Annals of Science and Allied Research Vol. 2 (1) June, 2024: 26-37.
https://doi.org/10.5281/zenodo.12599903
ISSN – 2584-2307 (Online)

THE CHEMISTRY OF HEALING: *HETEROATOMIC DERIVATIZATION AND THEIR MEDICINAL APPLICATIONS*

Aman Deep, Prachi and Hament Panwar*

Department of Chemistry, H.V.M. (P.G.) College, Raisi, Haridwar-247671, Uttarakhand., India.
*Corresponding author: *E-mail Id*: drhp.hvm@gmail.com; Orcid Id: orcid.org/0000-0002-5300-414X

(Received on April 12, 2024; Revised on May 31, 2024; Accepted on June 20, 2024)

ABSTRACT

Heterocyclic compounds are gaining attention for their medical and biological applications, with over 90% of new drugs containing them. Among all the heterocyclic molecules, mimics of nitrogen-based heterocycles occupy an exclusive position as a valuable source of therapeutic agents in medicinal chemistry. More than 75% of drugs approved by the FDA and currently available in the market are nitrogen-containing heterocyclic moieties. In the forthcoming decade, a much greater share of new nitrogen-based pharmaceuticals is anticipated. Many new nitrogen-based heterocycles have been designed. The number of novel *N*-heterocyclic moieties with significant physiological properties and promising applications in medicinal chemistry is ever-growing. In the present investigation, we amalgamate isatin and several aromatic aldehydes to produce a few thiazolidinone derivatives. This synthesis aims to contribute to the ongoing progress in the development of innovative nitrogen-containing heterocycles.

Keywords: Black pepper, chemical composition, biological activities.

INTRODUCTION

eteroatomic/cyclic compounds are a group of cyclic organic compounds that contain at least one atom other than carbon in their ring structure [1]. Heterocyclic organic chemistry is the branch of organic chemistry dealing with the synthesis, properties, and applications of organic heterocycles [2]. It is found that over 50% of identified compounds are heterocycles [3] and nitrogen heterocycles are present in 59% of drugs approved by the US FDA [4]. The most found heteroatoms in these compounds are nitrogen, oxygen, and sulfur. Heterocyclic compounds are abundant in both plants and animal products, and they make up a significant portion of natural organic compounds. They are found in various important substances such as alkaloids, natural dyes, drugs, proteins, and enzymes. These compounds can be classified based on their electronic structure, primarily as saturated and unsaturated. Saturated heterocyclic compounds exhibit similar properties to their acyclic counterparts but with modified steric properties. Examples of saturated heterocyclic compounds include piperidine and tetrahydrofuran. On the other hand, unsaturated heterocyclic compounds with 5- and 6-member rings have been extensively studied due to their unstrained nature. This category includes compounds like epoxides, thiadiazoles, triazoles, oxadiazole, tetrazoles, pyridine, thiophene, pyrrole, furan etc. Some important examples of benzo-fused heterocycles are quinoline, isoquinoline, indole, morpholine, piperazine, benzothiophene, and benzofuran etc. [Figure-1]. The advancement of various organic synthesis methods has significantly contributed to the field of chemical sciences [5-9]. N-heterocyclic compounds, which are widely found in nature, play a crucial role in the development of biologically important molecules such as vitamins, nucleic acids, pharmaceuticals, antibiotics, and agrochemicals [10-14]. These compounds are also essential components of pharmacologically active molecules, including the base pairs of DNA and RNA. With their unique properties and diverse applications, nitrogen-containing heterocyclic molecules have

become increasingly important in the fields of organic and medicinal chemistry, as well as in the pharmaceutical industry [15-17]. Pharmaceutical active ingredients frequently contain heterocyclic structures and are commonly sold as medications [Figure-2, 3]. Numerous nitrogen-containing heterocyclic compounds have been identified to demonstrate various pharmacological effects including anticancer, anti-HIV, antimalarial, anti-tubercular, antimicrobial, and diabetic activities [18-24]. The significance of nitrogen heterocycles in drug design is evident from the 97,400 plus publications on nitrogen heterocycles published between 2009 and early 2020 [Figure-4]. As per the literature review earlier, here we opted to utilize substituted isatin and aromatic aldehydes to produce substituted Schiff's bases. These were then reacted with thioglycolic acid in the presence of anhydrous zinc chloride to produce the desired substituted thiazolidinone mimics.

