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# A REVIEW ON BIOLOGICAL ACTIVITY OF DIHYDROPYRIMIDINONE (DHPM) DERIVATIVES:

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**ABSTRACT**

The most important heterocyclic ring systems that play a role in the synthesis of DNA and RNA are dihydropyrimidines. They were made synthetically using multi-component reactions such as the Biginelli reaction and the Hantzschdihydropyridine reaction. Due to the interesting pharmacological properties associated with this heterocyclic scaffold, Biginelli type dihydropyrimidones have received a lot of attention in recent decades. In this review, we concentrate on the DHPMs, which have recently been developed as calcium channel antagonist, anti-inflammatory, anti-tubercular, anticancer, and antibacterial activities.

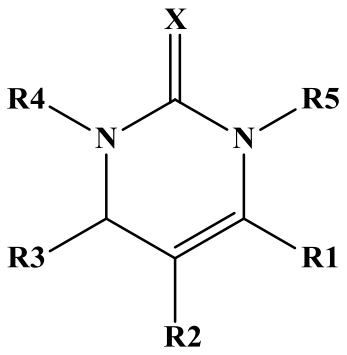
**KEYWORDS:** heterocyclic scaffold, Biginelli type dihydropyrimidones.

## 1. BACKGROUND

Dihydropyrimidinones are heterocycles with a pyrimidine moiety in the ring nucleus that have sparked interest in medicinal chemistry in recent decades due to their supposed wide range of biological activity. Because of the study of the biological activities of monastrol, a Biginelli adduct, this class of compounds became important in medicinal chemistry. Since then, other DHPMs have been synthesized, revealing a variety of new pharmacological properties.[1,2] In our biological system, heterocyclic compounds play a critical role. Many pharmacologically active chemicals, natural products, and nucleic acids contain them. Heterocyclic compounds such as purine, pyrimidine, and others make up the base pair of DNA and RNA (guanine, cytosine, adenine, and thymine). Antitumor, antibiotic, anti-inflammatory, antidepressant, antimalarial, anti-HIV, antimicrobial, antibacterial, antifungal, antiviral, antidiabetic, herbicidal, fungicidal, and insecticidal agents all include heterocyclic compounds.[3,4,5] The DHPMs are synthesized with the help of Multi-component reactions (MCR). MCRs are a form of synthetically useful organic reaction in which three or more starting materials react to produce a product.[6] MCRs have a number of advantages over traditional organic reactions, making them very common in areas where a large number of compounds must be synthesised and screened in order to find useful leads with a specific activity profile.[7,8]

The nucleus of dihydroprymidinone can also be present in synthetic analogues like monastrol. By the turn of the century, a structurally simple DHPM,(9) monastrol, had been identified as a novel cell permeable molecule that induces mitotic arrest by blocking the bipolar mitotic spindle in mammalian cells after screening a wide library of diverse small molecules. Monastrol is the first Eg5 inhibitor discovered, with an IC50 of 14 mM and a cell cycle block that is unique and reversible. It is a promising new lead in the production of anticancer drugs because it inhibits the mitotic kinesin Eg5 motor protein.[10] Monastrol's antimitotic activity isn't particularly high, so it's not a promising drug candidate.[11] HT-29 colon cancer cell lines have been examined with various monstraol analogues such as oxo-monastrol, thio, and 3,4-methylenedioxy derivatives of manostrol. Monastrol was found to be 30 times more active than a 3,4-methylenedioxy analogue.[12]

The general structure of these compounds is shown below:




X= O,NH or S

R1-5= H, alkyl, aryl, ester, amide, acyl, (thio)urea or an heterocycle

## 2. METHODOLOGY

### 2.1. Search strategy

The systemic search on dihydropyrimidinone for different types of activity was performed considering all the articles published until December 2020 through Pubmed and Google Schoolar for the electronic research. The search method in this systematic review aimed to involve studies that biological activity and toxicity both in vivo and in vitro of dihydropyrimidinone derivatives.[13]

### 2.2 Eligibility criteria

The review was carried out in two main steps. The first step includes screening of article titles and abstracts according to inclusion criteria. In second step, full text articles was studied and articles which match exclusion criteria were withdraw.[14]

#### 2.2.1 Inclusion criteria

For the eligibility of the review, studied had to meet the following inclusion criteria:

1) Bibliometric criteria: Articles to be published an original publication and to be published in English till 2020.

