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Structure- Activity Relationship Insights into Dihydropyrimidinones (DHPMs): A Versatile Scaffold for Multitarget Drug Discovery

Manjiri Mandar Shastri*[1,2], Archana Mukul Karnik[1], Somdatta Y. Chaudhari[3]

[1]Department of Pharmaceutical Chemistry, SCES's Indira College of Pharmacy (Now, Indira University, School of Pharmacy), Tathawade, Pune 411033, Maharashtra, India
[2] Department of Pharmaceutical Chemistry, JSPM's Rajarshi Shahu College of Pharmacy and Research, Tathawade, Pune 411033, Maharashtra, India
[3]Department of Pharmaceutical Chemistry, PES's Modern College of Pharmacy, Nigdi, Pune-411044, Maharashtra, India

***Corresponding author**: pranalkutkar@gmail.com

Abstract

Dihydropyrimidinones (DHPMs), a group of heterocyclic compounds that are considered versatile compounds bearing significant potential in multitarget drug discovery and development. Due to their adaptable nature, DHPMs demonstrate a wide range of pharmacological activities. Additionally, the implementation of green synthesis methods, such as solvent-free and microwave-assisted reactions, enhanced DHPM production efficiency by reducing reaction time from 2-4 hours to 10-20 minutes, increasing yields up to 95%, and lowering energy consumption by 40%, thereby improving environmental sustainability through a 60% reduction in hazardous waste. This review presents a wide-ranging consideration of the structural activity relationships (SAR) of DHPM derivatives, highlighting how specific substitutions (e.g. electron-donating, electron-withdrawing groups) at various positions on the DHPM core impact their biological activities. Hybridisation and In-silico methodologies have emerged as pivotal tools for enhancing lead identification and optimisation. Techniques such as quantitative structure-activity relationship (QSAR), virtual screening, and molecular modeling have allowed precise evaluation of DHPM-target interactions, facilitating SAR refinement. By elucidating the SAR of DHPMs, this review aims to guide future research in the rational design of more potent DHPM-based therapeutics, facilitating the development of more effective and safer drugs across various therapeutic areas.

Keywords: Electron-donating, Electron-withdrawing, Green Synthesis, Heterocyclic compounds, In-silico methodologies

Introduction

In recent years, heterocycles have gained importance in medicinal chemistry because of their medicinal and industrial applications (1). More than 85% of physiologically active compounds have heterocyclic structures, according to studies, highlighting their important role in modern drug design (2). Numerous N-heterocyclic compounds of biologically important molecules, such as vitamins, nucleic acids, medicines, dyes, and agrochemicals (3). Among the various nitrogen-containing heterocycles, Pyrimidines gained a notable position in medicinal chemistry. The pyrimidine scaffold can be easily modified at multiple positions due to its structural adaptability to enhance biological activity, selectivity, and pharmacokinetic properties (4,5). Dihydropyrimidinones (DHPMs), one of the Pyrimidine derivatives, also gained importance in drug design due to their

diverse pharmacological activities (6,7,8), like Anti-HIV (9), Antimicrobial (10), Anti-inflammatory (11), Analgesic (12), Anticancer (13), Antidiabetic (14), Antiulcer (15), Antimalarial (16), Antitubercular (17), Antihypertensive (18). Their synthesis and structural modifications offer vast potential for developing new drug candidates. They show structural similarities with natural pyrimidine bases of DNA, hence improving the binding affinity to various target enzymes. The objective of this review is to provide a systematic study of the structure activity relationship (SAR) of dihydropyrimidinone (DHPM) derivatives with a focus on the effect of the type and position of substituents on biological activity. Furthermore, the review emphasizes the importance of green synthetic approaches to enhance the efficiency and sustainability of DHPMs production. The underlying motive is to provide a systematic framework to rationally design novel DHPM analogs with better pharmacological profiles and environment friendly synthesis routes. This work is distinct from previous DHPM SAR studies that have primarily employed traditional synthesis and broad biological screening approaches, and also introduces eco-friendly green synthesis approaches in combination with in silico QSAR modeling. Moreover, the combination of sustainability and computational prediction in this study not only solves the environmental issues but also enhances the precision of SAR analysis. This study fills a key gap in the existing literature and paves the way for rational design of DHPM scaffolds. To compile this review, we performed an extensive literature search covering the period from around 2000 to 2025, using a diverse set of DHPM, SAR like keywords across multiple academic and general search engines including PubMed, Scopus, Web of science, and Google scholar.

Figure 1 shows the Dihydropyrimidinones (DHPMs) having similarities with natural pyrimidine bases like Thymine, Uracil, and Cytosine.

In medicinal chemistry, the structure-activity relationship (SAR) is essential in drug discovery and development. It describes

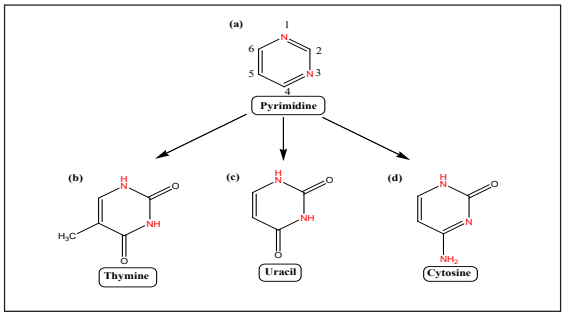

Figure 1. Dihydropyrimidinones (DHPMs) having similarities with natural pyrimidine bases like Thymine, Uracil, Cytosine.

how a molecule's pharmacological activity and chemical structure are related. Basically, SAR aids in understanding how modifications to a compound's molecular structure can affect its pharmacological effects (19, 20). SAR analysis is important in optimizing dihydropyrimidinone (DHPM)-based drug candidates. By examining how specific structural modifications influence biological activity, SAR drives the development of more effective and targeted medications.

Figure 2 shows the basic dihydropyrimidinone (DHPM) scaffold with R1, R2, R3, R4, and R5 positions where modifications can be possible.

