Iraqi Journal of Pharmacy 20(2) (2023) 99-110

Online ISSN: 2664-2522

Print ISSN: 1680-2594

Iraqi Journal of Pharmacy

Journal homepage: https://iphr.mosuljournals.com

Review Article:

The Influence of Dioxolane Ring Conjugates on Biological Activities: A Review Study

Moath Kahtan Bashir [1], Mahmood Khudhayer Oglah [1], Yasser Fakri Mustafa [1], Ahmed Abdul-jabbar Mahmood [1]

[1] *Department of Pharmaceutical Chemistry, College of Pharmacy, University of Mosul, Mosul, Iraq.*

Article Information

Article history:

Received on: 28 July 2023
Revised on: 17 August 2023
Accepted on: 22 August 2023
Published on: 01 December 2023

Keywords:

Dioxolane,
Heterocyclic,
Antibacterial,
Antifungal,
Antiviral,
Cytotoxic

Abstract

Background: The problem of drug side effects necessitates the design, synthesis, and development of novel therapeutic agents that possess high activity with minimal side effects. According to the structure-activity relationship, the dioxolane moiety is found in many natural therapeutic agents and plays an important role in their medical action. Synthetic dioxolane conjugates have been studied in a variety of biological fields, including cytotoxicity, antibacterial, antifungal, antiviral, antioxidant, and anti-inflammatory activity, and have demonstrated a distinct potency that encourages further research in this mode. **Aim**: This review highlights the most recent studies on dioxolane ring conjugates in various biological fields as a promising bioactive heterocyclic scaffold. **Conclusion**: The hydrogen bonding of the oxygen atoms in this heterocyclic ring with the target site may be responsible for the enhanced ligand-target interactions and improved bioactivity.

1.Introduction

1.1 Overview

Dioxolane is a non-polar, five-membered heterocyclic ring with two oxygen atoms that is fully saturated and located either adjacently, which is called 1,2-dioxolane, or separated by a methylene group and called 1,3-dioxolane, as shown in **Figure 1** (1, 2).

1,2-Dioxolane 1,3-Dioxolane

Figure 1. Dioxolane chemical structures

***Corresponding author:** *Moath Kahtan Bashir, Department of Pharmaceutical Chemistry, College of Pharmacy, University of Mosul, Mosul, Iraq.*

Email: moathkahtan@uomosul.edu.iq

How to cite:

Bashir, M., Kh., Oglah, M., Kh., Mustafa, Y., F., Mahmood, A., A. (2023). The Influence of Dioxolane Ring Conjugates on Biological Activities: A Review Study . Iraqi J. Pharm. 20(2), 99-110.

DOI: **https://doi.org/10.33899/iphr.2023.142073.1051**

As shown in **Figure 2**, the dioxolane ring is the backbone of many naturally occurring, semi-synthetic, and synthetic drugs with various biological activities such as antifungal (e.g., ketoconazole and itraconazole), antiviral (e.g., amdoxovir), and anticancer (e.g., Podophyllotoxin, Etoposide, and Teniposide) (3, 4).

1.2 Antibacterial bioactivity

The random utilization of antibiotics has led to an elevated level of antibiotic resistance. This fact necessitated the search for compounds with high antibacterial activities but less resistant properties. Dioxolane-containing compounds are important scaffolds in this field (5-10). Numerous investigations have been stimulated to investigate the impact of dioxolane conjugates as antibacterial agents, such as the one conducted by Küçük and colleagues, who synthesized a series of compounds (**Figure 3**) containing 1,3-dioxolane and investigated their effects against the bacteria which are positive to the gram stain, including S. epidermidis, S.aureus, and E.faecalis and those that are negative to this stain,like P. aeruginosa, using the microbroth dilution technique. The findings demonstrate

that everything except for one of these molecules had outstanding inhibition of S. aureus, with MIC values between 625 and 1250 g/mL, whereas none of these molecules had any discernible activity against gram-negative bacteria. All of the synthesized derivatives, with the exception of the compound c, were highly effective antibacterial agents against S. epidermidis. When tested against P. aeruginosa, the compounds d, f, and h showed great antibacterial activity. Compound d demonstrated flawless activity against E. faecalis with a MIC value of 625 g/mL. In this study, amikacine was used as a control (11).

