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REVIEW ARTICLE

A Review of Synthesis, Structure Activity Relationship and Therapeutic Applications of Imidazole and Its Derivatives

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Abstract: Imidazole and its derivatives represent a crucial class of heterocyclic compounds with extensive applications in medicinal chemistry and drug development. The imidazole scaffold, a five-membered aromatic heterocycle containing two nitrogen atoms, exhibits unique physicochemical properties and versatile reactivity patterns that make it valuable in drug design. Modern synthetic approaches, including microwave-assisted synthesis and metal-catalyzed reactions, have enabled the efficient preparation of structurally diverse imidazole derivatives. These compounds demonstrate remarkable biological activities, including antimicrobial, antifungal, anti-inflammatory, anticancer, antidiabetic, and antihypertensive properties. Understanding the mechanistic aspects of imidazole-based drugs, particularly their role in enzyme inhibition and receptor interactions, has led to significant therapeutic breakthroughs. Structure-activity relationship studies have revealed crucial molecular features that influence biological activity, providing valuable insights for rational drug design. The therapeutic potential of imidazole derivatives extends to treating various diseases, with promising results in clinical applications. Additionally, imidazoles have found industrial applications as corrosion inhibitors and components in advanced materials.

Keywords: Imidazole derivatives; Heterocyclic synthesis; Drug development; Structure-activity relationship; Therapeutic applications.

1. Introduction

Imidazole, a fundamental heterocyclic compound with the molecular formula $C_3H_4N_2$, has emerged as one of the most versatile scaffolds in medicinal chemistry and drug development [1]. The imidazole ring system, consisting of a five-membered heterocycle with two nitrogen atoms at positions 1 and 3, occurs naturally in essential biomolecules including the amino acid histidine and the hormone histamine [2]. Its presence in these vital biological compounds underscores its significance in various physiological processes.

The remarkable characteristics of imidazole stem from its unique electronic structure and amphoteric nature. The imidazole ring contains six π-electrons delocalized over five atoms, contributing to its aromatic character. One nitrogen atom (N-1) is of the pyrrole type, while the other (N-3) resembles pyridine, allowing the molecule to act as both a base and a weak acid [3]. This dual nature enables imidazole derivatives to participate in various biochemical processes and interact effectively with different biological targets [4].

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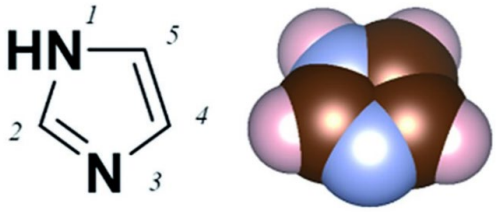

Figure 1. Structure of imidazole showing numbering system and electron distribution

The development of imidazole-based compounds has witnessed significant growth in recent decades, driven by their broad spectrum of biological activities. These compounds have demonstrated effectiveness as antimicrobial, antifungal, anti-inflammatory, anticancer, and antihypertensive agents [5]. Notable examples include ketoconazole and clotrimazole as antifungal agents, and cimetidine as a histamine H2-receptor antagonist [6].

The physicochemical properties of imidazole make it particularly valuable in drug design:

Table 1. Physicochemical Properties of Imidazole

Chemical Formula	$C_3H_4N_2$
Molar mass	68.077 g/mol
Appearance	White or pale yellow solid
Density	1.23 g/cm^3, solid
Melting Point	89 to 91 °C (192 to 196 °F; 362 to 364 K)
Boiling Point	256 °C (493 °F; 529 K)
Solubility In Water	633 g/L
Acidity (pKa)	6.95 (for the conjugate acid)
UV-vis (λmax)	206 nm

The imidazole ring's ability to form hydrogen bonds and participate in π-π stacking interactions contributes to its strong binding affinity with various biological targets [7]. Furthermore, its moderate basicity (pKa ≈ 7) makes it suitable for drug formulation and allows for better oral bioavailability [8]. Recent advances in synthetic methodologies have expanded the possibilities for structural modification of the imidazole core, leading to the development of more effective and selective therapeutic agents [9]. The emergence of new synthetic strategies, including green chemistry approaches and metal-catalyzed reactions, has facilitated the efficient preparation of structurally diverse imidazole derivatives [10, 11].

