

Heterocycles in Medicinal Chemistry II

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Carbon has a unique position among the elements, due to the fact that its valence shell has four electrons and is therefore quadrivalent in the excited state. Carbon atoms form strong covalent bonds and can also join together to form long chains or rings [1]. The most basic division of all organic compounds can be according to the representation of individual elements. One group contains only the “backbone” composed of carbons and hydrogens, while the second, much more comprehensive group also includes other atoms, so-called heteroatoms. Most often, the term “heterocyclic compounds” in the abbreviation “heterocycles” refers to organic cyclic substances that, in addition to carbon atoms, also have heteroatoms in the cycle. According to the type of heteroatom, these compounds can be divided into nitrogen, oxygen, and sulfur, but they can also contain other heteroatoms, such as selenium, phosphorus, iron, etc. [2,3]. According to the number of heteroatoms, they are divided into monovalent, divalent, and polyvalent. As cyclic hydrocarbons, heterocycles are most commonly five- and six-membered and may be saturated or unsaturated; depending on the structure and the actual type and number of heteroatoms, they may show signs of aromaticity. Heterocycles can combine to form various fused systems, e.g., with a benzene ring or with other heterocycles [1–3].

By introducing a heteroatom into the carbon backbone, the compound acquires completely different, often unique properties (reactivity, lipo-hydrophilic properties, polarity, or ability to interact with the environment) from the parent hydrocarbons [2,4–15]. Heterocycles thus form the most important traditional branch of organic chemistry, and research interest in heterocycles is growing due to their biological (medical) and industrial applications [4–20], as documented in Figure 1. Heterocycles are found in natural substances, and some are necessary for life (e.g., purine/pyrimidine backbones of DNA/RNA, building blocks of chlorophyll, hemoglobin, essential amino acids in proteins, vitamins, etc. [4,20–23]).

From the point of view of significance, it does not matter whether they are isosterically or bioisosterically substituted carbons or carbon substructures. Most biologically active chemical entities contain a heterocycle [4,19,24]. This fact reflects the central role of heterocycles in the modern design of drugs or even agrochemicals [4,5,18,19,21,24–31]. Many heterocyclic scaffolds can be considered privileged structures. There is no therapeutic group of drugs that does not contain heterocyclic drugs, so it can be stated that they have a wide spectrum of biological activities [19,24,26,27,31]. Therefore, heterocycles are of fundamental importance to medicinal chemists, as their use can expand the chemical universe from which to draw new compounds for biomedical research and streamline drug discovery programs. Historically, many procedures have been developed for the targeted synthesis of heterocycles (target-oriented synthesis or diversity-oriented synthesis), although there is still the possibility of their isolation from natural sources and their subsequent modification [2,3,32–38].



