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A REVIEW ON THE SYNTHESIS AND THERAPEUTIC POTENTIAL OF PYRIMIDINE DERIVATIVES

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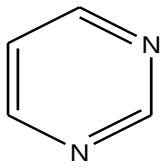
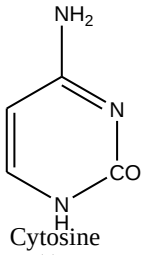
ABSTRACT

The chemistry of pyrimidine is a blossoming field. Numerous method for the synthesis of pyrimidine and also their diverse reactions offer enormous scope in the filed of medicinal chemistry. The utility of pyrimidines as synthon for various biologically active compounds has given impetus to these studies. The review article aims to review the work reported and the chemistry and biological activities of pyrimidines during past year.

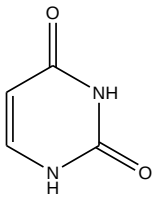
INTRODUCTION: Pyrimidines are the most important six member heterocyclic containing two nitrogen atoms



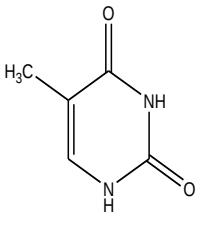
Pyrimidines are present among the three isomeric diazines. Several (mainly uracil, thymine and cytosine) Pyrimidines have been isolated from the nucleic acid hydrolyses. The nucleic acid are essential constituent of all cell and thus of all living matter cytosine is found to be present in both types of nucleic acid i.e. ribonucleic acid (RNA) and deoxyribonucleic acid (DNA) while uracil present only in RNA and thymine only in DNA.[1]



Cytosine
(I)

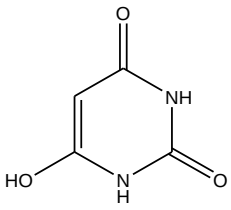


Uracil
(II)

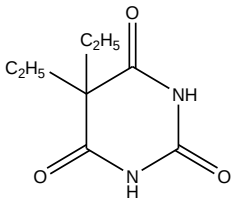


Thymine
(III)

In addition to this, Pyrimidines ring is also found in vitamin B_1, barbituric acid (2, 4, 6-trihydroxy pyrimidine) and its several derivatives e.g. Veranal) which are used as hypnotics.[2]



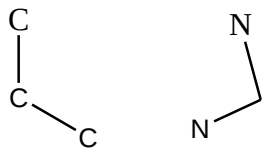
Barbituric acid
(IV)



Veranal
(V)

Numerous reports have appeared in the literature that highlights chemistry and uses of Pyrimidines.

Preparation of Pyrimidines: Synthetic strategies' of Pyrimidines have involved four main routes based on the condensation of two fragments as illustrated by VI-IX;



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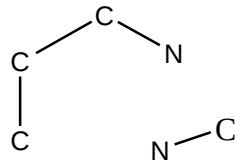
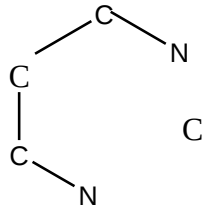
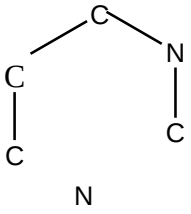


(VII)



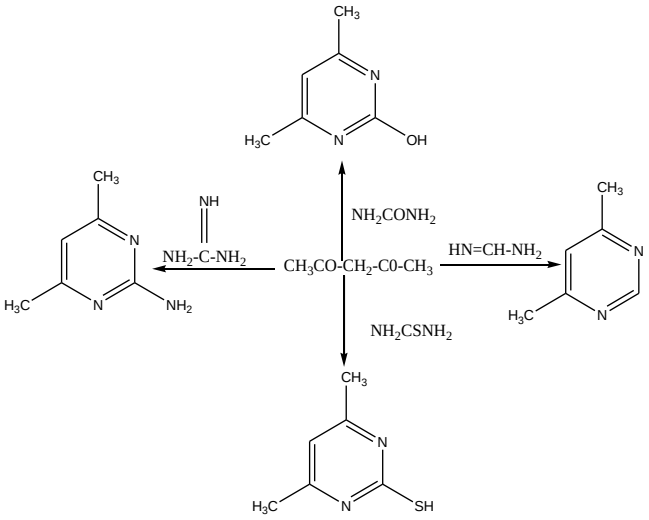
(VIII)



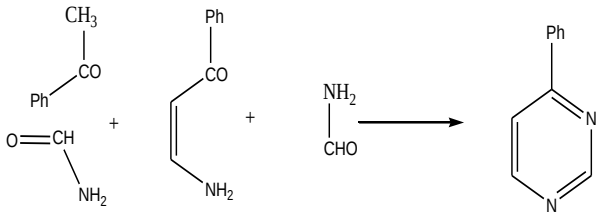
(IX)

Of these strategies that illustrated by VI i.e. the condensation of three carbon unit with an N-C-N fragment appears to most widely use this approaches has been called the common synthesis because of its general applicability to the synthesis of a whole range of Pyrimidine derivative. The great versatility in this synthesis rests with the fact that one or both of the group of three carbon atom fragments may be present as an aldehydes, Ketone, ester or nitrile group, β- Dialdehyde, β-ketoaldehydes, β-keto esters, malonic ester, β-aldehydo or β-keto nitrile and much other combination of these groups or their masked derivatives may be used.

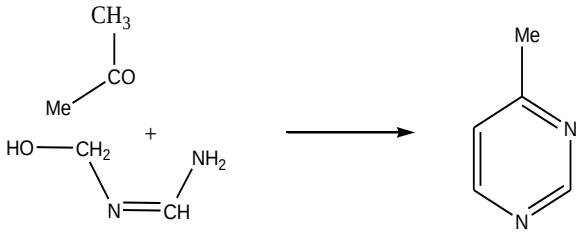
The nitrogen containing fragment may be an amidine, urea, thiourea or guanidine and acetyl acetone serves as an excellent illustrative example in that, it readily under goes reaction with formamidine[3], Guaidine[4], urea[5]or thiourea[6] to produce 4, 6 dimethyl pyrimidines.



