Al-Rafidain J Med Sci. 2023;4:60-67.
DOI: https://doi.org/10.54133/ajms.v4i.109

AJMS

Online ISSN (2789-3219)

Review Article

Anticancer Activities of Some Heterocyclic Compounds Containing an Oxygen Atom: A Review

Sumayah Saadi Abbas[1]*, Azhar Mahdi Jasim[1], Tayseer Hamid Shakir[1], Iman Saadi Abbas[2]

[1]*Department of Pharmaceutical Chemistry, College of Pharmacy, University of Baghdad, Baghdad, Iraq;*
[2]*Department of Pharmaceutics, College of Pharmacy, University of Baghdad, Baghdad, Iraq.*

Received: 14 March 2023; Revised: 15 April 2023; Accepted: 20 April 2023

Abstract

The purpose of this study is to underline the progression and development of research regarding oxygen-containing heterocycles, as well as to highlight the contribution that some oxygen-containing heterocycles have made as anticancer medicines. A series of publications about the antitumor effects of derivatives of heterocyclic compounds containing an oxygen atom, such as furan, benzofuran, oxazole, benzoxazole, and oxadiazole, were evaluated, and their anticancer activities showed encouraging results when compared to those of established standard treatments.

Keywords: Oxygen-containing heterocyclic compounds, Anticancer activity, Standard drugs, Benzo furan, Oxazole, Benzoxazole, Oxadiazole

الأنشطة المضادة للسرطان لبعض المركبات الحلقية غير المتجانسة التي تحتوي على ذرة الأوكسجين: مراجعة

الخلاصة

الغرض من هذه الدراسة هو التأكيد على تقدم وتطوير الأبحاث المتعلقة بالمركبات الحلقية غير المتجانسة المحتوية على ذرة الأوكسجين، وكذلك لتسليط الضوء على المساهمة التي قدمتها بعض المركبات الحلقية غير المتجانسة المحتوية على الأوكسجين كأدوية مضادة للسرطان. تم تقييم سلسلة من المنشورات حول التأثيرات المضادة للأورام لمشتقات المركبات الحلقية غير المتجانسة التي تحتوي على ذرة الأوكسجين، مثل الفوران، والبنزوفوران، والأوكسازول، والبنزوكسازول، والأوكساديازول، وأظهرت أنشطتها المضادة للسرطان نتائج مشجعة عند مقارنتها بتلك الموجودة في العلاجات القياسية المعمول بها.

* Corresponding author: Sumayah S. Abbas. Department of Pharmaceutical Chemistry, College of Pharmacy, University of Baghdad, Baghdad, Iraq; Email: sumayah.saadi@copharm.uobaghdad.edu.iq

Article Citation: Abbas SS, Jasim AM, Shakir TH, Abbas IS. Anticancer activities of some heterocyclic compounds containing an oxygen atom: A review. *Al-Rafidain J Med Sci.* 2023;4:60-67. doi: https://doi.org/10.54133/ajms.v4i.109

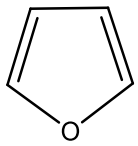
INTRODUCTION

Carcinoma is the abnormal growth of normal cells, frequently extending beyond of its original boundaries, including the surrounding area, and metastasizing to other organs, which is one of the main causes of mortality in cancer patients [1,2]. Globally, both cancer incidence and death are rapidly increasing [3]. Due to treatment resistance and adverse effects associated with their use, the quick and adaptive nature of cancer development makes it challenging to design new pharmaceuticals with the purpose of giving more effective therapeutic choices.

As a result, creating new therapeutic treatments is always necessary to address the side effects of existing pharmaceuticals [4]. With a range of biological factors, heteroromatic structures have developed into efficient scaffolds. Heterocyclic compounds play a significant role in the medical, pharmacological, chemical, physiological, and industrial fields. The final structure of more than 60% of the pharmaceutical industry's top-selling medications has at least one heterocycle motif [5]. The primary problems with treating cancer are the anticancer drugs' cytotoxicity and genotoxicity against healthy cells, which raise the possibility of subsequent malignancy. Finding and developing drugs that could efficiently cause apoptosis while also harming normal cells the least is therefore of great interest [6]. The majority of cancer illnesses are multifactorial, therefore a single monofunctional "targeted" medication could not be an efficient treatment option. The use of molecular hybridization is a helpful method for the design, discovery, and optimization of biologically active molecules. This method produces hybrid "multitarget-directed compounds" by fusing two various and independently active chemical entities into a single molecular scaffold [7].