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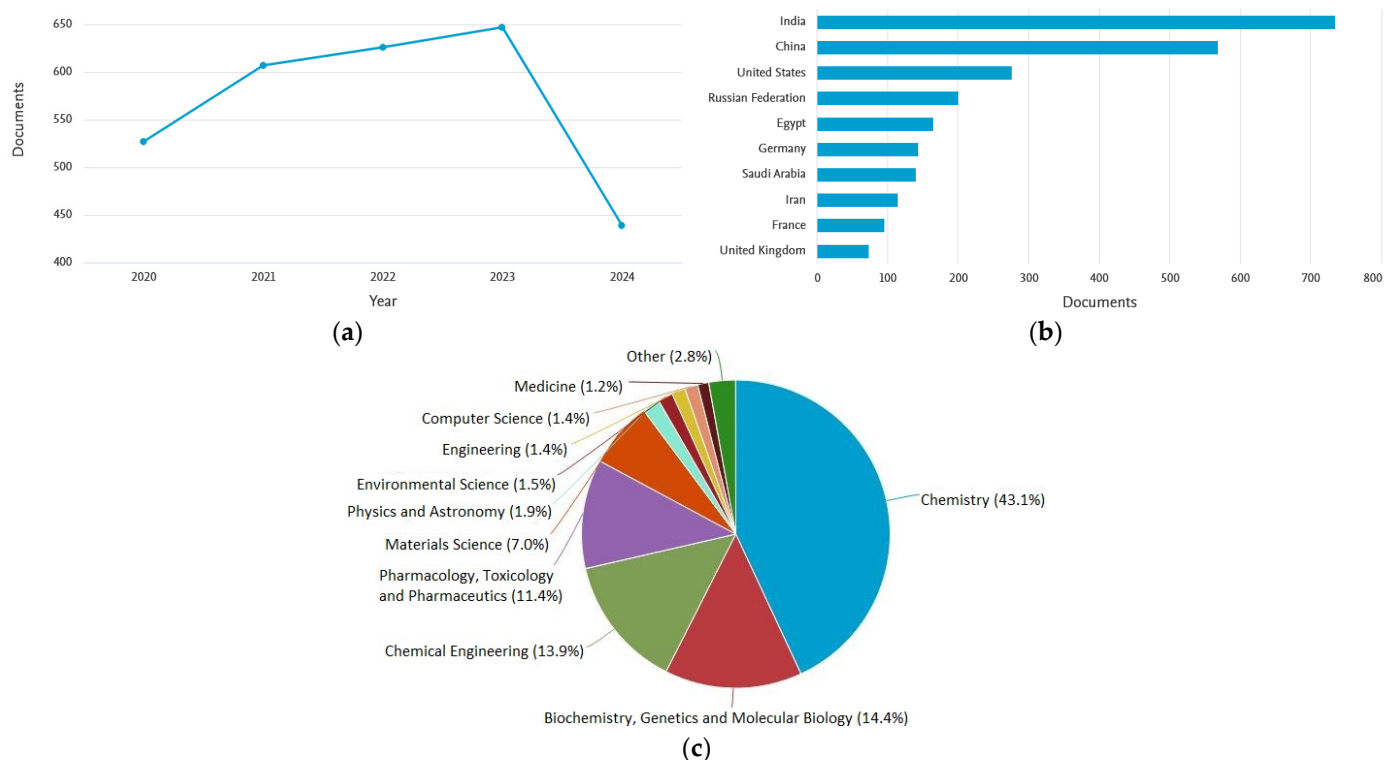


Figure 1. Number of publications according to Scopus database published in the years 2020–2024 (as of 30 September 2024) containing in the title of the article, the abstract or the keywords, “heterocycle” and “heterocyclic compounds” (a), publications by country (b), publications by subject areas (c).

The articles in this Special Issue provide some overview of recent developments in the field of heterocycle research. The study of drug lipophilicity combining experimental and chemometric methods (principal component analysis and cluster analysis) and comparison of chromatographically obtained and theoretical lipophilicity descriptors represents a useful concept for simplifying the prediction of drug-like properties of molecules [39]. Many heterocycles have the potential to act as anti-infective agents. Ring-substituted pyrazoles have been tested as potential agricultural fungicides against a number of phytopathogenic fungi, and some of the listed compounds showed activity comparable to pyraclostrobin [40]. The cyclic analogues of pyrazoles—a series of twenty-two indazole derivatives studied as antiprotozoa against *Entamoeba histolytica*, *Giardia intestinalis*, and *Trichomonas vaginalis*—appear to hold great promise as potential therapeutics [41]. Ahmad et al. prepared a series of substituted *N*-(4-methylpyridin-2-yl)-thiophene-2-carboxamides showing high activity against pathogenic extended-spectrum β -lactamase producing *Escherichia coli*, which, in addition to promising efficacy, have the ability to inhibit β -lactamases as well [42]. A series of new *N*-substituted benzimidazole carboxamides were evaluated for their overall anti-invasive activity, i.e., both antimicrobial (Gram-positive bacteria) and anticancer (H460, HCT 116, MCF-7, HEK293) efficacies [43]. Synthetic compounds (nitroimidazoles, 5-(indol-2-yl)pyrazolo[3,4-*b*]pyridines) [44,45] or semi-synthetic derivatives (steviol or isosteviol) [46] have been evaluated for their ability to eliminate cancer cells and prevent the emergence of cancer lines resistant to clinically used drugs. The above-mentioned indications of heterocyclic derivatives aimed at anti-infective agents and anticancer drugs are complemented by the following two publications: Zolotareva et al. provide a review of potential antidiabetic agents based on three heterocyclic compounds, namely morpholine, piperazine, and piperidine [47]; and Kim et al. investigated benzylidene-3-methyl-2-thioxothiazolidin-4-ones with antioxidant activities as potential tyrosinase inhibitors for the treatment of hyperpigmentation-related disorders [48].

