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Bioactive Dihydropyrimidines: An overview

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ABSTRACT

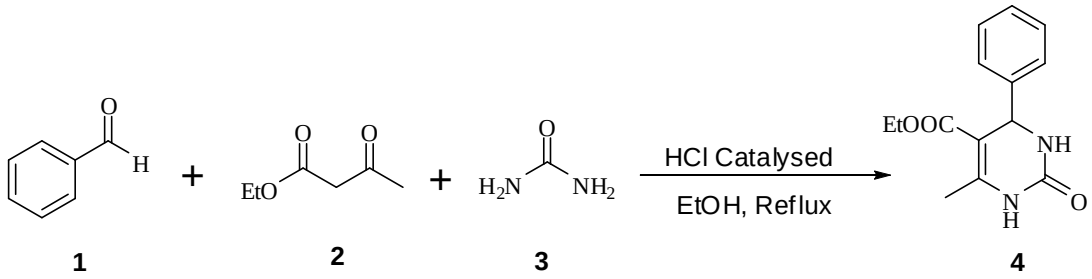
The Biginelli reaction, which is a three-component reaction for the synthesis of dihydropyrimidinone and corresponding dihydropyrimidinethiones (DHPMs) is known for more than a century. A large number researchers have shown consistent attention towards the study of Biginelli reaction, leading towards structurally diversified molecular libraries of DHPMs and it's analogues, having significant biological and pharmaceutical importance. Thus this chapter account for the Biginelli reaction giving novel DHPMs products, leading towards new drug discovery and drug like molecules.

INTRODUCTION

Nature is diversified with different variety of natural products with number of scaffolds and unique structures with specific activity. Among all the structures known, available and identified, heterocyclic scaffolds are ubiquitous in pharmaceuticals, natural products and biologically active compounds. The heterocyclic systems constitute privileged substructures and are present in a large number of compounds with remarkable biological activity [1]. Although a variety of methods are used to prepare these heterocyclic compounds with different core structure, the synthetic access to polysubstituted-polyfunctionalized heterocyclic derivatives remains a serious challenge [2] to scientific community. Although multistep sequences are widespread in the literature, but even in these cases the preparation of some substitution patterns and functional group combinations is particularly difficult. So of the available types of syntheses, an "ideal synthesis" [3] should lead to the desired product with the minimum steps as possible, in good overall yield and by using environmentally compatible reagents. The synthetic variables that have to be optimized are time, costs, overall yield, and simplicity of performance, safety, and environmental acceptability. Thus, multicomponent reactions (MCRs) are one-pot reaction procedures, which are easier to perform, isolate and diversify than multistep syntheses. Thus MCR strategy is a highly desirable approach in drug discovery development in the context of rapid identification, structural diversification and optimization of biologically active lead compounds of potential therapeutic importance within a short span of time which can generate large number of libraries of heterocyclic compounds with the aid of high-throughput biological screening [4]. Although in today's era, the concept of MCRs is highly popular and desirable procedure among the academic and industrial researchers, but this concept is not new in nature. It is observed that during evolution period, adenine [5], which is one of the major constituents of DNA and RNA was prebiotically formed by the condensation of five molecules of HCN, a plentiful component of prebiotic atmosphere, through the NH_3 catalyzed reaction. In the history of MCRs first contribution was made by Strecker [6] in 1850, with the discovery of α-amino nitrile synthesis, followed by Hantzsch's synthesis [7] of symmetrically substituted dihydropyridines, Biginelli's synthesis [8] of substituted dihydropyrimidines, Robinson's synthesis [9] of natural product alkaloid tropinone, Passerini's synthesis of acyloxy carboxamides [10], Bucherer and Bergs' synthesis of hydantoins [11], Asinger's synthesis of thiazolines [12], Ugi's synthesis of α-acylamino amides [13a, b], Gewald's synthesis of 2-amino thiophenes [13c] and which is finally followed by some organometallic and miscellaneous multicomponent reactions.

2. Discovery

In 1893, an Italian chemist Pietro Biginelli from University of Florence reported one of the most important multi-component reactions that allow the synthesis of dihydropyrimidinones and their sulfur analogues for the first time, which has given birth to this Biginelli reaction. In honor to his novel and excellent discovery this reaction is named as Biginelli reaction [8] after him. To achieve this reaction, he carried out a one-pot, three component, acid-catalyzed cyclocondensation reaction of 1, 3-dicarbonyl compounds, aldehyde and urea or thiourea by simply heating a mixture of the three components dissolved in ethanol with a catalytic amount of HCl at reflux temperature. On cooling he got a solid crystalline product of 3,4-dihydropyrimidin-2(1*H*)-one 6, represented as below.

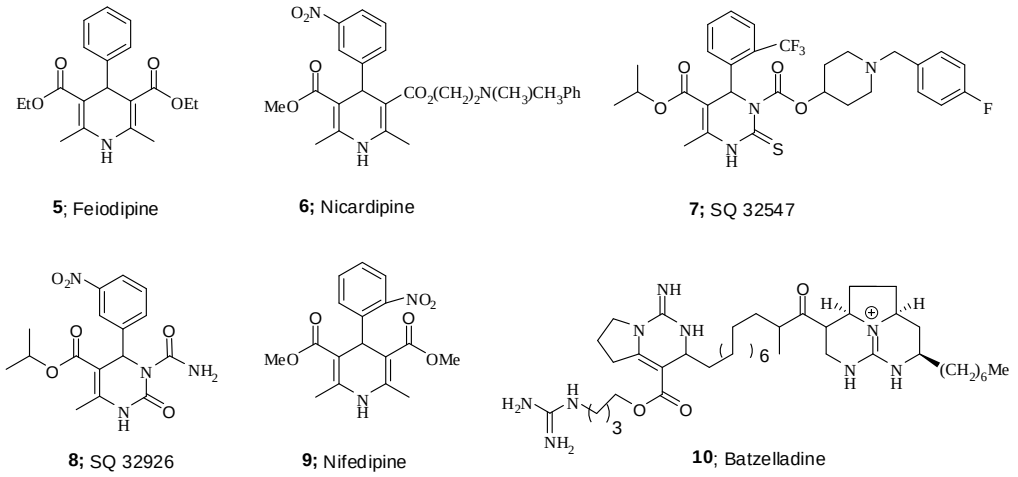


Scheme 1. Classical synthesis of Biginelli product.

Continuous research work has been undertaken by number of prominent scientist & researchers throughout last 100 years with highlighting mainly on variations in acid catalysts [14] ranging from mild Bronsted acids to strong Lewis acid. Being important building blocks and versatile synthons, 3, 4-dihydropyrimidinones are highly featured in organic synthesis due to their attractive pharmacological properties. Due to this, a large number of publications are shaded not only with motif modification but also with asymmetric synthesis.

Biological Activity of Dihydropyrimidines

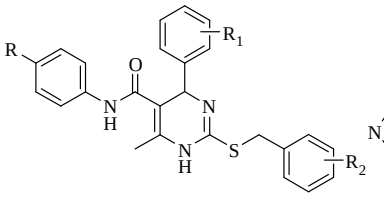
Taking into account of biological aspect of Biginelli product i.e. dihydropyrimidines, intensive investigation is carried out because they possess close resemblance of clinically used nicardipine, nifedipine etc. **5-9**, which are analogues of Biginelli product further they had resemblance to marine natural alkaloids batzelladine B **10**. Again biologists & chemists synthesized modified Biginelli product scaffolds, which showed activities like antiproliferative, antiviral, antitumor, anti-inflammatory, antibacterial, antifungal and antitubercular activity. Similarly, the structural core of quinoline is frequently associated with medicinal applications such as anticancer, antimicrobial, HIV-1 integrase inhibition, HIV protease inhibitors, antileishmanial activity, NK-3 receptor antagonists, PLT antagonists and antimalarial activity. In search of more potent and effective medicinally important molecules numerous Biginelli dihydropyrimidine related annulated or multifunctionallized pyrimidine heterocyclic have been investigated & tested against different life threatening diseases. To address its biological utility only selective molecules are presented which are having significant activity and they are examined with clinically used drugs in *vivo*/in *vitro* and establishing QSAR studies.



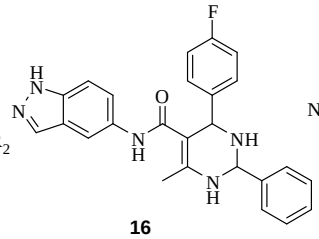
2.1 Antihypertensive agents

Many chemists and biologists saw Biginelli products in close resemblance to Hantzsch 1, 4-dihydropyridine as being aza-analogues of nifedipine and other related molecules which are well-known as calcium channel modulators

and Biginelli compounds like SQ 32547 *i.e.***7,** SQ 32926 *i.e.* **8**, which are effective orally active antihypertensive agents which seen to become very attractive target for becoming a promisable drug candidate. Ozair Alam *et. al.* [15] synthesized a number of 5-(4-substituted phenyl)-2-(substituted benzylsulfanyl)-4-(substituted phenyl)-6-methyl-1, 4-dihydro-5-pyrimidine carboxamides. Keeping in view the structural requirements as suggested in the pharmacophore model for antihypertensive activity. All the synthesized compounds were tested for antihypertensive activity by non-invasive blood pressure (NIBP) measurements (tail-cuff method) in rats. Almost all the tested compounds displayed considerable decrease in the blood pressure as compared to control. Thirteen compounds showed significant antihypertensive activity comparable to the standard drug nifedipine. Out of the all compounds synthesized only **11-15** show promising anti-hypertensive drug activity.