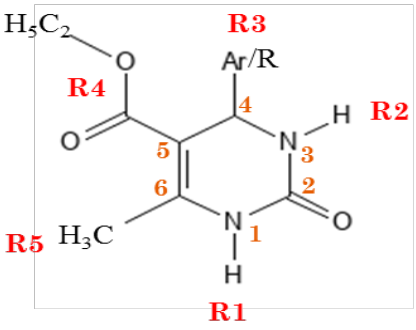

Figure 2. Basic Pharmacophore: Dihydropyrimidinone (DHPM) scaffold with R1, R2, R3, R4, R5 positions.

Synthesis of Dihydropyrimidinones

General synthesis

Multicomponent reactions (MCRs) are one-pot processes with three or more reactants in which the final product retains most of the at-

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oms from the starting materials. Because these reactions are economical, time-efficient, and have a wide range of exploratory possibilities, they provide strategic advantages over linear synthesis (21, 22). The Biginelli reaction is the earliest technique for the synthesis of dihydropyrimidinone among classical MCRs. In 1893, the Italian chemist Pietro Biginelli, proposed this MCR (23). It is basically a three-component reaction which includes the condensation of an aldehyde, a β-keto ester, and urea (or thiourea) in the presence of acidic conditions. This one-pot reaction, now widely recognised as the Biginelli reaction, was the first efficient method for synthesising 3,4-dihydropyrimidin-2(1H)-ones (24, 25). This reaction was a fast, cost-efficient, and high-yielding method. Figure 3 depicts the general Biginelli reaction.

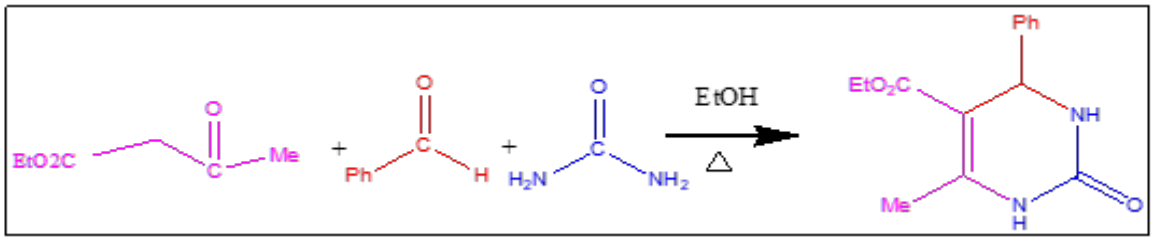

Figure 3. Classical Biginelli Reaction takes place between Ethylacetoacetate, Benzaldehyde, and Urea to give Dihydropyrimidinones.

Classical method of synthesis requires harsh acidic conditions and prolonged heating, leading to low yields, especially with substituted or aliphatic aldehydes. These conditions can also cause side reactions and limit the reaction's substrate scope. The main issue with homogeneous acid catalysts is the time-consuming separation procedure and problematic recycling, which results in hazardous waste. Environmental concerns arise due to the use of non-recyclable catalysts and organic solvents, developed the need for greener and more sustainable approaches. Recent advancements, such as employing solid acid catalysts and alternative energy sources like microwave irradiation, aim to address these challenges and enhance the reaction's efficiency and eco-friendliness (26, 27).

Modified and green chemistry approach

Green chemistry principles emphasise more on waste prevention, atom economy, and the use of safer solvents and renewable feedstocks. Widespread research and various modifications have been applied to the Biginelli reactions to improve their environmental sustainability(28). Modifications in the Biginelli reactions involve greener and efficient approaches (29), such as microwave-assisted reactions and solvent-free reactions, as well as asymmetric synthesis, solid-phase synthesis for combinatorial chemistry, chemical biology, and other fields have recently been used in the Biginelli reaction (30). Table 1 depicts the different green chemistry approaches and other modifications for Biginelli reactions in the comparative form.

Structural variability

As DHPM exhibits Structural variability, which allows various substitutions at different positions. These variations significantly influence their physicochemical properties and bio-

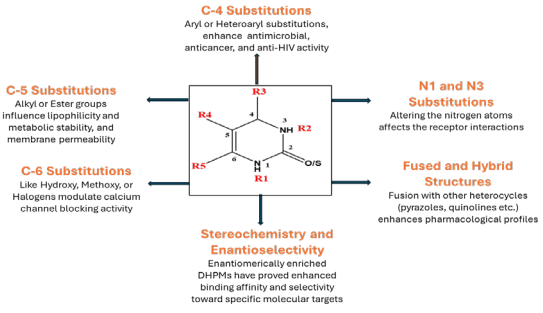

Figure 4. Structural Variability in DHPM's scaffold.

Table 1. Comparative study of Green Chemistry Approaches

Approach	Key Findings	Efficiency (Yield/Time)	Sustainability Impact	Scalability/Practicality	Reference
Solvent-free	Multicomponent reaction with heterogeneous catalyst; catalyst reusable	Moderate to high yields; easy separation	Eliminates solvent waste; reduces hazardous chemicals	Industrially attractive due to catalyst recyclability	Giovanna Bosica et al. (27)
Renewable solvent	Vegetable oils (e.g., palm oil) as eco-friendly solvents	Comparable yields to cyclohexane	Non-hazardous, renewable, less environmental damage	Readily scalable; oils widely available	Pakin Noppawan et al.(31)
Catalyst-free	Planetary ball-milling mechanochemical method	High yields under optimized conditions	Eliminates solvents and catalysts; maximizes atom economy	Promising but requires validation for scale-up	Mohamed Ould M'hamed et al. (32)
Ionic liquids	Brønsted acidic ionic liquids as sustainable catalysts	High catalytic efficiency	Reusable, less corrosive than H_2SO_4/HCl/ H_3PO_4	Cost and handling may limit large-scale use	Majid Vafaeezadeh et al. (33)
Renewable feedstocks	Biomass-derived HMF replacing aldehydes	Moderate to good yields	Introduces sustainable functionalities; reduces reliance on petrochemicals	Innovative, but feedstock supply chain critical	Weigang Fan et al. (34)
Microwave-assisted	Accelerated Biginelli reaction; library generation	Reaction time reduced from hours to minutes; yields often ≥90%	Supports solvent-free/green solvents; energy-efficient	Highly scalable for rapid screening	Majid M. Heravi et al., A Stadler et al. (35,36)
Asymmetric synthesis	Chiral ytterbium-based catalysts; enantioenriched DHPMs	Excellent yields; high enantioselectivity	Catalyst recyclable; reduces waste	Valuable for drug development; scalable with catalyst reuse	Eric Woerly et al. (37)

logical activities. Various positions include C-4, C-5, C-6, also, substitutions at the N1 and N3 position tends to enhances activity. Figure 4 depicts various structural modifications on the DHPM core nucleus.

