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Review Article

Pyrimidine As Anticancer Agent: A Review

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ABSTRACT

The chemistry of pyrimidines is a blossoming field for the study of their pharmacological uses. Numerous methods for the synthesis of pyrimidine as also their diverse reactions offer enormous scope in the field 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 the recent work on the anticancer synthetic pyrimidine compound and the chemistry and biological activities of pyrimidines during past year.

Keywords: Pyrimidine, Anticancer Activity, Nucleic acid.

1. INTRODUCTION

Pyrimidines are the most important six member heterocyclic containing two nitrogen atoms (Fig.1). Pyrimidines are present among the three isomeric diazines.

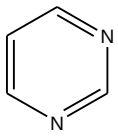


Figure 1

Several (mainly uracil, thymine and cytosine (Fig.2)) pyrimidines have been isolated from the nucleic acid hydrolyses. The nucleic acid are essential constituent of all cells and thus of all living matter cytosine is found to be present in both types of nucleic acids i.e. ribonucleic acid (RNA) and deoxyribonucleic acid (DNA) while uracil present only in RNA and thymine only in DNA [1].

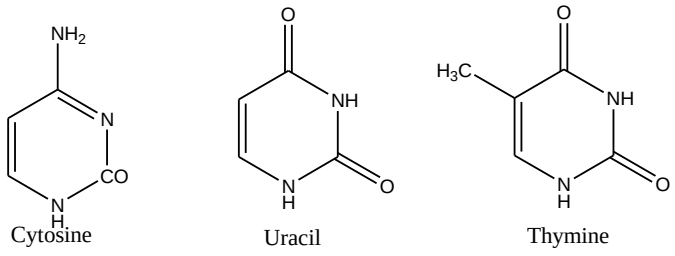


Figure 2

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 (Fig.3) which are used as hypnotics [2].

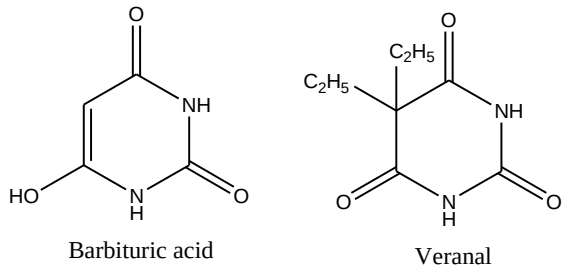


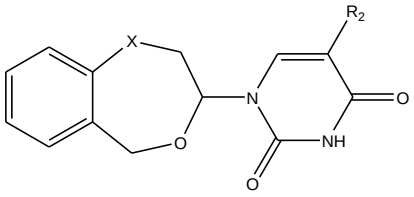
Figure 3

The literature indicated that compound having pyrimidine nucleus possesses broad range of biological activity like 5-flourouracil as anticancer; Idoxuridine & Triflouridine as antiviral; Zidovudine & Stavudine as anti-HIV; Trimethoprim, Sulphamethiazine, Sulphadiazine as antibacterial; Minoxidil & Prazosin as antihypertensive; Phenobarbitone as sedative-hypotic & anticonvulsant; Propylthiouracil as antithyroid; Thinozylamine as H_1-antihistaminics and Fervennuline as antibiotics [3] .

As a result of remarkable pharmacological activity of pyrimidine derivatives, intensive research has been made focused on anticancer activity. The present review highlights the anticancer activity of pyrimidine derivatives.

2. PYRIMIDINE AS A TEMPLATE FOR VARIOUS BIOLOGICAL ACTIVITIES

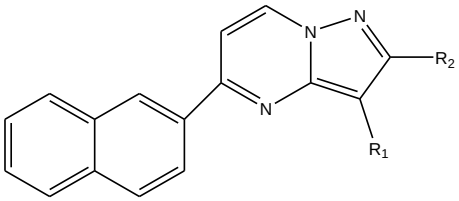
M. D. Gavilan *et al* [4] reported the synthesis of (1, 3, 5-tetrahydro-4, 1-benzoxazepine-3-yl)-pyrimidines and evaluated for anticancer activity, these compound (Fig. 4) showed significant antitumor activity (IC_{50} =1.25-6.75µM on MCF-7cell).



