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Dyhidropyrimidone Derivatives - A Review on Synthesis and Its Therapeutic Importance

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ABSTRACT

Dihydropyrimidones were generally synthesized via a three-component condensation reaction which was reported for the first time by P. Biginelli. Owing to the fascinating pharmacological properties associated with this heterocyclic scaffold, dihydropyrimidone derivatives are commonly used in the pharmaceutical industry. The main activities associated with this class of compounds are anti-tumor, anti-inflammatory, anti-bacterial, and calcium channel antagonists. In this review article, attempted to demonstrate the different synthetic procedures of Dihydropyrimidone derivatives and their respective therapeutic significance.

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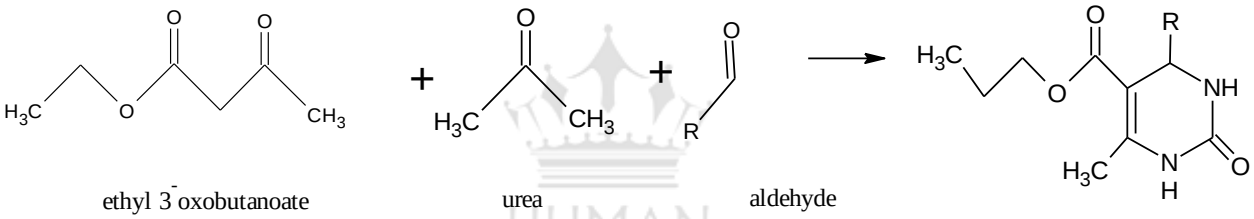
INTRODUCTION

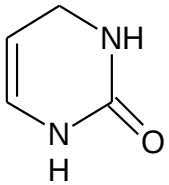
Heterocyclic chemistry constitutes at least half of all research related to organic chemistry worldwide. Heterocyclic structures in particular form the basis of various pharmaceutical, agrochemical, and veterinary products.[1-2]The aromatic heterocyclic compounds are compounds that have a heteroatom in the ring and, in most of their processes, behave in a manner close to benzene.[3] Dihydropyrimidone and its derivatives are aromatic heterocyclic compounds synthesized by multi-component reactions such as the Biginellireaction. Dihydropyrimidone has become an important construction moiety for novel drugs recently. [4]

Bignelli reaction is an acid-catalysed, three-component reaction between an aldehyde, a, ß-ketoester, and urea constitutes a rapid and facile synthesis of dihydropyrimidone. This reaction was developed by Pietro Biginelli in 1891. The reaction can be catalyzed by Bronsted acids and/or by Lewis acids such as copper (II) trifluoroacetate hydrate and boron.[5]



CHEMISTRY OF DIHYDROPYRIMIDONE

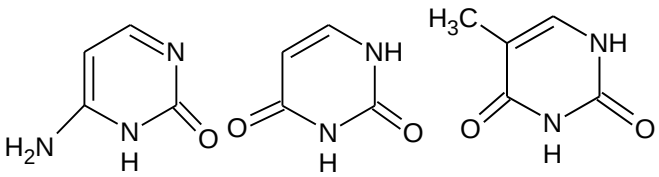
Dihydropyrimidinones are extremely advantageous molecules of small size which possess versatile pharmaceutical properties. They possess a large variety of biological activities with a molecular formula $C_4H_6N_2O$. It is a heterocyclic moiety with two N-atoms at the 1 and 3 positions. They are pyrimidine derivatives which contain an additional group of ketones. [6]



3,4-dihydropyrimidin-2(1*H*)-one

Pyrimidinones or Dihydropyrimidinones (DHPMs) are a wide range of bioactivities; antitumor, anti-inflammatory, antibacterial, and calcium channel antagonism/inhibition are

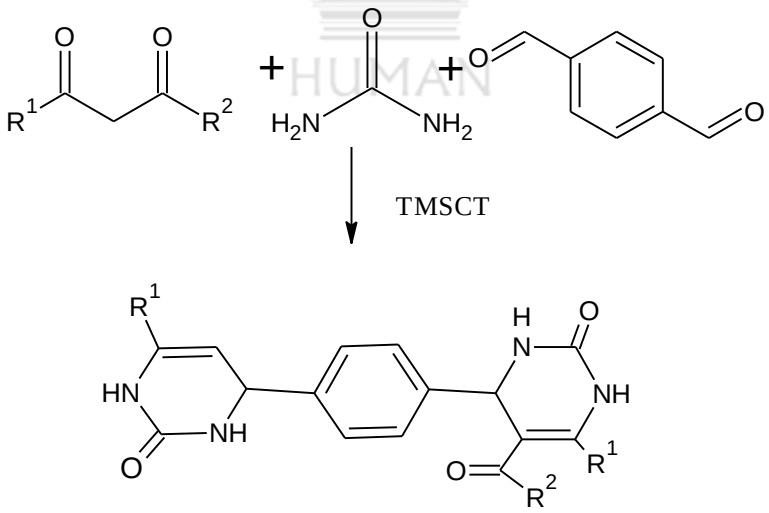
the main activities associated with this class of compounds. Their drug research applications have inspired the development of a large variety of synthetic methods for their preparation and chemical transformations. [7] Out of the five major bases in Nucleic acids three are pyrimidine derivatives which comprise of Cytosine which is found in DNA and RNA, Uracil in RNA, and Thymine in DNA. They have become very significant in the field of synthetic organic chemistry, because of their presence as bases in DNA and RNA. [8]