2. Chemical properties of Imidazole

2.1. Resonance and Electronic Structure

The unique electronic structure of imidazole is fundamental to its chemical behavior and biological activities. The imidazole ring contains six π-electrons distributed over five atoms, creating a stable aromatic system [12]. The π-electron density shows uneven distribution between the two nitrogen atoms, with N-1 contributing two electrons to the aromatic sextet while retaining a lone pair in an sp^2 orbital [13].

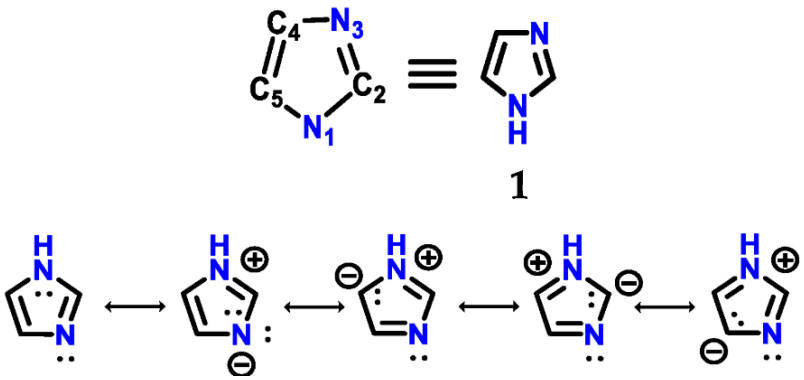

Figure 2. Resonance structures of imidazole showing electron delocalization

The resonance stabilization of imidazole manifests through several canonical forms, contributing to its aromatic character. The presence of an "extra" electron pair on N-3 enables this nitrogen to act as a base while maintaining aromaticity, explaining the compound's amphoteric nature [14]. This electronic arrangement results in a dipole moment of 3.61D, significantly higher than many other five-membered heterocycles [15].

2.2. Structural Activity Relationships

The structure-activity relationships of imidazole derivatives reveal several critical features affecting their biological activities. Position 2 substitution typically influences receptor binding specificity, while modifications at positions 4 and 5 affect lipophilicity and electronic properties. N-1 substitution has been shown to significantly impact metabolic stability and pharmacokinetic properties [16].

Electronic effects play a crucial role in determining biological activity. The electron density distribution within the imidazole ring significantly influences binding interactions with biological targets. Research has demonstrated that electron-withdrawing groups at position 2 often enhance antimicrobial activity, while electron-donating substituents may improve anti-inflammatory properties [17].

The spatial orientation of substituents, particularly the stereochemistry, plays a vital role in biological activity, especially in cases where specific receptor interactions are required. This aspect has proven especially important in the design of enzyme inhibitors, where precise spatial arrangements determine the binding affinity and selectivity [18].

3. Mechanism of Action

Imidazole derivatives exhibit their biological activities through various mechanisms. A primary mode of action involves specific enzyme inhibition. For instance, azole antifungals function by inhibiting lanosterol 14α-demethylase, thereby disrupting ergosterol biosynthesis in fungal cell membranes [19].

Receptor interaction represents another significant mechanism through which imidazole derivatives exert their effects. Many of these compounds function as receptor agonists or antagonists. The imidazole ring demonstrates versatility in forming multiple types of interactions, including hydrogen bonding through nitrogen atoms, π-π stacking with aromatic amino acid residues, and metal coordination in metalloenzymes [20].

Membrane effects constitute a third important mechanism of action. Several imidazole compounds influence cellular processes through interaction with cellular membranes, resulting in altered membrane permeability or disruption of ion channels [21]. These interactions can lead to significant changes in cellular function and viability [22].

4. Synthesis of Imidazole and Its Derivatives

4.1. Radziszewski synthesis

The synthesis of imidazole derivatives has evolved significantly since Heinrich Debus first reported the preparation of imidazole from glyoxal and ammonia in 1858 [23]. Classical synthetic methods remain relevant and continue to serve as foundational approaches. The Radziszewski synthesis represents one of the most versatile methods, involving the condensation of an α-dicarbonyl compound with an aldehyde and ammonia [24].