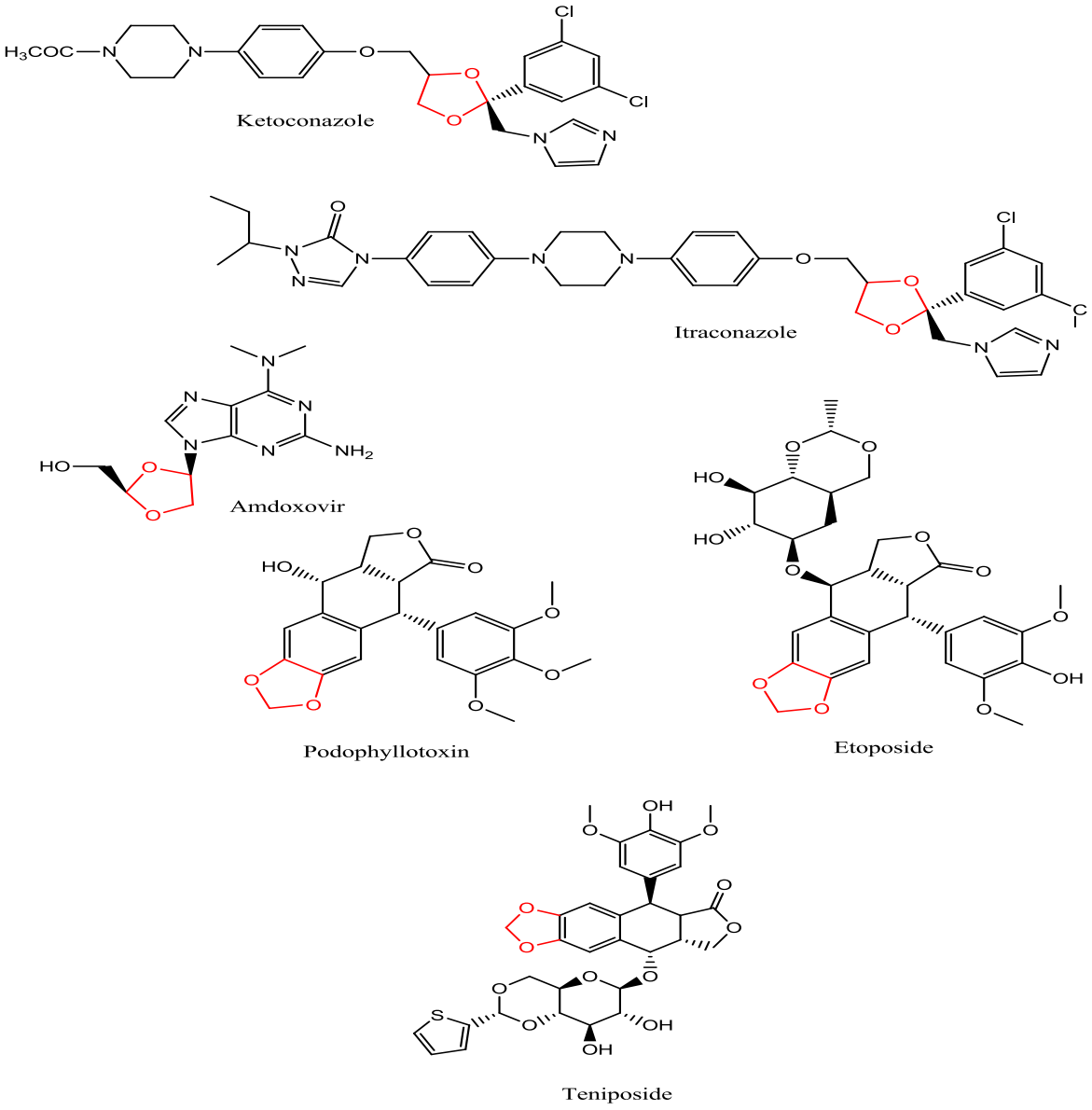


Figure 2. Drugs with a dioxolane scaffold in their chemical structures

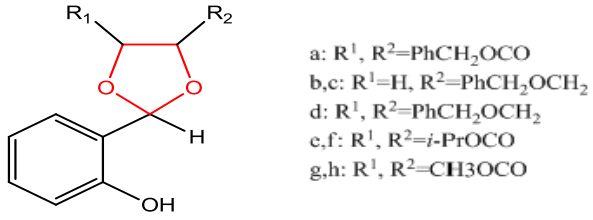
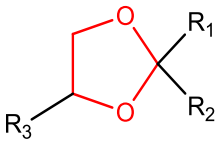


Figure 3. Compounds containing a 1,3-dioxolne scaffold prepared by Küçüket al.

Ovsyannikova and his colleagues synthesized a series of nine compounds containing a 1,3-dioxoane scaffold with substitution at positions 2 and 4 (**Figure 4**) and investigated their antibacterial effects on gram-positive (e.g., Staphylococcus) and gram-negative (e.g., Escherichia coli) bacteria using a method based on measurement of the intensity of the direct effects of tested compounds on live bacterial cells. Results showed that two compounds were the most effective, which may be related to the anti-radical activity of the test compounds, which depends on hydrophilic-hydrophobic balance (12).



	R_1	R_2	R_3
I	CH_3	CH_3	H
II	CH_3	C_2H_5	H
III	$(CH_2)_5$	$(CH_2)_5$	H
IV	CH_3	CH_3	CH_2OH
V	CH_3	C_2H_5	CH_2OH
VI	$(CH_2)_5$	$(CH_2)_5$	CH_2OH
VII	H	CH_3	CH_2OH
VIII	CH_3	CH_3	$CH_2OC_2H_5$
IX	CH_3	CH_3	CH_3COOCH_3

Figure 4. Compounds containing a 1,3-dioxolne scaffold prepared by Ovsyannikovaet al

Talismanov and colleagues prepared a series of substituted 1-((2-aryl-1,3-dioxolan-4-yl)methyl)-1H-azoles and investigated their antibacterial potencies against the gram-positive bacteria, includingE.faecalis, S.aureus, and B.subtilis, using the diffusion method and ciprofloxacin as a standard. Results showed that the activity of the synthesized compounds was comparable to that of the reference drug, and in addition, the compound named 2c (**Figure 5**) by the investigators showed activity above that of ciprofloxacin against S.aureus (13).

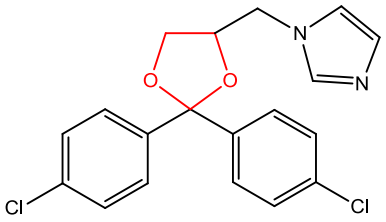


Figure 5. Compound 2c containing a 1,3-dioxolne scaffold prepared by Talismanovet al.

Jodeh and colleagues synthesized a novel naringin-based heterocyclic derivative (**Figure 6**), which was found to have the highest antibacterial activity against each of gram-negative (e.g., *E. coli* and *P. aeruginosa*) and gram-positive (e.g., *S. aureus*) bacteria using the microbroth dilution method with a minimal inhibitory concentration (MIC) of 0.125 mg/mL. Such a scaffold may be used as a template for future studies (14).

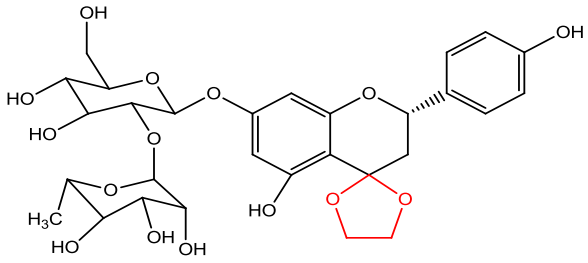


Figure 6. The naringin-based dioxolane derivative

Ramadan and colleagues synthesized a novel series of N-5 of 5H-1,2,4-triazino(5,6-b)indole-3-thiol connected with various 1,3-dioxolanes and examined its antibacterial activities against gram-positive bacteria (e.g.,S. aureus) and gram-negative bacteria (e.g.,E. coli, and P. aeruginosa), using imipenem as a standard. The results showed that many derivatives prepared by the investigators possessed an inhibition level in the range of 71-88% against the gram-positive bacteria, and the compound with a chemical structure displayed in **Figure 7** has the highest activity among tested compounds with no activity against gram-negative bacteria (15).

