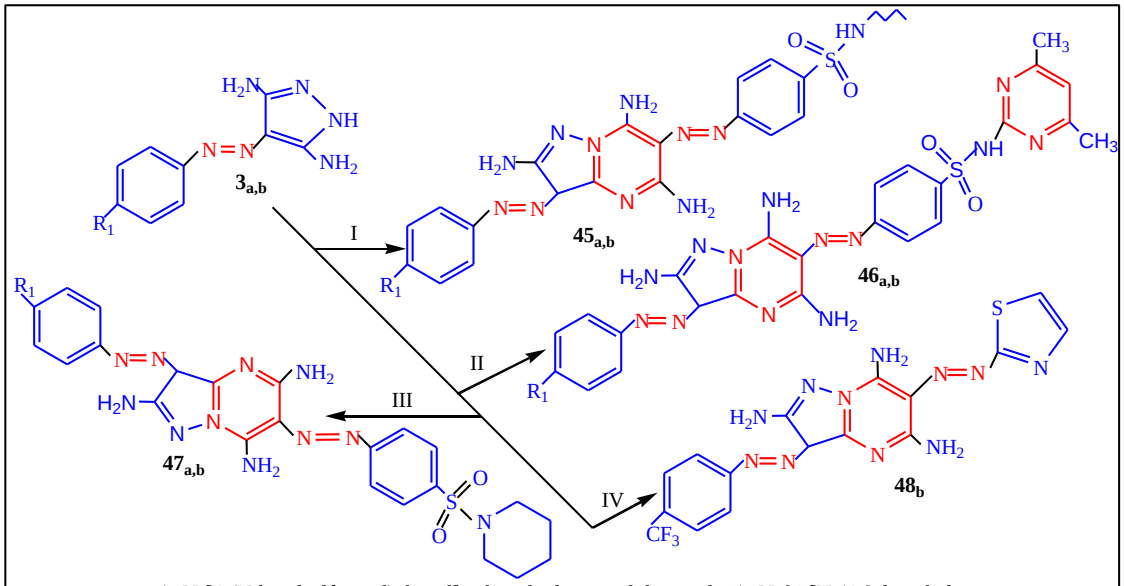
Synthesis of 6-[(4-trifluoromethyl/fluoro)phenylazo]-3-[(4-fluoro/trifluoromethyl)phenylazo -2,5,7-triaminopyrazolo[1,5-a]pyrimidine(**44a,b**): Compound **3a,b** and **2a,b** in ethanol, and pyrimidine are mixes and heated under microwave irradiation around 140°C. After 2min. the whole reaction solution is cooled at room temperature and solid precipitate(**44a,b**) is collected by purification.(**Scheme-6**)

Synthesis of N-butyl-4-{[2,5,7-triamino-3-(4-fluoro/trifluoromethyl)phenylazopyrazolo[1,5-a]pyrimidine-6-yl]azo}benzenesulfonamide(**45a,b**): Mixes the ethanolic solution of 3a,b and N-[4-(N-butylsulfamoyl)phenyl]carbonhydrazonoyldicyanide and are kept the whole mixture under the microwave around 140°C for 5 minute. A solid compound(**45a,b**) is formed at the end of the reaction after cooled and purification.

Synthesis of N-(4,6-Dimethylpyrimidin-2-yl)-4{[2,5,7-triamino-3-(4-fluoro/trifluoro-methyl-phenylazo)pyrazolo[1,5-pyrimidin-6-yl]azo}benzenesulfonamide(**46a,b**): In this step whole reaction has been occurred by mixing the ethanolic solution of **3a,b** and N-{4-[N-4,6-di-methyl-pyrimidin-2-yl]sulfamoyl]phenyl}carbonhydrazonyldicyanide compounds and kept inside the microwave at 140°C for 3min. Then the solution mixture is cooled at normal temperature and obtained pure compound after crystallization.

Synthesis of 3-[(4-fluoro/trifluoromethylphenylazo]-6-[4-(pyrimidine-1-ylsulfomyl)phenyl-azo]2,5,7-triaminopyrazolo[1,5-a]pyrimidine(**47a,b**): Compound **3a,b** and N-4-(piperidin-1-ylsulfonyl)phenyl]carbohydrazonoyldicyanide mixed and it is added into a ethanolic solution of pyridine and been heated the mixture around 140°C under microwave. A solid precipitate is obtained after 3-7min. and then purified.