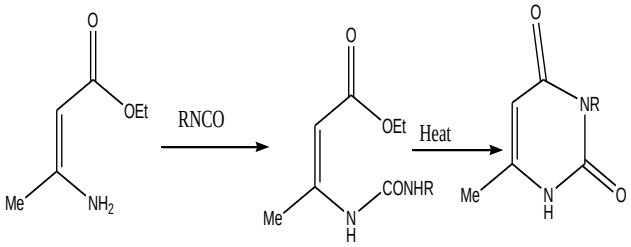
The formamide active methylene synthesis is illustrated by the condensation of acetophenone with two molecules of formamide in presence of zinc chloride at high temperature to give pyrimidine intermediate.[7]



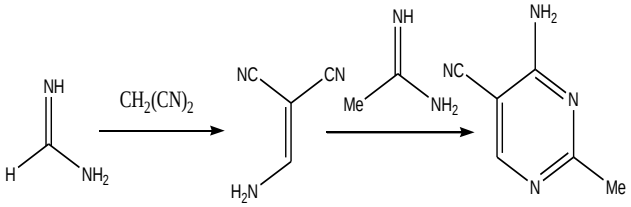
The synthesis may be used more effectively by combining the molecules of formamide as trisformamidomethane, which may then furnish N- formyl formamidine, thus acetone and this reagent with toluene sulphonic acid as catalyses yield 4-methyl pyrimidines.[7]



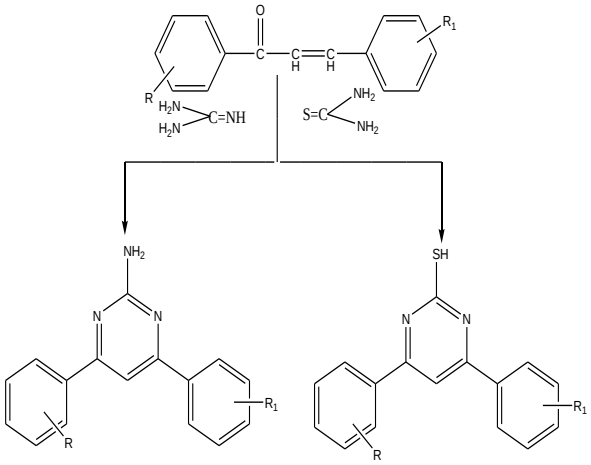
Ethyl β- aminocrotonate undergoes an extremely facile reaction with phenylisocyanate or methyl isocyanate to form an intermediate ureido derivative which undergo cyclization as treatment with base.[8]



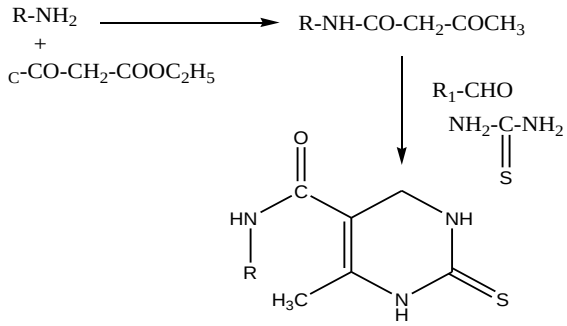
The condensation of maloenonitrile with amidines such as formamide or benzamidine result in the formation of 4-amino- 5-cyano pyrimidines.[9]



The 4, 6 di- substituted pyrimidines and 2 amino 4, 6 di-substituted pyrimidines formed by the reaction of chalcone with thiourea and guanidine hydrochloride in presence of sodium hydroxide.[10]

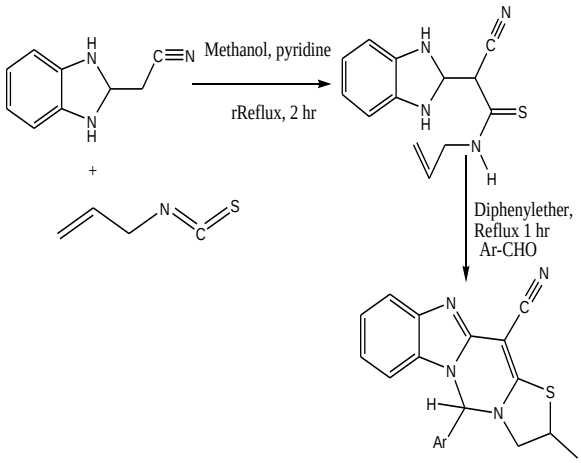


Anilido compound are produced by treatment of different aryl amine with ethyl aceto acetate which cyclized with various aromatic aldehyde and thiourea furnishing corresponding 4- aryl- 5- aryl carbomoyl 3, 4- dihydro- 6- methyl-2 (1H) pyrimidinethione.[11]

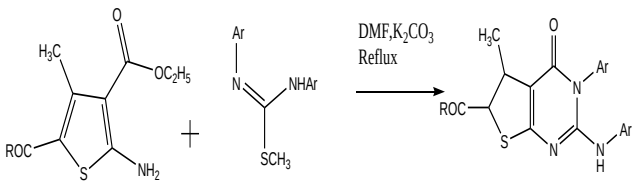


The 2-hydroxy-4-[P-methoxy phenyl] -5, 5, 7-trimethyl-5, 6-dihyrobenzo (d)-3, 4-dihydro pyrimidine, prepared by the cyclization with different aromatic aldehyde and urea.[12]

Reaction of 1H- benzimidazole- 2-aceto nitrile with allyl isothiocyanate in refluxing methanol with pyridine as catalyst gave 2- allyl amino- 1 (2, 3-dihydro- 1H- benzimidazol-2-yliden)- 2-thioxo ethyl cyanide which undergo ring closure with aromatic aldehyde to form 2, 3-dihydro benzimidazole[1, 2- c] [1, 3] thiazole [2, 3-f] pyrimidines.[13]



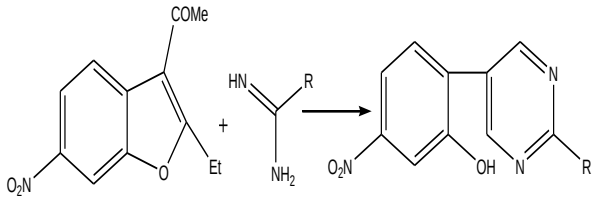
The 2- arylamino- 3- aryl- 5- methyl 6-substituted thieno [2, 3- d] pyrimidines -4- (3H)- ones synthesized by the condensation of equimolar quantities of the thiophene- o- amino ester with disubstituted aryl thiourea in DMF at reflux temperature in presence of catalytic amount of anhydrous K_2CO_3.[14]