cytosine uracil thymine

LITERATURE REVIEW

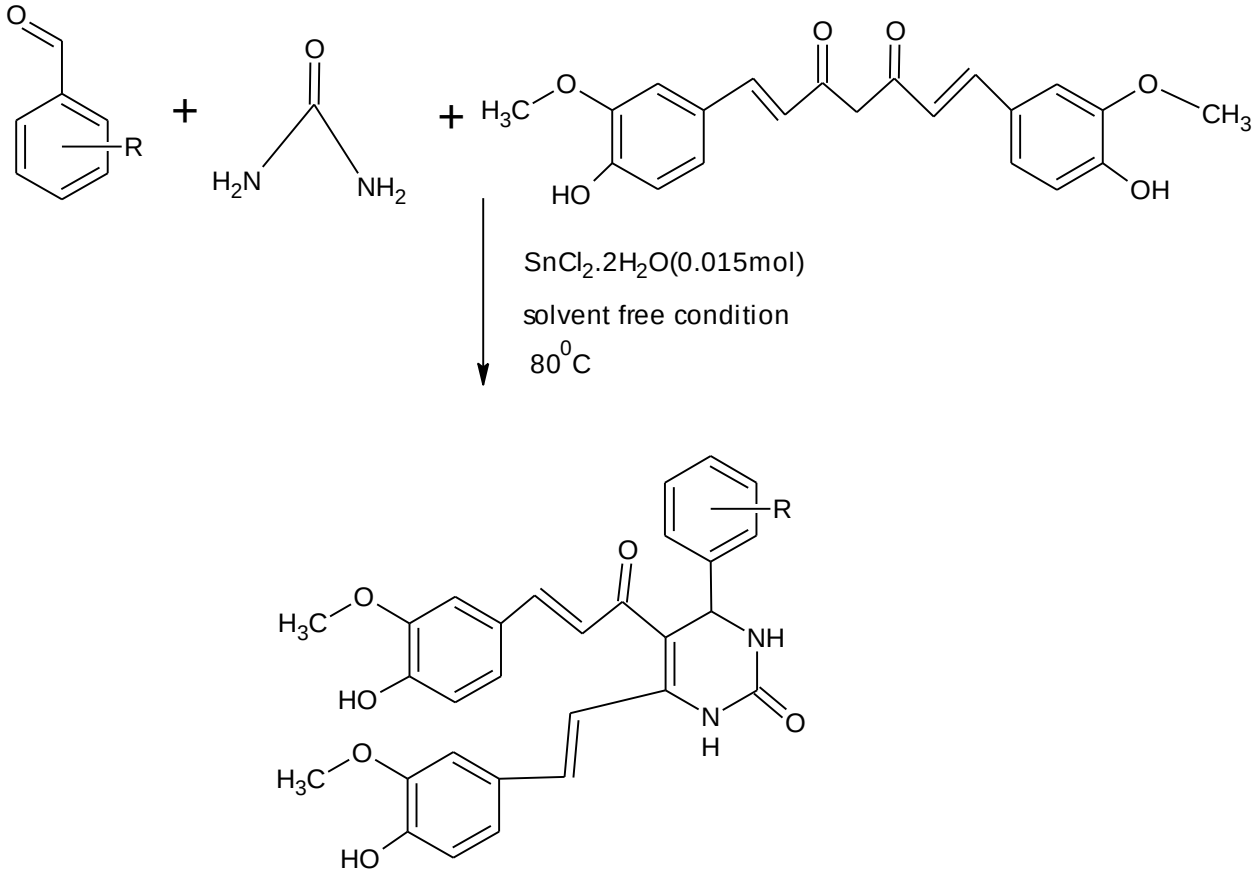
- Azizian J, *et al.*, (2010) synthesized bis(dihydropyrimidinone) benzenes by Microwave-Assisted Solvent-Free Synthesis and evaluated for their cytotoxic activity on five different human cancer cell lines.



Scheme 1

The cytotoxic activities of these compounds were evaluated on five different human cancer cell lines (Raji, HeLa, LS-180, SKOV-3, and MCF7). Their cytotoxic study indicated that they possessed a weak to moderate activity. [9]

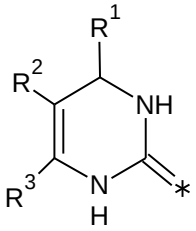
- Lal, *et al*., (2012) Design, synthesized and evaluated synergistic antimicrobial activity and cytotoxicity of 4-aryl substituted 3, 4-dihydropyrimidinones of curcumin.



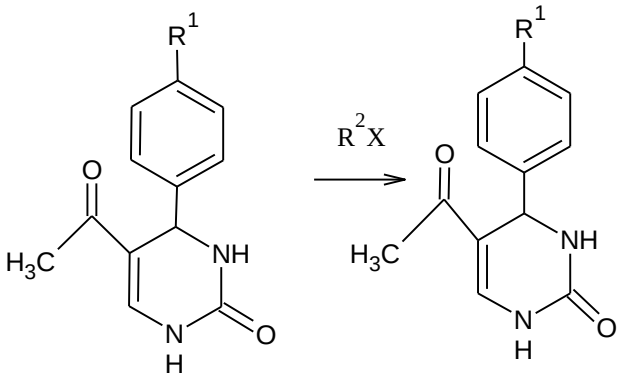
Scheme 2

The synthesized compounds evaluated for their synergistic antimicrobial (antibacterial and antifungal) activity against bacteria and fungi. The zone of inhibition is measured by adopting the disc diffusion method. In vitro minimum inhibitory concentrations measured using broth microdilution and food poisoning method. in vitro cytotoxicity of synthesized compounds evaluated against three human cancer lines Hep-G2, HCT-116, and QG-56.Most of the compounds showed interesting antimicrobial and cytotoxic activity as compared to curcumin, that is, the compounds derived from 2-hydroxy benzaldehyde, 4-hydroxy benzaldehyde, and 4-hydroxy-3-methoxy benzaldehyde showed the highest biological activity as compared to other compounds.[10]

