Moroccan Journal of Chemistry
ISSN: 2351-812X
http://revues.imist.ma/?journal=morjchem&page=login
M. Asif / Mor. J. Chem. 4N°4 (2016) 961-975

Mini Review on synthetic methods and biological activities of various substituted Pyrimidine derivatives

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Received 01 Aug 2016,
Revised 14 Oct 2016,
Accepted 02 Jan 2017

Abstract

Pyrimidines are versatile nitrogen containing heterocyclic compounds, possessing various types of biological and pharmacological activities like antimicrobial, hypotensive, antimalerial, antidepressant, antitubercular, anticoagulant, hypnotic, fungicidal, anti-inflammatory, analgesic, antiulcer, antiviral and anticancer and other useful activities. Pyrimidine nucleus is endowed with a variety of therapeutic activities and new Pyrimidine are known to be biologically active compounds possessing several pharmacological activities. Pyrimidines aroused our interest in synthesizing new Pyrimidines nucleus featuring different substitution with more potent pharmacologically active compounds.

Keywords: Pyrimidines, heterocycle, synthesis, biological activities

Introduction:

Heterocyclic compounds have great applicability in pharmaceutics because they have specific chemical reactivity and provide effectiveness biological activities. Heterocyclic compounds provide convenient building blocks to which biologically active substitutes can be attached. The interesting biological activities of heterocycles have stimulated considerable research work including the synthetic utility. Heterocyclic compounds can be synthesized by cyclization reactions, addition reactions, ring transformations or replacement involving groups.

Pyrimidine: Pyrimidine is one of the most important six member heterocyclic compounds containing two nitrogen (N) atoms (**Figure 1**) with molecular formula $C_4H_4N_2$ and molecular weight 80 dalton [1].

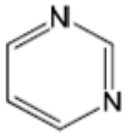
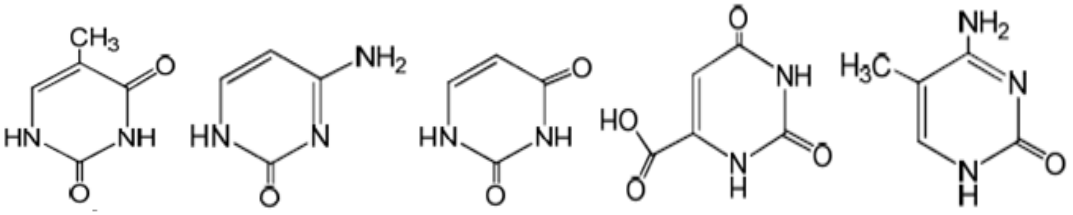


Figure 1. Structure of pyrimidine

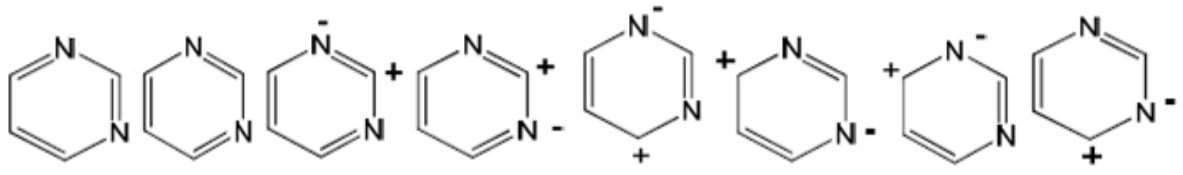
The first pyrimidine was isolated from natural sources. Later, thymine (**1**) was isolated from hydrolyzates bovine thymus or spleen in 1893 [2] and cytosine (**2**) was isolated 1894 from hydrolysis of calf thymus [3] and its structure was known in 1903104. Uracil (**3**) was isolated from the hydrolysis of herring sperm in 1900 and its structure was established by synthesis in 1901[4,5]. In 1905, orotic acid (**4**) was isolated from the whey of cow milk [6]. The 5-Methyl-cytosine (**5**) was synthesized in 1901 and its isolation from the hydrolyzates of tubercule bacilli was reported in 1925 [7].



1 **2** **3** **4** **5**

Physical Properties of Pyrimidine:

Pyrimidine is a colorless compound, having melting point 22.5°C and boiling point 124°C. Its dimensions have been determined by X-ray diffraction study of a crystal at -2°C and closely resemble those of pyridine (six membered hetrocyclics with one nitrogen atom in their ring). Pyrimidine is best considered as a resonance hybrid to which the uncharged equivalent kekule structures (**6,7**) and the charged structures (**8-13**) contribute (**Figure 2)**. The self consistent pai electone densities, calculated for ground state of pyrimidine are 0.776, 0.825 and 1.103 for positions 2, 4 and 5 respectively [8].



6 **7** **8** **9** **10** **11** **12** **13**

Figure 2. Resonance structures of pyrimidine; Kekule structure **(6, 7)**, unchanged equalent and structures **(8-13)** are charged structures.

Chemical Properties of Pyrimidine and its Derivatives:

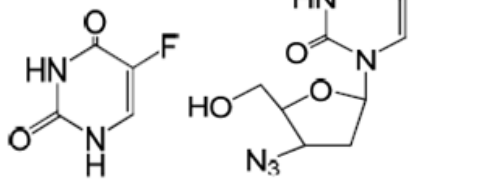
Pyrimidines can be considered best as derivatives of pyridine and to a lesser extent, as cyclic amidines. Pyrimidine, which accepts two protons under extremely acidic conditions (pKa1 1.3, pKa2 6.9) is much weaker base than pyridine (pKa 5.23), imidazole (pKa 7.2), or amidines. This is because, unlike imidazole and amidines, the addition of a proton does not increase the possibilities for resonance and hence the resonance energy. It is a surprisingly weaker base than pyridazine (pKa 2.33). Only one of the N- atoms of the pyrimidine alkylated by alkylating agents, such as methyl sulphate but the much more powerful agent triethyloxoniumborofluoride alkylates both N-atoms to give a ring bearing two positive charges. Chemically they are considered as the derivatives of pyridine and to a lesser extent as cyclic amidines. They are weaker base than pyridine, imidazole, or amidines. This is because the addition of protons does not increase the possibilities for the resonance and resonance energy. Though there is similarity in the shape of pyrimidine to that of benzene and pyridine, the differences between the bond angles and distance of these ring systems suggest that the pyrimidine is least aromatic amongst them.

