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HETEROCYCLICS AS A MEDICINES

Dr. Nathrao Ankushrao Kedar*

Department of Chemistry, Dayanand Science College, Latur – 413 512, Maharashtra, India.

***Corresponding Author: Dr. Nathrao Ankushrao Kedar**
Department of Chemistry, Dayanand Science College, Latur – 413 512, Maharashtra, India.

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ABSTRACT
Heterocyclic chemistry is a good example of a lack of clear boundaries; in fact, it pervades a wide range of other chemical specialties. Heterocycles are intricately linked to the processes of life. The pharmaceutical and agrochemical industries' keen interest in heterocycles is frequently linked to their natural occurrence. A cornucopia of heterocyclic systems may be found in synthetic chemistry. Heterocyclic compounds are found in more than 90% of novel medications, and they span the boundary between chemistry and biology, where so much new scientific insight, discovery, and application occurs. This review article discusses the most active heterocycles that have demonstrated antifungal, anti-inflammatory, antibacterial, anticonvulsant, antiallergic, herbicidal, and anticancer activity in animals.[1-20]

KEYWORDS: Heterocyclic, nitrogenous base, biological active, antimicrobial, essential, Gram Positive, Gram Negative.

1. INTRODUCTION

Heterocyclic chemistry is one of the most important areas of organic chemistry research. Heterocycles are the most important of the traditional organic divisions of organic chemistry, and their structural Skelton components make them extremely important physiologically and industrially.[21-24] They are common in our environment and can be found naturally in nucleic acid, vitamins, antibiotics, hormones, and other substances. From a biological and industrial standpoint, their contribution to society's evolution is of greater interest.[25-40] Heterocycles are also important in gaining a better knowledge of life processes and efforts to improve quality of life.[41-50] Heterocyclic compounds are found in more than 90% of novel medications, and they span the boundary between chemistry and biology, where so much new scientific.[51-60]

2. MEDICINAL APPLICATIONS

2.1. Anticancer Activity

Cancer is a collection of diseases distinguished by irregular or uncontrolled cell growth with the ability to occupy or spread to other parts of the body. This disease is caused by a variety of agents, including chemical compounds and radiant energy. Several medications are used to cure this disease, either by killing cancer cells or altering their growth.

Liu *et al.* reported the synthesis of phenanthroindolizidine **1** and phenanthroquinolizidine **2** alkaloids for potential use as anticancer drugs with IC_{50} values of 166 nM and 2.1 nM, respectively. The majority of synthesized compounds exhibited active proliferative action in opposition to BEL-7402 and A549 cells. In the primary screening, compound **2** was discovered to have the most potent activity. A mechanistic analysis revealed that compound **2** potently suppressed cell growth and colony formation, which are associated with a delay in S phase advancement via the inhibition of the DNA synthesis.[61]

Thigulla *et al.* described the synthesis of fused chromeno [4, 3-*b*] pyrrolo [3, 2-*h*] quinolin-7(1*H*)-one compounds **3**-**5** with IC_{50} values of 228.5 µM, 197.7 µM, and 70.74 µM, respectively. The synthesized compounds were tested for anticancer activity using murine melanoma cell lines (B16F10). To increase their efficacy, their molecules can be further replaced with different substituents (Figs. **1** and **2**).[62]

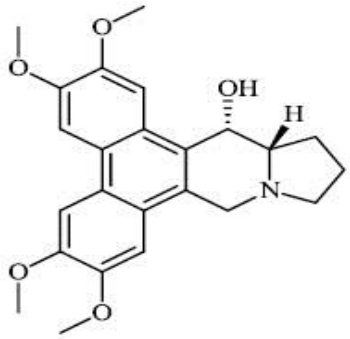


Fig. (1). Phenanthroquinolizidine.

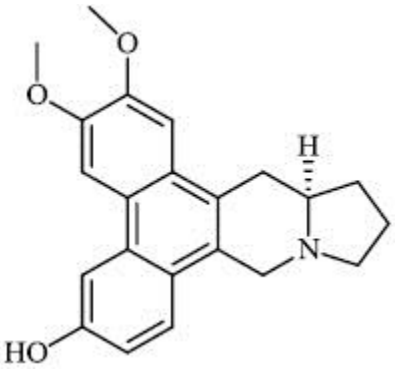


Fig. (2). Phenanthroquinolizidine.

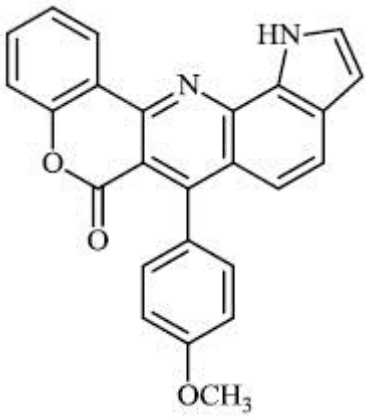


Fig. (3). 6-(4-methoxyphenyl)chromeno[4,3-b]pyrrolo [3,2-h]quinolin-7(1H)-one.

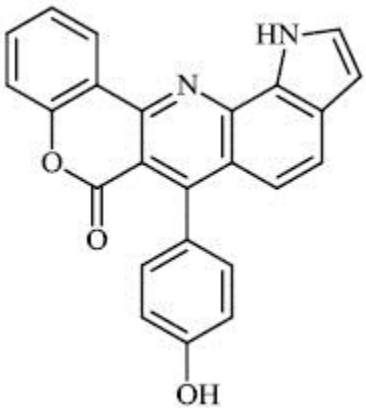


Fig. (4). 6-(4-hydroxyphenyl)chromeno[4,3-b]pyrrolo [3,2-h]quinolin-7(1H)-one.

