AMERICAN JOURNAL OF PHARMTECH RESEARCH

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Anticancer Activity of Assorted Annulated Pyrimidine: A Comprehensive Review

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ABSTRACT

Chemistry of heterocyclic organic compounds is as logical as that of aliphatic/aromatic compounds and of great interests both from the theoretical as well as practical synthetic view to design novel compounds that becomes one of the most important areas of research today. Electron-flux of six member/annulated N heterocycles plays vital roles to exhibit diverse potent biological activities from pharmaceuticals to industrial materials. The Pyrimidine and fused pyrimidine annulated rings in the chemistry of biological systems has attracted much attention due to availability in the substructures of therapeutic imperative natural products. As a result of their prominent and remarkable pharmacological activity, pyrimidine derivative's intensive research has been made especially focused on its anticancer activity. The present review gives brief information about anticancer activity of assorted six member/annulated pyrimidine derivatives.

Keywords: Annulated pyramidine, Heterocycles, anticancer activity, biological active

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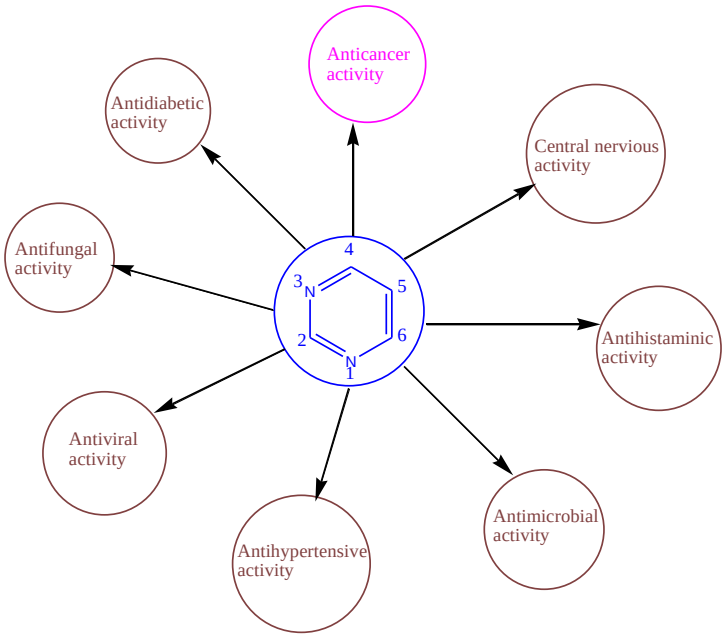
Received 16 December 2013, Accepted 26 December 2013

Please cite this article in press as: Dongre RS.*et al.*, Anticancer Activity of Assorted Annulated Pyramidines: A Comprehensive Review. American Journal of PharmTech Research 2014.

INTRODUCTION

Heterocycles play an important role in biochemical processes because the side groups of the most typical and essential constituents of living cells, DNA and RNA, are based on aromatic heterocycles. The presence of heterocycles in all kinds of organic compounds of interest in biology, pharmacology, optics, electronics, and material sciences and so on is very well known. Therefore heterocyles nucleus is present as a core structural component in an array of drug synthesis. Among large number of heterocycles found in nature, nitrogen-containing heterocyclic compounds are most abundant than those containing oxygen and sulphur owing to their wide distribution in nucleic acid instance and involvement in almost every physiological process of plants and animals. The foundation of this interest were their biological activities and unique structures that led to several applications in different areas of pharmaceutical and agrochemical research or, more recently, in material sciences. This review reflects the contribution of nitrogen heterocyles to the development of society from a biological point of view as well as to the understanding of life processes and to the efforts to improve the quality of life.



Pyrimidine

Figure 1: Diversity of potent biological activities

The chemistry of pyrimidines has become increasingly important as a result of recent developments in medicinal chemistry. Pyrimidines are the most important six member heterocyclic compounds containing two nitrogen atoms at 1 and 3 positions **(**Figure.1). They are present among the three isomeric diazines. The reactivities at 2, 4, 5 and 6 carbon atoms as well as substituent's attached them to vary individually.

Medicinal chemistry is the discipline concerned with determining the influence of chemical structure on biological activity and in practice, medicinal chemistry developed from an empirical one involving organic synthesis of new compound based largely on the modification of structure and then identifies their biological activity [1, 2]. Medicinal chemistry concerns with the discovery, development, interpretation and the identification of mechanism of action of biologically active compounds/drugs at the molecular level [3]. Annulated pyrimidine derivatives are one of the most prominent structures found in nucleic acid including uracil, thymine, cytosine, adenine, and guanine are fundamental building blocks for deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). Condensed pyrimidine derivatives have been reported as antiviral [4-6], antibacterial [7-9], antifungal [10,11], antihypertensive [12], antihistaminic [13], anti-inflammatory [14,15] and central nervous activities [16]. Cancer is a major health problem worldwide. Improvements in treatment and prevention have led to a decrease in cancer deaths, but the number of new diagnoses continues to rise [17]. Chemotherapy is one of the most commonly used treatment options, especially for un resectable patients. However, the use of conventional cytotoxic drugs, including doxorubicin, cisplatin and fluorouracil, has not shown any improvement in survival, and severe adverse effects have been frequently observed in treated patients [18]. Cytotoxic drugs remain the basis of cancer chemotherapy and are being administered with novel ways of therapy, therefore it is important to discover novel cytotoxic agents with spectra of activity and toxicity that differ from those current agents. It is well known that chemotherapy aims to destroy the cancer cells with various types of chemicals. The substances used are supposed to target mainly the cancer cells, and doses are calculated to minimize the collateral damage to surrounding tissues, which nevertheless occurs. This kind of treatment increases the entropy of the organism, suppresses the immune system, and forms a toxic cell environment which may destroy surrounding healthy cells So it is important to minimize curing doses to the least amount possible as well as trying to minimize the side effects of these drugs. Thus, it is urgent to develop novel chemotherapeutic agents for the treatment of cancer such as annulated Pyramidine derivatives, are important classes of heterocyclic compounds that exhibit a broad spectrum of biological activities such as anticancer [19-24]. The literature indicated that compound having pyrimidine nucleus shows

