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Dihydropyrimidinones: Recent Synthetic and Pharmacological Perspectives with Special Focus on Colon Cancer

Saba Beigh[1*], Rasha Mohammed Saleem[2], Ali Hassan Ahmed Maghrabi[3], Eman H Khalifa[4], Saima Mushtaq[5], Muneeb U Rehman[6] and Adil Farooq Wali[7]

[1]*Department of Public Health, Faculty of Applied Medical Science, Al Baha University, Al Baha, Saudi Arabia.*

[2]*Department of Laboratory Medicine, Faculty of Applied Medical Sciences, Albaha University, Albaha- 65431, Saudi Arabia.*

[3]*Biology Department, Umm Al-Qura University- 24382, Saudi Arabia.*

[4]*Laboratory Medicine Department, Faculty of Applied Medical Science , University of Al Baha, KSA.*

[5]*Veterinary Microbiology Department, Indian Veterinary Research Institute (IVRI), Bareilly 243122, Uttar Pradesh, India.*

[6]*Department of Clinical Pharmacy, College of Pharmacy, King Saud University, Riyadh 11451, Saudi Arabia.*

[7]*Department of Pharmaceutical Chemistry, RAK College of Pharmaceutical Sciences, RAK Medical and Health Sciences University, Ras Al Khaimah 11172, United Arab Emirates.*

***Correspondence author**
Saba Beigh
Department of Public Health
Faculty of Applied Medical Science
Al Baha University
Al Baha
Saudi Arabia
Email : sbeigh@bu.edu.sa

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Abstract

The most important heterocyclic complexes involved in the manufacture of DNA and RNA are dihydropyrimidines. Through multi-component synthetic procedures like the Biginelli reaction and the Hantzsch dihydropyridine reaction, they were created. Due to their extraordinary biological properties, dihydropyrimidin-2(1H)-ones/thiones (DHPMs) are notable heterocyclic compounds. Dihydropyrimidin-2(1H)-ones/thiones (DHPMs), among the most important heterocyclic compounds, have biologically important properties such as cytotoxic, antibacterial, antiviral, and anti-inflammatory effects. As a result, organic and medicinal chemists are paying increasing attention to the synthesis of DHPMs and their derivatives. Many DHPM compounds have recently been isolated, described, and identified, and they are currently undergoing human usage studies.

Dihydrpyrimidines have been discovered to improve the health of cancer patients. We are intrigued by dihydropyrimidine research and its focus on colon cancer. One of the most prevalent kinds of cancer is colorectal cancer (CRC), and it's also the second commonest fatal malignancy for both sexes combined and the third most frequent diagnosis. With the exception of younger persons, both the incidence of new cases and death have been consistently dropping over the past several years, maybe as a result of increased cancer screening and improved treatment options. Different dihydropyridine calcium channel blockers prevent calcium from entering certain human cancer cells, having anticancer effects. However, to our knowledge, the anticancer impact of dihydropyrimidine on colorectal cancer cells has never been studied (CRC). With an emphasis on colon cancer, we have attempted to discuss the significance of DHPM derivatives for a number of chronic and developmental problems in this article.

Keywords : *Dihydropyrimidinones*, Anti-inflammatory, Colon cancer, Drug Development, Calcium channel inhibition, anti-oxidant.

Introduction

In our biological system, heterocyclic molecules play a critical function. They are a crucial component of many naturally occurring chemicals, nucleic acids, and pharmacologically active compounds. Furthermore, heterocyclic substances like purine and pyrimidine, among others, make up the base pairs of DNA and RNA. Heterocyclic compounds have a wide range of therapeutic applications, including anticancer, antibiotic, anti-inflammatory, antidepressant, anti-HIV, antimicrobial, antibacterial, antifungal, antiviral, antidiabetic, herbicidal, fungicidal, and insecticidal medications (Kaur et al., 2017). For instance, vinblastine, vincristine, and quinine are all utilized

as antimalarial medications. Pyrimidine represents the most prominent heterocyclic moiety (Deya et al., 2020). Pyrimidine derivatives can be used therapeutically in a variety of ways, according to the biomedical field. One possible explanation for their action is that thymine, cytosine, and uracil, which are necessary components of nucleic acids, DNA, and RNA, include pyrimidine bases. Different biochemical compounds containing pyrimidine as its central nucleus were investigated for their hypertensive, antitumor, microbiological, antidiabetic, antiarrhythmic, anti-inflammatory, analgesics, bactericidal, anti-HIV, and anti-tuberculosis potential (Magid et al., 2020). Scientists are drawn to creating novel dihydropyrimidine compounds because of the vast spectrum of medicinal qualities. Human lactate dehydrogenase inhibitors: 2-thio-6-oxo-1,6-dihydropyrimidines. The DHPMs are produced by multicomponent reactions (MCR). MCRs are specialized organic reactions that include three or more initial components and generate the desired outcome. Combination synthesis processes often outperform continuous or unconventional methods in terms of time, speed, yield, and reproducibility (Magid et al., 2020). MCR with more than two starting elements is one of the organic reactions that is permitted to create a complex result. They consequently stand for a stronger instrument for diversity-focused complexity-generating synthesis for medication development. Two widely employed multi-component processes for the biosynthesis of heterocyclic compounds include the Biginelli reaction and the Hantzsch dihydropyridine reaction (Kaur et al., 2017). The dihydroprymidinone nucleus is present in the marine - derived alkaloids Batzelladine A and B, that are recognized to prevent HIV gp-120 from attaching to CD4 cells. Additional synthetic molecules have been produced, including monastrol, L-771,688 and SQ 32926 (Sancho et al., 2022). The most significant anticancer substance, monastrol, has the capacity to penetrate cell membranes. It triggers mitosis by selectively and irreversibly inhibiting Eg5 myosin. The HT-29 colon cancer cell lines have already created and tested against other manostrol precursors, including oxo-monastrol, thio, and 3,4-methylenedioxy analogues. It was discovered that the 3,4-methylenedioxy homologue was 30 times more powerful than monastrol (Russowsky et al., 2006). For several of the medications containing the dihyropyrimidinone nucleus, a variety of pharmacological interactions and adverse effects have been documented.