2) Exposure of interest: Articles which will related to the biological activities and synthesis of dihydropyrimidinone.

3) Search terms: "monastrol OR DHPM OR dihydropyrimidinone", "inhibitor OR mechanism OR activity OR toxicity OR cytotoxicity" were used.

4) Language: Articles should be published in English.[15,16]

#### 2.2.2 Exclusion criteria

Studies meeting the following criteria were excluded:

1) To include articles other than dihydropyrimidinone.

2) To provide incorrect or fake information about the chemistry and biological activity of dihydropyrimidinone.

3) It was necessary to exclude the term "Dynamic High-PressureMicrofluidization" since it has the same abbreviation as dihydropyrimidinones.

4) Fake journals which are not registered.

5) Not to mention reference or to give inaccurate details.[17,18]

### 2.3 Data collection

Mostly two databases(PUBMED, GOOGLE SCHOOLAR) were used for the collection of data. All articles contain biological activities and synthesis method for the dihydropyrimidinone was collected. For each activity different articles were studied.[19] Different reports were made for each activity also a report was made for different synthesis methods for dihydropyrimidinones. Also a report was made which contains marketed drugs which have dihydropyrimidinones nucleus.[20]

The following data were collected:

1. Biological activities and different synthesis methods for dihydropyrimidinones mentioned in the publications.
2. Marketed drugs contains dihydropyrimidinones nucleus.[21]

### 2.4 Data Analysis

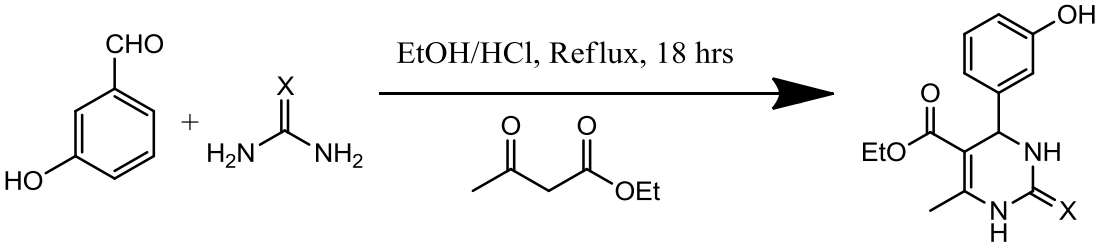
Primary outcome was to use report the data about the dihydropyrimidinones. Secondary outcomes were to report the synthesis methods and biological activities of dihydropyrimidinones. From all articles most active compounds were mentioned in the review there activities were also mentioned in the review.[22,23]

## 3. RESULTS

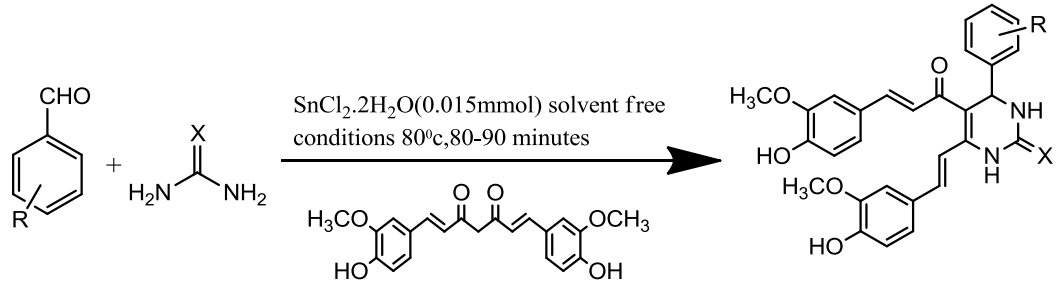
### 3.1 Synthetic strategies

In past years many research and development have done for introduction of various synthetic strategies for dihydropyrimidinones (DHPMs)**.** In 1893, Pietro Bignelli's was the first person who reported the synthetic method for preparation of DHPMs. He synthesized DHPMs by one pot cyclocondensation of ethyl acetoacetate, 3- hydroxybenzaldehyde and thiourea under slightly acidic condition using concentrated hydrochloric acid as catalyst in appropriate solvent system such as ethanol.[24] were synthesized DHPMs by condensation of aromatic aldehydes, urea/thiourea and curcumin in the presence of $SnCl_2$.2H2O under solvent free conditions using conventional heating. Were synthesized DHPMs by cationic Rh(II) cyclizations of propargyl ureas. were synthesized chromene dihydropyrimidinone (CDHPM) using recyclable Fe/Al pillared clay catalyst. were synthesized DHPMs by using Niobium Oxides as heterogeneous catalysts under the solvent free conditions.[25]