Synthesis of 6-(thiazol-2-yldiazenyl)-3-(4-(trifluoromethyl)phenyl-azo)-2,5,7-triaminopyraz-olo[1,5-a]pyrimidine(**48b**): Compound 3,5-diamino-4-[4-(trifluoromethyl)phenylazo]1H-pyra-zolo and compound N-(triazol-2-yl)carbonohydrazonoyldicyanide are well mixes together in ethanol solution and then pyridine is added to it and last of all the solution mixture is to heated under microwave at 140°C. After 8min., a solid precipitate is collected and purified[xvi]. (**Scheme-7**)



i)=N-[4-(N-butylsulfamoyl)phenyl]carbonohydrazonoyl dicyanide.ii)=N-{4-[N-(4,6 dimethyl pyrimidin-2yl)sulfamoyl]phenyl}carbon-hydrazonyldicya nide.iii)=N-[4-(piperidin1-ylsulfonyl) phenyl] carbon-hydrazonoyl dicyanide); iv)=N-(thiazol-2-yl)carbonohydrazonoyl dicyanide

Scheme-7

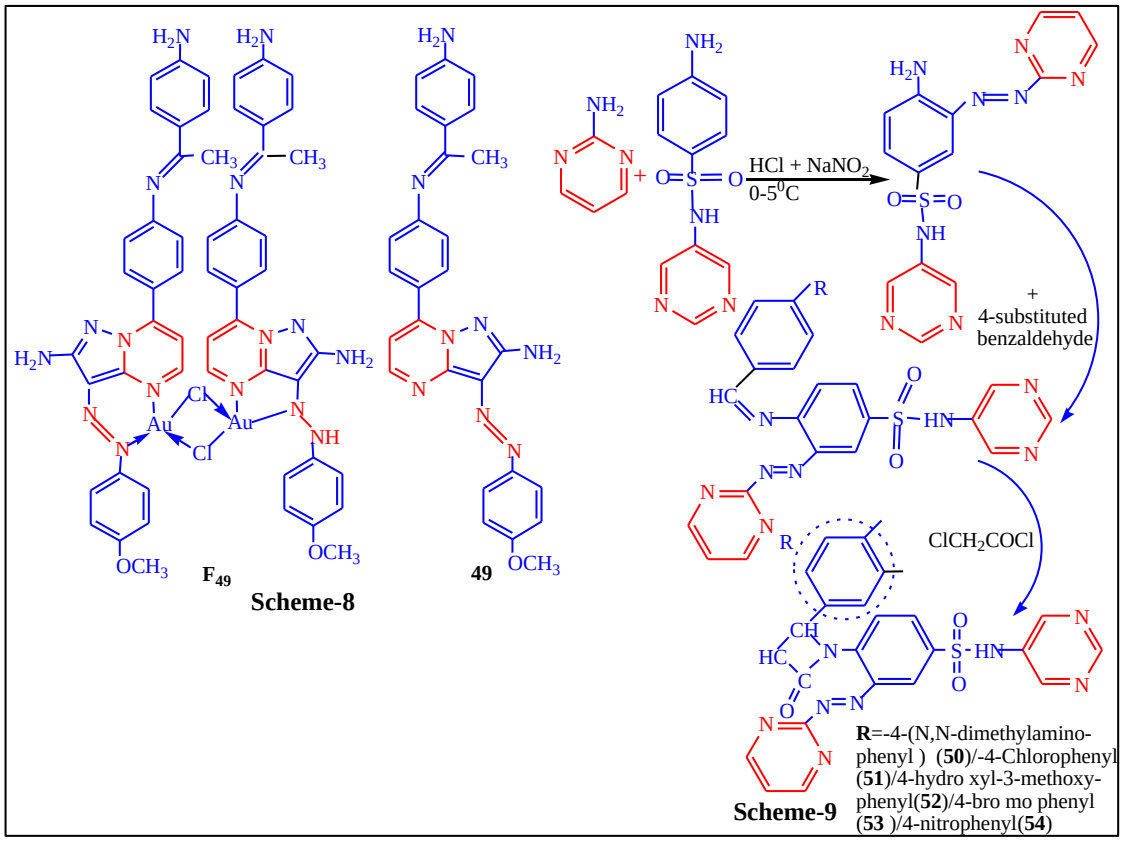
7. Synthesis of N-(1-(4-amino-phenyl)ethylidene)-4-(2-amino-3-(4-methoxyphenyl)diaze-nyl)[1,5-a]pyrimidin-7-yl)benzeneamine(49):