In analyzing the SAR patterns of the DHPM compounds, it is important to emphasize that observed effects are scaffold- and context-dependent rather than universal rules. The C-4 position is commonly substituted with aryl or heteroaryl groups, which have been shown to enhance antimicrobial, anticancer, and anti-HIV activity (9, 38, 39). Electron-withdrawing groups, e.g. Cl, NO2, tend to ncrease the potency in antibacterial assays by demonstrating larger inhibition zones against S. aureus and E. coli. Compounds with a chloro-group at the 3- or 4-position in the substituted ring of DHPM showed higher binding affinity for the human kinesin Eg5 enzyme (7.9 kcal mol 1) than the standard drug monastrol (7.8 kcal mol 1). Also in vitro cellular studies results indicate that a deactivating group (chlorine) at the 3- or 4-position in the substituted ring of DHPM might be a promising anticancer drug candidate (40). C-5 position substitutions involve the ester group and, alkyl group. These might influence

lipophilicity, metabolic stability, and membrane permeability, which is crucial for anti-inflammatory and CNS-targeted drugs. Bulkier esters such as benzyl or isopropyl groups reduce polarity and increase lipophilicity, resulting in higher logBB values and improved brain/plasma ratios compared to smaller esters Several substitutions at C-5 tend to enhance calcium channel blocking activity, thereby enhancing antihypertensive activity Aromatic substituents with electron-withdrawing groups and the ester alkyl group at C5 show the increasing potency in the order iso-propyl moieties > ethyl > methyl groups. (41). Substituents at C-6 positions generally involve electron-donating, electron-withdrawing groups, tend to enhance the antihypertensive and calcium channel blocking properties (41). Changes in ring nitrogen substitution tend to influence receptor binding and selectivity. Certain N-alkylation patterns have shown strong anticonvulsant action. α-glucosidase inhibitors, estrogen receptor antagonists (42). Integration with moieties like quinolines, pyrimidines, or pyrazoles might expands the activity spectrum. Notable impact in anticancer, antiviral, and antibacterial screening (43). Enantiomerically enriched DHPMs havetends to enhance binding affinity and selectivity toward specific molecular targets such as kinesin Eg5, a mitotic spindle motor protein overexpressed in cancer cells (44).

Therapeutic classes of DHPMs and their biological activities

Due to the versatility in the structure of DHPMs, they exhibit a variety of biological activities. Figure 5 depicts the various therapeutic classes of DHPM.

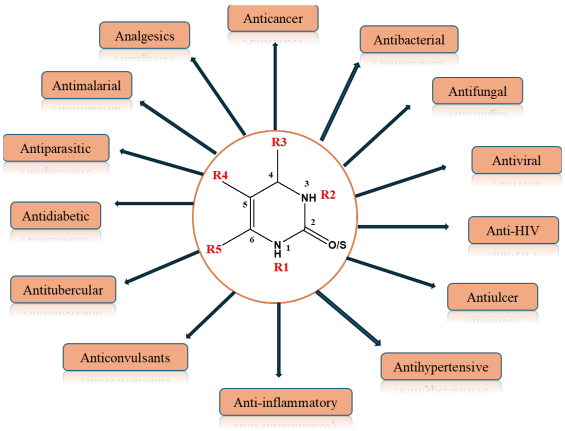

Figure 5. DHPM scaffold with various pharmacological activities.

Table 2 summarises the various therapeutic classes of DHPMs, and also shows the key findings of the substitution pattern.

Table 2. Summary of various therapeutic classes of DHPMs along with the SAR insights.

Therapeutic Class	Biological Activity	Representative Targets/Mechanisms	SAR insights	References
Anticancer	Antiproliferative and tubulin polymerisation inhibitory activities	MCF-7 and MDA-MB-231 breast cancer cell lines	The substitutions with a 4-methylphenyl ring on DHPM demonstrated the highest antiproliferation activity with good IC_{50} values (45).	Nagaraju Kerru et al.
Antibacterial	Inhibition of Gram +ve and Gram -ve bacteria	Cell wall synthesis disruption, DNA gyrase inhibition	Compounds with electron-releasing groups like hydroxyl, methyl exhibited good antibacterial activity against E.coli and Staphylococcus aureus (46).	Alka N Choudhary et al.
Antifungal	Inhibition of fungal species like Aspergillus niger & Penicillium notatum	Membrane disruption, ergosterol bio-synthesis interference	Pharmacophores with a nitro group (electron-withdrawing group) have exhibited the best antifungal activity (46).	Alka N Choudhary et al.