- Liu Y, *et al*., (2019) synthesized Compounds Derived from 3, 4-Dihydropyrimidin-2 (1H)-one and evaluated their anticancer activities.[11]

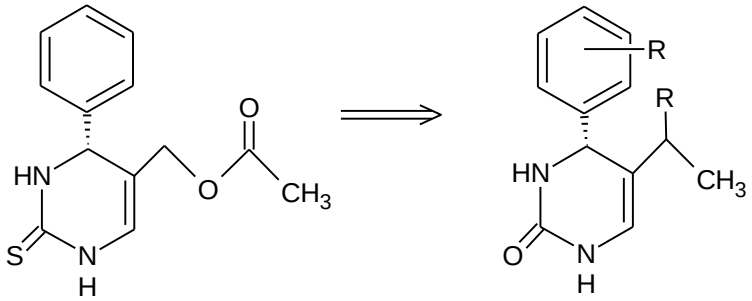


Preparation of N1 -alkylated DHPMs with different halo hydrocarbons.



Scheme 3

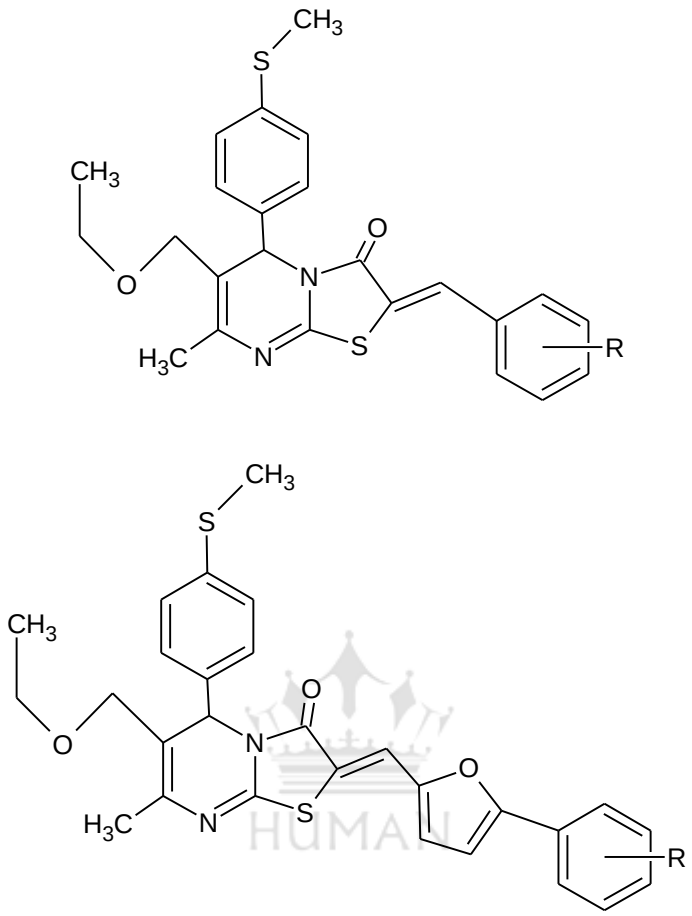
- Soumyanarayanan U, *et al*., (2012) synthesized Monastrol mimic Biginellidihydropyrimidinone derivatives. Cytotoxicity screened against HepG2 and HeLa clines.



Scheme 4

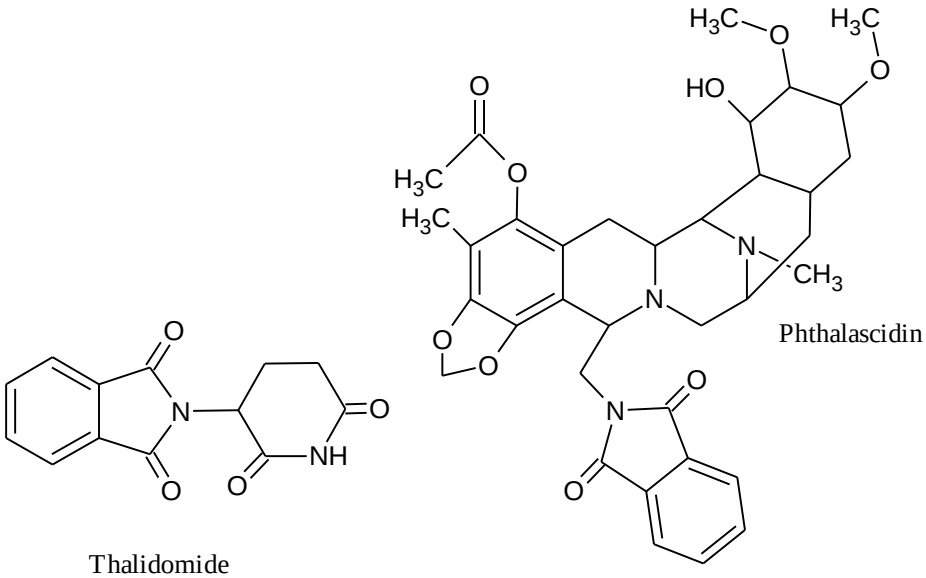
Recent progress in the DHPM class of the anticancer agent monastrol, an inhibitor of human kinesin Eg5 has led to the attention for efficient pharmacophore variation of Biginelli/ DHPMs. Human kinesin Eg5 plays a crucial role in bipolar spindle generation during mitosis, inhibition of which leads to mitotic arrest and subsequent apoptotic cell death It is therefore considered as one of the promising targets in cancer chemotherapy.[12]