Pyrimidine based azo ligand(L)(**49**) is prepared by as classical azo synthesis method. Metal complexes are prepared by the reaction between ethanolic solution of ligand(L) and corresponding metal salts in ethanol. [Ni(L).(2AcO)].H_2O, [Cu(L)(2AcO)].$2H_2O$, [4Pd(L-1H)$_2$4Cl($2H_2O$)], [Ag(NO_3)(L)$_2$].H_2O, [4Pt(L-H)$_2$$2H_2O$.4Cl] and [4Au(L-1H)$_2$(OH).5Cl](**F$_{49}$**).[lvi] (**Scheme-8**)

8. Synthesis of 4-(3-choloro-2-(4-(dimethylamino/choloro/hydroxyl-3-methoxy/bromo/nitro)phenyl)-4-oxoazitidine-1-yl)-N-(pyrimidine-2-yl)-3-(pyrimidine-2-yldiazenyl)benz-enesulfonamide(50-54):

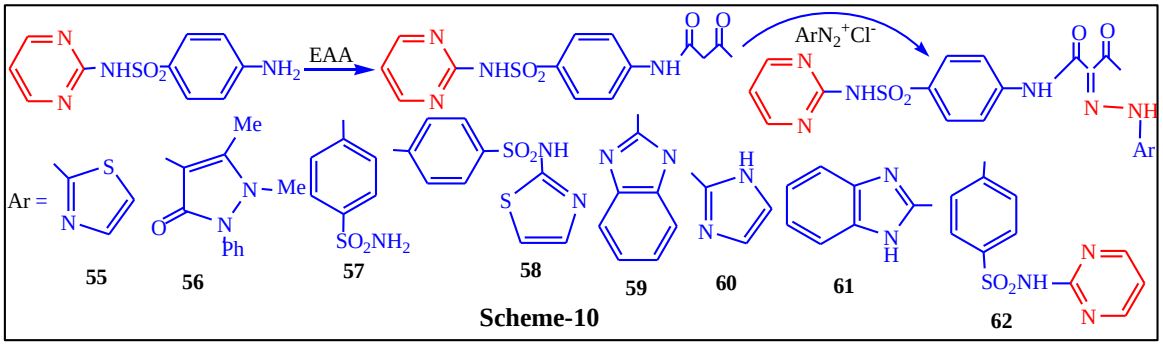
Synthesis of the β-lactam derivative of azo pyrimidine compound of {4-amino-N-(pyrimidine-2-yl)-3-(pyrimidine-2-yl-diazenyl)benzenesulfonamide(azo)} is carried out by first, diazotization of 2-aminopyrimidine with $NaNO_2$ and HCl at 0-5°C temperature then diazotized product is coupled with alkaline solution (5%NaOH) of sulfadiazine till the solution acidity reaches to neutral. Then azo compound poured into substituted benzaldehyde in glacial acetic acid medium and the solution mixture is reflux for 4hrs where azo compound form a Schiffbase of {(4-(dimethylamino)benzylidineamino)-N-(pyrimidine-2-yl)-3-(pyrimi-dineyldiazenyl)benzene-sulfonamide}. Schiff base with dioxane and triethyamine is added into a chloroacetylchloride and the whole solution mixture is stirred during 6hrs. Then the reaction

mixture is kept at room temperature for two days. After that the compound is transferred into crushed ice to form β-lactam derivative of azo pyrimidine compounds(**50-54**).[lvii](**Scheme-9**)