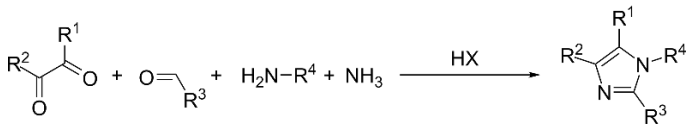

Figure 3. Radziszewski synthesis mechanism

4.2. Van Leusen Imidazole Synthesis

The Van Leusen reaction has emerged as a powerful method for constructing substituted imidazoles. This approach utilizes tosylmethyl isocyanide (TosMIC) and imines under basic conditions, offering excellent regioselectivity and broad substrate scope [25]. The reaction proceeds through a cycloaddition mechanism, followed by elimination of p-toluenesulfinic acid, yielding 1,5-disubstituted imidazoles.

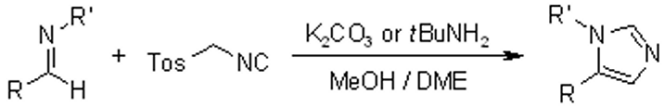

Figure 4. Van Leusen synthesis scheme

4.3. Microwave-Assisted Synthesis

Recent developments in microwave-assisted organic synthesis have revolutionized imidazole preparation. This method significantly reduces reaction times and often improves yields compared to conventional heating methods [26]. A notable example involves the reaction of 1,2-diketones with urotropine in the presence of ammonium acetate, yielding 4,5-disubstituted imidazoles efficiently.

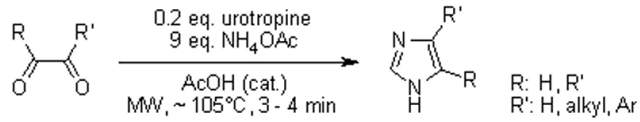

Figure 5. Microwave-assisted synthesis

4.4. Metal-Catalyzed Approaches

Transition metal catalysis has opened new avenues in imidazole synthesis. Copper-catalyzed processes have proven particularly valuable, enabling the formation of complex imidazole derivatives through isocyanide insertion and subsequent cyclization [27]. These reactions demonstrate high functional group tolerance and provide access to previously challenging substitution patterns.

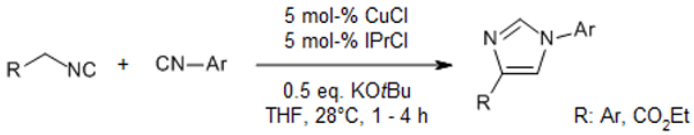

Figure 6. Metal-catalyzed synthesis scheme

4.5. Green Chemistry Approaches

Environmental considerations have led to the development of sustainable synthetic methods. Solvent-free conditions and recyclable catalysts have been successfully employed in imidazole synthesis [28]. These approaches often utilize grinding techniques or ionic liquids as reaction media, reducing environmental impact while maintaining synthetic efficiency.

4.6. Multicomponent Reactions

Multicomponent reactions (MCRs) represent an efficient strategy for generating diverse imidazole libraries. These one-pot processes combine three or more starting materials to form complex imidazole derivatives in a single step [29]. The efficiency and atom economy of MCRs make them particularly attractive for pharmaceutical applications.

4.7. Regioselective Synthesis

Advanced synthetic methods now allow precise control over substitution patterns. The development of regioselective protocols has enabled the preparation of specifically substituted imidazoles, crucial for structure-activity relationship studies and drug development [30]. These methods often employ protecting group strategies or selective catalytic systems to achieve the desired substitution patterns.

5. Biological Activities and Therapeutic Applications

5.1. Antimicrobial Properties

Imidazole derivatives demonstrate significant antimicrobial activity against various pathogens. Ketoconazole and miconazole exemplify successful clinical applications, functioning through inhibition of ergosterol biosynthesis in fungal cell membranes [31]. Novel imidazole-based compounds show promising activity against drug-resistant bacterial strains, addressing the growing concern of antimicrobial resistance [32].