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References

1. LibreTexts™ Chemsitry—Carbon-Why It Is Unique. Available online: [https://chem.libretexts.org/Courses/Prince_Georges_Community_College/CHM_1020:_General_Chemistry_II_\(Miller\)/09:_Organic_Chemistry/9.02:_Carbon-_Why_It_Is_Unique](https://chem.libretexts.org/Courses/Prince_Georges_Community_College/CHM_1020:_General_Chemistry_II_(Miller)/09:_Organic_Chemistry/9.02:_Carbon-_Why_It_Is_Unique) (accessed on 27 September 2024).
2. Katritzky, A.R.; Denisko, O.V. Heterocyclic Compound. Encyclopædia Britannica. Available online: <https://www.britannica.com/science/heterocyclic-compound> (accessed on 27 September 2024).
3. Ram, V.J.; Sethi, A.; Nath, M.; Pratap, R. *The Chemistry of Heterocycles*; Elsevier: Amsterdam, The Netherlands, 2019.
4. Kabir, E.; Uzzaman, M. A review on biological and medicinal impact of heterocyclic compounds. *Res. Chem.* **2022**, *4*, 100606. [CrossRef]
5. Qadir, T.; Amin, A.; Sharma, P.K.; Jeelani, I.; Abe, H. A review on medicinally important heterocyclic compounds. *Open J. Med. Chem.* **2022**, *16*, e187410452202280. [CrossRef]
6. Al-Mulla, A. A review: Biological importance of heterocyclic compounds. *Der Pharma Chem.* **2017**, *9*, 141–147.
7. Li, M.M.; Chen, X.; Deng, Y.; Lu, J. Recent advances of *N*-heterocyclic carbenes in the applications of constructing carbo- and heterocyclic frameworks with potential biological activity. *RSC Adv.* **2021**, *11*, 38060–38078. [CrossRef]
8. Li, X.; Liu, G.; Zheng, H.; Sun, K.; Wan, L.; Cao, J.; Asif, S.; Cao, Y.; Si, W.; Wang, F.; et al. Recent advances on heteroatom-doped porous carbon—Based electrocatalysts for oxygen reduction reaction. *Energies* **2023**, *16*, 128. [CrossRef]
9. Imramovsky, A.; Pejchal, V.; Stepankova, S.; Vorcakova, K.; Jampilek, J.; Vanko, J.; Simunek, P.; Kralovec, K.; Bruckova, L.; Mandikova, J.; et al. Synthesis and in vitro evaluation of new derivatives of 2-substituted-6-fluorobenzo[d]thiazoles as cholinesterase inhibitors. *Bioorg. Med. Chem.* **2013**, *21*, 1735–1748. [CrossRef] [PubMed]
10. Musiol, R.; Jampilek, J.; Nycz, J.E.; Pesko, M.; Carroll, J.; Kralova, K.; Vejsova, M.; O'Mahony, J.; Coffey, A.; Mrozek, A.; et al. Investigating the activity spectrum for ring-substituted 8-hydroxyquinolines. *Molecules* **2010**, *15*, 288–304. [CrossRef]
11. Waldman, A.J.; Ng, T.L.; Wang, P.; Balskus, E.P. Heteroatom-heteroatom bond formation in natural product biosynthesis. *Chem. Rev.* **2017**, *117*, 5784–5863. [CrossRef]
12. DrugBank—Indenes. Available online: <https://go.drugbank.com/categories/DBCAT000931> (accessed on 27 September 2024).
