Journal of Applied Pharmaceutical Science Vol. 12(05), pp 059-077, May, 2022
Available online at http://www.japsonline.com
DOI: 10.7324/JAPS.2022.120504
ISSN 2231-3354

N-Heterocycle derivatives: An update on the biological activity in correlation with computational predictions

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ARTICLE INFO

Received on: 14/11/2021
Accepted on: 20/01/2022
Available Online: 05/05/2022

Key words:
Oxazolone, oxazole, oxadiazole, benzoxazole, pharmacokinetics, target prediction.

ABSTRACT

This study focuses on selected potent N-heterocycle scaffolds, including oxazolone, oxazole, and oxadiazole. Numerous studies have examined their biological activity against cancer, infectious diseases, and, importantly, inflammation. Thus, efforts have been made to computationally predict and investigate the drug-like properties of these reported N-heterocycle derivatives. In this study, 19 articles have been reviewed for anticancer, antimicrobial, and anti-inflammatory activity of N-heterocycle compounds. The most potent compounds were examined for their pharmacokinetic properties and drug-like properties using the SwissADME web server. Moreover, a target prediction was performed using the Molinspiration web server to predict possible biological targets. A total of 30 compounds were selected for their potent biological activity as determined by IC_{50}, minimum inhibitory concentration, and edema inhibition for cancer, infection, and inflammation, respectively. Our computational predictions showed that all compounds have the recommended molecular weight except for C5, C6, and I5. Furthermore, the C2, C3, C8, M1, M2, M4, I1, and I4 compounds are expected to have blood–brain barrier permeability, suggesting central nervous activity. Additionally, most of the compounds showed acceptable gastrointestinal absorption. Target prediction studies suggested that compounds could modulate their biological responses via channel modulators and receptors to different degrees. The selected N-heterocycle derivatives possess promising medicinal properties that could be utilized for future drug discovery.

INTRODUCTION

The N-heterocycle is well known for its biological activity that increasingly attracts the development of novel biological entities, such as oxazole, oxazolone, benzoxazole, and oxadiazole (Vo and Bode, 2014). This class of compounds exhibits a wide variety of biological activities, including antidepressant, anticancer, antimicrobial, anti-inflammatory, anti-HIV, and analgesic effects (World Cancer Research Fund International, 2018). Currently, several available drugs contain N-heterocycle, including reclazepam, which is a benzodiazepine that has been used as an anxiolytic, thozalinone, an antidepressant, and cyclosporine, which is an immunosuppressant drug that is commonly utilized for several disorders (National Library of Medicine, 2004). N-heterocycle derivatives have been marketed and approved by the Food and Drug Administration (FDA) for numerous therapeutic indications. A promising opportunity appears to develop a novel and highly potent compound from this scaffold.

Therefore, the main objective of this review is to discuss the N-heterocycle biological activities such as the anticancer, antimicrobial, and anti-inflammatory activities and computationally predict the pharmacokinetics of the most potent compounds and their possible targets that mediate biological responses, as shown in Figure 1.

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REPORTED EXPERIMENTAL STUDIES FOR N-HETEROCYCLES

As potential anticancer agents

Background and current treatment

Cancer is defined as the uncontrolled proliferation of abnormal cells that tend to metastasize to other organs or regions of the body through several mechanisms, including mutation, deoxyribonucleic acid (DNA) lesions, cell division, and cell cycle checkpoints (Ames *et al*., 1995). It is the leading cause of death worldwide, accounting for an estimated 9.9 million deaths in 2020 (World Health Organization, 2020). Additionally, it is expected that the number of cancer mortality cases will continue to grow, reaching 21.4 million worldwide by 2030, due to changes in population demographics (World Health Organization, 2011). The most common types of cancer worldwide are lung and breast cancer, which contribute to 11.7% and 11.4% of the total cancer cases (World health organization, 2020).

Multiple therapeutic approaches are used to treat cancer, and the selection of therapy mainly depends on the type, stage, and patient comorbidities. Treatment is classified as local treatment (e.g., radiotherapy) or systemic treatment (e.g., chemotherapy) (American Cancer Society, 2021). Moreover, cancer cells tend to acquire resistance, which plays a major role in the failure of chemotherapy by several mechanisms (Gatti and Zunino, 2005; Ramos and Bentires-Alj, 2015). The first mechanism is drug inactivation, which occurs with most of the anticancer medications that require metabolic activation for their therapeutic effect, and platinum analogs are an example of this type of resistance by the formation of the platinum Glutathione (GSH) conjugate (Dasari and Bernard Tchounwou, 2014; Peklak-Scott *et al*., 2008). Second, drug efflux by P-glycoprotein, known as the multidrug resistance protein, is considered the most prevalent transporter to which the failure in treatment in over 90% of patients is attributed (Alfarouk *et al*., 2015; Aller *et al*., 2009). Third, DNA damage repair can reverse drug-induced damage, leading to anticancer drug resistance (Bonanno *et al*., 2014). Fourth, solid tumors metastasize by an epithelial-mesenchymal transition mechanism (Dudas *et al*., 2020). The fifth mechanism is drug target alteration that occurs due to mutation or modification of enzyme expression (Housman *et al*., 2014). The last mechanism is epigenetics, including DNA methylation and histone modification by either methylation or acetylation (Housman *et al*., 2014). As discussed earlier, cancer is the leading cause of death worldwide, and multiple resistance mechanisms are responsible for preventing therapeutic benefits for cancer patients.

Reported anticancer mechanisms for N-heterocycles

Numerous studies have investigated the oxazole and its related heterocycles, such as the oxadiazole and oxazolone scaffold, as a novel anticancer agent, and herein, we will discuss and summarize reported studies based on proposed mechanisms and important structural features that are essential for anticancer activity. According to Kemnitzer *et al*. (2009), the authors assessed the apoptosis-inducing activity of several oxadiazole derivatives by evaluating the ability to activate caspase, a protease enzyme that plays an essential role in cell death, using multiple cancer cell lines. The study demonstrated that oxadiazole compound C1 possesses EC_{50} equal to 0.38 µM against colorectal cancer (DLD-1) and 0.91 µM against breast cancer (T47D). However, C1 has no activity against the non-small cell lung cancer (H-1299) cell line. Furthermore, when C1 is given in combination with paclitaxel using MX-1 human breast cancer cells, it causes 80% growth inhibition with good tolerability. Overall, the authors concluded that C1 has significant anticancer activity against DLD-1 and T47D but has poor activity (EC_{50} > 10 µM) against H-1299 (Kemnitzer *et al*., 2009).

An additional study was conducted by Boulos *et al*. (2011) on oxazole derivatives using doxorubicin (DXR) as a reference drug. The results revealed that oxazole compounds C2 and C3 demonstrated an IC_{50} equal to 19.3 µg/ml using the breast (MCF7) cancer cell line. Both compounds showed a similar mechanism of action to DXR in which it interferes with DNA replication by inhibiting topoisomerase II, an enzyme responsible

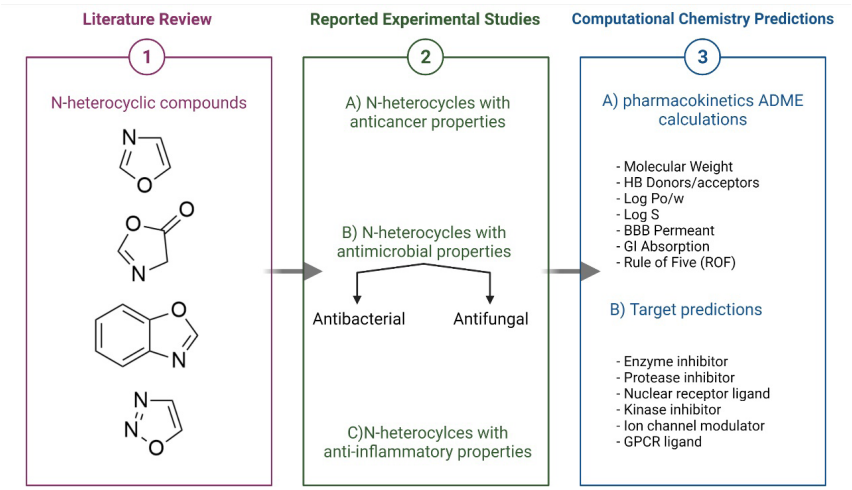


Figure 1. This article aims to review and discuss the anticancer, antimicrobial, and anti-inflammatory activity for N-heterocycle derivatives then computationally predict the pharmacokinetics and their possible targets that mediate biological responses.

for the separation of the DNA double helix, aiding its replication process (Boulos *et al*., 2011).