Despite being well-known as a mitotic kinesin inhibitor, neurotoxicity has been identified as one of the main adverse effects of monastrol (Russowsky et al., 2006). An exhaustive examination of the interactions between aminophylline and topiramate indicated that in the animal model of maximally produced seizures, aminophylline with the dihyroprymidinone nucleus significantly reduced topiramate's anticonvulsant effectiveness (Venere et al., 2015). Adenosine receptor blockade is primarily responsible for the aminophylline's seizure prolonging effects. However, RO 15-1788, a fractional benzodiazepine agonist, counteracted the aminophylline's ability to prolong seizures. Misonidazole and 5-fluorouracil interaction has shown that the former considerably inhibited the clearance of the latter. It has been demonstrated that the radiosensitizer misonidazole increases the antitumor effects of numerous chemotherapeutic medications in hypoxic cells (Marawar et al., 2004).

Synthetic Strategies

Over through the past couple of years, research & development have effectively achieved the objective of implementing a number of synthesized methodologies. The synthesis of DHPMs has been described using a variety of synthetic methods. Dihydropyrimidine is produced by reacting ethyl acetoacetate 3, 3-hydroxybenzaldehyde 1, and thiourea 2, using powerful hydrochloric acid as a catalyst in a solvent system such ethanol (Sancho et al., 2022). Matthews et al. combined b-keto ester 5 with aldehyde 1 and urea 2 to create DHPMs 6. In 2004, Holla et al. revealed a method for producing thiazolodihydropyrimidinones 8 in a pot by condensing of benzaldehyde, 2, 4-dichloro-5-fluoroacetophenones, and thiourea in the presence of sodium hydroxide and ethanolic potassium hydroxide under Claisen-Schmidt experimental conditions (Holla et al., 2004). Under somewhat acidic circumstances, 1-(piperidin-1-yl) butane-1, 3-dione 9, benzaldehyde 1, and an excess of thiourea 2 were used in ethanol. Later researchers were able to synthesis the desired DHPMs in good to outstanding yield (Kaur et al., 2017). The variety of the Biginelli reaction remains additional thoroughly investigated under the four-component reaction method because there are more combinations that may be made in four-component reactions than there are in three-component reactions (Hügel et al., 2009). In 2000, Kappe created an alternate synthetic method to the conventional Biginelli condensation for the synthesis of DHPMs. Under neutral circumstances, the protected urea or thiourea derivative was condensed with the enone.

Dihydropyrimidines were created when hydrochloric acid was used to deprotect an intermediate (Kappe et al., 2000). Sondhi et al. used 3-isothiocyanatobutanal 17 and easily obtainable functionalized amines 16 to generate 2-thiopyrimidine derivatives in 100% methanol to make 19 (Sondhi et al., 2005). In the last ten years, a number of effective techniques for the synthesis of dihydropyrimidines have been established, and these techniques are quite well characterized. Nevertheless, a number of recently published alternate methods for the production of this alluring molecule have been revealed. Multi-component reactions have produced complex molecules quite successfully in a single, uncomplicated synthetic method (Sondhi et al., 2005). Gong et al. reported using b-cyclodextrin-propyl sulfonic acid (2 mol%) as a catalyst in a one-pot, multi - component reaction comprising benzaldehydes 1, urea/thiourea 2, and ethyl acetoacetate 3, under solvent-free conditions at 80 ˚C to create 3,4-dihydropyrimidinones 20. A quick and effective way to make -aryl-6-methyl-5- (2-oxo-2Hchromene-3-carbonyl), Benazzouz et al. suggested using thiones 22 or 23 that are 3,4-dihydropyrimidin-2(1H)-ones (Benazzouz et al., 2015). Under the influence of refluxing acetonitrile, the reaction mixture was incubated with para-substituted benzaldehyde 1, urea/thiourea 3, and several 3-(acetoacetyl)

coumarin variations as the major synthon. Under the defined Bignelli reaction circumstances, 3, 4-dihyrdopyrimidin-2(1H)-one has been synthesized using a variety of synthetic methods (Guido et al., 2015).

The constitution of the solvents is crucial to the procedure because higher reaction yields result from better values of the dielectric constant. Kumaran et al. demonstrated a successful production of 3,4-dihydropyrimidinone 20 and the corresponding thione with 98% yield using lanthanium oxide (La2O3) as a catalyst despite the use of a solvent and under the influence of microwave radiation at 320 W for 20-60 s (Kuraitheerthakumaran et al., 2016).

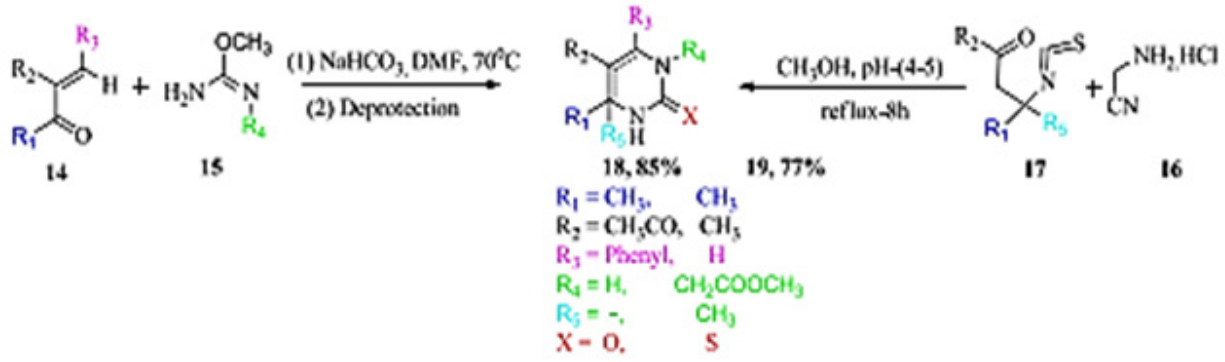


Figure 1: Different methods for creating 3,4-dihydropyrimidinones (Adopted Kaur et al., 2017)