F49 **Scheme-8** 49 **Scheme-9**

9. Synthesis of 3-oxo-N-(4-(N-pyrimidin-2ylsulfamoyl)phenyl-2-(2-(thiazol-2-yl)/4-sulfamoylphenyl/4-(N-thiazol-2-ylsulfamoyl)phenyl/4-(N-pyrimidine-2-ylsulfamoyl)-phenyl hydrazono)butanamide(55, 57, 58 and 62) and 2-(2-(1,5-Dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)/benzo[d]thiazol-2-yl/1H-Imidazol-2-yl/(1H-Benzo[d]-imidazol -2-yl)hydrazono)-3-oxo-N-4-(N-pyrimidin-2-ylsulfamoyl)butanamide(56, 59, 60 and 61) :
This 3-oxo-N-(4-(N-pyrimidine-2yl-sulfamoyl)phenyl)butanamide, compound is produced by the following steps of reactions. Firstly, reaction carried out between sulfonamide and ethyl-acetoacetate in dry boiling xylene medium. Subsequently coupling of this sulfonamide derivative with different hetero-aromatic diazonium salts: namely 2-amino-thiazole diazonium salt, 4-aminoantipyrine diazonium salt, sulfanilamide diazonium salt and sulfathiazolediazonium salt, 2-aminobenzthiazolediazonium salt, 2-aminoimidazole diazonium salt, 2-aminobenzimidazole diazonium salt, in pyridine at 0-5°C create the corresponding aryl/heteroaryl hydrazono derivatives(**55-62**).[lviii] (**Scheme-10**)



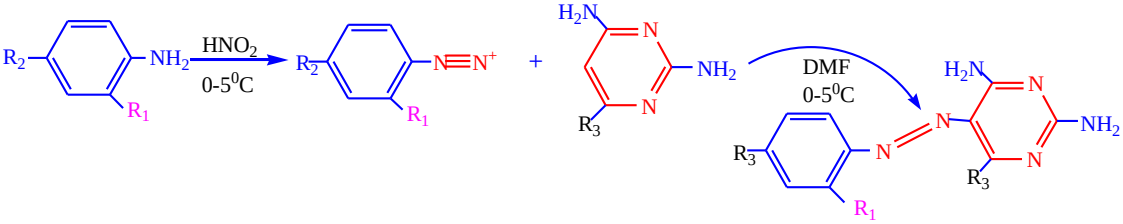
55 **56** **57** **58** **59** **60** **61** **62**

Scheme-10

10. Synthesis of 6-choloro-5-(2-nitrophenyl/diazenyl)pyrimidine-2,4-diamine/4-nitrophenyl/p-tolyl/4-methoxyphenyl(63,64,65&67), (N-(4-((2,4-diamino-6-choloropyrimidine

-5-yl)diazenyl)phenyl)acetamide(66) and 5-(4-nitrophenyl/4-methyoxyphenyl/2-nitro-phenyl/p-tolyl-diazenyl)pyrimidine-2,4,6-triamine(68-72):

Synthesized methods of pyrimidine azo derivatives (**63-67** & **68-72**) have normally described in literature[lix]. Where diazonium salt is to coupled with substituted phenyl-2,4,6-triaminopyrimidine or 2,6-diamino-4-chloropyrimidine in DMF to form pyrimidine based azo compounds.[lx] (**Scheme-11**)



Scheme-11

BIOLOGICAL ACTIVITIES SURVEY OF PYRIMIDINE BASED AZO COMPOUNDS(1-72):

A. Antibacterial activities of different azo-pyrimidine derivatives:

Antibacterial evaluation of **A1-3**, **B1-3** and **C1-3**compound: Metal-complexes(**A1-3**, **B1-3** & **C1-3**) containing pyrimidine-azo ligand that posses good antibacterial activities[xlviii]. All these complex compounds shows moderate to strong zone inhibition activities against the Bacillus Subtilis(BS) bacterial strain. Since azo-oxo-pyrimidine enhances their electron affinity due to the acidic character of metal-ion hence their interaction with the bacterial strain can easily happened. Among the nine metal complexes three Ni-metal complexes(**B1-3**) shows highest zone inhibition effect (28.0mm, 34.0mm, 31.0mm respectively) on the bacterial strains of BS. Where as Co-metal complexes (**C1-3**) exhibit little bit lowest activity(30.0mm, 25.0mm, 29.0mm) compare to Ni-complex(**B1-3**).