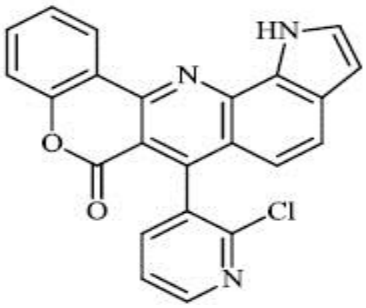


Fig. (5). 6-(2-chloropyridin-3-yl)chromeno[4,3-b]pyrrolo [3,2-h]quinolin-7(1H)-one.

Morsy *et al.* synthesized a series of coumarin-containing compounds **6-8** with IC_{50} values of 91.1±5.27 µg/ml, 5.5±0.19 µg/ml, and 52.0±3.55 µg/ml, respectively, and evaluated their activity against human tumor cell lines. The synthesized compounds were the most active against MCF-7 and HepG-2 cell lines (Figs. **3-5**).[63]

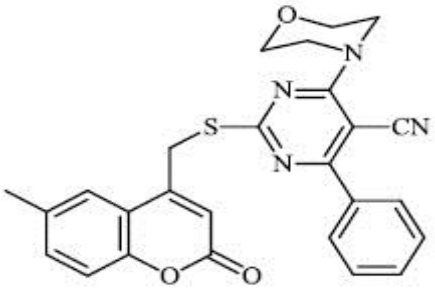


Fig. (6). 2-(6-methyl-2-oxo-2H-chromen-4-yl)methyl)thio)-4-morpholino-6-phenylpyrimidine-5-carbonitrile.

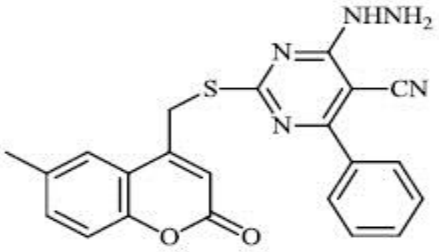


Fig. (7). 4-hydrazinyl-2-(6-methyl-2-oxo-2H-chromen-4-yl)methyl)thio)-6-phenylpyrimidine-5-carbonitrile.

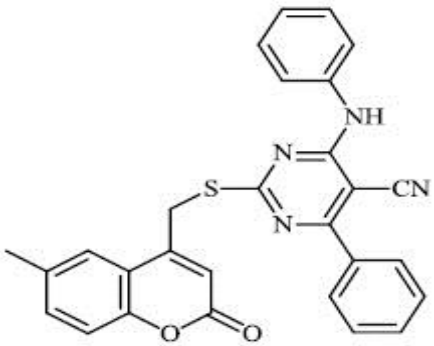
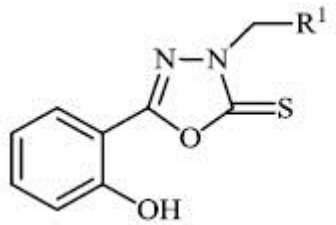


Fig. (8). 2-(6-methyl-2-oxo-2H-chromen-4-yl)methyl)thio)-4-phenyl-6-(phenylamino)pyrimidine-5-carbonitrile.

Aboraia *et al.* explored the synthesis of a series of 5-(2-hydroxyphenyl)-3-substituted-2, 3-dihydro-1, 3, 4-oxadiazole-2-thione derivatives **9** as potent anticancer agents (MCF-7: 32-104). In the primary assay, the synthesized compounds demonstrated high anticancer activity and were selected for a comprehensive anticancer screening in opposition to a 60-cell panel assay, where they demonstrated potential anti-cancer activity (Figs. **6-8**).[64]



R^1 = -NH-C_6H_4(2-COOH); -NH-C_6H_4(4-Cl); -NH-C_6H_4(4-COOH); -NH-C_6H_4(2-Cl); -NH-C_6H_4(3-Cl)

Fig. (9). 5-(2-hydroxyphenyl)-3-substituted-2, 3-dihydro-1, 3, 4-oxadiazole-2-thione derivatives.

Wang *et al.* synthesized C-11 labeled fluorinated 2-arylbenzothiazoles **10** (GI_{50}< 0.1 nM for MCF-7 and MDA 468 breast cancer cell lines), which are employed in positron emission tomography (PET) imaging of tyrosine kinase in cancer. Fluorinated 2-arylbenzothiazoles are novel prospective anticancer medicines that inhibit breast, lung, and colon cancer cell lines effectively and selectively (Fig. **9**).[65]

Kok *et al.* synthesized phthalimide-containing benzothiazole **11** with an IC_{50} value of 69 µM and tested its anticancer efficacy on human carcinoma cell lines. The authors discovered that the toxicity of synthesized benzothiazole-containing phthalimide on bone marrow cells was comparable to that of cancer cells [with 50% of cellular ATP content loss around 69 µM (25 µg/ml)] (Fig. **10**).[66]

Chitrakar *et al*. reported the synthesis and anticancer efficacy of sulfenylated 2-phenylimidazo [1, 2-*a*] pyridines **12-14**. All compounds demonstrated good to excellent activity against different human cancer cell lines, *i.e*., HepG2 (liver), MDA MB 231 (breast), A549 (lung), SKMEL-28 (skin melanoma), Hela (cervical), U87MG (glioblastoma), and DU-145 (prostate) cell lines by employing the MTT assay (Fig. **11**).[67]

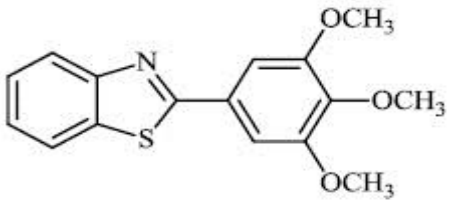


Fig. (10). C-11 labeled fluorinated 2-arylbenzothiazoles.