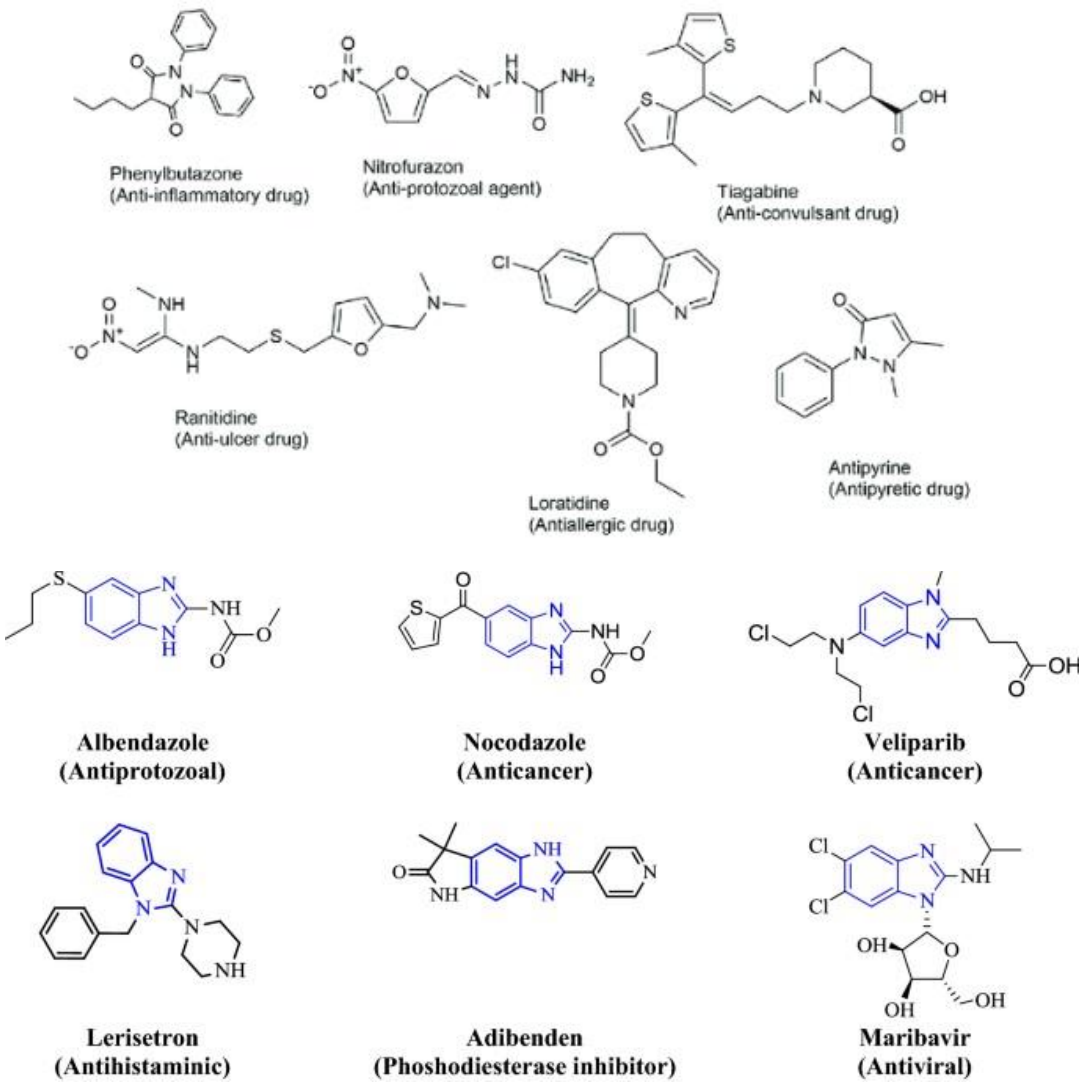


Figure-2

Annals of Science and Allied Research Vol. 2 (1) June, 2024: 26-37.
https://doi.org/10.5281/zenodo.12599903
ISSN – 2584-2307 (Online)

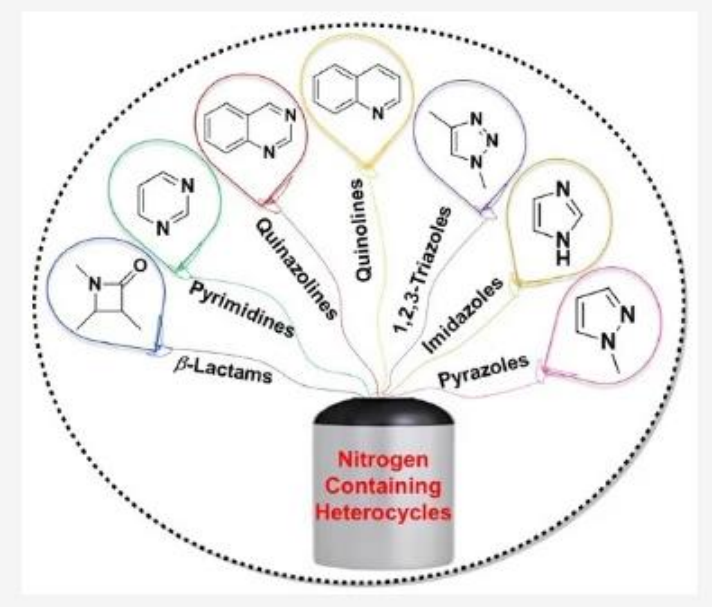


Figure-4

β-Lactams

The β-lactam ring, a four-membered cyclic amide ring system, commonly called "β-lactam ring" or "azetidinone", is highly valued in the design of antibiotics and organic synthesis. It plays a crucial role in the bioactivity profile of antibiotics and serves as a versatile building block for the synthesis of various bioactive heterocycles [25-29]. In addition to its role in antibiotics, β-lactams have other clinical applications such as β-lactamase inhibitors and cholesterol absorption inhibitor [30-31]. The wide range of applications has sparked interest in further developing the β-lactam ring, leading to the creation of various protocols for synthesizing four-membered ring β-lactams [32-33]. The emergence of bacterial resistance to existing β-lactam antibiotics has further fueled research in this field [Figure-5]. No cytotoxic effects were observed in the in vitro cytotoxic studies conducted on NIH-3T3 cell lines, even at concentrations higher than those demonstrated to possess antibiotic activity by Rosa et al. [34]. Similarly, Vigliotta et al. [35] devised a strategy to create a hybrid structure by merging a lactam ring with a cephalosporin moiety using chains of different lengths (n = 1 to 7). The synthesized compounds were then evaluated against specific strains of Gram-positive and Gram-negative bacteria, demonstrating their efficacy against Gram-positive bacteria. Notably, the compounds with longer carbon chains exhibited superior antibacterial activity compared to the reference drug. Furthermore, all the compounds exhibited no cytotoxicity on tested MRC-5 and Calu-1 cell lines at the active antimicrobial doses. Pagadala et al. [36] synthesized bicyclic ring

structures with monocyclic 2-azetidinone rings connected by spacers of varying lengths and flexibility. These compounds were tested in vitro for antibacterial activity against B. subtilis, S. aureus, E. coli, and K. pneumoniae. Results showed that all compounds had moderate to good activity, comparable to standard drugs. Notably, compounds with a methoxy-, nitro-, or amino-group on the phenyl ring at the C-4 position of the azetidinone ring exhibited the highest activity.

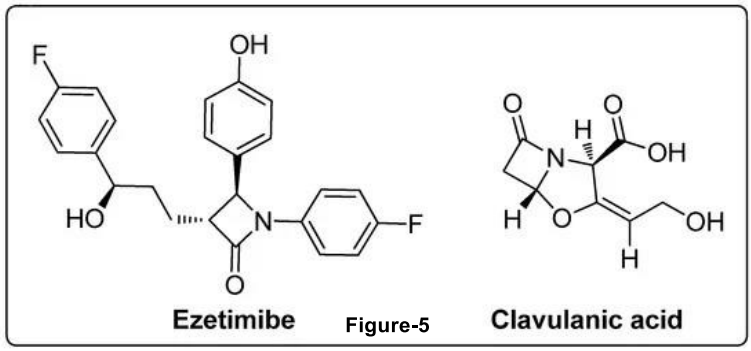


Figure-5

Triazoles

The 1,2,3-triazole moiety serves as a crucial pharmacophore system in nitrogen-based molecules and is a fundamental building block in the exploration of novel biological targets. These heterocyclic motifs, consisting of three nitrogen heteroatoms, can be easily synthesized through the application of 'click' chemistry, specifically copper-catalyzed azide-alkyne cycloaddition [Cu-AAC] reactions. Generally, 1,2,3-triazoles possess a stable 'linker' property that resists hydrolysis under both acidic and basic conditions, as well as metabolic degradation. These compounds exhibit interactions with diverse biological targets through hydrogen bonding, noncovalent interactions, van der Waals forces, and dipole-dipole bonding interactions. Additionally, triazoles display weak acidic and weak basic characteristics, making them more susceptible to reducing agents. Notably, the 1,2,3-triazole-based compound known as carboxyamidotriazole has undergone successful clinical evaluation for cancer treatment [37-39] (Figure-6).