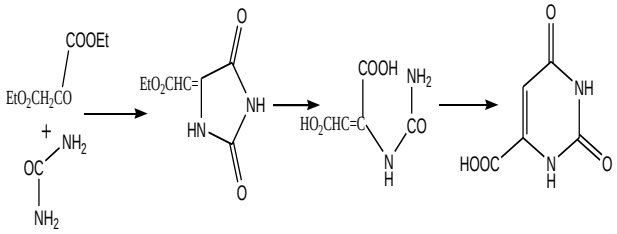
Where R= Me, NHPh, OEt
Ar = Ph,C_6H_5Cl

The pyrimidines synthesis from benzofuran is very specialized leading only to 5- (o- hydroxyphenyl) pyrimidines one example from a great many is the treatment of 3- acetyl- 2- ethyl- 6- nitro benzofuran with guanidine, acetamidine,

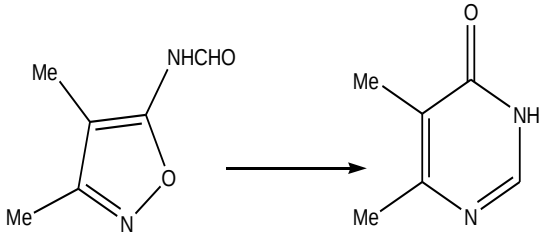
thiourea or urea to give in a good yield 4-ethyl- 5- (2′- hydroxy- 4′- nitrophenyl)- 6-methyl pyrimidines- 2- amine (R=NH_2) the methyl analogue (R=Me) and the corresponding pyrimidines- 2 (1H) thione and pyrimidinones respectively.[15]



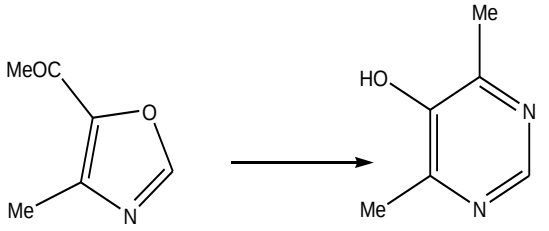
Hydantoins i.e. imidazole 2, 4 diones sometime arise in reactions designed to make pyrimidines. However they can usually be converted into the desired pyrimidines, often under hydrolytic conditions for example, diethyl oxaloacetate and urea under the usual conditions do not give the expected uracil carboxylic acid but the hydantoin however; this may be converted, on vigorous alkaline treatment, first in to the acyclic intermediate and thence into orotic acid.



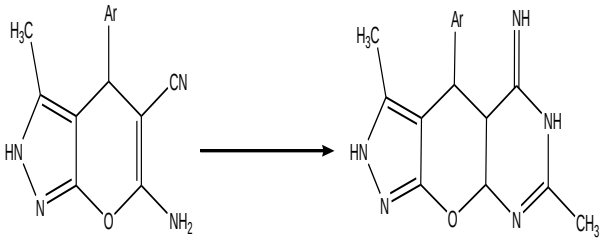
The 3, 4 dimethyl isooxazole-5-amine is easily acylated to it's formyl derivative which on catalytic hydrogenation, undergoes ring cleavage and recyclization to yield 5, 6-dimethyl-pyrimidine-4(3H)-one, other acyl derivatives give analogous 2-substituted pyrimidines.[15]



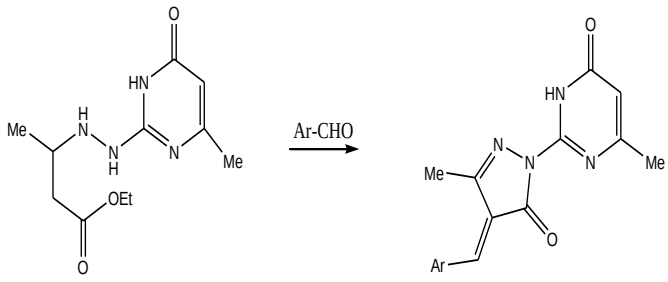
Treatment of the oxazole with ammonia converts it in to 5- hydroxy- 4, 6- dimethyl pyrimidines.[15]



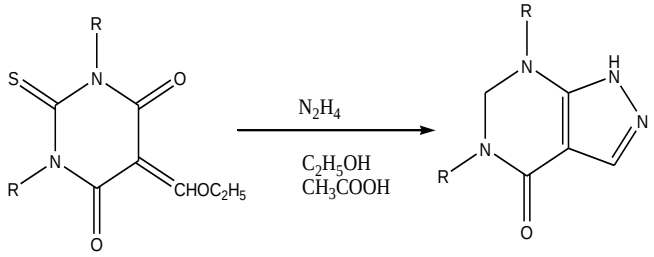
The synthesis of triazolopyrimidines fused to other heterocyclic moieties has been described by many heterocyclic moieties has been described by many investigator, the compounds proved to have pronounced biological activities 6- Amino-5- immino- pyrazolo [4' 3' 5, 6] pyrano [2,3- d] pyrimidines -5- yl hydrazine derivative were prepared starting from 6-amino -3-methyl -4- (p- nitrophenyl) - 2. 4-dihydropyrano [2, 3- c] pyrazolo- 5-carbonitrile.[16]



2- (pyrazol- 1- yl) pyrimidines prepared by condensation of ethyl aceto acetate (6- methyl- 4- oxo- 3, 4- di hydro pyrimidine- 2- yl) hydrazine with aromatic aldehyde.[17]



The 4- oxopyrazolo [3, 4- d] pyrimidines- 6- thione synthesized from 1, 3- diaryl- 5- ethoxy methylene- 2- thiobarbituric acid in the presence of hydrazine hydrate in ethanol/acetic acid for 8 hours.[18]



Molecular spectra of pyrimidines:-

U.V. spectra of pyrimidines: The U.V. spectrum of pyrimidines will depend on the state of the nucleus fully aromatic, partly reduced or fully reduced) on the position, number nature of any chromophoric substituent attached to it and on the ionic species present in the solution being measured. The U.V. absorption of pyrimidines occurs in two bands centered at 243 and 298 nm in cyclohexane. The second band is ascribed to the electronic transition from a nitrogen lone pair non bonding orbital to an empty π-orbital, in short an n to π * transition on account of the hypsochromic shift observed as changing solvent from cyclohexane to water .the lone pair become engaged in hydrogen bonding in water so that the absorbed radiation must be of higher energy (i.e. of lower wavelength) to provide for breaking the hydrogen bonds as well as bringing about the electronic transition. The more intense band at 243 nm is ascribed to a transition from the occupied π orbital of the ring having the highest energy to empty π orbital of lowest energy a π → π * transition akin to that which accounts for the 250 nm band of benzene, such bands are unaffected by solvent changes. In general electron releasing substituent cause a bathochromic shift of the n→ π* band while electron withdrawing substituent do the reverse.[19]

I.R. Spectra of pyrimidines: The I. R. spectra are essentially due to vibrational transition, many substitutes with single bands or isolated double bands give rise to characteristic absorption bands with in a limited frequency.