X=0 R_1=OCH_3,H R_2=H,F

Figure 4

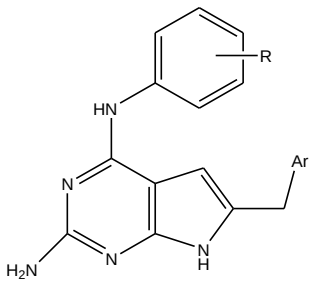
O.M, Ahmed *et al* [5] have studied the synthesis of Pyrazolo [1, 5-a] pyrimidine derivative. For evaluation of antitumor cytotoxicity of synthesised compounds, four different human cancer cell lines were used; HepG2 (liver carcinoma cell line), MCF-7 (breast carcinoma cell line), HCL 116 (colon carcinoma cell line). Pyrazolo [1, 5-a] pyrimidine derivative (Fig.5) exhibited potent anti-tumour activity against above human cancer cell lines.



R_1= CONH-C_6H_4, CONHC_6H_4-4CH_3, CONHC_6H_4-4Cl
R_2= SCH_3,NHC_6H_5

Figure 5

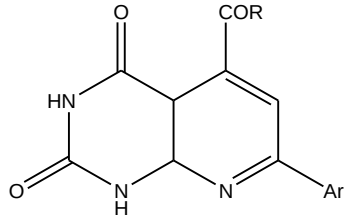
A. Gangjee *et al* [6] reported the synthesis of N^4-phenyl substituted-6(2,4-dichlorophenyl methyl)-7H-Pyrrolo[2,3-d] pyrimidine-2,4-diamines and evaluated for anticancer activity. *In-vivo* antitumor activity of compounds (Fig. 6) was tested at a dose of 35mg/kg and 10 mg/kg of standard compound three times a week by interperitonal route against the B16-F10 (lung clononizing) melanoma implanted in arrthymic male mice.



R=3-Br, 3-CF_3, 3-CCH
Ar= 2-MePh,2,5-diOMePh,2,4-diClPh

Figure 6

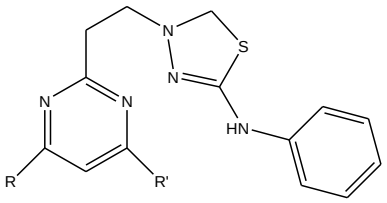
N.R. Mohamed *et al* [7] synthesised pyrido [2, 3-d] pyrimidines (Fig.7) the synthesised compound were tested for *in-vivo* antitumor activity against lung (H466) and liver (HEPG2) carcinoma cells. Compound showed moderate activity against lung carcinoma cell lines (H460).



R=2-thienyl, 2-furyl, 2-naphthuyl
Ar=Ph, C_6H_4.4-OCH_3

Figure 7

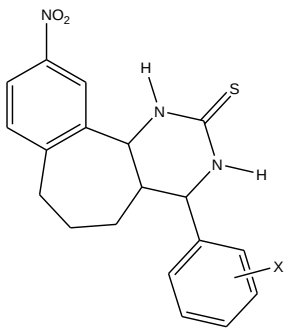
Azam *et al* [8] synthesised pyrimidine bridged thiadiazole derivatives .5-{(4, 6-disubstituted pyrimidine-2-yl) thio methyl}-N-phenyl-1, 3, 4, thiadiazol-2-amines (Fig.8) were tested for their anticancer and anti oxidant activity against human breast MCF 7cell lines.



R=-C_6H_5, -2OH.C_6H_4 and 4-NO_2, C_6H_4
R'=-C_6H_5, 4-OCH_3,C_6H_4,2OH.C_6H_4,-CH=CH-C_6H_5

Figure 8

E. Amr *et al* [9] have studied 10-nitro-4–(substituted phenyl)-1, 3, 4, 5, 6, 7-hexahydro-2H benzo [6,7]-cycloheptal [1, 2-d] pyrimidine-2-thione derivatives for its anticancer activities . 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 (Fig. 9) exhibited better in-vitro antitumor activities at low concentration ($\log_{10}GI_{50}$=-4.7) against the used human tumour cell lines.