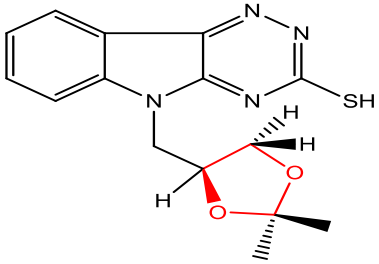
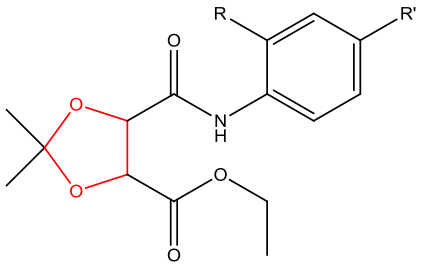


Figure 7. The most significant1,3-Dioxolane-thiol conjugates prepared by Ramadan *et al.*

Begum and co-workers prepared a novel amide derivative of 1,3-dioxolane from tartaric acid (**Figure 8**) and investigated their antibacterial activities against Enterobacterspp., Vibrio cholera, and Klebsiela spp. All prepared compounds showed good antibacterial activities against tested bacterial strains compared to the standard chloramphenicol. These compounds had the most significant results, which could be attributed to the presence of ortho- and para-halogen substitutions (16).



	R	R'
3a	H	H
3b	COOH	H
3c	H	I
3d	Cl	H
3e	Cl	Cl

Figure 8. Amide derivatives (3a- of a 1,3-dioxolane prepared by Begum *et al.*

Helesbeux and colleagues prepared many acetophenones that contain the 1,2-dioxolane moiety and investigated their activities against malarial-producing bacteria *Plasmodium falciparum*. Results showed that compounds named by the researchers as 10, 11, 20, and 21(**Figure 9**) had some activity against the chloroquine-resistant *P. falciparum* line. Such a scaffold may be the cornerstone for future studies against *P. falciparum* (17).

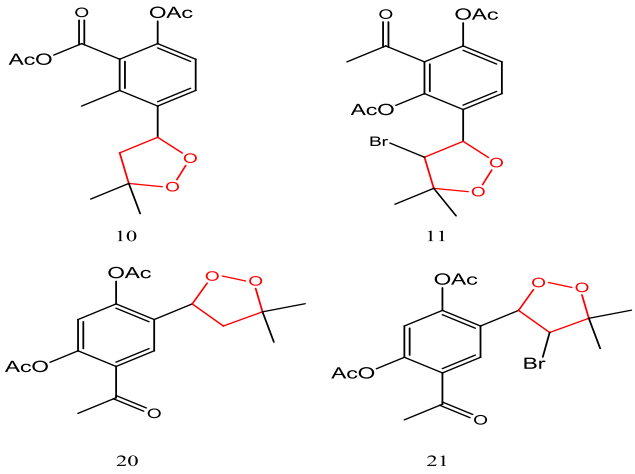


Figure 9. Acetophenones containing a 1,2-dioxolane scaffold prepared by Helesbeux*et al*

1.3 Antiviral bioactivity

Because of the epidemic infections caused in the last few decades, such as HIV and COVID-19, viral infections are a major concern all over the world. Such facts guided the scientists to design and synthesize proper antiviral agents (18-23). Dioxolane-pyrimidine nucleosides were created by Kim et al., who then tested their effectiveness versus HIV-1 in mononuclear cells from human peripheral blood. Comparing zidovudine as a control, results showed that the compound displayed in **Figure 10** has the most potent activity with the least cytotoxicity among the prepared series (24-29).

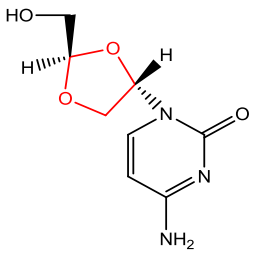
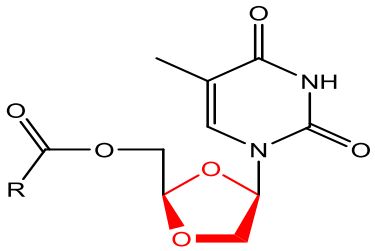


Figure 10. The active dioxolane-pyrimidine conjugate prepared by Kim *et al.*

Liang and colleagues synthesized a series of prodrugs by coupling aliphatic acid esters with (-)-b-D-(2R,4R)-dioxolane-thymine-5'-O-amino acid esters. These prepared compounds were investigated for their *in vitro* activities against HIV and hepatitis B virus (HBV) in human peripheral blood mononuclear cells. The prodrugs (1-8) with the structural backbone displayed in **Figure 11** showed improved anti-HIV activity with half-lives of 3-54 hours at pH 2 and good chemical stability (30).



1. R = CH_3 2. R= C_4H_9 3. R = C_7H_{15}
4. R = $C_{11}H_{23}$ 5. R = $C_{15}H_{31}$ 6. R = $(CH_3)_3C$
7. R = Cyclopropyl 8. R = Cyclohexyl

Figure 11. Prodrugs (1-8) of (-)-b-D-(2R,4R)-dioxolane-thymine

Franchini and collaborators synthesized a new series of 4-C-methyl and phenyldioxolane purines and pyrimidine nucleosides in an attempt to discover new antiviral scaffolds. Results showed that only the compound displayed in **Figure 12** weakly inhibited HIV-1 multiplication; however, manipulation of such conjugates may result in promising activities in future studies (31).

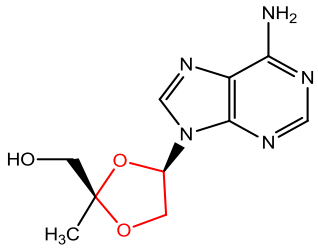


Figure 12. The dioxolane-nucleoside conjugate prepared by Franchini*et al.*

1.4 Cytotoxic bioactivity

Cancer is a global mortal disease that constitutes the second most common cause of death, and due to this fact, huge efforts have been made all over the world to fight this deadly disease, either through discovering natural compounds or synthesizing appropriate scaffolds in order to reduce its mortality rate (32-38). Dioxolane-containing compounds were found in many cytotoxic drugs of natural origin (3, 4), and they were also synthesized and investigated in many cytotoxic studies, for example the study made by Kim *et al.*, who prepared novel seven-membered ring platinum (II) complexes containing 1,3-dioxolane-2-(2-ethanamine)-2-methanamine. These complexes were tested for their in vitro cytotoxicity compared to the drugs cisplatin and carboplatin against cisplatin-resistant murine L1210 leukemia cell lines and cancer cell lines abstracted from human stomach (SNU-6, SNU-1, and SNU-5). Results showed that the complexes displayed in **Figure 13** are highly effective against these cytotoxic cell lines compared to the controls (39).