Antiviral	Antiviral activity against a wide range of DNA and RNA viruses	Reverse transcriptase inhibition, viral entry blockade	Out of all synthesised compounds, one compound with a long lipophilic side chain was found to be a potent and selective inhibitor of Punta Toro virus, a member of the Bunyaviridae (47).	Dhanabal Kumarasamy et al.
Anti-HIV	Activity against retroviruses like HIV	Reverse transcriptase inhibition	The presence of a small aliphatic group at the R1 position has been found to favour reverse transcriptase inhibitory activity as compared with aromatic and heteroaromatic substitution, which exhibits comparably low efficacy (9).	Titiksh L. Devale et al.
Antiulcer	Activity against the ulcers	Gastric ulcer models developed	Compounds with different R groups like 4-nitrophenyl substitution, 2-methoxy phenyl, dimethylaminophenyl and 2,3,4-trime thoxyphenyl, substitutions were shown good antiulcer activity among all synthesised compounds (15).	Mashooq Ahmad Bhat et al.
Antihypertensive	Vasodilation, calcium channel blocking	L-type calcium channel antagonism	Substituents at positions 3 and 5 with electron-withdrawing groups enhancing calcium channel blockade, Aromatic rings with alkyl chains facilitating membrane interaction (41).	Yasser M. Zohny, et al.
Anti-inflammatory	Reduction of inflammation markers	COX inhibition, cytokine modulation	C-4 substitution with a 4-methoxy group shows vital role in the activity. It was observed that 4-methoxyphenyl increases the activity of the compounds (70).	Ramandeep Kaur et al.
Anti-malarial	Inhibition of Plasmodium falciparum	Inhibition plasmodial parasite	When compared to traditional antimalarial drugs like chloroquine, the antimalarial activity is increased by the substitution of acetyl groups along with 2-thiooxo-1,2,3,4-tetrahydropyrimidine and 1,3,5-oxadiazole residues, including quinoline moieties (48).	Ibrahim Ali, et al.
Antitubercular activity	Activity against wild-type M. tuberculosis	Anti-TB evaluation against Mtb strains	Compounds with electron-withdrawing groups like OCH_3, Cl, Br at metaposition demonstrated a promising efficacy, but only the Br-substituted analogue retained good inhibitory activity when placed at the para position. The electron-donating groups (EDGs) such as alkyl and methoxy at the para position of the aromatic ring substituted on a pyrimidine scaffold showed moderate effectiveness (49).	Gobind Kumar et al.

Antidiabetic	Blood glucose regulation	Inhibition of α-glucosidase and α-amylase	Substitutions at the C5 and C6 positions of DHPM containing a fused heterocyclic ring exhibit significant inhibition of α-glucosidase (50).	Umair Ilyas et al.
Antiparasitic	Activity against Leishmania and Plasmodium species	DNA intercalation, redox imbalance	Derivative with 4-fluoro phenyl substitution possesses the potent antileishmanial activity (51).	Neeloo Singh et. al.
Anticonvulsant	Protection in seizure models, particularly in maximal electroshock (MES)-induced convulsions	Modulate the GABAergic system	Out of all synthesised compounds, one compound with promising activity, which includes both urea and thiourea derivatives, had compact lateral chains and phenyl rings that were either unsubstituted or para-substituted with a methyl group (52).	Matias et al.
Analgesics	Analgesic activity	Inhibition of COX enzymes	Substitutions like 4-hydroxy-3-methoxybenzaldehyde (vanillin) derivative was found to be a good analgesic agent. p-chloro benzaldehyde and p-methoxybenzaldehyde , derivatives were found to be a moderately effective (12).	D. Kumara Swamy et al.

Some target -specific SAR insights of DHPMs

Anti-HIV activity-non-nucleoside HIV-1 reverse transcriptase inhibitors (NNRTIs)

Titiksh L. Devale et al. determined that dihydropyrimidinone-isatin hybrids are new non-nucleoside HIV-1 reverse transcriptase inhibitors (NNRTIs). Two hybrids with better RT inhibitory activity than standard Rilpivirine were found through in vitro screening. The study showed that keeping the isatin moiety unsubstituted is important for increased RT inhibition and that small aliphatic substituents at the R^1 position are more advantageous than aromatic or heteroaromatic groups. Compound 9c was found to be the most potent with RT inhibitory activity (95.96%) among all synthesized compounds in series and as compared with standards (rilpivirine and nevirapine) (9). Figure 6 shows the Dihydropyrimidinone-Isatin hybrid structure.

Anti-HIV activity- HIV Integrase inhibitor

A series of dihydropyrimidinone and thiopyrimidine derivatives using an aryl

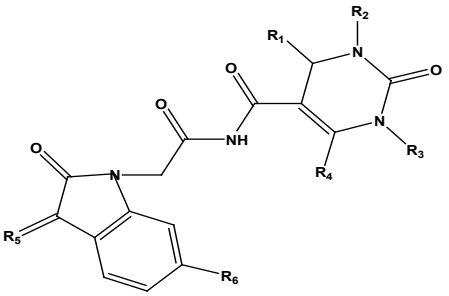

Figure 6. Structure of Dihydropyrimidinone-Isatin hybrid having NNRTI activity.

α,γ-diketobutanoic acid moiety were synthesised by Ozkan Sari et al. using the Biginelli multicomponent reaction and evaluated against HIV 1 Integrase enzyme According to the study, phenyl and isopropyl substituents exhibit the least amount of activity, and steric hindrance at the C6 position is poorly tolerated. Methyl and ethyl groups, on the other hand, produced better results, and a benzyl substituent at the C4 position showed encouraging inhibitory ef-

fects. Among them, compound 4c, substituted by a benzyl group at C-4 position, displayed a promising inhibition with an IC50 of 0.19 mM. Moreover, compounds with somewhat lower potency were produced when aryl substituents like Cl, F, OCH_3, and 3,5-dimethyl at the C4 position did not significantly affect the α,γ-diketobutanoic acid moiety at C2 (53). Figure 7 shows the structure of dihydropyrimidinone and thiopyrimidine derivatives

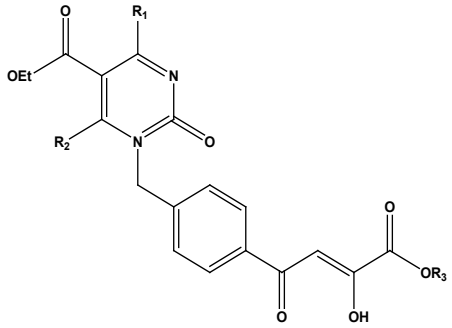

Figure 7. Structure of Dihydropyrimidinone and thiopyrimidine derivatives bearing aryl a,γ-diketobutanoic acid.