Range their spectra afforded reference data for identification of pyrimidines, for the identification of certain attached groups and as an aid in studying quantitatively the tautomerism of pyrimidines, pyrimdinethiones and pyrimidines in the solid state or in non protic solvents. Naturally pyrimidin-2-one give strong absorption bands for C=O and N-H band stretching vibration more ever, it is well established that six membered hetro- aromatic 'hydroxy' compounds

with oxygen in to a ring nitrogen give N-H stretching bands in the range 3360-3420 cm^{-1} while those with oxygen γ to a ring nitrogen have seen bands in the range 3415-3445 cm^{-1}. pyrimidin-2(and 4)-amine shows two 3500cm^{-1} representing the symmetric and anti- symmetric vibrations imines absorb at distinctly lover frequencies (3300 cm^{-1}) .

Mogilaian et al[20] studied the I. R. spectra of 2- (3- phenyl- 4- formyl pyrazol- 1-yl)- 3- (4- methyoxypheyl)- 1, 8 napthopyrimidine the structure of these compounds were confirmed as the basis of spectral studies the IR spectral of these compound exhibited absorption bands at 1687 and 1608 due to C=O and C=N stretching frequencies.

Alagarsamy et al[21] reported the I.R. spectra of 2- Allylamino- 1, 3, 4- thiazolo (2, 3- b)- 6, 7- dimetyl thizeno- (3, 2- e) pyrimidine -5 (4H)- one exhibited absorption band at 3280, 1690 and 1180 due to N-H, C=O and C=S respecting.

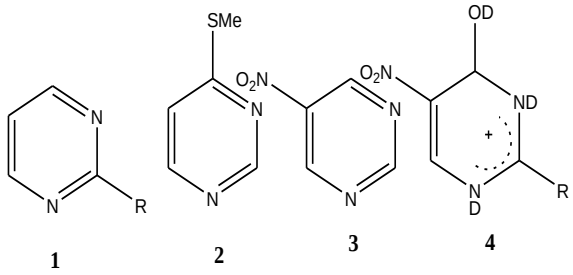
The I.R. spectrum of 6-[2' hydroxyl-3'-(2"– aryl thiazol- 4" yl) -5'- substituted phenyl]-4-aryl-2-amino pyrimidines studied by Rinde et al.[22] these compound show absorption bond at 2965, 2950 (-NH_2) and 3040(O-H phenolic).

Nuclear Magnetic resonance spectroscopy: The first proton NMR spectrum of pyrimidine appeared in 1960 and the data were confirmed subsequently. The relative deshielding of forer proton is H-2> h-4=H-5 as might be expected [S ($CDCl_3$)] 9.26 (H- 2), 8.78 (H- 4/6), 7.46 (H- 5)] the spectrum show little change from neat liquid to dilute carbon tetrachloride solution. The three mono-c-methylpyrimidines do show long range coupling between the methyl protons and ortho or para ring protons. For example, 2-methyl pyrimidine has 0.6 Hz and 4-methylpyrimidine has 0.4 Hz (both in $CDCl_3$).

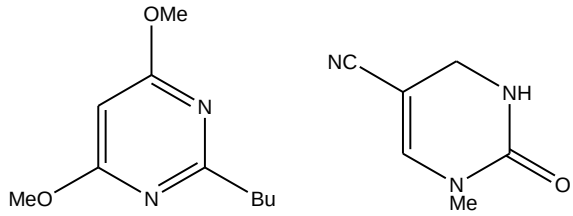
The NMR spectra of most other pyrimidines, which are mono substituted by a non tautomeric group, are unexceptional. Thus 2-substitued pyrimidines show a doublet and triplet with H-4/6 broadened by coupling to the adjacent nitrogen ; the chemical shift and $J_{4.5}$ naturally vary with the nature of the 2-substitutent : compare pyrimidine -2-carbonitrile(**1**; R= CN) [δ (Me_2CO) : 9.04, H-4/6; 7.86, $J_{4.5}$ 5.1 Hz,H- 5] and 2-bromopyrimidine (**1**; R= Br) [δ (Me_2CO) : 8.72, H-4/6; 7.57, $J_{4.5}$ 4.8 Hz, H- 5] .

The 4-substituted pyrimidines have no symmetry and show typical ABX pattern with small para- couplings involving H-2 as exemplified in 4-methylthiopyrimidine (2) [δ ($CDCl_3$): 9.02, $J_{2,5}$ 1.3 Hz, H- 2; 8.43, $J_{5,6}$ 5.6, H- 6; 7.25, H-5; 2.58, SMe]. The spectra of 5-substituted pyrimidines simply show two broad singlet with no meta-coupling evident across the ring-nitrogen atom, except in 5-nitropyrimidine (3) in which a small such coupling is manifest [δ ($CDCl_3$): 9.67,H-4/6;9.64, $J_{2,4}$ 0.3 Hz,H-2]. There is little change in the spectrum of 5-nitropyrimidine in D_2O, but when acidified the spectrum becomes three singlet [δ(D_2O/DCl) : 8.66,8.31,6.49], indicating a

covalently hydrated cation(4; R=H): the position of hydration is proven by the similarity in spectrum of the 2-methyl-5-nitropyrimidine cation (4; R=Me), in which 1, 2 (2, 3)- hydration is precluded.[23]



