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A Review Article - Pyrimidines as a Propitious Scaffold for Numerous Bioactive Compounds

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Pyrimidines, Synthesis, Biological Significance.

Abstract
In recent years, the resistance of organisms toward drugs has accelerated at an alarming rate. Hence, the search for newer drugs is incessant. Pyrimidines, six-membered heterocyclic compounds, form the basis of our DNA and RNA. This pharmacophore possesses an extensive array of biological activities, namely antimicrobial, anti-cancer, anticonvulsant, anthelmintic, etc. This review aims at describing recent reports in the field of pyrimidine synthesis along with the pyrimidine-based drugs employed to treat numerous disorders. A detailed summary of the pyrimidine moiety, including its structure, various reactions it undergoes, numerous substituted and fused pyrimidines, along with their biological significance, etc., has been reported. This panoramic study has been undertaken to facilitate a scaffold for discovering newer drugs.

1. Introduction

A microbe's genetic fundamentals bear a distinct signature in the sequence position as well as the lifestyle to which it is inhabited [1]. In recent years, there has been a growing resistance of organisms toward anti-bacterial agents. According to the clinical definition, microbial resistance is observed when a drug, given at the prescribed dose, cannot reach a particular concentration at the target site, which is needed to stop or kill bacterial growth [2]. This poses a significant threat and cause of concern. For example, Methicillin-resistant Staphylococcus aureus (MRSA) is accelerating at an alarming rate [3].

The rationale behind the resistance shown by the microbes can be attributed to various reasons. The resistance of drugs is mobile, i.e., the genes responsible for resistance traits can be transferred among bacteria of different taxonomic groups via mobile genetic elements such as plasmids, bacteriophages, naked DNA, or transposons [4].

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Hence the method of structural modification of existing drugs is employed to overcome the dilemma of drug resistance. This will, however soon reach a dead-end as most researchers and pharma companies work on the existing molecules which are on the verge of saturation, and there is no way but to synthesize a new and novel class of compounds [5]. In this regard, heterocyclic compounds have attracted much recognition [6].

The term "heterocyclics" is conformed to compounds containing atoms apart from carbon in their ring structure. These heterocyclic nuclei possess an outstanding ability to be able to serve as biometrics as well as pharmacophore of reactive nature [7]. Heterocyclic compounds are regarded as one of the major classes of organic compounds since they have shown activity against various types of illness [8]. Various biomolecules such as vitamins, enzymes, proteins, nucleic acid systems, and existing medicinal agents contain the heterocyclic skeleton [9].

One such class of heterocyclic compound is Chalcones. Chalcones (1,3-diarylprop-2-en-1-one) are α,β- unsaturated ketones that possess the reactive ketoethylenic group – CO – CH= CH –. Their biological activity is owed to the presence of this α, β-unsaturated carbonyl system. It has been reported that some derivates of chalcone, as well as substituted chalcones, exhibit many biological properties such as analgesic, antifungal, ulcerogenic, etc. [10]. They constitute a pivotal class of plant metabolites that serve as a basis for the biosynthesis of flavonoids and other compounds. Chalcones can endow some biological activity to the synthesized compound, and upon altering the method of synthesis, chalcones of various cores can be yielded. This is the justification for the great interest of scientists in chalcones [11].

Pyrimidines are one class of compounds that can be synthesized from chalcones. Generally, heterocyclic compounds containing nitrogen atoms have renowned importance in the field of medicinal chemistry has made an immense impact in terms of industrial as well as the biological point of view [12]. The pyrimidine structure contains six atoms in the ring structure, of which two are nitrogen atoms. They, however, do not exist in nature as such. Instead, they are found as derivatives. It has three isomeric diazines, and it constitutes a part of DNA as well as RNA which can attribute to its numerous biological activities [13].

Pinner coined the term-Pyrimidine which is an amalgamation of the words- pyridine and amidine [14].

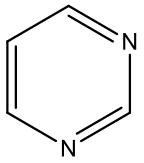

Figure 1: Basic pyrimidine nucleus

Cytosine, Uracil, and Thymine, which are primary components of nucleic acids, contain the pyrimidine nucleus.

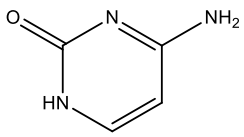

Figure 2: Cytosine

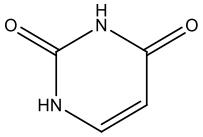

Figure 3: Uracil

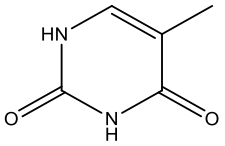

Figure 4: Thymine

Alloxan, an antidiabetic agent discovered by Justus von Liebig and Friedrich Wöhler was initially synthesized by oxidation of uric acid with the help of nitric acid and also contains a pyrimidine nucleus.

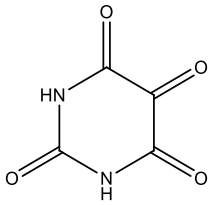

Figure 5: Alloxan

Many detailed reviews have been published regarding the synthesis of substituted pyrimidines. In all the synthesis methods, one of the below four routes of condensation is employed to yield the pyrimidine nucleus [14].

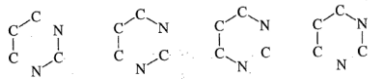

Figure 6: Routes of condensation

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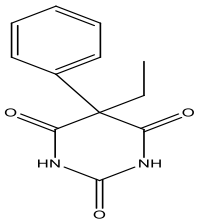
Amongst these, the most commonly used method is condensing a three-carbon compound with a compound containing an N-C-N fragment.

Pyrimidines can fuse with other heterocyclic rings, wherein are referred to as fused pyrimidines. One such example of fused pyrimidine is purine which possesses a remarkable range of biological activity [15].

A vast majority of organisms generate pyrimidines via the de novo pyrimidine synthetic pathway, while the Uracil salvage pathway is availed by the rest [16]. Pyrimidines have a minimal π electron density greater in extent than that of the pyridine molecules. This is why the ease of nucleophilic substitutions of pyrimidines, while electrophilic aromatic substitution proves to be less facile. Protonation/ alkylation occurs at only one ring of nitrogen of the pyrimidine. The basicity, also known as the lone pair electron density, is also lesser in pyrimidines than in pyridines [17].

An extensive literature survey highlights various pharmacological activities of compounds containing pyrimidine nuclei. For example, Barbiturates like phenobarbitone containing pyrimidine nuclei in their structure possess sedative, hypnotic, and anticonvulsant properties; the anti-cancer activity of 5-Fluorouracil is also observable [18].



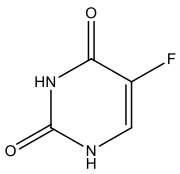


Figure 7: Phenobarbitone Figure 8: 5-Fluorouracil

Pyrimidines also interfere with the synthesis and role of nucleic acids. For example, Zidovudine which is an anti-HIV drug, possesses the Pyrimidine pharmacophore and acts by inhibiting the nucleoside reverse transcriptase enzyme [19].

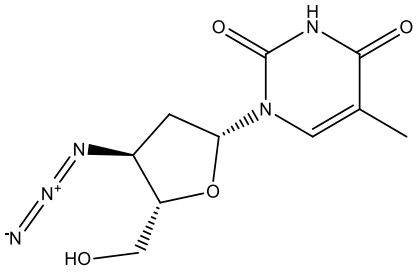


Figure 9: Zidovudine

Apricitabine, Broxuridine, also antiretroviral drugs, contains pyrimidine moiety.