Antibacterial activity of **4-14** compounds: Antibacterial activity studied of pyrimidine azo compounds (**4-14**) on four bacterial strain (viz; Salmonella Typhimurium(ST), Micrococcus Luteus(ML), BS and Pseudomonas Aeruginosa(PA)) under the broth culture in incubated in time 18hrs. and at 37°C temperature. Existence of highest electronegative element, fluorine that act as electron with-drawing group present at benzene ring which motivate the 5-(4-fluorophenyl)-azo-4,6-dihydroxypyrimidine compound(**9**), gives better inhibition result against four bacterial strain among the all compounds (**4-14**) and these inhibition effects are ST- 30mm, ML- 16mm, BS- 13mm and PS- 17mm.[lix]

Antibacterial screen of **15-26**, **D15, 19, 20, 21**&**E15**compounds: All the azo-pyrimidine compounds (ligands: **15-26** & complexes: **D15,19,20,21** & **E15**) are examined antibacterial activity by the disc diffusion method in the presence of two bacterial strain such as Staphylococcus Aureus(SA) and Escherichia Coli (EC)[xxxix]. Proposal concentrations of these azo samples in DMSO solvent are 100µg/ml, 200µg/ml, 300µg/ml, 500µg/ml. Presence of Sulfonamide group in phenyl ring increases electron with drawing property in the compound **24** gives the most inhibition activity (12-13mm &16mm) against two bacteria SA & EC where the concentration of the tested samples had 100µg/ml. This value also reported and compared with the standard drug sulfamerazine.[l]

Antibacterial activity of the compound **27-38**: The results of antibacterial activities of the synthesized compounds(**27-38**) against bacterial pathogens (EC, Se, ST, SP, Sf1, Sf2, PA,VC, KP, Ml, BC, SM, PC, BS, PA(f1), S_{Ares}, EC_{res}) revealed that the compounds **28, 31, 32, 33, 34, 35** and **38** exhibited significant inhibitory activities against majority of the pathogens when compared to the standard reference antibiotic. The zone inhibitory effect of the tested

compounds against bacterial strain may be attributed to the presence of electron withdrawing group as 4-nitropheny-l,4-(1,3-dimethyl-2-phenyl-3-oxopyrazolyl)-3-nitro- phenyl and 2-methyl-phenyl-substituent in C-5 position which are attached in 2-thio-azo-barbituric acid. However other compounds **27, 30, 36** and **37** showed moderately inhibition against towards previously referred test pathogens in comparison with the standard antibiotics (Gentamycin, Ciprofloxacin and Chloroamphonicol). Synthesized one compound, 5-(4-bromo-3-methylphenyl)diazenyl]-2-thiobarbituric acid gives the largest zone of inhibition effect(26.6±1.0mm) against the PC bacteria(test sample conc. 7.8µg/ml) whereas the value of standard reference antibiotic such as MIC shows 19.52µg/ml. Another compound, 5-[(4-nitrophenyl)diazenyl]-2-thiobarbituric acid can gives the strong zone of inhibition effect (24.2±1.6mm and 22.3±1.3 mm) against S. flexneri and B. circulans bacterial strain respectively. Because the presence of electron pulling group at the phenyl ring centers in these compounds as nitro/bromo, help to exhibit stronger antibacterial activities.[lvii]

Antibacterial evaluation of the compound **39-42**: Four synthesized compound(**39-42**) and their studies of antibacterial activities against different bacterial strain, viz: ST, PS, EC, BS, Surcina Lutea(SL), SA, Enterococccus Facealis(EF) are highlighted here. Again good inhibition activities of compound **42** against four gram positive microorganism (like; SL, SA, BS, EF) and one gram negative microorganism(like; PA) can explained the presence of thioxo group which is worked as electron pulling. Now it has been observed that among these four compounds, only compound **40** showed better zone of inhibition activity against gram positive microorganism(like; SL and BS).[liv]