Electrophilic Reactions:

From the consideration of the charged structures contributing to the resonance hybrids represent pyrimidine, pyridine and the pai electron densities, it is clear that the position 5 of pyrimidine which should correspond to position 3 of pyridine and be the most susceptible in the ring to electrophilic attack.

Nucleophilic Reactions:

In a similar way position 2,4 and 6 of pyrimidine formally correspond to those of 2 or 4 of pyridine and in the few cases investigated are attacked by nucleophilic reagents such as sodamide ($NaNH_2$) and phenyl magnesium bromide (PhMgBr). Pyrimidine is attacked at the 2 and 4-positions by the 4 nitro phenyl radical. Halogen atoms, methoxy and methyl mercapto groups at positions 2,4 or 6 of a pyrimidine can be replaced by amino groups on treatment with ammonia or by hydroxyl groups on hydrolysis with dilute mineral acid (HCl). Over the years, the pyrimidines system turned out to be an important pharmacophor, interacting with the synthesis and function of nucleic acids e.g. the cytostaticum fluorouracil (**14**) [9] or the HIV drug zidovudine (**15**) [10]. Ultrashort acting barbiturate such as thiopental sodium (**16**) (Pentothal) [11] are often used as general anesthetic, where as methyl phenobarbital (**17**) [12] still is in use as antiepilepticum. Some diaminopyridines such as pyrimethamine (**18**) [13] or trimethoprim (**19**) [14] are powerful antimalaria drugs. Used in combination with sulfonamides as potent antibacteriostaticum, whereas minoxidil (**20**) [15] is used as antihypertensivum. Sulfadiazine (**21**) [16] is one of the chemotherapeutic containing a pyrimidine moiety.



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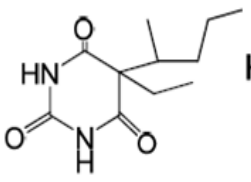

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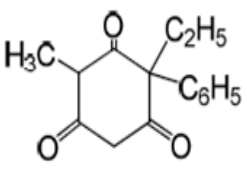

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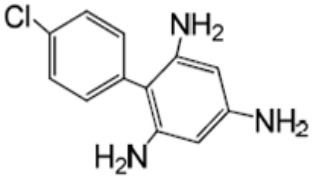
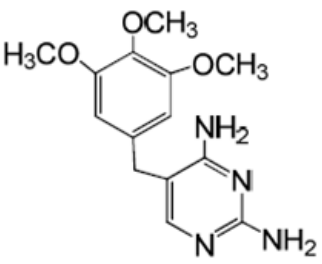
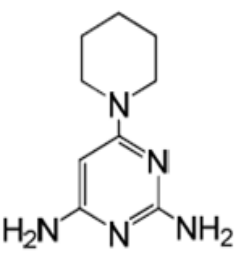
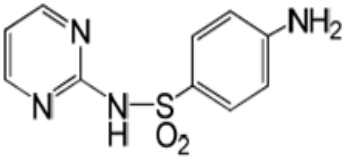






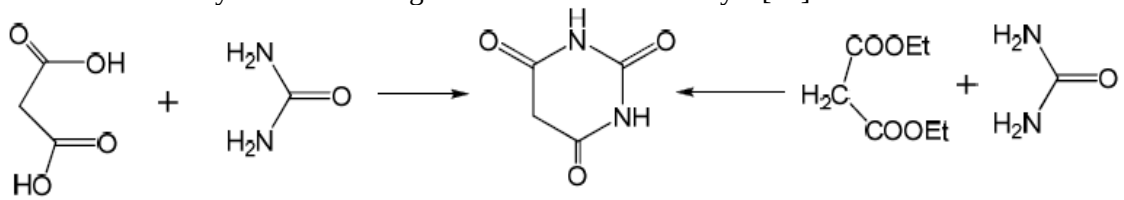


18 **19** **20** **21**

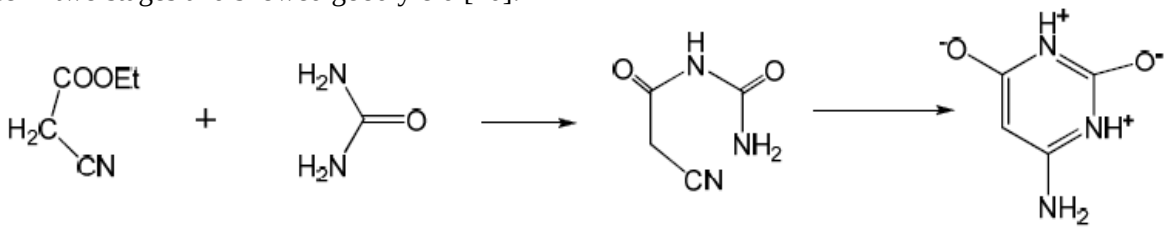
Synthetic Methods of Pyrimidines:

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-ketoesters, malonic ester, β-aldehydo or β-ketonitrile and much other combination of these groups or their masked derivatives may be used. The N-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 [17], guaidine [18], urea or thiourea [19] to produce 4,6-dimethyl pyrimidines. Although the pyrimidine ring system has been built up in a number of ways, the most common and versatile method is the one in which the ring is formed from two compounds, which contribute the N-C-N and C-C-C fragments. Some of the synthetic methods described below.

Method 1: Synthesis of barbituric acid from malonic acid, urea and phosphorus oxychloride was the earliest type. It was also synthesized from ethyl malonate using sodium ethoxide as catalyst [20].

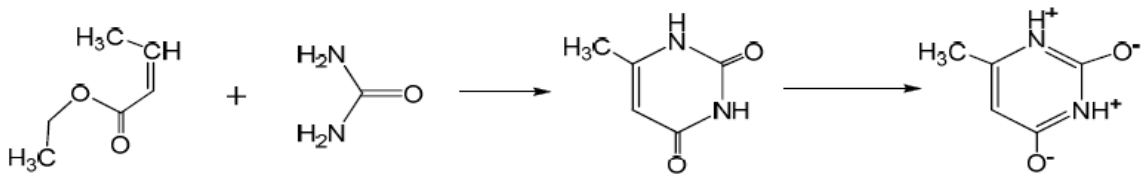


Method 2: A variation in general synthesis is to replace the ethylmalonate by ethylcyanoacetate. The reaction takes place in two stages and showed good yield [20].