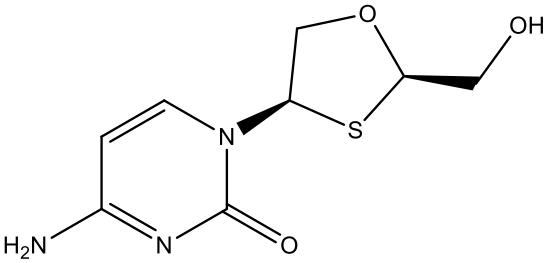


Figure 10: Apricitabine

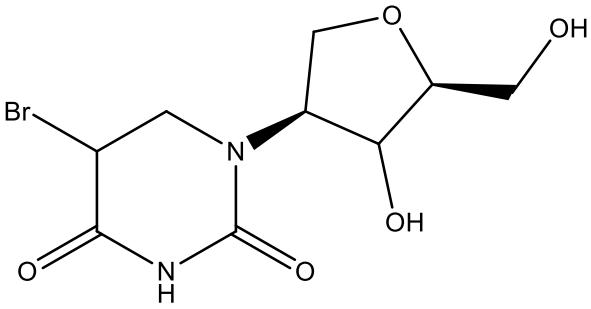


Figure 11 :Broxuridine

5-iodo-2'-deoxyuridine, also finds use in treating numerous viral infections.

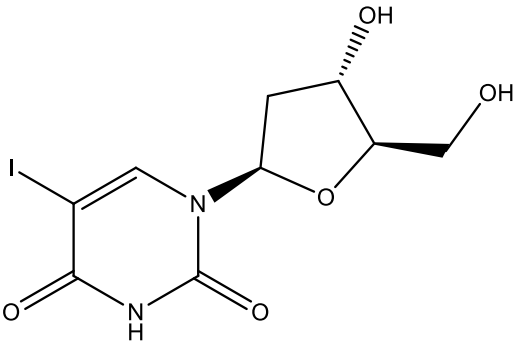


Figure 12: 5-iodo-2'-deoxyuridine

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Fervenulin, and Hexidine are antibiotics also owe their efficacy to the pyrimidine pharmacophore [20].

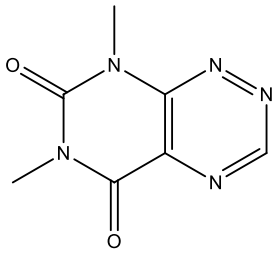


Figure 13: Fervenulin

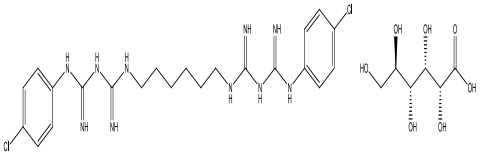
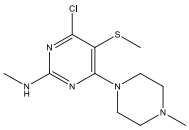


Figure 14: Chlorhexidine gluconate

Pyrimidines fused with other heterocycles are of high regard as potential bioactive molecules. These fused compounds demonstrate anti-cancer, antidepressant, antioxidant, and antiviral efficacy. For example, drugs such as Mezilamine, and Risoperidone possess the antipsychotic activity and are used to treat schizophrenia, autism-related irritability, etc. [21].



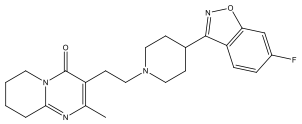


Figure 15: Mezilamine **Figure 16**: Risoperidone

Isolation of uric acid by Scheele in 1776 led to the commencement of chemistry of fused pyrimidine moieties [22], the most significant of them being purines and pteridines [23].

A few naturally occurring pteridine derivatives include xanthopterin [24] isoxanthopterin [25], and leucopterin [26], which are present in the wings of butterflies. From the medical point of view, Riboflavin prescribed for vitamin B2 deficiency contains pteridine ring [27].

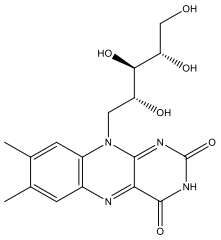


Figure 15: Riboflavin

Leucovorin, indicated for the treatment of osteosarcoma, also bears the same nucleus.

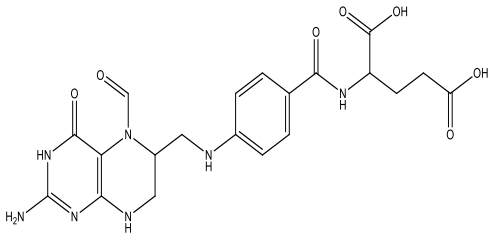


Figure 16 : Leucovorin

Gefitinib, Tandutinib also show anti-cancer efficacy.

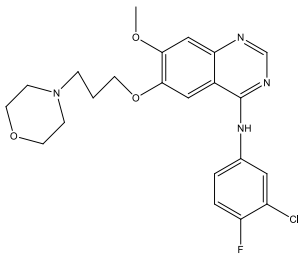


Figure 17: Gefitinib

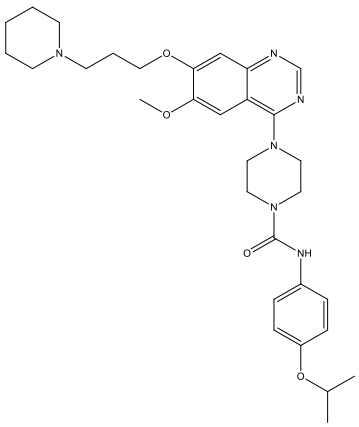


Figure 18: Tandutinib

Edema caused by liver cirrhosis, and congestive heart failure has been known to be treated by Triamterene,

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chemically known as 6-phenylpteridine-2,4,7-triamine [28].

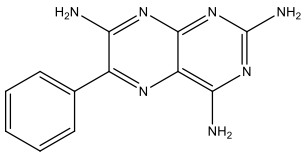

Figure 19 : Triamterene

Herpes infection of various body parts such as the skin, eye, etc can be treated with a relatively recent antiretroviral drug, Ara-A.

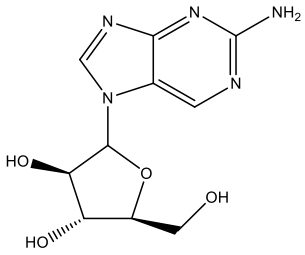

Figure 20: Ara-A (Adenine 9-β-D-arabinofuranoside)

The importance of fused pyrimidines in other fields, such as antithrombotic, antiplatelet, anti-cancer drugs, has led to the notion that further exploration of these derivatives is substantial [29].

2. Methodology

Pyrimidines as an antidepressant agent

Antidepressants represent a class of compounds that amend the chemical imbalance of the neurotransmitters present in the brain. Though there are many types of antidepressants, they primarily act on serotonin, norepinephrine in the brain, thereby restoring the chemical balance [30].

Sindhu et al. reported the synthesis and accounted for the anti-depressant activity of pyrimidine derivates using the in-vivo method of forced swimming test and tail suspension method with comparison against Fluoxetine HCl as the standard drug. Pyrimidines, synthesized from the chalcones of substituted acetophenone and benzaldehyde, were made to undergo Mannich reaction with various secondary amines to yield a series of compounds.

The following compounds (Figure 21 and Figure 22) showed significant antidepressant potential [31].