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

Figure 9

K. M, Amin *et al* [10] reported the synthesis of tetralin-6-yl pyrimidines and screened them for anticancer activity. The anticancer activity of some of the prepared compounds was evaluated using two human tumour cell lines representing liver and breast. The compounds tested were in most of the cases, selective towards liver cancer. K. M. Amin et al synthesised three tetralin-6yl pyrimidines. The compound 1 and 2 compounds (Fig.10) were active against liver cancer cell (Hep G2) with IC_{50}=8.66 and 7.11 µg/ml respectively, while 3 compound showed dual activity (IC_{50}=5.50 and 7.29 µg/ml) for liver and breast cancer respectively.

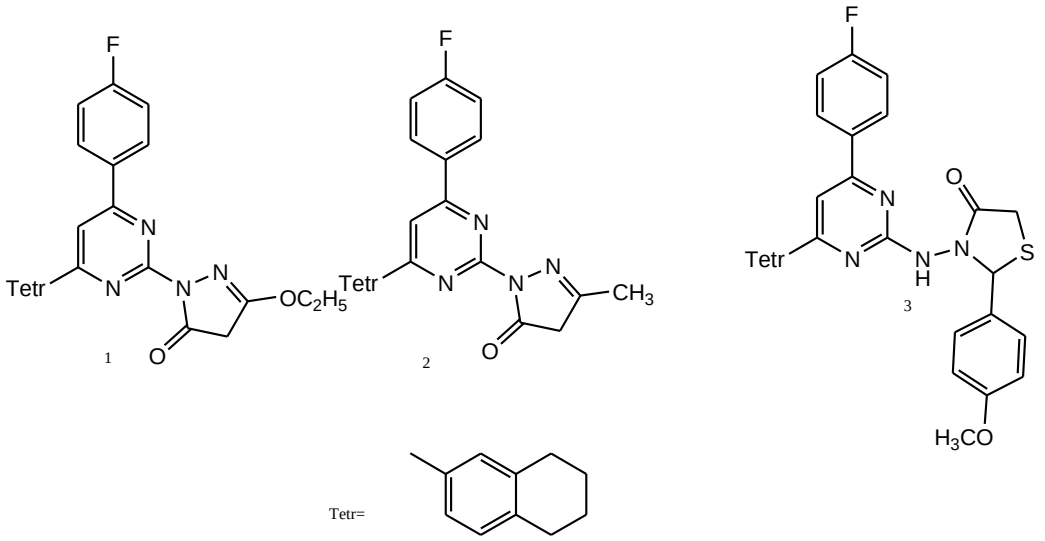


Figure 10

Pyrido (2,3-d) pyrimidine carboxylate were synthesised by P. Shanmugasundaram *et al* [11] , cytotoxic activity of synthesised pyrimidine derivatives using three human cancer cell lines that is colon cancer (HT29). Liver cancer (HepG2) cervical cancer (Hela) was evaluated with MTT assay showed significant activity. The LC50 of the synthesised pyrimidine derivatives (Fig.11) was found to be > 100 µg/ml for all these cell lines.

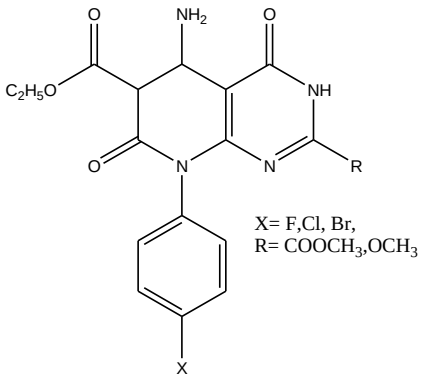
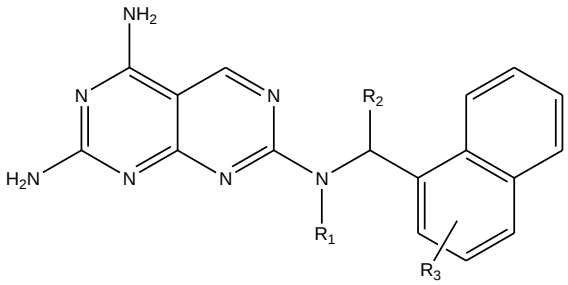


Figure 11

M. Banjane *et al* [12] synthesised pyrimido pyrimidines (Fig.12) as dihydrofolate reductase inhibitor. Inhibitiors of dihydrofolate reductase (DHFR), an enzyme that catalyzes NADPH dependent reduction of 7, 8-dihydrofolate to 5, 6, 7, 8 tetrahydrofolate, thus producing an important cofactor for a number of one carbon transfer reaction and is essential for biosynthesis of purines, pyrimidines and amino acids. Inhibition of DHFR leads to a deficiency of thymidylate (dTMP) thus causing cell growth.