- Ashok M, *et al*., (2007) synthesized some novel derivatives of thiazole[2, 3-b] dihydropyrimidinone possessing 4-methylthiophenyl moiety and evaluated of their antibacterial and antifungal activities.[13]



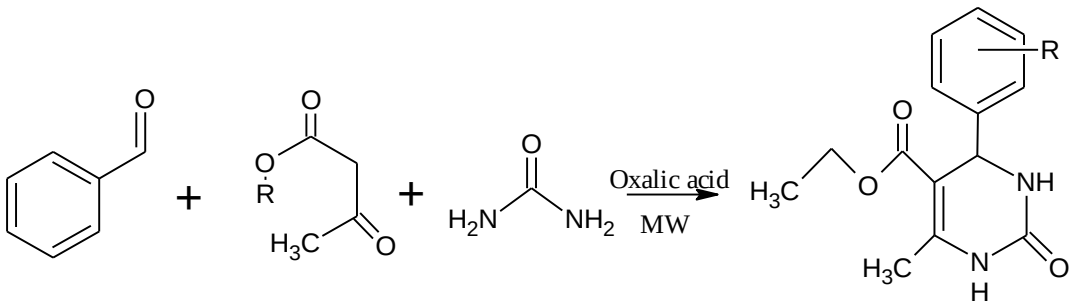
Scheme 5

- Kamal A, *et al*., (2008) synthesized series of phthalimido-dihydropyrimidones and naphthalimido-dihydropyrimidones and some representative compounds evaluated for their in vitro anticancer activity. Some compounds act selectively against leukemia while exhibiting moderate activity against a wide range of cancer cell lines.[14]



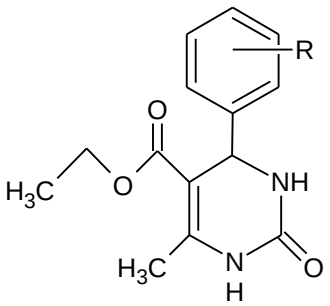
Scheme 6

- Adhikari A, *et al*., (2012) 3,4-Dihydropyrimidin-2(1*H*)-one derivatives were synthesized by Biginelli reaction under microwave irradiation using oxalic acid as a new, efficient, and environmentally benign catalyst. Antioxidant properties of synthesized compounds evaluated by three methods, viz., the radical-scavenging effect on 2,2-diphenyl-1-picrylhydrazyl radicals, reducing power, and Fe^{2+} chelating activities. The compounds having –OH group on the benzene ring was found to have higher activity.[15]



Scheme 7

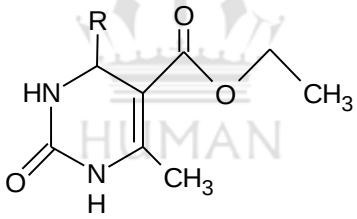
- Russowsky D, *et al*., (2006) synthesized and differential ant proliferative activity of control, Oxo-monastrol, and eight oxygenated derivatives on seven human cancer cell lines.[16]



Scheme 8

- Wang G, *et al*., (2013) investigated DNA binding properties of two medicinally important dihydropyrimidinones derivatives 5-(Ethoxycarbonyl)-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one (EMPD) and 5-(Ethoxycarbonyl)-6-methyl-4-(4-chlorophenyl)-3,4-dihydropyrimidin-2(1H)-one (EMCD) with calf-thymus DNA (ctDNA).

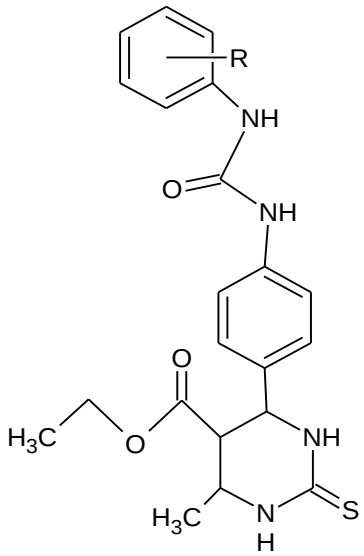
Evaluation of the two derivatives' antitumor activities against different tumor cell lines has shown that they exhibit substantial inhibition rate of tumor cells, thereby blocking transcription and replication of DNA.[17]