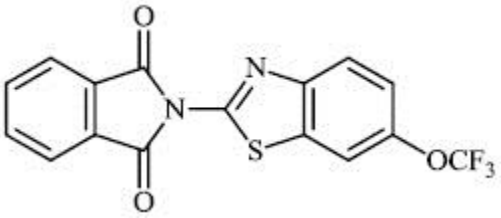


Fig. (11). Phthalimide-containing benzothiazole.

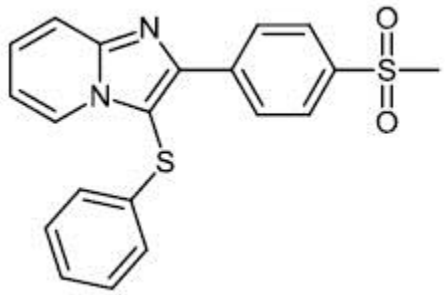


Fig. (12). 2-(4-(methylsulfonyl)phenyl)-3-(phenylthio)imidazo[1,2-a]pyridine.

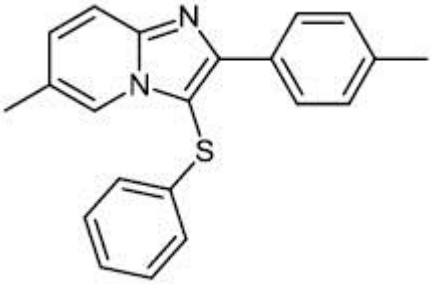


Fig. (13). 6-methyl-3-(phenylthio)-2-(p-tolyl)imidazo[1,2-a]pyridine.

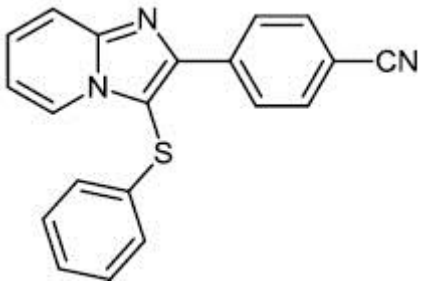


Fig. (14). 4-(3-(phenylthio)imidazo[1,2-a]pyridin-2-yl)benzonitrile.

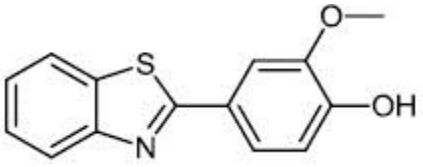


Fig. (15). 2-(4-hydroxy-3-methoxyphenyl)-benzothiazole.

Fu *et al.* reported the synthesis of 2-(4-hydroxy-3-methoxyphenyl)-benzothiazole. The synthesized compound inhibited breast cancer cell proliferation and invasiveness. Furthermore, compound **15** suppressed the capacity to form spheres and boosted the expression of

the carboxyl terminus of Hsp70-interacting protein, which inhibits the oncogenic pathway, and hence, lowers the tumorigenic and metastatic potential of breast cancer cells (Figs. **12-14**).[68]

2.2. Anti-Inflammatory Activity

Anti-inflammatory is a term used to describe drugs that are used to relieve or mitigate inflammation or swelling. Analgesics account for about half of all anti-inflammatory medications. In contrast to opioids, which damage the central nervous system and inhibit pain signaling to the brain, NSAIDs relieve pain by reducing inflammation. Aspirin, ibuprofen, and naproxen are the most commonly used anti-inflammatory drugs and are known as Non-steroidal Anti-inflammatory Drugs (NSAIDs); this term distinguishes these drugs from steroids. Though having a common mode of action, the newer specific cyclooxygenase inhibitors are not listed with the conventional NSAIDs. Prolonged use of NSAIDs can result in gastric erosions, and in acute situations, fatal hemorrhage. For adults aged 16-45, the chance of death from NSAIDs use is 1 in 12,000. For those above the age of 75, the chances almost double. Other risks of NSAIDs include asthma exacerbation and kidney injury. In addition to aspirin, pharmaceutical and over-the-counter NSAIDs raise the risks of stroke and myocardial infarction (Fig. **15**).

Sondhi *et al.* reported the synthesis of 2-thiopyrimidine derivatives, for example, 7, 7, 8a-trimethyl-Hexa-hydro-thiazolo [3, 2-*c*] pyrimidine-5-thione **16**. The synthesized compounds were tested for biological activity and showed good analgesic (50%), anti-inflammatory (37.4%), and kinase (CDK-1; IC_{50}: 0 µM, CDK-5; IC_{50}: >10 µM and GSK-3; IC_{50}: >10 µM) inhibitory activities. Carrageenan-induced paw edema in albino rats was used to screen their anti-inflammatory efficacy. Edema in one of the hind paws was generated by injecting 0.1ml of 1% carrageenan solution into the plantar aponeurosis.[69]

Perner *et al.* synthesized 6, 7-disubstituted 4-aminopyrido [2, 3-*d*] pyrimidine **17** (IC_{50} (enzyme): 350±50 nM and IC_{50} (intact cells): 1500±289 nM), and this compound has been stated to be effective in the treatment of inflammation, epilepsy, sepsis, *etc*. (Fig. **16**).[70]

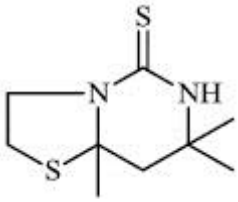


Fig. (16). 7, 7, 8a-trimethyl-hexa-hydro-thiazolo [3, 2-c] pyrimidine-5-thione.