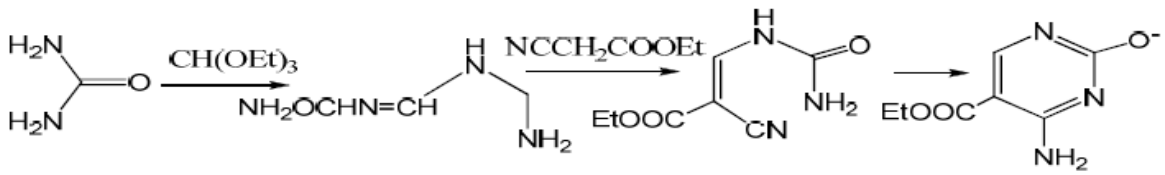
Method 3:

Another synthesis involves the condensation of amidines or ureas with the unsaturated compounds such as ethyl crotonate under basic conditions. Here the Micheal addition to the double bond is followed by the cyclization. The resulting dihydropyrimidine is readily oxidized [20].



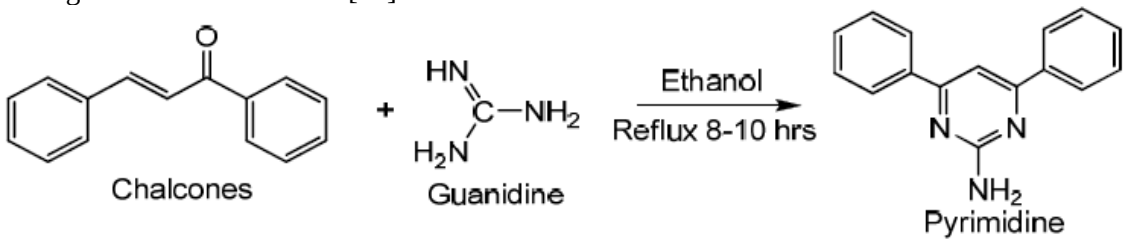
Method 4:

The very convenient method was to synthesize from ethyl orthoformate, which reacted with thiourea or urea to obtain the corresponding formamidines. These were then refluxed in the presence of the inert solvent to yield ethylenes. The reaction can also be carried out by heating the three reactants together in an inert solvent in the presence of sodium ethoxide as a catalyst. The overall yield from this method is very good [20].



Method 5:

The method of synthesis that is followed in the present research work is through chalcone as an intermediate. Here chalcone was condensed with guanidine nitrate in the presence of a base i.e. aqueous NaOH. The reflux condition was maintained during the course of reaction [21].

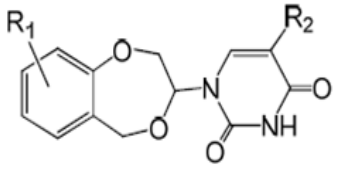


Various biological activities of Pyrimidine derivatives:

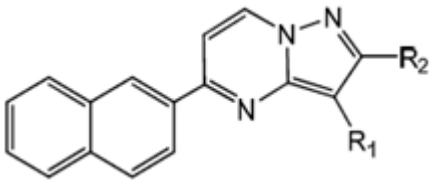
Pyrimidine derivatives have been reported to have some important activities.

Anticancer activity/Antitumor/Antiproliferative:

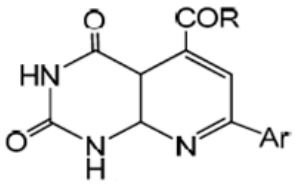
The synthesis of (1,3,5-tetrahydro-4,1-benzoxazepine-3-yl)-pyrimidines (**22**) and evaluated their anticancer activity, these compound showed significant antitumor activity (IC_{50} = 1.25-6.75 µM on MCF-7cell) [22]. The synthesis of pyrazolo[1,5-a]pyrimidine derivative (**23**). For evaluation of antitumor cytotoxicity of synthesized compounds, four different human cancer cell lines were used; HepG2 (Liver carcinoma cell line), MCF-7 (Breast carcinoma cell line), HCL 116 (Colon carcinoma cell line). Pyrazolo [1,5-a]pyrimidine derivative exhibited potent antitumor activity against above human cancer cell lines [23]. The synthesized pyrido [2,3-d]pyrimidines derivatives (**24**) and these compounds were tested for *in-vivo* antitumor activity against lung (H466) and Liver (HEPG2) carcinoma cells. Compound showed moderate activity against Lung carcinoma cell lines (H460) [24].



22 R_1=OCH_3; R_2=H,F



23 R_1= CONH-C_6H_4, $CONHC_6H_4$-4CH_3, CONHC6H4-4Cl; R_2=SCH_3, NHC_6H_5



24 R= 2-thienyl, 2-furyl, 2-naphthyl; Ar=C_6H_5, C_6H_4, 4-OCH_3

The synthesized pyrimidine bridged thiadiazole derivatives. 5-{(4,6-disubstituted pyrimidine-2-yl)thiomethyl}-*N*-phenyl-1,3,4-thiadiazol-2-amines (**25**) were tested for their anticancer and antioxidant activity against human Breast MCF 7cell lines [25]. The 10-nitro-4-(substituted phenyl)-1,3,4,5,6,7-hexahydro-2*H*-benzo[6,7]-cycloheptal[1,2-d]pyrimidine-2-thione derivatives (**26**) for its anticancer activities.