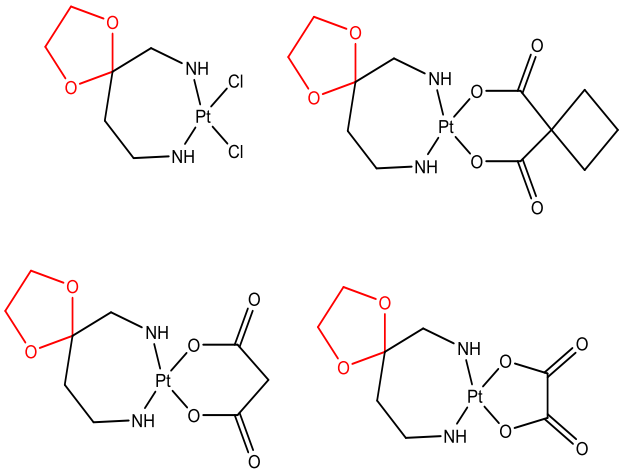


Figure 13. Novel platinum (II) complexes prepared by Kim *et al.*

Dzhumaev and colleagues synthesized a new series of ethers containing *gym*-dichloropropane and 1,3-dioxolane and then evaluated their*in vitro*cytotoxicity against SH-SY5Y (human neuroblastoma), A549 (human lung adenocarcinoma), and MCF-7 (adenocarcinoma of the human mammary gland ducts), tumor cell lines, and also the normal cell line from human named HEK293 (immortalized embryonic kidney cells). Results showed that the compound displayed in **Figure 14** was the most cytotoxic scaffold due to the presence of 1,3-dioxolane with an increased amount of *gym*-dichloropropane fragments, resulting in a modification in the cellular metabolism (40).

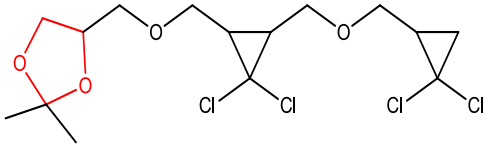
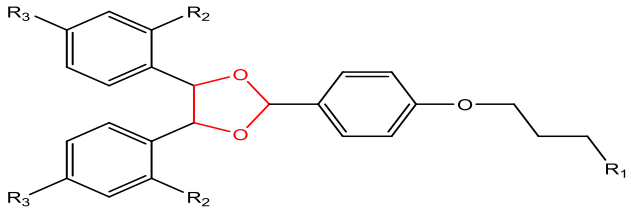


Figure 14. Cytotoxic active ether prepared by Dzhumaev*et al.*

Schmidt and his co-workers prepared novel 2,2-diphenyl-1,3-dioxolaneand 4,5-diphenyl-1,3-dioxolanederivatives, and examined their activities as effective modulators to reduce multi-drug resistance tumors (MDRTs) through interaction with P-glycoprotein, which is the major factor responsible for MDRTs. Different protonable basic moieties and lipophilic linker structures were synthesized and investigated. The most effective compounds, according to the findings, are piperazine derivatives with two basic centers and an ideal proximity of 5Å seen between basic functional group and the lipid soluble fragrant structure.. The *in vitro* investigations were made on human Caco-2 cells (colorectal adenocarcinoma), and the different isomers of the frameworkdisplayed in **Figure 15** were found to be the most effective (41).

Hawata and colleagues used a heterocyclization reaction to create a new series of substituted pyrazolo(3,4-b)pyridines linked to 1,3-dioxolane, oxadiazole, the fluorinated ring system, and acyclic sugar. The prepared compounds were investigated for their *in vitro* cytotoxicity against HTC116 (human colorectal carcinoma) and MCF7 cell lines. Results showed that the compound displayed in **Figure 16** with the 1,3-dioxolane side chain was one of the top cytotoxic agents with an IC_{50} value of 39±4 µM for the HTC116 cell line and 17.17±2.93 µM for the MCF7 cell line. Doxorubicin was used as a control in this *in vitro* study (42).



	R_1	R_2	R_3
22/cis	4-methylpiperazine	H	H
22/trans	4-methylpiperazine	H	H
22/RR	4-methylpiperazine	H	H
22/SS	4-methylpiperazine	H	H

Figure 15. New 1,3-dioxolane derivatives as effective modulators to reduce MDR

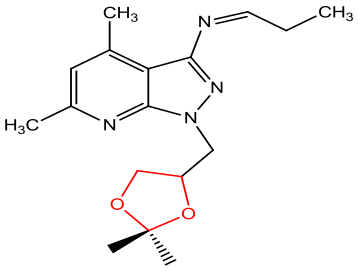


Figure 16. Pyrazolo-pyridine conjugated with 1,3-dioxolane prepared by Hawata*et al.*

A novel bioengineering of alternating copolymers and their organoboron amide-ester-carboxyl functionalized copolymers were synthesized by Kahraman and colleagues (**Figure 17**), then their*in vitro* activity against Hela (cervical cell carcinoma) cells was investigated. Results showed that the cytotoxicity was significantly increased for organoboron copolymer concentrations above 100 µM/mL. Such a cytotoxic effect may be attributed to the formation of complex hydrogen bonds that influence the destruction of biomacromolecules in cancer cells (43).

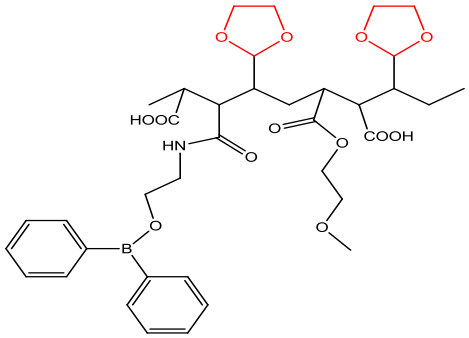


Figure 17. The organoboron amide-ester-carboxyl functionalized copolymers prepared by Kahraman*et al.*

Dung *et al.* designed and prepared a novel series of N hydroxyl propenamides containing 5' (7')-substituted-2'-oxospiro (1,3) dioxolane-2,3'-indoline, then evaluated their inhibitory activity against histone deacetylase (HDAC2), which plays an significant impact in the carcinogenesis. Results showed that these compounds possessed potent inhibitory activity, with an IC_{50} for the compound displayed in **Figure 18** of 0.284μM, which is comparable to the IC_{50} of vorinostat (0.265 μM) which is the positive control. Such a new series may be used as a template for future HDAC2 inhibitors (44).