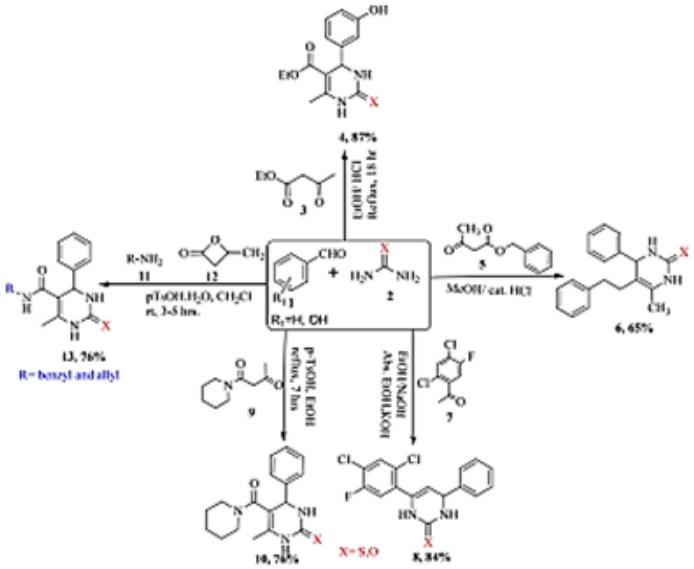


Figure 2: The methods used by Kappe and Sondhi to create 3,4-dihydropyrimidine (Adopted Kaur et al., 2017))

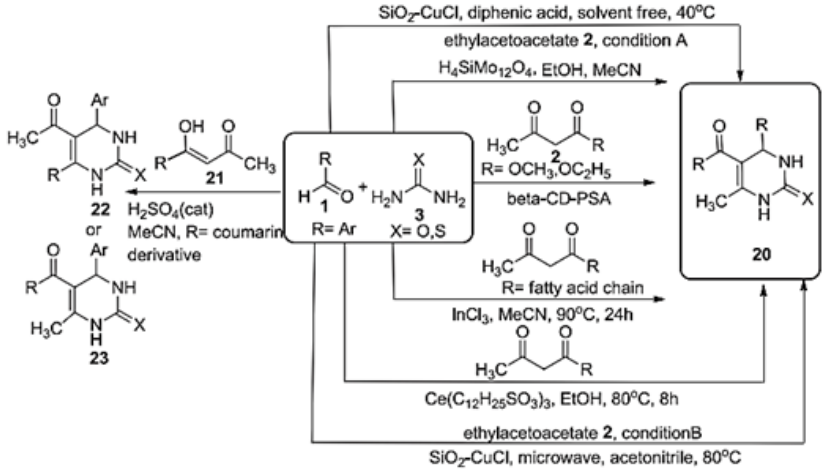


Figure 3: Alternative methods of synthesis were used to produce 3,4-dihydropyrmidin-2(1H)-ones ((Adopted Kaur et al., 2017).

Twenty novel compounds were created, and their enzymatic activity against HIV integrase was assessed. Inhibiting strand transfer and submicromolar activity were compounds 46, 48, 53, and 55 (Hajimahdi et al., 2016). hey discovered that C-6 substitution had a significant impact on the compounds' efficacy. An increase in activity was seen when methyl or ethyl groups were added to the R2. On the other hand, a decreasing effect in activity was seen when R2 was swapped with phenyl or isopropyl groups (Petrou et al., 2021). This shows that steric hindrance caused by C-6 was not tolerated. Novel dihydropyrimidines were created by Trivedi et al. in 2010 as a potential new class of antitubercular drugs. They used the multi-component Biginelli reaction to create thirty novel chemicals (Trivedi et al., 2010). Trivedi Initially, nine substances were examined using a strain of Mycobacterium tuberculosis. They were all 90e100% MTB inhibited. Two substances (58 and 59) inhibited MTB at the secondary level with MICs of 1 mg/mL, whereas three substances (61, 65, & 66) had MICs of 2 mg/mL. Compounds 58 and 59, out of all the compounds, were discovered to be the strongest (MIC of 0.02 mg/mL and SI > 500) in the series. In in vitro tests, the compounds were discovered to be significantly more effective than the medication INH (MIC: 0.03 mg/mL). The compounds provided guidance for creating a strong candidate for new antitubercular active chemicals. The pyrazolyl ring's C-3 fourth position plays a significant role in the activity of the newly created compounds. It was discovered that the compounds were more active when the methyl group at the C-3 position of the phenyl ring of the pyrazolyl was replaced with a different electronegative element (Horita et al., 2014). Figure 4 depicts the structures of effective drugs against TB.

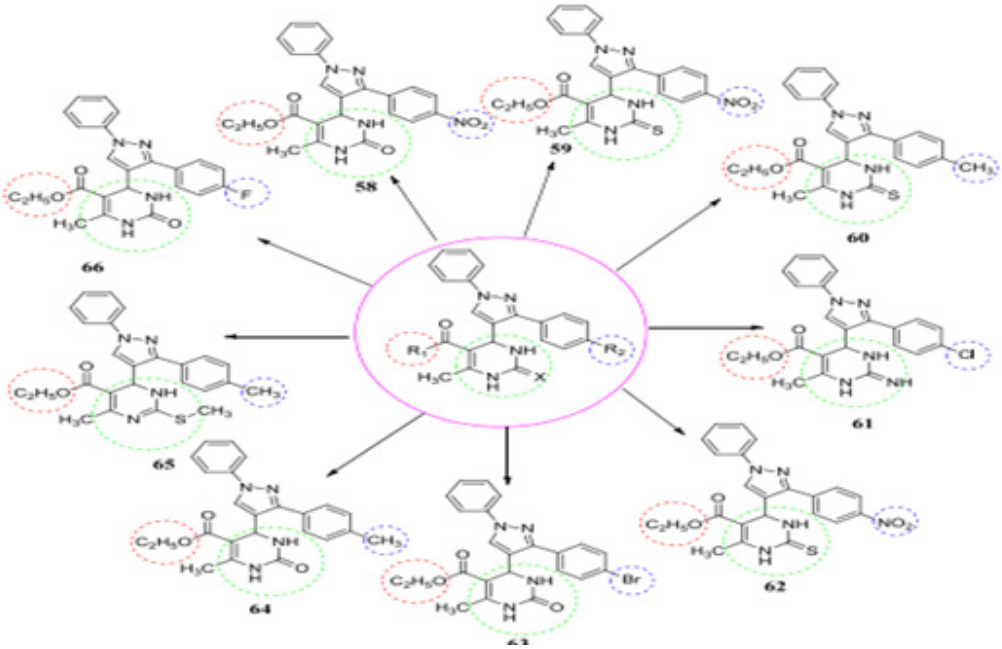


Figure 4: Dihydropyridines having antituberculosis activities (Trivedi et al., 2015)

Aly and Kamal created a brand-new family of fused pyrano [2,3-d] and chromeno [2,3-d] pyrimidine derivatives in 2012 (Aly et al., 2012). Prepared samples chemicals' antifungal efficacy was separately evaluated in vitro. The chemicals were tested against the two fungi Aspergillus flavus and Candida albicans on sabourround dextrose agar plates. The agar well diffusion method for evaluating antifungal effectiveness. Nine substances had their antifungal properties evaluated. Each fungus underwent the test three times. To gauge the potency of the confirmed complexes, they were compared to Amphotericin B in its conventional form. Zones of inhibition for synthetic drugs were identified. According to the findings, compound 72 was more effective against the Aspergillus flavus fungus than the common medication Amphotericin B. However, it was discovered to be ineffective against the fungus Candida albicans (Rajanarendar et al., 2010). Figure 5 depicts the structures of powerful compounds.