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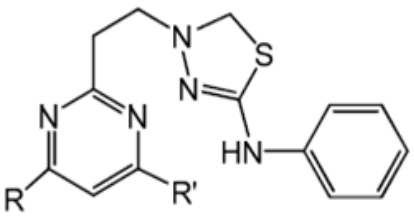
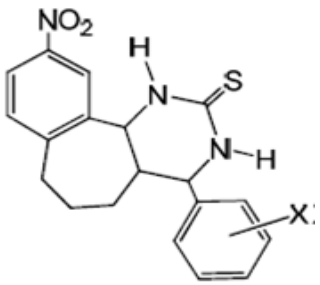
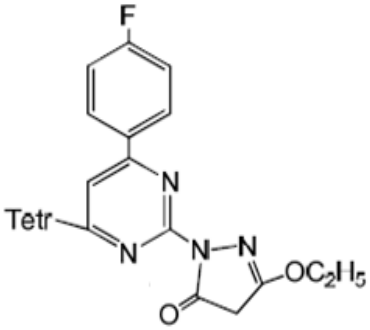


25 R=C_6H_5, 2-OC_6H_5, 4-NO_2C6H5; R'= C_6H_5, 4-$OCHH_3C_6H_5$, 2-OHC_6H_5, CH=CH C_6H_5

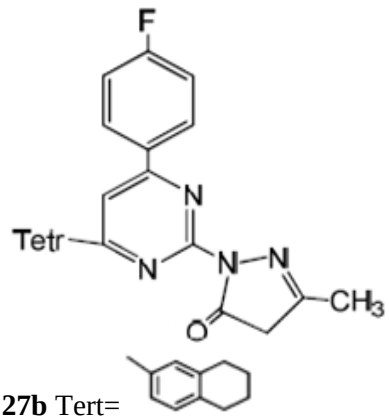


26 X=p-NO_2, 3,4,5-$(OCH_3)_3$

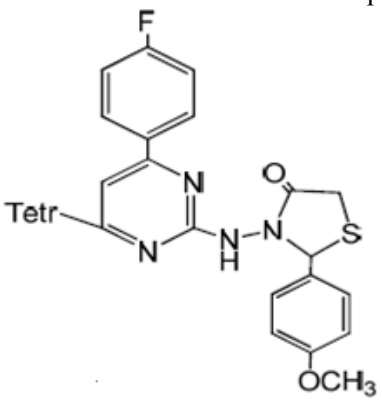
These compounds were tested at five different concentrations against 60 cell lines of nine types of human cancers namely Leukaemia, Lung, Colon, CNS, Melanoma, Ovarian, Renal, Prostate and Breast cancer. These compounds exhibited better *in-vitro* antitumor activities at low concentration (log10GI50 = -4.7) against the used human tumor cell lines [26]. The synthesis of three tetralin-6-ylpyrimidines (**27a, 27b** & **27c**) and screened them for anticancer activity. The anticancer activity of some of the prepared compounds was evaluated using two human tumor cell lines representing Liver and Breast. The compounds tested were in most of the cases, selective towards Liver cancer. The compounds (**27a** & **27b**) were active against Liver cancer cell (Hep G2) with IC_{50}=8.66 and 7.11µg/mL respectively while (**27c**) compound showed dual activity (IC_{50}=5.50 and 7.29µg/mL) for Liver and Breast cancer respectively [27].



27a

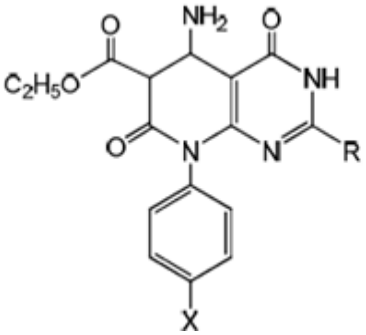


27b Tert=

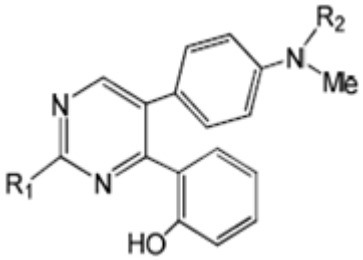


27c

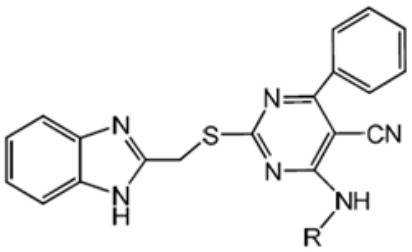
Pyrido(2,3-d)pyrimidine carboxylate derivatives (**28**) was synthesized, cytotoxic activity of synthesized pyrimidine derivatives using three human cancer cell lines that is Colon cancer (HT29), Liver cancer (HepG2) and Cervical cancer (Hela) was evaluated with MTT assay showed significant activity. The LC_{50} of the synthesized pyrimidine derivatives was found to be >100 µg/mL for all these cell lines [28]. New 2,4,5-substituted pyrimidine derivatives (**29**) and evaluated *in-vitro* for inhibition against human hepatocellular carcinoma BEL-74502 cell proliferation. Several compound show potent anticancer activity with an IC_{50} less than 0.10 µM from the current investigation. Structure activity relationship of these compound suggest electron donating group at the 2-position of pyrimidine will determine anticancer activity and *para* substitution of aromatic ring B with suitable less bulky electron donating group will increase anticancer activity [29].



28 X=F,Cl, Br R=$COOCH_3$, OCH_3



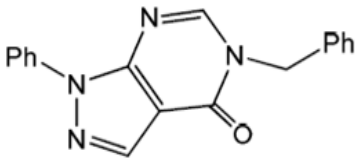
29 R1=CH_3, NH_2; R_2= H, CH_3, C_2H_5



30 R=NH_2, NHC_6H_5, C_6H_4N, $NHCSNH_2$, $CSNH_2$, $CONH_2$

The synthesis of novel benzimidazole pyrimidine conjugates (**30**) as potent antitumor agent, evaluation of the synthesized compounds for their *in-vitro* cytotoxic activity against twelve cell lines namely, Cervical carcinoma (KB), Ovarian carcinoma (SKOV-3), CNS cancer (SF-268), Lung cancer (NCI H460), Colonoadenocarcinoma (RKOP27),

Leukaemia (HL60, U937, K562), Melanoma (G361, SK-MEL-28) and Neuroblastoma (GOTO, NB-1) revealed their marked potency when compared with anticancer drug [30]. The pyrazolo (3,4-d) pyrimidine derivatives and tested it for *in-vitro* anticancer activity against ehrlich ascite carcinoma cell line. 5-Benzyl-1-phenyl-1,5-dihydropyrazolo(3,4-d)pyrimidin-4-one (**31**) showed intermediate anticancer activity compared to doxorubicin as positive control with IC50 values of 90 µg/Ml [31]. Novel pyrimidine derivatives of 2,3-dibenzyl-6-deoxy-L-ascorbic acid (**32a**) and 4,5-didehydro-5,6-dideoxy-L-ascorbic acid (**32b**) were synthesized. The synthesized compounds containing 5-flouro-substituted uracil ring showed the most significant antitumor activities against murine Leukaemia L1210/0 (IC_{50}=1.4 µg/mL) murine mammary carcinoma FM3A/0 (IC_{50} = 0.78 µg/mL) and CEM/0 cell lines (IC_{50} =20.9 µg/mL).