13. DrugBank—Benzimidazoles. Available online: https://go.drugbank.com/unearth/q?searcher=drugs&query=benzimidazole&button=&_gl=1*3tvvg*_up*MQ.*_ga*MTU1NzE3MTk0NC4xNzI3NzAyMTA4*_ga_DDLJ7EEV9M*MTcyNzcwMjEwNy4xLjAuMTcyNzcwMjEwNy4wLjAuMA (accessed on 27 September 2024).
14. DrugBank—Benzoxazoles. Available online: https://go.drugbank.com/unearth/q?searcher=drugs&query=benzoxazoles&button=&_gl=1*okm6e9*_up*MQ.*_ga*MTU1NzE3MTk0NC4xNzI3NzAyMTA4*_ga_DDLJ7EEV9M*MTcyNzcwMjEwNy4xLjEuMTcyNzcwMjEwNy4wLjAuMA (accessed on 27 September 2024).
15. DrugBank—Benzothiazoles. Available online: https://go.drugbank.com/unearth/q?searcher=drugs&query=benzothiazoles&button=&_gl=1*1hfxtqb*_up*MQ.*_ga*MTU1NzE3MTk0NC4xNzI3NzAyMTA4*_ga_DDLJ7EEV9M*MTcyNzcwMjEwNy4xLjEuMTcyNzcwMjEwNy4wLjAuMA (accessed on 27 September 2024).
16. Mahajan, N.D.; Jain, N. Heterocyclic compounds and their applications in the field of biology: A detailed study. *Nat. Vol. Essent. Oil* **2021**, *8*, 13223–13229.
17. Nehra, B.; Mathew, B.; Chawla, P.A. A medicinal chemist's perspective towards structure activity relationship of heterocycle based anticancer agents. *Curr. Top Med. Chem.* **2022**, *22*, 493–528. [CrossRef]
18. Karthikeyan, S.; Grishina, M.; Kandasamy, S.; Mangaiyarkarasi, R.; Ramamoorthi, A.; Chinnathambi, S.; Pandian, G.N.; Kennedy, L.J. A review on medicinally important heterocyclic compounds and importance of biophysical approach of underlying the insight mechanism in biological environment. *J. Biomol. Struct. Dyn.* **2023**, *41*, 14599–14619. [CrossRef] [PubMed]
19. Meanwell, N.A.; Lolli, M.L. *Applications of Heterocycles in the Design of Drugs and Agricultural Products*; Academic Press & Elsevier: Amsterdam, The Netherlands, 2021.
20. Pozharskii, A.F.; Soldatenkov, A.T.; Katritzky, A.R. *Heterocycles in Life and Society: An Introduction to Heterocyclic Chemistry, Biochemistry and Applications*, 2nd ed.; J. Wiley & Sons: Chichester, UK, 2011.
21. Li Petri, G.; Holl, R.; Spanò, V.; Barreca, M.; Sardo, I.; Raimondi, M.V. Emerging heterocycles as bioactive compounds. *Front. Chem.* **2023**, *11*, 1202192. [CrossRef]
22. Majumdar, K.C.; Chattopadhyay, S.K. *Heterocycles in Natural Product Synthesis*; Wiley-VCH: Weinheim, Germany, 2011.
23. Gao, B.; Yang, B.; Feng, X.; Li, C. Recent advances in the biosynthesis strategies of nitrogen heterocyclic natural products. *Nat. Prod. Rep.* **2022**, *39*, 139–162. [CrossRef] [PubMed]
24. Heravi, M.M.; Zadsirjana, V. Prescribed drugs containing nitrogen heterocycles: An overview. *RSC Adv.* **2020**, *10*, 44247–44311. [CrossRef]