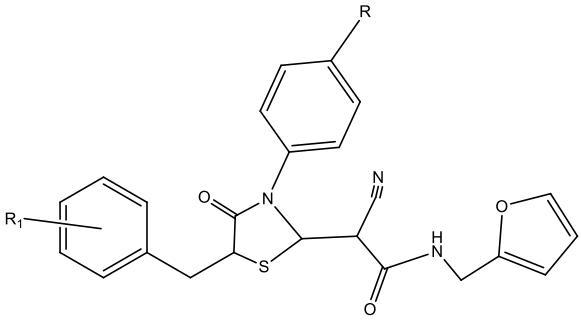
Furan

Furans (compound I) are five-membered ring heteroaromatic compounds containing one oxygen molecule [8].



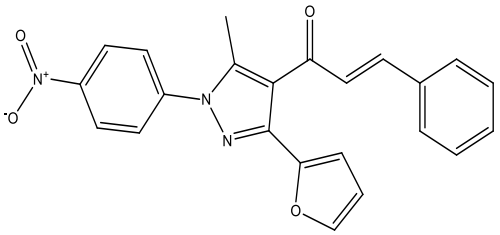
(Compound I)

Due to their chemotherapeutic-related behaviors, molecules containing furans have attracted a lot of interest in the field of pharmaceutical chemistry [9,10]. Ya *et al.* synthesized a number of derivatives from 2-cyano-N-(furan-2-ylmethyl)-2-(4-oxo-3-arylthiazolidin-2-ylidene)-acetamide, but the ultimate selective and effective antitumor action was discovered in 2-(5-R-benzyl-4-oxo-3-arylthiazolidin-2-ylidene)-2-cyano-N-(furan-2-ylmethyl)-acetamide (compound II) toward a line of lymphoblastic cells originally derived from a child with acute lymphoblastic leukemia (CCRF-CEM) (GP 13.77–29.32%) and spontaneously remission (SR) leukemia cell lines (GP 27.90–43.24%) [11].



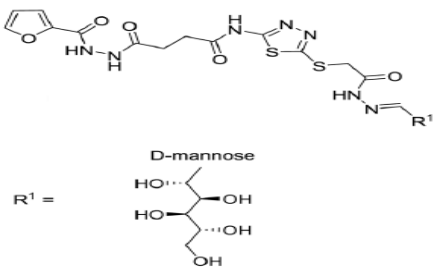
(compound II)

Helmy *et al.* prepared new furan derivatives, Compound III, (E)-1-(3-(furan-2-yl)-5-methyl-1-(4-nitrophenyl)-1H-pyrazol-4-yl)-3 phenylprop-2-en-1-one, demonstrated strong activity with 100% inhibition against BJ1, and were assessed against other 3 human cancer cell lines, which are MCF7 (human Caucasian breast adenocarcinoma), A549 (lung carcinoma), and HepG2 (human hepatocellular carcinoma), with percentages of cancer-related mortality of 100µg\ml of 87.2, 95.3, and 84.5, respectively [4].



(compound III)

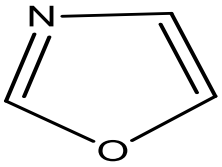
Kassem *et al.* synthesized brand-new furan derivatives containing 1,3,4-thiadiazole and sugar hydrazone moieties that were examined for their anticancer effects, *in vitro* on HepG-2 and RPE-1 cell lines. Compound IV exhibited significant antitumor activity with IC_{50} values of 4.2±1.2, compared to doxorubicin [12].



(compound IV)

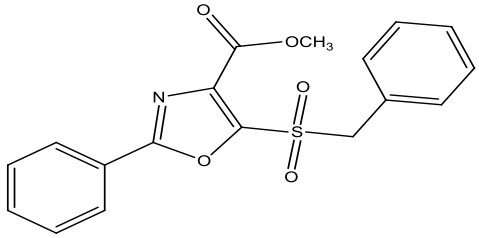
Oxazole

Oxazole, compound V, is a 5-membered aromatic heterocycle containing O and N atoms. Its structure allows non-covalent interactions with various enzymes and receptors in biological systems, allowing for a wide range of biological activities [13].



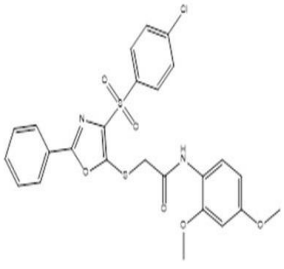
(compound V)

Pilyo *et al.* prepared new oxazole derivatives. Compound VI has the most potent antitumor activity against multiple cancer cell lines, ranging from -78.70% to 109.63% [14].

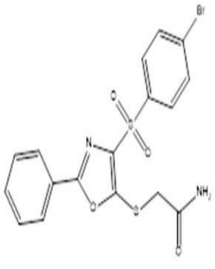


(compound VI)

Zyabrev *et al*. created a new class of 4-arylsulfonyl-1,3-oxazoles and tested them using 59 cancer cell lines to test the anticancer ability of all the synthesized chemicals. The greatest cytostatic effects were shown by compound VII against SNB75 and SF-539 (GI_{50} 0.50) of the central nervous system cancer subpanel, which are found in glioblastoma and gliosarcoma, respectively. While compound VIII has the largest antiproliferative activity in the non-small cell lung cancer subpanel (HOP-92 carcinoma) (GI_{50} 0.48) [15].