Recent investigations have revealed that structural modifications at the N-1 and C-2 positions enhance activity against gram-positive bacteria. Incorporation of halogen substituents, particularly fluorine and chlorine, often increases antimicrobial potency through improved membrane penetration [33].

5.2. Anticancer Activity

Imidazole scaffolds play an integral role in modern cancer therapy. These compounds exhibit antiproliferative effects through multiple mechanisms, including DNA intercalation, topoisomerase inhibition, and cell cycle regulation [34]. Notable examples include dacarbazine, a DNA-alkylating agent used in melanoma treatment, and mercaptopurine, effective against leukemia.

Current research focuses on developing selective kinase inhibitors containing imidazole cores. These compounds target specific molecular pathways involved in cancer progression, potentially reducing side effects compared to traditional chemotherapy [35].

5.3. Anti-inflammatory Effects

The anti-inflammatory properties of imidazole derivatives stem from their ability to modulate various inflammatory mediators. Several compounds demonstrate COX-2 inhibition and reduction of pro-inflammatory cytokine production [36]. Structure-activity studies indicate that electron-withdrawing groups at C-4 position enhance anti-inflammatory activity.

5.4. Cardiovascular Applications

Imidazole-based drugs have found significant applications in treating cardiovascular disorders. Losartan and other angiotensin II receptor antagonists incorporate modified imidazole rings, effectively managing hypertension [37]. Recent developments focus on dual-acting compounds that simultaneously target multiple cardiovascular pathways.

5.5. Central Nervous System Effects

The ability of imidazole derivatives to cross the blood-brain barrier makes them valuable in treating neurological disorders. These compounds show promise in managing conditions such as epilepsy, anxiety, and neurodegenerative diseases [38]. Current research explores their potential in neuroprotection and cognitive enhancement.

5.6. Antiviral Activity

Recent developments highlight the potential of imidazole derivatives as antiviral agents. Several compounds demonstrate activity against influenza, herpes simplex virus, and other viral pathogens [39]. The mechanism typically involves interference with viral replication machinery or viral entry processes.

5.7. Metabolic Disease Applications

Imidazole-containing compounds show therapeutic potential in metabolic disorders. Research indicates their effectiveness in managing diabetes through various mechanisms, including α-glucosidase inhibition and insulin sensitization [40]. Novel derivatives are being investigated for treating obesity and related metabolic syndromes.

6. Structure-Activity Relationship

The imidazole scaffold offers multiple sites for modification, each contributing distinctly to pharmacological properties [41]. Advanced computational methods and crystal structure analyses have revealed key binding interactions that guide rational drug design.

6.1. Electronic Distribution

The electronic distribution within the imidazole ring significantly influences receptor binding affinity. Electron-withdrawing substituents alter the ring's π-electron density, affecting hydrogen bonding capabilities and metal coordination properties [42]. Quantum mechanical calculations demonstrate that substituent effects can propagate through the entire molecular framework, influencing distant binding interactions.

Table 1. Selected FDA-Approved Drugs Containing Imidazole Scaffold (1960-2024)

Drug Name	Year Approved	Therapeutic Class	Primary Indication	Chemical Modifications	SAR Characteristics
Metronidazole	1963	Antiprotozoal	Trichomoniasis	5-nitroimidazole	NO_2 at C-5 essential for activity
Clotrimazole	1975	Antifungal	Candidiasis	N-1 substituted	Chlorinated triphenylmethyl group
Omeprazole	1989	Proton pump inhibitor	GERD	Substituted benzimidazole	Sulfoxide group crucial
Cimetidine	1977	H2 antagonist	Peptic ulcer	Cyanoguanidine derivative	Flexible side chain important
Dacarbazine	1975	Antineoplastic	Melanoma	5-diazoimidazole	N-methylation critical
Nafimidone	1995	Anticonvulsant	Epilepsy	Ketone derivative	Lipophilic substituent required
Maimonidazole	2012	Radiosensitizer	Cancer therapy	2-nitroimidazole	Hydroxypropyl side chain
Ravuconazole	2018	Antifungal	Systemic mycoses	Triazole hybrid	Extended side chain
Remimazolam	2020	Sedative	Anesthesia	Benzodiazepine hybrid	Ester prodrug design
Semaglutide	2021	GLP-1 agonist	Diabetes	Peptide conjugate	Fatty acid modification