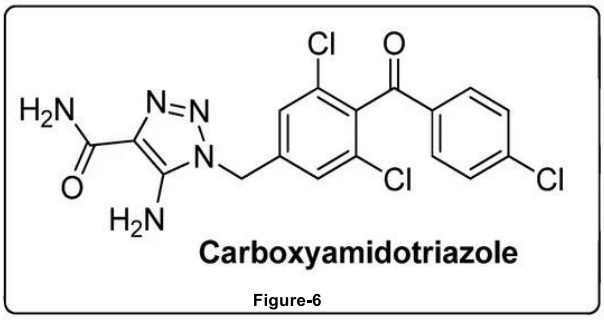


Figure-6

Meltem et al. [40] developed azole-functionalized fluoroquinolone hybrids and tested their antibacterial and antioxidant properties. Some of the fourteen hybrids exhibited stronger antibacterial effects against test microorganisms compared to ampicillin, with MIC values ranging from 0.03 to 0.25 µg/mL. The study conducted by Bektaş et al. [41] focused on the synthesis and antimicrobial properties of novel 1,2,4-triazole derivatives. The results indicated that compounds 3 and 8 displayed moderate antimicrobial effects against *Escherichia coli* and *Klebsiella pneumoniae*, while compounds 11 and 12 exhibited moderate activities towards Enterobacter aerogenes, *Staphylococcus aureus, Enterococcus faecalis*, and *Bacillus careus*. Compounds 13 and 14 demonstrated good antimicrobial activities against the tested microorganisms, and Mannich bases 15a,b showed either good or moderate antimicrobial effects. However, none of the synthesized compounds showed antimicrobial activity against *Candida tropicalis* and *Candida albicans*.

Imidazoles and Benzoimidazoles

The significant structural characteristics of the five-membered imidazole and benzoimidazole moieties set them apart as crucial heterocycles, and these formations are present in numerous natural products and synthetic compounds. The imidazole-based derivatives, known for their electron-rich nature, are valuable in their ability to readily bind with various receptors and

Annals of Science and Allied Research Vol. 2 (1) June, 2024: 26-37.
https://doi.org/10.5281/zenodo.12599903
ISSN – 2584-2307 (Online)

enzymes in the biological profile, thereby displaying a wide range of biological activities [42-43]. Several imidazole-based molecules (such as oxiconazole, dacarbazine, and clotrimazole) that exhibit potent antifungal and anticancer properties are currently utilized as drugs in clinical settings (Figure 16). The field of medicinal chemistry is witnessing a rapid expansion in the realm of imidazole and benzoimidazole possessed molecules [Figure-7]. El-Feky and colleagues [44] synthesized and tested various new quinoline derivatives to evaluate their anti-inflammatory and ulcerogenic properties. They conducted a docking study on the COX-2 binding pocket to assess the selectivity of these compounds against the COX-2 enzyme. The most potent compounds (5a, 8a, and 11a) exhibited superior activity compared to celecoxib. Compound 11a displayed the highest anti-inflammatory effects and showed the best binding affinity to the COX-2 binding site. Additionally, compounds 9c, 9e, 10a, and 11a did not exhibit any ulcerogenic activity. Yanhui et al. [45] conducted a study on the antibacterial and anti-biofilm effects of certain compounds on S. aureus. They found that ionic liquids containing imidazole chloride and alkyl chains of twelve and sixteen carbons exhibited varying levels of antibacterial effectiveness, with the effectiveness improving as the alkyl chain length increased. The researchers also investigated the impact of CnMIMCl ILs on S. aureus, and observed that toxicity increased as the length of the imidazolidinyl side chains increased. Among the ILs studied, C12MIMCl was selected for further analysis due to its ability to induce internal and external changes in S. aureus, ultimately leading to bacterial death. The researchers discovered that high levels of reactive oxygen species (ROS) caused oxidative stress, disrupted metabolism, and resulted in cell death. Additionally, damage to the cell membrane led to leakage and fragmentation. In vivo tests conducted on mice confirmed the antibacterial properties of the ILs against skin blisters.

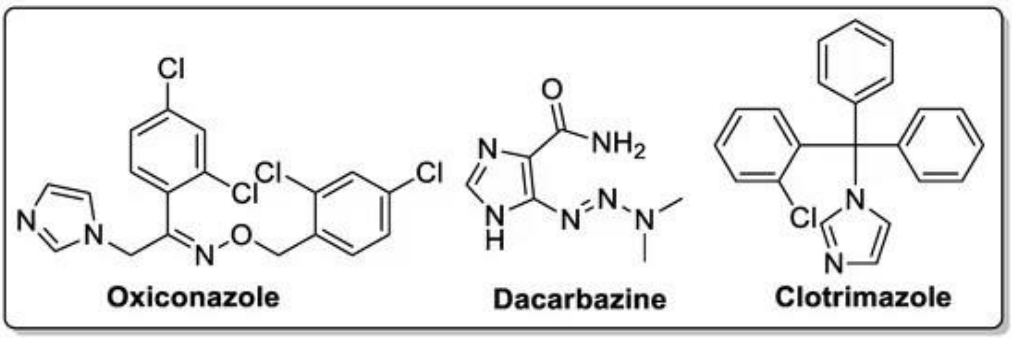


Figure-7

Pyrazoles

Pyrazole is a renowned heterocycle composed of five nitrogen-containing members, known for its diverse applications in both synthetic and biological contexts. Several drugs derived from pyrazole, including celecoxib, rimonabant, difenamizole, and fezolamine, have been developed with exceptional anti-inflammatory, anti-obesity, analgesic, and/or antidepressant effects. These drugs are employed in the management of various diseases (Figure 23) [46-49]. Akbas and colleagues [50] conducted the synthesis of a range of 1H-pyrazole-3-carboxylic acid derivatives and assessed their antibacterial properties against *Bacillus cereus, Staphylococcus aureus, Escherichia coli*, and *Pseudomonas putida*. The findings indicated that compound 151 stood out as the most effective compound in the series, demonstrating antibacterial efficacy against both Gram-positive and Gram-negative bacteria. Xiong et al. [51] reported synthesis, and biological evaluation of novel thiazolyl substituted bis-pyrazole oxime derivatives with potent antitumor activities by selectively inducing apoptosis and ROS in cancer Cells.