11, R= 4-F, R1=4-NO2, R2=4-F
12, R= 4-Br, R1=2,4-Cl, R2=2-Cl
13, R= 4-Br, R1=4-OCH3, R2=F
14, R= 4-NO2, R2=3-NO3, R2=H
15, R= 4-NO2, R2=3-NO3, R2=F



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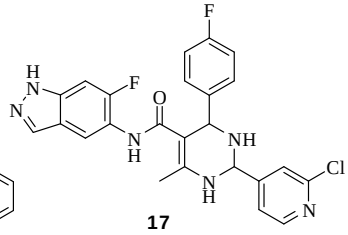

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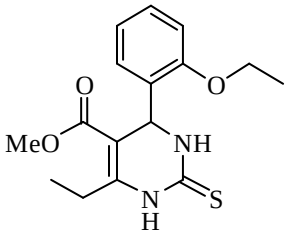
Clark A. Sehon *et. al.*[16] described that Rho-associated kinase isoform 1 (ROCK1*a*)1 is an enzyme involved in diverse cellular signaling functions such as smooth muscle contraction, cytoskeleton rearrangement, cell migration, and proliferation. Recent studies using ROCK1 inhibitors such as **16** (Fausidil) and **17** (Y-27632)3 along with cellular and molecular biology data have revealed a pivotal role of this serine-threonine kinase in many aspects of cardiovascular function. ROCK1 is a potential therapeutic target in the treatment of cardiovascular diseases such as hypertension. Their efforts focused on the optimization of dihydropyrimidine, resulted in the identification of a series of dihydropyrimidines with highly improved pharmacokinetics and P450 properties. Selma Sarac *et. al.* [17] also synthesized 4-aryl-6-ethyl-5-(methoxycarbonyl)-3, 4-dihydropyrimidin-2(1H)-thione compounds through Biginelli reaction which involved condensation reaction of methyl 3-oxopentanoate, aromatic aldehydes and thiourea with a catalytic amount of HCl at reflux temperature. But out of the sixteen compounds synthesized only compound **18** had shown promising antispasmodic and vasodilator activities in both screening paradigms utilized in their experiments.



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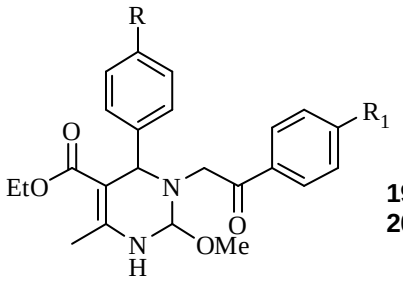


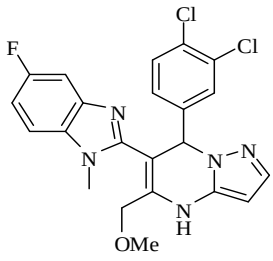
19, R=CH3, R_1=H
20, R=OCH3, R1=OCH_3

R.V. Chikhale *et. al.* **[**18] synthesized fifteen new ethyl 6-methyl-2-methoxy-3-(substituted 1-phenylethanone)-4-(substituted phenyl)-1, 2, 3, 4-tetrahydropyrimidine-5-carboxylates compounds following a two step sequence. All these compounds were tested for antihypertensive activity by non-invasive tail-cuff method and evaluated by carotid artery cannulation method for determining the diastolic blood pressure. Hypertension was induced by DOCA-salt. Anti-inflammatory activity was carried out by carrageenan induced rat-paw edema method. It is observed that compounds **19** & **20** possessed novel antihypertensive activity.

2.2 Potassium channel antagonists

John Lloyd *et. al.* [19] synthesized dihydropyrazolopyrimidines with a C6 heterocycle substituent were found to have high potency for block of KV1.5. Investigation of the substitution in the benzimidazole ring and the substituent in the 5-position of the dihydropyrazolo pyrimidine ring produced **21** with an IC_{50} for KV1.5 block of 0.030 µM without significant block of other cardiac ion channels. Because of the acceptable pharmacokinetic profile and ion channel selectivity, the methoxymethyl compound **21,** was chosen for further *in vivo* characterization. The pharmacodynamic activity was tested in a rabbit model, which measured the effective refractory period (ERP) in both atrium and ventricle. Like humans; rabbits express the I_{Kur} current in atrium but not in ventricle. The

compound was dosed at 0.3, 1.0, 3.0, and 10 mg/kg and prolonged atrial ERP by >20% at a dose of 3 mg/kg. There was no effect on ventricular ERP reflecting the selectivity for KV1.5 over ventricular ion channels. This compound also showed good bioavailability in rats and robust pharmacodynamic effects in a rabbit model. This compound also had good oral bioavailability in rats and showed a significant pharmacodynamic effect in rabbits. For these reasons, it was chosen for further preclinical development. Wayne Vaccaro *et. al*. [20] synthesized a series of dihydropyrazolo pyrimidine inhibitors of KV1.5 (I_{Kur}). Compounds **22** and **23** were evaluated for selectivity versus a panel of ion channels. Compounds **22** and **23** are both greater than 50 fold selective for KV1.5 versus hERG, INa, ICa (L-type), IKs, and IK1 ion channels. The ion channel selectivity of these compounds suggests that they may be useful for the treatment of atrial fibrillation without the risk of ventricular proarrhythmia. John Lloyd *et. al.* [21] designed and synthesized series of pyrazolo dihydropyrimidines as KV1.5 blockers which led towards the discovery of **24** as a potent and selective antagonist. This compound showed atrial selective prolongation of effective refractory period in rabbits and was selected for clinical development. The pharmacodynamic activity of **24** was tested in a rabbit model, which measured the effective refractory period (ERP) in both atrium and ventricle. Like humans, rabbits express the I_{Kur} current in atrium but not ventricle. The compound was dosed at 0.3, 1.0, 3.0, and 10 mg/kg and prolonged atrial ERP by >20% at a dose of 3 mg/kg. Reflecting the selectivity for KV1.5 over ventricular ion channels, **24** showed no effect on ventricular ERP up to the highest dose of 10 mg/kg with plasma concentration of nearly 7 µM. Plasma free fraction in rabbits for 7d was 3.0%. In conclusion, pyrrolidine amides of pyrazolo dihydropyrimidines were discovered as potent and selective KV1.5 blockers. A substituent at the 2-position significantly enhanced activity and the S-configuration is favored over the R-configuration. Compound **24** was chosen for more complete *in vitro* and *in vivo* evaluation and found to be potent in a pharmacodynamic model measuring effective refractory period. This compound was chosen for further pre-clinical toxicology studies and development as a clinical candidate.



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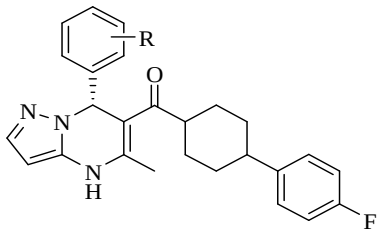
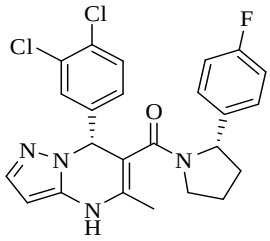


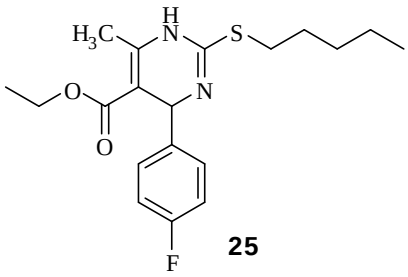
22, R= 2,3-Cl
23, R= 3,4-Cl



24

2.3 Antifilarial agents:

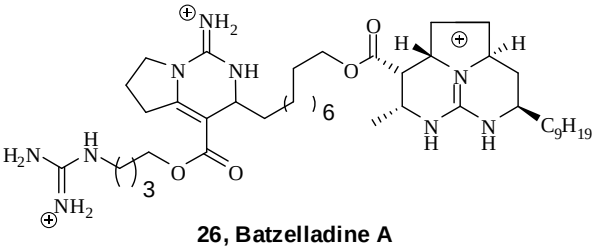
R. P. Tripathi *et. al* [22] synthesized a series of 2-sulfanyl-6-methyl-1, 4-dihydropyrimidines by alkylation of 5-methyl-6-phenyl-2-thioxo-1, 2, 3, 6- tetrahydropyrimidine-4-carboxylic acid ethyl esters with different alkyl or aryl halides in the presence of a combination of anhydrous K_2CO_3 and catalytic amount of tetrabutyl ammonium bromide. The title compound **25** was evaluated for their antifilarial activity against adult parasites of human lymphatic filarial parasite Brugia malayi (sub-periodic strain) *in vitro* and *in vivo* at various concentrations.



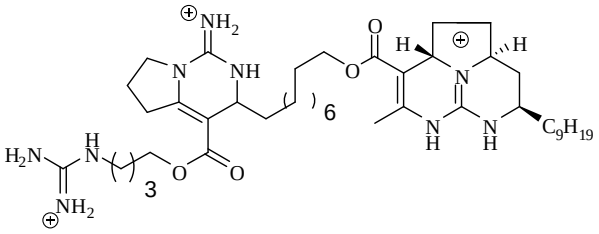
25

From the synthesized, compounds showing potent *in vitro* antifilarial activity were screened *in vivo* against B. malayi in Mastomys coucha model to see the effect of the compounds on parasitological parameters. It is evident from the observation that a significant effect on adult worms (50%; $P < 0.001$) was shown by compound **25** at 100 mg/kg. In terms of embryostatic activity, it exerted significant ($P < 0.01$) efficacy by sterilizing about 68% of the surviving female worms compared to 20% observed in the untreated controls. The efficacy of the compound was found to be lower at 50 mg/kg as compared to 100 mg/kg. In normal M. coucha at this dose the animals showed no mortality or adverse effect on general and gross health of the animals during the treatment and thereafter up to 15 days post-treatment. It is evident from the results that the standard antifilarial drug DEC (12.5 mg/kg, the effective dose of the drug against animal filariid, Litomosoides carinii) did not show any noticeable microfilaricidal activity and about 10% adulticidal activity was observed only as compared to untreated controls. However, the synthetic

compound **25** displayed about 46% adulticidal ($P < 0.01$) activity and 34% ($P < 0.05$) of the sterilized female worms were recovered. Untreated control animals showed no effect on mf (microfilariae) of peritoneal cavity of any of the animals. About 16% of live female worms recovered from these animals were sterile.