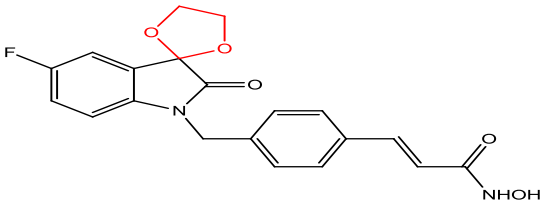


Figure 18. Compound with a 1,3-dioxolane-indoline system prepared by Dung *et al.*

All natural and synthetic nucleoside analogues are in the β-D-configuration; however, Grove and his co-workers prepared a novel unnatural nucleoside analogue thathas β-L-configuration. β-L-dioxolane-cytidine is an important compound from this series (**Figure 19**), with significant *in vitro* activity against a nasopharyngeal carcinoma (KB) cell line and two prostate cancer (DU-145 and PC-3) cell lines when compared to cytosine arabinoside. This compound's cytotoxic activity may be due to its resistance to degradation by the deoxycytidinedeaminase enzyme (45).

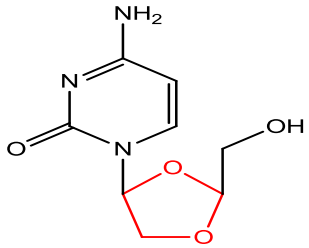


Figure 19. Theβ-L-dioxolane-cytidine prepared by Grove *et al.*

1.5 Antifungal bioactivity

Fungal infections are responsible for more than 1.5 million deaths globally, especially in people with AIDS, cancer, corticosteroid therapies, and organ transplantation. These facts help scientists develop more potent compounds with fewer side effects (46-51).

Xiao-hui and colleagues prepared a novel series of triazole compounds containing 1,3-dioxolane and investigated their*in vitro* activity against *Candida albicans, Candida tropicalis, Candida parapsilosis*, and *Candida neoformance* using itraconazole as a standard. Results showed that the compound with a structural backbone displayed in **Figure 20** was the most effective, with an IC_{50} of 0.125, 0.125, 0.5, and 4 μg/mL, respectively, compared to the IC_{50} of itraconazole (2, 2, 2, and 1) μg/mL, respectively. These triazole-dioxolane conjugates may be used as a scaffold for future studies because of the pronounced results obtained (52).

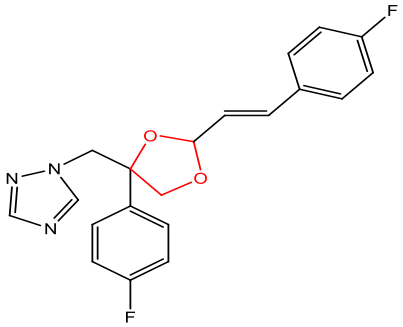


Figure 20. The structural backbone of the triazole-dioxolane conjugate prepared by Xiao-hui*et al.*

Talismanov and colleagues synthesized and examined the *in vitro* antifungal activity of some 4-azolylmethyl-1,3-dioxolane conjugates against six phytopathogens, which are *Venturiainaequalis, Sclerotiniasclerotiorum, Bipolarissorokiniana, Rhizoctoniasolani, Fusariummoniliforme,* and *Fusariumoxysporum.* The synthetic moietieswith structural frameworks displayed in **Figure 21** showed good retardant activity on radial mycelium growth of the tested fungi compared to triadimefon as a standard (53).

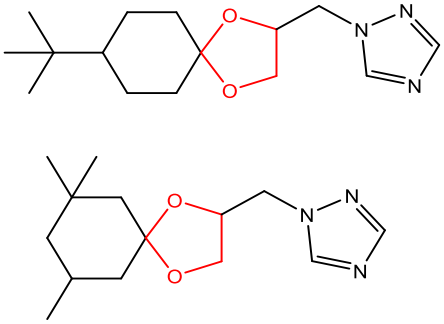


Figure 21. Triazole-1,3-dioxolane conjugates prepared by Talismanov*et al.*

Pinetand collaborators prepared a series of 3,5-disubstituted 1,2-dioxolanes and investigated their activity against *Candida albicans* and *Aspergillus fumigatus*. Results showed that the compounds with structural frameworks displayed in **Figure 22** possessed moderate antifungal activity compared to the standard antifungal drug fluconazole (54).

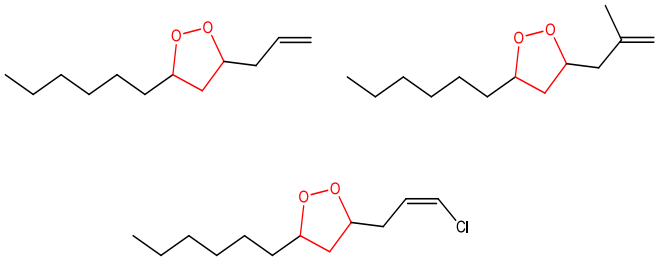


Figure 22. The 3,5-disubstituted 1,2-dioxolanes prepared by Pinet*et al.*

Delcourt and colleagues used 2-(2,4-dichlorophenyl)-1,3-dioxolane to prepare a new class of polyazole derivativesand examined their*in vitro* antifungal activities versusa series of pathogenic fungi that can attackanimals and humans. The results showed that the compounds with the structural frameworks displayed in **Figure 23** were the most effective,especially against *Cryptococcus neoformans* and *Candida glabrata*with an MIC below 12.5 µg/mL, which is somewhat similar to that of the standards ketoconazole and oxiconazole. The structure-activity relationship postulated that the four chlorine atoms and the oxime group increased the antifungal activity of the tested compounds (55).