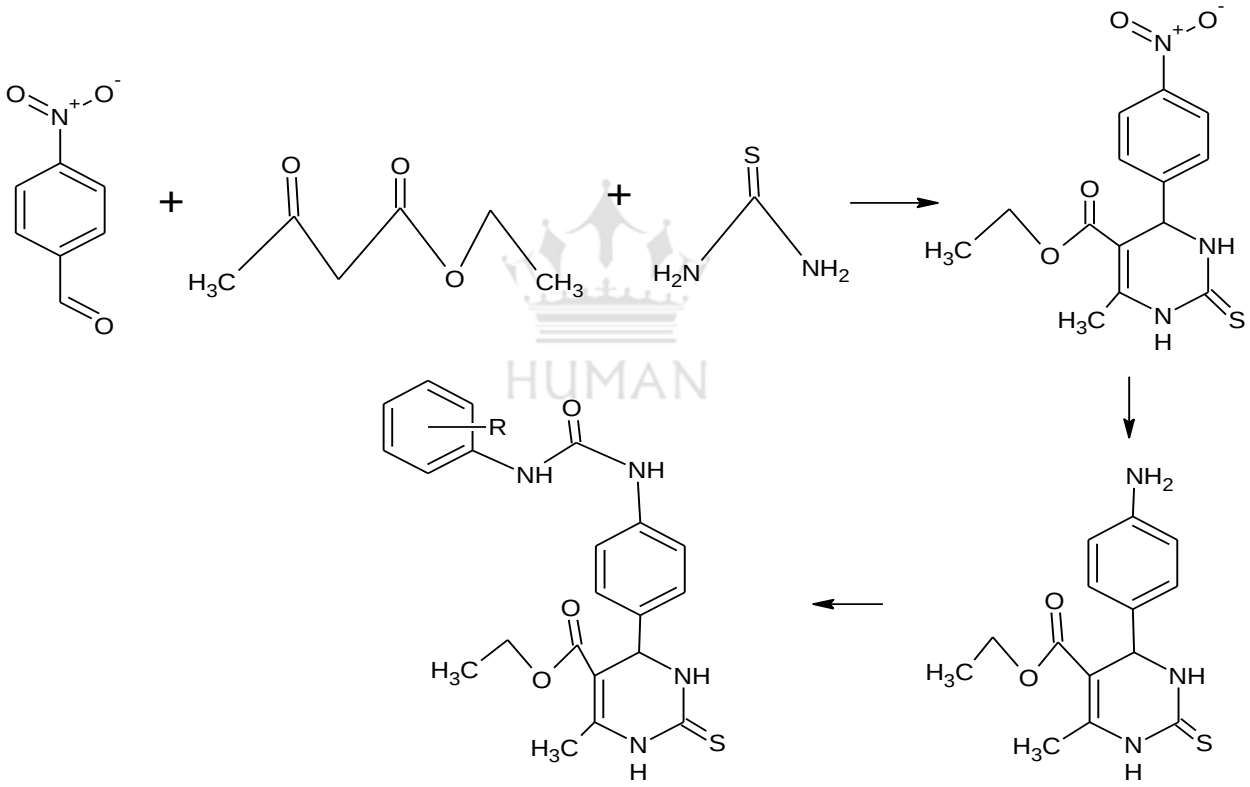
Scheme 9

- Attri P, *et al*., (2017) carried out Triethylammonium acetate ionic liquid assisted one-pot synthesis of dihydropyrimidinones and evaluation of their antioxidant and antibacterial activities All the synthesized compounds to reveal the significant antioxidant properties, these properties have been studied using 1,1-diphenyl-2-picrylhydrazyl (DPPH) free radical scavenging and cupric reducing antioxidant capacity (CUPRAC) assays. Also, to this, these compounds show good antibacterial activity against four human pathogenic bacteria.[18]

- Tale RH, *et al*., (2011) synthesized series of novel 3, 4-dihydropyrimidin-2(1*H*)-one urea derivatives of biological interest prepared by sequential Bigineli's reaction, reduction followed by reaction of resulting amines with different aryl isocyanates. All the synthesized compounds screened against the pro-inflammatory cytokines (TNF-α and IL-6) and antimicrobial activity (antibacterial and antifungal).[19]