R_1= CH_3, CH_2CH_3, CH_2CH_2OH,CH_2COOH,$CH_2CH_2NH_2$
$CH_2CH_2CH_2CH_3$,$CH_2CH_2CH_2NH_2$
R_2=H, CH_2OH
R_3= 4-CH_3, 4CH_2OH,2CH_2CH_3, 2OCH_2CH_3

Figure 12

F. Xie *et al* [13] synthesised novel 2, 4, 5- substituted pyrimidine derivatives. 2, 4, 5-substituted pyrimidine (Fig.13) derivative were 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.

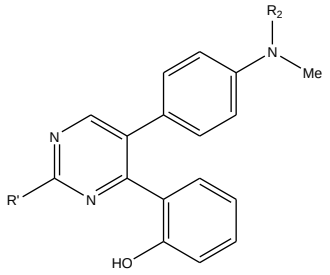


Figure 13

H. T. Abdel- Mohsen *et al* [14] have studied the synthesis of novel benzimidazole pyrimidine conjugates as potent antitumor agent. Evaluation of the synthesised 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 (Fig.14)when compared with anticancer drug.

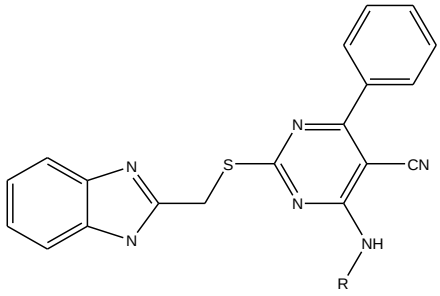


Figure 14

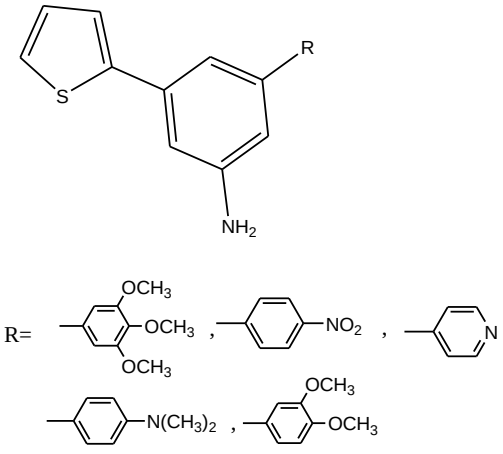


Figure 15

Ramesh B *et* al [15] reported the synthesis of some new pyrimidine derivative. Synthesized compounds were tested for their anticancer activity (prostate cancer) by MTT based cytotoxic assay. DU-145 cell lines were used for the experiment. The screening result revealed that they are not having any significant activity. These compound (Fig.15) used to test on other cancer cell lines in order to predict their activity and usefulness.

O. A. Fathalla *et al* [16] reported the synthesis of some pyrimidine derivatives. The synthesized compounds were evaluated for their antitumor activity against liver cancer (HEPG2) tumour cell line in comparison to known anticancer drug: 5- fluorouracil and doxorubicin. All compounds exhibited growth inhibition activity on the tested tumour panel cell line between 1-10 µg/ml concentrations in comparison the known anticancer drug. It is noticed from the result that the novel derivatives (Fig. 16) induced a significant growth inhibition towards liver cancer(HEPG2) cell line in comparison to 5-FU after treatment with IC_{50} value (ranged from 3.74 to 8.48 µg/ml concentrations) while theIC_{50} value for 5-FU was 5 µg/ml concentration.