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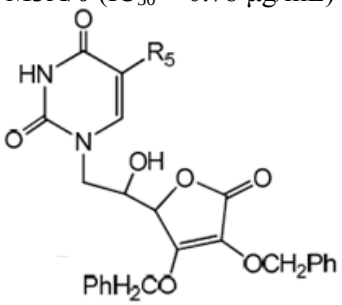
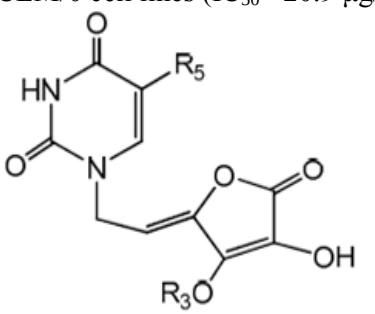
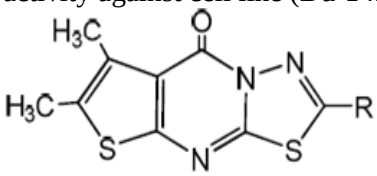


32a R_5=H,F,CF_3

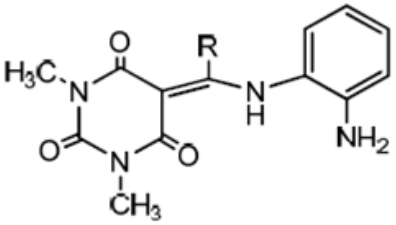


32b R_3=H. Benzyl

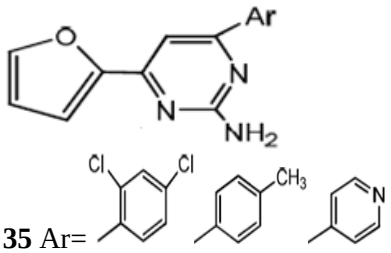
Anticancer activity of some substituted(1,3,4)thiadiazolo thieno[3,2-e]pyrimidin-5(4*H*)-ene (**33**). The compound showed activity against Lung, Breast and other cancer [33]. The 5-benzoyl/5-carbaldehyde-/5-(3-phenyl acryloxy-6-hydroxy-1*H*pyrimidine-2,4-diones with ammines provided the corresponding amines (**34**). The investigation for anticancer activity of molecule at 59 human tumour cell lines representing on Leukaemia, Melanoma and cancer of Lung, Colon, Brain, Ovary, Breast and Renal cancer [34]. The synthesis of some new pyrimidine derivatives (**35**). The synthesized pyrimidine derivatives were tested for anticancer activity on Du-145 cell line (Prostate cancer) by MTT based cytotoxicity assay. The IC_{50} value for pyrimidine revealed that they are not having any significant anticancer activity against cell line (Du-145) [35].



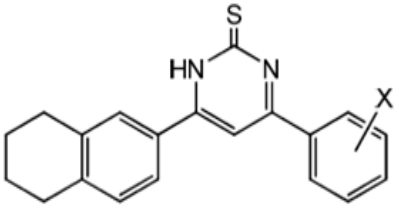
33 R=H,CH3, CH2CH2CH3, NHCH3, NHC6H5



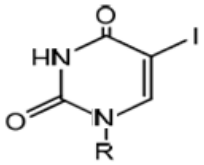
34 R=H,CH=CH-Ph,Ph



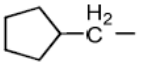
35 Ar=



36 X=2,6-Cl_2, 2,6-F_2



37 R= CH2CH2CH2CH3,

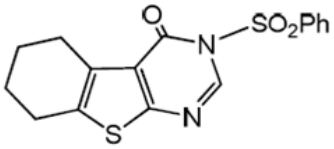


Some 2-thioxopyrimidine derivatives (**36**). The newly prepared compounds were evaluated for anticancer activity against two human tumour cell lines. Some compound showed the highest potency with IC_{50}=3.5 and 4.5 µg/mL against a Cervix carcinoma cell line (Hela) & Breast carcinoma cell line (MCF7), respectively [36]. The *N*-substituted-

5-iodouracils (**37**) and evaluated their anticancer activity. Cyclohexylmethyl analogues inhibited the growth of HepG2 cells significantly. *N*-1,*N*-3-dicyclohexylmethyl analogue displayed the most potent anticancer activity, with an IC**50** of 16.5 µg/mL [37].

Antimicrobial activity:

Some thienopyrimidine derivative and the synthesized compound (**38**) were screened for their antibacterial activity against *B. cereus* (BTCC 19), *S. dysenteriae* (AE 14396) and *S. typhi* (AE 14612). The compound were also screened for their antifungal activities against *M. phaseolina*, *F. equiseti*, *A. alternate* and *C. corchori* and showed good to excellent activity against all the fungi [38]. *N*-(*N*-Alkoxyphthalimido)-4,6-diaryl-5,6-dihydropyrimidine-2-thiones (**39**) prepared and tested against bacterial strains *K. pneumonia*, *E. coli*, *S. typhi*, *P.aeruginosa*, *P. mirabilis* and fungi (500ppm) *C. albicans and A. fumigates* [39]. Various derivatives of pyrimidines (**40**). The fungicidal activities of the compounds were evaluated against *P. infestans* and *C. falcatum* by the usual agar plate technique at 1000, 100 and 10 ppm concentration [40].