promising antitumor activity, as there are large numbers of pyrimidine-based anti-metabolites as well as presence of electron rich nitrogen atoms. Research in the field of pharmaceutical has its most important task in the development of new and better drugs and their successful introduction into clinical practice. Central to these efforts, accordingly stand the search for pharmaceutical substances and preparation which are new and original, such advantages may be qualitative or quantitative improvement in activity and absence of undesirable side effect, a lower toxicity, improved stability of decreased cost. As a result of remarkable pharmacological activity of annulated pyrimidine derivatives, intensive research has been made focused on anticancer activity. The present review highlights the anticancer activity of annulated pyrimidine derivatives.

Literature Review

P. Shanmugasundaram *et al* reported the synthesized of Pyrido[2,3-d] pyrimidine carboxylate. The anticancer activities of synthesized pyrimidine derivatives were evaluated using three human cancer cell lines, colon cancer (HT29), Liver cancer (HepG2) and cervical cancer (Hela) with MTT assay showed significant activity. The LC50 of the synthesized pyrimidine derivatives (Figure.2) was found to be > 100 µg/ml for all these cell lines.[25]

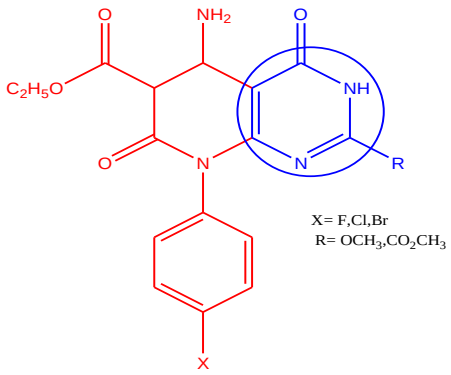


Figure 2: Pyrido[2,3-d] pyrimidine carboxylate derivatives

O.A Fathalla *et al* synthesized a few pyrimidine derivatives and 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 (Figure. 3 & 4) induced a significant growth inhibition towards liver cancer(HEPG2) cell line in comparison to 5- FU after treatment with IC50 value (ranged from 3.74 to 8.48 µg/ml concentrations) while the IC50 value for 5-FU was 5 µg/ml concentration.[26]

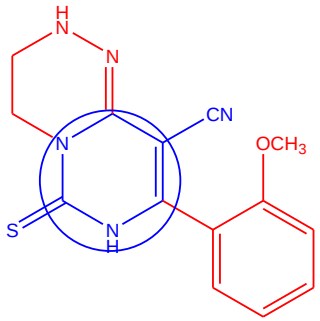


Figure 3: 3, 4, 6,7-tetrahydro-8- (2-methoxyphenyl)-6-thioxo-2H pyrimido [6, 1-c] [1,2,4] triazine-9- carbonitrile

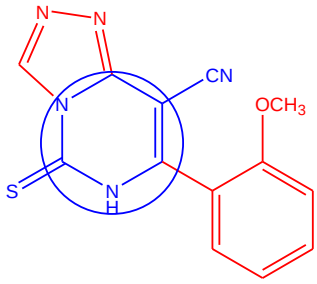


Figure 4: 5, 6-dihydro-7-(2-methoxyphenyl)-5-thioxo-[1,2,4]triazolo[4,3-*f*]pyramidine-8-carbonitrile

A series of Pyrrolo[2,3-d]pyrimidine derivatives (Fig. **5**) were synthesized by M. H. Jung *et al* and tested for in vitro anti proliferative activities against A375 human melanoma cell line and HS27fibroblast cell line.[27]

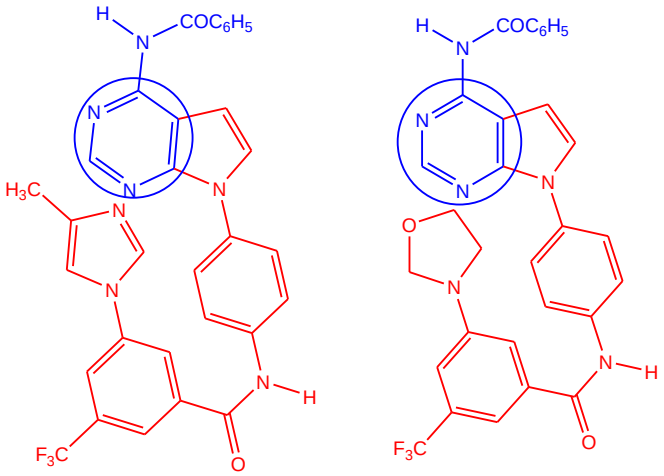


Figure 5: Pyrrolo[2,3-d]pyrimidine derivatives

O. A Fathalla *et al* reported novel derivatives of pyrimidine possessing a broader spectrum of antitumor activity and fewer toxic side effects than 5-FU and DOX have been sought. The antitumor activities of such compounds were assessed against HEPG2 cancer cell line in comparison to the traditional anticancer drugs: 5-FU and DOX. Regarding the antitumor activity

the compound (Figure.6) showed reasonable antitumor activity in comparison to 5-FU and DOX. Moreover, the study of the induced biochemical parameters of the tested compounds in mice showed insignificant differences relative to the control group, which indicates a moderate margin of safety for the selected compound. Comparable to 5-FU and DOX a dose augmentation of compound searching for possible higher potency and realizable without undesirable implications. Furthermore, the compound have important potential advantages over 5-FU and DOX because of their lower toxicity and their ability to induce lower biochemical parameters and fewer toxic side effects than 5-FU.[28]