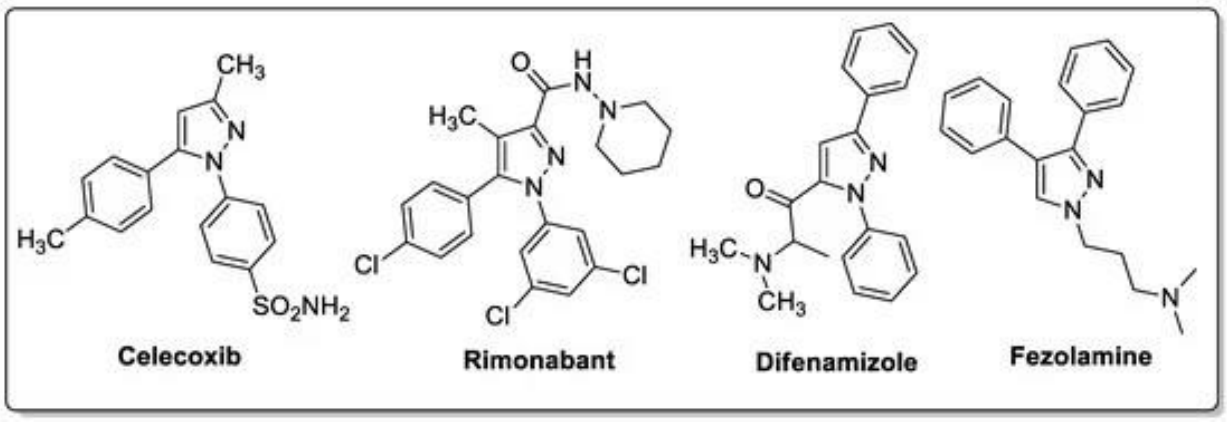


Figure-8

Quinolines

The quinoline moiety is a well-known entity and is a ubiquitous alkaloid subunit of many natural products. Quinoline is an important pharmacophore moiety as it has been described to possess various biological activities, which include antimalarial, antibiotic, antitubercular, antiproliferative, antiprotozoal, antihypertensive, anti-HIV properties [52-54] and many are commercially available in market [Figure-9]. Raynes et al. [55] are found to possess a good degree of antimalarial activity against both chloroquine-resistant and chloroquine-sensitive parasites. While 7-chloroquinolinyl thioureas synthesized by Mahajan et al. [56] and claimed their potential antimalarial potential.

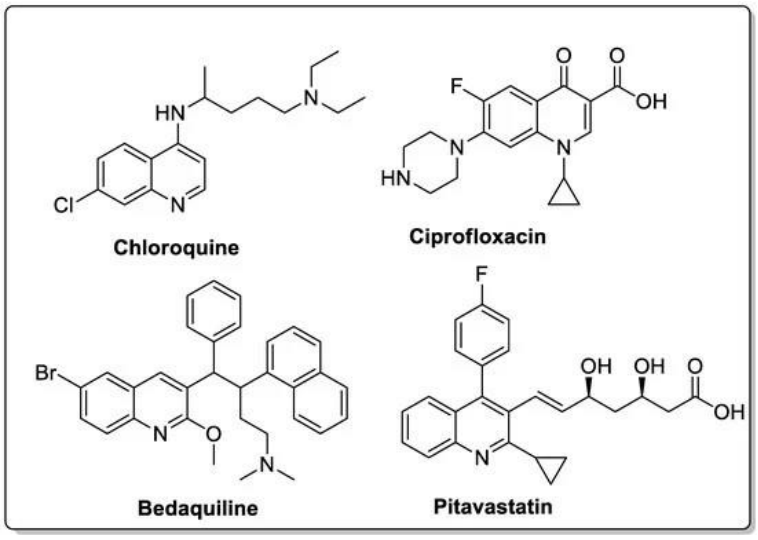


Figure-9

Quinazolines

Quinazoline are nitrogen-containing six-membered heterocyclic compounds that contain a benzene ring system fused to a pyrimidine at two adjacent carbon atoms. Quinazolines and their analogs possess a wide range of biological activities. Many quinazoline compounds were reported as growth factor receptor (EGFR) tyrosine kinase inhibitors, such as gefitinib, erlotinib, lapatinib and afatinib (**Figure**-10) [57].

Annals of Science and Allied Research Vol. 2 (1) June, 2024: 26-37.
https://doi.org/10.5281/zenodo.12599903
ISSN – 2584-2307 (Online)