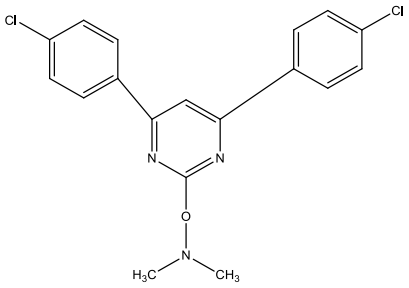

Figure 21: Test compound 1b(N-(4,6-bis(4-chlorophenyl)pyrimidin-2-yloxy) methyl) –N-ethylethanamine)

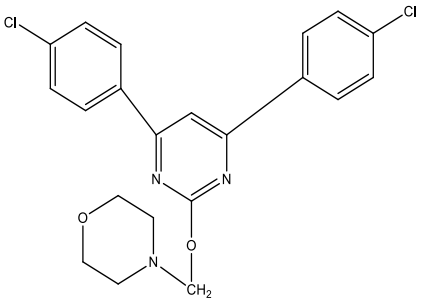

Figure 22: Test compound 1c4-(((4,6-bis(4-chlorophenyl)pyrimidin-2- yl) oxy)methyl)morpholine

Pyrimidines as antimycobacterial agent

Primarily, *Mycobacterium tuberculosis*, *M. bovis*, and *M. africanum* cause tuberculosis in humans. When a susceptible host inhales a carrier of the bacteria, it gives rise to infection [32]. Antimycobacterial drugs act rapidly on the above-mentioned freely replicating bacterial species and arrest their growth and development [33].

The synthesis and antimycobacterial activities of newly synthesized pyrimidines were reported by **Amit R et al**. The synthesis was done by employing the condensation of ethyl 2-(4-carboxyphenylazo) acetoacetate with various aromatic aldehydes in ethanolic NaOH solution to yield chalcones which, on further reaction with urea in an essential ethanolic medium resulted in the formation of pyrimidine derivatives. Assessment of the antimycobacterial activities of the synthesized compounds was carried out against *Mycobacterium tuberculosis* H37Rv.

The results showed that almost all the synthesized pyrimidines possessed good antimycobacterial activity (Fig.23) [34].

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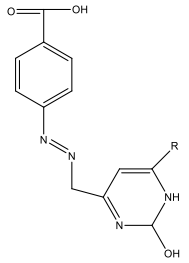
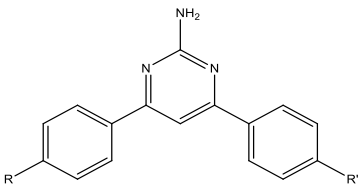


Figure 23: Substituted pyrimidines with good antimycobacterial activity

K Umaa et al. reported synthesizing and evaluation of anti-bacterial and antitubercular activities of some novel aminopyrimidines. Chalcones were first synthesized using acetophenone and benzaldehyde. After that, an equimolar concentration of chalcone and Guanidine Carbonate was refluxed for 6 hours, and the novel aminopyrimidine was obtained after recrystallization. Anti-bacterial activity of the synthesized compound was evaluated against Gentamycin as the standard, using Kirby bauer method against *Staphylococcus aureus, Pseudomonas aeruginosa*and *Escherichia coli*. The compounds were also screened for their anti-tubercular potential using Alamar blue assay technique with Isoniazid as the standard drug. The test organism used was *Mycobacterium tuberculosis* H37 RV strain maintained on Lowenstein Jensen medium. The results depicted that the synthesized compounds possessed insignificant anti-bacterial activity; however, three of the compounds, namely, [(2-amino-4,6-(4,4'-dichloro phenyl)pyrimidine, 2-amino-4-phenyl-6-(4-methoxyphenyl)pyrimidine, 2-amino-4,6-(4,4'-methoxy phenyl)pyrimidine)] possessed high anti-tubercular activity and were found to be equipotent to Isoniazid (standard drug) (Fig.24) [35].



R-Cl R'-Cl

R-OCH_3 R'-H

R-OCH_3 R'-OCH_3

Figure 24: Substituted pyrimidines with anti-TB activity

Pyrimidines as an analgesic and anti-inflammatory agent

Inflammation can be termed as a process of complex and defensive nature, which is primarily characterized by redness, pain, swelling of the area as well as site-specific function loss [36]. At the time of inflammation, the production of reactive oxygen species accelerates when free radicals act on molecular oxygen, which thereby causes an imbalance between the body's antioxidant system and the oxidizing molecules. As a result of oxidative stress, cellular components get damaged [37]. Literature review suggests that many drugs containing the pyrimidine nucleus with analgesic and anti-inflammatory efficacy.

Vishal D et al. synthesized various novel pyrimidine derivatives chalcones and evaluated their anti-inflammatory and analgesic activity. The synthesis of the chalcones was carried out with the help of Claisen condensation reaction between Furan-2-carbaldehyde and variously substituted acetophenones. The chalcones thus obtained were then refluxed with urea, thiourea, and guanidine hydrochloride to yield multiple pyrimidines. The structures of the compounds that were synthesized were analyzed through IR, NMR, and Mass spectroscopy. Carrageenan-induced paw edema and Rat caudal immersion method were used to evaluate the anti-inflammatory and analgesic activity, respectively. The results depicted that the following synthesized pyrimidines (Fig.25,26) had good anti-inflammatory and analgesic activity [38].

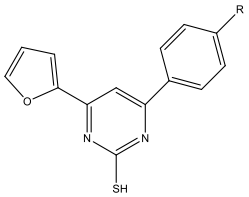


Figure 25: Compound D2: R- Cl

Compound E2: R- F

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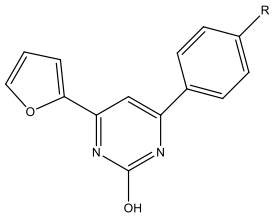

Figure 26: Compound D1: R- Cl

Compound E1: R- F

Synthesis of chalcones using the precursor 4-acetylpyridine and various aromatic aldehydes and thereby synthesizing novel pyrimidines from the chalcones obtained was reported by **Monica K et al. (2014).** The cyclization of chalcones with urea, thiourea, and guanidine HCl acquired the pyrimidine analogs. 1HNMR,13CNMR, Mass spectra, and IR characterized the synthesized compounds. Anti-tubercular, anti-bacterial and anti-inflammatory activities of the synthesized pyrimidines were assessed. It was reported that 4-fluoro substitution on the 2-amino pyrimidine analog showed commendable anti-tubercular activity at low concentrations. It exhibited good anti-bacterial and anti-inflammatory activity (Fig.27) [39].

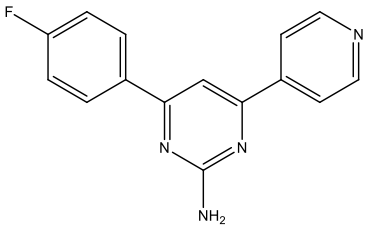

Figure 27: 4-(4-Fluorophenyl)-6-pyridin-4-yl-pyrimidin-2-ylamine

Wesam et al. (2018) reported the synthesis and the evaluation of anti-inflammatory & antioxidant properties of novel fused pyrimidine derivatives using chalcones as the precursor moiety. Chalcones were synthesized through Claisen condensation using 3-acetylpyridine and thiophene 2-carboxaldehyde , which then yielded pyrimidinthiol derivative on reaction with thiourea. These were then made to react with hydrazine hydrate to give 2-hydrazinylpyrimidine derivative. This was used as a scaffold to synthesize the other derivatives. In-vitro COX-1 and COX-2 inhibition using a screening assay kit were performed to assess the anti-inflammatory activity with Celecoxib as a standard reference drug. In-vivo studies too were done by employing Carrageenan-induced rat paw edema method in rats (10mg/kg.b.wt). Lipid peroxidation assay and DPPH free radical scavenging assay were performed to evaluate the antioxidant activity with Ascorbic as the standard drug. It was inferred that the synthesized compounds were equipotent to that of the standard drug. Compound 3 (Fig 28), however demonstrated maximum cyclooxygenase inhibitory potential, thereby possessing a high antioxidant property, and compound 5 (Fig 29) proved to be equipotent to that of the standard [40].