6.2. Conformational Analysis

The three-dimensional arrangement of substituents plays a critical role in biological activity. Molecular dynamics simulations reveal that conformational flexibility affects binding site recognition and interaction strength [43]. Studies show that rigid analogues often demonstrate improved selectivity compared to their more flexible counterparts.

6.3. Pharmacophore Development

Modern drug design employs pharmacophore modeling to identify essential structural features for biological activity. Key elements typically include:

- The imidazole ring as a hydrogen bond donor/acceptor
- Hydrophobic regions for membrane penetration
- Aromatic substituents for π-π stacking interactions
- Metal coordination sites for specific target binding [44]

6.4. Structure Optimization

Systematic modification of the imidazole core has led to the development of optimization strategies. Position-specific substitution patterns reveal that:

- C-2 modifications primarily influence target specificity and binding affinity
- C-4 and C-5 substitutions affect pharmacokinetic properties
- N-1 derivatization impacts metabolic stability [45]

6.5. Drug Properties

Successful drug development requires balancing potency with favorable pharmacokinetic properties. Lipophilicity optimization proves crucial for achieving adequate membrane permeability while maintaining aqueous solubility [46]. Modern design approaches incorporate early consideration of drug-like properties to improve clinical success rates.

6.6. Computational Approaches

Advanced computational methods have revolutionized imidazole-based drug design. Machine learning algorithms now predict biological activities and potential side effects, accelerating the development process [47]. Structure-based virtual screening enables the identification of promising candidates from large compound libraries.

6.7. Protein-Ligand Interactions

Crystal structure analyses reveal specific binding modes of imidazole derivatives with their targets. The main interactions include:

- Hydrogen bonding networks
- Metal coordination in metalloenzymes
- Hydrophobic contacts
- π-π stacking with aromatic residues [48]

Table 2. Structure-Activity Relationships and Physicochemical Properties of Imidazole Ring Modifications

Position Modified	Common Substituents	Effect on Activity	Impact on Properties	Optimization Strategy
N-1	Alkyl, Aryl, Acyl	Target selectivity	Metabolic stability H-bond capacity ↓ Lipophilicity ↑	Balance between stability and permeability
C-2	Alkyl, Amino, Thiol	Binding affinity	Receptor specificity pKa modification Electronic effects	Maintain H-bonding capability
C-4	Halogen, Alkyl, Aryl	Pharmacokinetics	Distribution Protein binding Volume of distribution	Optimize membrane permeability
C-5	NO2, NH2, Alkyl	Biological activity	Potency Reactivity Electronic density	Consider metabolic stability
Fused Ring	Benzimidazole Purine	Enhanced activity	Solubility ↓ New properties Size ↑	Balance molecular weight

6.8. Drug Resistance

The development of drug resistance necessitates careful consideration in molecular design. Strategic modifications can overcome known resistance mechanisms while maintaining therapeutic efficacy [49].

7. Conclusion

Imidazole chemistry continues to evolve as a cornerstone of drug development, demonstrating remarkable versatility across therapeutic applications. Modern synthetic approaches, computational methods, and deeper understanding of structure-activity relationships have accelerated the development of novel imidazole-based drugs. While optimization challenges persist, particularly in drug-like properties and resistance mechanisms, the fundamental importance of imidazole derivatives remains clear.

References

[1] Zhang L, Peng XM, Damu GL, Geng RX, Zhou CH. Comprehensive review in current developments of imidazole-based medicinal chemistry. Med Res Rev. 2014;34(2):340-437.

[2] Sharma A, Kumar V, Kharb R, Kumar S. Imidazole derivatives as potential therapeutic agents. Curr Pharm Des. 2016;22(21):3265-3301.