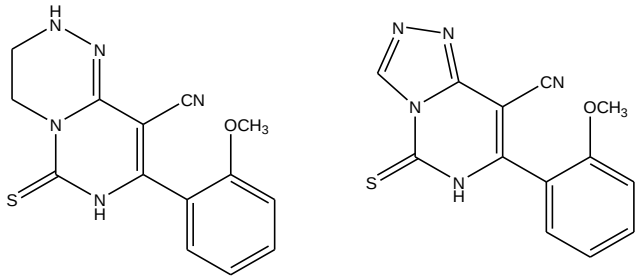


Figure 16

5, 6-disubstituted pyrimidine derivative were synthesized by T.G. Kraljevic *et al* [17]. The compounds were evaluated for their cytostatic activity against human malignant cell lines. All the tested compounds 2, 4-dimethoxy-5-methoxy tri-ethyl pyrimidine and 2, 4-dichloro -5-chloro ethyl pyrimidine exhibited (Fig.17& 18) the most prominent inhibitory effects. Furthermore 2, 4-dichloro-5-chloro ethyl pyrimidine showed marketed activity against human colon carcinoma (IC_{50}=0.4 µM).

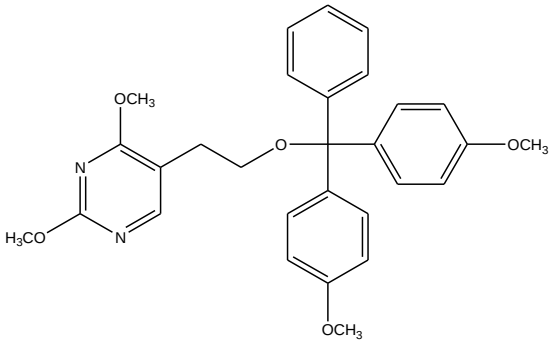


Figure 17

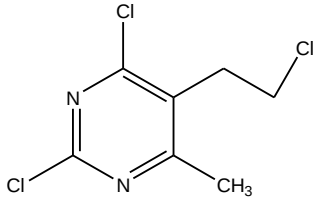


Figure 18

Pyrrolo [2,3-d] pyrimidine derivatives (Fig.19 &20) were synthesised by M. H. Jung *et al* [18]. There in vitro anti proliferative activities against A375 human melanoma cell line and HS27fibroblast cell line were tested. Among all of these derivatives compounds having imidazole & morpholine moieties respectively showed the most potent antiproliferative activity against A375.

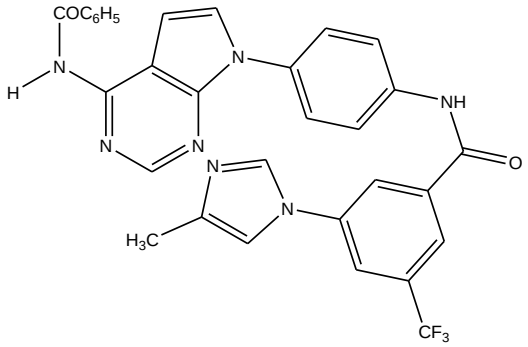


Figure 19

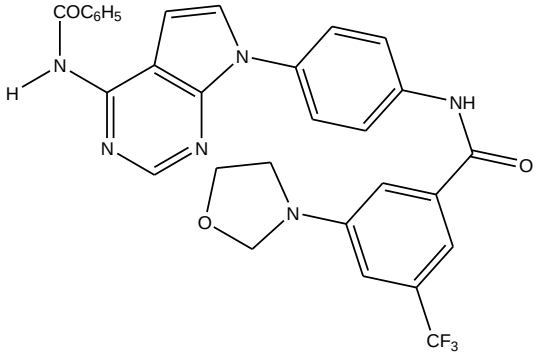


Figure 20

M. M. Ghorab *et al* [19] synthesised new pyrazolo (3, 4-d) pyrimidine derivatives & tested for *in-vitro* anticancer activity against Ehrlich Ascite Carcinoma cell line. 5-Benzyl-1-phenyl-1, 5-dihydropyrazolo (3, 4-d) pyrimidin-4-one showed intermediate anticancer activity compared to doxorubicin as positive control with IC_{50} values of 90µg/ml.