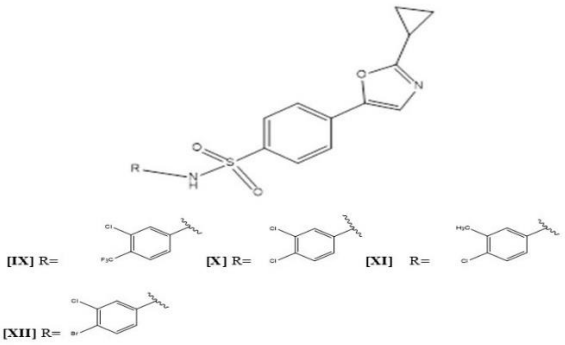


(compound VII)

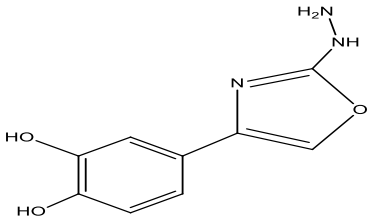


(compound VIII)

A variety of new 1,3-oxazole sulfonamides (IX-XII) were created by Sisco and coworkers and tested against the entire NCI panel of sixty human tumor cell lines for their potential to slow down the proliferation of cancer cells. Compounds IX-XII, GI_{50} 0.655, 0.416, 0.216, and 0.491, respectively, are specifically bound to tubulin, inhibit self-polymerization, and cause depolymerization of the intracellular microtubule network [16].



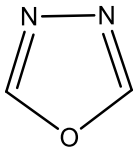
Naz and his coworkers synthesized new derivatives, including an oxazole moiety. The anticancer activity was investigated in vitro by an MTT assay using a glioblastoma cell line. Compound XIII containing an oxazole moiety with hydroxyl groups at the para and meta positions of the phenyl ring demonstrated excellent activity with an IC_{50} value of 13.17±0.06 µM [17].



(compound XIII)

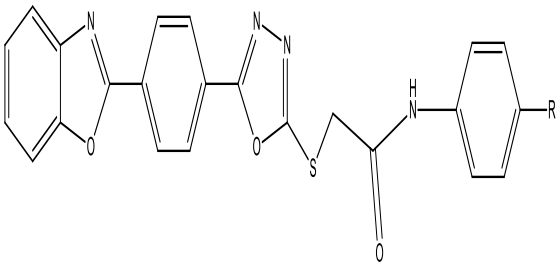
Oxadiazole

Oxadiazoles are well-known five-membered heterocyclic compounds with a structure that includes two nitrogen atoms and one oxygen atom. They are presented in several isomeric forms. 1,3,4-oxadiazole, compound IXV, is the best-known motif known for its biological impact [18].



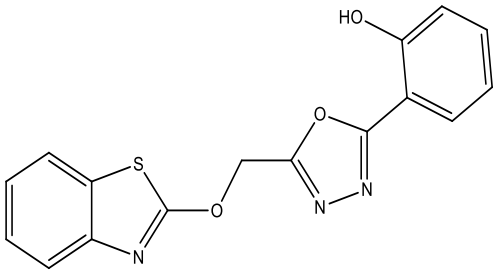
(compound IXV)

There are various literature findings that point to the fact that compounds that contain the 1,3,4-oxadiazole ring in their structure show several directions of action. These compounds show antibacterial [19], antimalarial [20], anti-inflammatory [21], anti-depressant [22], anti-cancer [23], analgesic [24], and antiviral effects [25,26]. Ravinaik *et al.* investigated the antitumor activity of a new 1,3,4-oxadiazole amide-linked benzoxazole analogue using the control drug combretastatin-A4 toward 4 human cancer cell lines, namely, lung, breast, melanoma, and colon cancer. In the number of substances produced, compounds XV and XVI showed strong activity to colorectal tumor cell lines, giving IC_{50} values equal to 0.018 and 0.093 µM, respectively, higher than standard drugs [27].



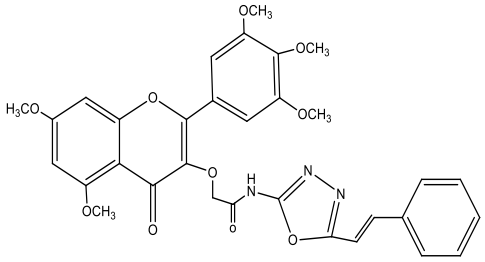
[XV] R= 4-OCH_3, [XVI] R= 4-NO_2

Alghamdi *et al.* synthesized benzothiazole clubbed with 1,3,4-oxadiazole; compound XVII was the most effective substance that demonstrated cytotoxicity (IC_{50} 1.8 ± 0.02 µM/mL). This is almost as potent as the reference drug doxorubicin (IC_{50} 1.2 ± 0.005 µM/mL) [28].