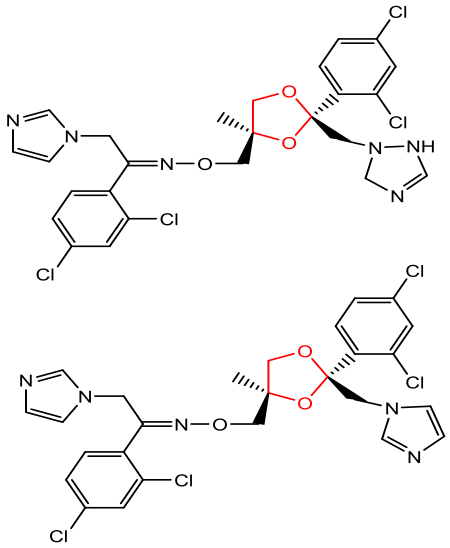


Figure 23. The 2-(2,4-dichlorophenyl)-1,3-dioxolane derivatives prepared by Delcour*et al.*

In the agricultural field, Hoshi and colleagues synthesized a new series of 1,2,4-triazole derivatives and investigated theiractivity against *Magnaportheoryzae*, which is the major fungus responsible for rice blast. Results showed that the compound with the chemical structure illustrated in **Figure 24** was the most effective, with an IC_{50} 3.8±0.5 µM compared to the IC_{50} of propiconazole, 3.7±0.2 µM. The antifungal effect was found to be increased in a dose-dependent manner and the chlorine atom possessed an important role in such activity according to the structure-activity relationship study (56).

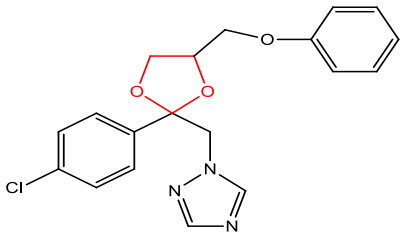


Figure 24. The active antifungal agent prepared by Hoshi *et al.*

1.6 Antioxidant bioactivity

A number of diseases, including Alzheimer's disease, atherosclerosis, chronic obstructive pulmonary disease, diabetes mellitus, and cancer are discovered to be triggered by oxidative stress, which results from an imbalance in the amount of oxidizing agents and physiological antioxidant defensive systems. In order to avoid and even consider such serious illnesses, it has been discovered that both natural and artificial compounds with antioxidant properties are crucial (57-64).

Sonmez and colleagues synthesized a novel series of spiro-isatin-based Schiff bases and investigated their ABTS (2,2-azinobis-(3-ethylbenzothiazoline-6-sulfonate), CUPRAC (cupric reducing antioxidant capacity), and DPPH (2,2-diphenyl-1-picrylhydrazyl),cation radical scavenging abilities. Results showed that all synthesized compounds were effective antioxidants, and the compound with the structural framework illustrated in **Figure 25** was the most active, with an IC_{50}=0.39 µM for ABTS, 4.49 µM for DPPH, and 0.42 µM for CUPRAC.These values of IC_{50} are even more significant than the standard quercetin, with an IC_{50}=15.49 µM for ABTS, 8.69 µM for DPPH, and 18.47 µM for CUPRAC. According to the structure-activity relationship study, the catechol moiety was found to exhibit this high antioxidant effect (65).

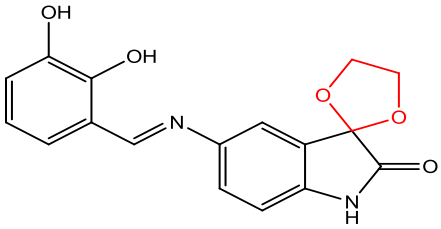


Figure 25. The most potent spiro-isatin-bases Schiff base prepared by Sonmez*et al.*

Nobre *et al.* prepared a new class of organochalcogen compounds from glycerol and investigated their antioxidant potency using different assay procedures such as ABTS, DPPH, nitric oxide (NO), and hydroxyl radical (OH•) scavenging activities. Results showed that the compound with the chemical structure illustrated in **Figure 26** was the most effective, and such activity was found to be influenced by tellurium in its structure (66).

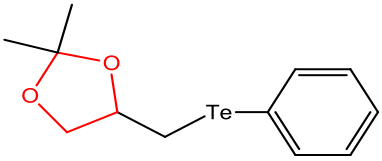


Figure 26. The2,2-dimethyl-4-(phenyltellanylmethyl)-1,3-dioxolane prepared by Bobre*et al.*

Talisnanov and colleagues prepared a new class of triazole derivatives functionalized with various cyclic ketals, then investigated their scavenging activity using the DPPH scavenging activity test and trolox as a standard. Results showed that the compound with the chemical framework illustrated in **Figure 27** was the most effective, and thisactivity was attributed to the hexylthiosulfonyl substituent in the *para* position of the arene ring (67).

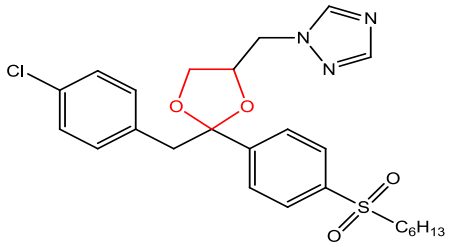


Figure 27. The active derivative prepared by Talisnanov*et al.*

1.7 Anti-inflammatory bioactivity

Inflammation is the body's response to an injury or insult, and it is essentially beneficial, but excessive mediating agent release in this protective process can lead to dire consequences for the body; that's why natural or synthetic anti-inflammatory agents gain great attention through selective inhibition of mediator synthesis (68-79). Niu and his research group extracted and identified 27 sesquiterpenoidproducts from the deep-sea sediment-derived fungus *Aspergillus sydowii*. They include bisabolanes and cuparene-containing compounds. All isolated compounds, including that with a dioxolane ring and the chemical structure displayedin **Figure 28**, exhibited a dose-dependent inhibition of the pro-inflammatory mediator nitric oxide secreted in lipopolysaccharide BV-2 microglia cells. Such results provided a new and novel scaffold with anti-inflammatory activity (80).

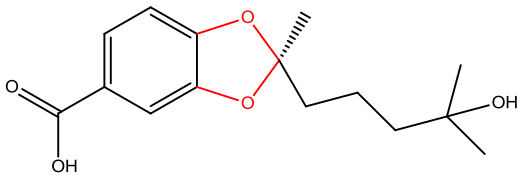


Figure 28. The novel seco-bisabolane skeleton with dioxolane ringisolated by Neu and his team

Guo and colleagues isolated and identified a novel sesquiterpenoidlindenane dimer with an unprecedented 1,3-dioxolane linkage (**Figure 29**). This compound was found to exhibit a potent inhibitory effect on the production of the pro-inflammatory mediator nitric oxide in RAW 264.7 (monocyte/macrophage-like) cells (81).

