IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

REVIEW OF ANTICANCER ACTIVITY OF DIHYDROPYRIMIDINONES

[1]PILLI ARCHANA, [2]TARANNUM FATHIMA

[1]Assistant professor, [2]Assistant professor

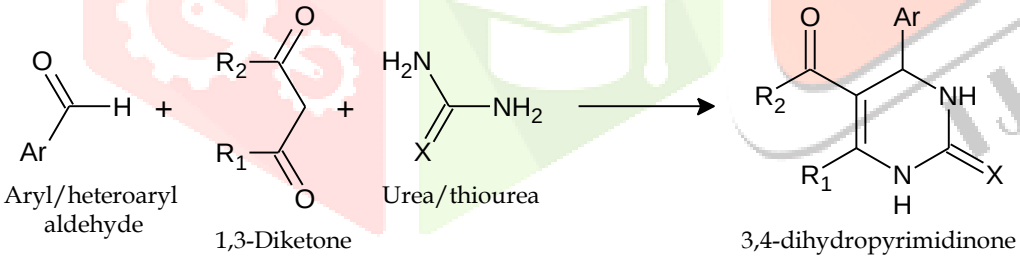
[1]Pharmaceutical Chemistry,

Rbvrr women's college of pharmacy, Barkatpura, Hyderabad, T.S, India

Abstract : Dihyropyrimidinones and their derivatives have desirable pharmacological properties like anti inflammatory, anti HIV ,anti tubercular, antifungal ,antibacterial anti filarial , anti hyperglycemic , anti tumour activities. Monostrol is a lead moiety for development of anticancer drugs specifically inhibits motor activity of mitiotic kinesin Eg5 which is derivative of dihydropyrimidiones .

INTRODUCTION

Dihydropyrimidinones compounds were first synthesized by Pietro biginelli.Thesynthesis of this type of compounds involves the condensation of numerous aldehydes with urea and beta-keto ester under acidic conditions using hydrochloric acid as catalyst and ethanol solvent to give tetrahydropyrimidinone.



Aryl/heteroaryl aldehyde | 1,3-Diketone | Urea/thiourea | 3,4-dihydropyrimidinone derivatives

Many synthetic approaches have been conducted under solvent free conditions for synthesis dihydropyriminones using biginellireaction, through nature of solvent is important as dielectric constant induces higher reaction yield. Many new dihydropyrimidinone derivatives with good yield are reported using lanthanum oxide or bismuth nitrate in acetonitrile or pph_3 as catalyst without using solvent

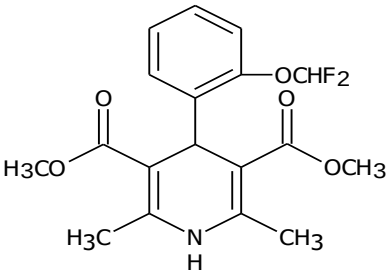
Dihydrpyrimidinones have potent anticancer activity by different actions like

- Anti VEGF/vegfr2 which act as anti apoptopic factor where it induces B-cell lymphoma 2 and breast cancer cells .Inhibition of vascular endothelial growth factor (VEGF) induce apoptosis of malignant cells.
- P^{53}mediated apoptosis, by preventing DNA re- replication when mitotic spindle is disrupted.
- Inhibits motor activity of mitiotic kinesin Eg5 leading to apotosis

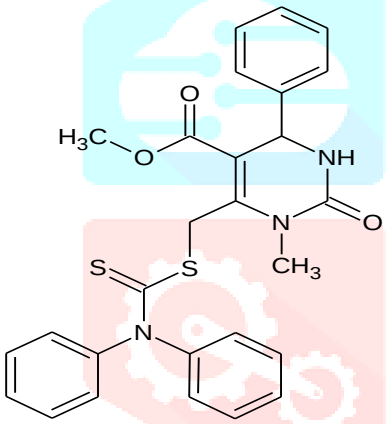
LITERATURE SURVEY

Surendra Kumar Nayak et.al., explained that dihydropyrimidiones based scaffolds provided the inhibition of p^{53}-MDM2 interaction thus prevent degradation of p^{53} and maintain high maintain high level for induction of apoptosis in cancer cells.