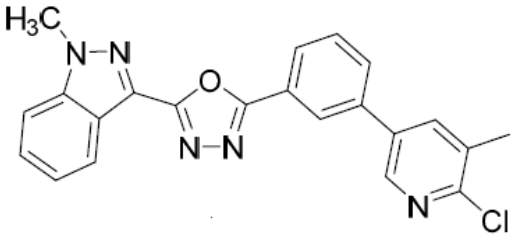
(compound XVII)

As prospective telomerase inhibitors, Han *et al.* developed 2-phenyl-4H-chromone compounds that have an amide and 1,3,4-oxadiazole moiety (compound XVIII) that have an IC50 0.44µM in comparison to the reference drug staurosporine (IC50 6.41 µM) [29].



(compound XVIII)

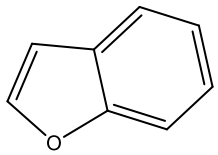
The anticancer potential of a new oxadiazole conjugated with an indazole that Malojirao and colleagues had produced was tested using several cancer cell lines. Among the novel substances, compound IXX always demonstrated the highest anticancer effect against cancer cells in the lung, with IC50 values ranging between 4.8–5.1 µM [30].



(compound IXX)

Benzofuran

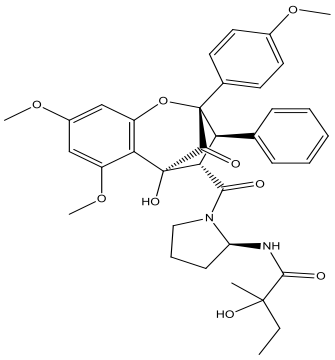
Structurally, benzofurans are describe by a unique motif formed by the fusion of benzene and furan (compound XX) [31].



(compound XX)

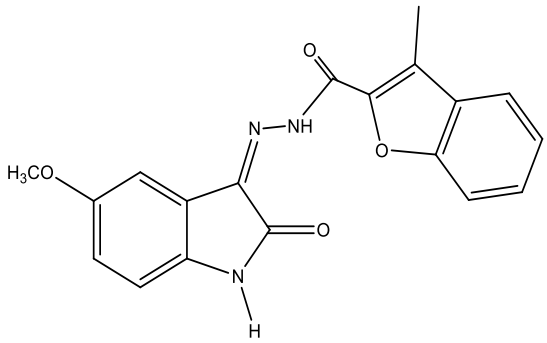
There are several different types of benzofuran compounds in nature. In higher plants, including Asteraceae, Rutaceae, Liliaceae, and Cyperaceae, benzofuran compounds are extensively distributed. The greatest number of these compounds have been found in Asteraceae [32]. Furthermore, benzofuran can be synthesized chemically through the dehydrogenation of 2-ethylphenol [33]. Benzofurans and their derivatives play a crucial role in treating malignant cells. Aglaodoratin (compound XXI), a tetrahydrocyclopenta-[b]-benzofuran derivative extracted from the leaves of *Aglaia odorata*, inhibits HepG2 hepatocellular carcinoma by arresting the

G2/M cell cycle phase and inducing apoptosis at a concentration of 25 μM [34].



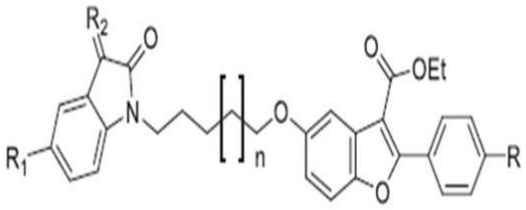
(compound XXI)

Eldehna and colleagues developed and synthesized a new class of benzofuran-isatin conjugates with carbohydrazide linkages. On fifty-five human cancer cell lines, compounds' anticancer efficacy was evaluated. Compound XXII was the most effective, and it was subjected to a five-dose screening process where it had great wide activity against almost all cancer subpanels that were tested in addition to an excellent inhibitory effect (IC_{50}: 6.5 and 9.8 mM) [35].



(compound XXII)

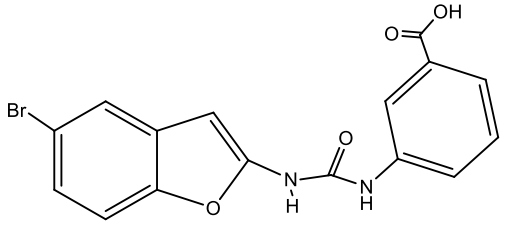
Xu and colleagues created and synthesized 14 benzofuran-isatin hybrids and tested their anticancer efficacy, *in vitro*, against a variety of cancer cell lines. The hybrids are linked through alkyl groups. The most active ones were XXIII (IC_{50}: 77.2–88.9 μM) and XXIV (IC_{50}: 65.4–89.7 μM), against wide-spectrum cancer cell lines: A549 (lung adenocarcinoma cells), HepG2 (liver cancer cells), MCF-7 (breast cancer cells), PC-3 (prostate cancer cells), and HeLa (human cervical carcinoma cells) [36].