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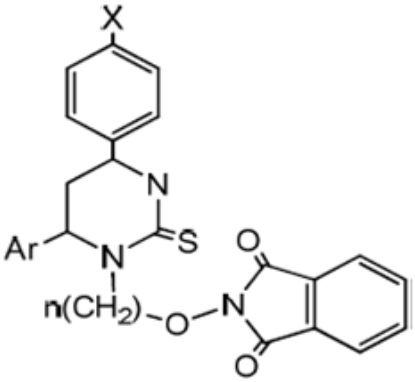
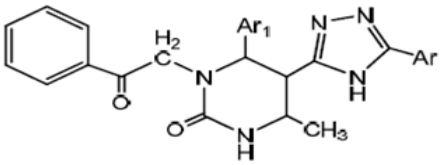


39 X=CH_3,Cl; Ar=C_6H_5, ClC_6H_4, $OCH_3C_6H_4$; n=2,3,4



Ar=C_6H_5, p-ClC_6H_4, m-$NO_2C_6H_4$, p-$OCH_3C_6H_5$

Ar_1= m-$NO_2C_6H_4$, p-$OCH_3C_6H_5$

The 5-[5'-substituted-1,3,4-oxadiazol-2-yl)dihydropyrimidinon (**41**) and screened for their antimicrobial activity against *S. aureus* and *E. coli* using Norfloxacin as standard. Antifungal activity was also evaluated by using *A. niger* and *C. albicans* using Grisofulvin as standard [41].

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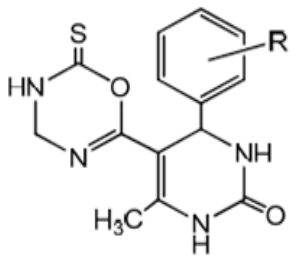
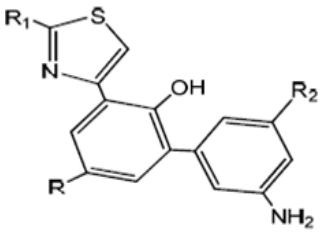


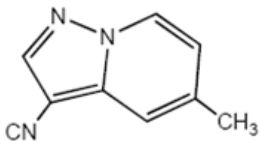
41R=H,4-OCH_3,3-NO_2



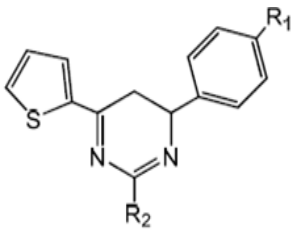
R=CH3,Cl

R1=C6H5, 4-C6H4Cl

R2=4-OCH3, 4-Cl



43



R1=Cl,Br

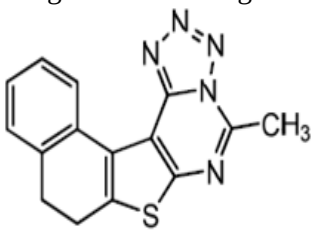
R2=SC_2H_5, NHNH2

The 2-amino-6-substituted thiazolyl pyrimidine compounds (**42**) with 4-chloro and 4-methoxy substituent at four position showed significant antifungal activity [42]. The 2-cyano-5-methylpyrazolo [1,5-a]pyrimidine derivatives (**43**) 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 [43]. Various 2,6-disubstituted pyrimidine (**44**), pyrazoline and pyran

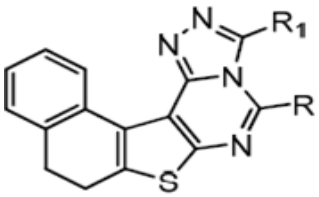
derivatives were synthesized starting from their chalcone derivative. The synthesized compounds displayed different degrees of antimicrobial activity against *B. subtilis* (Gram positive), *P. aeruginosa* (Gram negative) and *Streptomyces* species (Actinomycetes) [44]

Antiinflammatory, analgesic and ulcerogenic activity:

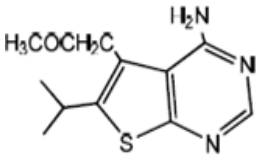
Thienotetrazolo pyrimidines (**45a**) and thienotriazolopyrimidine derivatives (**45b**) prepared and evaluated for their antiinflammatory activity. These synthetic derivatives showed patent activity in carrageenan test [45]. The thieno[2,3-d]pyrimidine derivatives (**46a-c**) as antiinflammatory, analgesic and ulcerogenic activity. 5-Methyl-6- phenyl-2-thioxothieno[2,3-*d*]pyrimidone derivative reacted with hydrazonoyl chloride derivatives to afford triazolo-thienopyrimidones. Also, acetone-1-(2-amino-5-isopropylthiophene-3-carbonitrile) reacted with functional and bifunctional groups to yield the corresponding compounds (**46b,46c**). The new products showed antiinflammatory, analgesic and ulcerogenic activities comparable to that of Indomethacin and acetylsalicylic acid, respectively [46].



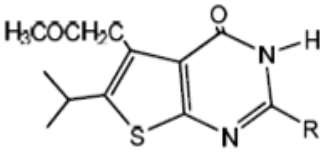
45a



45b R=C2H5 R1=H, CH3



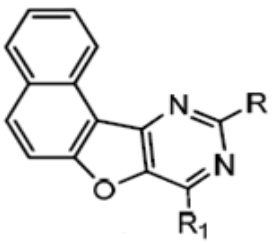
46a

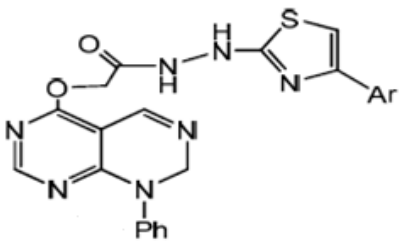


46b R=H

46cR=CH3

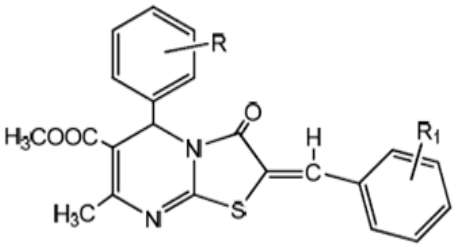
Naphtho[2,1-b]furo[3,2-d]pyrimidine derivatives (**47**) were reported and carrageen induced rat paw edema method was employed for evaluating their antiinflammatory activity. The compounds were given at a dose of 80 mg/kg body weight in albino rats weighing between 150 and 200 gm. The edema was produced by injecting carrageenan solution at the left hind paw [47]. Some new 2-[cl-phenyl-1*H*-pyrazolo[3,4-d]pyrimidin-4-yl)aceto hydazide derivatives (**48**) and screened for their analgesic activity by acetic acid induced writhing test using standard drug Diclofenac sodium [48].