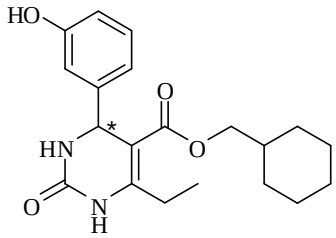
26, Batzelladine A



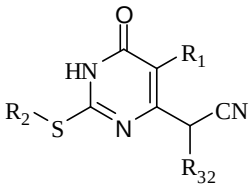
27, Batzelladine B

2.4 Anti-HIV agents

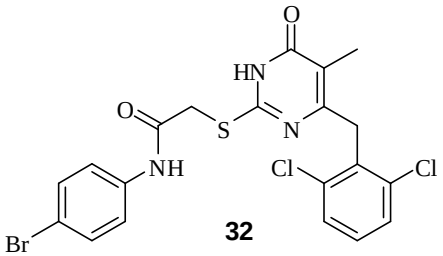
In 2009, it was observed that near about 33 million people were infected with the human immunodeficiency virus i.e HIV, a causative agent for acquired immunodeficiency syndrome *i.e.* AIDS, which currently on the top for the highest number of deaths by any single infectious agent, which is also increasing with time. Batzelladine A **26** and B **27** derivatives of DHPMs were obtained by Ashok D. Patil *et. al.* [23] from marine natural source were the first low molecular weight natural products reported showing promising anti HIV activity and, therefore, are potential leads for AIDS therapy. These low molecular weight natural products inhibit the binding of HIV envelope glycoprotein gp120 to CD4 receptors, and so are of potential interest for the treatment of HIV. The limited availability of the natural products renders them to be attractive targets for total synthesis. Zaesung No *et. al.* [24] synthesized 3, 4-Dihydropyrimidin-2(1H)-ones (DHPMs) were selected and derivatized through a HIV-1 replication assay based on GFP reporter cells, where compounds (R/S)-**28**/**29** exhibited significant inhibition of HIV-1 replication *in vitro*, with a good safety profile. Chiral separation of each enantiomer by fractional crystallization showed that only the (S)-**28**, enantiomer on C-4 in dihydropyrimidinone ring shown to have potent anti-HIV activity.



(S)-28, 98% ee
(R)-29, 98% ee



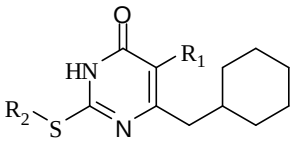
30: R1=Me, R2=benzoylmethyl, R3=1-naphthyl
31: R1=Me, R2= *i*-Pr, R3=Ph



32

Lei Ji *et. al.* [25] synthesized a series of S-DABO analogues and evaluated as inhibitiors of HIV type-1. Structural modification of compounds by replacement of 6-arylmethyl group by a 6-arylcarbonyl group, showed that two of them **30**, **31** posseses only micromolar potency against HIV-1 in MT-4 cells *in vitro* which are unusually potent (IC_{50}= 0.9 µM for **30**, **31**) and selective (SI= 1500 and 4600 respectively). Xinyong Liu *et. al.* [26] synthesized a series of novel 2-(phenyl aminocarbonylmethylthio)-6-(2, 6-dichlorobenzyl)-pyrimidin-4(3H)-ones have been designed and synthesized. All of the new compounds were evaluated for their anti-HIV activities in MT-4 cells. Most of these new compounds showed moderate to potent activities against wild-type HIV-1 with an EC_{50} ranging from 4.48 µM to 0.18 µ M .

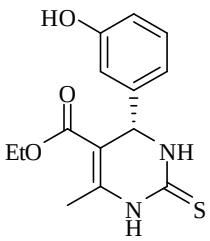
Among them, 2-[(4- bromophenylamino)carbonylthio]-6-(2, 6-dichlorobenzyl)-5-methylpyrimidin-4(3H)-one **32** was identified as the most promising compound (EC_{50} = 0.18 ± 0.06 l M, CC50 >243.56 l M, SI >1326) which is more effective than the reference drugs nevirapine and efavirenz. Yan-Ping He *et. al.* [27] synthesized novel dihydro-aryl/alkylsulfanyl-cyclohexylmethyl-oxopyrimidines (S-DACOs) combinatory library was synthesized and evaluated with C8166 cells infected by the HIV-1 IIIB *in vitro*, using Nevirapine (NVP) and Zidovudine (AZT) as positive control. The anti-HIV screening results revealed that C-6-cyclohexyl methyl substituted pyrimidinones possessed higher selective index than its 6-aryl methyl counter-parts. Compounds **33, 34, 35** and **36** showed potent anti-HIV activities with EC_{50} values of 0.012, 0.025, 0.088 and 0.162 *nM*, respectively.



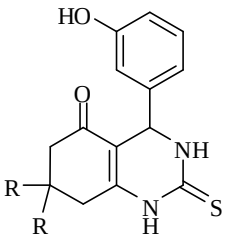
33: R1=i-Pr (4'-OCH3), R2=-PhCOCH2
34; R1=i-Pr ; R2=-PhCOCH2
35; R1=i-Pr, R2=-PhCH2
36; R1=Et; R2=-PhCOCH2

2.5 Antitumor activity

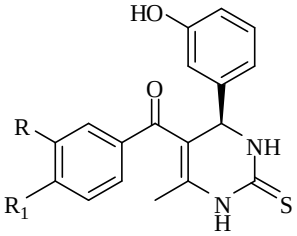
It is documented that, Human kinesin Eg5, plays an essential role in mitosis by establishing the bipolar spindle, which has proven to be an interesting drug target for the development of cancer chemotherapeutics. In this development, Monastrol **37** is the first Biginelli compound, which has excellent anticancer activity. So far, two structures of Eg5 in complex with dihydropyrimidine (DHPM)-derived inhibitors have been solved and employed for structure-based drug development.



37; (S)-Monastrol

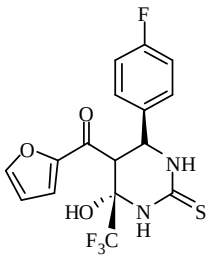


38;R=H; (S)-Enastron
39;R=Me; (S)-dimethylenastron



40

41;R=R1=H:(R)-mon-97
42;R=R1=F:(R)-Fluorastrol
43;R=H, R1=F: rac-1
44;R=F, R1=H: rac-2



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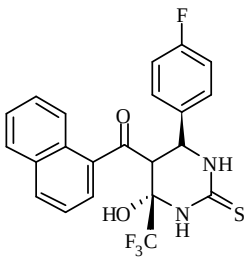

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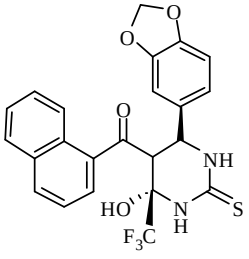

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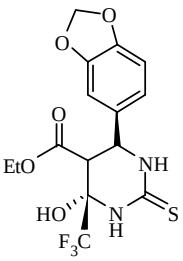

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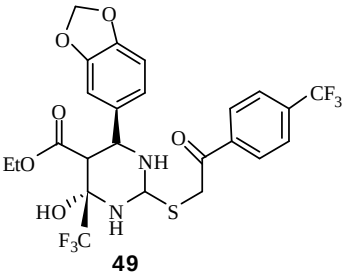

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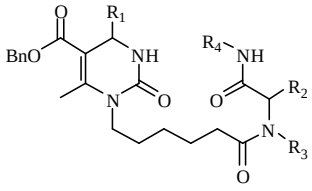
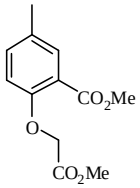
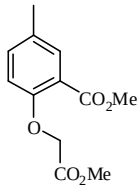
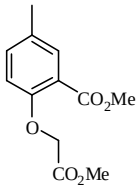
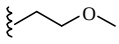
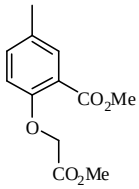
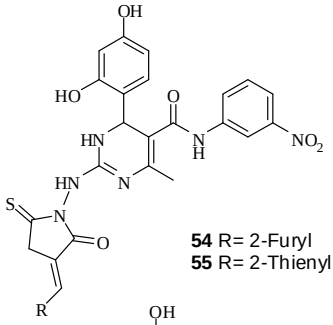
The crystal structures of the Eg5 motor domain complexed with enastron, dimethylenastron and fluorastrol has been reported. By comparing these structures to that of monastrol and mon-97, Frank Kozielski *et. al.* [28] identified the main reasons for increased potency of these new inhibitors, namely the better fit of the ligand to the allosteric binding site and the addition of fluorine atoms. He noticed preferential binding of the S-enantiomer of enastron and dimethylenastron to Eg5, while the R-enantiomer of fluorastrol binds preferentially to Eg5. In addition, he performed a multidrug resistance (MDR) study in cell lines overexpressing P-glycoprotein (Pgp). To be able to directly compare DHPM analogues developed by different groups, Kozielski *et. al.* investigated 11 compounds in proliferation assays in five different cell lines, including four tumor cell lines and one non-transformed (normal) cell line. Monastrol was included as a control and was a weak inhibitor throughout all cell lines. Dimethylenastron was stronger inhibitor than enastron and was approximately 6-fold more potent. Although there are some intercellular variations between racemic dimethylenastron and racemic fluorastrol, both compounds are almost equally potent, with the best EC_{50} values reaching about 300 *nM* in the colon cancer cell line HCT116. These compounds are also reported to be very active in the untransformed breast cancer cell line *hTERT-HME1*. Fluorastrol is about 5-fold more active than mon-97 when comparing the racemic mixtures and the more active enantiomers. Comparison of the racemic mixture of fluorastrol with **43** and **44** reveals that analogues with only one fluorine in either the meta or paraposition are less active in cell-based assays than analogues with two fluorines (fluorastrol). Comparison of the enantiomers of fluorastrol also clearly indicates that the R-enantiomer is at best about 30-fold more potent than the S-enantiomer. Cosmas O. Okoro *et. al.* [29] synthesized a series of trifluoromethylated hexahydropyrimidine and tetrahydropyrimidine derivatives were synthesized and their *in vitro* cytotoxic activities were determined in colon