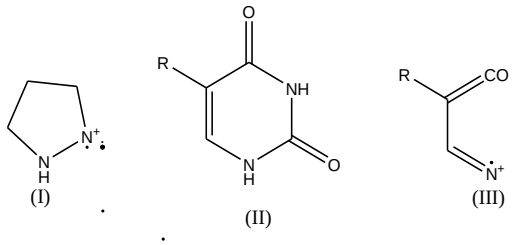
1 2 3 4



5 6

The NMR spectra of simple dihydropyrimidines are not easy to interpret but the spectrum of 2, 5-dihydropyrimidine (5) is particularly interesting in having $J_{2,5}$ 5.5 Hz (as shown by decoupling procedure) a large value for long range coupling. Work on dihydropyrimidiene has been more popular and rewarding. for example, the spectrum of 5- cyano- 1- methyle 3, 4 dihydropyrimidine- 2 (1H)- one (6) [δ ($CDCl_3$) : 6.80, $J_{4,6}$ 1.0 Hz, H- 6, 4.13, H-4; 3.12, NMe] clearly show the reduction of the 3,4-bond as do also those of its 3-methyl isomer and 1,3-dimethyl homologue. The NMR spectra of 6-[2'-hydroxy -3'- (2''- arylthiazol- 4''- yl)- 5'-substituted phenyl]- 4- aryl/heteryl- 2-amino pyrimidines reported by Rindhe et al .[24] Spectrum of this compound exhibited peak at [δ (DMSO- d_6): 5.0(s,1H,phenolic O-H), 4.0 (s, 2H, NH_2), 7.36 (s, 2H, aromatic), 7.07 (m, 4H, aromatic), 6, 90 (s, 1H, 2- pyrimidine), 7.409s, 1H, thiazole).

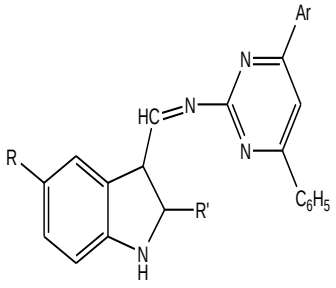
Mass spectra of pyrimidines: The mass spectra of pyrimidines and quninazolines are generally simple. The dominant fragmentation mode of pyrimidines is loss of HCN twice to give ionized acetylene…. 26, as base peak, whether C- 2 or C- 4 is involved in the initial loss of HCN appears to be unknown. Pyrimidines-2-amine also fragments by sequential loss of two molecule of HCN but the product from first loss appears to be the pyrazole radical cation (I) or possibly an imidazole, both of which are known to fragment according to the subsequent pattern for pyrimidine-2-amine behave similarly but pyrimidine-4-amino and it's derivative fallow a greatly modified and quite complicated pattern both uracil(II, R=H) and thymine (II,R=CH_3) undergo on retro-Diels-Alder reaction by losing HCNO to give fragment (III)(R=H or Me). The subsequent fragmentation is logical enough. Cytosine fragments by at least three pathway, of which are involve initial loss of CO. but barbituric acid proceeds by a logical loss of 2XHNCO in main.[25]



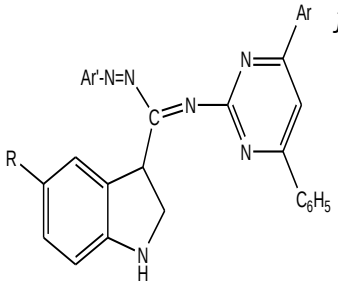
(I) (II) (III)

Biological Activities of pyrimidines:

Antimicrobial activity: Saundane et.al.[26] synthesised 2- (2', 5' substituted indolideneamino- 3'- yl) - 4, 6- diaryl pyrimidines (I) and 2 [2', 5'- substitutedindole- 3'- yl) (phenyl azo) methylene imino]- 4, 6- Diaryl pyrimidine(II) with a view to screening then for their antimicrobial activity. the compound were screened for their activity at concentration 1000 µg/ml in DMF against the gram negative Bacteria *E. Coli* and Gram-positive bacteria *S. Aureous* by cup plate method and show antifungal activity against *A. niger* and *A. flavus.*



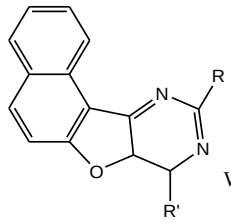
(I)



(II)

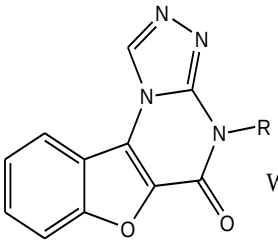
Where R= H, Cl, R'= H, C_6H_5, Ar= C_6H_5, $C_6H_4OCH_3$, $C_6H_4NO_2$
Ar'= $C_6H_5CH_3$, $C_6H_4OCH_3$, C_6H_4Cl

Padamshali et.al.[27] prepared Naptho [2, 1- b] furo [3, 2- a] pyrimidine which were useful in the preparation of pharmacologically active compound like anti-inflammatory, anti- anthelmintic, antimicrobial agents.



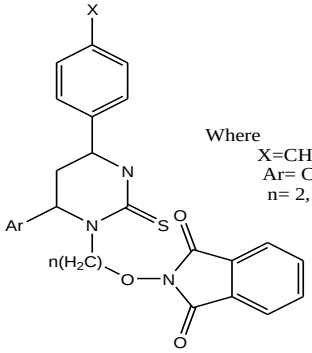
Where R=CH_3, C_6H_5
R'=OCH_3,OC_2H_5,NHC_2H_5,NHC_6H_5

Synthesis of 1, 2, 3, 4- tetrahydro-4- oxo-2- thiobenzo furo [3, 2- d] (IV) pyrimidine was reported by Basavaraja et al [28] and examined for their activity against *S. Aureus* and *E. Coli.*



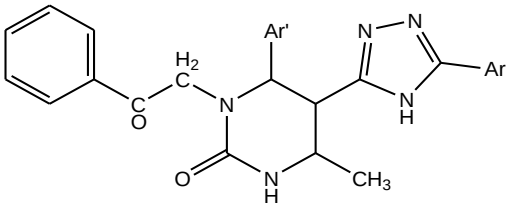
Where
R= CH_3, C_6H_5, $C_6H_4CH_3$, $C_6H_4OCH_3$

N- (N- Alkoxy phthalimido)- 4, 6- diaryl- 5, 6 Dihydropyrimidine - 2- Thiones prepared by Talesara et.al.[29] and tested against bacterial strains *K. Pneumonia, E. Coli*, *S. Typhi*, *P. Aeruginosa,P. Mirabilis* and fungi (500ppm) *C. Albicans, A. fumigatus.*



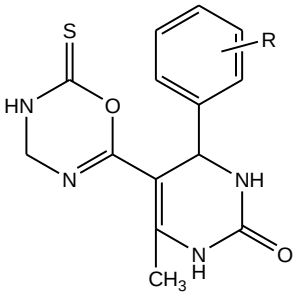
Where
X=CH_3, Cl
Ar= C_6H_5, ClC_6H_4, $OCH_3C_6H_4$
n= 2, 3, 4

Mishra et.al.[30] synthesized various derivatives of pyrimidines. The fungicidal activities of the compound were evaluated against *P. infestans* and *C. falcatum* by the usual agar plate technique at 1000, 100 and 10 ppm concentration.