(XXIII): [n]=2, R=OCH_3, R_1=F, R_2=$NOCH_3$

(XXIV): [n]=2, R=F, R_1=F, R_2=$NOCH_3$

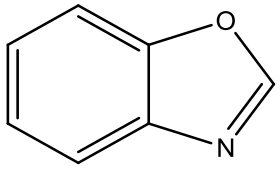
Currently, carboxylic acid derivatives are coupled to 5-bromobenzofuran through a ureido linker, as prepared by Eldehna *et al.* Some of the compounds investigated *in vitro* for potential breast cancer (MCF-7 and MDA-MB-231) antiproliferative effects, more specifically compound XXV, demonstrated a hopeful antiproliferative effect (IC_{50} = 2.52 ± 0.39 μM), the pro-apoptotic effects spread in MDA-MB-231 cells [37].



(compound XXV)

Benzoxazole

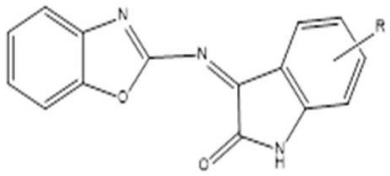
Benzoxazole (compound XXVI) is an organic heterocyclic compound that has a benzene ring fused with an oxazole ring [38,39]. Benzoxazole derivatives are found to have different anticancer activities [40].



(compound XXVI)

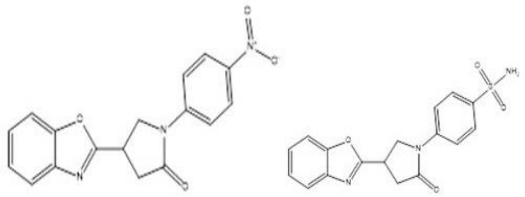
Susithra and colleagues created several new benzoxazole-isatin conjugates by treating substituted isatin derivatives with 2-amino benzoxazoles. The researchers then used the MTT method to test the antitumor activity, *in vitro*, of the conjugates toward the cancer cell lines HeLa, IMR-32, and MCF-7. Compounds XXVII, XXVIII, XXIX, XXX, and XXXI had the strongest cytotoxic activity against 3D

cancer cell lines. The IC_{50} values for all the synthetic test compounds ranged between 176.31 and 82.33 µM [41].



[XXVII] (R=5-F), [XXVIII] (R=Br), [XXIX] (R=Cl), [XXX] (R=CH_3) and [XXXI] (R=7-Cl)

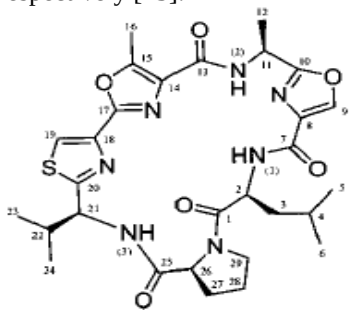
Afzal *et al*. synthesized benzoxazole and 2-pyrrolidinone derivatives. Anticancer screening revealed that compounds XXXII and XXXIII have significant anticancer activity against CNS cancer cell lines. These compounds were the most active inhibitors of monoacylglycerol lipase (MAGL), with IC_{50} of 8.4 and 7.6 nM, respectively [42].



(compound XXXII) (compound XXXIII)

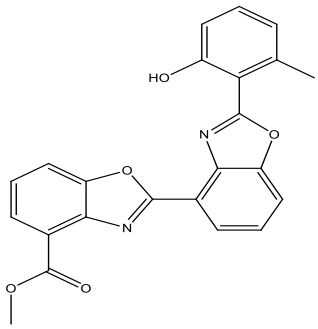
Some Natural Compounds Containing Oxygen-Heterocycles with Anticancer Activity

Leucamide A (compound XXXIV), composed of methyloxazole and thiazolyl subunits, was isolated from the Australian sponge *Leucetta microraphis*. Leucamide A was found to inhibit the growth of three tumor cell lines, HM02, HepG2, and Huh7, with GI50 values of 5.2 µg/mL, 5.9 µg/mL, and 5.1 µg/mL, respectively [43].



(compound XXXIV)

Nataxazole (compound XXXV) is a benzoxazole compound isolated from Streptomyces spp. that exhibits high cytotoxic activity against mouse leukemia (P388) cells and human AGS (gastric adenocarcinoma), MCF7 (breast adenocarcinoma), and HepG2 (hepatocellular carcinoma) cell lines. Cell cycle analysis showed that nataxazole and UK-1 induce S-phase cells and decrease G2/M-phase cells by about 44 percent [44].