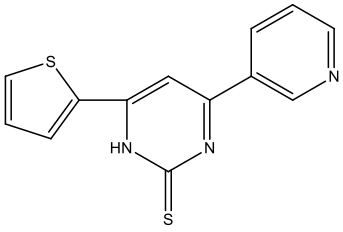

Figure 28: Compound 3

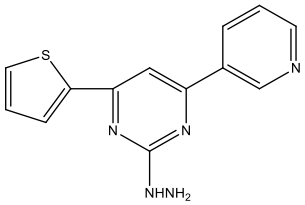

Figure 29: Compound 5

Pyrimidines as muscarinic antagonist

Neurons of the mammalian central nervous system are embedded with both nicotinic and muscarinic types of receptors [41]. Though nicotinic receptors are not known to demonstrate much activity, relaxation of smooth muscle, secretion from the glands, memory, thermoregulation, motor control, etc, are mediated via the muscarinic receptors. Anti-muscarinic agents competitively inhibit the binding of acetylcholine to these receptors and thereby can be successfully utilized in diseases of the heart, anesthesiology, gastric disorders, etc. [42].

Aaron M et al. (2018) synthesized 4,6- disubstituted pyrimidines and evaluated them for their CNS penetrant pan-muscarinic antagonistic activity. After a

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high throughput screening, 4,6- disubstituted pyrimidines were found as a lead molecule as M4 muscarinic antagonist. In one of the synthesis schemes, amide coupling between N-Boc-isonipecotic acid and 1,2,3,4 tetrahydroisoquinoline yielded the disubstituted pyrimidines. Subsequent Boc-deprotection and nucleophilic substitution yielded the final 4,6- disubstituted pyrimidine analogs, which showed many M4 antagonistic activity with a commendable rat in-vivo pharmacokinetic profile. A possible new generation series of compounds were also obtained by one-pot SNAr/methyl ester hydrolysis followed by amide coupling. Among the many synthesized compounds, the isoindoline derivative (Fig 30) was a potent antagonist at both human and rat M4and it also proved to be a pan-mAChR antagonist [43].

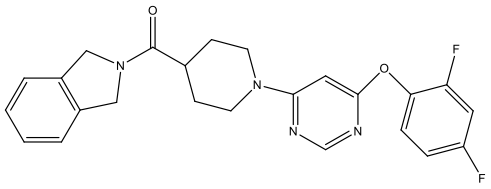

Figure 30: Isoindoline derivative of disubstituted pyrimidine

Pyrimidines as antimicrobial agents

Agents which lead to the fatality of microorganisms or cause retardation of their growth are termed as antimicrobial agents. They may be effective against bacteria, fungi, viruses, parasites, etc [44].

The synthesis of novel pyrimidine derivatives and the evaluation of anti-bacterial and antinociceptive activity, was reported by **Akhlaq et al. (2008).** Chalcones synthesized from 3-acetyl Coumarin, and various aldehydes were employed to produce numerous pyrimidine derivatives. Chalcones, upon condensation with 3-guanidinyl carboxy-7-methyl, 1-ethyl, 1,4 dihydro,1,8 napthyridine-4-one produced a series of pyrimidines. The structures were confirmed through spectral analysis. The biological evaluation inferred that the pyrimidines (especially the ones substituted with p-chloro and 2,4- dichloro) (Fig 31) had considerable activity against the Gram-ve strains, with meta Bromo substitution having the highest activity. Tail flick model was employed to evaluate the antinociceptive activity. It was observed that pyrimidine derivative with bromine at Meta position had the highest activity, while the other derivatives showed considerable activity [45].

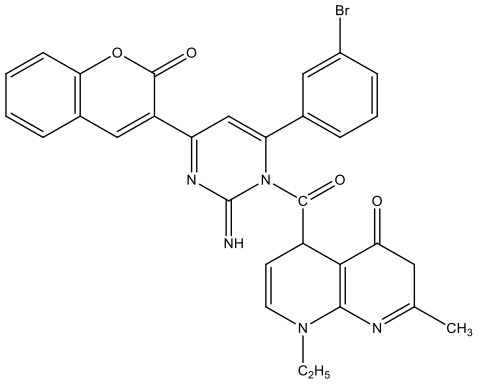

Figure 31: p-chloro and 2,4- dichloro substituted pyrimidine

Eshwara R et al. (2016) reported the synthesis of pyrimidines from chalcones. Initially, the chalcones were synthesized by 24 hours of stirring of equimolar concentrations of 4-imidazolyl acetophenone and variously substituted benzaldehydes along with a few drops of potassium hydroxide. The chalcones obtained were then refluxed with Guanidine HCl and KOH to yield the respective pyrimidine derivatives. The structures of the synthesized compounds were assessed with IR, ^{1}H NMR, and Mass spectroscopy. The anti-bacterial assay against *Escherichia coli*, *Staphylococcus aureus*, was performed per the Disc Diffusion method using Ciprofloxacin as the standard drug. The screening results portrayed that the compounds exhibited significant anti-bacterial activity at both 500µg/ml and 1000 µg/ml concentration levels, with the following pyrimidine (Fig 32) showing maximum activity [46].

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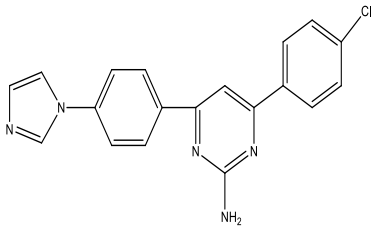


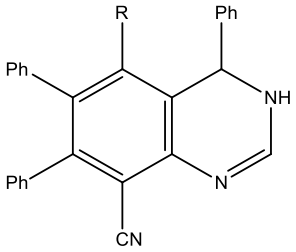
Figure 32: 4-(4-(1H-imidazol-1-yl)phenyl)-6-(4-chlorophenyl)pyrimidine-2-amine

Mistry N et al. (2004) reported the synthesis of Some Novel Heterocyclic Chalcones, Pyrazolines, Pyrimidine - 2 - One, Pyrimidine - 2 - Thione, *para*-Acetanilide Sulphonyl, and Benzoyl derivatives along with their antimicrobial screening. Chlorosulphonation of 1, 2 - Dichloro benzene followed by condensation with p–amino acetophenones and 2,4- dichlorobenzaldehyde and subsequent reaction with 99% hydrazine hydrate and glacial acetic acid yielded 1-[acetyl]-3- [1', 2' - (dichloro) - dibenzsulphonamide] -5 - [2", 4" - dichloro phenyl] - 2 - pyrazoline derivatives. These subsequent reactions with various aldehydes gave rise to corresponding chalcones.