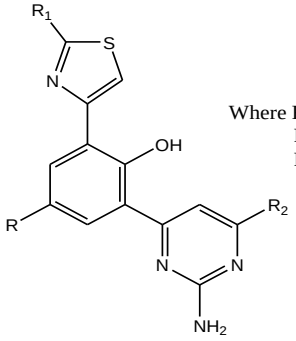
Ar=C_6H_5, p- ClC_6H_4, m- $NO_2C_6H_4$, p- $OCH_3C_6H_4$
Ar'= m- $NO_2C_6H_4$, p- $OCH_3C_6H_4$

Purohit et al [31] synthesized 5- [5'- substituted 1, 3, 4 oxadiazol- 2' yl) Dihydropyrimidinon and screened for their antimicrobial activity against *S.Aureus* and *E.Coli* using Norfloxacin as standard antifungal activity was evaluated by using *A.Niger* and *CAalbicans* using Grisofulvin as standard.



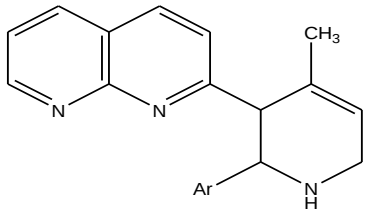
Where R= H
4-0CH_3
3-NO_2

Rindhe et.al.[32] prepared 2-Amino-6-substituted thiazolyl pyrimidine compounds with 4-chloro and 4-methoxy substituent at four position showed significant antifungal activity.



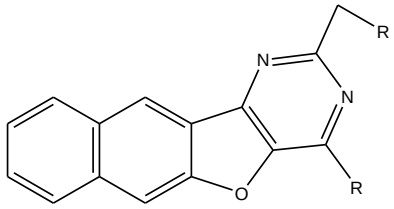
Where R =CH_3, Cl
R_1= C_6H_5, 4-C_6H_5Cl
R_2= 4-OCH_3, 4-Cl

1, 8 Napthopyridine derivatives reported by Mogilaiah et.al.[33] compounds were tested for their antibacterial activity in-vitro against Escherichia coli and *B. Subtilis* using filter paper disc technique.



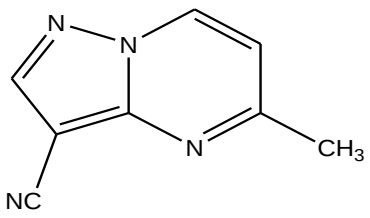
Ar=C_6H_5, p-$CH_3C_6H_5$, $CH_{30}C_6H_4$,o-ClC_6H_4
p-ClC_6H_4, p-OHC_6H_4

Naptho [2, 1- b] furo [3, 2- d] pyrimidine were prepared by Vaidya et.al.[34] the antimicrobial activity of the selected synthesized compounds was determined by cup plate method. The in-vitro antimicrobial activity was carried against 24 hr cell culture of two bacteria and two fungi. The bacterial strains used were *S. Aureus* and *P. Aerugenosa*. The fungi used were *A. Niger* and *C. Albicans*.

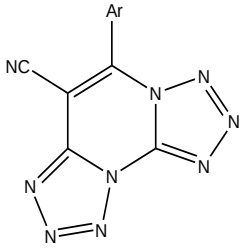


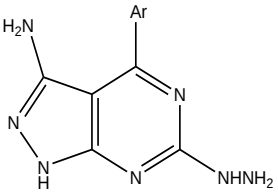
R= OH, -NHC_2H_5, -NHC_6H_5

Ming li et.al.[35] synthesized 2 -cyano- 5-methyl pyrazolo [1, 5- a] pyrimidine derivatives which showed various biological activities in the terms of antibacterial, antischistosomal and xanthine oxidase inhibitor. The preliminary biological test showed that the compound exhibit activity against four fungi *G. Zeave*, *A. Solani*, *P. Asparangi* and *C. Aracnidicola* hori.

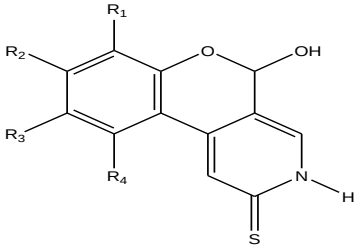


Aly et al.[36] synthesized a series of 1-glycosyl thio pyrimidines, annulated pyrimidines derivatives, pyrazolo [3,4-d]-pyrimidines, ditetrazolo [1,5-a,1,5'-c] pyrimidines thieno [2,3-d] pyrimidines derivative. The antimicrobial were determined in vitro using cup plate and paper disc method.

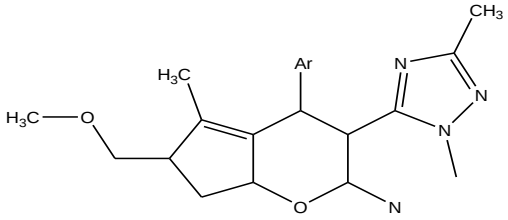




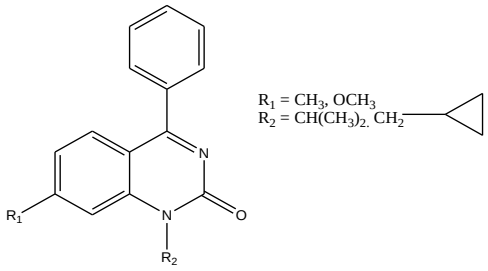
2- Thio- 5- hydroxy- 5H- [1] benzopyron [4, 3- d] pyrimidines derivative was reported by Karale et.al.[37] ,compound were screened for their antibacterial activity against gram negative bacteria *E.Coli* and gram positive bacteria *S. Albus* using filter paper disc method.



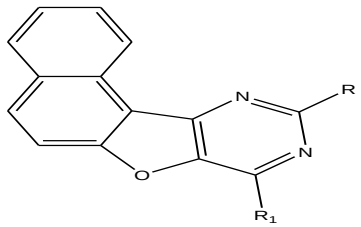
The 9 (2- Methoxyethyl) - 2, 5, 10-trimethyl- 11 (p- nitrophenyl)- 9, 11-dihydro pyrazolo [4' 3: 5, 6] pyrano [2, 3-e] [1, 2, 4] triazolo [1, 5 -c] pyrimidines derivative was synthesized by A. H. Shamroukn et.al.[38] compounds were screened for their antibacterial activity against gram-positive and gram negative bacteria and antifungal activity against *A. Niger* and *C. Albicans*.