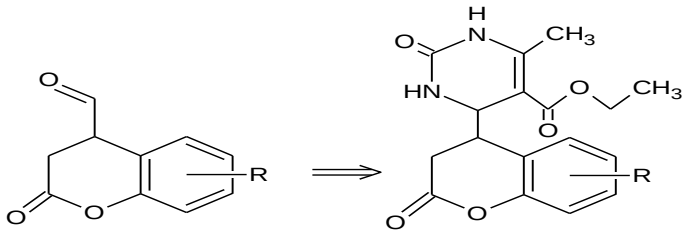


R= different substituent



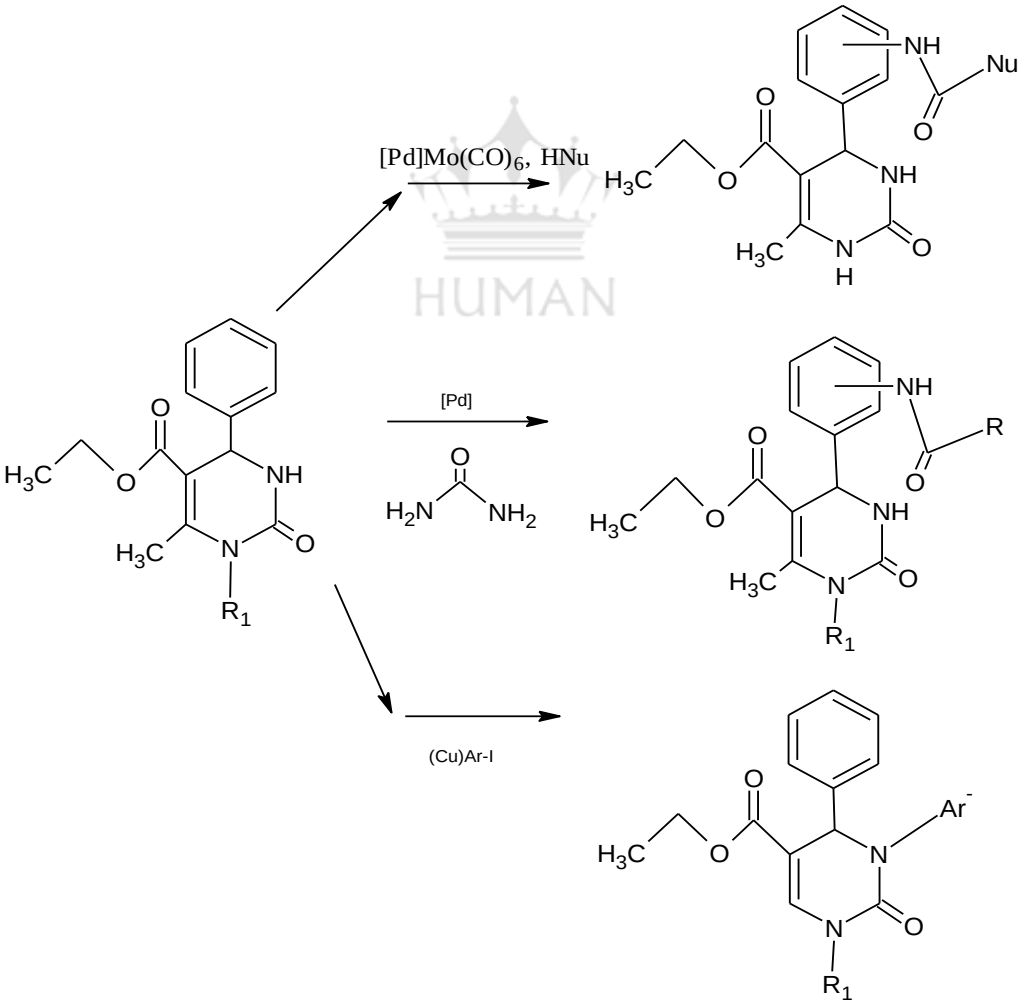
Scheme 10

- Naik NS, *et al*., (2017) synthesized the dihydropyrimidin-2(1*H*)-one/thione derivatives of coumarin from substituted 4-formylcoumarins and ethyl acetoacetate using urea/thiourea in the presence of the catalytic amount of ceric ammonium nitrate. All the synthesized compounds were evaluated for their antibacterial activity against four bacterial strains by the broth dilution method.[20]