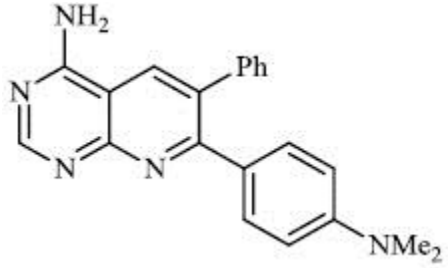


Fig. (17). 6, 7-disubstituted 4-aminopyrido [2, 3-d] pyrimidine.

Balkan *et al.* described the synthesis of some thiazolo [4, 5-*d*] pyrimidine-7 (6*H*)-one derivatives and investigated them for different biological activities. Compound **18** (**(**ED_{50}: 129 mg/kg) demonstrated anti-inflammatory and analgesic properties similar to acetylsalicylic acid, while compound **19** showed high anti-inflammatory activity (35%) (Fig. **17**).[71]

Shehata *et al.* synthesized imidazo [2, 1-*a*] [1, 2, 4] triazolo [1, 5-*c*] pyrimidine **20** and 1, 2, 4-triazolo [1, 5-*c*] pyrimido [2, 1-*a*] pyrimidine **21**, and explored them for their potent anti-inflammatory action on carrageenan-induced edema in rat paws (Figs. **18** and **19**).[72]

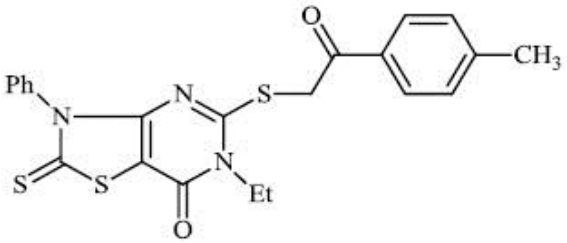


Fig. (18). 6-ethyl-5-((2-oxo-2-(p-tolyl)ethyl)thio)-3-phenyl-2-thioxo-2,3-dihydrothiazolo[4,5-d]pyrimidin-7(6H)-one.

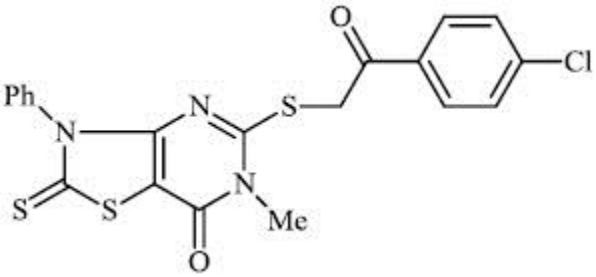


Fig. (19). 5-((2-(4-chlorophenyl)-2-oxoethyl)thio)-6-methyl-3-phenyl-2-thioxo-2,3-dihydrothiazolo[4,5-d]pyrimidin-7(6H)-one.

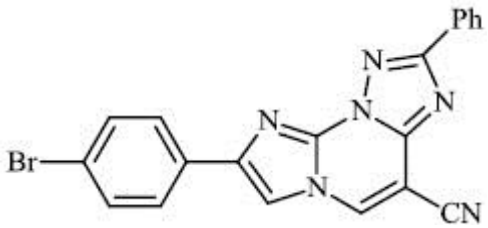


Fig. (20). imidazo [2, 1-a] [1, 2, 4] triazolo [1, 5-c] pyrimidine.

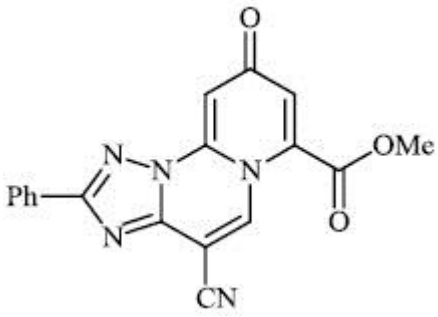


Fig. (21). 1, 2, 4-triazolo [1, 5-c] pyrimido [2, 1-a] pyrimidine.

Mochona *et al.* accomplished the synthesis of tetrahydro pyridine derivatives **22** and **23** with substantial anti-inflammatory activity. The impact of substituents on pharmacological activity was tested in male Sprague-Dawley rats using the carrageenan-induced paw edema experiment. Analogs containing electron-donating substituents at positions 4 and 2 of the benzene moiety displayed strong anti-inflammatory effects, similar to indomethacin (Figs. **20** and **21**).[73]

Amir *et al.* synthesized 2-substituted aryl 1, 3, 4-oxadiazoles **24** and tested them for anti-inflammatory action (22.34% to 72.34%). Several synthesized compounds were found to have anti-inflammatory properties similar to the standard drug ibuprofen. Furthermore, when compared to standard antibiotic ofloxacin, all of these compounds exhibited considerable antibacterial efficacy against *S. aureus* and *E. coli* (Figs. **22** and **23**).[74]

Kanchappa *et al.* synthesized benzofuran pyrazole heterocycles **25** and screened them for their anti-inflammatory efficacy. The synthesized compounds exhibited the ability to inhibit the edema caused in the rat's hind paw following injection of a phlogistic agent, such as carrageenan (Fig. **24**).[75]

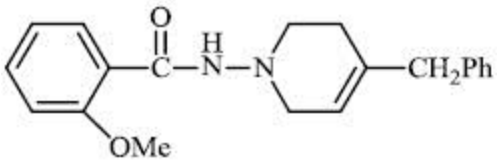


Fig. (22). N-(4-benzyl-5,6-dihydropyridin-1(2H)-yl)-2-methoxybenzamide.