cancer cell line (COLO 320 HSR). They represent promising new leads for the development of highly potent and selective anticancer compounds. All the compounds are lipophilic due to the trifluoromethyl group, and are thus expected to penetrate the membrane in appreciable concentration. They examined the antiproliferative activity of the variably substituted fluorinated hexahydropyrimidine derivatives on human colon (COLO 320 HSR) cancer cell line in the 72 h drug exposure Alamar blue™ Assays. The dose of the compound that inhibited 50% cell proliferation (IC_{50}) was calculated using the data generated from the assay. Among the 17 fluorinated Hexahydropyrimidine derivatives synthesized, only two derivatives **46** and **47** containing naphthyl-substituted analogs (R= naphthyl) showed the highest activity with IC_{50} values of 9.3 and 9.9 µM, respectively. Compound **45** also showed good activity of IC_{50} value of 11. 5 µM. Further upon modifications they synthesized compound **48**, which was also converted into **49** a fluorinated sulfanyl tetrahydropyrimidine. Both compounds showed good antiproliferative activity against colon cancer cell line COLO 320 with IC_{50} values of 12.2 and 8.1 µM, respectively. Jeffrey L. Brodsky *et. al.* [30] described that the heat shock proteins, molecular chaperones, such as Hsp70 and Hsp90, are responsible for a variety of protective, anti-apoptotic functions. The heat shock protein Hsp70, and its constitutively expressed counterpart Hsc70, play essential roles in many diverse cellular processes, including protein folding and transport, and the rearrangement of multi-protein complexes. The J domain interacts with the Hsp70 ATPase domain through a conserved His-Pro-Asp sequence to stimulate Hsp70 ATP hydrolysis. The TAg J domain can stimulate Hsp70 ATP hydrolysis, an activity that is required for maximal tumorigenesis. SV40 is highly related to at least four human polyomaviruses, two of which have been definitively linked to two-disease states progressive multifocal leukoencephalopathy (PML) and kidney transplant rejection—in immunocompromised patients. Notably, a number of MAL3-101 derivatives inhibited SK-BR-3 cell growth; GI50s for sixteen compounds ranged from 6.0 ± 0.4 µM to 42.6 ± 6 µM, with nine compounds yielding GI50 values < 10 µM. We then examined the effects of select compounds with activity in this assay on the growth of two other cell lines: MCF7 breast cancer cells and HT29 colon cancer cells. DMT003088-**50** and DMT003132-**51** and DMT003052-**52** exhibited GI50s in SK-BR-3 cells at a range from 6.2–8.8 µM, and similarly inhibited MCF7 and HT29 growth with GI50s ranging from 2.4–7.8 µM. Of interest, MAL3-101 also inhibited MCF7 growth but had no effect on HT29 cells. This result suggests that MAL3-101-**53** exhibits some specificity of action with regard to different cancer cell lines, as previously proposed. Diaa A. Ibrahim *et. al.* [31] synthesized novel derivatives of 2, 4, 5, 6-tetrasubstituted pyrimidine cyclin-dependent kinase (CDK2) inhibitors where they built a library of proposed pyrimidine derivatives using pharmacophore and docking techniques. Synthesis of novel highly selective CDKs as candidates for CDK-target therapy in cancer treatment is currently in high demand. The newly synthesized compounds showed potent and selective CDK2 inhibitory activities and inhibited *in vitro* cellular proliferation in cultured human tumor cells. In general, compounds **54, 55** and **56a** showed better CDK2 and cell division inhibitory activities than the other compounds. Compounds **54**, **55** were much more active than the reference compounds (roscovitine and olomoucine) with IC_{50}= 0.4 and 0.3 respectively, whereas compound **54** had no inhibitory activity on cell division. Compounds **56b** and 5**7** exhibited potent CDK2 inhibitory activity and reasonable cell division inhibitory activity. B. R. Prashantha Kumar *et. al.* [32] carried out synthesis of novel Biginelli dihydropyrimidines of biological interest using p-toluene sulphonic acid as an efficient catalyst. All the thirty-two synthesised dihydropyrimidines, Biginelli compounds were subjected for their *in vitro* anticancer activity against MCF-7 human breast cancer cells. The title compounds were tested at the concentration of 10 mg. Compounds exhibited activity ranging from weak to moderate and, from moderate to high in terms of percentage cytotoxicity. Among them, compounds **59** and **60** exhibited significant anticancer activity. In order to study the three-dimensional structure–activity relationships (3D QSAR) towards their anticancer activity, they did comparative molecular similarity indices analysis (CoMSIA).

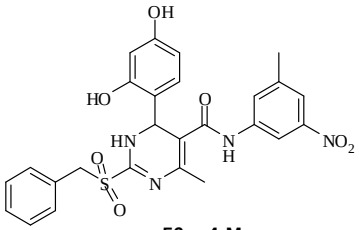


dihydropyrimidinone-peptoid

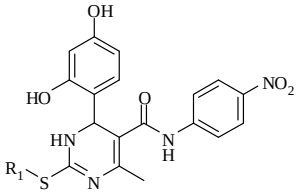
	R1	R2	R3	R4
50	Phenyl		*n*-hexyl	*n*-butyl
51	c-propyl		*n*-hexyl	*n*-butyl
52	p-biphenyl			*n*-butyl
53	p-biphenyl		*n*-hexyl	*n*-butyl



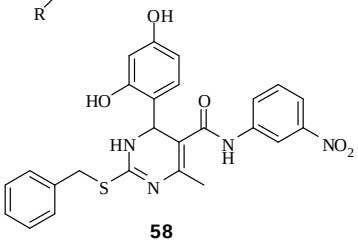
54 R= 2-Furyl
55 R= 2-Thienyl



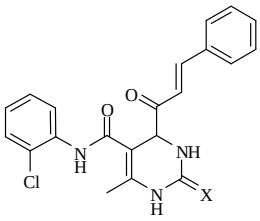
56a; 4-Me
56b; 3-NO_2



57. R=Sulphamethisoxazole



58

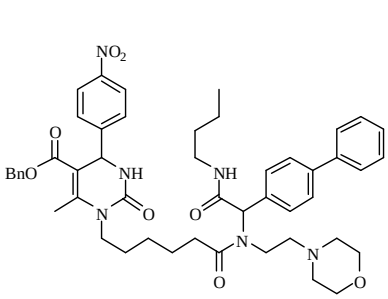


59; X=O & **60**; X=S

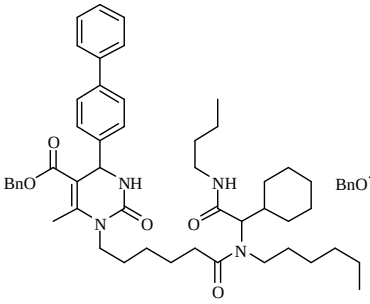
2.6 Anti-malarials

Pyrimidinone-amide derivatives of DHPMs **61-69**, a new class of Hsp70 modulators, could inhibit the replication of the pathogenic *P. falciparum* stages in human red blood cells. Jeffrey L. Brodsky *et. al.* [33] described these nine molecules as anti-malarial agents are being investigated further. *Plasmodium falciparum,* the *Apicomplexan parasite* that is responsible for the most lethal forms of human malaria, is exposed to radically different environments and stress factors during its complex lifecycle. In any organism, Hsp70 chaperones are typically associated with tolerance to stress. Therefore, the inhibition of *P. falciparum* Hsp70 chaperones would adversely affect parasite homeostasis was hypothesized. To test this hypothesis, measurements were carried whether pyrimidinone-amides, a new class of Hsp70 modulators, could inhibit the replication of the pathogenic P. falciparum stages in human red blood cells.

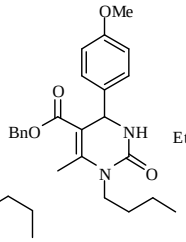
Nine compounds **61-69** with IC_{50} values from 30 nM to 1.6 µM were identified. Each compound also altered the ATPase activity of purified *P. falciparum* Hsp70 in single-turnover assays, although higher concentrations of agents were required than was necessary to inhibit *P. falciparum* replication. The impact of JAB75 on [^{3}H] hypoxanthine uptake, they used the chloroquine (CQ)-resistant Dd2 clone and employed CQ as an internal control because CQ is known to inhibit Dd2 with an IC_{50} value of 0.2 µM. Thus from initial analysis of 157 compounds, they identified nine molecules with IC_{50} values between 30 nM and 1.6 µM. To ensure that the compounds were not generally cytotoxic, they also determined the 50% growth inhibitory concentrations (G_{I50}) for each of these nine agents in two human cell lines, HepG2 hepatocellular carcinoma cells and WI-38 embryonic diploid lung cells. Based on this analysis, all G_{I50} values in these cells were >10 µM, which is well above the concentration needed to inhibit P. falciparum growth. As a control for this experiment, we found that the G_{I50} values for paclitaxel in HepG2 and WI-38 cells were 1.0 ± 0.6 nM and 13.7 ± 0.2 nM, respectively. In next assessesment, the effects of the nine compounds on Hsp70 ATPase activity, they examined the ability of each pyrimidinone to modulate the ATP hydrolytic rate of purified yeast Hsp70, Ssa1, and also compared the effects of these agents on human and *P. falciparum* Hsp70. The three chaperones are 71–74% identical to one another at the amino acid.



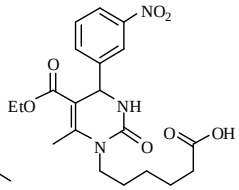
61; DMT3024



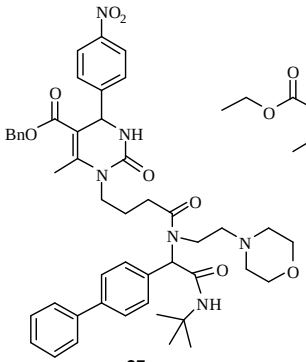
62; DMT2264



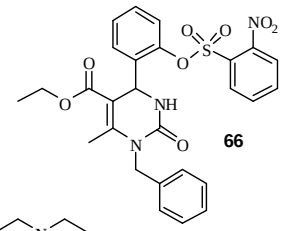
63 DMT3024



64; DMT3024



65



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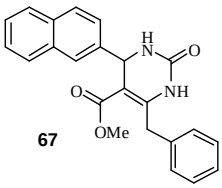

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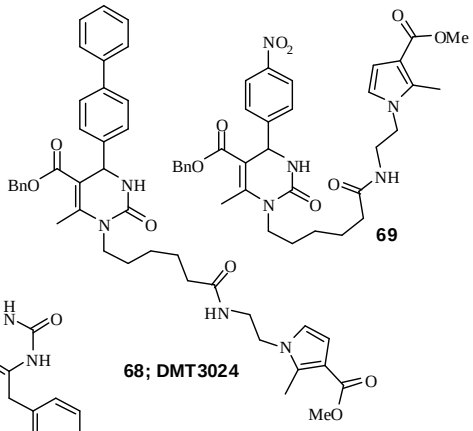
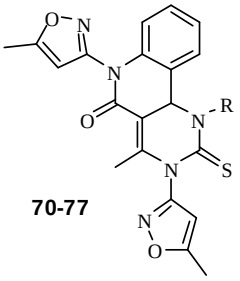
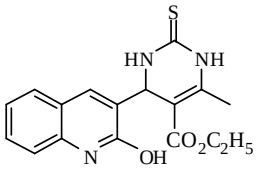