In another report, using a human liver cancer cell line (HepG2), Abdelhameid *et al*. (2020) compared the anticancer activity of sorafenib (SOR), an FDA-approved chemotherapy drug used to treat liver cancer, to several oxazolone derivatives. The study results showed that oxazolone derivatives possess a promising cytotoxic activity via inhibition of vascular endothelial growth factor receptor-2 (VEGF-2) that is responsible for angiogenesis in tumor cells (Pons-Cursach and Casanovas, 2019), as well as suppression of β-tubulin (TUB) polymerization. Nevertheless, both SOR and the oxazolone compound C4 were found to cause morphological changes within cancer cells, increasing the percentage of apoptosis during the cell cycle at the sub-G1 phase and the percentage of 3/7 caspase by induction of p53, a tumor suppressor gene, which activates cell apoptosis (Abdelhameid *et al*., 2020). Several triazole derivatives have been investigated by El Bourakadi *et al*. (2020) for their *in vitro* antiproliferative activity. The reported human cancer cell lines were colorectal adenocarcinoma (HT-29), non-hormone-dependent breast cancer (MDA-MB-231), and mammary gland/breast adenocarcinoma (SKBR3). Compound C5 exhibited significant activity against all the cell lines tested at IC_{50} values ranging from 1.28 to 7.72 µg/ml. Compound C5 underwent further mechanistic investigation to determine whether the cell growth inhibition was mediated by caspase activation. The HT-29 and MDA-MB-231 cells exhibiting caspase 3/7 activity increased from 6.87% and 6.73% to 21.48% and 39.46%, respectively, which indicates that compound C5 induces caspase activation (El Bourakadi *et al*., 2020).

A similar study was conducted by Minhas *et al*. (2006) to assess a series of macrocyclic compounds that contain four to seven oxazole units for their antitumor activity. Oxazole derivatives were evaluated for their ability to stabilize G-quadruplex DNA and induce cell death. Unlike hexaoxazoles, tetraoxazole macrocycle showed little or no binding to G-quadruplex DNA. Hence, the selected hexaoxazole compound C6 binds selectively to G-quadruplex DNA with moderate antitumor activity. Additionally, the reported IC_{50} values (µM) were 0.5 for murine leukemia (P388) and 0.4 for the human lymphoblastoma (RPMI 8402) (Minhas *et al*., 2006).

Reported anticancer structural requirements for N-heterocycles

To obtain effective anticancer agents, Savariz *et al*. (2012) reported that having a good electron-donating substituent is crucial for anticancer activity. The study investigated the *in vitro* cytotoxic activity of four oxazolone moieties against six cancer cell lines, including glioma (U251), melanoma (UACC-62), breast (MCF7), prostate (PC-3), ovarian (OVCAR-03), and colon (HT-29) cells. The study results demonstrated a potent activity with IC_{50} < 10 µM against three cancer cell lines, glioma (U251), prostate (PC-3), and ovarian (OVCAR-03), for two out of the four compounds. On the contrary, due to a lack of an electron-donating substituent at the phenyl ring, the other two compounds showed activity *only* in melanoma (UACC-62). Thus, it is apparent from this study that having a good electron-donating substituent at the phenyl ring at C-1 is important for cytotoxic activity in cancer cells. The most potent compound, C7, with $IC_{50} \leq 1.50$ µM for U251, PC-3, and OVCAR-03 showed promising activity as a novel anticancer agent (Savariz *et al*., 2012).

Along with the above-discussed study having *p*-fluorophenyl at the C-2 position equally important for the activity as reported by Kumar *et al*. (2010), the anticancer activity was determined using a formazan dye [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT)] conversion assay to determine the antitumor activity for 18 oxazole derivatives against 6 human cancer cell lines, prostate (PC-3, DU145, and LnCaP), breast (MCF7 and MDA231), and pancreatic (PaCa2) cells. Five compounds demonstrated an IC_{50} < 50 µM against numerous cancer cell lines. Compound C8 showed selective and potent cytotoxic activity against PC-3 (42.8), DU143 (31.8), MCF7 (28), and PaCa2 (40.6). The study highlighted that *p*-fluorophenyl at the C-2 position is necessary for the activity, as seen in C8, which demonstrated promising anticancer activity against all cancer cell lines (Kumar *et al*., 2010).

Reported anticancer activity for N-heterocycles (miscellaneous)

As summarized in Fadda *et al*.'s (2020) study, the authors synthesized derivatives that possess a moderate to strong cytotoxic effect against several cancer cell lines. No proposed mechanism or structural requirement has been reported. Moreover, the most potent compound, C9, showed IC_{50}s of 8.9, 9.2, 13.1, and 12.1 µg/ml against liver cancer (HepG2), colon cancer (HTC-116), prostate cancer (PC-3), and breast cancer (MCF7), respectively, suggesting a remarkable anticancer activity for the tested compound (Fadda *et al*., 2020). In a similar attempt, Sengupta *et al*. (2008) studied oxadiazole derivatives that possessed anticancer activity against Ehrlich ascites carcinoma (EAC) cells and originated from human breast cancer cells (T47D) by spontaneous passaging. The experiment was performed using Swiss albino mice by measuring the ability of oxadiazole derivatives to inhibit cancer cell growth in ascitic fluid. One of the synthesized oxadiazole compounds, C10, demonstrated the ability to reduce the percentage of tumor weight inhibition (% TWI) by 37.93 and inhibit the tumor cell count (% TCI) by 37.86 (Sengupta *et al*., 2008). All reviewed studies are summarized in Table 1.

As potential antimicrobial agents

Background and current treatment

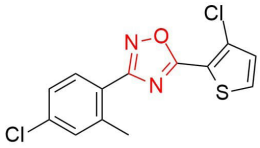
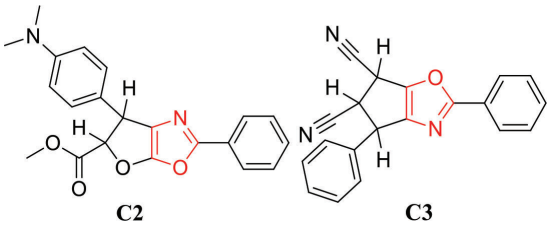
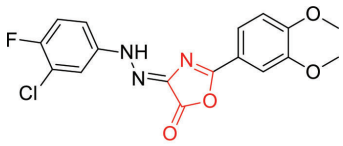
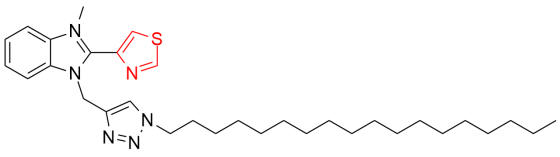
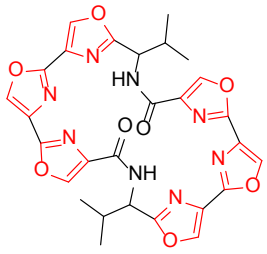
Infectious diseases kill 17 million people per year. Approximately 50,000 people, whether adults or children, die every day because of infectious diseases (World Health Organization, 1996). Lower respiratory infections were considered the fourth leading cause of death globally in 2019 by the WHO (2020). Fortunately, an infectious disease can be prevented by a vaccine and treated using the correct antimicrobial drugs. The first antibiotic, penicillin, was discovered by Alexander Fleming in 1928, followed by the major development of different antibiotic classes, which contributed to a significant reduction in the mortality and morbidity of some infectious diseases such as pneumonia and gonorrhea (Silver, 2011).

To cure a patient of infection, the clinician needs to identify the microbe type, and based on the findings, the treatment can be initiated with a specific antibiotic, anti-viral or antifungal (Standing up to infectious disease, 2019). However, antimicrobial

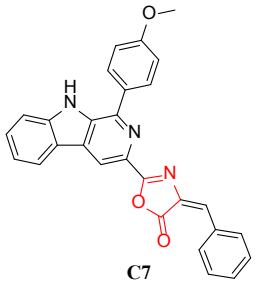
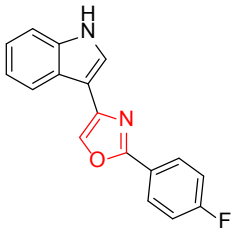
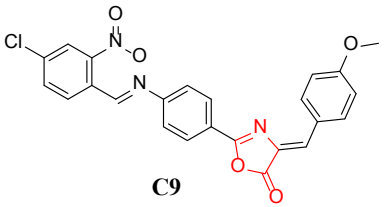
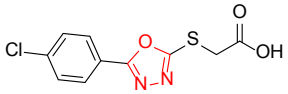
therapy may fail due to multiple causes (Cunha and Ortega, 1995). Among the leading causes is antimicrobial resistance (AMR), which is the most challenging one, affecting the quality of life and economy (Septimus, 2018). Furthermore, statistics indicate that, by the year 2050, there will be a rise in AMR that will lead to 10 million people dying every year, and the global economic cost would be up to 100 trillion USD (Review on Antimicrobial Resistance, 2014). Additionally, AMR extends hospital stays, additional doctor visits, and high costs, which pose a high risk of the occurrence of chronic diseases (Centers for Disease Control and Prevention, 2020).

The microorganism can develop resistance through numerous mechanisms, such as destruction of drugs by enzymes, pumps, or changing of the entryways (Centers for Disease Control

Table 1. The reported anticancer activity for N-heterocycles.