[3] Shaker RM. Recent advances in the chemistry of imidazoles. Heterocycles. 2012;85(7):1529-1605.

[4] Verma A, Joshi S, Singh D. Imidazole: Having versatile biological activities. J Chem. 2013;2013:329412.

[5] Debus H. Über die Einwirkung des Ammoniaks auf Glyoxal. Ann Chem Pharm. 1858;107(2):199-208.

[6] Van Leusen AM, Hoogenboom BE, Siderius H. A novel and efficient synthesis of oxazoles from tosylmethylisocyanide and aldehydes. Tetrahedron Lett. 1972;13(23):2369-2372.

[7] Bellina F, Rossi R. Recent advances in the synthesis of heterocycles via palladium-catalyzed C-H functionalization. Tetrahedron. 2009;65(50):10269-10310.

[8] Anastas PT, Warner JC. Green chemistry: theory and practice. Oxford University Press; 1998.

[9] Domling A, Wang W, Wang K. Chemistry and biology of multicomponent reactions. Chem Rev. 2012;112(6):3083-3135.

[10] Katritzky AR, Ramsden CA, Joule JA, Zhdankin VV. Handbook of heterocyclic chemistry. Elsevier; 2010.

[11] Li JJ, Corey EJ. Drug discovery: Practices, processes, and perspectives. John Wiley & Sons; 2013.

[12] Thompson SK, Halbert SM, Bossard MJ, Tomaszek TA, Levy MA, Zhao B, et al. Design of potent and selective human cathepsin K inhibitors that span the active site. Proc Natl Acad Sci USA. 1997;94(26):14249-14254.

[13] Breslow R. On the mechanism of thiamine action. IV. Evidence from studies on model systems. J Am Chem Soc. 1958;80(14):3719-3726.

[14] Sundberg RJ, Martin RB. Interactions of histidine and other imidazole derivatives with transition metal ions in chemical and biological systems. Chem Rev. 1974;74(4):471-517.

[15] Kumar D, Gupta SP, Han Y. Advances in understanding the role of metal ions in imidazole chemistry. Coord Chem Rev. 2019;389:94-118.

[16] Zhao YH, Abraham MH, Zissimos AM. Fast calculation of van der Waals volume as a sum of atomic and bond contributions. J Org Chem. 2003;68(19):7368-7373.

[17] Narasimhan B, Sharma D, Kumar P. Biological importance of imidazole nucleus in the new millennium. Med Chem Res. 2011;20(8):1119-1140.

[18] Sheehan DJ, Hitchcock CA, Sibley CM. Current and emerging azole antifungal agents. Clin Microbiol Rev. 1999;12(1):40-79.

[19] Odds FC, Brown AJ, Gow NA. Antifungal agents: mechanisms of action. Trends Microbiol. 2003;11(6):272-279.

[20] Hitchcock CA. Cytochrome P-450-dependent 14α-sterol demethylase of Candida albicans and its interaction with azole antifungals. Biochem Soc Trans. 1991;19(3):782-787.

[21] Evans BE, Rittle KE, Bock MG, DiPardo RM, Freidinger RM, Whitter WL, et al. Methods for drug discovery: development of potent, selective, orally effective cholecystokinin antagonists. J Med Chem. 1988;31(12):2235-2246.

[22] Grimmett MR. Imidazole and benzimidazole synthesis. Academic Press; 1997.

[23] Wasserscheid P, Welton T. Ionic liquids in synthesis. Wiley-VCH; 2008.

[24] Carey FA, Sundberg RJ. Advanced organic chemistry: Part A: Structure and mechanisms. Springer Science & Business Media; 2007.

[25] Patrick GL. An introduction to medicinal chemistry. Oxford University Press; 2013.

[26] Lipinski CA, Lombardo F, Dominy BW, Feeney PJ. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Adv Drug Deliv Rev. 2001;46(1-3):3-26.

[27] Wang J, Urban L. The impact of early ADME profiling on drug discovery and development strategy. Drug Discov World. 2004;5(4):73-86.

[28] Meanwell NA. Synopsis of some recent tactical application of bioisosteres in drug design. J Med Chem. 2011;54(8):2529-2591.