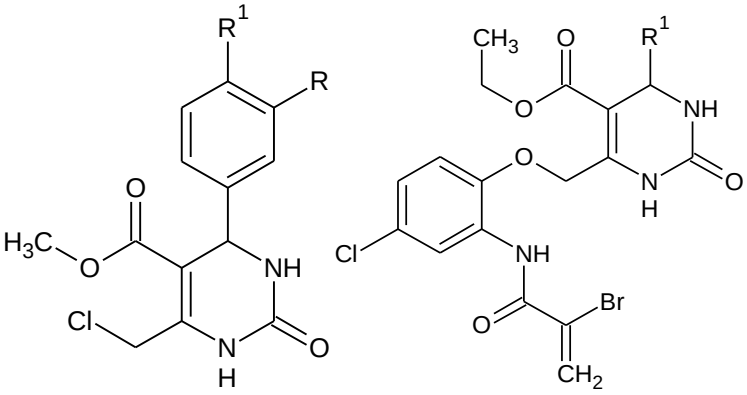
Anti-lipoxygenase activity of riodipine (1,4-dihydropyridine analogue), a bioisosteric molecule of DHPM is documented in literature.



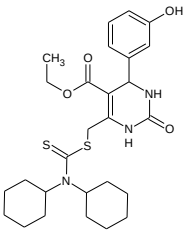
Amnay et.al., synthesized and evaluated new dihydropyrimidinone derivatives with N-heterocyclic moieties. Dihydropyrimidinones with dithiocarbamate moiety was identified as potent anti cancer drug. The inhibitory activities against VEGFR-2 and mTOR as well as the induction of apoptosis were reported.



Sana et.al., studied the cytotoxic and tubulin inhibitory actions of aryl alpha –haloacryl amide linked dihydropyrimidinone derivatives. The screening was done in human cancer cell lines like MCF-7, MDA-MB-231 FOR human breast cancer. These compounds were found to inhibit tubulin polymerization with microtubule destabilizing activity.



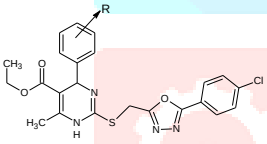
Amnay et.al., synthesised DHMP various heterocyclic moieties. DHPM wiithdithiocarbamate ring system compound showed significant activity against NCI-H460, SK-MEL-5, and HL-60 (TB) cell lines against against mTOR (IC50 ¼ 0.64 mM) and VEGFR-2 (IC50 ¼ 1.97 mM) to show high potency .Benzimidazole thioether with nitro group at 5-position shows high cytotoxic activity against PC-3, HCT-116 and MCF-7, while p-tolyl substituent on the oxadiazole ring has moderate activity



Ethyl 6-((dicyclohexylcarbamothioylthio)methyl)-1-methyl2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate

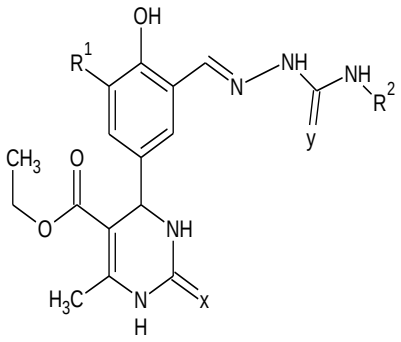
Fatma Ragab et.al., synthesized DHMPS with oxadiazole moiety showed potent activity against leukemia cell lines HL-60(TB) and MOLT 4.The compound 2(IC50 = 0.056 µM) 3- chlorophenyl substituted showed potent activity against leukemia HL-60(TB) cell line and non small cell lung cancer NCI-H522 with GI% values 80.42 and 74.59 % respectively. (IC50 = 0.153 µM)2,4 dichlorophenyl substituent showed potent activity against leukemia CCRF-CEM; non-small cell lung cancer HOP-92 and colon cancer HCT-116 cell lines with GI% range of 71.24-73.64 .

R =3cl/4cl/4-cl/2,4-di cl



Konenisashidhara et.al., selectively synthesized dihydropyrimidinone with semi carbazone hybrids. IN compound withR^1=$C(CH_3)_3$,Xand y =O,R^2=$OMeC_6H_4$ Which showed selective anti proliferative activity against hepG_2cells by regulating Yh2AX and p53 leading to apoptosis.

The in silico docking study explained the binding of synthesized compounds to hlig 1 enzyme preventing its nick sealing activity and leading to cancer cell death and Anti metastatic activity at concentration ranging from 10µM -20µM confirmed by ANOVA



R^1=aryl/phenyl/pyridyl
R^2=ester/amide
R^3=alkyl
x=o,s

Shanmugam et.al., newly synthesized compound Ethyl-6-methyl-2-oxo-4- (3,4,5-trichlorophenyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate and evaluated for anti cancer activity by assay tetrazolium dye on breast cancer MCF-7 cell line which growth inhibition and cytotoxic activity at IC_{50} of 45µM.The compound on molecular docking analysis showed a binding affinity to receptor of estrogen by london dispersion force of interactions at hydrophobic residues ALA 359, GLU 353, ARG 394, LEU 391, THR 347, VAL 418, ILE 424, with a best glide score- 8.955 k/mol and binding energy of -25.277 kcal/mol.