Chemical structure	N-heterocycle	Cell line	Activity	Mechanism	Reference
 **C1**	Oxadiazole	Breast (T47D) Non-small cell lung cancer (H-1299) Colon (DLD-1)	EC_{50} (µM): T47D: 0.91 ± 0.09 H1299: >10 DLD1: 0.38 ± 0.06	Caspase activation	Kemnitzer *et al.*, 2009
 **C2** **C3**	Oxazole	Breast (MCF7)	IC_{50} (µg /ml): 19.3[e]	Intercalation into DNA and inhibition of topoisomerase II	Boulos *et al.*, 2011
 **C4**	Oxazolone	Liver cancer cell (HepG2) Normal human liver cell (HL-7702)	IC_{50} (µM): HepG-2: 2.91 ± 0.15 HL-7702: 131.78 ± 11.33 VEGF-2: 0.21536 ± 0.01072 µM	-Increase p53 induction by either BAX/ BCL-2 or Fas-L which increases the percentage of 3/7 caspase -An increase of accumulation of the cells at G2/M phase -Suppressing β-TUB polymerization.	Abdelhameid *et al.*, 2020
 **C5**	Triazole		IC_{50} (µM): HT-29: 1.28 ± 0.32 MDA-MB 321: 3.45 ± 0.25 SKBR3: 7.72 ± 0.20	—	El Bourakadi *et al.*, 2020
 **C6**	Hexaoxazole	Murine leukemia (P388) Human lymphoblastoma (RPMI 8402)	IC_{50} (µM): P388: 0.5 RPMI 8,402: 0.4	Stabilize G-quadruplex DNA	Minhas *et al.*, 2006

Continued

Chemical structure	N-heterocycle	Cell line	Activity	Mechanism	Reference
 **C7**	Oxazolone	Glioma (U251) Prostate (PC-3) Ovarian (OVCAR-03) Melanoma (UACC-62) Colon (HT-29) Breast (MCF7)	IC_{50} (μM): U251: 0.48 PC-3: 1.50 OVCAR-03: 1.07 UACC-62: 10 HT-29: 67.88 MCF7: 23.44	—	Savariz *et al.*, 2012
 **C8**	Oxazole	Prostate (PC-3) Prostate (DU145) Prostate (LnCaP) Breast (MCF7) Breast (MDA231) Pancreatic (PaCa2)	IC_{50} (μM): PC-3: 42.8 DU145: 31.8 LnCaP: 59.8 MCF7: 28 MDA231: 90.4 PaCa2: 40.6	—	Kumar *et al.*, 2010
 **C9**	Oxazolone	Liver (HepG2) Prostate (PC-3) Breast (MCF7) Colon (HTC-116)	IC_{50} (μg /ml): HepG2: 8.9 ± 0.30 PC-3: 13.1 ± 1.06 MCF7: 12.1 ± 1.06 HTC-116: 9.2 ± 0.63	—	Fadda *et al.*, 2020
 **C10**	Oxadiazole	EAC Originated from human breast carcinoma	% TWI: 37.93 % TCI: 37.86	—	Sengupta *et al.*, 2008

C1: compound 1 with anticancer activity, C2: compound 2 with anticancer activity, C3: compound 3 with anticancer activity, C4: compound 4 with anticancer activity, C5: compound 5 with anticancer activity, C6: compound 6 with anticancer activity, C7: compound 7 with anticancer activity, C8: compound 8 with anticancer activity, C9: compound 9 with anticancer activity, C10: compound 10 with anticancer activity.
LC_{50}: the concentration required to kill half the cells in the cell culture, IC_{50}: compound concentration required to inhibit tumor cell proliferation by 50%. Values are means of three experiments, GI_{50}: the concentration of drug causing 50% inhibition of cell growth, EC_{50}: the dose (or concentration) causing 50% of maximum effect for any measured biological effect of interest, ND: not determined.
e according to the American National Cancer Institute guidelines, medications with IC_{50} < 30 mcg/ml are active.

and Prevention, 2020). Moreover, the most common examples of AMR are modifications of the bacterial structure and membrane, which inhibit the medication that acts on the membrane to attach and produce actions such as penicillin (beta-lactam antibiotic) (Capita and Alonso-Calleja, 2013). The second mechanism is enzymatic inactivation, which more commonly happens to beta-lactam medications as the bacteria produce a lactamase enzyme that degrades the medication, thus yielding to the inactivation of the drugs (Capita and Alonso-Calleja, 2013). The third mechanism is efflux pumps, which transport the drugs outside the cell, thus reducing the intracellular drug concentration (Alanis, 2005). The fourth mechanism is target remodeling. As some drugs bind to the ribonucleic acid (RNA) to produce activity, such as fluoroquinolones, mutation of the binding site will decrease the affinity and antibacterial effect (Alanis, 2005). Lastly, through the development of new metabolic pathways. For example, sulfonamide and trimethoprim interfere with the bacterial folic acid synthesis, so the bacteria form changes in the target enzyme. Thus, reducing their affinity.

N-heterocycles have been reported to possess antimicrobial activity that could overcome some of the discussed challenges. Thus, herein, we will discuss and review several articles based on structural requirements for antimicrobial activity against multiple organisms such as *Staphylococcus aureus*

Bacillus subtilis, Pseudomonas aeruginosa, Candida albicans, and Aspergillus niger.

Reported antibacterial structural requirements for N-heterocycles

Olomola *et al*. (2018) synthesized oxazolone derivatives and screened them against several Gram-positive and Gram-negative bacteria, including *S. aureus, Bacillus cereus, Streptococcus pneumonia, Enterococcus faecalis, Corynebacterium pyogenes, P. aeruginosa, Proteus vulgaris, Klebsiella pneumoniae, Escherichia coli*, and *Shigella* sp. Using streptomycin and ampicillin as control drugs, Olomola *et al*. (2018) found that M1 exhibits a higher minimum inhibitory concentration (MIC) in *E. coli* and *S. pneumonia* relative to ampicillin which was due to the presence of the bromo group in the phenyl ring. Moreover, the authors proposed that this derivative demonstrates its activity via bacterial cell wall disruption. However, the exact mechanism was not specified (Olomola *et al*., 2018). Moreover, Rawat and Shukla (2016) investigated the activity of the oxazole compound M2 as an antimicrobial agent. Ampicillin was used as a reference drug against the *S. aureus, B. subtilis, P. aeruginosa*, and *E. coli* bacterial strains. Using the zone of inhibition, compound M2 demonstrated antibacterial activity with a zone of inhibition greater than 15 mm, and the authors concluded that the presence of an electron-withdrawing group at the para position is essential for the antibacterial activity (Rawat and Shukla, 2016).

An additional study conducted by Shukla *et al*. (2016) assessed the antimicrobial effect of oxadiazoles while using ciprofloxacin and fluconazole as reference drugs. The authors highlighted the importance of the electron-donating group for antibacterial activity. The tested bacteria strains were *S. aureus, E. faecalis, E. coli*, and *P. aeruginosa*, and the antibacterial activity of ciprofloxacin (MIC) was between 62.5 and 125 µg/ml, while the oxadiazole derivative M3 values were between 15.62 and 125 µg/ml against the same bacterial strains (Shukla *et al*., 2016). One study investigated 13 oxazolone derivatives, and the results indicated that the oxazolone derivative M4 had an MIC value of 166.4 µg/50 µl against *B. subtilis* and 160 µg/50 µl against *E. coli*. Pasha *et al*. (2007) highlighted that the halogen derivatives of substituted oxazolones appear to have a significant impact on antibacterial activity. Additionally, Andrejević *et al*. (2020) have assessed the antibacterial activity using two Gram-positive, *S. aureus* and *Listeria monocytogenes*, and two Gram-negative, *P. aeruginosa* and *E. coli*, species. In this study, they investigated the antimicrobial activity of zinc (II) complexes with different N-heterocycles. Consider that zinc shows a significant reduction in child mortality in the treatment of infections causing uncontrollable diarrhea in Asian and African countries (Larson *et al*., 2009). Considerable zones of inhibition for M5 have been detected for all organisms except for *P. aeruginosa* (Andrejević *et al*., 2020).

A recent piece of evidence added by Arshad (2018) revealed the antibacterial activity of oxazole derivatives on the Gram-positive bacteria *S. aureus* and *Staphylococcus epidermidis* as well as the Gram-negative bacteria *E. coli* and *Proteus mirabilis*. It is worth mentioning that the author did not report any structural requirements nor mechanisms for activity. However, the author reported that derivative M6 exhibited significant antibacterial activity ≤24.32 against the four bacteria strains which were measured by the zone of inhibition (mm) (Arshad, 2018). A similar investigation was conducted by Singh *et al*. (2017) on a few oxazolone derivatives, which were found to possess antimicrobial activity against the bacteria *E. coli*, *P. aeruginosa, S. aureus*, and *Streptococcus pyogenes*, along with the fungi *C. albicans, A. niger*, and *Aspergillus clavatus*. Compound M7 exhibited high activity against the four bacterial species with an MIC value equal to or below 125 µg/ml comparable to the antibacterial drugs ampicillin (MIC value 100–250 µg/ml) and chloramphenicol (MIC is 50 µg/ml) (Singh *et al*., 2017).