Pyrimidine-2-one derivatives were obtained by the reaction of the chalcones with urea, whereas Pyrimidine-2-thione derivatives were synthesized by the reaction of the chalcones with thiourea. Condensation of Chalcones with 99 % hydrazine hydrate yielded various pyrazolines, which acted as a precursor to obtaining sulphonyl and benzoyl derivatives upon reaction with p-acetanilide sulphonyl chloride and benzoyl chloride, respectively. IR and ^{1}H NMR confirmed the structures of the compounds. The antimicrobial assay was carried out using the cup-plate method wherein the evaluation of the synthesized compounds (at a conc. of 50 µg/ml) was done against *Staphylococcus aureus*, *Escherichia coli*, and *Candela albicans*. Standard drugs employed included, Ampicillin, Penicillin, and Tetracycline. The synthesized compounds showed moderate to good activity [47].

Microwave-assisted synthesis of 3,4-dihydrobenzo[2,3-d]pyrimidines and a screening of antimicrobial potential, was performed and reported by **Kidwai M et al. (2003).**

2-amino-3-cyano-4,5-diphenyl furan and chalcones(0.01mol) were dissolved in ethanol and adsorbed on 20 g of neutral alumina and irradiated in the microwave for 5–6 min to yield 1,3-cyclohexadiene derivatives. These further reactions with formamide under the same reaction conditions yielded various 5-substituted-8-cyano-4,6,7-triphenyl-3,4-dihydrobenzo[2,3-d]pyrimidines. The structures of synthesized compounds were validated through IR and ^{1}H NMR. The Antifungal and anti-bacterial activities of the compounds were evaluated using the paper disc diffusion method and cup diffusion method, respectively. *Aspergillus niger* and *Aspergillus flavus* were the organisms used to assess antifungal activity while *E. coli*, *Rhizobium japonicum*, *Enterobactor aerogenes*, *Burkholderiacepacia*, and *Bacillus mojavensis* were the microorganisms used to evaluate anti-bacterial activity. The following compounds (Fig 33) showed moderate activity [48].



R- C_6H_5

4-CH_3C6H_4

4-CH_3OC6H_4

4-ClC_6H_4

Figure 33: 5-substituted-8-cyano-4,6,7-triphenyl-3,4-dihydrobenzo[2,3-d]pyrimidines

K. H. Chikhalia*et al* **(2007)** synthesized pyrimidine derivatives and evaluated them for their anti-bacterial efficacy. Refluxing of a mixture of 1-(2,4-dichloro-5-fluorophenyl)-3(aryl)-2-propene-1-one(0.05 mole),guanidine nitrate (0.15 mole) and sodium methoxide in methanol for six hours resulted in the formation of 2-amino-4-(2,4-dichloro-5-fluorophenyl)-6-(aryl)- pyrimidine. Anti-bacterial assay of the synthesized compounds was performed through Agar cup method against *S.aureus*, *E.coli*,

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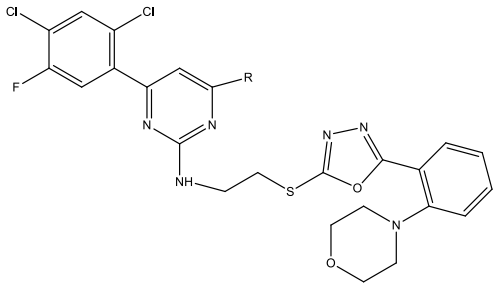
*S.typhi*and *B.subtilis* using Tetracyclin as the standard drug. Results depicted that the following two compounds showed maximum activity against the selected species [49].



R-4-$CH_3C_6H_4$

3,4,5-$(OCH_3)_3C_6H_2$

Figure 34: 2-amino-4-(2,4-dichloro-5-fluorophenyl)-6-(aryl)- pyrimidines

One pot synthesis of novel 1-5 benzodiazepine derivatives containing pyrimidine moiety was reported by **Mishra et al. (2018).** IR, ^{1}H NMR, ^{13}C NMR, and mass spectral analysis confirmed the structures of the synthesized compounds. The benzodiazepines were synthesized from pyruvonitrile and benzoylacetonitrile. *Staphylococcus aureus* (MTCC 9886) and *Escherichia coli* (MTCC 433) were the organisms used to evaluate the anti-bacterial efficacy of the compounds. IC_{50} values were determined, and Field emission scanning electron microscope (FE-SEM) along with Leakage study was performed to confirm the test compound's deleterious potential on the cell membrane. Molecular docking using Argus Lab 4.0 docking software was performed to illustrate the interaction and possible mechanism of association of the synthesized compounds with Dihydrofolate reductase (PDB ID-4XE6) enzyme obtained from *S. aureus*. The results showed that the following compounds (Fig 35, Fig 36) showed significant membrane damaging effects and hence possessed significant anti-bacterial activity [50].

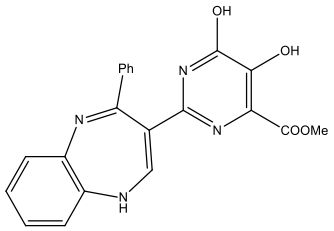


Figure 35 :1-5 phenyl benzodiazepine substituted pyrimidine

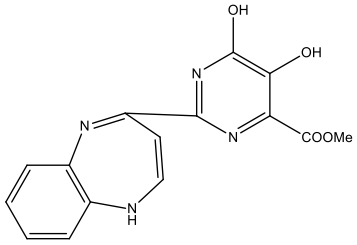


Figure 36:1-5 benzodiazepine substituted pyrimidine

Pyrimidines as Anti-Alzheimer Agents

Alzheimer's disease is a long-term neurodegenerative disorder wherein cognitive functions deteriorate at an accelerating rate, and loss of memory occurs [51]. Various studies over the years have indicated that tau proteins, Amyloid β, and calcium hemostasis contribute to the acceleration of the disease, which ultimately leads to neuroinflammation [52]. Current literature reviews highlight the role of pyrimidines in reducing this neuroinflammation, thereby modifying Alzheimer's [53].

Investigation of chalcones as a lead molecule for radiotracers in Alzheimer's disease was reported by **Hsieh CJ et al. (2018).** Chalcones were synthesized by condensation reaction between 2-acetyl benzothiazole and the substituted benzaldehyde with more focus on 4-OCH_3, 4-$N(CH3)_2$, and 4-NO_2 substitutions. Benzothiazole analogs proved to have an excellent affinity to Aβ fibrils. Further, pyrazole and isoxazole analogs were synthesized. It was concluded that both these derivatives possessed an affinity for Asyn and good selectivity versus Aβ and tau fibrils. Molecular modeling studies were also conducted to examine the properties of the ligands contributing to this selectivity. This led to the identification of the (E)-5-(4-methoxystyryl)-3-(thiazol-2-yl)isoxazole (Fig 37) as a novel lead for the development of PET radiotracers having a good

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affinity for Asyn fibrils and a modest selectivity for Asyn versus Aβ fibrils [54].

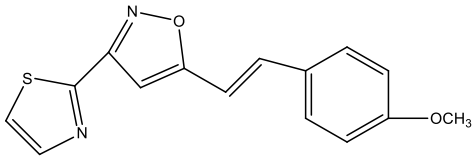
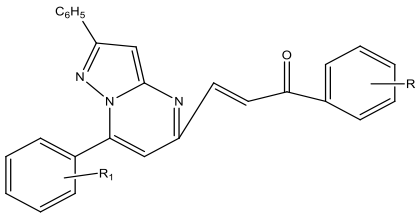


Figure 37: (E)-5-(4-methoxystyryl)-3-(thiazol-2-yl) isoxazole

Pyrimidines as anti-cancer agents

Cancer refers to the uncontrolled and abnormal growth of cells in our body. Since the pharmacophore pyrimidine is a building unit of DNA and RNA, its role as an anti-cancer, antiviral, and antimicrobial agent is well supported via the vast literature available. Furthermore, thiouracil carbonitrile ring has been reported to possess chemotherapeutic activity and is a constituent of many marketed anti-cancer drugs [55].