CONCLUSION:

Dihydropyrimidinones and its derivatives revolutionized the chemistry of purines as well as pyrimidines for their potent anti cancer activity. Drugs like 5-flourouracil containing dihydropyrimidinones are already used in treatment of cancer.

REFERENCES

1. Nowsheen, S., Aziz, K., Kryston, T. B., Ferguson, N. F. & Georgakilas, A. The interplay between inflammation and oxidative stress in carcinogenesis. *Curr. Mol. Med.* **12**, 672–680 (2012).
2. Shalini, V. *et al.* Molecular mechanisms of anti-inflammatory action of the flavonoid, tricin from Njavara rice (*Oryza sativa* L.) in human peripheral blood mononuclear cells: Possible role in the inflammatory signaling. *Int. Immunopharmacol.* **14**, 32–38 (2012).
3. Brooks-Worrell, B. & Palmer, J. P. Immunology in the clinic review series; focus on metabolic diseases: development of islet autoimmune disease in type 2 diabetes patients: potential sequelae of chronic inflammation. *Clin. Exp. Immunol.* **167**, 40–46 (2012).
4. Marchant, D. J. *et al.* Inflammation in myocardial diseases. *Circ. Res.* **110**, 126–144 (2012).
5. Neau, D. B. *et al.* Crystal structure of a lipoxygenase in complex with substrate the arachidonic acid-binding site of 8R-lipoxygenase. *J. Biol. Chem.* **289**, 31905–31913. https ://doi.org/10.1074/jbc.M114.59966 2 (2014).
6. Funk, C. D., Chen, X. S., Johnson, E. N. & Zhao, L. Lipoxygenase genes and their targeted disruption. *Prostaglandins Other Lipid Mediat.* **68–9**, 303–312. https ://doi.org/10.1016/S0090 -6980(02)00036 -9 (2002)
7. Newcomer, M. E. & Brash, A. R. The structural basis for specificity in lipoxygenase catalysis. *Protein Sci.* **24**, 298–309. https ://doi.org/10.1002/pro.2626 (2015).
8. Gilbert, N. C. *et al.* The structure of human 5-lipoxygenase. *Science* **331**, 217–219. https ://doi.org/10.1126/scien ce.11972 03 (2011).
9. Lin, H. C. *et al.* 5-Lipoxygenase inhibitors attenuate TNF-alpha-induced inflammation in human synovial fibroblasts. *PLoS ONE* **9**, e107890. https ://doi.org/10.1371/journal.pone.01078 90 (2014).
10. Bomalaski, J. S. & Clark, M. A. Phospholipase A2 and arthritis. *Arthritis Rheum.* **36**, 190–198 (1993).
11. Honnappa Nagarajaiah, Arindam Mukhopadhyay, Jarugu Narasimha Moorthy: Biginelli Reaction: An Overview: Tetrahedron Letters, 57, 2016, 5135-5149
12. Sanchez-Galan, E. *et al.* Leukotriene B4 enhances the activity of nuclear factor-kappaB pathway through BLT1 and BLT2 receptors in atherosclerosis. *Cardiovasc. Res.* **81**, 216–225. https ://doi.org/10.1093/cvr/cvn27 7 (2009).
13. Ye, Y. N. *et al.* Dual inhibition of 5-LOX and COX-2 suppresses colon cancer formation promoted by cigarette smoke. *Carcinogenesis* **26**, 827–834 (2005).
14. Sravani Sanaa, Ramya Tokalaa, Deepti Madanlal Bajaj, Narayana Nageshd, Kiran Kumar Bokarad, Gaddam Kiranmaid, Uppu Jaya Lakshmia, Swapna Vadlamanic, Venu Tallab, Nagula Shankaraiaha: Design and synthesis of substituted dihydropyrimidinone derivatives as cytotoxic and tubulin polymerization inhibitors: Bioorganic Chemistry, 93, 2019, 103317.
15. Amany S. Mostafa, Khalid B. Selim: Synthesis and Anticancer Activity of New Dihydropyrimidinone Derivatives, 156, 2018, 304-315.

16. Dhanabal Kumarasamy, Biswajit Gopal Roy, Joana RochaPereira, Johan Neyts, Satheeshkumar Nanjappan, Subhasis Maity, Musfiqua Mookerjee, Lieve Naesens: Synthesis and Invitro Antiviral Evaluation of 4 Substitued 3, 4- Dihydropyrimidinones: Bioorganic & Medicinal Chemistry Letters 2016
17. B.P. Kumar, G. Sankar, R.N. Baig, S. Chandrashekaran, Novel Biginelli dihydropyrimidines with potential anticancer activity: a parallel synthesis and CoMSIA study, Eur. J. Med. Chem., 44 (2009) 4192-4198