In another study done by Naganagowda *et al*. (2011) the authors synthesized 23 oxazolone and imidazolone derivatives and tested for their antibacterial activity against Gram-negative bacteria *P. aeruginosa* and *E. coli* and Gram-positive bacteria (*S. aureus and B. subtilis*). The study results showed that compound M8 had a zone of inhibition (mm) of less than 20, suggesting N-heterocycle derivatives hold great promise as active antimicrobial candidates (Naganagowda *et al*., 2011). A similar study conducted by Gadhe *et al*. (2010) found that compound M9 has a similar zone of inhibition (in mm) to ampicillin sodium against *B. subtilis* and *S. aureus* (Gram-positive bacteria) and *E. coli* and *Salmonella typhi* (Gram-negative bacteria). All the examined studies are compiled in Table 2a.

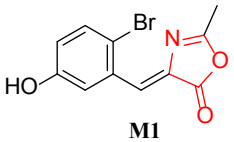
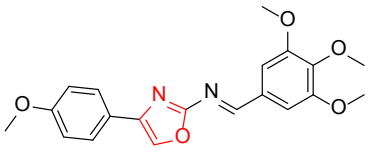
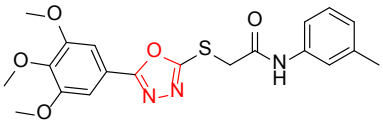
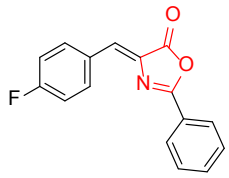
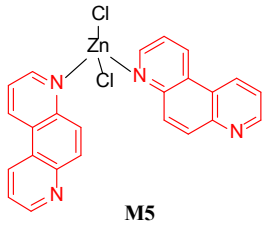
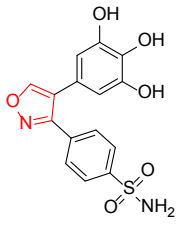
Reported antifungal activity for N-heterocycles

A considerable amount of literature has been published on N-heterocycle activity as a novel antifungal agent. However, little to no detailed information was found about the structural requirements for this type of activity. For example, Andrejević *et al*. (2020) evaluated the antifungal activity of M5 against two *Candida* strains, *C. albicans and C. parapsilosis*. The author reported that M5 shows inhibition zones (mm) equal to 3 and 7 for *C. albicans and C. parapsilosis*, respectively (Andrejević *et al*., 2020). In a similar attempt, Gadhe *et al*. (2010) explored the antifungal properties of oxazole derivatives, and their analogs were evaluated against *C. albicans and A. niger* using clotrimazole as a reference drug. The study results showed that M9 had a zone of inhibition (mm) equal to 30 and 21 against *C. albicans* and *A. niger* (Gadhe *et al*., 2010).

In Singh *et al*.'s (2017) study, the authors determined the antifungal activity of the oxazole compound M10 against *C. albicans and A. niger*. This compound showed a MIC of under 500 µg/ml and was compared with the antifungals nystatin (MIC 100 µg/ml) and griseofulvin (MIC 100–500 µg/ml). However, there was barely any reported activity shown against *A. clavatus* fungi (Singh *et al*., 2017). Compound M11 was synthesized by Shukla *et al*. (2016) and showed promising antifungal activity against two fungal strains, *C. albicans and A. niger*. The synthesized oxadiazole agent (MIC range from 31.25 to 62.5 µg/ml) demonstrated higher potency relative to fluconazole (MIC values between 62.5 and 125 µg/ml) (Shukla *et al*., 2016).

In a similar attempt Rawat and Shukla (2016), compared the antifungal activity of ketoconazole with oxazole derivatives. Compound M12 was reported to be the most potent among the other derivatives with antifungal efficacy against *C. albicans and A. niger* fungal strains. Furthermore, the action was measured using the zone of inhibition. Rawat and Shukla (2016) concluded that compounds with a zone of inhibition greater than 15 mm

Table 2a. The reported antibacterial activity of N-heterocycles.

Chemical structure	N-heterocycle	Bacteria	Activity	Mechanism	Reference
 **M1**	Oxazolone		MIC (mg/ml)	Cell wall disruption	Olomola *et al*., 2018
		E. coli	0.31		
		P. aeruginosa	0.625		
		P. vulgaris	ND		
		K. pneumoniae	ND		
		S. aureus	ND		
		C. pyogenes	ND		
		S. pneumoniae	0.31		
		B. cereus	ND		
 **M2**	Oxazole		Zone of inhibition (mm)	—	Rawat and Shukla, 2016
		S. aureus	16		
		B. subtilis	18		
		P. aeruginosa	17		
		E. coli	18		
 **M3**	Oxadiazole		MIC (µg/ml)	—	Shukla *et al*., 2016
		S. aureus	15.62		
		E. faecalis	125		
		E. coli	62.5		
		P. aeruginosa	31.5		
 **M4**	Oxazolone		MIC (µg/50µl)	—	Pasha *et al*., 2007
		B. subtilis	166.4		
		E. coli	160.4		
 **M5**	Phenanthroline		Zone of inhibition (mm)	—	Andrejević *et al*., 2020
		S. aureus	3		
		E. coli	3		
		L. monocytogenes	1.5		
 **M6**	Oxazole		Zone of inhibition (mm)	—	Arshad, 2018
		S. aureus	22.22 ± 0.33		
		S. epidermidis	23.18 ± 0.34		
		E. coli	24.32 ± 0.30		
		P. mirabilis	22.24 ± 0.20		

Continued

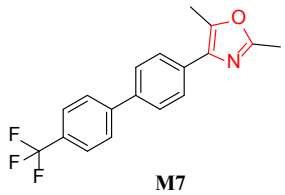
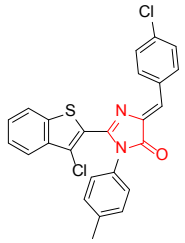
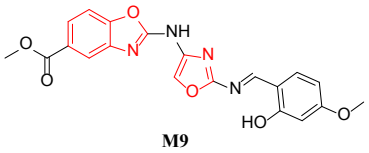
Chemical structure	N-heterocycle	Bacteria	Activity	Mechanism	Reference
			MIC (µg/ml)		
 **M7**	Oxazole	*E. coli*	62.5	—	Singh *et al*., 2017
		P. aeruginosa	100		
		S. aureus	125		
		S. pyogenes	125		
 **M8**	Imidazolone	*S. aureus*	Zone of inhibition (mm) 16	—	Naganagowda *et al*., 2011
		B. subtilis	15		
		P. aeruginosa	11		
		E. coli	15		
 **M9**	Oxazole/ benzoxazole	*B. subtilis*	Zone of inhibition (mm) 24	—	Gadhe *et al*., 2010
		S. aureus	22		
		E. coli	21		
		S. typhi	20		

exhibit strong antifungal activity against microbes. The activities of the compounds in the discussed studies are outlined in Table 2b.

As potential anti-inflammatory agents

Background and current treatment

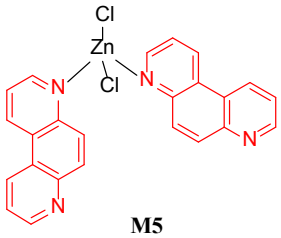
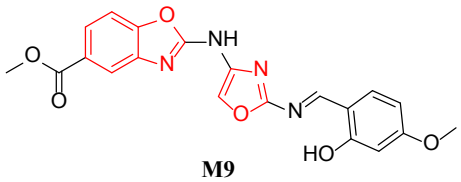
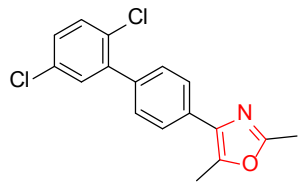
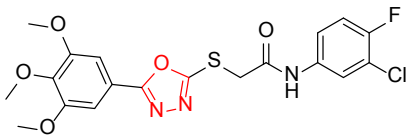
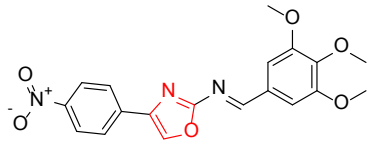
Inflammation reflects the immune system's response to a foreign object, which could manifest as redness, heat, swelling, pain, and loss of function (Stone *et al*., 2021). Inflammatory diseases include a wide range of disorders such as diabetes, cardiovascular diseases, chronic respiratory diseases, cancer, arthritis, and joint diseases (Desai *et al*., 2012). The prevalence of arthritis affects approximately 350 million people worldwide and 43 million people in the United States. It was reported that inflammatory diseases might increase mortality in a situation in which three out of five people die from chronic inflammatory diseases (Pahwa *et al*., 2020). Inflammation is classified into two types: acute inflammation and systemic chronic inflammation. Acute inflammation is triggered by pathogen-associated molecular patterns that are functional components of the microorganisms, such as peptidoglycan, double-stranded RNA, and lipopolysaccharide (Akira *et al*., 2006; Janeway Jr and Medzhitov, 2002). Besides, acute inflammation is triggered by damage-associated molecular patterns which are related to tissue destruction or damage (Rubartelli and Lotze, 2007).

As for the treatment of inflammation, numerous choices are available depending on the inflammation type and disease. For example, nonsteroidal anti-inflammatory drugs (NSAIDs) and cyclooxygenase (COX) inhibitors are used to relieve pain caused by arthritis or a musculoskeletal injury (Crofford, 2013; Mathew *et al*., 2011; Wongrakpanich *et al*., 2018). In comparison, corticosteroids are used for a variety of conditions such as systemic lupus, asthma, and sarcoidosis (Barnes, 2006; Grutters and Van den Bosch, 2006; Stojan and Petri, 2013). Approved drugs, such as NSAIDs, are commonly prescribed but can exhibit nephrotoxicity and gastrointestinal (GI) side effects.