Synthesis of chalcone linked pyrazolo [1,5-a]pyrimidines and their anti-cancer activity against A549, MDA-MB-231, and DU-145 cell lines, was demonstrated by **Chandrakant et al. (2017).** Condensation of various acetophenones withpyrazolo[1,5-a]pyrimidine-5-carbaldehydes and various aldehydes with 1-(pyrazolo[1,5-a]pyrimidin-5-yl)ethan-1-ones gave rise to two series of chalcone linked pyrazolo [1,5-a]pyrimidines. After evaluating anti-proliferative activity, compounds 6h, 6b, and 6i (Fig 38) showed maximum activity against the MDA-MB-231 cell line with an IC50 of 2.6 µm. Western blot and RT-PCR analyses proved that these series of compounds triggered cell death through apoptosis. Exhibition of the binding mechanism of these compounds to the EFGR of ATP binding sites was done by molecular docking studies [56].



6b: R= 4-OCH_3 R_1=OCH_3

6h: R=3,4-diOMe R_1=3,4-diOMe

6i: R=3,4,5-triOMe R_1=3,4-diOMe Figure 38: Chalcone linked pyrazolo [1,5 a]pyrimidines

Ayyakannu A et al (2015) reported the synthesis of novel furo-pyrrolo-pyrido-pyrimidine derivatives. In-silico docking studies were also performed to evaluate the anti-cancer efficacy of the synthesized derivatives. Schiff bases were synthesized by condensation of furfural and p-anisidine. They were then reduced and condensed with formyl uracil to give Compound-4 : 6-((furan-2-ylmethyl)(4-methoxyphenyl)amino)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydro pyrimi dine-5-carbaldehyde, which when reacted with diethtyl aminomalonate hydrochloride yielded the final compound-6: diethyl 11-(4-methoxyphenyl)-1,3-dimethyl-2,4-dioxo-1,2,3,4,4b,5,10,11-octahydrofuro [2",3":3',4']pyrrolo[2',3':4,5]pyrido[2,3-d]pyrimidine-6,6(6aH)-dicarboxylate via 1, 3-dipolar cycloaddition reaction. IR, NMR analysis confirmed the structures of the compounds.

The binding interactions of the compounds, as well as the standards (5-fluorouracil, methotrexate) with thymidylate synthase, were performed using Autodock v.1.5.6. The results obtained from the molecular docking studies showed that the compounds 4 (Fig 39) and 6 (Fig 40) are having good binding interaction towards thymidylate synthase receptor. Compound 4 had a docking score of -7.0, whereas compound 6 shows -8.7, more significant than standard 5-fluoro uracil (-5.0) and methotrexate (-8.6). It can be inferred from the results that the synthesized compound 6 had an excellent binding interaction with thymidylate synthase and be further examined through in-vitro and in-vivo studies as a potential anti-cancer agent [57].

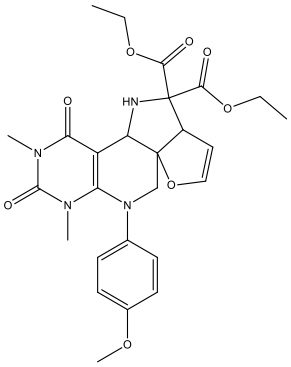


Figure 39: Diethyl 11-(4-methoxyphenyl)-1,3 dimethyl-2,4- dioxo 1,2,3,4,4b,5,10,11

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octahydrofuro [2'',3'':3',4']pyrrolo[2',3':4,5] pyrido[2,3-d]pyrimidine 6,6(6aH)dicarboxylate

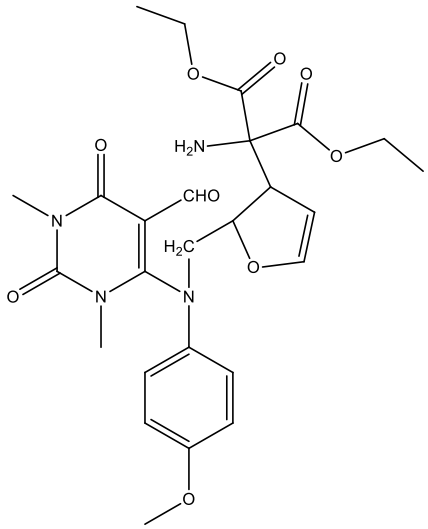
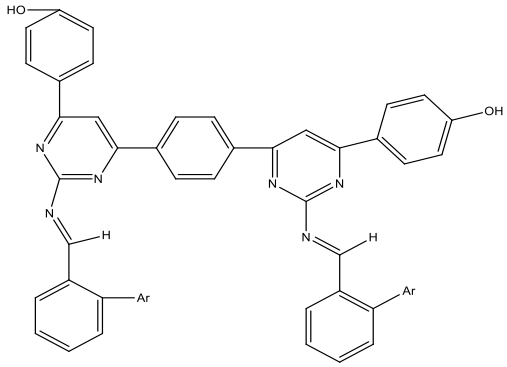


Figure 40: 6-((furan-2-ylmethyl)(4-methoxyphenyl)amino)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydro pyrimi dine-5-carbaldehyde

Kumar et al. (2017) synthesized bis-pyrimidine Schiff base derivatives and screened them for antimicrobial and anti-cancer activity. They also performed docking studies to assimilate the interaction of the synthesized compounds with the receptor. By Claisen-Schmidt condensation, the bis-chalcones were yielded by reacting 1-(4-hydroxyphenyl) ethanone with terephthalaldehyde. Thereupon on the condensation of the bis-chalcones with guanidine HCl, bis-pyrimidines were obtained. The reaction of bis-pyrimidine with corresponding substituted aldehydes yielded the final compounds. $^{1}H/^{13}C$-NMR, FT-IR, mass spectral studies, and elemental analysis established the synthesized compounds. Tube dilution technique was employed to screen the compounds for their antimicrobial efficacy against Gram +ve bacterial species: *Staphylococcus aureus*, *Bacillus subtilis*, the Gram −ve bacterium *Escherichia coli*, and fungal species: *Aspergillus niger* and *Candida albicans* using norfloxacin (anti-bacterial) and fluconazole (antifungal)as the standards. It was observed that the following compounds had activities higher than that of the standard drugs, while the others had moderate activities.



Compound q1: Ar= C_6H_5OH

Compound q19: Ar= $C_6H_5N\ (C_2H_5)_2$

Compound q20: Ar= $C_6H_5OCH_3$

Figure 41: Bis-pyrimidine Schiff base derivatives

The anti-cancer activity was performed against the human colorectal cancer cell line (HCT-116 (ATCC CCL-247) with an inference that the bis-pyrimidine Schiff bases are equipotent to the standard 5-fluorouracil. Molecular docking studies suggested that compound **q1** being the most active molecule, has the most hydrogen bond interactions (four) compared to the other bis-pyrimidine derivatives [58].