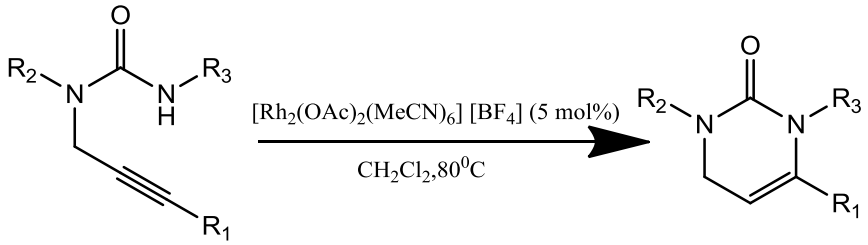
Pietro Bignelli's strategy for synthesis of dihydropyrimidinones:



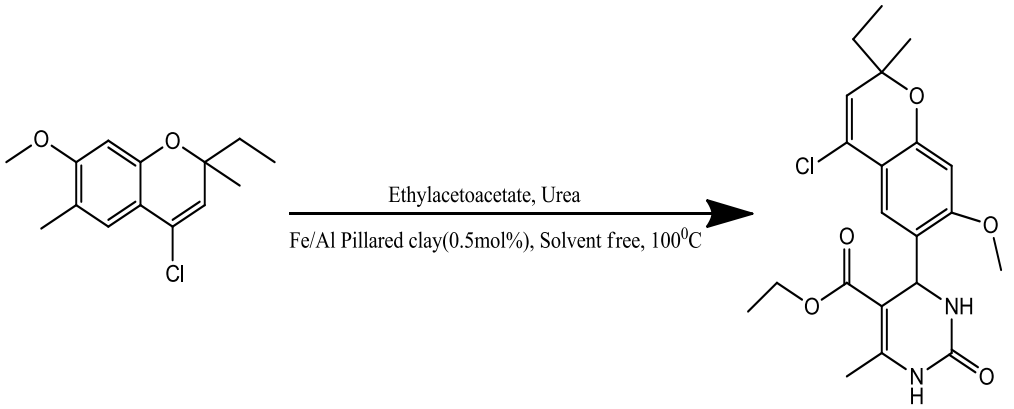
Lal's strategy for synthesis of dihydropyrimidinones:



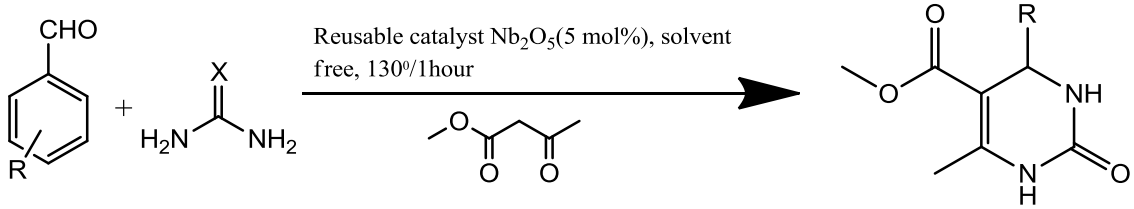

Yang's strategy for synthesis of dihydropyrimidinones:



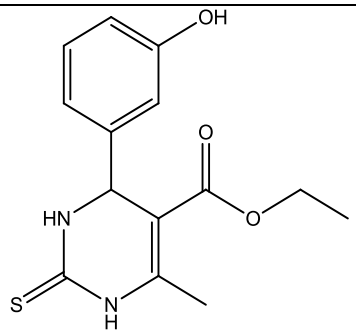

Dash's strategy for synthesis of dihydropyrimidinones:

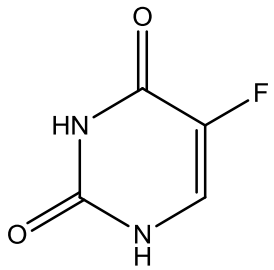
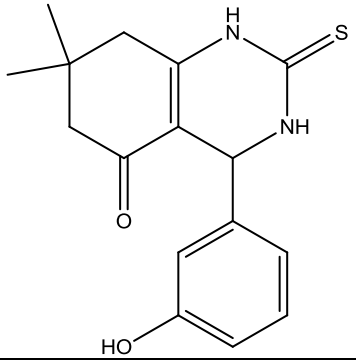