Reported anti-inflammatory mechanisms and structural requirements for N-heterocycles

A lot of research was conducted to discover novel anti-inflammatories with minimal side effects. Moreover, the unique

Table 2b. The reported antifungal activity of N-heterocycles.

Chemical structure	N-heterocycle	Fungi	Activity	Mechanism	Reference
 **M5**	Phenanthroline		Zone of inhibition (mm)	—	Andrejević *et al.*, 2020
		C. albicans	3		
		C. parapsilosis	7		
 **M9**	Oxazole/ benzoxazole		Zone of inhibition (mm)	—	Gadhe *et al.*, 2010
		C. albicans	30		
		A. niger	21		
 **M10**	Oxazole		MIC (µg/ml)	—	Singh *et al.*, 2017
		C. albicans	250		
		A. niger	500		
		A. clavatus	>1,000		
 **M11**	Oxadiazole		MIC (µg/ml)	—	Shukla *et al.*, 2016
		C. albicans	62.5		
		A. niger	31.25		
 **M12**	Oxazole		Zone of inhibition (mm)	—	Rawat and Shukla, 2016
		C. albicans	17		
		A. niger	16		

MIC: minimum inhibitory concentration, ND: not determined.
M1: compound 1 with antimicrobial activity, M2: compound 2 with antimicrobial activity.
M3: compound 3 with antimicrobial activity, M4: compound 4 with antimicrobial activity, M5: compound 5 with antimicrobial activity, M6: compound 6 with antimicrobial activity, M7: compound 7 with antimicrobial activity, M8: compound 8 with antimicrobial activity, M9: compound 9 with antimicrobial activity, M10: compound 10 with antimicrobial activity, M11: compound 11 with antimicrobial activity, M12: compound 12 with antimicrobial activity.

anti-inflammatory properties of the N-heterocycle scaffold have been an object of research since the 1980s. Herein, we reviewed and summarized the recent advances and updates regarding the anti-inflammatory properties of the N-heterocycle scaffold.

The study conducted by Mohamed *et al.* (2017) designed and synthesized a series of oxazolones to evaluate the inhibitory activity against both the COX-1 and COX-2 enzymes. Using IC_{50} (µmol) as a measurement tool and celecoxib as a reference drug, seven oxazolone derivatives have been evaluated, and the results showed higher inhibitory activity against the COX-2 than COX-1 enzymes. Compound I1 was associated with a lower IC_{50} against COX-2 relative to the reference drug, suggesting a better inhibitory activity that could overcome the GI side effects (Mohamed *et al.*, 2017). In another attempt to investigate the anti-inflammatory activity of oxadiazole by inhibition of the COX enzyme, Bezerra *et al.* (2005) reported the ability of 1,2,4-oxadiazole derivatives to reduce carrageenan-induced edema in mice. The test was conducted with the use of aspirin and ibuprofen as standard drugs in comparison to oxadiazole derivatives. The results suggested that compounds I2 and I3 had

a proportional anti-inflammatory effect with aspirin and ibuprofen in the inhibition of the COX enzyme. Further analysis showed the presence of a decapentyl group at the C-5 position enhances the anti-inflammatory activity (Bezerra *et al*., 2005).

Additionally, Gökhan-Kelekçi *et al*. (2009) assessed the anti-inflammatory activity for 12 benzoxazolone derivatives. Using indomethacin as a reference compound and a carrageenan-induced hind paw edema model as a screening tool, the authors reported a significant positive correlation between bearing no substituent at the phenyl ring and expressing significant activity at the 50 and 100 mg/kg doses in compound I4 when compared to indomethacin. The proposed mechanism is via inhibition of either the COX-1 and/or COX-2 enzymes (Gökhan-Kelekçi *et al*., 2009). In a recent study conducted by Abd El-Hameed *et al*. (2021) that investigated several pyridazinone derivatives, the author found that compound I5 can inhibit both the COX and lipoxygenase (LOX) enzymes. The dual inhibition of COX/LOX shows a higher anti-inflammation efficacy and lower incidence of vascular adverse events that could occur in potent COX-2 inhibitors (Abd El-Hameed *et al*., 2021). In a study conducted by Husain and Priyanka Ahuja (2009) to evaluate the biological activity of oxadiazole compounds as anti-inflammatory agents, the authors tested carrageenan-induced paw edema in rats and compared the activity of the compounds in percent of inhibition with that of indomethacin. Among the 17 oxadiazoles, compound I6 was shown to have the highest anti-inflammatory efficacy, with 56.2% inhibition of inflammation (Husain and Priyanka Ahuja, 2009).

Zheng *et al*. (2015) synthesized 10 compounds and examined their anti-inflammatory activity using a carrageenan-induced rat paw edema test and aspirin as a reference drug. Interestingly, compound I7 demonstrated anti-inflammatory activity, equal to 56.6%, which showed higher potency relative to aspirin. The study concluded that benzoxazolone derivatives have remarkable anti-inflammatory activity as highlighted (Zheng *et al*., 2015). A study conducted by Narayana *et al*. (2005) tested the anti-inflammatory activity of 1,3,4-oxadiazole. The results showed that derivative I8 possesses a higher percentage of edema inhibition (71.1%) than indomethacin (69.2%). Thus, derivative I8 possesses a promising anti-inflammatory activity that could be further developed and optimized to discover novel treatments for inflammatory-based diseases (Narayana *et al*., 2005). All the related measurements of the discussed studies are summarized in Table 3, and all the proposed mechanisms of N-heterocycles for the three activities are shown in Figure 2.

COMPUTATIONAL CHEMISTRY PREDICTIONS

Pharmacokinetics (ADME) properties of N-heterocycles

The most potent N-heterocycle derivatives that were discussed above were selected and evaluated for their physicochemical properties. Moreover, all the generated SMILES for the chemical structures are summarized in Tables T1S–T3S. The values were measured and calculated using the SwissADME web server, which is a tool that gives access to computer models (e.g., the ESOL model) that can predict the physicochemical properties, pharmacokinetics, and drug-likeness (Daina *et al*., 2017). Each compound has been drawn by using ChemAxon's Marvin JS, which enables the user to draw a 2D chemical structure. After drawing completion, the system starts the calculations and runs the computation. The results are shown in Tables 4–6.

Molecular weight (MW)

MW can have a significant role in determining solubility, penetration, absorption, and distribution of compounds (Gleeson, 2008). Aside from compounds C5, C6, and I5, all of the measurements fall within the recommended range (150–500 g/mol) as recommended in the SwissADME web server (Daina *et al*., 2017).

Hydrogen bond-donor/acceptor (HB-donor/acceptor)

An increase in the number of HB-donors and/or acceptors can suppress the permeability of the molecule to the cell membrane (Desai *et al*., 2012). According to Lipinski *et al*. (2001) [rule of five (ROF)], HB-D should be ≤5, and HB-A should be ≤10 to predict drugs with high absorption ability. Except for C6, all the compounds follow this rule.

Lipophilicity log Po/w (WLOGP)

LogPo/w [(log P method developed by Wildman and Crippen (WLOGP)] plays a major role with topological polar surface area in classifying compounds into blood–brain barrier (BBB) permeant and GI absorption in the BOILED egg model in SwissADME. It is stated that compounds with log P ranging from +0.4 to +6.0 can penetrate the BBB. Thus, activity on the central nervous system (CNS) can be predicted. All of the anticancer compounds have a Log Po/w less than or equal to 5, except C5. Compounds M5, M7, and M8 of the antimicrobials, as well as I2 and I3 of the anti-inflammatory compounds, fall outside this range.

Solubility log S (SILICOS-IT)

Solubility can be affected by MW, hydrogen bonding, and lipophilicity. As the MW decreases, the solubility increases. According to SwissADME, the classification of compounds that possess Log S > −4 is considered water-soluble. However, compounds with Log S < −6 are moderately soluble (Daina *et al*., 2017). Therefore, C10, M1, and I7 are highly soluble compounds, while the rest of the compounds were found to be moderate to poorly soluble.

BBB permeability

For CNS activity, BBB permeability is essential. Besides, lipophilicity, MW, and hydrogen bonds may influence brain permeation positively (Di, 2008). As demonstrated in Tables 4–6, the compounds capable of BBB penetration are C2, C3, C8, M1, M2, M4, I1, and I4.

GI absorption

Oral absorption is highly affected by solubility, permeability, and MW (Di, 2008). Because of their poor solubility, compounds C5, C6, M5, M6, M7, M9, M11, I2, and I3 demonstrated poor GI absorption.