Antibacterial activity of compound **43a,b-47a,b** & **48b**: Another five synthesized compounds (**43a,b-47a,b** & **48b**) and their antimicrobial evaluation has been done on the six bacterial strain. Whereas three gram-positive bacteria (SA, BS and Stephylococccus Mutants(SM)) and the three gram negative bacteria is taken (EF, Proteus vulgaris(PV) and EC) as tested bacteria. Compound **46b** demonstrated more potent significantly activities against tested EF and PV bacteria that show an inhibition zone diameter between 25mm & 40mm. One more compound **46a** gives mild inhibition activity against on the three gram positive bacteria shows zone of inbitions like 18mm, 12mm & 9mm against SA, BS, SM bacteria respectively and also find out zone of inhibition against on three gram negative bacteria (EF, PV, EC) and their obtained results are 13mm, 9mm & 11mm respectively. All these fact can be chemically rationalize by the presence of electron dragging group at the phenyl ring and also possess sulfamoyl phenyl moiety in pyazole-azo-pyrimidine derivatives(**46a,b**) gives the higher activity compare to compounds **43a,b** & **44b** where exhibited low antibacterial activity on EC(10mm), BS(8mm) SA(10mm) respectively due to their absence of such group. The author also compared all these values with the standard antibiotic drugs like Gentamycin and Ketoconazole.[xvi]

B. Antifungal activities of azo pyrimidine compounds:

Antifungal activity of compound $\mathbf{A_{1\text{-}3}}$, $\mathbf{B_{1\text{-}3}}$ and $\mathbf{C_{1\text{-}3}}$: It has been study of antifungal activities of three pyrimidine azo ligands(**1-3**) and their metal(Cu, Ni and Co) complexes ($\mathbf{A_{1\text{-}3}}$, $\mathbf{B_{1\text{-}3}}$ and $\mathbf{C_{1\text{-}3}}$) against Aspergillus Niger fungus up to minimum concentration limit 25.0mg/ml, which exhibited positive results. But with lowering the concentrations of the tested samples only Ni-complexes with the ligands($\mathbf{C_{1\text{-}3}}$) give positive values but other Cu and Co metals complexes($\mathbf{A_3}$, $\mathbf{B_3}$ and $\mathbf{C_3}$) also give positive result. It has been chemically observed that here ligand(**1-3**) contains larger number of N-atom with higher electronegative around it which enhances the interaction with the fungus in the metal-complexes.[xlviii]

Antifungal activity of compound **43a,b – 47a,b**&**48b**: It is observed from the article[xvi] that the antifungal (Aspergillus fumigates, Aspergillus flavus and Candida albicans) activities of eleven compounds(**43a,b-47a,b** & **48b**) on the three fungal strain gives the zone of inhibition and these data are compared with the standard Ketoconazole antibiotic where concentration limit

is up to the 15μg/ml. Analysis of the antifungal activities, it is noticed here that the compound **46b** shows moderate inhibition effect on the above three fungal strains among those eleven compounds and these results are 20mm, 17mm, and 15mm.