Donascimento's strategy for synthesis of dihydropyrimidinones:




**3.1 Marketed drugs**

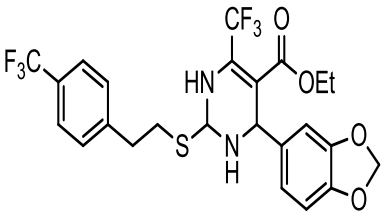
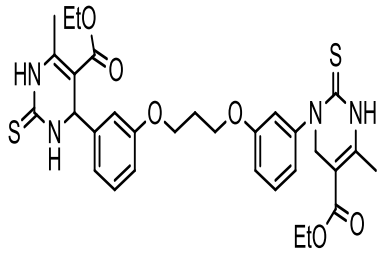
| S.NO. | Drug name | Chemical structure | Activity | Mode of action |
|---|---|---|---|---|
| **1** | **Monastrol** |  | Anticancer | Kinesin-5 (also known as KIF11, Kinesin Eg5), a motor protein essential for spindle bipolarity, was found to be inhibited by monastrol. (Thomas U. Mayer et. al., 1999) |

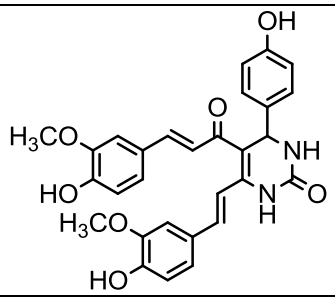
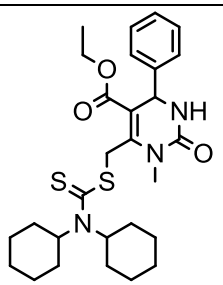
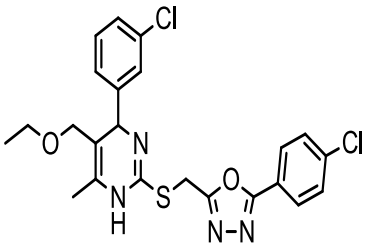
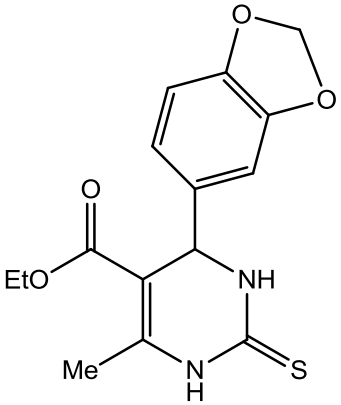
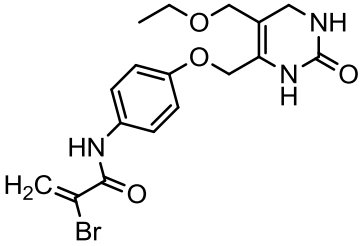
| | | | | |
|---|---|---|---|---|
| **2** | **5-Fluorouracil** |  | Anticancer | 5-Fluorouracil (5-FU) can activate p53 through a number of mechanisms, including the incorporation of fluorouridine triphosphate (FUTP) into RNA, the incorporation of fluorodeoxyuridine triphosphate (FdUTP) into DNA, and the inhibition of thymidylate synthase (TS) by fluorodeoxyuridine monophosphate (FdUMP), resulting in DNA damage. (Dushinsky et. al., 1957) |
| **3** | **Dimethylenastron** |  | Anticancer | Dimethylenastron inhibits the mitotic motor kinesin Eg5 in a precise and reversible manner. In cell-based assays, dimethylenastron inhibits bipolar spindle formation as well as proliferation, migration, and invasion of many pancreatic cancer cell lines.(Sun et. al.,2011) |