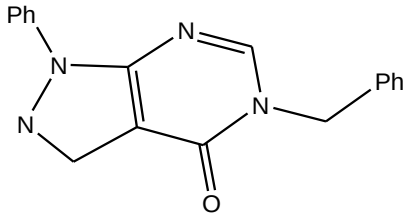
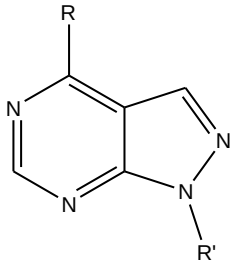


Figure 21

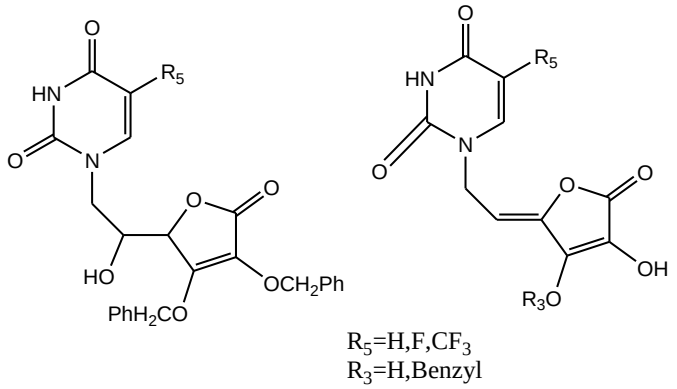
S. Schenone *et al* [20] reported the synthesis of new 1-aryl 4-amino-1H-Pyrazolo(3,4-d) pyrimidine derivatives. A preliminary cellular assay system using the tumour cell line A431 responding to epidermal growth factor (EGF) for its growth shows that the new compounds are potent inhibitors of cell growth.



R=NHC_3H_7,NHCyclopropyl,1-Pyrrolidinyl
1-Piperidinyl,4-Morpholinyl,NHCyclohexyl
R'=CH_2CHCl

Figure 22

Novel pyrimidine derivatives of 2, 3, dibenzyl-6-deoxy-L-ascorbic acid & 4, 5-didehydro- 5, 6- dideoxy-L-ascorbic acid were synthesised by S. R. Malic *et al* [21]. The synthesized compound containing 5-flouro-substituted uracil ring showed the most significant antitumor activities against murine leukaemia L1210/0 (IC_{50}=1.4µg/ml), murine mammary carcinoma FM3A/0 (IC_{50}=0.78 µg/ml) & CEM/0 cell lines (IC_{50}= 20.9 µg/ml).



R_5=H,F,CF_3
R_3=H,Benzyl

23 a **23b**

Figure 23

E. Nassar *et al* [22] synthesized some pyrimidine derivatives linked to indole moiety& evaluated for their antitumor activities against both of human breast cell lineMCF-7& liver carcinoma cell line HEPG2.some compound have significant antiproliferative activities against human breast cell line MCF-7 compared to standard reference drug 5-Flourouracil.

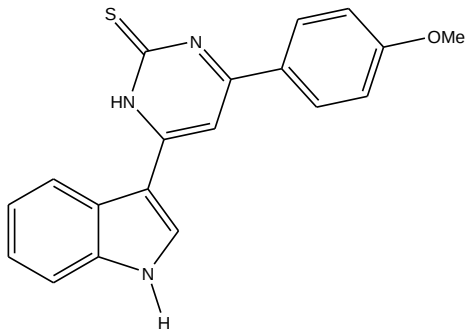
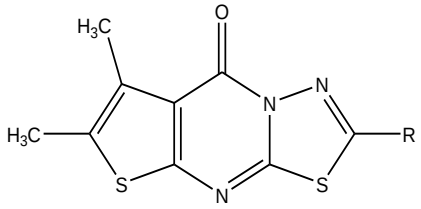


Figure 24

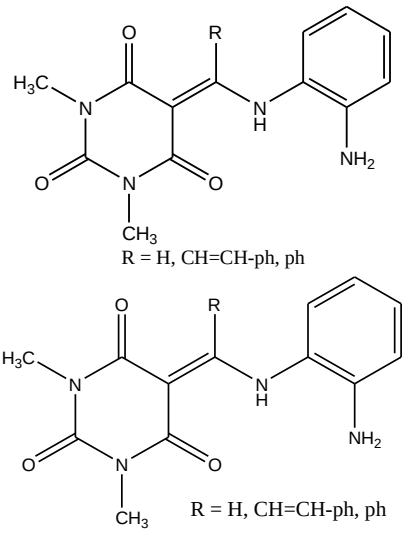
Alagarsamy *et al* [23] described anticancer activity of some substituted (1, 3, 4) thiadiazolo thieno[3, 2-e]pyrimidin-5(4H)-ene. The compound showed activity against lung, breast and other cancer.