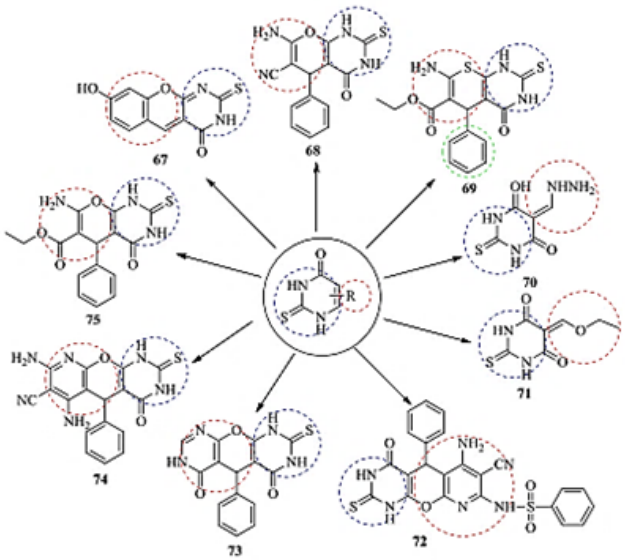


Figure 5: Antifungal activities of Dihydropyridines (Aly et al., 2012).

The new piperazine and morpholine related substituted pyrimidine compounds were created by Rajanarendar et al. as antibacterial medications (Rajanarendar et al., 2010). Using the broth dilution procedure, the newly produced compounds were tested for in vitro antibacterial activity against several kinds of Gram-positive and Gram-negative bacteria. The findings demonstrated that the compounds were significantly more efficient than the often-prescribed antibiotic Ciprofloxacin at killing germs.

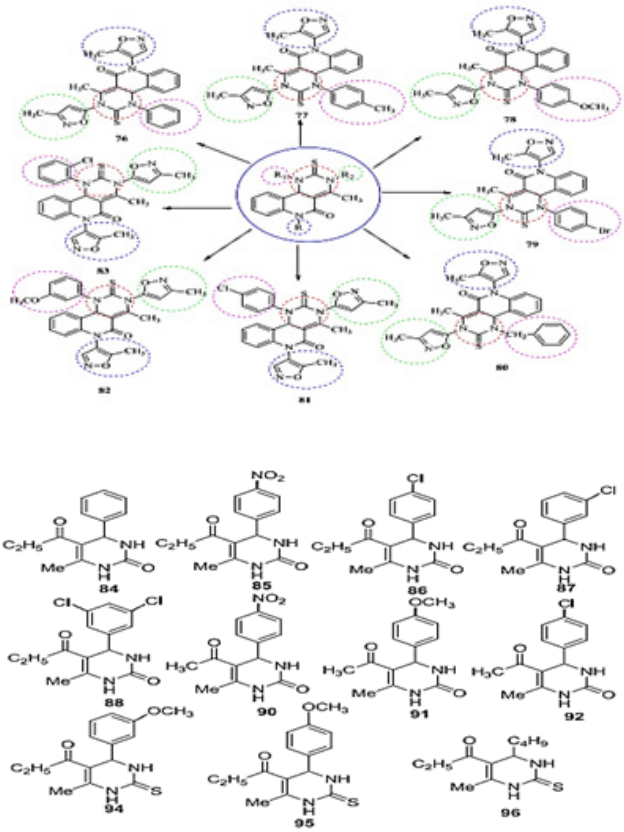


Figure 6: Antibacterial activity of dihydropyridines.

Antibacterial activity of dihydropyridines.

Antibacterial activity of the produced molecules (84e96) was also demonstrated. These medicines were examined using the disk diffusion test, and the zone of inhibition was determined. In a laminar flow hood, nutritional agar (25 mL) is aseptically added to petri dishes as part of the test method. 100 mL of the fresh culture was then put on top of the plates' hardened medium once it had solidified. The plates were then laminarly dried for a short while. Five straightforward, sterile disks with varying concentrations of test solution (*250.000e15.625 ppm) were placed into the plate, dried, and then filled with the test solution. All of the substances had inhibitory activity that was between moderate and excellent. The range of 31,250e15,625 ppm was found to be the acceptable limit for the MIC of compounds 86, 87, 88, and 89 against E. coli. The remaining compounds had MIC values extending since 62.5 to 125.0 ppm, however compounds 94, 95, and 96 had MIC values of 250 ppm and were completely inactive. Compounds 87, 88, and 92 had MIC values that were in line with the norm and were effective against S. aureus. The presence of halogen atoms in compounds 86, 87, and 88 may have contributed to their significant antibacterial effect overall against every microorganism. Comparatively to compounds 86 and 87, compound 88 was shown to be more efficient against bacteria with lower MICs. This is because compound 88 has two halogen atoms, which tend to increase the antibacterial action. Sondhi et al. created a few mono, bi, and tricyclic pyrimidine compounds in 2005 and tested them for their analgesic potential. They created 10 compounds and used the phenyl quinone writhing test to screen them. Ibuprofen was used as a reference medication to compare the evaluated compounds' analgesic efficacy (Sondhi et al., 2005). At a dosage of 100 mg/kg, the synthetic compounds 113, 114, and 115, respectively, showed 100%, 70%, and 75% activity. The makeup of potent compounds is shown in Fig. 7.