**3.3 Biological activities**

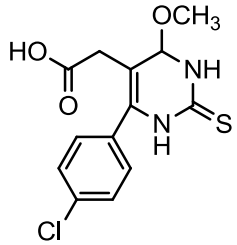
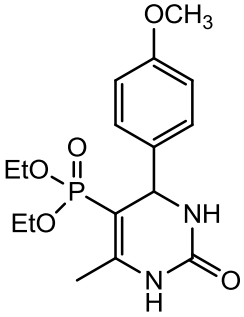
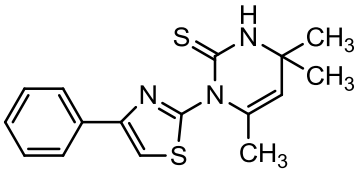
The main objective of this review is to provide detailed information about the dihydroprymidinones. In this review we discuss wide range of activity of the dihydroprymidinones. Dihydroprymidinone have wide range of biological activity. They involve different type of mechanisms like receptor mediated mechanism, enzymatic action and activity against the ion channel etc. The biological study suggest that substitution of different groups at different positions on ring impart different biological activity.[26,27]

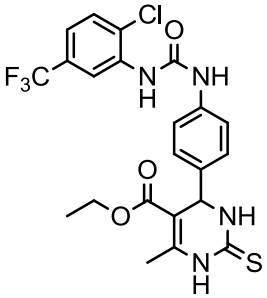
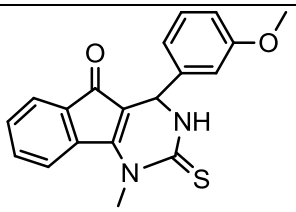
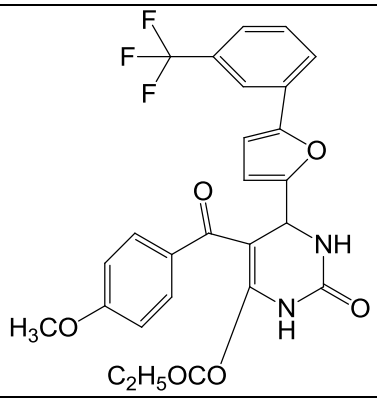
**3.3.1 Anticancer activity**

| Sr. No. | Chemical Structure | Cancer Cell line | Mechanism of action | $IC_{50}$ | Yield (%) | Reference |
|---|---|---|---|---|---|---|
| 1 |  | COLO 320 HSR | Inhibit mitotic motor Eg5(Kinesin spindle protein, KSP) | 8.1(μM) | 86 | Agbaje et. al., 2011 |
| 2 |  | MCF-7 | Inhibit Eg5 and causing a specific and reversible cell cycle block. | 16(μg/ml) | | Kamal et. al., 2011 |

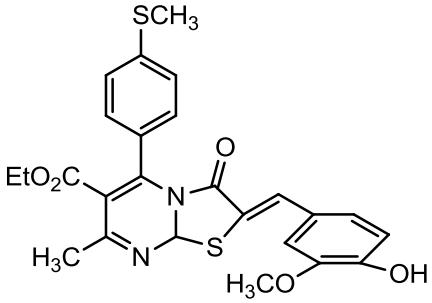
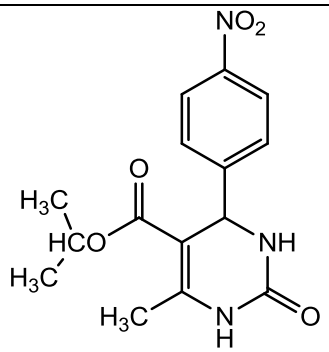
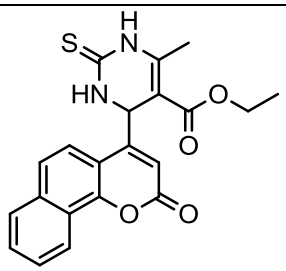
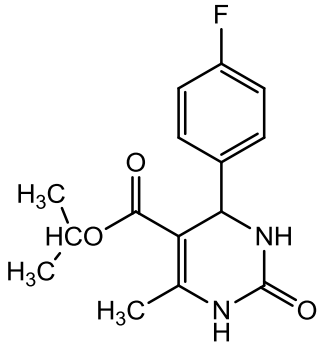
| | | | | | | |
|---|---|---|---|---|---|---|
| 3 |  | HCT-116 | | 12.5 (µM/ml) | 95 | Lal et. al., 2012 |
| 4 |  | NCl-H460 | Inhibit VEGFR-2 and mTOR enzymes | 88% GI | | Mostafa et. al., 2018 |
| 5 |  | HL-60(TB) | Cause Pro-apoptosis | 0.056(µM) | | Ragab et. al., 2017 |
| 6 |  | MCF-7 | Inhibit Eg5 | 1.9(µg/ml) | 65 | Russowsky et. al., 2006 |
| 7 |  | MCF-7 | Tubulin polymerization inhibition | 0.54±0.12(µM) | | Sana et. al., 2019 |