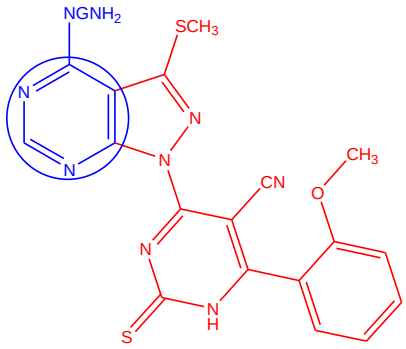


Figure 6: 4-[4-Hydrazinyl-3-(methylsulfanyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-6-(2-methoxyphenyl)-2-thioxo-1,2-dihydropyrimidine-5-carbonitrile

A. M. Mohamed *et al* were synthesized newly pyridopyrimidine derivatives and were evaluated for in vitro antitumor activities using 59 different human tumor cell lines, representing cancers of CNS, ovary, renal, breast, colon, lung, leukemia, and melanoma, prostate as well as kidney. The compounds (Figure. 7 & 8) with –NH group exhibited greater in vitro antitumor activities at low concentrations (log 10 [GI50] =-4.6) against the human tumor cell lines.[2]

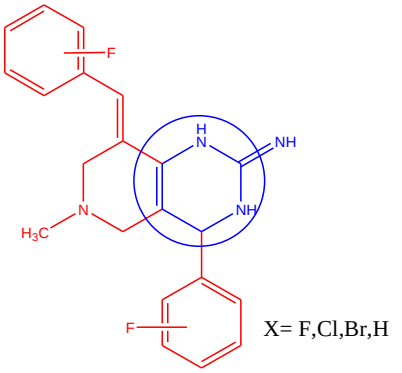


Figure 7: pyrido-[4,3-d]pyrimidine-2(1H)imine derivatives

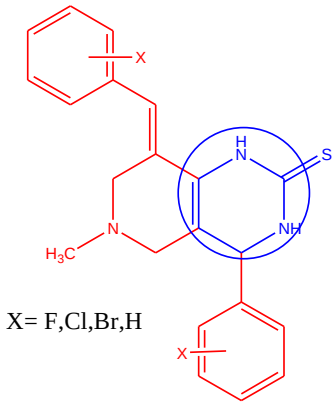


Figure 8: Methyl-pyrido[4,3-d]pyrimidine-2-(1H)thione derivatives

M. M. Ghoraba *et al* reported noval thiazolo[4,5-b]pyrano[2,3-d]pyrimidine derivatives and evaluated for their in vitro anticancer activity against human breast cancer cell line (MCF7). The screened compound (Figure. 9) with IC50 values 12.08 µM exhibited higher cytotoxic activities than the reference drug (32.00**)** doxorubicin [30]

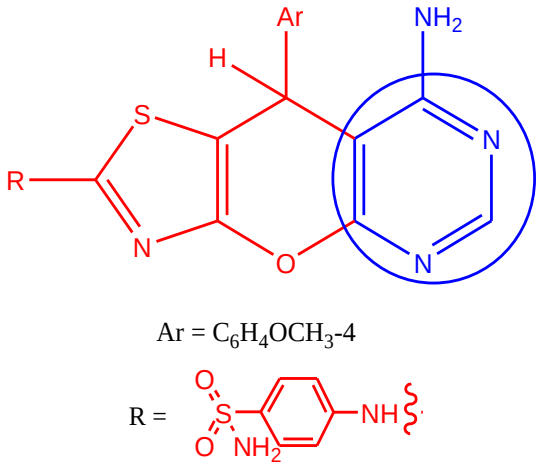


Figure 9: 8-Amino-9H-9-(4-methoxyphenyl)-2-(4-sulphamoylphenylamino)-thiazolo[4,5-]pyrano [2,3-d]pyrimidine

S.A. Al-Issa synthesized the noval pyrimidine derivatives and tested for their in vitro antitumor activity against human liver cancer cell line (HEPG2) in comparison to the traditional anticancer drug (Doxorubicin) on the basis of monitoring the inhibition of the growth of human cancer cells. The potent compounds (Figure. 10 & 11) have (IC50, 45.9 lg/ml and 39.8 lg/ml respectively) enhance antitumor activity.[31]

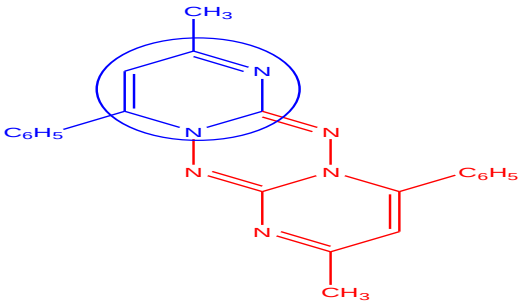


Figure 10: 6, 12-Dimethyl-4, 10-diphenyl pyrimido[3,2-b]-1,2,4,5- tetrazino[3,2-b] pyrimidin

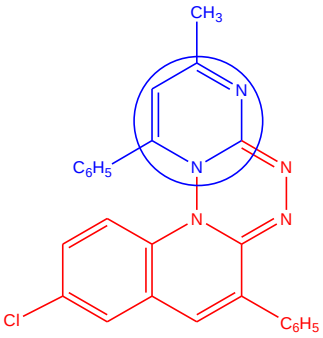


Figure 11: 4,12-Diphenyl-14-methyl pyrimido[3,2-b]-1,2,4,5-tetrazino[4,3-a] quinoline

H.Y.He et al reported novel Pyrazolo[3,4-*d*]pyramidine derivatives. In a cell-based screen of novel anticancer agents, the hit compound (Figure.12) which bears a pyrazolo[3,4-*d*]pyrimidine scaffold exhibited high inhibitory activity against a panel of four different types of tumor cell lines. In particular, the IC50 for A549 cells was 2.24 μM, compared with an IC50 of 9.20 μM for doxorubicin, the positive control. Flow cytometric analysis revealed that compound could significantly induce apoptosis in A549 cells *in vitro* at low micromolar concentrations. These results suggest that the target compound and its analogs with the pyrazolo[3,4-*d*]pyrimidine scaffold might potentially constitute a novel class of anticancer agents, which requires further studies.[32]