(compound XXXV)

Conclusion

Heterocyclic compounds that contain oxygen atoms somewhere in their structure, as well as derivatives of those compounds, are extremely specialized molecules that have a wide range of uses in medicinal chemistry and play an important part in the functioning of biological systems. In pharmaceutical applications, these compounds have demonstrated broad-spectrum anticancer activity in a variety of cell lines derived from cancerous tumors. This demonstrates that there is potential for the development of new cancer medicines in the near future.

Conflicts of interest

The authors declare no conflicts of interest.

Source of fund

No specific fund received

Data availability statement

N/A

REFERENCES

1. Angre T, Kumar A, Singh AK, Thareja S, Kumar P. Role of collagen regulators in cancer treatment: A comprehensive review. *Anticancer Agents Med Chem*. 2022;22(17):2956-2984. doi: 10.2174/1871520622666220501162351.

2. Singh AK, Kumar A, Thareja S, Kumar P. Current insights into the role of BRAF inhibitors in treatment of melanoma. *Anticancer Agents Med Chem*. 2023;23(3):278-297. doi: 10.2174/1871520622666220624164152.

3. Bhattacharya S. Development of 5-FU loaded poly lactic-co-glycolic acid nanoparticles for treatment of lung cancer. *Iraqi J Pharm Sci*. 2022;31(1):130-143. doi: 10.31351/vol31iss1pp130-143.

4. Helmy MT, Sroor FM, Mahrous KF, Mahmoud K, Hassaneen HM, Saleh FM, et al. Anticancer activity of novel 3-(furan-2-yl) pyrazolyl and 3-(thiophen-2-yl) pyrazolyl hybrid chalcones: Synthesis and in vitro studies. *Archiv der Pharmazie*. 2022;355(3):2100381. doi: 10.1002/ardp.202100381.

5. Khatana K, Gupta A. An update on natural occurrence and biological activity of benzofurans. *Acta Sci Med Sci*. 2020;4:114. doi: 10.31080/asms.2020.04.0748.

6. Osmaniye D, Çelikateş BK, Sağlık BN, Levent S, Çevik UA, Çavuşoğlu BK, et al. Synthesis of some new benzoxazole derivatives and investigation of their anticancer activities. *Eur J Med Chem.* 2021;210:112979. doi: 10.1016/j.ejmech.2020.112979.

7. Makowska A, Wolff L, Sączewski F, Bednarski PJ, Kornicka A. Synthesis and cytotoxic evaluation of benzoxazole/benzothiazole-2-imino-coumarin hybrids and their coumarin analogues as potential anticancer agents. *Int Res J Pharm.* 2019;74(11):648-657.

8. Davies DT. Aromatic heterocyclic chemistry. Oxford: Oxford University Press; 1992. Chapter 2, Pyrroles, Thiophenes, and furans; p.10.

9. Alper-Hayta S, Arisoy M, Temiz-Arpaci Ö, Yildiz I, Aki E, Özkan S, et al. Synthesis, antimicrobial activity, pharmacophore analysis of some new 2-(substituted phenyl/benzyl)-5-[(2-benzofuryl) carboxamido] benzoxazoles. *Eur J Med Chem*. 2008;43(11):2568-2578. doi: 10.1016/j.ejmech.2007.12.019.

10. Al-Omari NA, Omar AO, Taher IM. Preliminary cytotoxic study of some novel Furo-2-quinolone compounds. *Iraqi J Pharm Sci*. 2009;18(Suppl.):32-38.

11. Horishny VY, Arshad M, Matiychuk VS. Synthesis and anticancer activity of 2-cyano-N-(furan-2-ylmethyl)-2-(4-oxo-3-arylthiazolidin-2-ylidene) acetamide derivatives. *Russ J Org Chem.* 2021;57(2):212-218. doi: 10.1134/s1070428021020111.

12. Kassem AF, Nassar IF, Abdel-Aal MT, Awad HM, El-Sayed WA. Synthesis and anticancer activity of new ((Furan-2-yl)-1, 3, 4-thiadiazolyl)-1, 3, 4-oxadiazole acyclic sugar derivatives. *Chem Pharm Bull.* 2019;67(8):888-895. doi: 10.1248/cpb.c19-00280.

13. Zhang HZ, Zhao ZL, Zhou CH. Recent advance in oxazole-based medicinal chemistry. *Eur J Med Chem.* 2018;144:444-492. doi: 10.1016/j.ejmech.2017.12.044.