Anti-HIV 1- replication inhibitor

Junewon Kim et al. showed a detailed study of the DHPMs scaffold as an anti-HIV-1 replication inhibitor. The study focused towards optimising the metabolic stability of the Ester group. Various modifications studied are 1) The Lactone derivatives proved inactive, indicating that a bulky lipophilic substituent on the right-hand side is crucial for anti-HIV activity, 2) The Ketone derivatives revealed moderate activity, with ring size 5-7 moderately improved activity; phenyl analogues completely lost activity, Variations in the ring size of R1 displayed moderately improved antiviral activities depending on the ring sizes from five-membered 16a (EC50= 420nM), six-membered 16b (EC50=403nM), and seven-mem bered 16c (EC50=329nM), 3) Bioisosters like oxazole/oxathiazole exhibited similar activity with EC50 of 116 and78 nM, respectively. Imidazole did not show activity (54). Figure 8. depicting various modifications at the ester moiety.

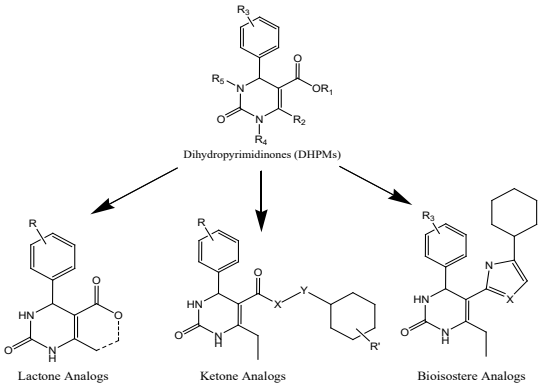

Figure 8. Dihydropyrimidinone scaffold with various modifications at the ester moiety.

Antimicrobial activity

Novel 1,2,3,4-tetrahydropyrimidines with biological significance were synthesised and analysed by Karthikeyan Elumalai et al. It was revealed that the presence of a sulphanilamide group at the fifth position contributed to both cytotoxic and antimicrobial activities. Because fluoride and chloride have strong electron-withdrawing effects, substituting them at the fourth position of the phenyl ring increased potency. Additionally, derivatives with sulphur in the second position were more active than their oxygen-substituted counterparts. Among all synthesized compounds 7p showed the best antimicrobial and cytotoxicity of all the 1,2,3,4 tetrahydropyrimidine derivatives, antimicrobial activity with an MIC value of 11.4 μM, 12.1 μM and cytotoxicity CTC50 value of 19.0 μM.(10). Figure 9 showing structure of 1,2,3,4-tetrahydropyrimidines derivatives.

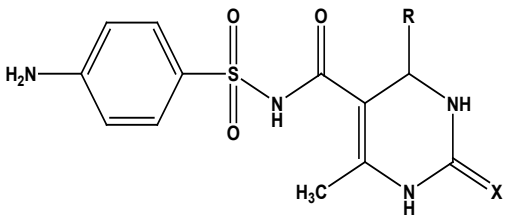

Figure 9. Structure of 1,2,3,4-tetrahydropyrimidines with sulphanilamide group, where (X= O/S)

Analgesic activity

D. Kumara Swamy et al. synthesised and screened the dihydropyrimidinone deriva-

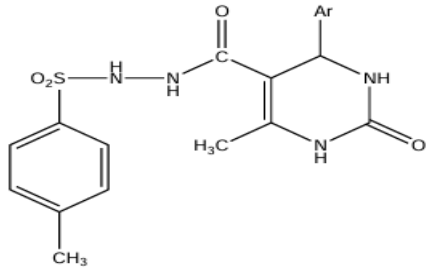

Figure 10. Structure of Dihydropyrimidinone derivatives with sulphonamide derivative.

Antihypertensive and calcium channel blocking activity

A series of DHPMs was synthesised and screened for antihypertensive and calcium channel blocking activity by Hiren M. Marvaniya et al. by comparing with bioisosteric nucleus Nifedipine. Compound with 4-morpholinyl substitution showed better antihypertensive activity, and the derivative with chloro and diethyl amino substitution possesses better calcium channel blocker activity. Compound 6c was found to have better antihypertensive activity with percent inhibition 31.44 and compound 6f found to have better calcium channel blocker activity with percent inhibition 50.00 (55). Figure 11 shows the structures of the standard drug Nifedipine and bioisosteric dihydropyrimidinone derivative.

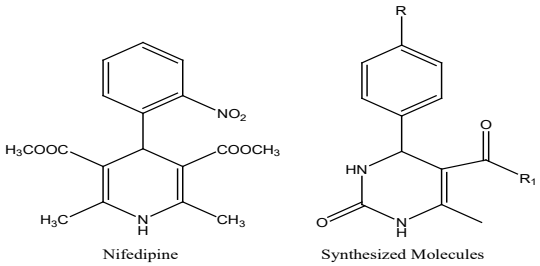

Figure 11. Structures of Dihydropyrimidinones for antihypertensive and calcium channel blocking activity, along with the standard drug Nifedipine.

Anti-HIV 1- replication inhibitor

A series of dihydropyrimidinone analogues were synthesised and evaluated as HIV-1 replication inhibitors in vitro by Junwon Kim et al. Several derivatives demonstrated notable inhibitory activity in cell-based assays. The study explored that the presence of an oxygen atom at position 2nd is crucial for activity, whereas sulphur substitution reduces potency. Furthermore, the R^2 position was found to be highly sensitive to both steric and electronic effects, with para-substituted electron-withdrawing groups on the phenyl ring sustaining significant inhibitory activity Results showed that a hydrophobic alicyclic R1is preferred and 8 e xhibited EC50 of 0.529l M(56). Figure 12 depicts structures of dihydropyrimidinone analogues as HIV-1 replication inhibitors.