68; DMT3024

69



70-77



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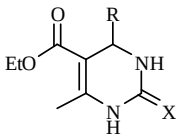
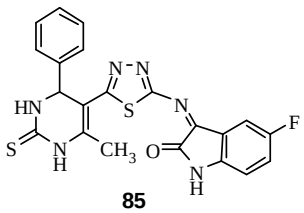




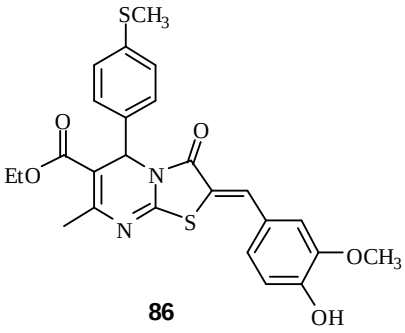
85

70: R= C6H5, **71**: R= 4-CH3C6H4, **72**: R= 4-CH30C6H4
73: R= 4-BrC6H4, **74**: R= C6H5CH2, **75**: R= 4-ClC6H4,
76: R= 3-CH30C6H5, **77**: R= 2-ClC6H4

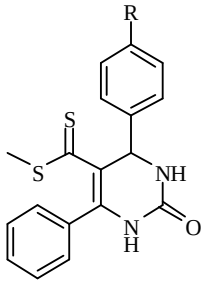
79: R=C6H5, X=O, **80**: R=C6H5, X=S,
81: R=2-HOC6H4, X=O, **82**: R=2-HOC6H4, X=S,
83: R=4-Me2NC6H4, X=S, **84**: R=4-Me2NC6H4, X=O,

4.7 Anti-microbials

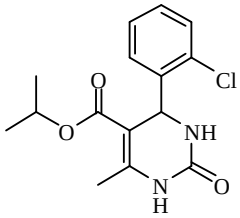
The increasing incidences of bacterial and fungal resistance to a large number of antimicrobial agents have prompted studies on the development of new potential antimicrobial compounds. It is well documented in the literature that isoxazole, pyrimidine derivatives and heterocyclic annulated pyrimidines display a wide variety of interesting pharmacological properties. So an attempt is made by E. Rajanarendar *et. al.* [34] by synthesizing new hybrid moieties secured by embedding fused molecular frame work isoxazoles with pyrimidines and quinolines which can offer promising and fascinating tri heterocyclic scaffolds and also to improve specificity and efficacy of these scaffolds against microorganisms. Thus the synthesis and biological evaluation of a novel series of 1-aryl-4-methyl-3,6-bis-(5-methylisoxazol-3-yl)-2-thioxo-2,3,6, 10b-tetrahydro-1H-pyrimido[5,4-c]-quinolin-5-ones is carried out. The newly synthesized compounds **70**-**77** were evaluated for *in vitro* antibacterial and antifungal activity against various gram-positive, gram-negative bacteria and fungal strains using broth dilution method and agar cup bioassay method, respectively. The bacterial strains used in the present investigation are *Bacillus subtilis* (MTCC 441), *Bacillus sphaericus* (MTCC 511), *Staphylococcus aureus* (MTCC 96), *Pseudomonas aeruginosa* (MTCC 741), *Klebsiella aerogenes* (MTCC 39), and *Chromobacterium violaceum* (MTCC 2656) and it is shown that the antibacterial activity of compounds **70**-**77** exhibited moderate to good antibacterial activity and are more active than standard drug Ciprofloxacin. The antibacterial activity of **73** and **77** is promising as compared to standard Ciprofloxacin, and they can be exploited for the formulation of bactericides after further study. The antifungal activity of the compounds **70**-**77** showed that they are significantly toxic towards all the five pathogenic fungi *i.e.* Aspergillus niger (MTCC 282), Chrysosporium tropicum (MTCC 2821), Rhizopus oryzae (MTCC 262), Fusarium moniliformae (MTCC 1848), and Curvularia lunata (MTCC 2030) and they are lethal even at 100 µg/mL concentration in comparison with standard Clotrimazole at the same concentration. Adhikari *et. al.* [35] synthesized dihydropyrimidines containing quinoline and shown that compound **78** posseses highest biological activity against Escherichia coli, Staphylococcus aureus and Pseudomonas aeruginosa. The antibacterial and antifungal screening revealed that **85** and it's derivatives showed moderate to good inhibition at 10 mg/ml concentration. Singh *et. al.* [36] carried out synthesis of dihydropyrimidinones by the Biginelli reaction and of which six compounds were selected for their antifungal activities against the radial growth of three fungal species viz., *Trichoderma hammatum, Trichoderma koningii* and *Aspergillus niger*. It was observed that inhibitory effects of the six compounds on each test fungus were different. Thus compound **79** was the most potent against *T. hammatum* resulting in 100% growth inhibition with *MIC* value of 0.*35 µg/mL*. The radial growth of *T. koningii* after 24 and 48 h were found to be inhibited completely (100%) by compound **81** and compounds **80**, **83** and **84** were the most potent against *A. niger*, with *MIC* value of *0.35 µg/mL* each. Jignesh Priyakant Raval *et. al.* [37] synthesized various 5- substituted-3-[{5-(6-methyl-2-oxo/thioxo-4-phenyl-1,2,3,4 tetrahydro pyrimidin-5-yl)-1,3,4-thiadiazol-2-yl}imino]-1,3-dihydro-2H-indol-2-one derivatives using one pot multicomponent Biginelli reaction. Newly synthesized compounds were also tested for their *in vitro* antibacterial activity against selected human pathogens viz. Escherichia coli, Pseudomonas aeruginosa, Klebsiella pneumoniae, Salmonella typhi, Staphylococcus aureus, Staphylococcus pyogenus, Bacillus subtilis and antifungal activity against Candida albicans, Aspergillus niger, Aspergillus clavatus strains. Where compound **86**, showed showed better activity (25 mg/ml) compared to other analoges. Okram M. Singh *et. al.* [38] synthesized 5-methyl mercaptothiocarbonyl-4-aryl-3, 4-dihydropyrimidin-2(1*H*)-ones by the Biginelli reaction. Of which six pure compounds selected, were examined for their antifungal activities against the radial growth of two fungal species *Curvularia oryzae* and *Fusarium moniliforme* using poison food technique and antibacterial activities against two bacteria viz. *Bacillus cereus* and *Bacillus amyloliquefaceins* using Agar well diffusion method. Where it is observed that compounds **87** and **88** were more potent not only in their antibacterial activity when compared with that of the standard drug ciprofloxacin but also more potent in their antifungal activity as the % inhibition of the tested fungi was more than the standard antifungal agent Amphotericin. B. K. Pandiarajan *et. al.* [39] synthesized 4-aryl-5-isopropoxycarbonyl-6-methyl-3, 4-dihydropyrimidin-2(1H)-ones and 4-phenyl-5-isopropoxycarbonyl-6-methyl-3,4-dihydropyrimidin-2(1H)-thione. All the compounds were screened for their antibacterial activity against *Staphylococcus aureus*, *Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa* and *Salmonella typhi* and antifungal activity against *Candida albicans, Aspergillus flavus, Rhizopus and Mucor*. Compounds **89, 90, 91 & 92** exhibited excellent *in vitro* antibacterial activity against Staphylococcus aureus, Salmonella typhi and Pseudomonas aeruginosa and potent *in vitro* antifungal activity against *Candida albicans, Rhizopus and Mucor*. Compounds **91 & 92** showed more activity than the standard drugs.



86



87: R=H;
88: R=Me



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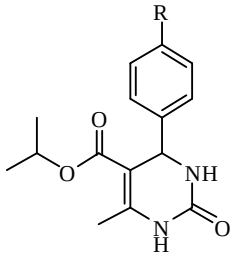
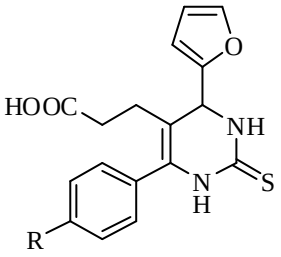


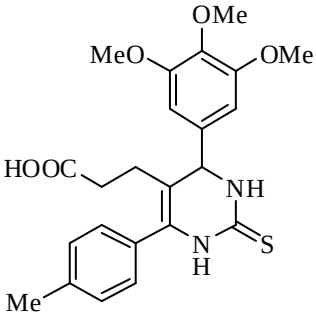
90-92; R=Cl, NO2, F

4.8 Anti-inflammatories

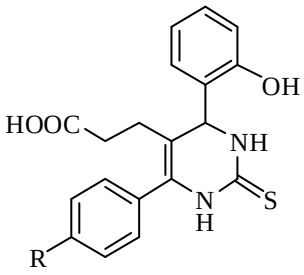
It is observed that, gastrointestinal adverse effects can be reduced through suppressing acid production, by concomitant use of a proton pump inhibitor, for example, omeprazole or the prostaglandin analogue Misoprostol. It was observed that acetic acid containing 2-thioxo/amino-1, 2, 3, 4-tetrahydropyrimidine moiety act as anti-inflammatory agent due to its lower lipophilicity. Santosh N. Mokale *et. al.* [40] synthesized series of 3-(4, 6-disubtituted-2-thioxo-1, 2, 3, 4-tetrahydropyrimidin-5-yl) propanoic acid derivatives, by condensation of thiourea, 5-(4-subtituted phenyl)-5-oxopentanoic acid and substituted aldehyde. The synthesized compounds were screened for their anti-inflammatory activity using rat paw edema method. Most of the compounds from the series showed significant ($p < 0.05$) anti-inflammatory activity which were found to be equipotent with diclofenac. The anti-inflammatory effect was found to be most significant ($p < 0.05$) at 1 h and gradually reduced at subsequent hours. Overall looking at duration of action and percent inhibition, the sustained and significant ($p < 0.05$) action was reported with **93a-93b, 94** and **95.**



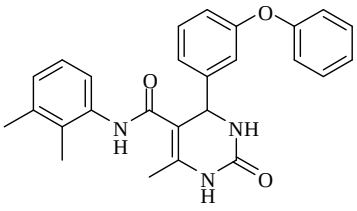
93a-93b; R=H, CH3



94



95; R=H, CH3



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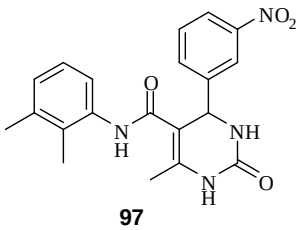