14. Pilyo SG, Kozachenko OP, Zhirnov VV, Kachaeva MV, Kobzar OL, Vovk AI, et al. Synthesis and anticancer activity of 5-sulfonyl derivatives of 1, 3-oxazole-4-carboxylates. *Ukr Bioorg Acta*. 2020;15(2):13-21. doi: 10.15407/bioorganica2020.02.013.

15. Zyabrev V, Demydchuk B, Zhirnov V, Brovarets V. Synthesis, Characterization, and in vitro anticancer evaluation of 2-Aryl-4-Arylsulfonyl-5-RS-1, 3-oxazoles. *Biointerface Res Appl Chem.* 2022;13(3):1-53. doi: 10.33263/briac134.336.

16. Sisco E, Barnes KL. Design, synthesis, and biological evaluation of novel 1, 3-Oxazole Sulfonamides as tubulin polymerization inhibitors. *ACS Med Chem Lett.* 2021;12(6):1030-1037. doi:10.1021/acsmedchemlett.1c00219.

17. Naz A, Qazi SU, Javed A. Anticancer studies of Imine analogues. *Research Sequare*. 2022;1-9. doi: 10.21203/rs.3.rs-1537397/v1.

18. Joule JA, Mills K. Heterocyclic Chemistry. 5th ed. UK: John Wiley & Sons; 2010. Chapter 29, Heterocycles Containing More Than Two Heteroatoms: p.p.564.

19. Ahmed MN, Sadiq B, Al-Masoudi NA, Yasin KA, Hameed S, Mahmood, et al. Synthesis, crystal structures, computational studies and antimicrobial activity of new designed bis((5-Aryl-1,3,4-Oxadiazol-2-Yl)thio)Alkanes. *J Mol Struct*. 2018;1155:403-413. doi: 10.1016/j.molstruc.2017.11.011.

20. Verma G, Chashoo G, Ali A, Khan MF, Akhtar W, Ali I, et al. Synthesis of pyrazole acrylic acid based oxadiazole and amide derivatives as antimalarial and anticancer agents. *Bioorg Chem*. 2018;77:106-124. doi: 10.1016/j.bioorg.2018.01.007.

21. Abd-Ellah HS, Abdel-Aziz M, Shoman ME, Beshr EAM, Kaoud TS, Ahmed ASFF. New 1,3,4-oxadiazole/oxime hybrids: Design, synthesis, anti-Inflammatory, COX inhibitory activities and ulcerogenic liability. *Bioorg Chem.* 2017:74:15–29. doi: 10.1016/j.bioorg.2017.06.003.

22. Tantray MA, Khan I, Hamid H, Alam MS, Dhulap A, Kalam A. Synthesis of benzimidazole-linked -1,3,4-oxadiazole carboxamides as GSK-3 inhibitors with in vivo antidepressant activity. *Bioorg Chem.* 2018;77:393-401. doi: 10.1016/j.bioorg.2018.01.040.

23. Yadagiri B, Gurrala S, Bantu R, Nagarapu L, Polepalli S, Srujana G, et al. Synthesis and evaluation of benzosuberone embedded with 1,3,4-oxadiazole, 1,3,4-thiadiazole and 1,2,4-triazole moieties as new potential antiproliferative agents. *Bioorg Med Chem Lett.* 2015;25:2220-2224. doi: 10.1016/j.bmcl.2015.03.032.

24. Manjunatha K, Poojary B, Lobo PL, Fernandes J, Kumari NS. Synthesis and biological evaluation of some 1,3,4-oxadiazole derivatives. *Eur J Med Chem.* 2010;45:5225-5233. doi: 10.1016/j.ejmech.2010.08.039.

25. Hajimahdi Z, Zarghi A, Zabihollahi R, Aghasadeghi MR. Synthesis, biological evaluation, and molecular modeling studies of new 1,3,4-oxadiazole- and 1,3,4-thiadiazole-substituted 4-oxo-4H-pyrido[1-a] pyrimidines as anti-HIV-1 agents. *Med Chem Res.* 2013;22(5):2467-2475. doi: 10.1007/s00044-012-0241-5.

26. Xu WM, Li SZ, He M, Yang S, Li XY, Li P. Synthesis and bioactivities of novel thioether/sulfone derivatives containing 1,2,3-thiadiazole and 1,3,4-oxadiazole/thiadiazole moiety. *Bioorg Med Chem Lett.* 2013;23(21):5821-5824. doi: 10.1016/j.bmcl.2013.08.107.

27. Ravinaik B, Ramachandran D, Rao MV. Synthesis and anticancer evaluation of amide derivatives of 1, 3, 4-oxadiazole linked with benzoxazole. *Russ J Gen Chem.* 2019;89(5):1003-1008. doi: 10.1134/s1070363219050219.

28. Alghamdi A, Nazreen S. Synthesis, characterization and cytotoxic study of 2-hydroxy benzothiazole incorporated 1, 3,

4-oxadiazole derivatives. *Egypt J Chem*. 2020;63(2):471-482. doi: 10.21608/ejchem.2019.17265.2059.