Matias M et al. (2017) synthesized and evaluated in-vitro a series of potential antitumoral 3,4-dihydropyrimidin-2- (1H)-thiones via the Biginelli three-component condensation reaction. The reaction mixture containing ZrCl4 (5 mol), a mixture of aldehydes (1mmol), thiourea (1.3 mmol) and β-ketoester/acetylacetone (1 mmol) was heated at 70C with continuous stirring and subsequently cooled and filtered to yield the corresponding 3,4-dihydropyrimidin-2- (1H)-thione derivatives. IR, ^{1}H NMR, ^{13}C NMR, and mass spectral analysis confirmed the structures of the synthesized compounds. *In-vitro* antiproliferative assay performed on various cell lines such as hepatic (HepaRG), colon (Caco-2) and breast (MCF-7) cancer cell lines, demonstrated that compounds containing Chlorine had a profound effect on the proliferation of the cell lines. Also, they showed no signs of cytotoxicity towards the regular dermal cell line. A QSAR model was also developed based on *in-silico* molecular

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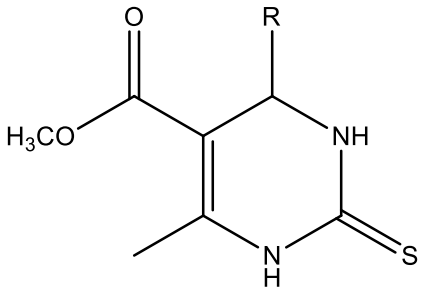
descriptors- BLI, GATS1m, and GATS5v. These models could effectively predict the relative cell proliferation in the cell lines used in this study. Compounds 2 and 15 (Fig 42) were the most potent molecules compared to the other synthesized compounds [59].



Compound 2: R- C_6H_5

Compound 15: R- 2,4-(Cl)$2C_6H_3$

Figure 42: 3,4-dihydropyrimidin-2- (1H)-thiones

Pyrimidines as anticonvulsant agents

When the neurons are fired excessively and uncontrollably, it leads to a neurodegenerative condition known as convulsions. Some marketed anticonvulsants also possess the pyrimidine nucleus, such as Phenobarbital, Hexobarbital, etc. [60-64].

The anticonvulsant activity, as well as the synthesis of some novel pyrimidine derivatives, was reported by **Kikkeri N et al. (2013)**. With 5-bromo-2,4-dichloropyrimidine and hydrazine hydrate as the precursors, various fused pyrimidines were prepared. IR, 1H-NMR, and Mass spectroscopy formed the basis of structural conffirmation. Male Wistar rats (190-220g) were administered the test compounds orally at 100mg/kg. The anticonvulsant activity was tested by MEZ method using Phenytoin as the standard drug. This was followed by neurotoxicity screening wherein the test compounds were evaluated against Phenytoin as standard in Rotorod test method.

The results established that the following compound (Fig 43) having electron-withdrawing groups showed excellent anticonvulsant activity while other compounds showed substantial activity [65].

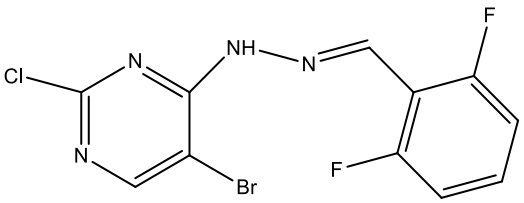
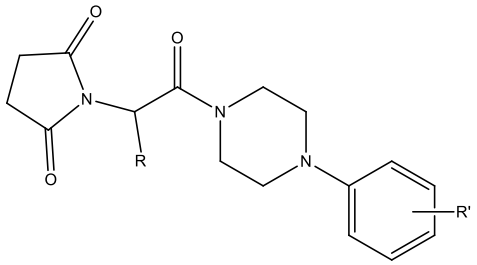


Figure 43: (E)-5-bromo-2-chloro-4-(2-(2,6-difluorobenzylidene) hydrazinyl)pyrimidine

Kaminski K et al (2018) synthesized an array of 1-(4-phenylpiperazin-1-yl)- or 1-(morpholin-4-yl)-(2,5-dioxopyrrolidin-1-yl)propanamides and (2,5-dioxopyrrolidin-1-yl) butanamides derivatives and evaluated them for their anticonvulsant potential. These compounds bore a resemblance to the marketed antiepileptic drugs namely, ethosuximide and levetiracetam. In the first step, the fusion of the alkylamide moiety and pyrrolidine 2,5-dione ring by a two-step condensation reaction was carried out. Subsequently, 3-methoxypropanamide derivatives of the most effective compound from the series of 2-(2,5-dioxopyrrolidin-1-yl)alkylamides were prepared. MES model was employed to evaluate the in-vivo anticonvulsant efficacy followed by scPTZ (subcutaneous pentylenetetrazole) and 6Hz seizure models wherein the compounds were administered to mice at a dose of 300 mg/kg (i.p). Prolonged and satisfactory anticonvulsant activity with an acceptable safety profile was displayed by the following compound (Fig 44) [66].



R-CH_3 R'-3-CF_3

Figure 44: (2,5-dioxopyrrolidin-1-yl) butanamides derivatives

Mohammad R et al. (2015) synthesized a hybrid molecule containing both pyrimidine nucleus and Schiff base. In this regard, 2-mercapto-6-oxo-4-aryl-

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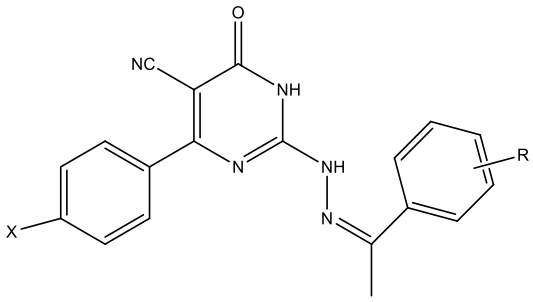
1,6-dihydropyrimidine-5-carbonitrile derivatives were obtained via Biginelli condensation of an aromatic aldehyde, ethyl cyanoacetate, and thiourea using potassium carbonate as a catalyst followed by a nucleophilic reaction using hydrazine hydrate. Dissolving 1 mole of these compounds in acetic acid: ethanol (2:8) followed by the addition of substituted acetophenones resulted in 6-oxo-4-aryl-1,6-dihydropyrimidine-5-carbonitrile derivatives. The structures were evaluated using IR, NMR and mass spectroscopy. In-vivo activity was carried out using Maximal electroshock and Pentenyltetrazole method followed by neurotoxicity of selected compounds using Rotarod test.

The activity of the two below-depicted compounds (Fig 45) proved commendable at a dose of 30 mg/kg in both models. Furthermore, they exhibited no neurotoxicity, even at high doses [67].



X= 4-Cl R= 4-NO2

X= 4-Cl R= 4-Br

Figure 45: 6-oxo-4-aryl-1,6-dihydropyrimidine-5-carbonitrile derivatives

A series of novel 7-substituted-[1,2,4]triazolo[4,3-f]pyrimidine derivatives were synthesized by **Guan et al. (2012)** and evaluated for their anticonvulsant efficacy using Maximal electroshock test. 4-Chloro-6-(4-methoxyphenoxy) pyrimidine was refluxed with hydrazine hydrate and ethanol to yield 1-(6-(4-Methylphenoxy) pyrimidin-4-yl) hydrazine. This on further reaction with triethylorthoester and ethanol resulted in the final substituted pyrimidine compounds. Out of the synthesized compounds, 7-(4-chlorophenoxy)-[1,2,4]triazolo[4,3-f] pyrimidine (Fig 46) proved to be the most effective with a reported effective dose of 34.7 mg/kg and a protective index of 7.6. Low neurotoxicity was ascertained using the Rotarod test [68].