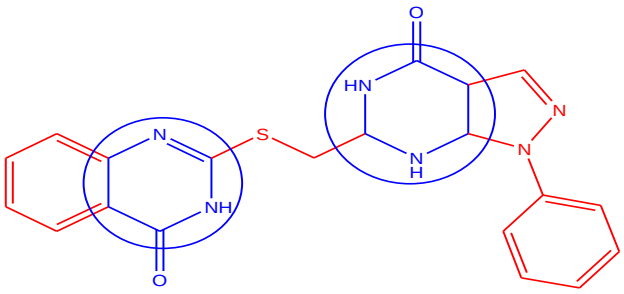


Figure13:2-((4-Oxo-1-phenyl-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6 yl)methylthio) quinazolin 4(3H) -one

A. M. Mohamed *et al* reported Some new Thiazolo[3,2-a]Pyrido[4,3-d]Pyrimidine derivatives and evaluated for antitumor activities utilizing 60 different human tumor cell lines, representing leukemia, melanoma, lung, colon, brain, ovary, breast and prostate as well as kidney. The anticancer activity is generally enhancing due to the presence of nitrogen heterocyclic rings. From the in vitro observed data it has been noticed that, the synthesized compounds (Figure. 14) seem to be the most active prepared derivatives against all the tested cell lines.[33]

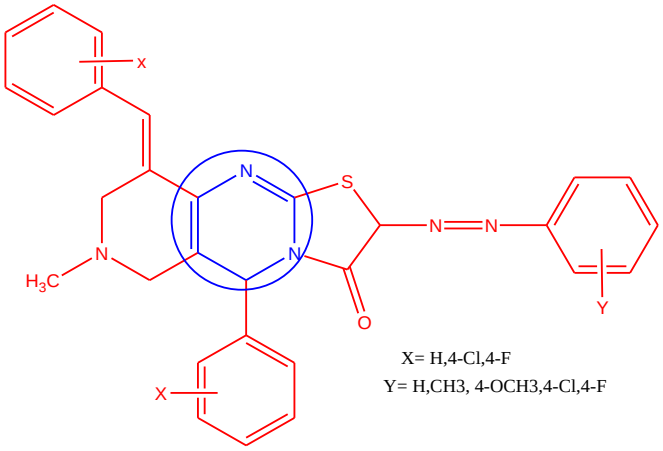


Figure 14: 5-Aryl-9-arylmethylene-6,7,8,9- tetrahydro-7-methyl-2-arylyldiazenyl-2H-thiazolo[3,2-a]pyrido[4,3-d]pyrimidin-3(5H)-ones

Q. Ren *et a* synthesized the novel tetrahydrobenzo[40,50]thieno[30,20:5,6]pyrido[4,3-d]pyrimidin-4(3H)-ones and showed effective to both KB cells (KB cells were the drug sensitive human oral carcinoma cells) and their KBv200 cells (multidrug resistant cells) with the over expression of ABCB1 induced by vincristine. The compounds (Figure. 15) showed the best inhibition against KB and KBv200 cells with IC50 values of 17.4 and 25.4 µM, respectively.[34]

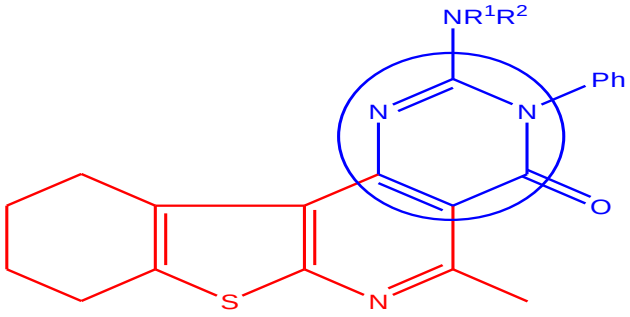
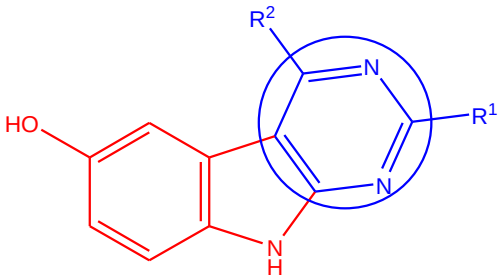


Figure15: tetrahydrobenzo[40,50]thieno[30,20:5,6]pyrido[4,3-d]pyrimidin-4(3H)-ones

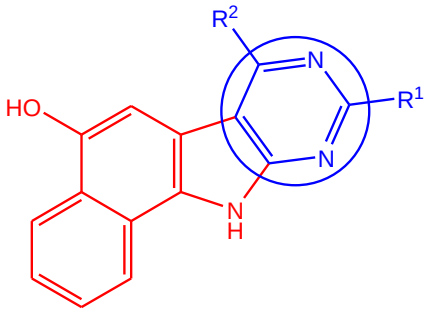
B. Dotzauer *et al* reported 2,4-Diamino-9H-pyrimido[4,5-b]indol-5-ols and the in vitro cytotoxic activities were evaluated against four human cancer cell lines originating from solid tumors. Two

human bladder cancer cell lines 5637 (ACC 35) and RT-4 (ACC 412), and two human lung cancer cell lines A-427 (ACC 234) and LCLC-103H (ACC 384). An increase in activity was observed when a N type heteroaromatic ring was annulated on the pyrimido[4,5-b]indole system to give compounds (Figure. 16, 17, 18, 19, 20 & 21) with activities comparable to ellipticine and cisplatin.[35]