29. Han X, Yu YL, Ma D, Zhang ZY, Liu XH. Synthesis, telomerase inhibitory and anticancer activity of new 2-phenyl-4H-chromone derivatives containing 1, 3, 4-oxadiazole moiety. *J Enzyme Inhib Med Chem.* 2021;36(1):345-361. doi: 10.1080/14756366.2020.1864630.

30. Malojirao VH, Girimanchanaika SS, Shanmugam MK, Sherapura A, Metri PK, Vigneshwaran V, et al. Novel 1, 3, 4-oxadiazole targets STAT3 signaling to induce antitumor effect in lung cancer. *Biomedicines*. 2020;8(9):368. doi: 10.3390/biomedicines8090368.

31. Eicher T, Hauptmann S. The Chemistry of Heterocycles: structures, reactions, synthesis, and applications. John Wiley & Sons; 2003; Chapter 5; p.63-64.

32. Proksch P, Rodriguez E. Chromenes and benzofurans of the Asteraceae, their chemistry and biological significance. *Phytochemistr*y. 1983;22(11):2335-2348. doi: 10.1016/0031-9422(83)80118-6.

33. Heravi MM, Zadsirjan V, Hamidi H, Tabar Amiri PH. Total synthesis of natural products containing benzofuran rings. *RSC Adv*. 2017;7:24470-24521. doi: 10.1039/C7RA03551A.

34. An FL, Wang JS, Wang H, Wang XB, Yang MH, Guo QL, et al. Cytotoxic flavonol-diamide [3+2] adducts from the leaves of *Aglaia odorata*. *Tetrahedron*. 2015;71(16):2450-2457. doi: 10.1016/j.tet.2015.02.028.

35. Eldehna WM, Salem R, Elsayed ZM, Al-Warhi T, Knany HR, Ayyad RR, et al. Development of novel benzofuran-isatin conjugates as potential antiproliferative agents with apoptosis inducing mechanism in colon cancer. *J Enzyme Inhib Med Chem*. 2021;36(1):1423-1434. doi: 10.1080/14756366.2021.1944127.

36. Xu K, Liu Y, Wang R, Cai P, Fang Y. Design, synthesis, and anticancer activities of benzofuran–isatin hybrids tethered by pentylene and hexylene. *J Heterocycl Chem*. 2019;56(7):2052-2055. doi: 10.1002/jhet.3586.

37. Eldehna WM, Nocentini A, Elsayed ZM, Al-Warhi T, Aljaeed N, Alotaibi OJ, et al. Benzofuran-based carboxylic acids as carbonic anhydrase inhibitors and antiproliferative agents against breast cancer. *ACS Med Chem Lett*. 2020;11(5):1022-1027. doi: 10.1021/acsmedchemlett.0c00094.

38. Rahim NA, Abbas SS, Aljuboori SB, Mahmood AA. Synthesis, antimicrobial evaluation and Docking study of new Schiff bases of benzo [d] oxazol-5-amine derivatives. *Res J Pharm Technol.* 2021;14(8):4129-4136. doi: 10.52711/0974-360X.2021.00715.

39. Alheety N. Synthesis, characterization and antimicrobial activity study of some new substituted benzoxazole derivatives. *Baghdad Sci J.* 2019;16(3):616-625.40.

40. Ghoshal T, Patel TM. Anticancer activity of benzoxazole derivative (2015 onwards): a review. *Future J Pharm Sci*. 2020;6(1):1-24. doi: 10.1186/s43094-020-00115-0.

41. Susithra E, Rajkumar S, Pansare SK, Praveena S, Arun PP, Chekkara R, et al. Design, synthesis, antimicrobial and anticancer activity of some novel benzoxazole-isatin conjugates. *Biointerface Res Appl Chem.* 2022;12:2392-403. doi: 10.33263/BRIAC122.23922403.

42. Afzal O, Altamimi AS, Shahroz MM, Sharma HK, Riadi Y, Hassan MQ. Analgesic and anticancer activity of benzoxazole clubbed 2-pyrrolidinones as novel inhibitors of monoacylglycerol lipase. *Molecules.* 2021;26(8):2389. doi: 10.3390/molecules26082389.

43. Kehraus S, König GM, Wright AD, Woerheide G. Leucamide A: A new cytotoxic heptapeptide from the Australian sponge Leucetta microraphis. The Journal of Organic Chemistry. 2002 Jul 12;67(14):4989-92.

44. Sommer PS, Almeida RC, Schneider K, Beil W, Süssmuth RD, Fiedler HP. Nataxazole, a new benzoxazole derivative with antitumor activity produced by Streptomyces sp. Tü 6176. The Journal of antibiotics. 2008 Nov;61(11):683-6.