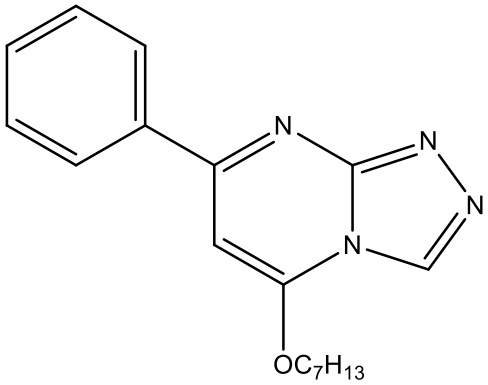


Figure 46: 7-substituted-[1,2,4]triazolo[4,3-f] pyrimidine derivatives

The introduction of triazole molecule into pyrimidine ring structure and evaluation of the synthesized compounds for anticonvulsant activity was carried out by **Nan Jiang et al. (2011)**. 5-Phenyl-[1,2,4]triazolo[1,5-a]pyrimidin-7-ol was synthesized by the reaction of 0.15 mole of 1-phenylpentane-1,3-dione along with 0.2 mole of 2H-1,2,4-triazol-3-amine at 160°C for 2 hours. The compound obtained was refluxed with variously substituted alkyl bromides along with NaOH and DMF to yield 7-Alkoxy-5-phenyl-[1,2,4]triazolo[1,5-a] pyrimidine derivatives. Out of the synthesized compounds, 7-(heptyloxy)-5-phenyl-[1,2,4] triazolo[1,5-a] pyrimidine (Fig 47) proved to have maximum anticonvulsant potency having an effective dose of 84.9 mg/kg [69].

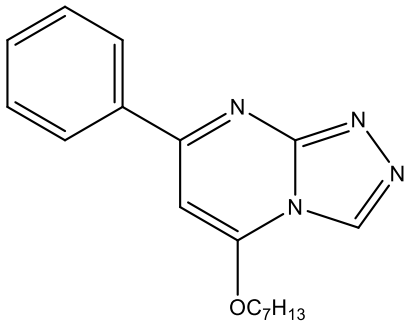


Figure 47: 7-(heptyloxy)-5-phenyl-[1,2,4] triazolo[1,5-a] pyrimidine

Amir M et al. (2013) synthesized derivatives and tested their anticonvulsant efficacy against albino mice. Treatment of anthranilic acid with various aryl/propyl isothiocyanate yielded an intermediate compound which, on reaction with corresponding phenacyl bromide, produced an array of 2-[2-(aryl)-2-oxo-ethyl-sulfanyl]-3-(aryl/propyl)- 3H-quinazolin-4-ones. IR, ^{1}H-NMR, ^{13}C-NMR, and mass spectroscopic

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analysis confirmed the structures of the compounds. MES model employed to evaluate the anticonvulsant showed that all the synthesized compounds had satisfactory activity, with the activity of the following compound (Fig 48) being the maximum [70].

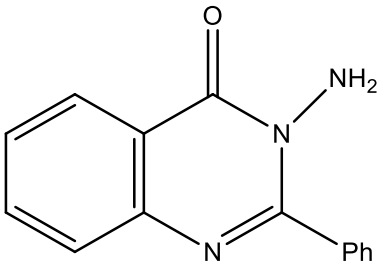


Figure 48: [(4-butoxy-benzylidene)- amino]-2-phenyl-3H-quinazolin-4-one

Pyrimidines as anthelmintic agents

Helminthes comprise one of the most frequently occurring infections in man, affecting many people [71-74]. Anthelmintics help remove parasitic worms from our bodies by either stopping their growth or killing them.[75-78]

David I et al. (2017) reported a method for synthesizing and evaluating the anthelmintic activity of pyrimidine derivatives containing carboxamide and sulphonamide moieties**.**

N-benzoyl substituted benzenesulphonamide derivatives synthesized from the reaction between substituted benzenesulfonamide and benzoyl chloride, were refluxed with 4- or 2-aminopyrimidine (1.0 mmol) and boric acid (0.1 mmol) to yield the novel pyrimidine derivatives. ^{1}H-NMR and ^{13}C-NMR confirmed the structures of the synthesized compounds. Garg and Atal method was performed against *Giardia duodenalis* to evaluate the anthelmintic activity using Albendazole as the standard drug wherein the test compounds were given at a dose of 2mg/ml. Results depicted an increase in anthelmintic activity with an increase in the concentration of the drug. Among all the synthesized compounds, 2-aminopyrimidines were found to have increased activity in comparison to the 4-aminopyrimidine derivatives except 4-hydroxy-1-[(4--nitrophenyl)sulfonyl]-N-(pyrimidin-4-yl)pyrrolidine-2-carboxamide, which has the highest activity [79].

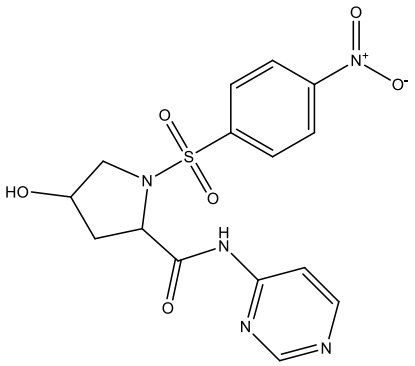
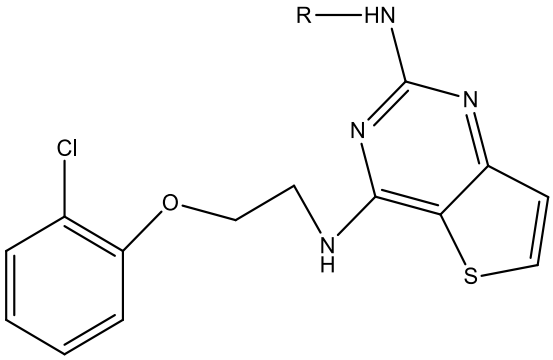


Figure 49: 4-hydroxy-1-[(4- -nitrophenyl)sulfonyl]-N-(pyrimidin-4-yl)pyrrolidine-2-carboxamide

Frederick A et al. (2018) have described the significance of 2,4 Diaminothieno[3,2-d]pyrimidines as anthelmintic agents against ***Trichuris trichiura. The microwave-assisted synthesis used*** 2-chlorothieno[3,2-***d***]pyrimidine and differently substituted amines in an argon atmosphere. The structures of the compounds were analyzed via Mass and NMR spectral analysis. In-vitro and in-vivo studies were done to establish the whipworm infection using 100 infected eggs for in-vitro, and 40 eggs were given to mice for the latter. Results proved that the synthesized DTAPs proved effective against both the adult and egg stage of the worms [80].



R= CH_3

R=CH_2C6H_50

Figure 50: 2,4 Diaminothieno[3,2-*d*]pyrimidines

3. Conclusion:

Employing an extensive and elaborate literature survey led to an inference that pyrimidine moiety possesses a wide range of biological activity, and its

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chemistry will continue to attract attention for scaffolding therapeutically active drugs.

Further structural modification may lead to many compounds capable of treating many disorders.

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