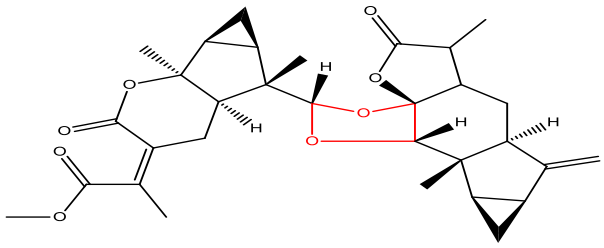


Figure 29. The novel sesquiterpenoidlindenane dimer with 1,3-dioxolane linkage

Hadjipavlou-Litina and colleagues synthesized and investigated the anti-inflammatory activity of a series of coumarins and coumarin-conjugates. The dioxolane-coumarine conjugated compound with the chemical structure illustrated in **Figure 30** has been shown to have a significant anti-inflammatory *in vivo* effect using carrageenan-induced rat paw edema at a concentration of 0.01 mmole/kg with a protection percentage of 57.4% compared to 47%, which is the protection percentage of indomethacin at equivalent concentration. Such enhanced activity was attributed to the potent inhibition of the lipoxygenase enzyme (82).

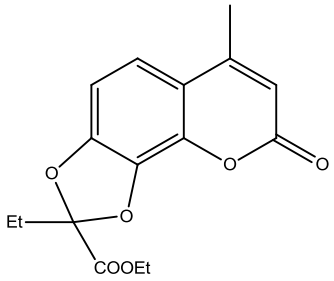


Figure 30. Dioxolane-coumarin conjugate prepared by Hadjipavlou-Litina*et al.*

2. Conclusion

Many scientific studies of various pharmacological fields have discovered the presence of the dioxolane heterocyclic ring in conjugation with many other chemical groups to be a basic motif. The positive findings in these studies with dioxlane conjugation may be attributed to the hydrogen bonding of the oxygen atoms in this heterocyclic ring with the target site, leading to enhanced ligand-target interactions.

3. Acknowledgments

The authors are very grateful to the University of Mosul/College of Pharmacy for their provided facilities, which helped to improve the quality of this work.

4. References

1. Ferrié L. Advances in the synthesis of 1,2-dioxolanes and 1,2-dioxanes. In Scriven E and Ramsden C (eds), Advance in Heterocyclic Chemistry. Elsevier, USA. 2021: pp 57-145.

2. Aitken RA. and Hill L. 1,3-Dioxoles and 1,3-oxathioles. In Black D, Cossy J, and Stevens C (eds), Comprehensive Heterocyclic Chemistry IV. Elsevier, USA. 2021: pp 525-567.

3. Ram VJ, Sethi A, Nath M, and Pratap R. The chemistry of heterocycles: Nomenclature and chemistry of three-to–five membered heterocycles. Elsevier, USA. 2017: pp 149-478.

4. Rad JS, Ozleyene A, Tumer TB, Adeetunji CO, El-Omari N, Balahbib A, Taheri Y, Bouyahya A, Martorell M, Martins N, Cho WC. Natural Products and Synthetic Analogs as a Source of Antitumor Drugs. *Biomolecules* 2019; 9:679-731.

5. Mustafa YF, Khalil RR, Mohammed ET. Antimicrobial activity of aqueous extracts acquired from the seeds of two apples' cultivars. *Systematic Reviews in Pharmacy* 2020; 11(2):382-387.

6. Jebir RM, Mustafa YF. Natural Coumarin-Lead Compounds: A Review of Their Medicinal Potentials. *Iraqi Journal of Pharmacy* 2022; 18(2):139–61.

7. Waheed SA, Mustafa YF. Synthesis of coumarin-based derivatives from different starting materials: A review of ongoing developments. *Iraqi Journal of Pharmacy* 2022; 18(2):126–38.

8. Oglah MK, Mustafa YF, Bashir MK, Jasim MH. Curcumin and its derivatives: A review of their biological activities. *Systematic Reviews in Pharmacy* 2020; 11(3):472–81.

9. Jasim SF, Mustafa YF. A review on coumarin backbone: An attractive scaffold for promising bioactive compounds. *Iraqi Journal of Pharmacy* 2022; 18(2):104–25.

10. Ismael RN, Mustafa YF, Al-Qazaz HK. Coumarin-based products: Their biodiversity and pharmacology. *Iraqi Journal of Pharmacy* 2022; 18(2):162–79.

11. Küçük HB, Yusufoğlu A, Mataracı E, and Döşler S. Synthesis and biological activity of new 1,3-Dioxolanes as potential antibacterial and antifungal compounds. *Molecules* 2011; 16:6806-6815.

12. Ovsyannikova MN, Vol'eva VB, Belostotskaya IS, Komissarova NL, Malkova A V, Kurkovskaya LN. Antibacterial activity of substituted 1,3-dioxolanes. Pharm Chem J, 2011, 47(3):142-145.

13. Talismanov VS, Popkov SV, Zykova SS, Karmanova OG. Design, synthesis and antibacterial activity of substituted 1-((2-aryl-1,3-dioxolan-4-yl)methyl)-1H-azoles. *Pharmaceutical Chemistry Journal* 2018; 1(2):328-332.

14. Jodeh S, Shawarb N, Jaradat N, Warad I, Hussein F, El-Masri M, Salghi R. Synthesis and biological activities of a novel naringin based heterocyclic derivatives. *Moroccan Journal of Chemistry* 2015; 3:242-250.

15. Ramadan E, Rasheed HA, El-Ashry EH. Synthesis and antimicrobial screening of novel 1,3-dioxolanes linked to N-5 of 5H-1,2,4-triazino(5,6-b)indole-3-thiol. *Journal of the Serbian Chemical Society* 2019; 84(1): 1-10.

16. Begum Z, Khan M, Khan SW, Imran M, RehmanN, Umar MN, Kamil A, Muhammad T. Synthesis, characterization, antifungal and antibacterial activities of novel amide derivatives of 1,3-Dioxolane. *International Journal of Chemistry* 2019; 11(1): 71-78.

17. Helesbeux J, Peyronnet D, Labaïed M, Grellier P, Frappier F, Seraphin D, Richomme P, Duval O. Synthesis and antimalarial activity of some new 1,2-Dioxolane derivatives. *Journal of Enzyme Inhibition and Medicinal Chemistry* 2002; 17(6): 431–437.