**3.3.2 Anti-inflammatory activity**

| Sr. No. | Chemical Structure | Standard Drug | Method of testing | Activity in % | Reference |
|---|---|---|---|---|---|
| 1 |  | Diclofenac | Carragneenan induced rat paw edema test by winter et. al. | 66 | Bahekar et. al., 2004 |
| 2 |  | Indomethacin | Carrageenan induced hind paw edema method | 58.42 | Essid et. al., 2017 |
| 3 |  | Ibuprofen | Carragneenan induced rat paw edema test by winter et. al. | 34.5 | Sondhi et. al., 2005 |

| Sr. no. | Chemical Structure | Mechanism of action | Activity | Reference |
|---|---|---|---|---|
| 4 |  | Inhibit TNFα,IL-6 | 68% inhibit TNFα, 92% inhibit IL-6 | Tale et.al., 2011 |
| 5 |  | Inhibit TRPA1 | $IC_{50}$ 0.003(μM) | Gijsen et. al., 2012 |
| 6 |  | Inhibit mPGES-1 | $IC_{50}$ 4.016±0.47(μM) | Lauro et. al., 2014 |

**3.3.3 Anti-Bacterial activity**

| Sr. No. | Chemical Structure | Activity Against | Standard Drug | MIC (µg/ml) | Yield(%) | Reference |
|---|---|---|---|---|---|---|
| 1 |  | Staphylococcus aureus | Ciprofloxacin | 12.5 | 80 | Ashok et. al., 2007 |
| 2 |  | Salmonella typhi | Ciprofloxacin | 12.5 | 90 | Chitra et. al., 2010 |
| 3 |  | Staphylococcus aureus | Ciprofloxacin | 0.4 | 78 | Naik et. al., 2017 |
| 4 |  | Staphylococcus aureus | Ciprofloxacin | 12.5 | 94 | Chitra et. al., 2010 |

**3.3.4 Calcium Channel Antagonism**

| Sr. No. | Chemical Structure | Standard Drug | Method | Yield(%) | Reference |
|---|---|---|---|---|---|
| 1 | 4a | Nifedipine | Evaluated by check the ability to relax a membrane depolarization induced contraction of vascular smooth muscle. | 90% | Singh et. al., 2009 |
| 2 | 2d | No Standard drug was used | Evaluated by whole cell patch clamp recording assay with $Ca_v$ 1.2 and $Ca_v$ 3.2 channels at 10 micro | 76.3% | Teleb et. al., 2017 |

| | | | | | |
|---|---|---|---|---|---|
| | | | molar concentration. | | |
| 3 | 11 | Nicardipine | Activity was studied on isolated rat ileum. | 23.59% | Zarkun et. al., 2006 |

**3.3.5 Antitubercular activity**

| Sr. No. | Chemical Structure | Method | Mechanism of action | Activity | Reference |
|---|---|---|---|---|---|
| 1 | 4p | Compound was explored in tuberculosis infected macrophages model | Inhibit mycobacterium tuberculosis dihydrofolate reductase | MIC: 0.39(µg/ml) | Desai et. al., 2016 |
| 2 | 5e | Compound was tested for inhibitory potential against mycobacterium tuberculosis chorismate mutase | Inhibit mycobacterium tuberculosis chorismate mutase | % inhibition: 63% | Mallikajunarao et. al., 2013 |
| 3 | 7d | Resazurin microplate assay plate method | No specific mechanism of action mentioned | MIC: 10(µg/ml) | Venugopala et. al., 2016 |

## 4. CONCLUSION

DHPMs, a class of traditional heterocyclic small molecules with diverse bioactivities, are gaining regular growing interest in the search for new lead compounds. Because of their exceptional ability to bind to various proteins and enzymes, compounds and drugs are commonly used. The availability of far more structurally diverse DHPMs makes it possible to perform research in the sense of rapid growth in modern synthetic chemistry. Much further research into the pharmacology of this scaffold is needed. As a result, promising results in the discovery of excellent drugs containing the central backbone of heterocyclic scaffolds should be expected.

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