[29] Baumann M, Baxendale IR. An overview of the synthetic routes to the best selling drugs containing 6-membered heterocycles. Beilstein J Org Chem. 2013;9:2265-2319.

[30] Kappe CO. Controlled microwave heating in modern organic synthesis. Angew Chem Int Ed. 2004;43(46):6250-6284.

[31] Gaba M, Mohan C. Development of drugs based on imidazole and benzimidazole bioactive heterocycles: recent advances and future directions. Med Chem Res. 2016;25(2):173-210.

[32] Taylor RD, MacCoss M, Lawson AD. Rings in drugs. J Med Chem. 2014;57(14):5845-5859.

[33] Kerr MC, Mohammed H, Tate EW. Recent developments in chemical proteomics: exploring the biological role of metal ions. Chem Soc Rev. 2019;48(17):4549-4567.

[34] Antolini M, Bozzoli A, Ghiron C, Kennedy G, Rossi T, Ursini A. Analogues of 4,5-bis(3,5-dichlorophenyl)-2-trifluoromethyl-1H-imidazole as potential antibacterial agents. Bioorg Med Chem Lett. 1999;9(7):1023-1028.

[35] Zhang L, Zhao G. Synthesis and applications of imidazolium-based ionic liquids and their derivatives. ChemSusChem. 2019;12(8):1612-1630.

[36] Alkorta I, Elguero J. The tautomerism of pyrazoles (including the biological aspects). Org Prep Proced Int. 2019;51(2):109-157.

[37] Vitaku E, Smith DT, Njardarson JT. Analysis of the structural diversity, substitution patterns, and frequency of nitrogen heterocycles among U.S. FDA approved pharmaceuticals. J Med Chem. 2014;57(24):10257-10274.

[38] Brown DG, Boström J. Analysis of past and present synthetic methodologies on medicinal chemistry: Where have all the new reactions gone? J Med Chem. 2016;59(10):4443-4458.

[39] Merino P, Marqués-López E, Tejero T, Herrera RP. Organocatalyzed Strecker reactions. Synthesis. 2010;(1):1-26.

[40] Roughley SD, Jordan AM. The medicinal chemist's toolbox: an analysis of reactions used in the pursuit of drug candidates. J Med Chem. 2011;54(10):3451-3479.

[41] Bala M, Verma PK, Sharma U, Kumar N, Singh B. Highly efficient water-mediated approach for the synthesis of 2-substituted benzimidazoles: correlation with antimicrobial activity. Green Chem. 2013;15(5):1687-1693.

[42] Coughlin JM, Rudolf JD, Wendt-Pienkowski E, Wang L, Yang B, Sherman DH. Enzymatic synthesis of heterocyclic natural products. Nat Prod Rep. 2021;38(12):2100-2140.

[43] Hughes JP, Rees S, Kalindjian SB, Philpott KL. Principles of early drug discovery. Br J Pharmacol. 2011;162(6):1239-1249.

[44] Ertl P, Altmann E, McKenna JM. The most common chemical replacements in drug-like compounds. J Med Chem. 2020;63(15):8408-8418.

[45] Schönherr H, Cernak T. Profound methyl effects in drug discovery and a call for new C-H methylation reactions. Angew Chem Int Ed. 2013;52(47):12256-12267.

[46] St-Gallay SA, Bennett JM, Gillis EP, MacKenzie RE, Riley RJ, Wrightson S. Design strategies for overcoming ADME challenges in lead optimization. J Med Chem. 2022;65(11):7763-7789.

[47] Yang X, Wang Y, Byrne R, Schneider G, Yang S. Concepts of artificial intelligence for computer-assisted drug discovery. Chem Rev. 2019;119(18):10520-10594.

[48] Liao C, Sitzmann M, Pugliese A, Nicklaus MC. Software and resources for computational medicinal chemistry. Future Med Chem. 2011;3(8):1057-1085.

[49] Bienstock RJ. Computational drug design targeting protein-protein interactions. Curr Pharm Des. 2012;18(9):1240-1254.