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

Figure 25

Palwinder Singh *et al* [24] reacted 5 benzoyl/ 5-carbaldehyde-/ 5-(3-phenyl acryloyl0-6-hydroxy-1H-pyrimidine-2, 4-diones with ammines provided the corresponding amines. The investigation for anticancer activity of molecule at 59 human tumour cell lines representing leukaemia, melanoma and cancer of lung, colour, brain, ovary, breast as well as kidney.

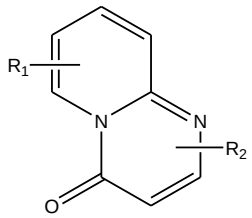


R = H, CH=CH-ph, ph

R = H, CH=CH-ph, ph

Figure 26

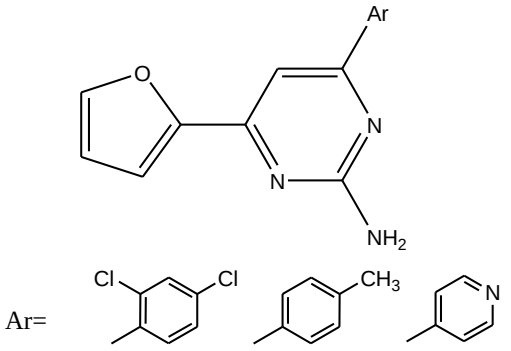
Organic compounds and their complex with various ligand have found many application in biomedicine Al Allaf *et al* [25] describe the preparation of R_2SnCl_2 complex of some 4H-pyrido[1,2-a] pyrimidin-4-one derivatives as donating ligand having multiple doner sites and examine the cytotoxic activity 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

Figure 27

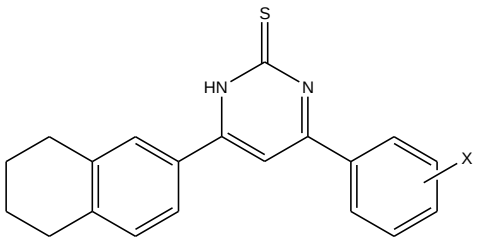
Rao *et al*[25] reported the synthesis of some new pyrimidine derivatives. The synthesized pyrimidine derivatives were tested for anticancer activity on Du-145cell line (prostate cancer) by MTT based cytotoxicity assay. The IC_{50} value for pyrimidine revealed that they are not having any significant anticancer activity against cell line (Du-145).



Ar=

Figure 28

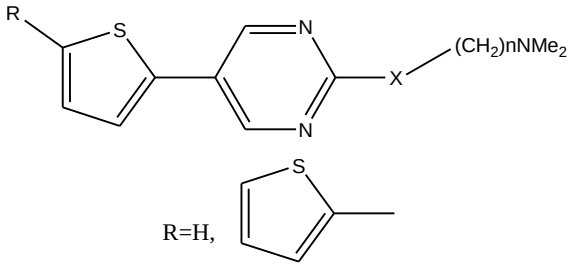
Abdulla *et al* [26] synthesized 2-thioxopyrimidine derivatives. The newly prepared compound were evaluated for anticancer activity against two human tumour cell line. Some compound showed the highest potency with IC_{50} =3.5&4.5µg/ml against a cervix carcinoma cell line (Hela) & breast carcinoma cell line (MCF7) respectively.



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

Figure 29

Chou *et al* [27] synthesized a series of bithienyl pyrimidines having cationic side chain .The compound have been developed as antitumor agents, the use of bithienyl group leads to improve binding & cytotoxicity.



R=H,

Figure 30

Hashem *et al* [28] reported the synthesis of some new thiazolopyrimidine, Pyrrolothiazolo pyrimidine & thiazlopyrrolothiazolopyrimidine derivatives. The newly synthesized compound was screened for their antitumor activity using in vitro Ehrlich used as cite assay. The series of compound proved to have the

best cytotoxic activity. The viability of the cell determined by the microscopically examination using haemocytometer & using tryphan blue strains (stain only the dead cells).

