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Review Article

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A Systematic Review on the Recent Advances in the Pharmacological Activities of Dihydropyrimidinones

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Abstract Dihydropyrimidinones (DHPM's) are well known for their wide range of medicinal and therapeutic properties. In the recent years, DHPM's have attained considerable interest in the field of natural and synthetic organic chemistry, in the areas of drug research and exhibits diverse range of biological activities. This review focuses on important bioactivities of dihydropyrimidinone with greater prominence to recent literatures.

Keywords Dihydropyrimidinone, Biginelli, Antitumor, Antioxidant, Antimicrobial, Antialzheimer, Anti-inflammatory

Introduction

Medicinal chemistry in conjunction with other scientific disciplines are involved in the design, discovery and development of new chemical entities and their analytical and pharmacological characterization. Heterocyclic compounds contain a minimum of one atom and a component aside from carbon like atomic number 7, gas or sulfur, inside the ring structure. N-containing heterocycles received greater attention because of its interesting pharmaceutical and biological activities and forms important structural moieties for drug development [1].

Classical synthetic reaction was first reported by Pietro Biginelli in 1893 and involves the one pot condensation of an aromatic aldehyde, ethyl acetoacetate and urea under acidic conditions (Fig: 1) [2].

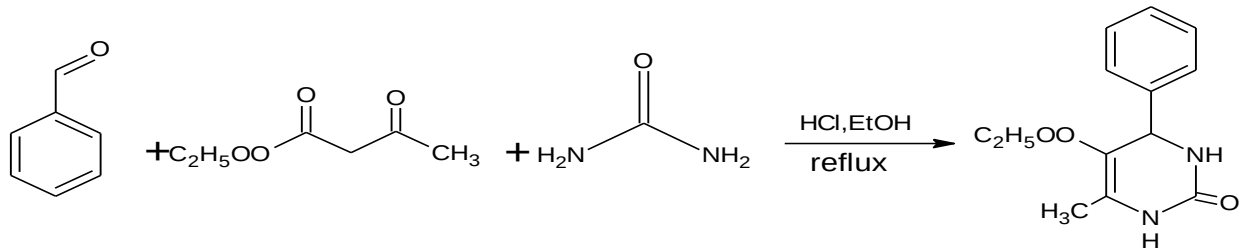


Figure 1: Classical Biginelli Condensation reaction

Literature Review

Anti-Tumor Activity

Amany S. Mostafa *et al* 2018, synthesized series of dithiocarbamate – DHPM derivatives. Cytotoxic activity screened for twelve compounds against sixty cancer cell lines. A DHPM derivative with dithiocarbamate moiety showed significant activity against a panel of cancer cell lines. Effects on levels of active caspase 3 and caspase 9, effect on cell cycle progression, detection of apoptosis and inhibitory activities against mTOR and VEGFR were evaluated [3].

Koneni V. Sashidhara *et al* practiced the synthesis of new diydropyrimidinone – semicarbazone hybrids by regioselective multicomponent reaction. Out of the synthesized compounds, DHPM – semicarbazone hybrids inhibit hLig1 activity and presented good to moderate activity. One compound suppressed the proliferation of cancer cells by binding directly with enzyme hLig1 and inhibited the nick sealing activity (Fig. 2). Anti-metastatic property and hLig1 inhibition capacity can be utilized since ligase inhibitors can become promising targets in cancer therapy [4].