Figure 12. Structure of Dihydropyrimidinone analogues as HIV-1 replication inhibitors.

The compilation of SAR insights based on base modifications mainly at C4, C5, C6 positions and core atom O, underscores the importance of scaffold engineering in rational drug design. Figure 13 showed the compiled SAR discussions in accordance with Base modifications.

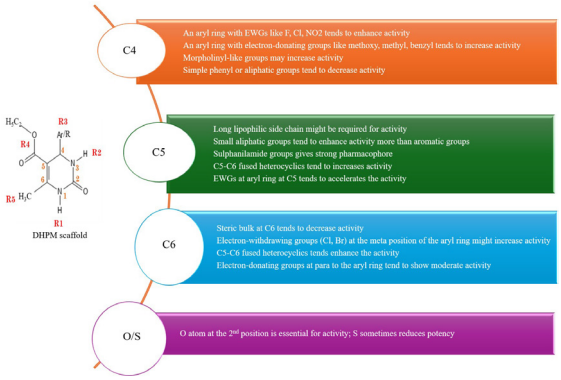

Figure 13. SAR discussions compiled in accordance with base modifications

Effect of substituents on DHPM activity

The biological activity of dihydropyrimidinones (DHPMs) is predominantly influenced

by the position, type, and nature of substituents on their aromatic rings. Changes in functional group substitution can alter the reactivity and thermal stability of these analogues (57). Both electron-withdrawing groups (EWGs) and electron-donating groups (EDGs) can modulate the pharmacological activities of DHPM derivatives, as shown in Figure 14.

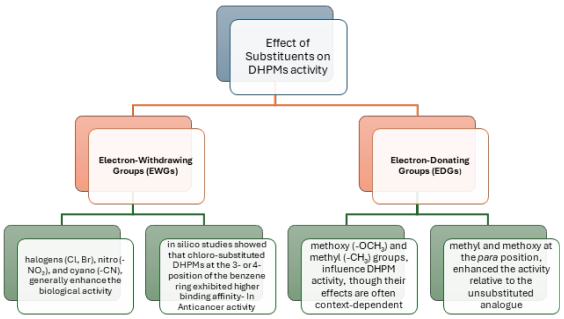

Figure 14. Effect of Substituents on DHPMs Activity.

Electron-Withdrawing Groups (EWGs)

EWGs, like halogens (Cl, Br), nitro ($-NO_2$), and cyano (-CN), generally enhance the biological activity of DHPMs. These groups stabilise the molecular framework through inductive and resonance effects, potentially increasing binding affinity to biological targets (58). It has been reported that the activity of DHPM derivatives is increased by chloro and bromo substituents on the benzene ring. In silico analyses showed that chloro substitution at the 3- or 4-position imparts higher binding affinity to the human kinesin Eg5 enzyme than the reference drug Monastrol, promising their potential as anticancer agents (59). Structure-activity relationship (SAR) studies discovered that electron-withdrawing substituents, mainly chloro and bromo, on the benzene ring improve the activity of DHPM compounds. Some chloro and bromo-derivatives of DHPMs exhibit potent antibacterial activity, comparable to the standard drug ciprofloxacin (7). A study on DHPMs with chloro or bromo substituents, along with a free NH group in the pyrimidine moiety, showed increased and significant antibacterial activity (60).

Electron-Donating Groups (EDGs)

EDGs, like methoxy ($-OCH_3$) and methyl (-CH), can also influence DHPM activity, though their effects are often context-dependent. The introduction of EDGs, such as methyl and methoxy at the *para* position, enhanced the activity relative to the unsubstituted analogue. However, their potency remained lower than that of their halogenated counterparts, signifying that EDGs improve activity (17). The incorporation of a para-methoxy group on the phenyl ring, along with thiazole and thiazine scaffolds, was associated with moderate cytotoxic activity (61). The effect of a methoxy group on DHPM activity is not universally positive or negative. It depends on the specific DHPM scaffold, the position of the methoxy group, and the specific biological target.

DHPMs Modifications

Various modifications have been carried out on the DHPM scaffold, including the formation of ring-fused hybrids and side-chain alterations to improve biological activity. Figure 15 shows the various modification approaches in DHPMs.

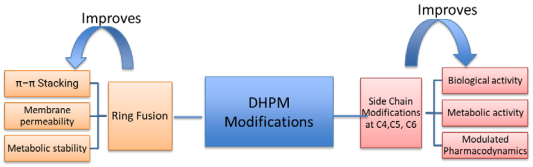

Figure 15. Modification approaches in DHPMs: ring fusion and side-chain modifications, with their advantages.

Ring fusion hybrid molecules in Dihydropyrimidinones (DHPMs)

Ring fusion strategies in DHPM derivatives have proven to be a successful approach to enhance their biological potential. These hybrid molecules exhibit improved binding affinity, selectivity, and pharmacokinetic behaviour due to increased molecular rigidity and planarity. Ring-fused DHPMs are therefore a promising avenue for the manufacture of multitarget ther-

apeutic agents, demanding further investigation through SAR and in vivo pharmacological studies.

Ring fusion facilitates stronger π–π stacking and interaction with biological targets, enhancing membrane permeability and metabolic stability. Multicyclic systems can occupy a larger binding site volume, thereby improving selectivity. Various heterocyclic-DHPM derivatives showed enhanced biological activities like anticancer, antibacterial, antifungal, etc (42).

A series of Chromone dihydropyrimidine hybrids having ester and hydrazide substituents at the C5 position of the ring was designed and synthesised by Tiwari et al. Synthesised derivatives were tested for antibacterial activity against Staphylococcus aureus and two E.coli strains. Among all derivatives, one compound was most potent and had comparable activity with D-cycloserine against S. aureus but was slightly more potent against E. coli (62).