R^1R^2 = NH_2,NMe_2,NEt_2,OMe,pyrolidine-1-yl,4-methylpiperizine-1-yl

Figure 16: pyrimido[4,5-b]indol-6-ol derivatives



R^1R^2 = NH_2,NMe_2,NEt_2,OMe,pyrolidine-1-yl,4-methylpiperizine-1-yl

Figure 17: benzo[g]pyrimido[4,5-b]indol-5-ol derivatives

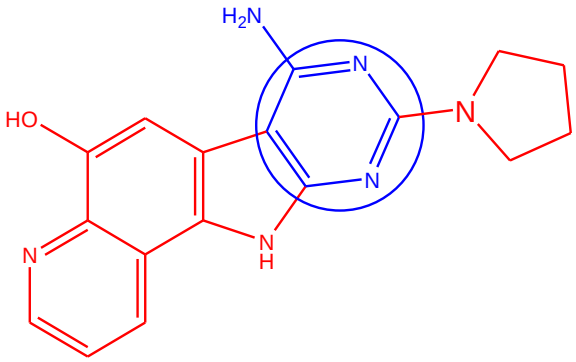


Figure 18: 7-Amino-9-pyrrolidin-1-yl-11H-pyrimido[50,40:4,5]- pyrrolo[2,3-f]quinolin-5-ol

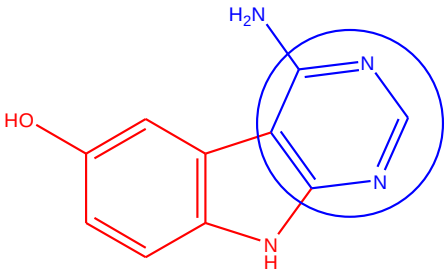


Figure 19: 4-Amino-9H-pyrimido[4,5-b]indol-6-ol

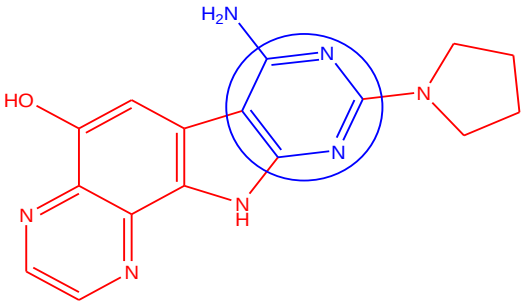


Figure 20: 7-Amino-9-pyrrolidin-1-yl-11H-pyrimido[50,40:4,5]-pyrrolo[2,3-f]quinolin-5-ol

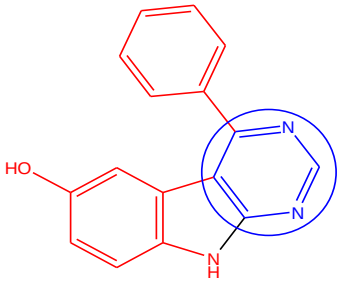


Figure 21: 4-Phenyl-9H-pyrimido[4,5-b]indol-6-ol

E. M. Grivsky *et al* reported 2,4-Diamino-6-(2 ,5-dimeth oxybenzyl)-5-methyl pyrido[2,3-d]pyrimidine (Figure. 22) and has found significant Antitumor activity against the Walker 256 carcinosarcoma in rats. [36]

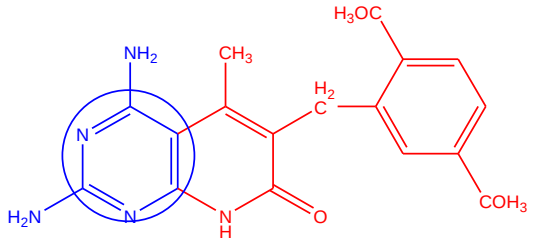


Figure 22: 2,4-Diamino-7,8-dihydro-6-(2,5-dimethoxybenzyl)-5- methyl-7-oxopyrido[2,3-d]pyrimidine

I. Antonini *et al* reported Bis(pyrimido[5,6,1-*de*]acridines) and were selected for a cytotoxic screening against six human cancer cell lines (large cell lung carcinoma H460M, gastric cancer MKN45, prostatic carcinoma PC3, colon adenocarcinoma HCT116, LoVo, sensitive, and

LoVo/Dx, doxorubicin-resistant). The results of compounds (Figure. 23) indicate that: (i) The target derivatives are extremely potent cytoxic agents, which often present IC50 values inferior to the minimum drug concentration tested (10-3 μM). (ii) The potency of selected derivatives in relation to the nature of substituent's are order in potency seems to be (X) = OH) > H) > OMe) > NO2). (iii) Finally, it can be remarked that the derivatives are cross resistant with Dx, but the grade of cross resistance of compounds appear to be inferior. [37]

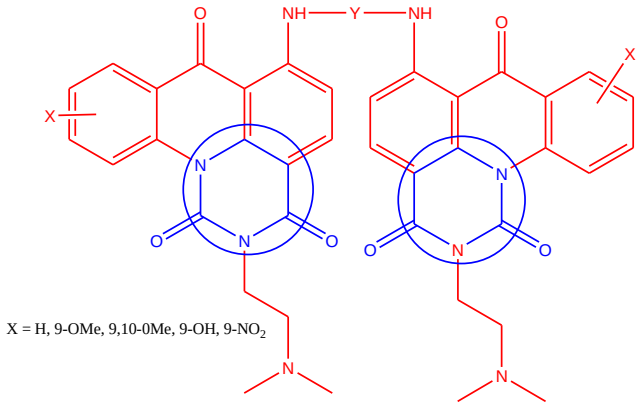


Figure 23: Bis{2-[2-(dimethylamino)ethyl]-1,3,7-trioxo-2,3-dihydro-1*H*,7*H*-pyrimido[5,6,1-*de*]acridin-6-yl}-5-methyl-1,5,9-triazanonane