25. Rusu, A.; Moga, I.-M.; Uncu, L.; Hancu, G. The role of five-membered heterocycles in the molecular structure of antibacterial drugs used in therapy. *Pharmaceutics* **2023**, *15*, 2554. [\[CrossRef\]](#)
26. Rotella, D.P. Heterocycles in drug discovery: Properties and preparation. In *Advances in Heterocyclic Chemistry*; Meanwell, N.A., Lolli, M.L., Eds.; Academic Press & Elsevier: Amsterdam, The Netherlands, 2021; pp. 149–183.
27. Pibiri, I. Recent advances: Heterocycles in drugs and drug discovery. *Int. J. Mol. Sci.* **2024**, *25*, 9503. [\[CrossRef\]](#) [\[PubMed\]](#)
28. Lamberth, C. Heterocyclic chemistry in crop protection. *Pest Manag. Sci.* **2013**, *69*, 1106–11014. [\[CrossRef\]](#) [\[PubMed\]](#)
29. Lamberth, C.; Dinges, J. *Bioactive Heterocyclic Compound Classes: Agrochemicals*; Wiley-VCH: Weinheim, Germany, 2012.
30. Al-Harb, E.A.; Wafaa, A.G. Nitrogen-containing heterocycles in agrochemicals. *Agri. Res. Tech. Open Access J.* **2018**, *16*, 555986. [\[CrossRef\]](#)
31. Roche, V.F.; Zito, W.S.; Lemke, T.L.; Williams, D.A. *Foye's Principles of Medicinal Chemistry*, 8th ed.; Wolters Kluwer: Alphen aan den Rijn, The Netherlands, 2019.
32. Schreiber, S.L. Target-oriented and diversity-oriented organic synthesis in drug discovery. *Science* **2000**, *287*, 1964–1969. [\[CrossRef\]](#)
33. Burke, M.D.; Lalic, G. Teaching target-oriented and diversity-oriented organic synthesis at Harvard University. *Chem. Biol.* **2002**, *9*, 535–541. [\[CrossRef\]](#)
34. Quin, L.D.; Tyrell, J.A. *Fundamentals of Heterocyclic Chemistry: Importance in Nature and in the Synthesis of Pharmaceuticals*; J. Wiley and Sons: Hoboken, NJ, USA, 2010.
35. Majee, S.; Shilpa; Sarav, M.; Banik, B.K.; Ray, D. Recent advances in the green synthesis of active N-heterocycles and their biological activities. *Pharmaceutics* **2023**, *16*, 873. [\[CrossRef\]](#) [\[PubMed\]](#)
36. Zeleke, D.; Damena, T. Advance in green synthesis of pharmacological important heterocycles using multicomponent reactions and magnetic nanocatalysts (MNCs). *Res. Chem.* **2024**, *7*, 101283. [\[CrossRef\]](#)
37. Hashmi, S.Z.; Bareth, D.; Dwivedi, J.; Kishorea, D.; Alvi, P.A. Green advancements towards the electrochemical synthesis of heterocycles. *RSC Adv.* **2024**, *14*, 18192–18246. [\[CrossRef\]](#)
38. Singh, K.; Sharma, S.; Tyagi, R.; Sagar, R. Recent progress in the synthesis of natural product inspired bioactive glycohybrids. *Carbohydr. Res.* **2023**, *534*, 108975. [\[CrossRef\]](#) [\[PubMed\]](#)
39. Wardecki, D.; Dolowy, M.; Bober-Majnusz, K.; Jampilek, J. Comparative study of the lipophilicity of selected anti-androgenic and blood uric acid lowering compounds. *Molecules* **2023**, *28*, 166. [\[CrossRef\]](#) [\[PubMed\]](#)