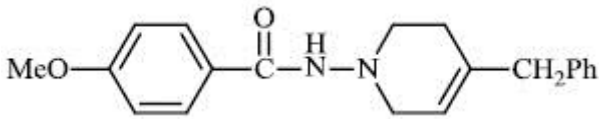


Fig. (23). N-(4-benzyl-5,6-dihydropyridin-1(2H)-yl)-4-methoxybenzamide.

Fig. (24). 2-substituted aryl 1, 3, 4-oxadiazoles.

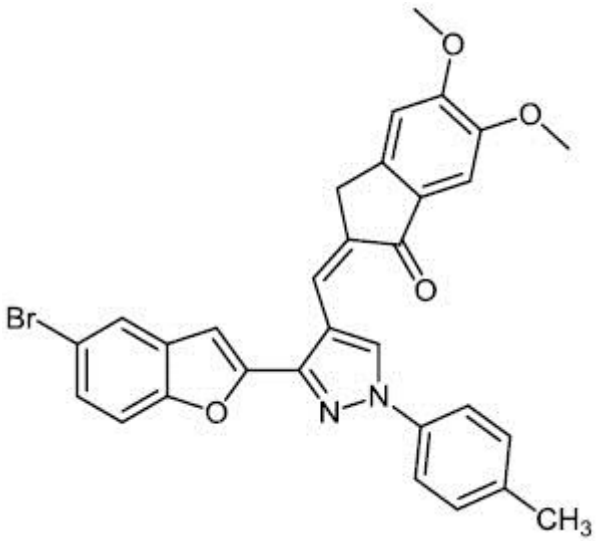


Fig. (25). (Z)-2-((3-(5-bromobenzofuran-2-yl)-1-(p-tolyl)-1H-pyrazol-4-yl)methylene)-5,6-dimethoxy-2,3-dihydro-1H-inden-1-one.

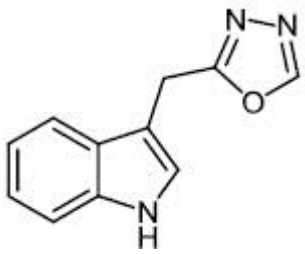


Fig. (26). 2-(1H-indol-3-yl)methyl)-1,3,4-oxadiazole.

Kumar *et al.* synthesized indole functionalized oxadiazoles **26** as anti-inflammatory agents. The anti-inflammatory and analgesic efficacy of indole functionalized oxadiazole derivatives was investigated; they displayed anti-inflammatory and analgesic properties equivalent to the reference drugs (Fig. **25**).[76]

2.3. Antiviral Activity

A virus is a parasitic organism that cannot replicate on its own. On the other hand, a virus can direct the cell machinery to develop more viruses once it has infected a susceptible cell. The genetic material in most viruses is either RNA or DNA. The nucleic acid and an outer protein shell make up the whole infectious virus particle,

known as a virion. The FDA has approved antiviral agents for the treatment of viral infections. Antiviral drugs mainly target different stages of the viral life cycle.

Held *et al.* reported the synthesis of 4, 5, 7, 8-substituted quinazolines **27**-**30** ($EC_{50:}$ 0.6±0.1 µM). The synthesized compounds exhibited significant activity against HCMV (Fig. **26**).[77]

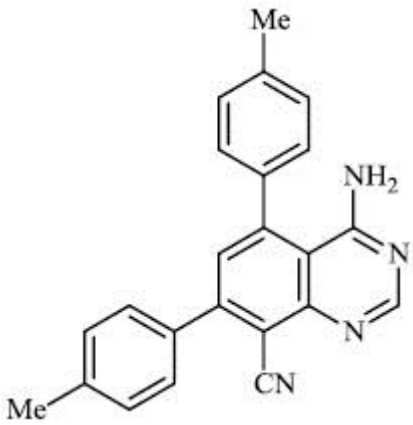


Fig. (27). 4-amino-5,7-di-p-tolylquinazoline-8-carbonitrile.

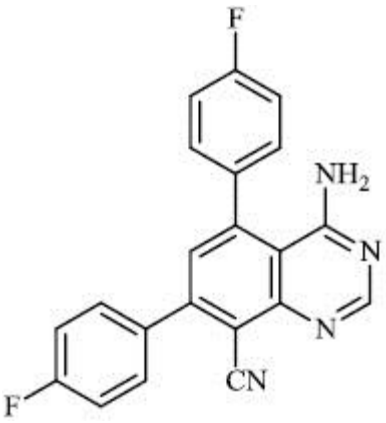


Fig. (28). 4-amino-5,7-bis(4-fluorophenyl) quinazoline-8-carbonitrile.