M.Y. Cha *et al* reported novel series of (S)-1-acryloyl-N-[4-(arylamino)-7-(alkoxy)quinazolin-6-yl]pyrrolidine-2-carboxamides and were used to measure the inhibitory activities towards the human vaginal epidermoid cancer cell line, A431 (ATCC: CRL-1555), a human breast cancer cell line, SK-Br3 (ATCC: HTB-30), Gefitinib/Erlotinib resistant non-small cell lung cancer cell line, H1975 (ATCC: CRL-5908), and a primary human fibroblast cell-line, Hs27 (ATCC: CCL-34). The synthesized compounds (Figure. 24) seem to be the most active prepared derivatives against all the tested cell lines due to presence of nitrogen heteroatom and substituted phenyl rings. [38]

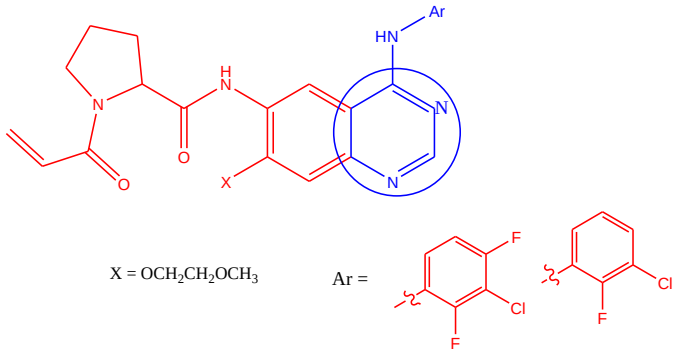


Figure 24: 4-7-[(2-methoxyethoxy)quinazolin-6-yl]pyrrolidine-2-carboxamide derivatives

M. M. Gineinah *et al* Synthesized new pyrido[2,3-d]pyramidine derivatives and screened for antitumor activity which possess high and potential efficacy with minimal side effects. As a result, interaction of antitumor agents with DNA should produce as little DNA damage as possible. The newly synthesized compounds had been subjected to bleomycin-dependant DNA damage assay[39] to screen their antitumor activity and the degree of DNA damage caused by these compounds. The antitumor activity of synthesized compounds is evaluated in terms of sample absorbance (A). As sample absorbance (A) increases, DNA damage increases and the sample efficiency as antitumor agent decreases. The novel Compounds (Figure.25) showed the lowest absorbance (0.052), and hence exhibited the highest antitumor activity.[40]

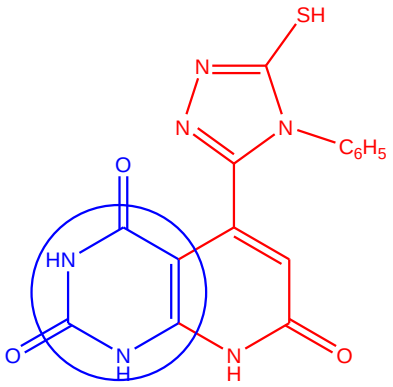


Figure 25: 5-(4-Phenyl-5-sulfanyl-4H-[1,2,4]triazol-3-yl)1H,3H,8Hpyrido[2,3-d]pyrimidine-2,4,7-trione

M. Bakavolia reported cytotoxic effects of triazolopyrimidooxadiazine moiety on different malignant cancer cell lines including human breast cancer cell line (MCF-7) and hepatocellular carcinoma with various concentrations (50–500 μM). The result showed compound (Figure. 26) decreased cell viability of cells as a concentration-dependent manner. The IC50 values against MCF-7 after 24 h and against HepG2 after 48 h were determined 439.6 and 280.5 μM, respectively.[41]

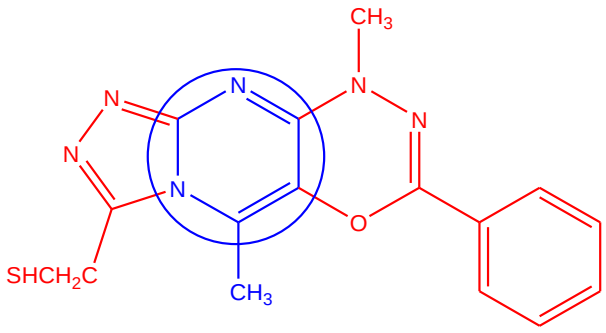


Figure 26 [(1,5-Dimethyl-3-phenyl-1H-[1,2,4]triazolo[4',3':1,2]pyrimido[4,5-e][1,3,4]oxadiazin-7 yl)sulfanyl]methyl cyanide

CONCLUSION

Due to the presence of nitrogen in the heterocyclic compounds skeleton, they show diverse biological activities. Pyrimidine and fused pyrimidine are the important six membered heterocyclic compounds because it is an essential constituent of all cells and potential therapy for the treatment of large number of diseases, This review focus on the various potent annulated Pyramidine derivatives and observed that cyclic N-type structure with different electron withdrawing and electron donating substitution groups showed better anticancer activity.