40. Zhao, T.; Sun, Y.; Meng, Y.; Liu, L.; Dai, J.; Yan, G.; Pan, X.; Guan, X.; Song, L.; Lin, R. Design, synthesis and antifungal activities of novel pyrazole analogues containing the aryl trifluoromethoxy group. *Molecules* **2023**, *28*, 6279. [\[CrossRef\]](#)
41. Rodriguez-Villar, K.; Yopez-Mulia, L.; Cortes-Gines, M.; Aguilera-Perdomo, J.D.; Quintana-Salazar, E.A.; Olascoaga Del Angel, K.S.; Cortes-Benitez, F.; Palacios-Espinosa, J.F.; Soria-Arteche, O.; Perez-Villanueva, J. Synthesis, antiprotozoal activity, and cheminformatic analysis of 2-phenyl-2H-indazole derivatives. *Molecules* **2021**, *26*, 2145. [\[CrossRef\]](#) [\[PubMed\]](#)
42. Ahmad, G.; Khalid, A.; Qamar, M.U.; Rasool, N.; Saadullah, M.; Bilal, M.; Bajaber, M.A.; Obaidullah, A.J.; Alotaibi, H.F.; Alotaibi, J.M. Antibacterial efficacy of N-(4-methylpyridin-2-yl)thiophene-2-carboxamide analogues against extended-spectrum- β -lactamase producing clinical strain of *Escherichia coli* ST 131. *Molecules* **2023**, *28*, 3118. [\[CrossRef\]](#)
43. Bec, A.; Zlatic, K.; Banjanac, M.; Radovanovic, V.; Starcevic, K.; Kralj, M.; Hranjec, M. Design, synthesis and biological activity of novel methoxy- and hydroxy-substituted N-benzimidazole-derived carboxamides. *Molecules* **2024**, *29*, 2138. [\[CrossRef\]](#)
44. Liew, L.P.; Shome, A.; Wong, W.W.; Hong, C.R.; Hicks, K.O.; Jamieson, S.M.F.; Hay, M.P. Design, synthesis and anticancer evaluation of nitroimidazole radiosensitisers. *Molecules* **2023**, *28*, 4457. [\[CrossRef\]](#)
45. Ramirez, D.; Mejia-Gutierrez, M.; Insuasty, B.; Rinne, S.; Kiper, A.K.; Platzk, M.; Muller, T.; Decher, N.; Quiroga, J.; De-la-Torre, P.; et al. 5-(Indol-2-yl)pyrazolo [3,4-b]pyridines as a new family of TASK-3 Channel blockers: A pharmacophore-based regioselective synthesis. *Molecules* **2021**, *26*, 3897. [\[CrossRef\]](#) [\[PubMed\]](#)
46. Heise, N.V.; Heisig, J.; Meier, K.; Csuk, R.; Mueller, T. F16 Hybrids derived from steviol or isosteviol are accumulated in the mitochondria of tumor cells and overcome drug resistance. *Molecules* **2024**, *29*, 381. [\[CrossRef\]](#) [\[PubMed\]](#)
47. Zolotareva, D.; Zazybin, A.; Dauletbakov, A.; Belyankova, Y.; Giner Parache, B.; Tursynbek, S.; Seilkhanov, T.; Kairullinova, A. Morpholine, piperazine, and piperidine derivatives as antidiabetic agents. *Molecules* **2024**, *29*, 3043. [\[CrossRef\]](#) [\[PubMed\]](#)
48. Kim, H.J.; Jung, H.J.; Kim, Y.E.; Jeong, D.; Park, H.S.; Park, H.S.; Kang, D.; Park, Y.; Chun, P.; Chung, H.Y.; et al. Investigation of the efficacy of benzylidene-3-methyl-2-thioxothiazolidin-4-one analogs with antioxidant activities on the inhibition of mushroom and mammal tyrosinases. *Molecules* **2024**, *29*, 2887. [\[CrossRef\]](#)

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