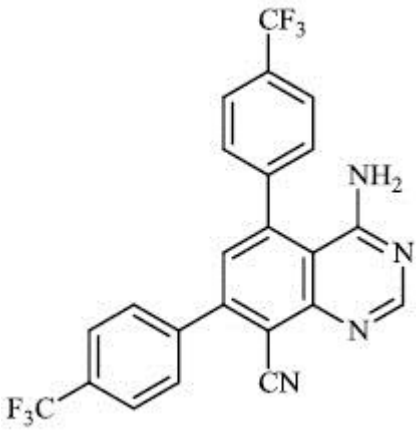


Fig. (29). 4-amino-5,7-bis(4-(trifluoromethyl)phenyl) quinazoline-8-carbonitrile.

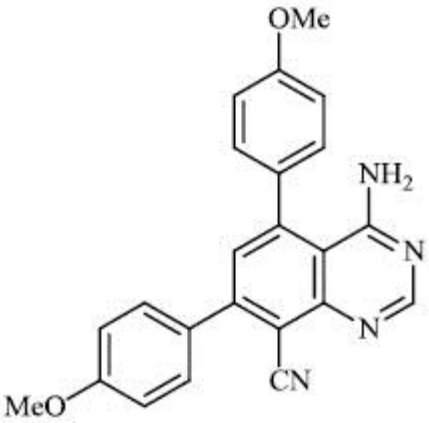


Fig. (30). 4-amino-5,7-bis(4-methoxyphenyl) quinazoline-8-carbonitrile.

Schwarz *et al.* reported the synthesis of kaempferol and kaempferol glycosides as good candidates for 3a channel proteins of coronaviruses. The kaempferol compound **31** with an IC_{50} value of 20 µM could be used to produce novel antiviral agents with increased bioavailability. In particular, the glycosides of kaempferol **32** and **33** with IC_{50} values of 2.3 µM and 10 µM, respectively, appear to be important candidates for exploration as anti-coronaviral drugs. The significance of multi-target medicines is highlighted by the fact that they block the 3a channel, inhibiting virus replication and obstructing other viral life cycle stages (Figs. **27**-**30**).[78]

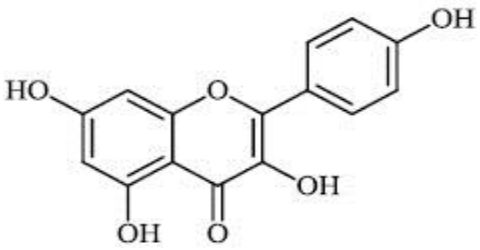


Fig. (31). Kaempferol.

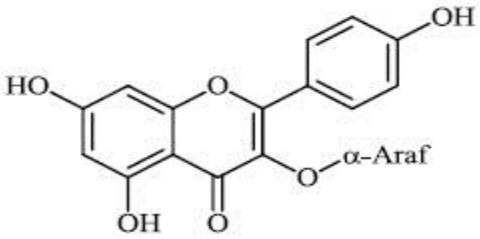


Fig. (32). Juglanin Araf: Arabinofuranose Rha: Rhamnose.

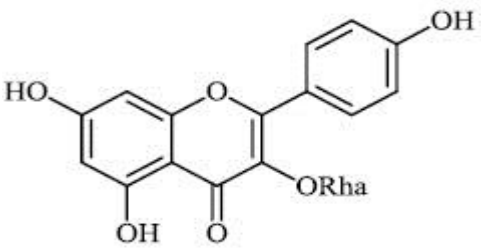


Fig. (33). Afzelin.

Diwani *et al*. investigated benzimidazole derivatives **34-36** with IC_{50} values of 0.6 µM and 1.5 µM, respectively, and screened them for their anti-HCV efficacy. Compound **36** was found to exert significant activity (Figs. **31-34**).[79-81]

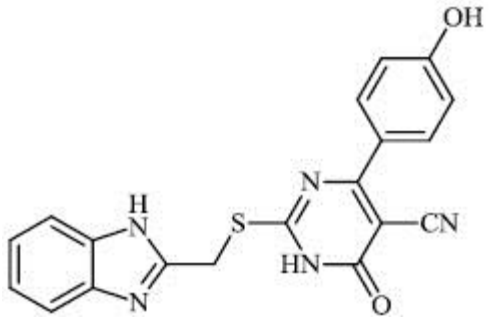


Fig. (34). 2-(1H-benzo[d]imidazol-2-yl)methyl)thio)-4-(4-hydroxyphenyl)-6-oxo-1,6-dihydropyrimidine-5-carbonitrile.

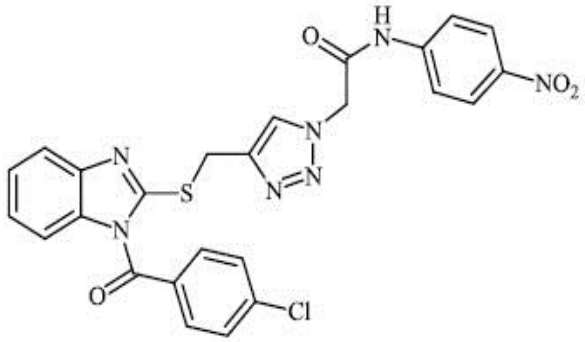


Fig. (35). 2-(4-(1-(4-chlorobenzoyl)-1H-benzo[d]imidazol-2- yl)thio)methyl)-1H-1,2,3-triazol-1-yl)-N-(4-nitrophenyl)acetamide.

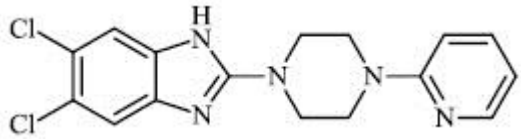


Fig. (36). 5,6-dichloro-2-(4-(pyridin-2-yl)piperazin-1-yl)-1H-benzo[d]imidazole.