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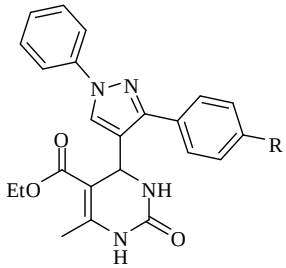
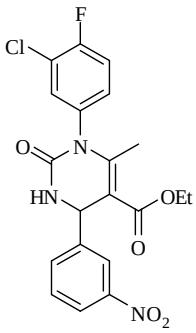


98, R=F;**99**, R=NO2

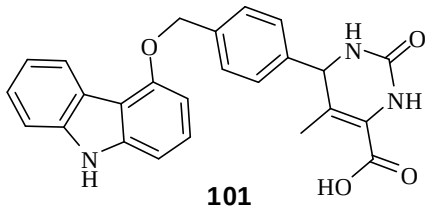


100

4.9 Anti-tubercular activity

One-third of the world's population is infected with Mycobacterium tuberculosis, which is the leading cause around 2 million peoples death in the developing world. The development of resistance by M. tuberculosis to commonly used antitubercular drugs necessitates a longer duration of therapy. The emergence of multi-drug resistance has forced the development of new structural classes of antitubercular agents, with several of them showing promising activity against *M. tuberculosis.* Dihydropyrimidines also were evaluated for their antitubercular activity against Mycobacterium tuberculosis H37Rv. This study was in vitro only. Evans C. Coutinho *et. al.* [41] synthesized new structural classes of antitubercular agents. They carried out the synthesis, evaluation and 3D-QSAR analysis of a set

of substituted N-phenyl-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamides as antitubercular agents. All compounds were screened for antitubercular activity against Mycobacterium tuberculosis H37Rv strain and out of which compound **96** & **97** showed 65% and 63% inhibition. Viresh H. Shah *et. al.* [42] synthesized a small library of 30 dihydropyrimidiines and evaluated for their *in vitro* antitubercular activity against Mycobacterium tuberculosis H37Rv. Two compounds, ethyl 4-[3-(4-fluorophenyl)-1-phenyl-1H-pyrazol-4-yl]-6-methyl-2-oxo-1,2,3,4- tetrahydro pyrimidine-5 carboxylate **98** and ethyl 4-[3-(4-nitrophenyl)-1-phenyl-1H-pyrazol-4-yl]-6-methyl-2-oxo-1,2,3,4tetrahydropyrimid-idine-5-carboxylate **99** were found to be the most active compounds *in vitro* with MIC of 0.02 µg/mL against MTB and were more potent than isoniazid (Antitubercular drug). Again Zalavadiya *et. al.* [43] synthesized different DHPMs, in which compound **100** exhibited moderate antimycobacterial activity against *Mycobacterium tuberculosis* H_{37} RV



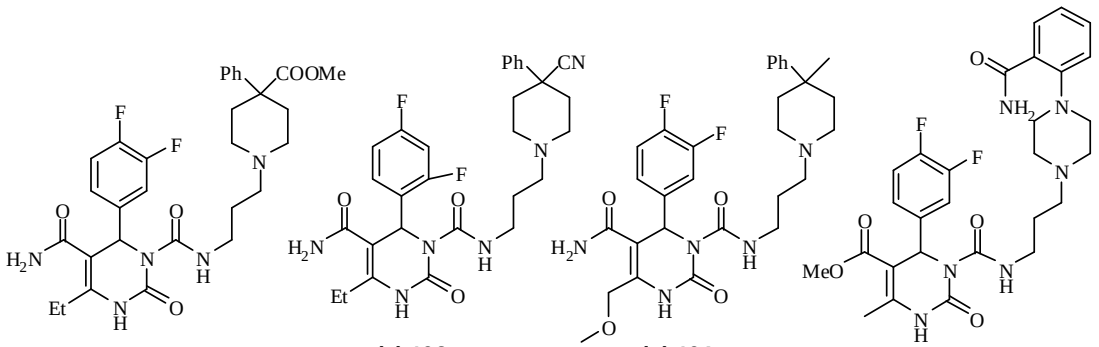
101

PPAR γ Activators

Type 2 diabetes mellitus (T2DM) accounts for more than 90% of all diabetics. A vast population in the world suffers from diabetics partly due to a dramatic increase in the incidence of obesity and sedentary lifestyle. The peroxisome proliferators activated receptor *γ* (PPAR Gamma) is a member of nuclear harmone receptor superfamily of ligand dependent transcription factors, which play a pivotal role in regulating adipogenesis, insulin sensitivity and glucose homeostasis. Synthetic agonists of PPAR*γ* including pioglitazone and rosiglitazone, has been proved clinically beneficial in decreasing the elevated plasma glucose levels in T2Dm. However, edema and weight gain have been reported in patients after treatment with some of PPAR*γ* agonist. It is unclear whether the side effects observed are PPAR receptor mediated or compound mediated. Rakesh Kumar *et. al.* [44] synthesized a novel series of 6-methyl-2-oxo-1, 2, 3, 4-tetrahydro-pyrimidine-5-carboxylic acid derivatives that are high affinity ligands for peroxisome proliferators activated receptor gamma have been reported as a potential substitute of 2, 4-thiazolidinedione head group. The Flex X docking and radioligand binding affinity of following promising compounds of this series is comparable to that of thiazolidinedione based antidiabetic drugs currently in clinical use. From the results it is observed that compound **101** fitted the best in the active site of PPAR*γ* and attained the best score of -23.7 kcal/mol amongst all the molecules synthesized. Again it showed all the prime interactions to anchor well in the active sites of the receptors.

***α*-1A Adrenergic receptor antagonists**

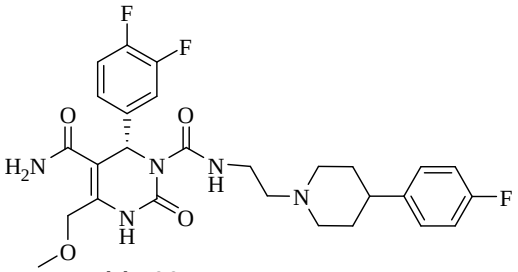
Benign prostatic hyperplasia (BPH) is a progressive condition characterized by a nodular enlargement of the prostate resulting in obstruction of the urethra.



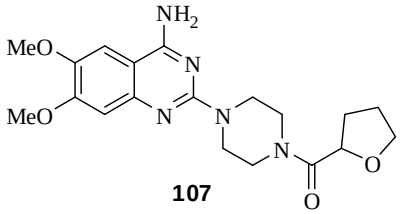
(+) 102 **(+) 103** **(+) 104** **(+) 105**

Nonselective R1 adreno receptor antagonists such as prazosin and terazosin are presently used for the symptomatic relief of BPH. It has been reported that the functional potency of a number of R1 antagonists to relax the agonist-induced contraction of prostatic smooth muscle correlates well with the binding affinity for these antagonists for the R1a subtype at the cloned human receptors. The data seem to suggest that a potent R1a-selective antagonist can be an attractive drug candidate for treatment of BPH with fewer undesirable side effects that may be associated with the other subtypes. Dhanapalan Nagarathnam *et. al.* [45] synthesized dihydropyrimidinones leading to the

identification of highly potent and subtype-selective compounds (+)-**102**, with high binding affinity (*K*i) 0.2 nM for R1a receptor and greater than 1500-fold selectivity over R1b and R1d adreno receptors. The compounds were found to be functional antagonists in human, rat, and dog prostate tissues. Among these, compound (+)-**102** exhibited excellent selectively to inhibit intraurethral pressure (IUP) as compared to lowering diastolic blood pressure (DBP) in mongrel dogs (*K*b(DBP)/*K*b(IUP)) suggesting urethra selectivity for R1a-selective compounds. The results from a number of *in vivo* and *in vitro* experiments on **(**+**)-102** and terazosin suggested, terazosin has no subtype selectivity for the R1a receptor, but (+)-**102** showed >1000-fold selectivity for the R1a receptor over a number of recombinant human G-protein coupled receptors such as R2 and 5HT (1A, 1B, 1D, and 2A) receptors as well as the rat L-type calcium channel. The selectivity for the R1a receptor over the histamine H1 receptor was found to be 140-fold, based on the binding affinities of (+)-**102** for the cloned human receptors. Further M. R. Marzabadi *et. al.* **[**46] synthesized several dihydropyrimidinone analogues with the goal of either minimizing the formation of 4-methoxycarbonyl-4-phenylpiperidine by modification of the linker or finding alternative piperidine moieties which when cleaved as a consequence of metabolism would not give rise to *í*-opioid activity. Modification of the linker gave several compounds with good R1a binding affinity (*K*i) < 1 nM) and selectivity (>300-fold over R1b and R1d). In vitro analysis in the microsomal assay revealed these modifications did not significantly affect *N*-dealkylation and the formation of the 4-methoxycarbonyl-4-phenylpiperidine. The second approach, however, yielded several piperidine replacements for 4-methoxycarbonyl-4-phenylpiperidine, which did not show significant *í*-opioid activity. Then he carried out synthesis of compounds (+)-**103** and (+)-**104** which on detailed *in vitro* and *in vivo* characterization shown to have excellent selectivity (>880-fold) over R1b and R1d, also showed good selectivity over several other recombinant human G-protein coupled receptors. Compounds (+)-**103** and (+)-**104** displayed good functional potency in isolated human prostate tissues, with *K*bs comparable to their *in vitro* R1a binding data. In addition, compound (+)-**103** also exhibited good uroselectivity (DBP *K*b/IUP *K*b > 20-fold) in the *in vivo* experiments in dogs, similar to **102**. Bharat Lagu *et. al.* [47] identified compound **(**+**)-105** as a lead compound with a binding and functional profile comparable to that of **102**. The putative metabolite 2-carboxamidophenylpiperazine has negligible affinity for the *í*-opioid receptor. James C. Barrow *et. al.* [48] synthesized many compounds and evaluated *in vivo* activity. Few of the compounds found to be more potent than terazosin in both a rat model of prostate tone and a dog model of intra-urethral pressure without significantly affecting blood pressure. While many of the compounds tested displayed poor pharmacokinetics, compound **106** was found to have adequate bioavailability (>20%) and half-life (>6 h) in both rats and dogs. Due to its selectivity for the R1a over the R1b and R1d receptors as well as its favorable pharmacokinetic profile, **106** has the potential to relieve the symptoms of BPH without eliciting effects on the cardiovascular system. It has displayed sufficient bioavailability and plasma half-life in animal models to warrant further consideration for the treatment of BPH.