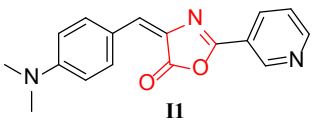
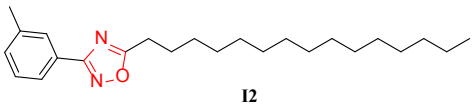
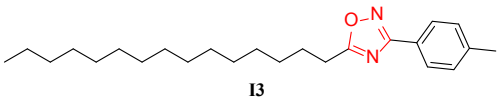
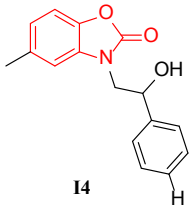
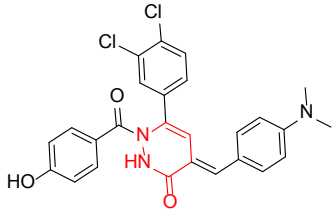
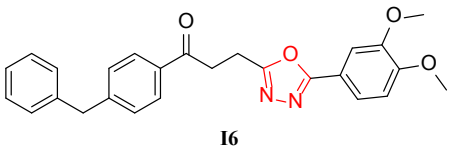
Rule of five

The ROF, which is also called Lipinski's rule, is a set of structural characteristic guidelines for drug-like structures (MW ≤ 500, Log P ≤ 5, HB-D ≤ 5, and HB-A ≤ 10) (Di, 2008). All the compounds follow the ROF with zero violations except C5 violated MW > 500, Moriguchi octanol-water partition coefficient (MLOGP) > 4.15, C6 violated MW > 500, NorO > 10, and M8, I2, I3, I5, I8 have one violation, which is MLOGP > 4.15.

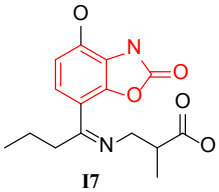
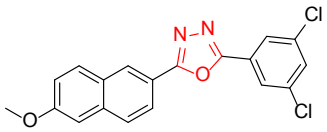
Target predictions of N-heterocycles

Using the Molinspiration web server (Molinspiration software), Tables 7–9 summarize the bioactivity scores of the most potent anticancer, antimicrobial, and anti-inflammatory N-heterocycle derivatives to predict the probability of the compounds being bioactive at a specific target. As reported in the web server, the higher the bioactivity score (positive value), the more likely it will be active at that target (Molinspiration software).

Table 3. The reported anti-inflammatory activity of N-heterocycles.

Chemical structure	N-heterocycle	Activity	Mechanism	Reference
 **I1**	Oxazolone	IC_{50} COX-1 µmol: 0.08 IC_{50} COX-2 µmol: 0.019	Inhibition of COX-1 and COX-2 enzymes	Mohamed *et al*., 2017
 **I2**	Oxadiazole	Edema inhibition (%) 67	COX inhibition	Bezerra *et al*., 2005
 **I3**	Oxadiazole	Edema inhibition (%) 67	COX inhibition	Bezerra *et al*., 2005
 **I4**	Benzoxazolone	Swelling in thickness (× 10−2 mm): 90 minutes: 37.9 180 minutes: 43.9 270 minutes: 15 360 minutes: 22.4	Inhibition of COX-1 and COX-2 enzymes	Gökhan-Kelekçi *et al*., 2009
 **I5**	Pyridazinone	IC_{50} COX-2 (µm): 0.04 ± 0.00 IC_{50} LOX (µm): 3.17 ± 0.06 IC_{50} TNF-α: 2.90 ± 0.10	—	Abd El-Hameed *et al*., 2021
 **I6**	Oxadiazole	Anti-inflammatory activity* (% inhibition ± SEM) 56.20 ± 2.32	—	Husain and Priyanka Ahuja, 2009

Continued

Chemical structure	N-heterocycle	Activity	Mechanism	Reference
 I7	Benzoxazolone	Anti-inflammatory activity: 56.6% Activity relative to the reference drug (aspirin = 100): 136	—	Zheng *et al*., 2015
 I8	Oxadiazole	Edema inhibition (anti-inflammatory activity) (%) 71.1	—	Narayana *et al*., 2005

SEM: standard error of the mean, COX-1: cyclooxygenase-1, COX-2: cyclooxygenase-2, LOX: lipoxygenase, TNF-α: tumor necrosis factor-α, I1: compound 1 with anti-inflammatory activity.
I2: compound 2 with anti-inflammatory activity, I3: compound 3 with anti-inflammatory activity, I4: compound 4 with anti-inflammatory activity, I5: compound 5 with anti-inflammatory activity, I6: compound 6 with anti-inflammatory activity, I7: compound 7 with anti-inflammatory activity, I8: compound 8 with anti-inflammatory activity.

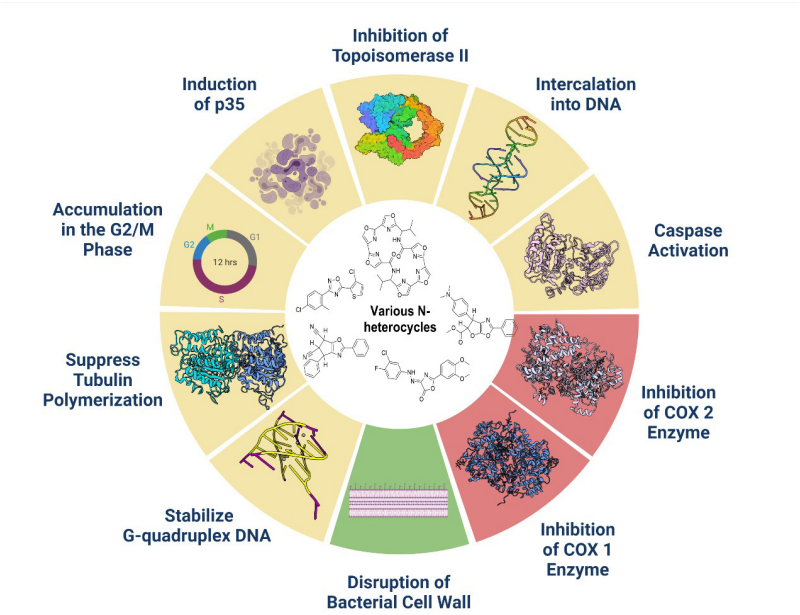


Figure 2. This figure highlight all the reported mechanisms of N-heterocycle derivatives, it works on several sites on cancer cell lines such as DNA itself and cell cycle. Moreover, it disrupts the bacterial cell wall to produce anti-microbial activity. Furthermore, it works on COX-1 and/or COX-2 for anti-inflammatory activity.

G Protein-coupled receptor (GPCR) ligands

GPCRs are the largest superfamily of membrane receptors (Trzaskowski *et al*., 2012). The GPCR plays a role in the enhancement of phagocyte migration to infected cells so that the phagocytes can easily kill the invading bacteria and fungi and reduce inflammation (Sun and Richard, 2012). As shown in Table 7, C5, C6, and C8 demonstrated positive values for the GPCR target protein, which could potentially mediate anticancer activity. Moreover, among 11 antimicrobial compounds, M6, M7, and M10 possess a positive value, which indicates their good activity at this target, while in the anti-inflammatory compounds the highest positive value is I7, with a score of 0.28, followed by I2 and I3.

Ion channel modulators

Modulators enrich the movement of ions through the cell membrane. Additionally, ion channels such as K+ and Ca2+ are essential for cell proliferation (Paramashivam *et al*., 2015). Of the anticancer compounds, none were active at this target. However, M6, M7, and M10 are the best antimicrobial derivatives that could serve as ion channel modulators. Moreover, only compound I7 showed considerable ion channel activity.

Kinase inhibitors (KIs)

KI subfamilies facilitate signaling pathways and regulate the invasion, adhesion, and migration of particles and

Table 4. The pharmacokinetics ADME properties of N-heterocycles with anticancer activity.

Compounds code	Molecular weight	HB-donors	HB-acceptors	Log Po/w (WLOGP)	Log S (SILICOS-IT)	BBB permeant	GI absorption	ROF
N-heterocycles								
C1	311.19 g/mol	0	3	5.08	−6.77	No	High	Yes; 0 violations
C2	364.39 g/mol	0	5	3.47	−6.24	Yes	High	Yes; 0 violations
C3	311.34 g/mol	0	4	4.23	−6.57	Yes	High	Yes; 0 violations
C4	377.75 g/mol	1	7	3.07	−6.58	No	High	Yes; 0 violations
C5	549.84 g/mol	0	3	9.29	−9.19	No	Low	No; 2 violations: MW > 500, MLOGP > 4.15
C6	600.54 g/mol	2	14	3.44	−9.9	No	Low	No; 2 violations: MW > 500, NorO > 10
C7	445.47 g/mol	1	5	5.25	−10.15	No	High	Yes; 0 violations
C8	278.28 g/mol	1	3	5.05	−7.44	Yes	High	Yes; 0 violations
C9	461.85 g/mol	0	7	5.23	−8.03	No	High	Yes; 0 violations
C10	270.69 g/mol	1	5	2.57	−3.89	No	High	Yes; 0 violations

Table 5. The pharmacokinetics ADME properties of N-heterocycles with antimicrobial activity.