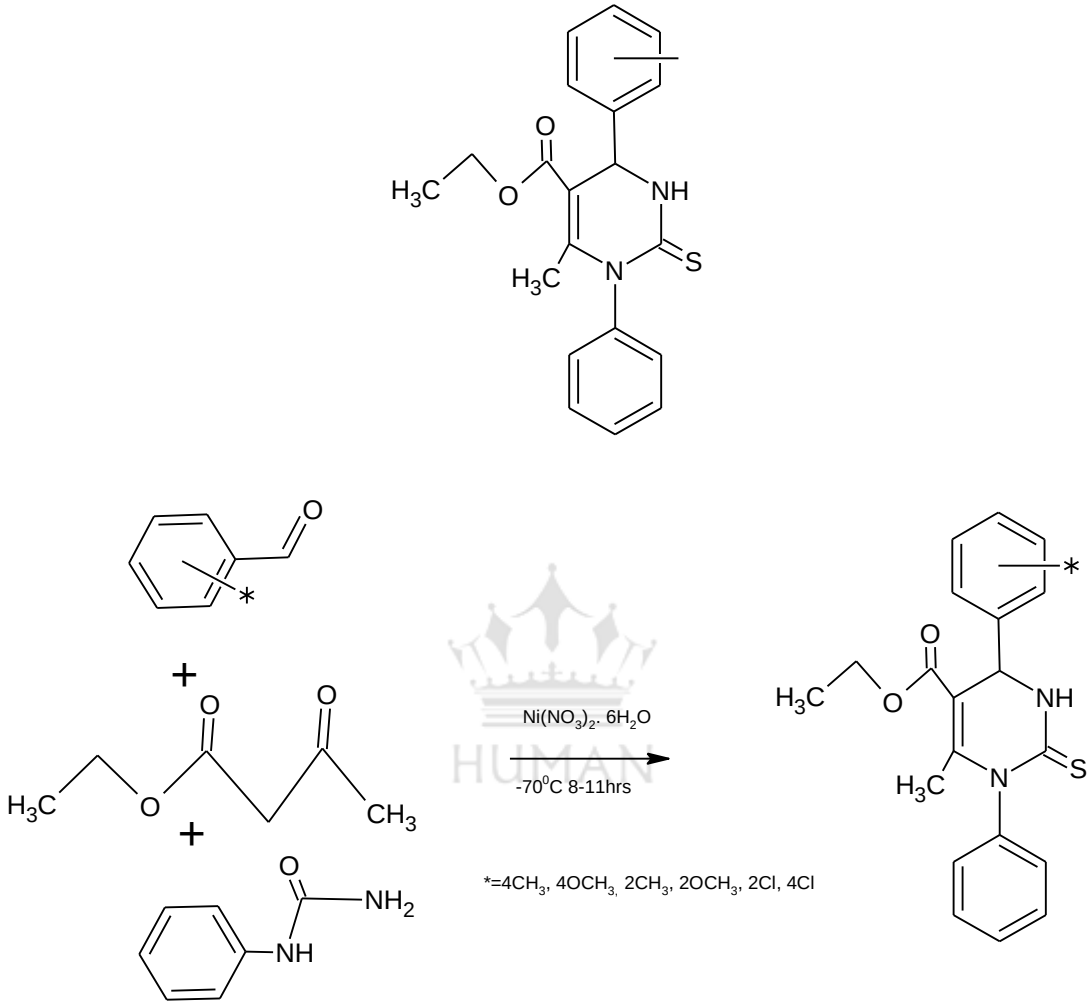
Scheme 11

- Wannberg J, *et al*., (2005) conducted a synthesis of Microwave-enhanced and metal-catalysed functionalization's of the 4-aryl-dihydropyrimidone template. Palladium-catalyzed cross-coupling, Heck reactions, amino- and alkoxycarbonylation, and direct N-amidations of 4-(bromophenyl)-dihydropyrimidones were performed. Further, the first N3-arylations of the dihydropyrimidone ring system were completed using the copper-catalyzed Goldberg reaction. [21]



Scheme 12

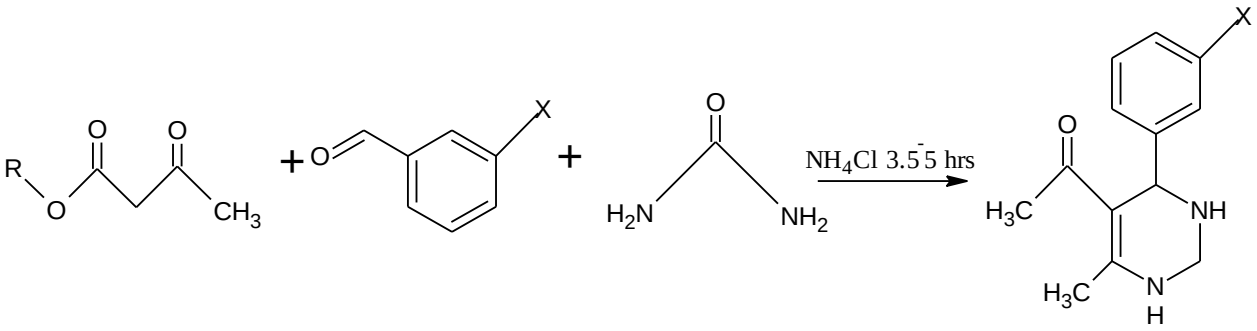
- Akhter K, *et al.*, (2019) Synthesized 1-phenyl-3,4-dihydropyrimidin-2(*1H*)-thiones by one-pot Biginelli like reaction coupling of 1-phenyl thiourea, ethyl acetoacetate, and aromatic aldehydes by using nickel nitrate hexahydrate [Ni(NO3)2.6H2O] as a new catalyst under the solvent-free condition to avoid the usage of hazardous organic solvents.[22]



Scheme 13

- Tawfik HA, *et al.*, (2009) carried out Tumour anti-initiating activity of some novel 3, 4-dihydropyrimidinones. Halting the tumor initiation process by targeting the inhibition of the carcinogens metabolic activators (CYP), the induction of the carcinogen detoxification enzymes (glutathione-S-transferases, GSTs), and the induction of antioxidant activity is an effective strategy. Twelve compounds were synthesized and structurally elucidated. All compounds not toxic against tumor cells, but some compounds were noncytotoxic inhibitors of cytochrome p450 inducer of GST activity, scavenger of OH, and inhibitor of DNA fragmentation.[23]

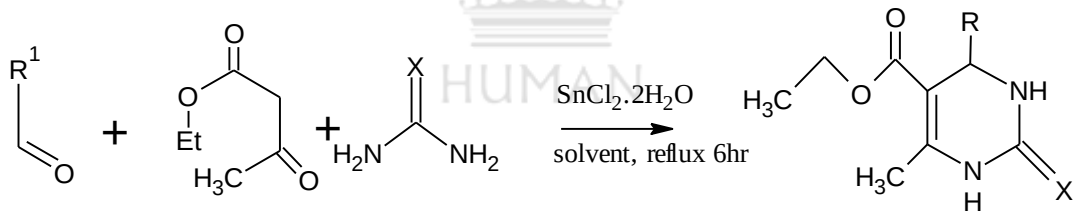
- Stefani HA, *et al*., (2006) synthesized several new dihydropyrimidinones, under ultrasound irradiation in the presence of NH_4ClSome of the synthesized compounds tested *in Vitro* for their antioxidant activity. All the compounds selected exhibited some antioxidant activity. Some analogs exhibited strong activity against lipid peroxidation induced by Fe + EDTA and the most potent in reducing ROS levels.[24]



X= H, NO_2

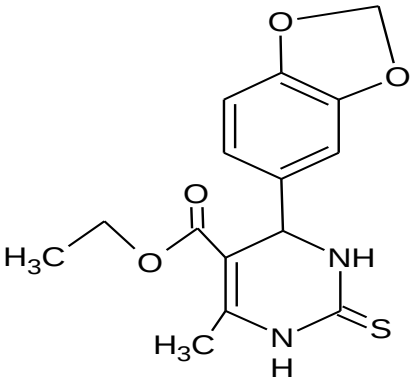
Scheme 14

- Russowsky D, *et al*., (2004) Multicomponent Biginelli's synthesis of 3, 4-dihydropyrimidin-2 (1H)-ones promoted by $SnCl_2.2H_2O$.[25]