By combining the pharmacophore hybridisation approach with a regioselective multicomponent reaction, Koneni V. Sashidhara et al. created several novel dihydropyrimidinone–semicarbazone hybrids. The majority of the synthesised compounds were found to be good to moderately active when their hLig1 inhibition potency was assessed. Compound 6f demonstrated dose-dependent selective anti-proliferative activity against HepG2 cells, and in silico docking studies revealed good binding affinity. Additionally, they have examined their pharmacokinetic parameters with favourable drug-like properties (63).

After reviewing ten years of research on DHPM and its modifications, Dhirajkumar Nikam et al. discovered that molecular hybridisation of DHPMs with other heterocyclic analogues has established remarkable anti-breast cancer potential, greater selectivity, and significant growth inhibition in preclinical research in comparison to current anti-breast cancer drugs like tamoxifen, fluorouracil, doxorubicin, and monastrol (64).

Side chain modifications in Dihydropyrimidinones (DHPMs)

Side chain modifications in DHPMs play a critical role in modulating their biological activity, selectivity, solubility, and metabolic stability. These modifications typically occur at three main positions in the DHPM scaffold, specifically at the Carbon 4^{th}, 5^{th} and 6^{th} positions, during or after the Biginelli reaction.

Types of side chain modifications and their effects on DHPM activity

Structural modifications at the side chains of dihydropyrimidinones (DHPMs) significantly influence their pharmacological profile. One distinguished modification involves the conversion of an ester to an amide at the C-4 position, which enhances hydrogen bonding capacity and improves metabolic stability (7). This alteration has been associated with increased anticancer and anti-inflammatory activities. At the C-5 position, various aryl substitutions have shown activity-dependent effects based on the electronic nature of the substituents. Electron-withdrawing groups such as nitro (NO_2) or chloro (Cl) tend to enhance antibacterial efficacy, and antifungal (46), while electron-donating groups like methoxy (OCH_3) and methyl (CH_3) are more favourable for anti-inflammatory actions (7).

The incorporation of bulkier or long alkyl side chains has also been reported to improve anti-HIV activity (54). Additionally new series of compounds where pyrrolidine, piperidine and morpholine are attached to the side chain of dihydropyrimidinones through amide linkage has shown improved metabolic stability (65). Finally, the use of metal-complexed derivatives, like DHPM-thione derivatives, which have been shown to directly bind copper ions, triggering metal-dependent rescue of βamyloid toxicity in cellular models, showed a clear indication that metal coordination can significantly modulate pharmacodynamics and target engagement (66) or bioisosteric substitutions (55) offer novel avenues to modulate pharmacodynamic behaviour and introduce unique mechanisms of action.

Computational and Insilico approaches

In recent years, molecular modelling has emerged as a basis in modern in silico drug design, driving the discovery and optimisation of drug candidates across diverse therapeutic areas. Structure-based modelling techniques, including molecular dynamics (MD) simulations, virtual screening, and molecular docking, enable high-throughput identification of potential ligands and detailed insights into binding interactions, significantly accelerating lead generation and optimisation while reducing experimental burden (67,68). Figure 16 depicts the journey of DHPM drug discovery by traditional methods and the advantages of in silico approaches to develop optimised DHPM analogues.

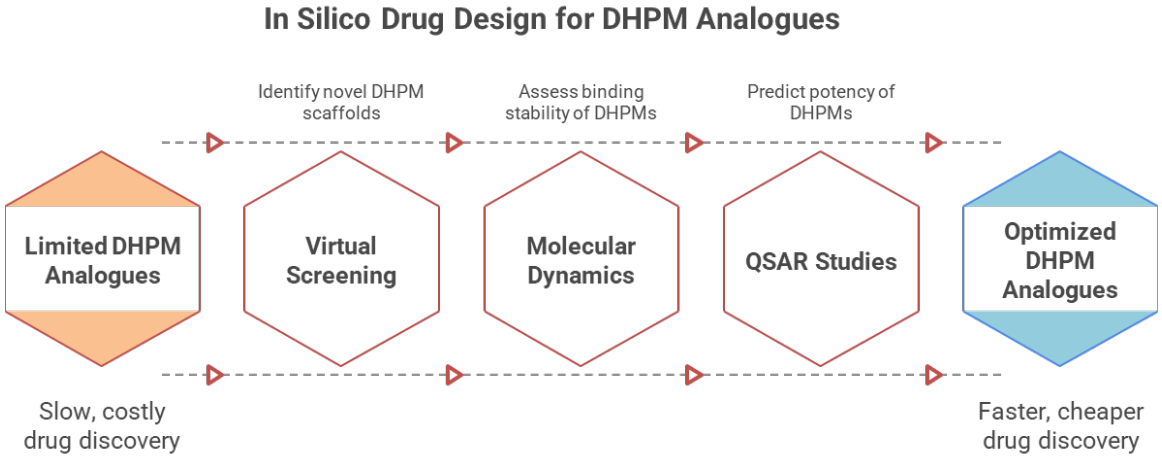

Figure 16. In silico drug design approaches for the development of DHPM analogues, with their advantages over traditional methods.

Itamar et al. synthesised a novel series of N-1 aryl dihydropyrimidin-2-thiones to create Monastrol derivatives having anticancer activity against glioma cell lines. All compounds were subjected to molecular modeling studies with N-1 modifications to enhance interactions with the P3 pocket, leading to strong Eg5 inhibition. The binding poses predicted by GOLD were consistent with the experimental inhibition data. Remarkably, two newly developed N-1 aryl-substituted derivatives exhibited approximately double the activity of monastrol against glioma cells, thereby validating the effectiveness of N-1 aromatic ring incorporation in DHPMs (69).

Molecular dynamics studies further supported binding stability when the binding pattern and influence of DHPMs derivatives on Eg5 behaviour were studied by Bruna C. Guindo et al. by performing Molecular dynamics assays. The binding patterns found for the DHPM derivatives demonstrate the importance of the interaction between a few Eg5 residues and the DHPM derivative. This is represented by the 4bc derivative, which strongly ties the ligand-binding site through two water-mediated interactions with Glu116 in addition to direct interactions with Leu214 and Arg119. Similar to Monastrol, the 4bc derivative interacts with Arg119, but it bonds to Glu116 rather than Glu118, ensuring the stability of the α-helix (70).