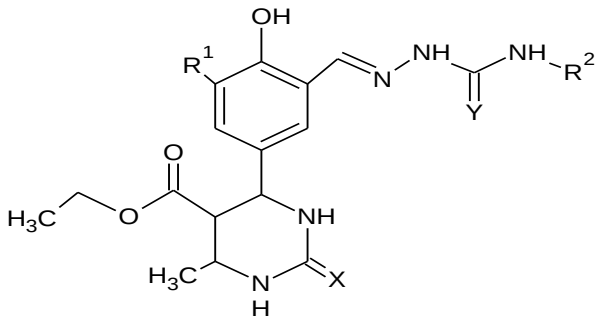
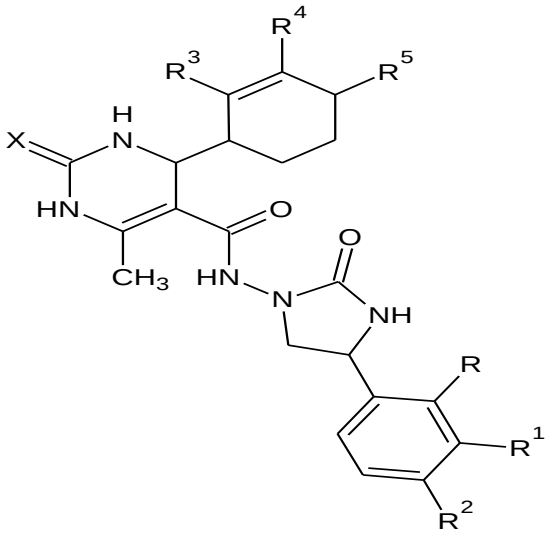


Figure 2: Dihydropyrimidinone- semicarbazone hybrid with antitumor activity

R^1: C $(CH_3)_3$, X: O, Y: O, R^2:3-$OMeC_6H_4$

Anti-oxidant activity

Beena K P *et al* performed the synthesis of novel imidazolidinone linked DHPM derivatives via multicomponent Biginelli condensation (Fig. 3). Melting point determined by open and capillary method. Structure elucidated by spectral data obtained from FTIR, ^{1}H NMR, ^{13}NMR, Mass spectral analysis. Anti-oxidant potency evaluated by DPPH method. Percentage inhibition calculated with ascorbic acid as the reference by comparing absorbance values of test and control. The study stated that most of the synthesized compounds were found to have notable antioxidant activity [6].



X=O, R=OH, R^1=H, R^2=H, R^3=H, R^4=OCH_3, R^5=OH

Figure 3: Dihydropyrimidinone derivative with antioxidant activity

Gejalakshmi S and Harikrishnan N *et al* described the synthesis of 2, 3 – dihydropyrimidin-2(1H)-one derivatives (Fig. 4) by Biginelli cyclocondensation reaction. Characterization of compounds carried out and evaluated the antioxidant and in - vitro anti-inflammatory activity. Antioxidant activity performed by DPPH and hydrogen peroxide free radical scavenging assay against ascorbic acid as standard. Nitro group at third position responsible for better antioxidant and anti-inflammatory activity than the isopropyl derivative [5].

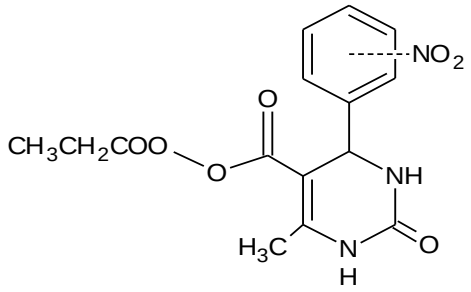
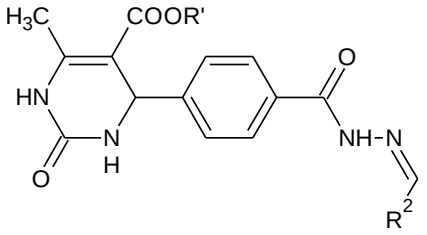


Figure 4: 2, 3- dihydropyrimidin-2(1H)-one derivative possessing antioxidant activity

Anti-microbial activity

Hua-Nan Peng *et al* synthesized series of 3, 4- dihydropyrimidin-2(1H)-one derivatives with a hydrazine moiety [Fig: 5]. Structure of compounds characterized by IR, ^{1}NMR, ^{13}NMR and HRMS analysis. Evaluated antimicrobial activity against bacterial and fungal strains. All compounds exhibited moderate inhibition against *E. coli* and *A. niger*. Five compounds showed excellent antibacterial activity which is approximately equal to the standard antibiotic Ciprofloxacin [7].