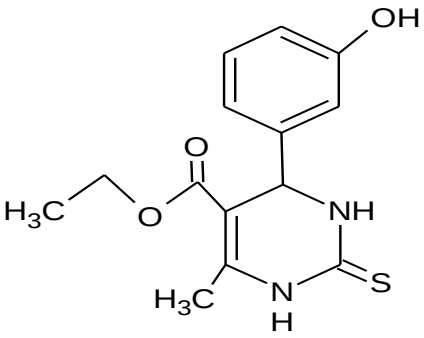


Scheme 15

- de Fatima A, *et al*., (2015) carried out A mini-review on Biginelli adducts with notable pharmacological properties. This mini analysis discusses over 100 Biginelli adducts which are promising anticancer, calcium channel inhibitors, anti-inflammatory, antimicrobial, and antioxidant. Bignelli adducts are promising compounds for cancer treatment, of which monastrol is among the most studied.[26]



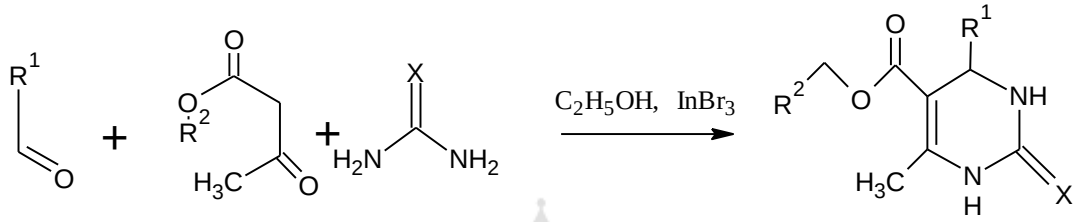
PIPERASTROL



MONASTROL

Scheme 16

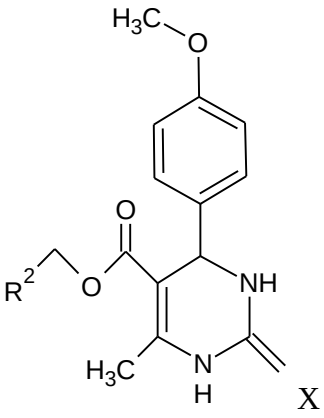
- Fu NY, *et al*., (2002) design and synthesized Indium (III) bromide-catalyzed preparation of dihydropyrimidinones.



Scheme 17

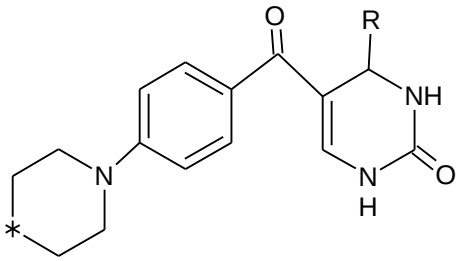
This new protocol for the Biginelli reaction contains the following important features: it produces excellent yields, enables catalyst recycling without loss of activity and contributes to zero-discharge during the process. [27]

- Ali F, *et al*., (2016) synthesized a series of dihydropyrimidone derivatives via a 'one-pot' three-component reaction according to well-known Biginelli reaction by utilizing $Cu(NO_3)_2 \cdot 3H_2O$ as a catalyst and screened for their *in vitroβ-glucuronidase* inhibitory activity. [28]



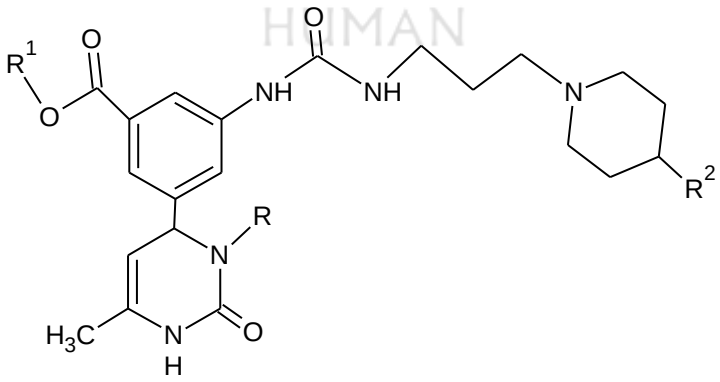
Scheme 18

- Bhat M, *et al.*, (2018) synthesized Enaminones, 4-methyl-1-[4-(piperazin/morpholin-1-yl) phenyl] pent-2-en-1-one by refluxing 1-[4-(piperazin/morpholin-1-yl) phenyl] ethan-1-one with dimethylformamide dimethyl acetal (DMF–DMA) without any solvent. The enaminone's three-dimensional structure, including morpholine moiety, is verified by single crystal X-ray crystallography. Finally, the dihydropyrimidinone derivatives were obtained in the presence of glacial acetic acid by reacting enaminones with urea and various substituted benzaldehydes.[29]



Scheme 19

- Bruce M A, *et al.*,(1999) synthesized a series of piperidine derivatives of 4-phenyl-1, 4-dihydropyrimidinones. As antagonists of NPY-induced feeding behaviour, these compounds are expected to act as effective anorexiant agents in promoting weight loss and treating eating disorders.[30]



Wherein R, R' and R are defined herein.

Scheme 20

SUMMARY

This review article discusses the different synthetic processes and pharmacological activities of Dihydropyrimidone derivatives. The activities include anticancer Activity, β-glucuronidase

inhibitory activity, inhibitors of calcium channel, anti-inflammatory, antimicrobial and antioxidant, antibacterial activity.

ACKNOWLEDGMENT

I, express my sincere gratitude to all faculties and friends at Malik Deenar College of Pharmacy for completing the review work successfully.

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