C. Anti-HIV activities of azo-pyrimidine compounds (15-26 & $D_{15,19,20,21}$ & E_{15}):

Synthesized compounds(**15-26**) and their metal-complexes(**$D_{15,19,20,21}$&E_{15}**) are tested based on MTT assay for their studies of anti-HIV-1(strain IIIB) and anti-HIV-2(strain ROD) activity of human T-lymphocyte (MT-4) cells[lxi]. These results also comparable with the two standard drugs Nevirapine (BOE/BIRG587)[lxii] and Azidothymidine (DDN/AZT)[lxiii]. Compounds **24** and **D_{15}** are found to be the only compounds from the total of these compounds which are inhibiting HIV-1 & HIV-2 replication in cell culture that showed an IC_{50} values are greater than 2.07μg/ml and also more than 3.02μg/ml. But the compounds **20**, **23, 25** and **E_{15}** exhibited moderate activity against both virus types where their IC_{50} values each the following 9.56μg/ml, 8.11μg/ml, 5.23μg/ml, 8.06μg/ml and 10.01μg/ml respectively are greater than such these value. Sulfadiazine/ sulfamerazine or sulfamethazine incorporated at the C-5 of the pyrimidine of azo derivatives are the backbone that shows anti-HIV activity. In addition, the coordinated Pt(II) with the carbonyl oxygen (C-4) and nitrogen (C-5)that come from the azo pyrimidine derivatives i.e compound **D_{15}** improves the anti-HIV activity as well. Therefore, in these both compounds (**24** and **D_{15}**) should be use as new anti-HIV agents by further structural modification and pharmacological evaluation as per the author concept[l]. Author also studies a computational molecular modeling analysis with the compound **24** for knowing their mode with the HIV-RT binding pocket(NIBP) (PDB code: IDTT[lxiv]). The SyByL-X1.1 software is used and the results are visualized with PYMOL[lxv] which revealed a selective interaction with the amino acids of the RT-HIV enzyme and aromatic ring of the sulfonamide group of 24 fitted into an aromatic rich pocket surrounded by the aromatic side chains of Tyr179 that form a hydrogen bond between the hydroxyl group of Tyr179 and the nitrogen atom of the azo group is observe. Overall, the binding of ASN-130 with HIV-RT is the chemical combination of hydrophobic and π-stacking interaction.[l]

D. Anti-Cancer activities of azo pyrimidine compounds:

Anticancer activity of compounds **43b, 46b, 47b** and **48b**: The antitumor activity of the Pyrimidine azo derivatives are studies against on three human cancer cell-lines (breast adenocarcinoma(MCF), hepatocelluler carcinoma(HePG2) and human colon carcinoma (HCT-116)) is to possessive. The IC_{50} values among the tested compounds only **43b** & **47b** exhibited the most potent cytotoxic profile on cancer cells (MCF-7, HePG2 and HCT-116) with IC_{50} values ranging from 0.3μg/ml to 3.4μg/ml. But compound **43b** is most highly common effective among all of them on all types of cancer cells.

Compounds **46b** and **48b** have demonstrated significant effect on MCF-7 & HePG2 cells respectively with IC_{50} values ranging from 2.7μg to 9.8μg. Here the activity of **46b** compound gives significantly more when study on HCT-116 having IC_{50} is 1.2μg & 2.4μg. Furthermore, the compounds **43a** and **45a** shows moderate effects on cancer cells when IC_{50} values ranging from 6.7μg to 12.9μg, whereas the compound **43a** was the most significant on HePG2 cells with IC_{50} of 4.9μg. This is established from the all experimental results that the anticancer(MCF-7: 0.3±0.01, HePG2: 0.6± 0.02, HCT: 0.4±0.02) activity of **43b** compound and others compounds is be comparable with the standard doxorubicin drug(MCF-7: 1.2 ±0.2 , HepG2: 0.9±0.3, HCT: 1.6±0.2) .

Anticancer activity of compound **F_{49}**: The azo dye compounds might have promising potential anticancer applications, since such ligand can lead to possible alternative modes of cytotoxic action such as intercalative DNA lesion[lii] square planar metal complexes with aromatic ligandsbind to DNA by intercalation[liii]. Among all of the six metal-complexes only the gold complex(**F_{49}**) shows moderate cytotoxicity activity against MCF-7 human tumor cell lines[lxvii].

The reported result in IC_{50} value for 48μg/ml is comparison with the cytotoxicity of cisplatin which act as standard antitumor drug that are evaluated IC_{50} is 0.426μg/ml under the same conditions. Most of the soluble compounds having hydrophilic part as depicted in the complex have noticeable cytotoxicity activity. The activity of the gold complex could be explained by its greater solubility and lipophilicity of pyrimidine derivatives. The lipophilicity increases with increasing bulkiness and may facilitate transport through the cellular membrane[lxviii].