Compounds code	Molecular weight	HB-donors	HB-acceptors	Log Po/w (WLOGP)	Log S (SILICOS-IT)	BBB permeant	GI absorption	ROF
N-heterocycles								
M1	282.09 g/mol	1	4	1.98	−3.58	Yes	High	Yes; 0 violations
M2	368.38 g/mol	0	7	4.13	−6.82	Yes	High	Yes; 0 violations
M3	415.46 g/mol	1	7	3.61	−7.09	No	High	Yes; 0 violations
M4	267.25 g/mol	0	4	3.1	−5.72	Yes	High	Yes; 0 violations
M5	496.70 g/mol	0	2	6.94	−4.73	No	Low	Yes; 0 violations
M6	348.33 g/mol	4	8	2.85	−4.08	No	Low	Yes; 0 violations
M7	317.31 g/mol	0	5	6.8	−7.91	No	Low	Yes; 0 violations
M8	463.38 g/mol	0	2	6.48	−9.97	No	High	Yes; 1 violation: MLOGP > 4.15
M9	408.36 g/mol	2	9	3.81	−6.48	No	Low	Yes; 0 violations
M10	318.20 g/mol	0	2	5.93	−8.26	No	High	Yes; 0 violations
M11	453.87 g/mol	1	8	4.52	−7.57	No	Low	Yes; 0 violations
M12	383.35 g/mol	0	8	4.03	−6.07	No	High	Yes; 0 violations

Table 6. The pharmacokinetics ADME properties of N-heterocycles with anti-inflammatory activity.

Compound code	MW	HB-donors	HB-acceptors	Log Po/w (WLOGP)	Log S (SILICOS-IT)	BBB permeant	GI absorption	ROF
N-heterocycles								
I1	293.32 g/mol	0	4	2.00	−5.17	Yes	High	Yes; 0 violations
I2	370.57 g/mol	0	3	7.68	−9.77	No	Low	Yes; 1 violation: MLOGP > 4.15
I3	370.57 g/mol	0	3	7.68	−9.77	No	Low	Yes; 1 violation: MLOGP > 4.15
I4	269.30 g/mol	1	3	2.31	−4.78	Yes	High	Yes; 0 violations
I5	511.40 g/mol	3	4	5.04	−8.88	No	High	Yes; 1 violation: MW > 500
I6	428.48 g/mol	0	6	5.16	−9.73	No	High	Yes; 0 violations
I7	306.31 g/mol	3	6	2.14	−3.74	No	High	Yes; 0 violations
I8	371.22 g/mol	0	4	5.87	−8.88	No	High	Yes; 1 violation: MLOGP > 4.15

Table 7. The target predictions of N-heterocycles with anticancer activity.

Compounds code	GPCR ligand	Ion channel modulator	KI	NR ligand	PI	EI
			N-heterocycles			
C1	−0.25	−0.23	−0.43	−0.63	−0.29	−0.23
C2	−0.14	−0.45	−0.33	0.15	−0.17	−0.05
C3	−0.13	−0.59	−0.31	0.17	−0.35	−0.16
C4	−0.48	−0.68	−0.05	−0.71	−0.67	−0.31
C5	0.07	−0.26	−0.05	−0.72	−0.08	0.11
C6	0.04	−0.68	−0.35	−0.39	0.02	−0.17
C7	−0.28	−0.55	0.14	−0.49	−0.58	0.06
C8	0.21	0	0.49	0.27	−0.17	0.35
C9	−0.92	−1.18	−0.43	−0.71	−0.99	−0.54
C10	v1.15	−1.54	−0.75	−1.18	−0.72	−0.53

Table 8. The target predictions of N-heterocycles with antimicrobial activity.

Compounds code	GPCR ligand	Ion channel modulator	KI	NR ligand	PI	EI
			N-heterocycles			
M1	−1.38	−1.31	−0.78	−1.48	−1.56	−0.64
M2	−0.17	−0.18	−0.09	−0.28	−0.3	0.03
M3	−0.81	−1.17	−0.4	−1	−0.52	−0.57
M4	−0.83	−1.24	−0.28	−0.75	−1.02	−0.34
M5	−0.01	0.41	0.16	−0.5	−0.09	0.36
M6	0.07	−0.02	0.23	0.06	0.13	0.27
M7	0.27	0.32	0.26	0.3	0.06	0.29
M8	−0.38	−0.79	−0.2	−0.53	−0.53	−0.4
M9	−0.17	−0.29	0.01	−0.16	−0.28	−0.03
M10	0.22	0.26	0.26	0.17	−0.07	0.33
M11	−0.75	−1.09	−0.28	−0.92	−0.56	−0.56
M12	−0.3	−0.21	−0.21	−0.38	−0.42	−0.07

Table 9. Target predictions of N-heterocycles with anti-inflammatory properties.

Compounds code	GPCR ligand	Ion channel modulator	KI	NR ligand	PI	EI
			N-heterocycles			
I1	−0.64	−1.1	−0.02	−0.77	−0.82	−0.23
I2	0.06	−0.03	−0.21	−0.27	−0.09	−0.05
I3	0.03	−0.04	−0.23	−0.3	−0.11	−0.07
I4	−0.13	−0.66	−0.8	−0.12	−0.94	−0.11
I5	−0.13	−0.33	0.15	0.05	−0.2	−0.09
I6	−0.09	−0.19	−0.11	−0.17	−0.07	0.06
I7	0.28	0.14	−0.44	0.3	−0.12	0.15
I8	−0.08	−0.3	0	−0.1	−0.22	−0.06

immune cells to cell membranes to reduce the risk of invading microbes (Cheng *et al*., 2017). Moreover, the protein kinase raises proinflammatory cytokine expression, which causes inflammation. Thus, compounds with a small MW act as KIs by targeting kinase and downregulating its gene level or blocking (adenosine triphosphate)-kinase binding to reduce inflammation (Negi *et al*., 2021; Patterson *et al*., 2014). For the anticancer compounds, C8 exhibited remarkable cytotoxic activity against the liver cell line (IC_{50} 2.91 for HepG2) and has been reported to inhibit VEGF-2, which is one of the tyrosine kinases enzymes (Abdelhameid *et al*., 2020). The antimicrobial compounds that revealed high KI activity are M5, M6, M7, and M10, while anti-inflammatory derivatives, compounds I5 and I8, demonstrated positive values as KIs.

Nuclear receptor (NR) ligands

The NR is one of the major receptor groups because it covers both intra- and extracellular signals to regulate biological

functions such as enhancement of macrophage survival by inhibiting bacterial-induced apoptosis decreasing proinflammatory cytokines and chemokines production and reducing inflammation. Moreover, agonists and antagonists of several NRs are commonly utilized as anticancer agents (Bourguet *et al*., 2000; Leopold Wager *et al*., 2019). As shown in Table 1, C2, C3, and C8 exhibited moderate activity with values equal to 0.15, 0.17, and 0.27, respectively. Compounds M7 and M10 demonstrated the highest activity, equal to 0.30 and 0.17, respectively, among the antimicrobial derivatives. Moreover, for the anti-inflammatory I7, the highest value as a NR ligand was 0.30.

Protease inhibitors (PIs)

In Europe, proteasome inhibitors are the backbone of one of the hematologic cancers, multiple myeloma. Because of the proteasome inhibitor resistance, multiple patients were left without active therapy (Driessen *et al*., 2016; Toscani *et al*., 2021). Moreover, PIs act against infections by reducing the presence of amino acids inside microorganisms. PIs make channels in the cell membrane and take out cellular content, which results in cell death (Shamsi and Fatima, 2016). Furthermore, they reduce inflammation by inhibiting proinflammatory cytokine production (Fei *et al*., 2017). C6, which showed activity on leukemia and lymphoblastoma (see Table 1), exhibited positive bioactivity as a PI. While compound M6 shows promising results in inhibiting the protease enzyme, compound M7 follows suit. In contrast, none of the anti-inflammatory derivatives demonstrated a positive bioactivity score as a PI.

Enzyme inhibitors (EIs)

Topoisomerase II, which is one of the important enzymes that regulate DNA replication, is a reported target for C4 and C5 (Boulos *et al*., 2011). Surprisingly, these two compounds had predicted values of −0.05 and −0.16, respectively, as EIs. Moreover, compounds C5, C7, and C8 exhibited positive values, suggesting enzymes are potential targets for these derivatives. Furthermore, bacteria produce certain enzymes as one way of resisting mechanisms, so targeting enzymes might be a promising approach to overcome bacterial drug resistance. As shown in Table 8, compound M5 (0.36) had the highest value, followed by M10 (0.33), M7 (0.29), and M6 (0.27). Moreover, COX enzyme inhibition is a crucial mechanism of anti-inflammatory compounds. In Table 9, half of the studied compounds were reported to have activity on COX-1 and/or COX-2. Interestingly, I6 and I7 have not been reported in their original studies as COX-1 and/or COX-2 inhibitors (Husain and Priyanka Ahuja, 2009; Zheng *et al*., 2015). However, both reveal the highest activity, equal to 0.06 and 0.15, respectively.

CONCLUSION AND FUTURE DIRECTION

The discussed studies examined the anticancer activity of a variety of N-heterocyclic compounds, which showed encouraging results against breast, liver, prostate, ovarian, and colorectal cell lines. Most of the studies focused on specific cancer cell lines, and further research could be performed to examine the cytotoxic activity against lung cancer and other types of cell lines that were not covered here. In addition to the fact that most of the studies assessed the efficacy *in vitro* without further confirmation of efficacy using *in vivo* models, only two studies investigated the cytotoxic activity against hematological malignancies (melanoma and leukemia).