(+)-106

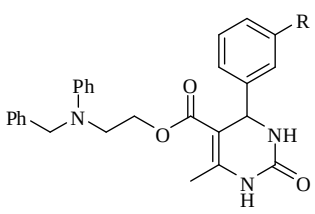


107
Terazosin

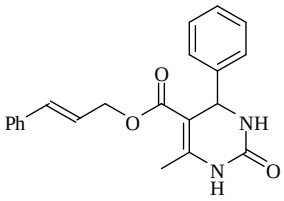
4.11 Antioxidant Activity

Free radicals play an important role in the pathogenesis of many diseases, accounting for continuing interest in the identification and development of novel antioxidants that prevent radical-induced damage. In humans, several pathologies involve the overproduction of reactive oxygen species (ROS): such as the superoxide radical anion (O_2) and hydrogen peroxide (H_2O_2) are formed in biological system by the partial reduction of molecular oxygen. Additionally, there are a large number of other reactive species that are formed from the reaction of ROS with biological molecules [e.g. polyunsaturated lipids, thiols and nitric oxide (NO)]. In the pathologic conditions an overproduction or scavenger diminution of the reactive oxygen species (ROS) can occur. In fact, ROS overproduction has been implicated in the installation and/or progression of a variety of human diseases, including diabetes and various neurodegenerative diseases. Hélio A. Stefani *et. al.* [49] synthesized different DHPMs. Some of the synthesized compounds were tested *in vitro* for their antioxidant activity. All of the selected compounds showed some antioxidant activity. Analogues compounds **108** and **109** exhibited a strong activity against lipid peroxidation induced by Fe + EDTA, while compounds **108** and **109** were the most potent in reducing ROS levels. Again Bernard Refouvelet *et. al.* [50] synthesized new hexahydropyrimido[5,4-c]quinoline-2,5-diones and 2-thioxohexahydropyrimido[5,4-c]quinoline-5-ones. Their antioxidant properties were evaluated by two methods:

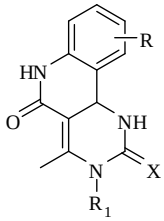
scavenging effect on 2,2-diphenyl-1-picrylhydrazyl (DPPH) radicals and scavenging effect on hydroxyl radicals. The results show that the compounds containing thiourea moiety **113**, have better activity.



108; R=H, **109**; NO2



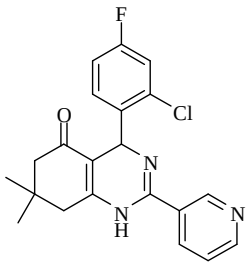
110



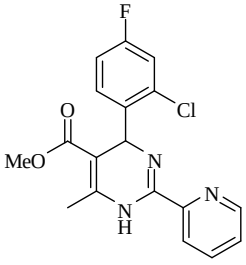
111; X=O, R=7-Cl,R1=Me
112;X=O, R=7-Cl,R1=Et
113; X=S, R=8-Cl,R1=Me

Anti- hepatitis B virus (HBV) agents

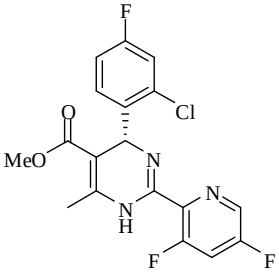
More than 350 million people around the world are chronically infected with the hepatitis B virus (HBV), and estimated one million patients die each year due to the long-term complications of liver cirrhosis or hepatocellular carcinomas. So far, six antiviral agents have been approved for treating chronic hepatitis B (CHB): two immune modulators (IFN-α and pegIFN-α), and four polymerase inhibitors (lamivudine, entecavir, telbivudine and adefovir). However, there are several disadvantages of current treatments, such as the emergence of resistant mutants, poor tolerability, and the inefficiency of eradicating HBV from CHB patients. Therefore, development of more effective therapeutic agents for HBV infection is still highly necessary. Xuejun Zhu *et. al.* [51] synthesized a series of novel 2, 4-diaryl-4, 6, 7, 8-tetrahydroquinazolin-5(1H)-one derivatives were designed and synthesized as potent inhibitors of HBV capsid assembly. These compounds arose from efforts to rigidify an earlier series of heteroaryl dihydropyrimidines (HAPs), and compound **114**, showed potent inhibition of HBV capsid assembly, with IC_{50} value at sub-micromolar range. Stephen J. Stray *et. al.* [52] observed that heteroaryl dihydropyrimidines (HAPs) are a new class of antivirals inhibiting production of hepatitis B virus (HBV) virions in tissue culture. He examined the effect of a representative HAP molecule **115**, methyl 4-(2-chloro-4-fluorophenyl)-6-methyl-2-(pyridin-2-yl)-1, 4-dihydropyrimidine-5-carboxylate (HAP-1) on the *in vitro* assembly of HBV capsid protein (Cp). HAP-1 enhances the rate and extent of Cp assembly over a broad concentration range. Aberrant particles, dominated by hexagonal arrays of Cp, were observed from assembly reactions with high HAP-1 concentrations. Deres *et. al.* [53] reported that the IC_{50} and the *K*d of BAY 39-5493 i.e. **117**, another HAP, for capsid were very similar (30 nM), suggesting that the biological effect is exerted at substoichiometric concentrations. Reduced secretion of mature virus in tissue culture was reported with treatment using low [BAY 39-5493] (less than the *K*d of drug for capsid), whereas a significant reduction of total Cp levels required higher drug concentrations. At low HAP-1, apparently normal capsids were assembled more rapidly *in vitro*; large-scale misdirection of assembly required considerably higher drug concentrations. The pure active isomer of BAY41-4109 i.e. **116** shows similar activity to racemic HAP-1 in our *in vitro* assays, but at one-fifth the concentration. Thus, simply deregulating the rate of assembly may be sufficient to reduce the production of normal virus particles. Similarly, F97L, a common, naturally occurring mutant associated with replication defects and secretion of immature virus particles in some cell lines, increased rates and extents of assembly *in vitro*.



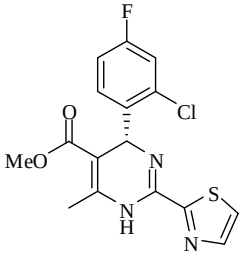
114



115;HAP



116; Bay 41-4109



117; Bay 39-5493

CONCLUSION

In the current chapter, we have collectively reviewed DHPMs having novel biological activity. This review also throws light on the past to present development in the synthesis of medicinally useful DHPMs using Biginelli reaction, which can lead towards identification of unique lead drug candidates useful against various life threatening diseases and saving life of every affected human beings in our society surrounding us.