REFERENCES

1. Williams DA and Lemke TL. Foye's Principles of medicinal chemistry. Lippincott Williams and Wilkins 2002; 5-36.
2. Pandeya Nath SN. A Text Book of medicinal chemistry.SG publisher 2004; 1(3): 2-3.
3. Singh H and Kapoor VK. Medicinal and Pharmaceutical Chemistry Vallabh Prakashan 2008; 2:1 -2.
4. Summa V, Petrocchi A, Bonelli F, Crescenzi B, Donghi M, Ferrara M, Fiore F, Gardelli C, Paz OG, Hazuda DJ, Jones P, Kinzel O, Laufer R, Monteagudo E, Muraglia E, Nizi E, Orvieto F, Pace P, Pescatore G, Scarpelli R, Stillmock K, Witmer MV, Rowley M. Discovery of raltegravir, a potent, selective orally bioavailable HIV-integrase inhibitor for the treatment of HIVAIDS infection. J. Med. Chem. 2008; 51:5843-5855.
5. Tagat JR, McCombie SW, Nazareno D, Labroli MA, Xiao Y, Steensa RW, Strizki JM, Baroudy BM, Cox K, Lachowicz J, Varty G, Watkins R. Piperazine-based CCR5 antagonists as HIV-1 inhibitors. IV. Discovery of 1-[(4, 6-dimethyl-5-pyrimidinyl) carbonyl] - 4-[4-[2-methoxy-1(R)-4-(trifluoromethyl) phenyl] ethyl-3(S)-methyl-1-piperazinyl]- 4-methylpiperidine (Sch- 417690/Sch-D), a potent, highly selective, and orally bioavailable CCR5 antagonist. J. Med. Chem. 2004; 47: 2405-2408.
6. Huckova D, Holy A, Masojidkova M, Andrei G, Snoeck R, De Clercq E, Balzarini J, Synthesis and antiviral activity of 2,4- diamino-5-cyano-6-[2-(phosphonomethoxy) ethoxy] pyramidine and related compounds, Bioorg. Med. Chem. 2004; 12(12): 3197-3202.
7. Deshmukh MB, Salunkhe SM, Patil DR, Anbhule PV. A novel and efficient one step synthesis of 2-amino-5-cyano-6-hydroxy-4- arylpyrimidines and their anti bacterial activity. Eur. J. Med. Chem. 2009; 44: 2651–2654.
8. Bhat AR, Dongre RS, Selokar RS. Potent in-vitro antibacterial and antifungal activities

of pyrano[2,3-d]pyrimidine derivatives with quantitative yield. Int. J Pharm Bio Sci. 2014 Jan; 5(1): (P) 422 - 430

9. Chandrashekaran S, Nagarajan S. Microwave-assisted synthesis and anti-bacterial activity of some 2-Amino-6-aryl-4-(2-thienyl) pyrimidines. IL Farmaco. 2005; 60:279-282.
10. Mai A, Rotili D, Massa S, Brosch G, Simonetti G, Passariello C, Palamara AT. Discovery of uracil-based histone deacetylase inhibitors able to reduce acquired antifungal resistance and trailing growth in Candida albicans. Bioorg. Med. Chem. Lett. 2007; 17:1221-1225.
11. Ingaral N, Saravanan G, Amutha P, Nagarajan S. Synthesis, in vitro antibacterial and antifungal evaluations of 2-amino-4-(1- naphthyl)-6-arylpyrimidines. Eur. J. Med. Chem. 2007; 42: 517-520.
12. Alam O, Khan SA, Siddiqui N, Ahsan W, Verma SP, Gilani SJ. Antihypertensive activity of newer 1, 4-dihydro-5-pyramidine carboxamides. Synthesis and pharmacological evaluation. Eur. J.Med. Chem. 2010; 45:5113-5119.
13. Rahaman SA, Pasad YR , Kumar P , Kumar B. Synthesis and anti-histaminic activity of some novel pyrimidines. Saudi Pharmaceutical Journal.2009; 17: 255-258.
14. Da S. Falcao EP, De Melo SJ, Srivastava RM, De A.Catanho MTJ, Nascimento SCD. Synthesis and anti-inflammatory activity of 4-amino-2-aryl-5-cyano-6-{3- and 4-(*N*-phthalimidophenyl)} pyrimidines. Eur. J. Med. Chem. 2006; 41:276-282.
15. Isobe Y, Tobe M, Inoue Y, Isobe M, Tsuchiya M, Hayashi H. Structure and activity relationships of novel uracil derivatives as topical anti-inflammatory agents. Bioorg. Med. Chem. 2003; 11:4933-4940.
16. Gillespie RJ, Bamford SJ, Clay A, Gaur S, Haymes T, Jackson PS, Jordan AM, Klenke B, Leonardi S, Liu J, Mansell HL, Ng S, Saadi M, Simmonite H, Stratton GC, Todd RS, Williamson DS, Yule IA. Antagonists of the human A (2A) receptor. Part 6: Further optimization of pyrimidine-4-carboxamides. Bioorg. Med. Chem. 2009; 17:6590-6605.
17. Jemal A, Siegel R, Xu J, Ward E. Cancer Statistics 2010. CA Cancer J. Clin. 2010; *60*, 277-300.
18. Simonetti RG, Liberati A, Angiolini C, Pagliaro L. Treatment of hepatocellular carcinoma. A systematic review of randomized controlled trials. Ann. Oncol. 1997;*8*, 117-136