Anti-inflammatory Activity: Vega et.al[39] synthesized 3- substituted derivatives of 4-phenyl- 2- thioxobenzo [4' 5] thieno [2, 3-d] pyrimidine and evaluated for their anti-inflammatory activity against carrageen induced edema in rates. They were compared with these obtained for acetyl salicylic acid, piroxicam and ibuprofen which were chosen as reference standard.

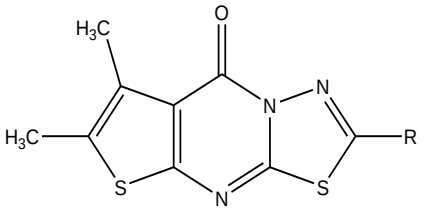


Naphtho [2, 1- b] furo [3, 2- d] pyrimidine was reported by Padama shale[40] et al carrageen induced rat paw edema method was employed for evaluating the anti -inflammatory activity. The compounds were given at a dose of 80 mg/kg body weight in albino rats weighing between 150 and 200 g. The edema was produced by injecting carrageenan solution at the left hind paw.



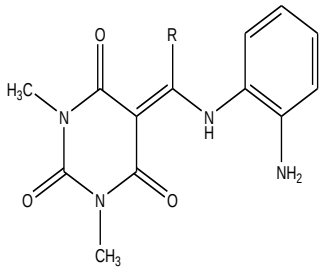
R = CH_3, C_6H_5
R_1 = OCH_3, OC_2H_5, NHC_2H_5, NHC_6H_5

Anticancer Activity: Alagarsamy et al [41] described anticancer activity of some substituted (1, 3, 4) thiadiazolo thieno[3, 2-e]pyrimidin 5(4H)-ene. The compound showed activity against Lung, Brest and other cancer.



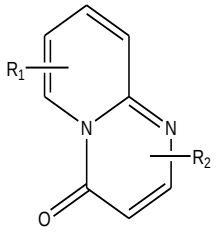
R = H, $-CH_3$, $-CH_2CH_2CH_3$, $NHCH_3$,NHC_6H_5

Palwinder Singh et al [42] reacted 5 benzoyl/ 5-carbaldehyde-/ 5- (3- phenyl acryloyl 0- 6- hydroxy- 1H- pyrimidine- 2, 4 diones with ammines provided the corresponding enamines. The investigation for anticancer activity of molecule at 59 human tumor cell lines representing Leukemia , Melanoma and cancer of lung ,color , brain, ovary, Brest as well as kidney.



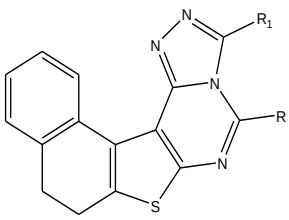
R = H, CH=CH-ph, ph

Organic compounds and their complex with various ligand have found many application in biomedicine Al Allaf et.al.[43] describe the preparation of R_2SnCl_2 complex of some 4H-pyrido[1,2-a] pyrimidin-4-one derivatives as donating ligand having multiple doner sites and examine the cytotoxic activity of some of these complex against fine tumor cell lines.

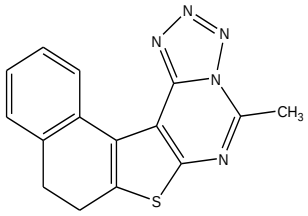


R_1 = H, 7-CH_3, 8-CH_3
R_2 = 2-CH_2Br, 3-CH_3COO

Thienotetrazolo pyrimidines and thienotriazolopyrimidine derivatives prepared by Rashand et.al.[44] compounds were tested as potent at anti-inflammatory agent and derivatives showed patent activity in Carrageenan test.

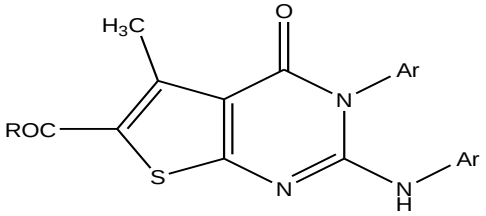


Thienotriazaoeo pyrimidine derivative
R = H_2CH_3 ,
R1 = H, CH_3



Thientetrazolo pyrimidine

Analgesic Activity: Rathod et al[45] synthesized 2- aryl amino- 3- aryl- 5- methyl- 6- (substituted) thione [2, 3- d] pyrimidin- 4 (3H)- ones. All the synthesized compounds were screened for the analgesic activity by tail flick method an albino rats and by writing method on albino mice.

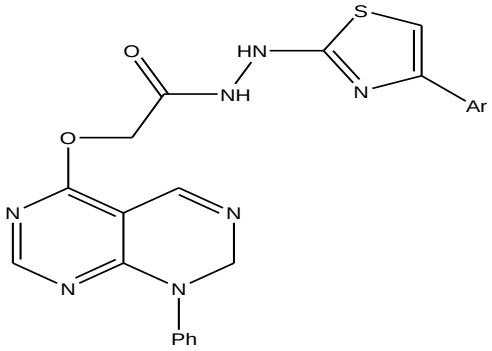


4- Amino- 5- substituted- 7- phenyl pyrido [2, 3-d] pyrimidin-2 (1H) - ones & 44- aino- 5- substituted- 7- phenylpyrido [2, 3- d]- pyrimidin- 2- (1H) - thione were

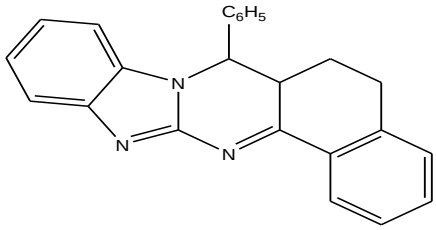
synthesized by shah et al [46] these compound were tested for analgesic activity.

Pirisino et al[47] have studied 2-phenyl pyrazolo-4-ethyl- 4, 7- dihydro [1, 5- a] pyrimidine- 7- one for it's analgesic, antipyretic and anti-inflammatory activities the anti-inflammatory properties of synthesized compound were evaluated by carrageen an induced paw edema and cotton pellets induced granuloma method and found to posses the activity similar to indomethacin, phenylbutazone and isoxicam similarly this compound was shown to passes analgesic and antipyretic activity comparable to the former drugs. Sondhi et al [48] synthesized some mono, bi and tricyclic pyrimidine derivatives and evaluated them for analgesic activity using phenyl quinine writhing assay.