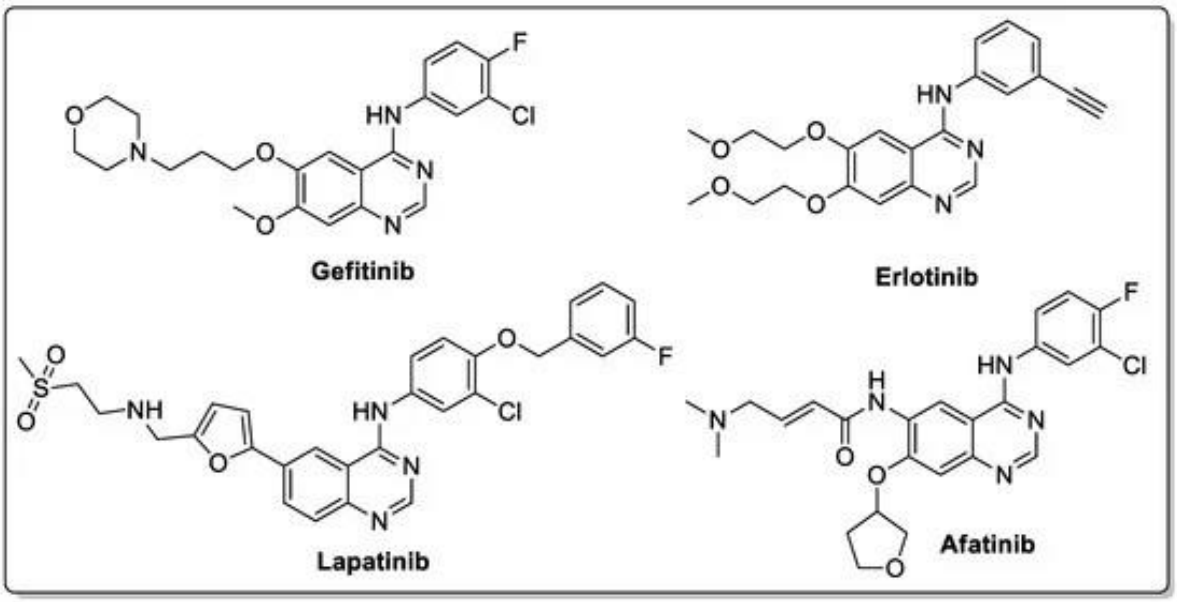


Figure-10

Pyrimidines and pyrimidinones

Derivatives of pyrimidines and pyrimidinone derivatives are highly regarded in organic synthesis due to their diverse biological activities. The pyrimidine nucleus is composed of a six-membered 1,3-diazine ring with a ketone group. These analogs play a crucial role in various biologically active compounds, including natural products and nucleic acids. Additionally, this type of heterocyclic compound is utilized in medicinal chemistry for its therapeutic applications, serving as a fundamental component in numerous drug candidates and nucleic acids, sharing a structural similarity with purines [57]. Recently, the US FDA has approved several pyrimidines and pyrimidinone derivatives (ibrutinib, capecitabine, folinic acid, and monastrol) as anticancer agents [Figure-11].

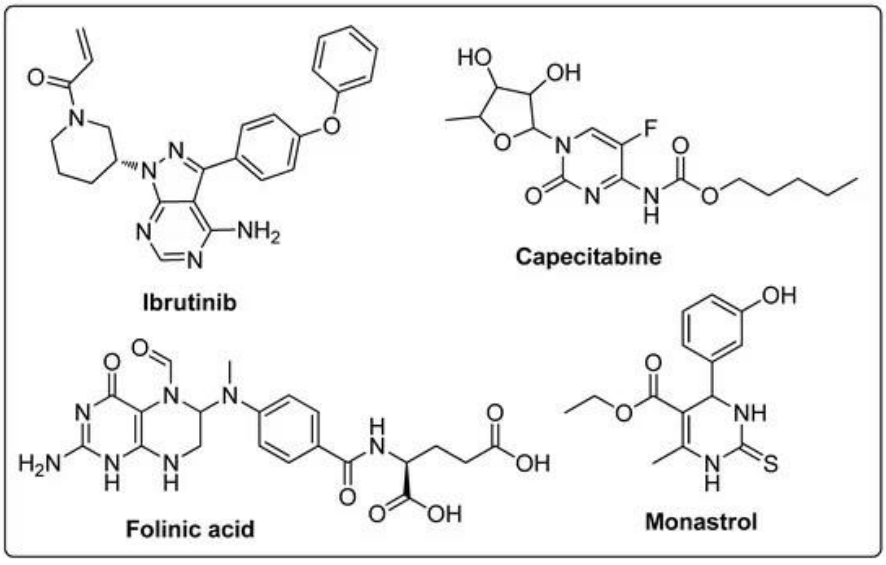
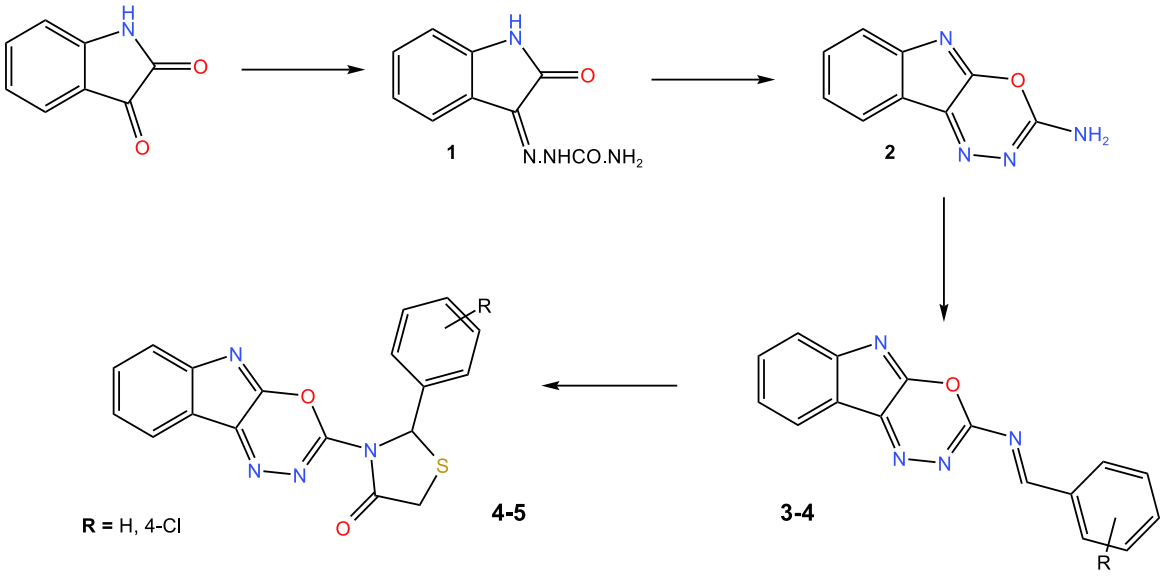


Figure-11

Designing and synthesis

In the current study, we selected aromatic aldehydes, indole-2,3-diones, thioglycolic acid to yield targeted heterocyclic moieties as depicted in scheme-1.



Scheme-1

3-Thiosemicarbazido indole-2-one [1]: A mixture of indole-2,3-dione (2 g), semicarbazide (1.23 g) in methanol (50 mL) was refluxed for 1 hr. The completion of reaction was checked by TLC and excess ofmethanol distilled out. The cooled, refluxed residual was poured into ice water, filtered, washed with water, dried and recrystallized from methanol to obtain compound **1** (80%), m.p. 200 ºC; IR (KBr, cm^{-1}): 1200, 1610, 1682, 1710, 3144, 3419; ^1H NMR ($CDCl_3$+DMSO-d_6,): 6.75-6.95 (d, $1H_d$), 7.02-7.10 (t, $1H_c$), 7.22-7.30 (t, $1H_b$), 7.5707.62 (d, $1H_a$), 8.90 (bs, 2H), 9.36 (bs, 1H) ppm. Anal. Calcd for $C_9H_8N_4SO$: C, 49.09; H, 3.63; N, 25.45. Found: C, 49.38; H, 3.41; N, 25.60%. MS: $[M]^+$ at m/z 220.