Complementing docking and dynamics, quantitative structure–activity relationship (QSAR) studies have identified structural determinants of activity within DHPM scaffolds. Itamar Luís Gonçalves et al. synthesised biphenyl-bearing DHPM-2-thione derivatives, among which several exhibited enhanced antiproliferative activity against glioma and bladder cancer cell lines compared to Monastrol, while maintaining favourable safety in *C. elegans* models.

A QSAR study was conducted to explain structural features associated with the antiproliferative effect, revealing that electron-withdrawing substituents were strongly correlated with cytotoxic potency and modulation of reactive oxygen species (71).

Collectively, these in silico approaches provide a strong pipeline for the identification and optimisation of DHPM analogues, including virtual screening of novel scaffolds via docking, stability assessment via molecular dynamics, and predictive potency modelling via QSAR. This integrative strategy enables rational design of DHPM compounds with enhanced inhibitory property, cytotoxicity profiles, and mechanistic insights bridging structure to function. In addition to streamlining the drug discovery process, the in silico framework offers a strategic basis for the creation of DHPM-based treatments of the future.

Challenges and future prospects in the development of DHPM drug candidates

The development of DHPM derivatives presents several challenges, both synthetic and biological. One of the primary challenges is the low yield and prolonged reaction time associated with the traditional Biginelli reaction, which typically requires up to 20 hours and often fails with certain aldehydes.(72) Although modified protocols have been introduced to improve efficiency, the reaction still requires precise optimisation of conditions such as pH, temperature, and catalysts to achieve desirable yields (72). Additionally, the structural complexity of DHPMs, especially due to lone pair and π-interactions, complicates purification and biological prediction, as revealed through SCXRD and Hirshfeld surface analysis (73). Furthermore, traditional synthetic approaches often use hazardous chemicals and reagents, thereby posing environmental and sustainability challenges (73).

Despite these challenges, DHPM derivatives hold immense promise in medicinal chemistry. Recent advances in green synthesis, such as the use of *Citrus macroptera* juice as a bio-catalyst, have demonstrated improved yields, shorter reaction times, and solvent-free conditions, making the process more eco-friendly and scalable (73). All DHPMs exhibit a wide range of pharmacological activities, including anti-HIV, antibacterial, anticancer, antioxidant, and calcium channel modulating properties. Notably, compounds like Monastrol (antimitotic) and GLS4 (antiviral) have proceeded to clinical trials, underlining their therapeutic potential (42). The integration of multicomponent reactions (MCRs) and computational modeling is also accelerating the design of novel DHPM analogues with enhanced selectivity and potency (74). As the demand for sustainable and targeted drug development grows, DHPM derivatives are poised to play a pivotal role in addressing unmet medical needs, particularly in cancer, neurodegenerative diseases, and infectious disorders (73,74).

Application of AI-Assisted Molecular Design Advances in AI, such as deep generative modeling, explainable AI, and hybrid frameworks, hold promise for exploring chemical space more efficiently, prioritising scaffold modifications with high predicted biological activity and drug-likeness (75). Recent advances in computational chemistry and artificial intelligence have revolutionized the exploration of DHPM derivatives for drug discovery. AI-assisted molecular design can quickly produce new DHPM scaffolds by predicting the substituents and structural modifications that are likely to improve biological activity. Techniques such as deep generative models and reinforcement learning algorithms can be used to propose new analogs with optimized pharmacokinetic and pharmacodynamic properties, reducing the reliance on trial-and-error synthesis (76). Meanwhile, QSAR studies based on machine learning provide quantitative insights on the structural activity relationship of DHPM derivatives. In this models have been trained on experimental datasets (e.g., IC50, Ki, % inhibition) and used algorithms including Random Forest, Support Vector Machines and Neural Networks to predict the biological activity of untested

compounds with high accuracy. The models do more than just identify important molecular descriptors (hydrophobicity, electronic parameters, steric effects); they also identify non-linear interactions that might be missed by traditional regression methods (77).

Conclusion

The exploration of Dihydropyrimidinones (DHPMs) as a versatile scaffold underscores their potent and adaptable nature in modern drug discovery. This review elucidates the rich structure-activity relationship (SAR) landscape of DHPM derivatives, revealing how strategic modifications at the C4, C5, and C6 positions, alongside functional group diversification, critically influence pharmacological outcomes across therapeutic targets.

Remarkably, DHPMs exhibit compelling interactions with a broad spectrum of biological receptors, including antitumor agents, anti-inflammatory, calcium antagonists, antibacterial, and antiviral targets, etc. The scaffold's inherent synthetic accessibility via the Biginelli reaction, coupled with its structural tunability, provides an ideal platform for multitarget drug development, aligning well with polypharmacological strategies.

Future research should focus on computational SAR modelling integrated with AI-driven predictive algorithms, hybridisation of DHPMs with other privileged scaffolds, and Eco-friendly synthetic modifications to enhance therapeutic indices.

In summary, the DHPM scaffold provides a robust platform for designing and developing novel therapeutic agents. Continued SAR studies, coupled with advancements in synthetic methodologies and nanotechnology, are expected to further expand the utility of DHPMs in addressing complex diseases through multitargeted approaches.

Abbreviations

DHPMs: Dihydropyrimidinones; MCR: Multicomponent Reaction; SAR: Structural Activity Relationship; EWGs: Electron-withdrawing groups; EDGs:Electron-donating groups; QSAR: Quantitative Structural Activity Relationship; HIV: Human Immunodeficiency Virus; DNA: Deoxyribose Nucleic Acid

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Author's Contribution

Conceptualisation, literature search, writing original draft, editing: Manjiri Shastri; Reviewing, supervision: Archana Karnik, Reviewing, supervision: Somdatta Chaudhari

Conflict of Interest

The authors declare that there are no conflicts of interest.

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