REFERENCES

[1] Eicher T, Hauptmann S, *The Chemistry of Heterocycles*, 2nd ed, Wiley-VCH: Weinheim, Germany, **2003,** pp 316.
[2] Larsen LD, Cai D, In *Six-Membered Hetarenes with One Nitrogen or Phosphorus Atom;* Black D, Ed, Science of Synthesis, Vol. ; Georg Thieme Verlag: Stuttgart, Germany, **2005**, 15, pp 551.
[3] Wender P.A., Miller B. L. "Organic Synthesis: Theory and Applications", T. Hudlicky Ed., Greenwich: JAI Press, **1993**, 2, pp 27.
[4] Armstrong R W, Combs A P, Tempest P A, Brown S D, Keating T A, *Acc. Chem. Res.*, **1996**, 29, 123. Ugi I, *Pure Appl. Chem*., **2001**, 73, 187. Dömling A, Ugi I, *Angewandte Chemie International Edition.*, **2000**, 39, 3151.
[5] Oró J, Kimball A P, *Archives of biochemistry and biophysics*, **1961**, 94, 217. Shapiro R, *Origins of Life and Evolution of Biospheres*, **1995**, 25, 83.
[6] Strecker A, *Annalen der Chemie und Pharmazie;* **1850**, 75, 27.
[7] Hantzsch A, *Chemische Berichte*, **1881**, 14, 1637.
[8] Biginelli P, *Ber.* , **1891**, *24*, 1317 & 2962; b) Biginelli P, *Ber.*, **1893**, *26*, 447.
[9] Robinson R, *Journal of the Chemical Society, Transactions 111:* **1917**, *762*. Nicolaou, K C, Vourloumis D, Winssinger N, Baran P S, *Angewandte Chemie International Edition***, 2000,** 39, 44.
[10] Passerini M, Simone L, *Gazz. Chim. Ital.* **1921**, *51*, 126. Passerini M, Ragni G, *Gazz. Chim. Ital.*, **1931**, *61*, 964. Banfi L, Riva R, *Org. React.*, **2005**, 65**,** 1.
[11] Bucherer H T, Fischbeck H T , *J. Prakt. Chem.*, **1934**, *140*, 69. Bucherer H T, Steiner W, *J. Prakt. Chem.*, **1934**, *140*, 291. Bergs H, Ger. pat. **1929,** 566, 94. Ware E, *Chem. Rev.*, **1950**, *46*, 403.
[12] Asinger F, Angewandte Chemie, **1956**, *68*, 413. Asinger F, Thiel M, *Angewandte Chemie*, **1958**, *70*, 667–683.
[13] Ugi I, Meyr R, Fetzer U, Steinbrückner C, *Angewandte Chemie*, **1959**, 71**,** 373.
Ugi I, Steinbrückner C, *Angewandte Chemie* , **1960**, 72, 267. Ugi I, *Angewandte Chemie International Edition in English*, **1962**, **1**, 8. Gewald K, Schinke E, Böttcher H, *Ber.* **1966**, *99*, 94.
[14] Oliver C K, *Eur. J. Med. Che.*, **2000**, 35, 1043 Wan J P, Yunyun Liu Y, *Synthesis*, **2010**, 23, 3943. Topics in Heterocyclic Chemistry 23, 2010, pp 227. Suresh, Sandhu J S, ARKIVOC, ***2012*** *(i) 66.* Srinivasa Rao J, Verma D, Jain S, *Der Chemica Sinica, 2012, 3(3):636. Priya G, Srivasthava Y K, Der Chemica Sinica, 2012, 3(2), 318. Suneel Kumar K, Reddy K T, G J M G Reddy. Omprakash, Dubey P K, Der Pharmacia Sinica, 2011, 2(6), 127.* Nazeruddin N *G M, Pandharpatte M S, Der Chemica Sinica, 2010, 1(2):15.*
[15] Ozair A, Khan S A, Siddiqui N, Ahsan W Verma S P, Gilani S J, *Europeon Journal of Medicinal Chemistry***, *2010,*** 45, 5113.
[16] Clark A S, Wang G Z, Viet A Q, Goodman K B, Dowdell S E, Elkins P A, Semus S F, Evans C, Jolivette L J, Kirkpatric R B, Dul E, Khandekar S S, Yi T, Wright L L, Smith G K, Behm D J, Bentley R, Doe C P, Hu E, Lee D, *Journal of Medicinal Chemistry***, *2008,*** 51, 6631.
[17] Zorkun I S, Sarac S, Celebib S, Erolb K**,** *Bioorganic & Medicinal Chemistry*, **2006,** 14, 8582.
[18] Chikhale R V, Bhol R P, Khedekar P B, Bhusari K P, *European Journal of Medicinal Chemistry*, ***2009,*** 44, 3645.
[19] Lloyd J, Finlay H J, Atwal K, Kover A, Prol J, Yan L, Rao B, Vaccaro W, Huynh T, Huang C S, Conder M, Jenkins-West T, Sun H, Li D, Paul L, *Bioorganic & Medicinal Chemistry Letters*, ***2009,*** 19 5469.
[20] Vaccaro W, Huynh T, Lloyd J, Atwal K, Finlay H J, Levesque P, Conder M L, Jenkins-West T, Hong S, Sun L, *Bioorganic & Medicinal Chemistry Letters*, ***2008,*** 18, 6381.
[21] John Lloyd J, Finlay H J, Vacarro W, Hyunh T, Kover A, Rao B, Yan L, Atwal K, Conder M L, Jenkins-West T, Hong S, Huang C, Li D, Sun H, Levesque P, *Bioorganic & Medicinal Chemistry Letters*, ***2010,*** 20, 1436.
[22] Singh B K, Mishra M, Saxena N, Yadav G P, Maulik P R, Sahoo M K, Gaur R L, Murthy P K, Tripathi R P, *European Journal of Medicinal Chemistry*, ***2008,*** 43, 2717.
[23] Patil A D, Kumar N V, Kokke W C, Bean M F, Freyer A J, De Brosse C, Shing M, Trunch A, Faulkner D. J, Carte B, Breen A L, Hertzberg R P, Johnson R K, Westley J W, Potts C M B, *Journal of Organic Chemistry*, **1995**, 60, 1182.
[24] Kim J, Park C, Ok T,; So W, Jo M, Seo M Kim, Y Sohn, J H, Park Y, Moon K J, Kim J, Han S J, Kim T H, Cechetto J Nam J, Sommer P No Z, *Bioorganic & Medicinal Chemistry Letters*, ***2012,*** 22, 2522.
[25] Ji L, Chen F E, De Clercq E, *Journal of medicinal chemistry*, **2007**, 50, 1778.
[26] Yu M, Liu X, Li Z, Liu S, Pannecouque C, Clercq E D, *Bioorganic & Medicinal Chemistry*, ***2009,*** *17*, 7749.
[27] He Y P, Long J, Zhang S S, Li C, Lai C C, Zhang C S, Li D X, Zhang D H, Wanga H, Cai Q Q, Zheng Y T, *Bioorganic & Medicinal Chemistry Letters*, ***2011,*** 21, 694.
[28] Kaan H Y K, Ulaganathan V Rath O, Prokopcov H, Dallinger D, Kappe C O, Kozielski, *Journal of Medicinal Chemistry*, ***2010***, *53*, 5676.
[29] Agbaje O C, Fadeyi O O, Fadeyi S A, Myles L E, Okoro C O, *Bioorganic & Medicinal Chemistry Letters*, **2011**, 21989.

[30] Wright C M, Chovatiya R J, Jameson N E, Turner D M, Zhu G, Werner S, Huryn D M, Pipas J M, Day B W, Wipf P, Brodsky J L, *Bioorganic & Medicinal Chemistry*, **2008**, 16, 3291.
[31] Ibrahim D A, El-Metwally A M, *European Journal of Medicinal Chemistry*,**2010,** 45, 1158.
[32] Prashantha Kumar B R, Sankar G, Nasir Baig R B, Chandrashekaran S, , *European Journal of Medicinal Chemistry*, **2009,** 44, 4192.
[33] Chiang A N, Valderramos J C, Balachandran R, Chovatiya R J, Mead B P, Schneider C, Bell S L, Klein M G, Huryn D M, Chen X S, Day B W, Fidock D A, Wipf P, Brodsky J L, *Bioorganic & Medicinal Chemistry***, *2009,*** 17, 1527.
[34] Rajanarendar E, Reddy M N, Murthy K R, Reddy K G, Raju S, Srinivas M, Praveen B, Rao M. S, *Bioorganic & Medicinal Chemistry Letters***, *2010,*** 20, 6052.
[35] Adhikari A, Kalluraya B, Sujith K V, Gouthamchandra, Mahmood R. *Saudi Pharmaceutical J*.**, 2012,** *20*, 75.
[36] Singh O M, Singh S Y, Devi M B, Devi L N, Singh N I, Lee S G, *Bioorganic & Medicinal Chemistry Letters***, 2008**, *18*, 6462.
[37] Akhaja T N, Raval J P, *European Journal of Medicinal Chemistry*, ***2011***, *46*, 5573.
[38] Singh O M, Nepram S D, Laishram R D, Khumanthem N, *International Journal of Drug Design and Discovery*, **2010**, 1, 258.
[39] Chitra S, Devanathan D, Pandiarajan K, *European Journal of Medicinal Chemistry*, **2010**, 45, 367.
[40] Mokale , S. N, Shinde, S. S, Elgire, R. D, Sangshetti, J. N, Shinde, D. B, Synthesis and anti-inflammatory activity of some 3-(4,6-disubtituted-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl) propanoic acid derivatives, *Bioorganic & Medicinal Chemistry Letters*, **2010**, 20, 4424–4426.
[41] Virsodia V, Raghuvir R S, Pissurlenkar Manvar D, Dholakia C, Adlakha P, Shah A, Coutinho E C, *European Journal of Medicinal Chemistry*, **2008**, 43, 2103.
[42] Trivedi A R, Bhuva V R, Dholariya B H, Dodiya D K, Kataria V B, Shah,V H, *Bioorganic & Medicinal Chemistry Letters*,**2010**, 20, 6100.
[43] Zalavadiya P, Tala S, Akbari J, Joshi H, *Arch. Pharm. Chem. Life Sci.*, **2009,** 342, 469.
[44] Kumar R, Mittal A, Ramachandran U, *Bioorganic & Medicinal Chemistry Letters*, **2007**, 17, 4613.
[45] Nagarathnam D, Miao S W, Lagu B, Chiu G, Fang J, Murali Dhar T G, Zhang J, Tyagarajan S,; Marzabadi, M. R, Zhang F, Wong W C, Sun W, Dake T, Wetzel J M, Forray C, Chang, R. S. L, Broten, T. P, Ransom, R. W, Schorn, T. W, Chen, T. B, O'Malley, S, Kling, P, Schneck, K, Bendesky, R, Harrell, C. M, Vyas, K. P, Gluchowski, C, *Journal of Medicinal Chemistry*, **1999**, 42, 4764.
[46] Murali Dhar, T. G, Nagarathnam D, Marzabadi M R, Lagu B, Wong W C, Chiu G, Tyagarajan S, Miao S W, Zhang F, Sun W, Dake T, Shen Q, Zhang J, Wetzel J M, Forray C, Chang R S L, Broten T P, Schorn T W, Chen T B, O'Malley S, Ransom R, Schneck K, Bendesky R, Harrell C M, Vyas K P, Zhang K, Gilbert J, Pettibone D J, Pataner M A, Bockr M G, Freidingerr R M, Gluchowski C, *Journal of Medicinal Chemistry*, **1999**, 42, 4778.
[47] Lagu B, Dake T, Nagarathnam D, Marzabadi M, Wong R W C, Miao S W, Zhang F, Sun W, Chiu G, Fang J, Forray C, Chang R S L, Ransom R W T, Chen B O'Malley S, Zhang K, Vyas K P, Gluchowski C, *Journal of Medicinal Chemistry*,**1999**, 42, 4794.
[48] Barrow J C, Nantermet P G, Selnick H G, Glass K L, Rittle K E, Gilbert K F, Steele T G, Homnick C F, Freidinger R M, Ransom R W, Kling P, Reiss D, Broten, Theodore P T, Schorn W, Chang R S L, O'Malley S S, Olah T V, Ellis J D, Kassahun A B K, Leppert P, *Journal of Medicinal Chemistry*, **2000**, 43, 2703.
[49] Stefani H. A, Oliveira C. B, Almeida R B, Pereira C M P, Braga R C, Cella R, Borges V. C, Savegnago L, Nogueira C W, *European Journal of Medicinal Chemistry*, **2006**, 41, 513.
[50] Ismaili L, Nadaradjane A, Nicod L, Guyon C, Xicluna A, Robert J F, Refouvelet B, *European Journal of Medicinal Chemistry*, **2008**, 43, 1270.
[51] Zhu X, Zhao G, Zhou X, Xu X, Xia G, Zheng Z, Wang L, Yang X, Li S, *Bioorganic & Medicinal Chemistry Letters*, **2010**, 20, 299.
[52] Stray S. J, Bourne C R, Punna S, Lewis W G, Finn M G, Zlotnick A A, *Proceedings of the National Academy of Sciences*, **2005**, 102, 8138.
[53] Deres K, Schröder C H, Paessens A, Goldmann S, Hacker H J, Weber O, Krämer T, Niewöhner U, Pleiss U, Stoltefuss J, Graef E, Koletzki D, Masantschek R N.A, Reimann A, Jaeger R, Groß R, Beckermann B, Schlemmer K. H, Haebich D, Rübsamen- WaigmannInhibition H, *Science***, 2003**, 299, 893.