Moreover, the reported studies demonstrated significant antimicrobial activity. However, the lack of certain important information, such as the mechanism of action, may affect the prediction of the microbe's mechanism of resistance, thus affecting the efficacy of the developed agents. Future studies could be performed on the mechanism of action of the N-heterocycles as antimicrobial agents. Furthermore, several studies confirmed the possibility of N-heterocycle-containing compounds to attenuate inflammation with a similar mechanism to NSAIDs via COX enzyme inhibition and with lower toxicity (Bezerra *et al*., 2005; Gökhan-Kelekçi *et al*., 2009; Mohamed *et al*., 2017). The discussed studies suggest that the N-heterocycle-derived compounds possess promising medicinal properties that could be utilized for future drug discovery and the development of novel drug entities.

ACKNOWLEDGMENTS

The authors acknowledge financial support from the King Abdullah International Medical Research Center (KAIMRC), Ministry of National Guard Health Affairs, Riyadh, Kingdom of Saudi Arabia. Grant # (SP20.444.R). The authors want to express their sincerest gratitude to the College of Pharmacy (COP) at King Saud bin Abdulaziz University for Health Sciences (KSAU-HS) for their continued support.

List of Abbreviations

AMR: Antimicrobial resistance, BBB: Blood–brain barrier, C1: Compound 1 with anticancer activity, C2: Compound 2 with anticancer activity, C3: Compound 3 with anticancer activity, C4: Compound 4 with anticancer activity, C5: Compound 5 with anticancer activity, C6: Compound 6 with anticancer activity, C7: Compound 7 with anticancer activity, C8: Compound 8 with anticancer activity, C9: Compound 9 with anticancer activity, C10: Compound 10 with anticancer activity, COX: Cyclooxygenase, DNA: Deoxyribonucleic acid, EAC: Ehrlich ascites carcinoma, EC_{50}: Dose (or concentration) causing 50% of maximum effect for any measured biological effect of interest, FDA: Food and Drug Administration, GI_{50}: Concentration of drug causing 50% inhibition of cell growth, GPCR: G protein-coupled receptor, HB-acceptor: Hydrogen bond-acceptor, HB-donor: Hydrogen bond-donor, I1: Compound 1 with anti-inflammatory activity, I2: Compound 2 with anti-inflammatory activity, I3: Compound 3 with anti-inflammatory activity, I4: Compound 4 with anti-inflammatory activity, I5: Compound 5 with anti-inflammatory activity, I6: Compound 6 with anti-inflammatory activity, I7: Compound 7 with anti-inflammatory activity, I8: Compound 8 with anti-inflammatory activity, IC_{50}: Compound concentration required to inhibit tumor cell proliferation by 50%, LC_{50}: Concentration required to kill half the cells in the cell culture, LOX: Lipoxygenase, M1: Compound 1 with antimicrobial activity, M2: Compound 2 with antimicrobial activity, M3: Compound 3 with antimicrobial activity, M4: Compound 4 with antimicrobial activity, M5: Compound 5 with antimicrobial activity, M6: Compound 6 with antimicrobial activity, M7: Compound 7 with antimicrobial activity, M8: Compound 8 with antimicrobial

activity, M9: Compound 9 with antimicrobial activity, M10: Compound 10 with antimicrobial activity, M11: Compound 11 with antimicrobial activity, M12: Compound 12 with antimicrobial activity, MIC: Minimum inhibitory concentration, NSAIDs: Nonsteroidal anti-inflammatory drugs, RNA: Ribonucleic acid, ROF: Rule of five, % TWI: Percentage of tumor weight inhibition, % TCI: Percentage of tumor cell count inhibition,VEGF-2: Vascular endothelial growth factor receptor-2.

AUTHOR CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the international committee of medical journal editors (ICMJE) requirements/guidelines.

CONFLICTS OF INTEREST

The authors report no financial or any other conflicts of interest in this work.

ETHICAL APPROVALS

This study does not involve experiments on animals or human subjects.

DATA AVAILABILITY

All data generated and analyzed are included within this research article.

PUBLISHER'S NOTE

This journal remains neutral with regard to jurisdictional claims in published institutional affiliation.

SUPPLEMENTARY MATERIAL

Supplementary material is available on the publisher's website along with the published article.

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How to cite this article:
Alghamdi SS, Suliman RS, Alshehri RA, Almahmoud RS, Alhujirey RI. N-Heterocycle derivatives: An update on the biological activity in correlation with computational predictions. J Appl Pharm Sci, 2022; 12(05):059–077.

SUPPLEMENTARY FILE

T1S. SMILES of the compounds with anticancer activity.

	SMILES
C1	ClC1=C(C2=NC(C3=C(C)C=C(Cl)C=C3)=NO2)SC=C1
C2	COC(C([H])(C1(C2=CC=C(C=C2)N(C)C)[H])OC3=C1N=C(C4=CC=CC=C4)O3)=O
C3	[H]C(C#N)(C(C#N)(C1(C2=CC=CC=C2)[H])[H])C3=C1N=C(C4=CC=CC=C4)O3
C4	COC1=CC=C(C2=N/C(C(O2)=O)=N\NC3=CC=C(F)C(Cl)=C3)C=C1OC
C5	CCCCCCCCCCCCCCCCCCCCN1N=NC(CN2C3=CC=CC=C3[N+](C)=C2C4=CSC=N4)=C1
C6	CC(C)C(NC(C1=COC(C2=COC(C3=COC(C(NC4=O)C(C)C)=N3)=N2)=N1)=O) C5=NC(C6=NC(C7=NC4=CO7)=CO6)=CO5
C7	O=C1OC(C2=CC3=C(NC4=CC=CC=C43)C(C5=CC=C(C=C5)OC)=N2)=N/C1=C/C6=CC=CC=C6
C8	FC(C=C1)=CC=C1C2=NC(C3=CNC4=CC=CC=C43)=CO2
C9	O=C1OC(C(C=C2)=CC=C2/N=C/C3=C([N]([O])=O)C=C(Cl)C=C3)=N/C1=C\C4=CC=C(C=C4)OC
C10	OC(CSC1=NN=C(C2=CC=C(Cl)C=C2)O1)=O

T2S. SMILES of the compounds with antimicrobial activity.

	SMILES
M1	CC(OC/1=O)=NC1=C/C2=C(Br)C=CC(O)=C2
M2	COC1=C(OC)C=C(C=NC2=NC(C3=CC=C(OC)C=C3)=CO2)C=C1OC
M3	O=C(NC1=CC=CC(C)=C1)CSC(O2)=NN=C2C3=CC(OC)=C(OC)C(OC)=C3
M4	O=C1OC(C2=CC=CC=C2)=N/C1=C\C3=CC=C(F)C=C3
M5	Cl[Zn]([N]1=C(C=CC2=C3C=CC=N2)C3=CC=C1)(Cl)[N]4=CC=CC5=C4C=CC6=C5C=CC=N6
M6	NS(C(C=C1)=CC=C1C2=NOC=C2C3=CC(O)=C(O)C(O)=C3)(=O)=O
M7	CC1=NC(C(C=C2)=CC=C2C3=CC=C(C(F)(F)F)C=C3)=C(C)O1
M8	ClC1=C(C2=N/C(C(N2C3=CC=C(C)C=C3)=O)=C\C4=CC=C(Cl)C=C4)SC5=C1C=CC=C5
M9	O=C(C1=CC=C2OC(NC3=COC(/N=C/C4=C(C=C(C=C4)OC)O)=N3)=NC2=C1)OC
M10	CC1=NC(C(C=C2)=CC=C2C3=C(Cl)C=CC(Cl)=C3)=C(C)O1
M11	O=C(NC1=CC=C(F)C(Cl)=C1)CSC(O2)=NN=C2C3=CC(OC)=C(OC)C(OC)=C3
M12	COC1=C(OC)C=C(C=NC2=NC(C3=CC=C([N+]([O-])=O)C=C3)=CO2)C=C1OC

T3S. SMILES of the compounds with anti-inflammatory activity.

	SMILES
I1	O=C1OC(C2=CC=CN=C2)=N/C1=C/C3=CC=C(N(C)C)C=C3
I2	CC1=CC(C2=NOC(CCCCCCCCCCCCCCCC)=N2)=CC=C1
I3	CC(C=C1)=CC=C1C2=NOC(CCCCCCCCCCCCCCCC)=N2
I4	O=C1OC2=CC=C(C=C2N1CC(C3=CC=C(C=C3)[H])O)C
I5	ClC(C(Cl)=C1)=CC=C1C(N(C(C2=CC=C(O)C=C2)=O)NC/3=O)=CC3=C/C4=CC=C(N(C)C)C=C4
I6	O=C(C1=CC=C(CC2=CC=CC=C2)C=C1)CCC3=NN=C(O3)C4=CC=C(OC)C(OC)=C4
I7	OC1=C2C(OC(N2)=O)=C(C=C1)/C(CCC)=N\CC(C)C(O)=O
I8	COC1=CC=C2C(C=CC(C3=NN=C(C4=CC(Cl)=CC(Cl)=C4)O3)=C2)=C1