19. Mahboobi S, Sellmer A , Hocher H, Eichhorn E, Bar T, Schmidt M, et al., [4-(imidazol-1-yl)thiazol-2-yl]phenylamines: a novel class of highly potent colchicine site binding tubulin inhibitors: synthesis and cytotoxic activity on selected human cancer cell lines, Beckers TL J. Med. Chem. 2006; 49: 5769-577.
20. Ghorab MM, Ragab FA, Alqasoumi SI, Alafeefy AM, Aboulmagd SA. Synthesis of some new pyrazolo[3,4-d]pyrimidine derivatives of expected anticancer and radioprotective activity. Eur J Med Chem. 2010; 45: 171–178.
21. Abou El Ella DA, Ghorab MM, Noaman E, Heiba HI, Khalil AI. Molecular modeling study and synthesis of novel pyrrolo[2,3-d]pyrimidines and pyrrolotriazolopyrimidines of expected antitumor and radioprotective activities. Bioorg. Med. Chem. Lett.2008;16: 2391–2402.
22. Abdel Mohsen HT, Ragab FAF, Ramla MM, El Diwani HI. Novel benzimidazole–pyrimidine conjugates as potent antitumor agents. Eur. J. Med. Chem. 2010; 45(6):2336-2344.
23. Xie F, Zhao HB, Zhao L, Luo L, Hu Y. Synthesis and biological evaluation of novel 2, 4, 5-substituted pyrimidine derivatives for anticancer activity. Bioorg. Med. Chem. Lett. 2009; 19:275-278.
24. Kamal A, Dastagiri D, Ramaiah MJ, Reddy JS, Bharathi EV, Reddy MK, Prem Sagar MV, Reddy TL, Pushpavalli S.N.C.V.L., Bhandra M. Synthesis and Apoptosis Inducing Ability of New Anilino-Substituted Pyrimidine Sulfonamides as Potential Anticancer agents. Eur. J. Med.Chem. 2011; 46:5817-5824.
25. Banjanac M, Tatic I, Ivezic Z, Tomi S, Dumic J. Biotechnol, 2009; 47(3): 236–245.
26. Fathalla OA, Zeid IF, Haiba ME, Soliman AM, Elmoez SIA, Serwy WSE. World J Chem, 2009; 4: 127-132.
27. Jung MH, Hwan Ki, Won-Kyoun C ,Mohammed I. Gama El, Jin-Hun P, Kyung HY,Tae BS, Leea SH, Daejin B, Jung-Mi H, Jung-Hyuck C,Chang-Hyun O. Synthesis of pyrrolo[2,3-d]pyrimidine derivatives and their antiproliferative activity against melanoma cell line. Bioorganic & Medicinal Chemistry Letters 2009; 19: 6538–6543
28. Fathalla O A, Mohamed NA, El-Serwy WS, AbdelHamid HF, Abd El-Moez SI, Soliman AM. Synthesis of some new pyrimidine derivatives and evaluation of their anticancer and antibacterial activities. Res Chem Intermed 2013 ;39:821–841

29. Mohamed AM, El-Sayed WA, Alsharari MA, Al-Qalawi HR, Germoush MO. Anticancer activities of some newly synthesized pyrazole and pyrimidine derivatives, Arch. Pharm. Res. 2013; 36:1055–1065.
30. Ghorab1 MM, Shaaban MA, Refaat HM, Heiba1 HI, Ibrahim1 SS. Novel Thiazolopyrane and Thiazolopyranopyrimidine Derivatives Carrying a Sulfonamide Moiety of Expected Cytotoxic and Radio sensitizing Activities. Journal of Materials Science and Engineering 2011; 747-758.
31. S.A. Al-Issa. Synthesis and anticancer activity of some fused pyrimidines and related heterocycles, Saudi Pharmaceutical Journal 2013; 21, 305–316.
32. He HY, Zhao JN, Jia R, Zhao YL, Yang SY, Yu LT, Yang L. Novel Pyrazolo[3,4-*d*]pyrimidine Derivatives as Potential Antitumor Agents: Exploratory Synthesis, Preliminary Structure-Activity Relationships, and in Vitro Biological Evaluation, Molecules 2011;16: 10685-10694.
33. Mohamed AM Abdel-Galil EA, Alsharari MA, Al-Qalawi RM, Germoush MO, Al-Omar MA. Anticancer Activities of Some New Synthesized Thiazolo[3,2-a]Pyrido[4,3-d]Pyrimidine Derivatives, Am J Biochemistry and Biotechnology2011; 7 (2): 43-54.
34. Qingyun R, Yong-Ju L, Hongwu H, Liwu F, Yucheng G. A facile synthesis and biological activity of novel tetrahydrobenzo[40,50]thieno[30,20:5,6]pyrido[4,3-d]pyrimidin-4(3H)-ones, Bioorganic & Medicinal Chemistry Letters 2009; 19:6713–6716.
35. Bernd D, Renate G, Patrick JB, Harald L, Jens L, Reinhard T. 2,4-Diamino-9H-pyrimido[4,5-b]indol-5-ols: Synthesis, in vitro cytotoxic activity, and QSAR investigations, Bioorganic & Medicinal Chemistry 2006; 14 :7282–729.
36. Eugene MG, Shuliang L, Sigel CW, Duch DS, Nichol CA , Synthesis and Antitumor Activity of 2,4-Diamino-6-(2 ,5-dimeth oxybenzyl)-5-meth ylpyrido[2,3- *d]*pyrimidine, J. Med. Chem. 1980,23, 327-329.
37. Ippolito A, Paolo P, Amelia M, Silvia S, Sante M, Rational Design, Synthesis, and Biological Evaluation of Bis(pyrimido[5,6,1-*de*]acridines) and Bis(pyrazolo[3,4,5-*kl*]acridine-5-carboxamides) as New Anticancer Agents**,** J. Med. Chem. 2004**;**47: 5244-5250
38. Cha MY, Lee KO, Kim JW, Lee CG, Song JY, Kim YH, Lee GS, Park SB, Kim MS. Discovery of A Novel Her-1/Her-2 Dual Tyrosine Kinase Inhibitor for the Treatment of

Her-1 Selective Inhibitor-Resistant Non-small Cell Lung Cancer, J. Med. Chem. 2009; 52: 6880–6888

39. Ayyad SEN, Ezmirly ST, Basaif SA, Alarif WM, Badria AF, Badria FA. Antioxidant, cytotoxic, antitumor and protective DNA damage metabolites from the red sea brown alga Sargassum sp. Pharmacogn Res 2011b; 3:160–165
40. Magdy MG, Magda NA, Sahar MB, El-Husseiny WM. Synthesis and antitumor activity of new pyrido[2,3-d]pyramidine Derivatives. Med Chem Res 2013; 22:3943–3952
41. Mehdi B, Mohammad R, Ali S, Marzieh A, Seyed-Hadi M, Hoda AM, Zahra TN. Synthesis and anticancer evaluation of new derivatives of 3-phenyl-1,5-dimethyl-1*H*-[1,2,4]triazolo[4',3':1,2]pyrimido[4,5-*e*][1,3,4]oxadiazine. Journal of chemical Research 2010: 403–406