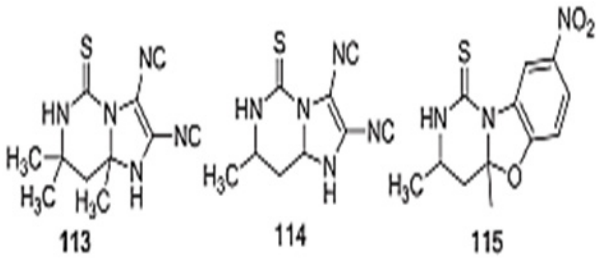


Figure 7: dihydropyrimidines structures with analgesic effects.

Using the 2,2-diphenyl-1-picrylhydrazyl method, Kumar et al. in 2009 synthesized 32 compounds and assessed each one's antioxidant properties (Kumar et al., 2009). Out of the 32 title compounds, compounds 126 and 127 discovered to be among the strongest compounds. With an IC50 value of 58 and 63 mg, respectively, the 3-nitro phenyl moiety at the fourth position of the dihydropyrimidine demonstrated a strong antioxidant action. When they interact with hydrogen donors, the DPPH free radicals generated during this experiment will be reduced to a matching hydrazine. The absorbance decreased and was measured. The 96-well microtiter plate was used for the test. In the presence of antioxidant molecules, the black DPPH radical solution changes into yellow diphenylpicrylhydrazine, causing the solution's absorbance to decrease. Different test solution concentrations, such as 100 mg/mL, 50 mg/mL, 25 mg/mL, and 12.5 mg/mL, were added to test tubes, and the volume was then adjusted to 3 mL using methanol. Separately, 1 mL each of the sample, standard, and DPHH solution were combined (0.1 mM). After being vortexed, the samples were kept in the dark for 30 minutes. It was possible to measure the shift in absorbance at 517 nm using a spectrophotometer. It is claimed that substances do not exhibit antioxidant action at lower concentrations.

Dihydropyridine with anticancer activity

The interaction of the pyrimidines and their derivatives with several enzymes and the anticancer action is brought on by tyrosinase, cytochrome P450, glutathione assistance, and receptors like somaostatin, estrogen, and progesterone receptors. Dihydropyridines are heterocyclic substances created by the Hantzsch dihydropyridine synthesis method, which entails the condensation of two beta ketoesters and two

aldehydes (Kaur et al., 2017). According to a review of the literature, N-containing heterocyclic compounds have attracted a lot of attention lately because of their powerful biological and pharmacological characteristics. The biological relevance of the 1,2,3-triazole moiety has been demonstrated in the production of powerful compounds with a range of properties, including those that are antioxidant, antibacterial, antifungal, anti-HIV, anti-inflammatory, antitubercular, and anticancer (Kumar et al., 2009). This is due to the 1,2,3-triazole's capacity to quickly connect with a variety of enzymes and receptors via a variety of linkages. It is common practice to produce 1,2,3-triazoles via the click reaction, often referred to as the Huisgen 1,3-dipolar cycloaddition process utilizing organic azides and alkynes in the presence of copper (I) catalyst. However, 1,4-dihydropyridines (DHP) are a crucial N-containing heterocyclic scaffold that exhibits a number of biological actions, including calcium channel antagonist, anticancer, anti-inflammatory, antibacterial, antihistamine, anticonvulsant, and analgesic properties. The particular quality of the DHP scaffold is the ability to structurally vary by placing different chemical substituents in various places of the DHP ring, leading to significant pharmacological profile alterations. Due to long-standing interest in and competence in this subject, it was also discovered that 1,4-dihydropyridine-based compounds facilitate the production of bioactive molecules with better and wider biological activity, such as anti-tubercular and cancer reversers (Kaur et al., 2017). More focus has recently been placed on the synthesis of hybrid bioactive compounds made up of two or more heterocyclic scaffolds in the preceding few years. According to studies, new hybrid compounds that are more effective as medications than their parent molecules are formed when two heterocyclic scaffolds with different biological functions are joined.

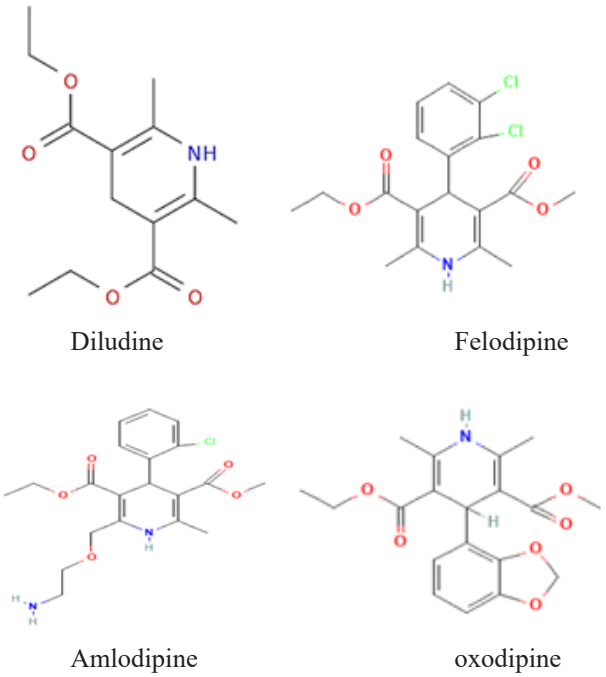


Figure 8: Illustrates a variety of DHP derivatives and their anticancer properties.

Colorectal cancer and dihydropyridines

Researchers have created derivatives of hexahydropyrimidine (Agbaje et al., 2011). Seventeen molecules in all were created, and the resultant compounds were evaluated for their capacity to cause cytotoxicity in the COLO 320 cell line (Agbaje et al., 2011). Only four of the seventeen molecules in the series (128, 129, 130, and 131) were discovered to be powerful analogs. With IC50 values of 11.5, 9.3, and 9.9 mM, respectively, the compounds 128, 129, and 130 demonstrated the maximum activity. With an IC50 of 14 8.1 mM, compound 130 was discovered to be the most powerful chemical. The anticancer research revealed that chemicals 128, 129, 130, and 131 offer potential development leads. Figure 9 displays the architectures of powerful compounds together with their IC50 values.