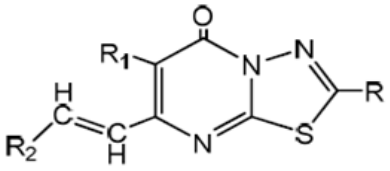
47 R=CH_3, C_6H_5 R_1=OCH_3, OC_2H_5, NHC_2H_5, **48** NHC_6H_5

A series of new 2-benzylidene-7-methyl-3-oxo-5-(substituted phenyl)-2,3-dihydro-5*H*-thiazolo[3,2a]pyrimidine-6-carboxylic acid methyl esters (**49**) by reacting 1,2,3,4-tetrahydropyrimidine-2-thiones with chloroacetic acid and substituted benzaldehydes. The synthesized compounds were tested for their antiinflammatory activity by using carrageenan inducing rat paw edema method. Test results observed that compounds **49a-49d** showed moderate antiinflammatory activity at the 100 mg/kg dose level compared with standard drug Indomethacin [49]. The thiadiazolopyrimidines derivative (**50**) and evaluated their antiulcer activity in albino rats. The synthetic compound showed moderate activity as compared with standard drug [50].



49a-49d

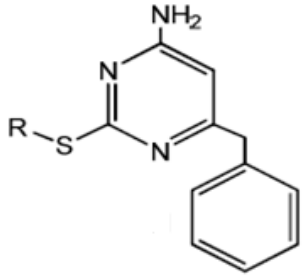
49a R=Br R1=4-OCH3
49b R=Br R1=4-OCH3
49c R=F R1=4-H
49d R=F R1=4-OCH3



50 R=4-Tolyl
R1= Alkyl
R2=3-Pyridyl

Anti-HIV activity:

Novel 2-aryalkylthio-4-amino-6-benzylpyrimidines (**51a-51h**), which can be considered as S-DABO and TMC-125 analogue hybrid molecules have been designed and synthesized as inhibitors of HIV-1 RT. The results clearly indicated that the changes at the N-3/C-4 position of pyrimidine ring could affect the hydrogen bonds strength and number between N-3/C-4 and the Lys101 residue which are indispensable for anti-HIV-1 RT activity. The biological activity results are also in accordance with the docking study [51].

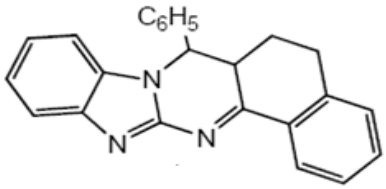


51a-51h

51a R=$C_6H_5CH_2$
51b R=$C_6H_5CH_2CH_2CH_2$
51c R=(m-CH_2)$C_6H_4CH_2$
51d R=$C_6H_5(CH_3)CH_2$
51e R=$C_6H_5CH_2CH_2$
51f R=(OCH_3)$C_6H_4CH_2$
51g R=(m-OCH_3)-$C_6H_4CH_2$
51h R=naphthylmethyl

Antidiabetic activity:

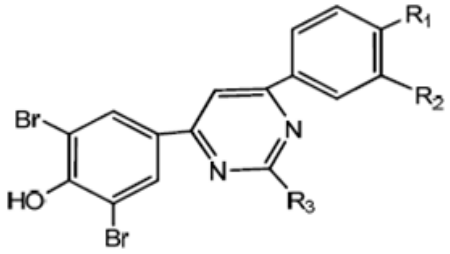
Azolopyrimidine derivatives (**52**) and synthetic compounds were evaluated for their hypoglycemic activity. The result showed moderate to remarkable activity [52].



52

Herbicidal activity:

The 2-piperidinye/1-pyriralidinyl-4-substitutedphenyl-6(3,5-di bromo-4-hydroxyphenyl)-pyrimidines (**53**). The 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. The minimum sample used in this test was 250mg [53]. Herbicidal activity has been reported in 5,7,7-trimethyl-7(*H*)-1,3,4-thiadiazolo(3,2-a) pyrimidines (**54**) for mono and dicotyledenous weeds in sugar beet [54]. Some thiadiazolopyrimidines derivatives (**55**) as a potential herbicidal agents [55].



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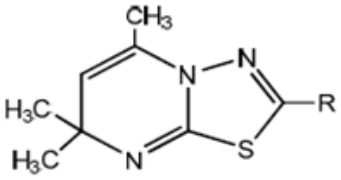
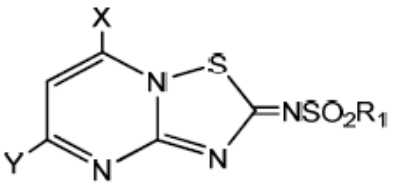


54 R=phenyl, substituted phenyl



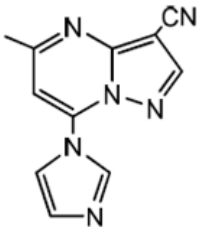
55

R= **substituted phenyl, pyridazinyl**

X,Y=CH3, C2H5, CH3OH, C2H5O

Hypnotic activity:

Synthesized and hypnotic activity of pyrazolo[1,5-a] pyrimidine derivatives (**56**). The newly designed target compounds, resemble the structural feature of Zaleplon with caronitrile substituents at the position of pyrazolo[1,5-a] pyrimidine ring [56]. A series of 3-phenyl/ethyl-2- thioxo-2,3-dihydrothiazolo[4,5-d]pyrimidin-7-yl urea and thiourea derivatives (**57a,57b**). All the synthesized compounds were evaluated for their antiparkinsonism activity in catalepsy induced by haloperidol in mice after intraperitoneal administration. Most of the compounds exhibited significant antiparkinsonism activity [57]. A series of thiazolo[4,5-d]pyrimidinethiones and ones (**58**) and evaluated their antipsychotic activity by antagonizing the activity of corticotrophin releasing factor. Compounds showed better antipsychotic activity [58]. The (1-substituted)thienotriazolopyrimidines derivatives (**59**) and screened their anticonvulsant activity in mice and reported to be potential anticonvulsant agents.