2-Amino-1,3,4-oxadiazino(6,5-*b*) indole [2]: Compound **1** (3 g) mixed with small quantity of cold, concentrate sulfuric acid (1.52 mmole) and left at room temp for 16 hr. After this, reaction mixture was poured into ice-cold water, neutralized with liquid ammonia to obtain solid mass, which was filtered, washed with water, dried, and recrystallized from methanol to yield compound **2** (60%), m.p. 340 ºC; IR(KBr, Cm^{-1}): 1295, 1611, 1683, 3144, 3420; ^1H NMR ($CDCl_3$+DMSO-d_6): 6.89-6.97 (d,$1H_d$), 7.00-7.05 (t,$1H_c$), 7.26-7.31 (t,$1H_b$), 7.56-7.59 (d,$1H_a$), 8.58 (bs,2H) ppm. Anal. Calcd for $C_9H_6N_4S$: C, 53.46; H, 2.97; N, 27.72. Found: C, 53.26; H, 3.15; N, 27.94%. MS: $[M]^+$ at m/z 202.

General procedure of arylidenamino-1,3,4-oxadiazino[6,5-*b*]indole [3-4]: The equimolar mixture (0.01 mole) of compound **2**and aromatic aldehydes (0.01 mole) in ethanol was refluxed for 6 hr in presence of glacial acetic acid. The completion of reaction was checked by TLC and excess of methanol distilled off. After this, refluxed reaction mixture was poured into ice-water, filtered, washed with water, and dried. Dried mass was recrys tallized from ethanol to yield compound **3-4.**

Benzylidenamino-1,3,4-oxadiazino[6,5-*b*]indole [3]: m.p. 188ºC; IR (KBr, Cm^{-1}) 1296, 1611, 1682, 31; ^1H NMR ($CDCl_3$+DMSO-d_6,): 6.47-6.68 (m,5H), 6.86-6.96 (d,$1H_d$), 7.02-7.12 (t,$1H_c$), 7.23-7.28 (t,1H), 7.56-7.60 (d,1H), 8.29 (s,1H) ppm. Anal. Calcd for $C_{16}H_{10}N_4O$: C, 66.20; H, 3.44; N, 19.31. Found: C, 65.96; H, 3.61; N, 19.18%. MS: $[M]^+$ at m/z 274.

2-[4-Chlorobenzylidenamino]-1, 3, 4-oxadiazino[6,5-*b*]indole 4: m.p. 222ºC (methanol-water); IR (KBr, cm^{-1}): 673, 1062, 1297, 1612, 1680, 3145, 3420; ^1H NMR ($CDCl_3$+DMSO-d_6): 3.72 (s, 3H), 6.72 (s, 1H), 6.90-6.92 (d, 1H), 7.01-7.06 (t, 1H), 7.27-7.32 (t, 1H), 7.76-7.79 (d, 1H), 7.87-7.90 (d, 1H). Anal. Calcd for $C_{16}H_9N_4OCl$: C, 60.71; H, 3.57; N, 16.66. Found: C, 60.50; H, 3.32; N, 16.39%. MS: [M] at m/z 308.5.

General procedure of 2-Aryl-4-thiazolidinon-3-yl-]-1,3,4-oxadiazino[6,5-*b*]indole [5-6]:

An ethanolic mixture of derivatives 3 & 4 refluxed for 5-7 hrs in presence of glacial acetic acid. On

Annals of Science and Allied Research Vol. 2 (1) June, 2024: 26-37.
https://doi.org/10.5281/zenodo.12599903
ISSN – 2584-2307 (Online)

completion, excess of solvent distilled and residue poured in ice-water to yield residues [5-6].

2-Phenyl-4-thiazolidinon-3-yl-]-1,3,4-oxadiazino[6,5-*b*]indole [5]: m.p. 188 ºC (acetic acid-water); IR (KBr, cm^{-1}): 1055, 1300, 1605, 1697, 3200, 3466; ^1H NMR ($CDCl_3$+DMSO-d_6): 3.70 (s, 2H), 6.56-6.97 (m, 5H), 7.25 (s, 1H,N-CH-), 7.56-8.17 (m, 4H). Anal. Calcd for $C_{18}H_{12}N_4O_2S$: C, 62.06; H, 3.44; N, 16.09. Found: C, 61.89; H, 3.31; N, 16.12%. MS: [M] at m/z 348.

2-[4-Chlorophenyl-4-thiazolidinon-3-yl-]-1,3,4-oxadiazino[6,5-*b*]indole [6]: m.p. 209 ºC (acetic acid-water); IR (KBr, cm^{-1}): 1055, 1300, 1605, 1697, 3200, 3466; ^1H NMR ($CDCl_3$+DMSO-d_6): 3.61 (s, 2H), 6.46-6.88 (m, 4H), 7.25 (s, 1H,N-CH-), 7.56-8.17 (m, 4H). Anal. Calcd for $C_{18}H_{11}N_4O_2SCl$: C, 56.47; H, 2.87; N, 14.64. Found: C, 56.70; H, 2.80; N, 14.60%. MS: [M] at m/z 382.5.

Conclusion

The field of nitrogen-based compounds in medicine is expanding daily, and their various analogs offer a viable and important avenue for the discovery of drugs with diverse biological applications. N-heterocyclic frameworks provide a high level of structural diversity, which has proven to be valuable in the search for new therapeutic agents that can improve pharmacokinetics and other physicochemical features. Many drugs currently in clinical use have severe side effects and have developed resistance to multiple drugs. Despite this, they have been extensively utilized to treat various diseases due to their high therapeutic potency. The research and development of nitrogen-based compounds in medicinal chemistry is a rapidly growing and increasingly active area of study. Significant progress has been made in the field of N-heterocyclic skeleton medicinal chemistry. The numerous advantages of nitrogen-containing drugs in the field of medicine, such as easy preparation, low toxicity, minimal adverse effects, high bioavailability, reduced drug resistance, and good biocompatibility, provide strong motivation for further research and development. Therefore, understanding the properties of these scaffolds is crucial in the current drug discovery and design system. In this review, we have extensively covered the current trends in families of nitrogen-based heterocyclic molecules, including β-lactam, pyrazole, imidazole, 1,2,4-triazole, pyrimidine, quinoline, and quinazoline derivatives. These molecules exhibit highly promising biological properties, such as anticancer, anti-inflammatory, antibacterial, antifungal, antitubercular, antidiabetic, antioxidant, anti-HIV, and other medicinal properties.

Statement of Declaration

This work is part of the dissertation works of M.Sc. final semester students Aman Deep and Prachi.