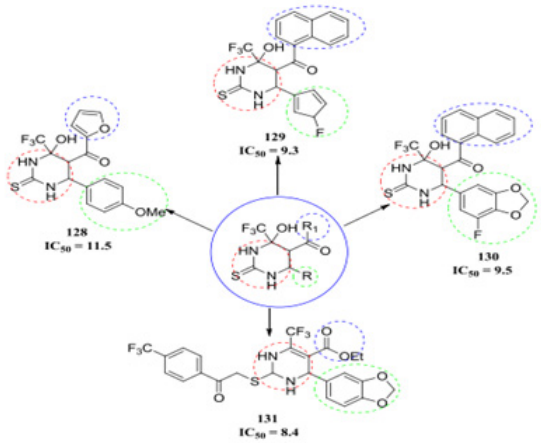


Figure 9: Dihydropyrimidines compounds against colon cancer

The varied colors used to distinguish the many replacements on the fundamental ring. Colon cancer one of the deadliest illnesses in the world, ranks third in terms of cancer morbidity and second in terms of cancer death. The 5-year relative survival rate of CRC patients is still poor despite major improvements in surgical techniques and CRC medicines over the past few decades (Xi & Xu, 2021). Therefore, it is critical to comprehend the molecular processes that control the development and spread of CRC. Numerous studies have shown that the formation and progression of certain malignancies are also directly tied to the instigation of calcium channels. The use of therapeutic methods to shut down calcium channels in tumors is becoming more popular. Nowadays, the main treatment for high blood pressure is the use of calcium channel blockers, which predominantly target L-type calcium channels in vascular smooth muscle cells. The L-type calcium channel, a kind of voltage-gated calcium channel (VGCC) that controls calcium inflow in response to membrane depolarization, is present in the majority of neurons, muscle cells, and neuroendocrine cells (Xi & Xu, 2021). More and more people are turning to therapeutic techniques to block calcium channels in malignancies. At the moment, calcium channel blockers mainly influence vascular smooth muscle cells. High blood pressure is mostly treated using L-type calcium channels. The L-type calcium channel, a kind of voltage-gated calcium channel (VGCC) that controls calcium

inflow in response to membrane depolarization, is present in the majority of neurons, muscle cells, and neuroendocrine cells. There are two kinds of high (L-, N-, P/Q-, and R-types) and low (T-type) voltage-activated channels. There are just a few therapeutic applications for calcium channel inhibitors, and it is still unknown how they impact tumor growth and immune regulation (Cain et al., 2012).

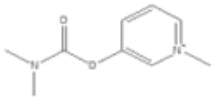
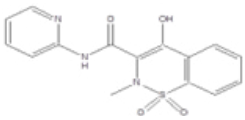
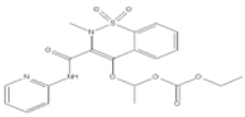
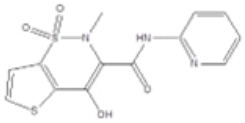
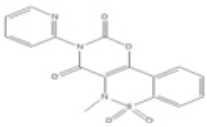
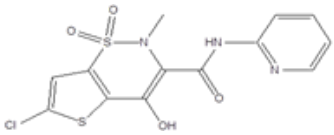
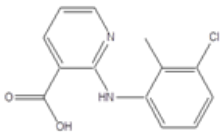
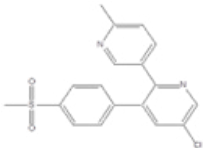
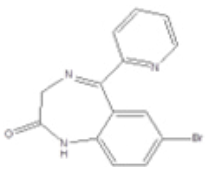
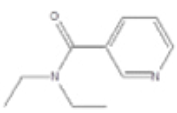
The dihydropyridine L-type calcium channel blocker nifedipine (NIFE), one of the most efficient and secure therapies for all types of hypertensions, is listed on the World Health Organization (WHO) list of essential medications. By NIFE, Ca2+ influx is reduced. So often is it the sole option for the therapeutic long-term usage of antihypertensive medications (Wu et al., 2020). It may be demonstrated how NIFE has anticancer properties using a case study that was released in Lancet in 2001.

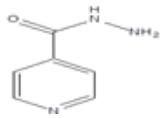
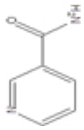
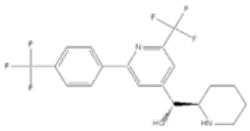
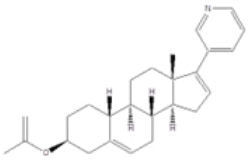
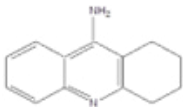
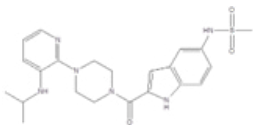
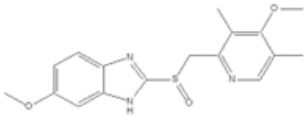
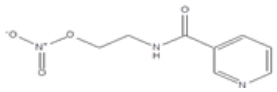
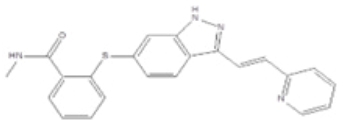
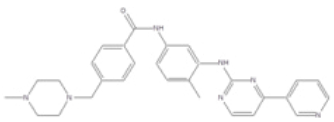
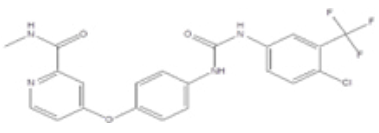
Following then, researchers' attention has been gradually drawn to NIFE's anticancer properties (Hu et al., 2016). Though its direct anticancer effect and mechanism are unclear, recent research on NIFE in malignancies has been concentrated on treatment resistance. Numerous studies have shown that NIFE suppresses the growth and invasion of CRC cells. Calcium channel blockers significantly decreased the growth and spread of CRC nodules, and studies in mice indicated that they also lengthened mice's lives (Hu et al., 2016). According to reports, NIFE also stimulates lymphocytes to reawaken tumor immunity, allowing for complete CRC prevention and therapy based on both the tumor and tumor immunity. By preventing the manufacture of PD-L1 in tumor cells and the expression of the co-inhibitory receptor Programmed Cell Death-1 (PD-1) in T lymphocytes, NIFE replicates the actions of PD-1/PD-L1 inhibitors in tumors, enhancing the immune identification of tumor cells by T lymphocytes (Valentini et al., 2018).