Hagar *et al*. studied some nitrogen-containing heterocyclic compounds as inhibitors for Covid-19, including favipiravir **37**, amodiaquine **38**, 2'-fluoro-2'-deoxycytidine **39**, ribavirin **40**, hydroxychloroquine **41**, and remdesivir **42**, with a binding affinity of −4.06, −7.77, −4.47, −4.69, −6.06, and −4.96 kcal/mol, respectively (Figs. **35** and **36**).[82]

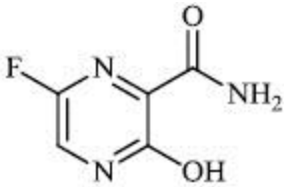


Fig. (37). Favipiravir.

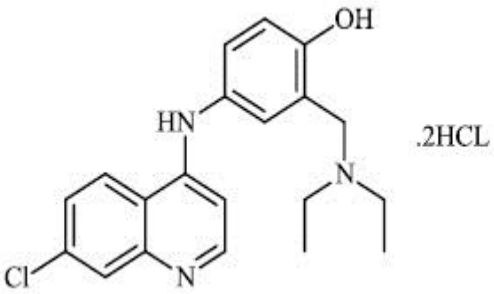


Fig. (38). Amodiaquine.

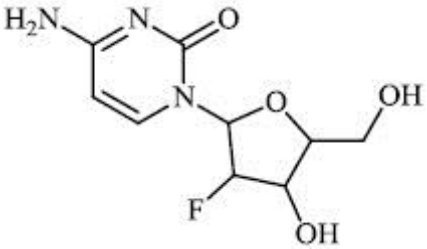


Fig. (39). 2'-fluoro-2'-deoxycytidine.

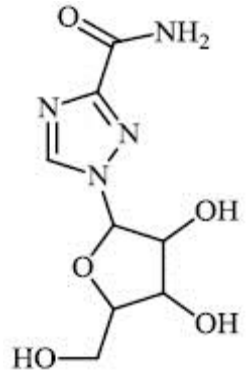


Fig. (40). Ribavirin.

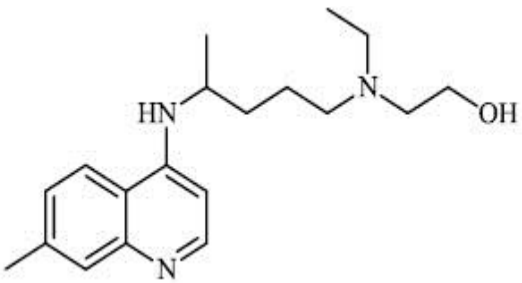


Fig. (41). Hydroxychloroquine.

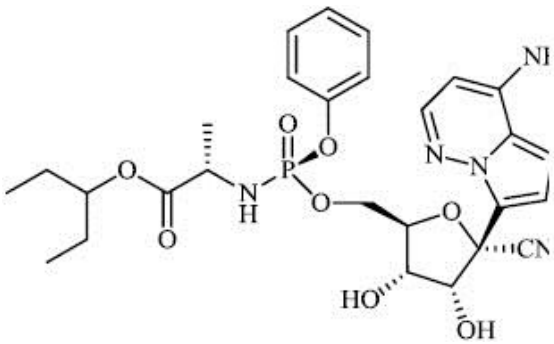


Fig. (42). Remdesivir.

Hwa *et al.* explored some coumarin-based heterocyclic compounds **43** (CC_{50}: 178µM, 117µM and 144 µM respectively; EC_{50}: 19.1µM, 10.2µM and 17.2 µM respectively) and **44** (CC_{50}: 126µM and 107 µM; EC_{50}: 58µM and 19.0 µM) as the most potent inhibitors against the chikungunya virus (CHIKV) (Figs. **37**-**42**).[83, 84]

Diaz *et al.* synthesized and tested quinoline derivatives **45** for antiviral activity. The synthesized quinoline derivatives displayed remarkable antiviral activity (Figs. **43** and **44**).[85]

Kovaleva *et al*. synthesized *N*-heterocyclic hydrazine derivatives of camphor. Compound **46** showed the highest activity against the H1N1 influenza virus (Figs. **45** and **46**).[86]

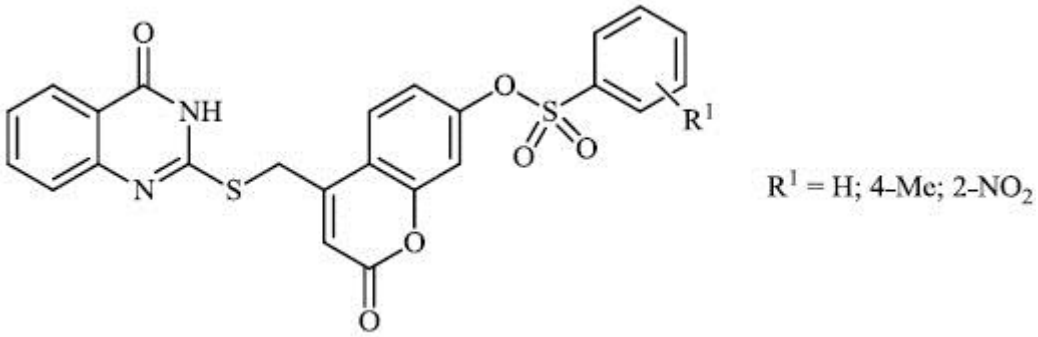


Fig. (43). 2-oxo-4-(4-oxo-3,4-dihydroquinazolin-2-yl)thio)methyl)-2H-chromen-7-yl benzenesulfonate.