R^1=Me, R^2= 4-$OCH_3C_6H_4$

Figure 5: Dihydropyrimidinone derivative containing hydrazine moiety with good Antibacterial activity

Hanane Kaoukabi *et al* described the series of mono and bis 1, 2, 3-triazole derivatives (Fig. 6), synthesized by the combination of dihydropyrimidinone and 1, 2, 3-triazole hybrid heterocycles. Evaluated antiviral activity against Varicella Zoster virus. Out of 18 compounds synthesized, nine derivatives exhibited moderate to good activity and 4 compounds came out as valuable antiviral agent against VZV TK^+ strains [8].

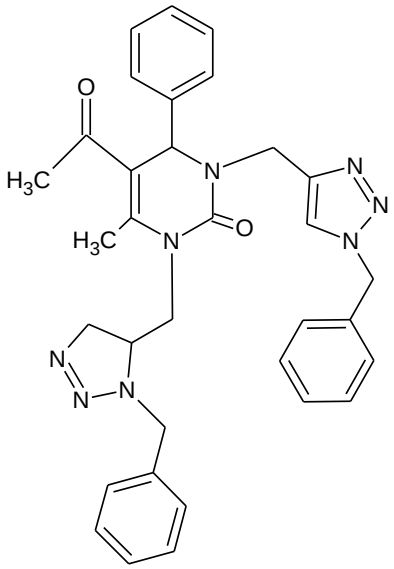


Figure 6: Dihydropyrimidinone triazole hybrid compound with antiviral activity

Anti-Alzheimer Activity

Flavio A.R. Barbosa *et al* performed the synthesis of DHPM derived selenoesters in two step pathway (Fig. 7), functionalized with electron donating or withdrawing group on the DHPM aromatic portion. Evaluated antioxidant activity by TBARS assay and iron chelation assay. The compounds exhibited excellent lipid peroxidation inhibition and good iron chelation activity. Also presented AChE inhibitory activity and some showed activity superior to standard drug Galantamine. DHPM functionalized with selenocyanides evaluated as valuable multi targeted therapy for Alzheimer's disease. One among the derivatives displayed excellent inhibition in a dose dependent manner and better pharmacokinetic profile [9].

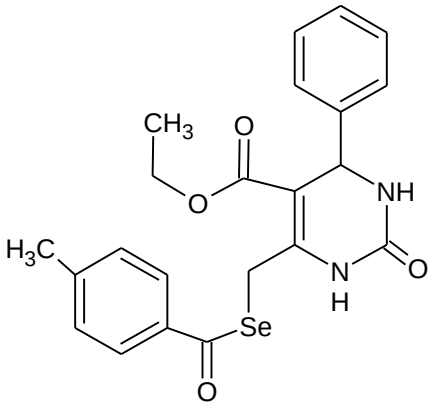


Figure 7: DHPM derived selenoester with prominent anti-alzheimer activity

Anti-inflammatory Activity

Naresh Podilla *et al* synthesized some novel DHPM derived aldehydes (Fig. 8) from a mixture of substituted aldehydes by the reaction of acetyl acetone or ethyl acetoacetate, urea or thiourea and lemon juice, refluxed for one hour at 80°C. Toxicity and anti-inflammatory study conducted and prominent activity exhibited by compounds possessing nitro and chloro groups. Groups in para position displayed better activity compared to groups in ortho position [10].

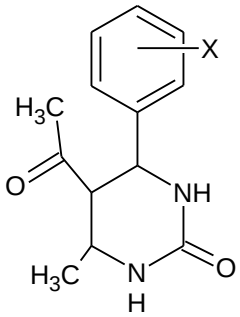


Figure 8: Substituted DHPM derivative exhibiting anti- inflammatory activity

Conclusion

Owing to the diverse range of medicinal and therapeutic properties, dihydropyrimidinone has developed an interest to synthesize more potent pyrimidine derivatives using multicomponent reaction which is extremely economical. Nowadays pyrimidine nucleus remains the main focus of new advances carried out in the field of modern drug discovery. Since several synthetic strategies and methodologies have been made, future work should be designed to develop novel approaches for the efficient synthesis of dihydropyrimidinones.

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