Conflicts of interest

The author states there are no conflicts of interest

REFERENCES

1. IUPAC Gold Book (2006), Heterocyclic compounds.
2. Thomas LG (1997). Heterocyclic chemistry, Addison Wesley: Essex, England 3:414.
3. Rees CW (1992). Polysulfur-Nitrogen Heterocyclic Chemistry. J Heter Chem 29(3): 639–651. doi:10.1002/jhet.5570290306.
4. Edon V, David TS, Jon TN (2014). Analysis of the Structural Diversity, Substitution Patterns, and Frequency of Nitrogen Heterocycles among U.S. FDA Approved Pharmaceuticals. J Med Chem 57(24): 10257–10274.
5. Li X, He L, Chen H, Wu W, Jiang H (2013). Copper-catalyzed aerobic C(sp^2)–H functionalization for C–N bond formation: Synthesis of pyrazoles and indazoles. J Org Chem 78: 3636–3646.
6. Santos CMM, Freitas M, Fernandes EA (2018). Comprehensive review on xanthone derivatives as α-glucosidase inhibitors. Eur J Med Chem 8(157): 1460–1479.
7. Kalaria PN, Karad SC, Raval DK (2018). A review on diverse heterocyclic compounds as the privileged scaffolds in antimalarial drug discovery. Eur J Med Chem 158: 917–936.
8. Kerru N, Bhaskaruni SVHS, Gummidi L, Maddila SN, Maddila S, Jonnalagadda SB (2019). Recent advances in heterogeneous catalysts for the synthesis of imidazole derivatives. Synth Commun 49: 2437–2459.
9. Kerru N, Singh P, Koorbanally N, Raj R, Kumar V (2017). Recent advances (2016-2016) in anticancer hybrids. Eur J Med Chem 142:179–212.
10. Eftekhari-SB, Zirak M, Akbari A (2013). Arylglyoxals in synthesis of heterocyclic compounds. Chem Rev 113: 2958–3043.

11. Kerru N, Maddila S, Jonnalagadda SB (2019). Design of carbon–carbon and carbon–heteroatom bond formation reactions under green conditions. Curr Org Chem 23: 3156–3192.
12. Ju Y, Varma RS (2006). Aqueous N-hetero-cyclization of primary amines and hydrazines with dihalides: microwave-assisted syntheses of N-azacycloalkanes, isoindole, pyrazole, pyrazolidine, and phthalazine derivatives. J Org Chem 1: 135–141.
13. Zarate DZ, Aguilar R, Hernandez-Benitez RI, Labarrios EM, Delgado F, Tamariz J (2015). Synthesis of α-ketols by functionalization of captodative alkenes and divergent preparation of heterocycles and natural products. Tetrahedron 71: 6961–6978.
14. Leeson PD, Springthorpe B (2006). The influence of drug-like concepts on decision-making in medicinal chemistry. Nat Rev Drug Discov 6: 881–890.
15. Fang WY, Ravindar L, Rakesh KP, Manukumar HM, Shantharam CS, Alharbi NS, Qin HL (2019). Synthetic approaches and pharmaceutical applications of chloro-containing molecules for drug discovery: A critical review. Eur J Med Chem 173: 117–153.
16. Kerru N, Singh-Pillay A, Awolade P, Singh P (2018). Current anti-diabetic agents and their molecular targets: A review. Eur. J. Med. Chem 152: 436–488.
17. Smith BR, Eastman CM, Njardarson JT (2014). Beyond C, H, O, and N analysis of the elemental composition of U.S. FDA approved drug architectures. J Med Chem 57: 9764–9773.
18. Chaudhari K, Surana S, Jain P, Patel HM (2016). Mycobacterium tuberculosis (MTB) GyrB inhibitors: An attractive approach for developing novel drugs against TB. Eur J Med Chem 124: 160–185.
19. Sameem B, Saeedi M, Mahdavi M, Shafiee AA (2017). Review on tacrine-based scaffolds as multi-target drugs (MTDLs) for Alzheimer's disease. Eur J Med Chem 128: 332–345.
20. Akhtar J, Khan AA, Ali Z, Haider R, Yar MS (2017). Structure-activity relationship (SAR) study and design strategies of nitrogen-containing heterocyclic moieties for their anticancer activities. Eur J Med Chem 125:143–189.
21. Ma X, Lv X, Zhang J (2018). Exploiting poly-pharmacology for improving therapeutic outcome of kinase inhibitors (KIs): An update of recent medicinal chemistry efforts. Eur J Med Chem 143: 449–463.
22. Kaur R, Dahiya L, Kumar M (2017). Fructose-1,6-bisphosphatase inhibitors: A new valid approach for management of type 2 diabetes mellitus. Eur J Med Chem 141: 473–505.
23. Patel RV, Keum Y.S., Park S.W. Sketching the historical development of pyrimidones as the inhibitors of the HIV integrase. Eur. J. Med. Chem. 2015, 97, pp. 649–663.
24. Martins P, Jesus J, Santos S, Raposo LR, Rodrigues CR, Baptista PV, Fernandes AR (2015). Heterocyclic anticancer compounds: Recent advances and the paradigm shift towards the use of nanomedicine's toolbox. Molecules 20: 16852–16891.
25. Newman DJ, Cragg GM (2016). Natural products as sources of new drugs from 1981 to 2014. J Nat Prod 79: 629–661.
26. Robb MJ, Moore JS (2015). A retro-staudinger cycloaddition: Mechanochemical cycloelimination of a β-lactam mechanophore. J Am Chem Soc 137: 10946–10949.
27. Baiula M, Galletti P, Martelli G, Soldati R, Belvisi L, Civera M (2016). New β-lactam derivatives modulate cell adhesion and signaling mediated by RGD-binding and leukocyte integrins. J Med Chem 59: 9721–9742.
29. Majewski MW, Miller PA, Oliver AG, Miller MJ (2017). Alternate "drug" delivery utilizing β-lactam cores: Syntheses and biological evaluation of β-lactams bearing isocyanate precursors. J Org Chem 82: 737–744.
30. Cele ZED, Arvidsson PI, Kruger HG, Govender T, Naicker T (2015). Applied enantioselective aminocatalysis: α-Heteroatom functionalization reactions on the carbapenem (β-lactam antibiotic) core. Eur. J. Org. Chem 3: 638–646.
31. Wang Y, Zhang H, Huang W, Kong J, Zhou J, Zhang B (2009). 2-Azetidinone derivatives: Design, synthesis and evaluation of cholesterol absorption inhibitors. Eur J Med Chem 44: 1638–1643.
32. Kamath A, Ojima I (2012). Advances in the chemistry of β-lactam and its medicinal applications. Tetrahedron 68: 10640–10664.
33. Hosseyni S, Jarrahpour A (2018). Recent advances in β-lactam synthesis. Org Biomol Chem 16: 6840–6852.
34. Han WT, Trehan AK, Wright JJK, Federici ME, Seiler SM, Meanwell NA (1995). Azetidin-2-one

derivatives as inhibitors of thrombin. Bioorg Med Chem 3: 1123–1143.