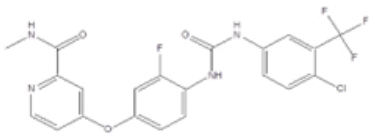
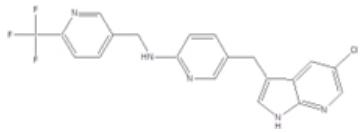
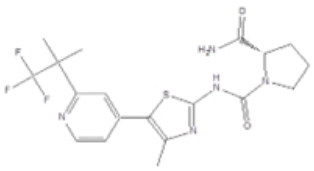
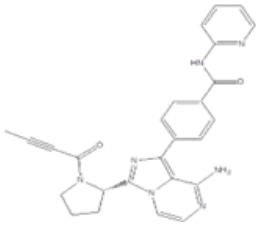
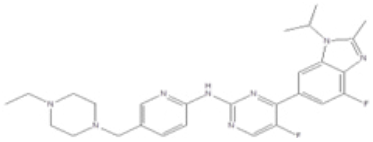
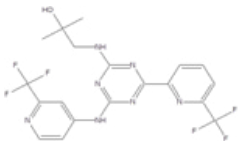
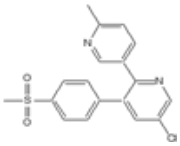
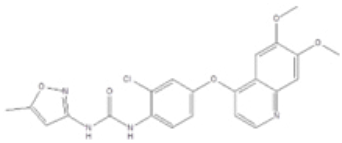
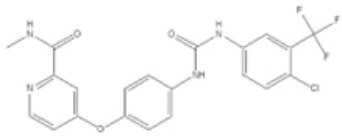
Amlodipine was shown in another investigation to be involved in preventing the formation of CRC cells that are aggressive. The modulatory action of amlodipine may be due to calcium channel blockage as well as suppression, or at the at least, intracellular calcium release, which may contribute to the development of CRC. Additionally, the cell cycle arrest of CRC cells may help to explain other findings regarding the anti-proliferative effect of amlodipine (Alqudah et al., 2022).

Application of DHPM derivatives on colon cancer

Every nation struggles with the serious public health issue of cancer. According to statistical statistics, cardiovascular illnesses continue to be the leading cause of disease-related mortality, but malignant neoplasia has a tendency to overtake them (ReFaey et al., 2021). Unfortunately, normal, actively growing tissues are frequently and severely affected negatively by conventional cytotoxic chemotherapy. This is a key consideration for selecting the best chemotherapy and determining the effectiveness of the therapeutic intervention. Therefore, it is a crucial and real duty to design effective and focused anticancer medications (Schirrmacher, 2019). Although little is known about how protein kinase inhibitors influence the body, they are an example of a focused therapeutic therapy that has a high selectivity to malignant cells and little harm. Particularly, there is a severe lack of information about the histology of cancer patients' healthy tissues. Therefore, the development of innovative targeted protein kinase inhibitors, thorough in vivo testing, and in-depth investigation of side effects are necessary. Considering major advancements in detection and treatment, malignancy remains the second leading cause of death globally. There were around 10.0 million cancer-related deaths in 2020 alone (Xi & Xu, 2021). The WHO predicts that by the end of 2030, this number will increase to 13.1 million if the current trend holds. Cancer continues to be a major research topic due to medication resistance and the toxicity of its treatments. To address these issues in cancer therapy, additional medication research and development initiatives are necessary. Since they still display important biological characteristics, heterocyclic compounds continue to be desirable candidates for synthesis. Particularly dihydropyrimidinones (DHPMs) are quite well known for its wide range of bioactive components. Applications for DHPMs are crucial in the realm of drug development since they are important. Cytosine, which can be found in both DNA and RNA, uracil, which can be found in RNA, and thymine, which can be found in DNA, are the three pyrimidine derivatives that make up nucleic acid bases (Xu et al., 2017). Monastrol's structural analogues are found in the DHPM family of chemicals. Because of the numerous biological actions, they are crucial to medicinal chemistry. Intriguing biological properties like antiviral, anticancer, and antibacterial properties, as well as calcium channel modifying properties, are also present in these molecules. The main character of the DHPMs class is Monastrol. Apoptosis results from the inhibitory effect of DHPM on human kinesin Eg5, according to several studies. Monastrol has inspired medicinal chemists to create innovative anticancer medications based on the DHPM scaffold or its modification with other substituents (Gong et al., 2015). Compounds 1, 2, and 3 have extensive substitutions (R1, R2, R3, R4, and X) applied to various ring sites in order to get crucial anticancer specialists. The creation of medications that stop the mitotic phase of cell division is a popular strategy in cancer treatment. Cancer treatment makes the mitotic spindle a key target, and kinesin Eg5, a key spindle motor protein, is viewed as a crucial targeted therapy because of its unique function during mitosis in assembling. DHPMs which have recently been discovered to selectively block Eg5 activity, are substances that do this. Because mitotic kinesins play a unique role in the formation of the mitotic spindle, the inhibition of Eg5 by DHPMs is a promising strategy for the treatment of cancer. DHPMs, has key biological features like anticancer, antibacterial, antiviral, and anti-inflammatory actions. As a result, organic and medicinal chemists are paying increasing attention to the synthesis of DHPMs and their derivatives. Many different synthetic procedures have recently been revealed for the production of DHPMs. The first synthesis of DHPMs was described in a three-component, one-pot condensation of alpha-ketoesters, aldehydes, and urea under very acidic conditions (Matos et al., 2018).

S.No.	Drug	Indication	Mechanism
1	 Pyridostigmine	Myasthenia gravis	AChE inhibition
2	 Piroxicam	Arthritis	COX inhibition
3	 Ampiroxicam	Anti-inflammatory	COX inhibition
4	 Tenoxicam	Rheumatoid arthritis and osteoarthritis	COX inhibition
5	 Droxicam	Rheumatoid arthritis and osteoarthritis	COX inhibition
6	 Lornoxicam	Rheumatoid arthritis	Inhibition of both COX1 and COX2
7	 Clonixin	Arthritis, migraine, and tissue disorders	COX inhibition
8	 Etoricoxib	Analgesic	Inhibition of COX2 isoform 2
9	 Bromazepam	Anxiety	Binds to the GABA-A receptor
10	 Nikethamide	Respiratory stimulant	increases the development of tension of a muscle stimulated indirectly at low frequencies and produces a depression of muscular contraction when the stimuli are of higher frequencies