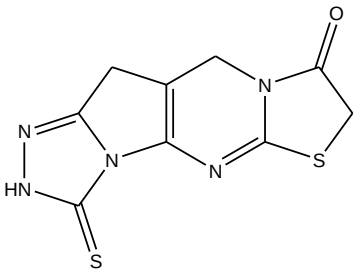


Figure 31

Prachayasittikul *et al* [29] synthesized *N*-Substituted 5-Iodouracils & evaluated for 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.

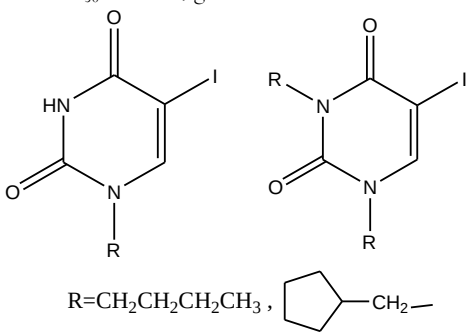


Figure 32

Lee *et al* [30] designed and synthesized a new series of N-substituted-2-aminopyrimidines based on the '4-(pyridin-3-yl) pyrimidin-2-amine' scaffold of Imatinib. A selected group from the target compounds was tested over a panel of 60 cancer cell lines at a single dose concentration of 10 µM and observed that the two compounds, 25b and 30 were most active against the most cell lines and they were further tested in a five-dose testing mode to determine their IC_{50} values over the 60 cell lines. Compound 30 has showed good potencies and high efficacies, tested at a single dose concentration of 10 µM over a panel of 54 kinases. At this concentration, the compound has showed multiple inhibitions over a number of oncogenic kinases, including ABL1, AKT1, LCK, C-SRC, PIM1, FLT3, FYN, and KDR.

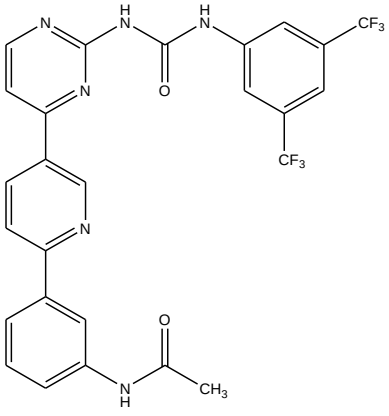


Figure 33

A series of novel pyrrolo[2,3-d]pyrimidine derivatives, pyrazolopyrrolopyrimidine, pyrrolo triazolo pyrimidine and pyrrolopyrimidotriazine were synthesized by Ghorab *et al* [31]. The design of these compounds was based upon the molecular modeling simulation of the fitting values and conformational energy values of the best-fitted conformers to vascular epithelial growth factor receptor tyrosine kinase (VEGFRTK) inhibitor hypothesis. This hypothesis was generated from its corresponding lead compounds using CATALYST software. Compounds 4-(2-Methyl-9-phenyl-7H-pyrrolo[3,2-e][1,2,4]triazolo[1,5-c]pyrimidin-7 yl) benzenesulfon amide 6 and 4-(3-(3-phenyl thioureido)-4-imino-5-phenyl-3, 4-dihydropyrrolo[2, 3-d] pyrimidin-7-yl) benzenesulfonamide showed interesting in vitro antitumor activity compared to doxorubicin as positive control. These results are nearly consistent with the molecular modeling studies.

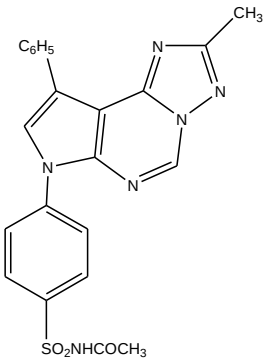


Figure 34

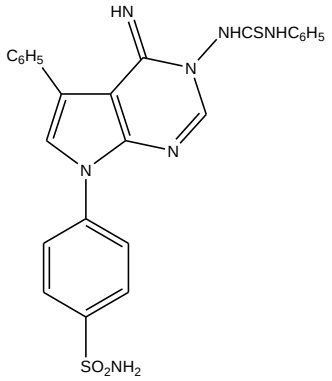


Figure 35

3. 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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