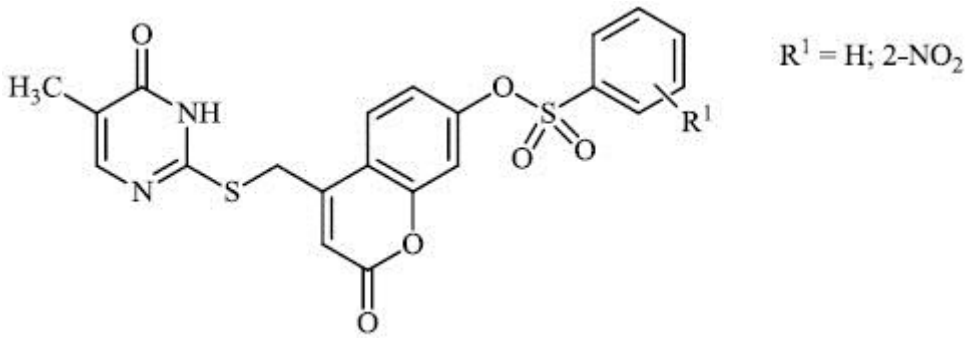


Fig. (44). 4-(5-methyl-6-oxo-1,6-dihydropyrimidin-2-yl)thio)methyl)-2-oxo-2H-chromen-7-yl benzenesulfonate.

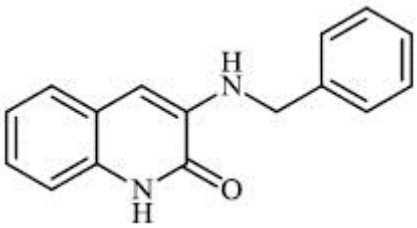


Fig. (45). 3-benzylamino-1H-quinolin-2-one.

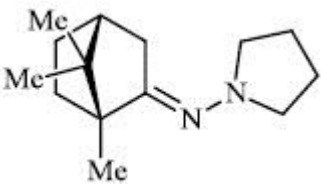


Fig. (46). (E)-N-((1R,4R)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylidene)pyrrolidin-1-amine.

2.4. Antibacterial Activity

Bacteria are single-cell organisms that can be found individually or in groups. Many effective and generally non-toxic medications available to treat bacterial infections pose challenges for medicinal chemists. Antibacterials, often known as antibiotics, are used to prevent or cure bacterial infections by either killing or inhibiting the development of bacteria.

Azab *et al.* synthesized novel heterocyclic compounds with a sulfonamide moiety, such as aminopyrazole derivatives **47**, pyrazolopyrimidine derivative **48**, and pyrimidine and thiazine derivatives **49** and **50,** and assessed them for their antibacterial efficacy. Most of the synthesized compounds exhibited promising antibacterial properties againstGram-positive and Gram-negative bacteria.[87]

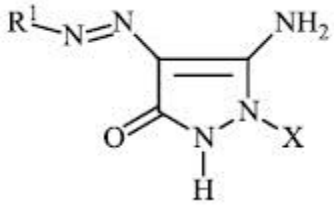


Fig. (47). Aminopyrazole derivatives. X = H; Ph; CSNH2.

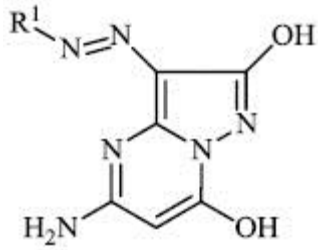
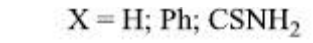


Fig. (48). Pyrazolopyrimidine derivatives.



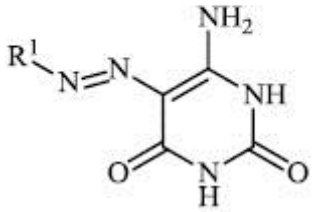


Fig. (49). Pyrimidine derivatives.

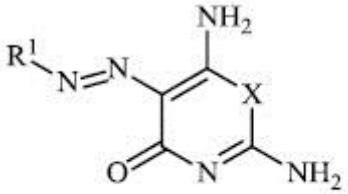
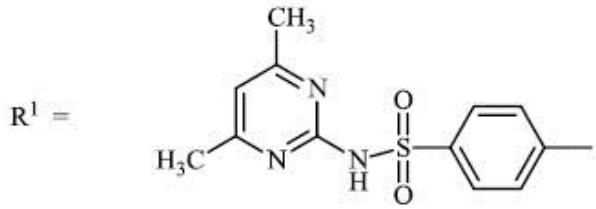


Fig. (50). Thiazine derivatives.



CONCLUSION

Heterocyclic compounds are one of the most significant types of organic molecules in medicinal chemistry and they are used as medications for various diseases. Numerous impressive accomplishments have shown that heterocyclic compounds have a wide range of therapeutic drug applications. Heterocyclic compounds are versatile synthetic targets and key structural units in organic synthesis and medicinal chemistry because of their exciting biological activities. The potential applications of heterocycles as anticancer, anti-inflammatory, antifungal, antibacterial, anti-Alzheimer's, antiviral, antidiabetic agents, *etc*., have attracted substantial interest within the pharmaceutical community. Interestingly, an increasing number of heterocycles have been identified as potential drug candidates in ongoing drug development.

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