11	 Isoniazid	Tuberculosis	Inhibits InhA, the enoyl reductase from Mycobacterium tuberculosis, by forming a covalent adduct with the NAD cofactor
12	 Nicotinamide	Pellagra	Signaling molecule transcription via NF-κB inhibition of nuclear PARP1
13	 Enpiroline	Malaria	Inhibition of β-hematin formation and hemin peroxidation
14	 Abiraterone	Prostate cancer	Inhibition of the steroidal enzyme CYP17A1 in a selective and irreversible manner
15	 Tacrine	Alzheimer's disease	Accumulation of acetylcholine at cholinergic synapses as a result of inhibition of the hydrolysis of acetylcholine produced by active cholinergic neurons
16	 Delavirdine	HIV/AIDS	It binds directly to viral reverse transcriptase and blocks RNA-dependent and DNA-dependent DNA polymerase activity by disrupting the enzyme's catalytic site.
17	 Omeprazole	Ulcer	Regulates H+/K+/–ATPase of the proton pump, expressed in high quantities by the parietal cells of the stomach
18	 Nicorandil	Vasodilator	Two main mechanisms: an activator, and :as an opener of ATP-sensitive (ATP-dependent) potassium channels
19	 Axitinib	Cancer	Oral VEGFR and kinase inhibitor
20	 Imatinib	Cancer	Inhibition of protein-tyrosine kinase
21	 Sorafenib	Cancer	Inhibition of CRAF, BRAF and mutant BRAF and KIT, FLT-3, VEGFR-2, VEGFR-3, and PDGFR-β

22	 Regorafenib	Cancer	Inhibition of multiple membrane-bound and intracellular kinases
23	 Pexidartinib	Tenosynovial giant cell tumors	Kinase Inhibition
24	 Alpelisib	Cancer	Kinase Inhibition
25	 Acalabrutinib	Lung cancer	Kinase Inhibition
26	 Abemaciclib	Breast cancer	Kinase Inhibition
27	 Enasidenib	Leukemia	Inhibition of the enzyme leads to decreased levels of 2-hydroxyglutarate and promotion of proper differentiation and clonal proliferation of cells of the myeloid lineage
28	 Tivozanib	Renal cell carcinoma	Kinase inhibition
29	 Etoricoxib	Rheumatoid arthritis, osteoarthritis, ankylosing spondylitis	Inhibition of COX2 isoform 2
30	 Sorafenib	Liver carcinoma and advanced renal carcinoma	Targets the Raf/Mek/Erk pathway via inhibition of these kinases, genetic transcription involving cell proliferation and angiogenesis is also inhibited.

A wide range of DHPM compounds were initially developed as a result of the well-known drug monastrol. The Eg5 kinesin is notably blocked by the antimitotic inhibitor monastrol. Cefatrizine, a beta-lactum antibiotic, has the 1,2,3-triazole unit. The medication may be able to affect many targets at once due to the union of these two unique heterocyclic rings into a single molecule (Bidram et al., 2020). Due of their structural properties, the creation of hybrids containing a DHPM or a 1,2,3-triazole ring has lately attracted attention. The 1,2,3-triazole ring is robust and resistant to hydrolysis, oxidation, and reductions. In addition, it could behave as a donor or acceptor for hydrogen bonds, take part in stacking interactions, and be a bioisostere of several important functional groups like amides and esters. The usage of DHPM or 1,2,3-triazole ring hybrids has tremendously aided the development of anti-cancer drugs. In a separate investigation, 21 new 1,2,3-triazole hybrids of the 1,4-disubstituted 1,2,3-trzl-DHPM type were created and examined. Non-small cell lung cancer, cervical cancer, breast cancer, and colon cancer have all been demonstrated to respond well to A549 and SW1573, HBL-100 and T-47D for the breast, HeLa for the cervix, and WiDr for the colon, respectively (Azab et al., 2021).

According to reports, monastrol inhibits the growth of quite a few malignance cell types, including glioma, breast, and renal cell lines. In contrast to taxol, this substance has not demonstrated neuronal cytotoxicity as an antimitotic agent. Due to their extensive spectrum of biological actions, including their anticancer, antiinflammatory, antihypertensive, antiviral, and, most critically, calcium channel modulator properties, DHPMs have recently assumed a key position in medicinal chemistry (Hosseinzadeh et al., 2020). The pharmacological effects of pyridine derivatives are also well documented to include protection against HIV, cancer, bacterial infection and anti-inflammatory, cardiotonic, anti-parkinsonism properties. Several 4,6-diaryl-substituted, tricyclic 2, amino-3-cyanopyridines have shown anticancer activity when tested on the female cell lines for breast cancer T-47D and ZR-75-1. Tumors that are extremely toxic and/or drug-resistant are the consequence of the majority of cancer therapies (Hosseinzadeh et al., 2020). The cytotoxic activity profiles of 2,6-diaryl-substituted pyridine and DHPMs on the human breast adenocarcinoma cell line (MCF-7), stomach adenocarcinoma (AGS), and human embryonic kidney (HEK293) cells have not yet been studied, despite substantial research on pyrimidine and pyridine derivatives. The usefulness of several DHPM compounds in the treatment of colon cancer has been the subject of numerous investigations. Dihydropyrrol derivatives exhibit in vitro cytostatic action against cell lines including HT29, HCT-15, and COLO-205. They were created as new tyrosine kinase ATP-binding site blockers (colorectal cancer). This exemplifies how they could combat cancer.

Discussion

Dihydropyrimidinones are a prototype that exhibit promise in the treatment of a variety of diseases through a number of pathways. Dihydropyrimidinones have changed the chemistry of pyrimidines and purines due to their numerous biological roles, which make them important scaffolds (Kaur et al., 2017). Due to their animosity toward pyrimidines found in nature, they are excellent candidates for the synthesis of a number of successful and successful compounds. Dihydropyrimidinone-containing medications, such as 5-fluorouracil, idoxuridine, methythiouracil, emivirin, and aminophylline, have been discovered and are now being effectively used in the prevention or treatment of a number of illnesses (Ling et al., 2021). The DPHMS and its variants are versatile drugs that have been investigated for a range of conditions, such as those caused by infection, hypertension, HIV, cancer, and other conditions. The researchers examined its SAR as well as binding way using molecular modeling investigations. Furthermore, a rational comprehension of the appropriate substitutions responsible for its efficacy and toxicity may in the future be used as a foundation for finding and resolving the toxicity problems related to dihydropyrimidinones.

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