34. De Rosa M, Vigliotta G, Palma G, Saturnino C, Soriente A (2015). Novel penicillin-type analogues bearing a variable substituted 2-azetidinone ring at position 6: Synthesis and biological evaluation. Molecules 20: 22044–22057.
35. Vigliotta G, Giordano D, Verdino A, Caputo I, Martucciello S, Soriente A, Marabotti A, De Rosa M (2020). New compounds for a good old class: Synthesis of two β-lactam bearing cephalosporins and their evaluation with a multidisciplinary approach. Bioorg Med Chem 28, (4): 115302.
36. Pagadala R, Kusampally U, Rajanna KC, Meshram JS (2015). Synthesis and antimicrobial studies of novel imidazole containing bisazetidinones and bisthiazolidinone derivatives. J Heterocycl Chem 52: 403–410.
37. Bozorov K, Zhao J, Aisa HA (2019). 1,2,3-Triazole-containing hybrids as leads in medicinal chemistry: A recent overview. Bioorg Med Chem 27: 3511–3531.
38. Dheer D, Singh V, Shankar R (2017). Medicinal attributes of 1,2,3-triazoles: Current developments. Bioorg Chem 71: 30–54.
39. Qiana J, Hana Y, Lia J, Zhang J, Hu C (2018). Toxic effect prediction of cefatirizine amidine sodium and its impurities by structure-toxicity relationship of cephalosporins. Toxicol Vitro 46: 137–147.
40. Meltem M, Neslihan D, Arif M, Serpi D, Ahmet D, Faik AA (2018). Novel azole-functionalited flouroquinolone hybrids: Design, conventional and microwave irradiated synthesis, evaluation as antibacterial and antioxidant agents. Lett Drug Des Discov 15: 46–64.
41. Bektaş H, Karaali N, Şahin D, Demirbaş A, Karaoglu ŞA, Demirbaş N (2010). Synthesis and antimicrobial activities of some new 1,2,4-triazole derivatives. Molecules 15: 2427–2438.
42. Adib M, Peytam F, Shourgeshty R, Mohammadi-Khanaposhtani M, Jahani M, Imanparast S, Faramarzi MA, Larijani B, Moghadamni AA, Esfahani EN, Fatmeh B, Mohammad M (2019) Design and synthesis of new fused carbazole-imidazole derivatives as antidiabetic agents: In vitro α-glucosidase inhibition, kinetic, and in silico studies. Bioorg Med Chem Lett 29: 713–718.
43. Bolousa M, Arumugam N, Almansour AI, Kumar RS, Maruok K, Antharam VC, Thangamani S (2019). Broad-spectrum antifungal activity of spirooxindolo-pyrrolidine tethered indole/imidazole hybrid heterocycles against fungal pathogens. Bioorg Med Chem Lett 29: 2059–2063.
44. El-Feky SA, Thabet HK, Ubeid MT (2014) Synthesis, molecular modelling and anti-inflammatory screening of novel fluorinated quinoline incorporated benzimidazole derivatives using the Pfitzinger reaction. J Fluorine Chem 161: 87–94.
45. Yanhui H, Yuyuan X, Peng Y, Haikuan Y, Xianglei M, Yuting S, Gongying W, Yanyan D (2023). The antibacterial activity and mechanism of imidazole chloride ionic liquids on Staphylococcus aureus. Front Microbiol 14: 1-10.
46. Baumann M, Baxendale IR, Ley SV, Nikbin N (2011). An overview of the key routes to the bestselling 5-membered ring heterocyclic pharmaceuticals. Beilstein J Org Chem 7: 442–495.
47. Karrouchi K, Radi S, Ramli Y, Taoufik J, Mabkhot YN, Al-Aizari FA, Ansar M (2018). Synthesis and pharmacological activities of pyrazole derivatives: A Review. Molecules 23: 134.
48. Fatima EB, Latifa D, Yahia C, Youssef R, Khalid K, M'hammed A, My El Abbes F (2020). Overview of recent developments of pyrazole derivatives as an anticancer agent in different cell line. Bioorg Chem 97: 103470.
49. Karrouchi K, Radi S, Ramli Y, Taoufik J, Mabkhot, YN, Al-Aizari FA, Ansar M (2018). Synthesis and Pharmacological Activities of Pyrazole Derivatives: A Review. Molecules 23(1):134.
50. Akbas E, Berber I., Sener A, Hasanov B (2005). Synthesis and antibacterial activity of 4-benzoyl-1-methyl-5-phenyl-1H-pyrazole-3-carboxylic acid and derivatives. Farmaco 60: 23–26.
51. Xiong B, Chen S, Zhu P, Huang M, Gao W, Zhu R, Qian J, Peng Y, Zhang Y, Dai H, Ling Y (2019). Design, Synthesis, and Biological Evaluation of Novel Thiazolyl Substituted Bis-pyrazole Oxime Derivatives with Potent Antitumor Activities by Selectively Inducing Apoptosis and ROS in Cancer Cells. Med Chem 15(7): 743-754.
52. Chu XM, Wang C, Liu W, Liang LL, Gong KK, Zhao CY, Sun KL (2019). Quinoline and quinolone

dimers and their biological activities: An overview. Eur J Med Chem 161: 101–117.
53. Nainwal LM, Tasneem S, Akhtar W, Verma G, Khan MF, Parvez S, Shaquiquzzaman M, Akhter M, Alam MM (2019). Green recipes to quinoline: A review. Eur J Med Chem 164: 121–170.
54. Bharate JB, Vishwakarma RA, Bharate SB (2015). Metal-free domino one-pot protocols for quinoline synthesis. RSC Adv 5: 42020–42053.
55. Raynes K, Foley M, Tilley L, Deady LW (1996). Novel bisquinoline antimalarials: synthesis, antimalarial activity, and inhibition of haem polymerisation. Biochem Pharmacol 52: 551–559.
56. Mahajan A, Yeh S, Nell M, Rensburg CEJ, Chibale K (2007). Synthesis of new 7-chloroquinolinyl thioureas and their biological investigation as potential anti-malarial and anticancer agents. Bioorg Med Chem Lett 17: 5683–5685.
57. Yang Y, Zou W, Peng L, Yang Z, Tang Q, Chen M, Jia S, Zhang H, Lan Z, Zheng P, Zhu W (2018). Design, synthesis, antiproliferative activity and docking studies of quinazoline derivatives bearing 2,3-dihydro-indole or 1,2,3,4-tetrahydroquinoline as potential EGFR inhibitors. Eur J Med Chem 154: 29–43.