Anticancer activity of compound **50-54**: The anticancer action of the pyrimidine-azo-derivative (**50-54**) in vitro is resolute against a human breast MCF-7 cancer line using MTT cell feasibility assay. In general the outcome of the pyrimidine-azo compound present better anticancer potentiality (IC_{50} = 2.90μM) on an after 72hrs of culture study. In this case, the toxicity result for 4-(3-chloro-2-(4-(dimethylamino)phenyl)-4-oxoazitridine-1-yl)-N-(pyrimi-dine-2-yl)-3-pyrimidine-2-yldiazenylbenzenesulfonamide increases with rise in concentration level. The author is also reported the half cell lethal concentration i.e IC_{50} = 2.9μM which kill the half number of cancer cell and it will be totally lethal with increase concentration, where for normal (IC_{50}) embryonic cells is 9.59μM. This means that the compound is likely to be killed the cancer cell without affecting the normal cells when used it as lethal concentration for half cell[lvii]. The use of N-heterocyclic compounds as pyrimidine azo has a noteworthy role in the treatment of cancer and its taking away strategy[lxix]. Heterocycles are generally used as blended materials on which pharmaceuticals company are coordinated to give effective and diverse drugs. This is preferably used for five member-ring heterocyclic compounds[lxx] which served as the core components of a huge number of compounds that have a broad motivating range in biological action[lxxi-lxxii].

Anticancer activity of compound **55-62**: In this section azo-pyrimidine compounds are elucidated and screened in vitro for prevention of the growth of HePG2(human hepatocellular liver carcinoma cell lines), WI38(human lung fibroblasts), VERO(cell line was initiated from the kidney of a normal adult African green monkey) and MCF-7(breast cancer cell lines) are compared with the uses of known anticancer drug 5-flurouracil (5-Fu) and as a trial the result is to more potent with lower toxicity.[xxxv]The in vitro elucidation of only **61** compound give strong action against two various cell lines among the other azo-pyrimidine-sulfonamide derivatives(**55-62**). Another compound, **63,** shows similar effect as former which contain long π-conjugation system joined by thiazole-pyrimidine rings, in addition the presence of azo-functional groups and benzene ring. These outcomes demonstrate that variable molecular structure and orientation could enhance the observed antitumor action against the four examined cancer cells.

E. Mushroom tyrosine inhibition assay(IC_{50}) of azo pyrimidine compounds(63-67&68-72):

Tyrosine is examined in the presence of synthesized product using formerly described procedure with some alteration[lxxiii]. In this case all compounds are evaluated for their inhibitory effect on tyrosinase activity according to the procedure mentioned in the materials and methods section and kojic acid is used as the reference inhibitor. The outcome indicated the percent of inhibition in all compounds as compared to kojic acid compounds that exposed the most potent inhibitory effects on the mushroom tyrosinase activity with IC_{50} values of 24.45μM and 24.69μM, respectively (Ref. = 25.24μM). The lowest inhibitory activity of compound **71** on mushroom tyrosinase among the other synthetic compounds gives IC_{50} = 43.80μM. All synthetic compounds(**63-67** & **68-72**) are capable to inhibition effect on mushroom tyrosinase dependent on the concentration level. From the data analysis of inhibitory activity it is shown that the presence of -Cl group at the R_3 position have more effect than the presence of an $–NH_2$ group at the same position. The compounds of **66** & **64** are possessing $–NHCOCH_3$ and $-NO_2$ groups respectively at the R_2 position and –Cl group at R_3 position have shown more potent

inhibitory effect of mushroom tyrosinase than the other compounds. In this situation IC_{50} values are slightly better than the reference compounds.

CONCLUSION:

Most of the drugs belong into the heterocyclic family. This review article is the unique wall-frame picture where maximum numbers of biologically active azo-pyrimidine potential compounds are incorporated in it. Pharmaceutically important synthetic organic compounds are day to day developed for high demand in drug industry. Here, review of all the pyrimidine azo-compound it enlighten higher biological activities in the presence of S-atom into the pyrimidine moiety whereas it decreases to some extent their biological activity in the absence of such S-atom in pyrimidine azo derivatives. Again, overall observation shows that lowering the carbon atom and addition of more hetro-atom into heterocyclic ring that increase their hydrophilic nature which reveals to their activity towards biological molecules. This article arranged the maximum number of tinted azo-pyrimidine derivative as their biological motivation that can help to next generation researcher for further developing of new drugs as nitrogen based heterocyclic compounds.

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