Vijay Raj et al[49] synthesized some new 2-[cl- phenyl- 1H- pyrazolo [3, 4- d] pyrimidin- 4- yl) acetohydazide derivative have been prepared and screened for their analgesic activity by acetic acid induced writhing test using standard drug diclofenac sodium.

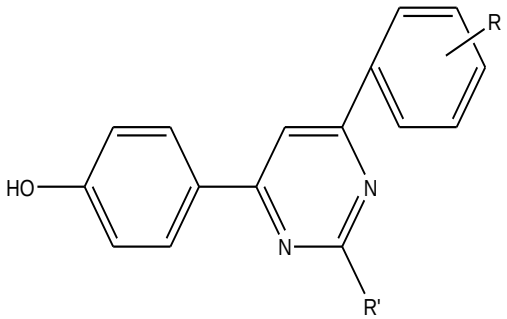


Antidiabetic Activity: Desenko et al [50] synthesized azolopyrimidine derivatives and compounds were evaluated for hypoglycemic activity.

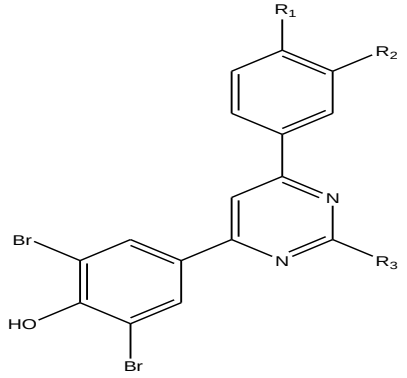


Lee et al [51] synthesized same novel pyrimidines derivative having thiazolidinedione. These compounds were evaluated for their glucose and lipid lowering activity using pioglitazone and rosigeitazone as reference compound.

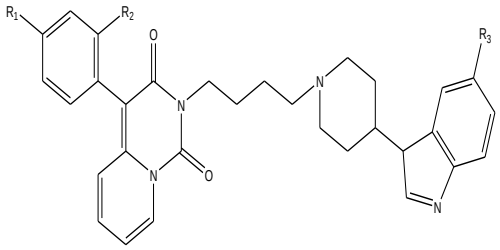
Miscellaneous activity: A small library of 20 tri-substituted pyrimidines was synthesized by Anu et al [52] evaluated for their in vitro anti-malarial and anti-tubercular activities. Out of the total screened compound, 16 compounds have shown in-vitro anti-malarial activity against *Plasmodium falciparum* in the range of 0.25-2 µg/ml and 8 compounds have shown anti-tubercular activity against Mycobacterium tuberculosis at a concentration of 12.5 µg/ml.



Verma et.al.[53] synthesized 2-91-piperidinye/1- pyriralidinyl0- 4-substituted phenyl -6 (3, 5- di bromo-4-hydroxy phenyl)-pyrimidines. The herbicidal activity was carried out by Cyanamid India Ltd. valsad plant valsad in collaboration with Cyana mid U. S. A. compound were tested both pre and post emergence against 18 species in an 80% acetone solution ± 0.2% in general 1 Kg activity compound at volume of 1600 lit/hec was used for this test. The minimum sample used in this test was 250 mg.

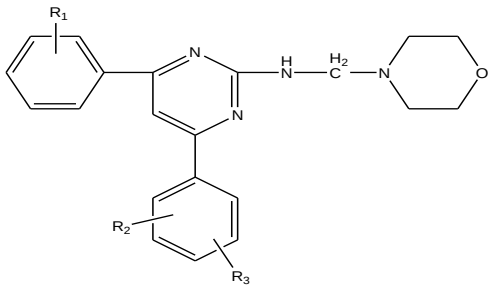


Herald et al [54] synthesis novel 4-aryl-pyrido[1,2-c] pyrimidines and compound were evaluated for antidepressant activity target compounds were tested for their affinity for $5HT_{1A}$ receptor and 5-HT reuptake inhibition using radio ligand binding assay.

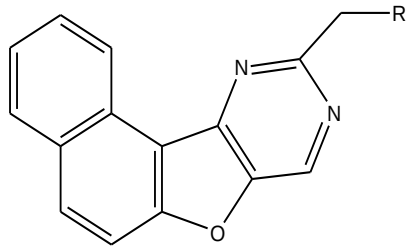


Bernier et al [55] synthesized pyrimido [4, 5-d]pyrimidines derivative and evaluated for antidepressant activity, binding at presynaptic α-receptor site spectral data determined in solution and in the solid state allowed establishment of the relationship between activity and conformation of the molecule.

Abignente et al [56] synthesized a group of imidazol [1, 2- a] pyrimidines- 2-carboxylic esters, acid and amides. All the synthesized compounds were tested in vitro for anti-inflammatory and analgesic as well as for ulcerogenic action in the rat paw edema, while almost all compounds displayed significant analgesic activity in the acetic acid writhing test. All new compounds were found to be lacking in inhibitory activity on cyclooxygenase in-vitro. Nasr et al [57] synthesized pyrido [2, 3- d] pyrimidines and pyrimido [5, 4: 5, 6] pyrido [2, 3-d] pyrimidines and investigated as antiviral agents compounds were subjected to antiviral activity testing against herpes simplex virus (HSV). 2- morpholino methyl amino-4 (4'-fuoro phenyl)- 6- (3" 4" - dimethoxy phenyl pyrimidines derivatives reported by Khan et al [58] and evaluated for anticonvulsant activity using phenyntoin as standard drug.



2-Alkyl/aryl amino methyl-4-alkyl/aryl naphtha [2, 1- b] furo [3, 2- d] pyrimidines prepared by vaidya et al [59] the activity was evaluated as earth worms *pheretima posthuma* by reported method. The compounds were tested at a dose of 0.001 mol/ml suspended in tween-80 piperazine citrate suspension was taken as standard.



Apart from these activities, pyrimidines also possess hypnotic, [60] CNS stimulants, [61] diuretic, [62] antihistaminic, [63]and calcium channel blocking activity.[64]

CONCLUSION: As a result of vigorous research; a vast literature has been accumulated over the years and chemistry of pyrimidines continue to be blossoming field it would also be interesting to see development of pyrimidines as potentially active therapeutic compound.

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