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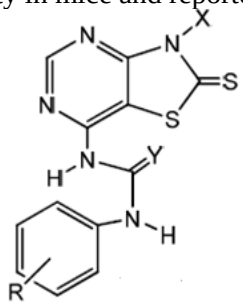
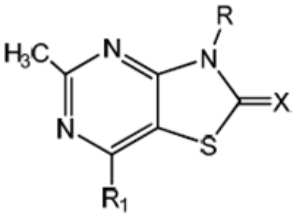


57a, X=C_6H_5, Y=O R=2-OCH_3

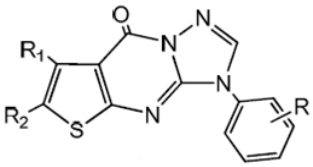
57b X=C_2H_5, Y=S R=2-OCH_3



58 X=O,S

R=2-Br-4-isoprpyl-C6H5; 2,4,6-Trimethyl-C6H5

R1=Morpholino; N(C6H5)2 NC2H5But; N(CH2CH2OCH3)2



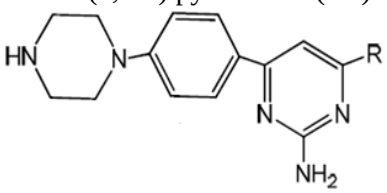
59

R=H,4-OCH3, 2-Chloro

R1=R2=Methyl, (CH2)4

Antihistaminic activity:

A pyrimidines derivatives (**60**) by the condensation of chalcones of 4-piperazine acetophenone with guanidine HCl and evaluated their antihistaminic activity [60]. The 6-(2-cyclohexylethyl)1,3,4-thiadiazolo(3,2-a)pyrimidin-5(4*H*)-ones derivatives (**61**) and have reported as allergy inhibitors [61]. The (2-substituted)-1,3,4-thiadiazolo(3,2-a)1,2,3-triazolo(4,5-d) pyrimidin-9(3*H*)-ones derivatives (**62**) and evaluated their antiallergic activity [62].



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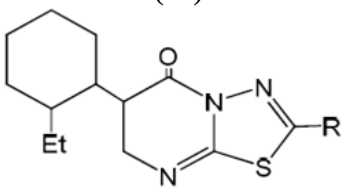
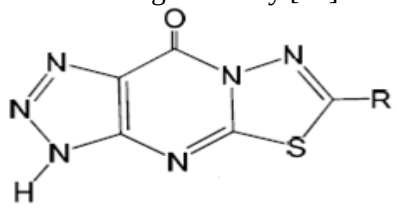


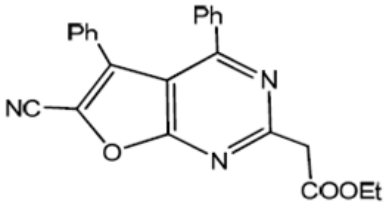
61 R= Akyl, Halogen, alkenyl



62 R=Cyclopentyl, cyclopentylpropyl, cyclopentylmethyl

Molluscicidal activity:

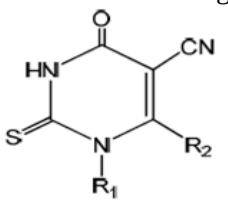
Molluscicidal activity of some substitute furan and furo[2,3-d] pyrimidine derivatives (**63**). The molluscicidal activity of the synthesized compounds towards *Biomphalaria alexanrina* snails was investigated and showed weak to moderate activity [63].



63

Antinociceptive activity:

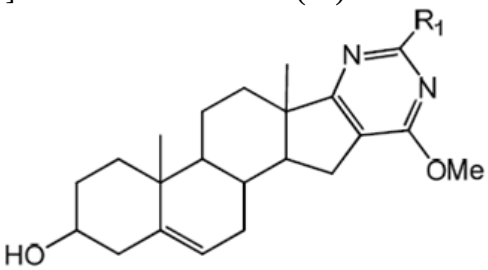
The *N*-1,6-disubstituted-5-cyano-2-thiouracil derivatives (**64**). The titled compounds were screened for antinociceptive activity using acetic acid induced writhing in mice in the dose of 5mg/kg body weight by *intraperitoneal* [64].



64

Steroidal like compound:

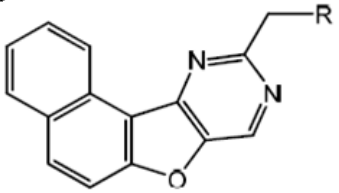
Steroidal heterocycles containing the pyrazole and pyrimidine ring fused to the 16, 17-position of steroidal nucleus and reported. androstenolone acetate reacted with carbon disulfide, indomethane and sodium hydride to furnish 3-acetoxy-16-[bis(methylthio) methylene]-5-androst-5-en-17-one (**65**).



65

Anthelmintic activity:

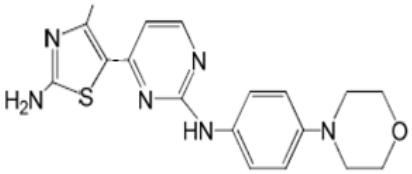
2-Alkyl/aryl amino methyl-4-alkyl/arylnaphtha[2,1-b]furo[3,3,2-d]pyrimidines (**66**) prepared and screened their anthelmintic activity on earth worms *Pheretima posthuma*. The compounds were tested at a dose of 0.001 mol/mL suspended in tween-80 piperazine citrate suspension was taken as standard and showed remarkable activity [66].



66

Some anticancer drugs (marketed, under clinical and preclinical studies):

Some biologically active anticancer agents having benzimidazole and other related heterocyclic moiety, for example, CYC116 (**67**) [67].



67

Some biologically active anticancer agents having pyrimidine and other related heterocyclic moiety for example, CGP60474 [68], Olomoucine (R_1=H, R_2=Me), *N*-9-Isopropylolo-moucine (R_1=H, R_2=iPr) [69], Fluorouracil [70], NU6027 [71], Troxacitabine [72], Mercaptopurine [73], Cytarabine [74], Gemcitabine [75], Tegafur [76], Capecitabine [77], Decitabine [78], ClNK4 [79], Thiarabine [80], Ara-C [81], Uramustine [82], CNDAC [83], Forodesine [84], Nimustine [85] and Trimetrexate [86].

In view of these points, some new pyrimidines and pyrimidine endowed with other heterocyclic ring system; with the hope of getting promising agents. Therefore, a number of hybrid molecules were synthesized and screened.

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