18. Collins LF, Sheth AN, Mehta CC, Naggie S, Golub ET, Anastos K, French A, Kassaye S, Taylor T, Fischl MA, Adimora AA, Kempf M, Palella F, Tien P, Ofotokun I. The prevalence and burden of non-AIDS comorbidities among women living with or at risk for human immunodeficiency virus infection in the united states. *Clinical Infectious Diseases* 2021; 72(8): 1301-1311.

19. Mustafa YF, Waheed SA, Jasim SF, Jebir RM, Ismael RN, Qutachi O. A Narrative Review of Benzo-Fused Coumarins, Shedding Light on Their Medicinal Activities. *Iraqi Journal of Pharmacy* 2023; 20(1):7–16.

20. Akendengue B, Ngou-Milama E, Bourobou-Bourobou H, Essouma J, Roblot F, Gleye C, et al. Acaricidal activity of Uvaria versicolor and Uvaria klaineana (Annonaceae). *Phytotherapy Research* 2003; 17(4):364–7.

21. Mustafa YF. Chemotherapeutic applications of folate prodrugs: A review. *NeuroQuantology* 2021; 19(8):99–112.

22. Mahmood AAJ, Mustafa YF, Abdulstaar M. New coumarinic azo-derivatives of metoclopramide and diphenhydramine: Synthesis and in vitro testing for cholinesterase inhibitory effect and protection ability against chlorpyrifos. *International Medical Journal Malaysia* 2014; 13(1):3–12.

23. Mustafa YF, Abdulaziza NT, Jasima MH. 4-Methylumbelliferone and its derived compounds: A brief review of their cytotoxicity. *Egyptian Journal of Chemistry* 2021; 64(4):1807–16.

24. Kim HO, Ahn SK, Alves AJ, Beach JW, Jeong LS, Choi BG, Roey PV, Schinazi RF, Chu CK. Asymmetric synthesis of 1,3-Dioxolane-Pyrimidine nucleosides and their anti-HIV activity. *Journal of Medicinal Chemistry* 1992; 35(11): 1987-1995. 11.

25. Mustafa YF, Abdulaziz NT. Hymecromone and its products as cytotoxic candidates for brain cancer : A brief review. *NeuroQuantology* 2021; 19(7):175–86.

26. Mustafa YF, Al-dabbagh KA, Mohammed MF. Synthesis of new metronidazole derivatives with suspected antimicrobial activity. *Iraqi Journal of Pharmacy* 2008; 7(1):34–41.

27. Mohammed ET, Mustafa YF. Coumarins from Red Delicious apple seeds : Extraction, phytochemical analysis, and evaluation as antimicrobial agents. *Systematic Reviews in Pharmacy* 2020; 11(2):64–70.

28. Mustafa YF, Abdulaziz NT. Biological potentials of hymecromone-based derivatives : A systematic review. *Systematic Reviews in Pharmacy* 2020; 11(11):438–52.

29. Mustafa YF. Synthesis, characterization, and biomedical assessment of novel bisimidazole–coumarin conjugates. *Applied Nanoscience (Switzerland)* 2023;13(3):1907–18.

30. Liang Y, Sharon A, Grier JP, Rapp KL, Schinazi RF, Chu CK. 5'-*O*-Aliphatic and amino acid ester prodrugs of ()-b-D-(2R,4R)-dioxolane-thymine (DOT): Synthesis, anti-HIV activity, cytotoxicity and stability studies. *Bioorganic & Medicinal Chemistry* 2009; 17: 1404–1409.

31. Franchini S, Battisti UM, Sorbi C, Tait A, Cornia A, Jeong LS, Lee SK, Song J, Loddo R, Madeddo S, Sanna G, Brasili L. Synthesis, structural characterization and

biological evaluation of 4'-C-methyl- and phenyl-dioxolane pyrimidine and purine nucleosides. *Archives of Pharmacal Research* 2016; 39(8): 1-15.

32. Oglah MK, Mustafa YF. Synthesis, antioxidant, and preliminary antitumor activities of new curcumin analogues. *Journal of Global Pharma Technology* 2020; 12(2): 854-862.

33. Khalil RR, Mustafa YF. Phytochemical, antioxidant and antitumor studies of coumarins extracted from Granny Smith apple seeds by different methods. *Systematic Reviews in Pharmacy* 2020; 11(2):57–63.

34. Mustafa YF. Synthesis, characterization and antibacterial activity of novel heterocycle, coumacine, and two of its derivatives. *Saudi pharmaceutical journal* 2018; 26(6):870–5.

35. Mustafa YF. Synthesis, characterization and preliminary cytotoxic study of sinapic acid and its analogues. *Journal of Global Pharma Technology* 2019; 11(9):1–10.

36. Mustafa YF, Khalil RR, Mohammed ET. Synthesis and antitumor potential of new 7-halocoumarin-4-acetic acid derivatives. *Egyptian Journal of Chemistry* 2021; 64(7):3711–6.

37. Mustafa YF, Bashir MK, Oglah MK. Original and innovative advances in the synthetic schemes of coumarin-based derivatives: A review. *Systematic Reviews in Pharmacy* 2020; 11(6):598–612.

38. Mustafa YF. Classical approaches and their creative advances in the synthesis of coumarins: A brief review. *Journal of Medicinal and Chemical Sciences* 2021; 4(6):612–25.

39. Kim D, Gam J, Kim K. Synthesis and in vitro cytotoxicity of 1,3-dioxolane-2-(2-ethanamine)-2-methanamine platinum (II) complexes. *Bioorganic & Medicinal Chemistry Letters* 1994; 4(7): 911-916.

40. Dzhumaev SS, Borisova YG, Raskil'dina GZ, Kuzmina US, Daminev RR, Zlotskii SS. Synthesis of ethers containing 1,3-dioxolane and gem-dichlorocyclopropane fragments. *Fine Chemical Technologies* 2021; 16(2): 156–166.

41. Schmidt M, Ungva´ri J, Glo¨de J, Dobner B, Langner A. New 1,3-dioxolane and 1,3-dioxane derivatives as effective modulators to overcome multidrug resistance. *Bioorganic & Medicinal Chemistry* 2007; 15: 2283–2297.

42. Hawata MA, El-Essawy FA, El-Sayed WA, El-Bayaa MN. Synthesis and cytotoxic activity of new substituted pyrazolo(3,4-b)pyridine derivatives and their acyclic nucleoside analogs. *Egyptian Journal of Chemistry* 2022; 65(3): 161-169.

43. Kahraman G, Türk M, Rzayev ZMO, Söylemez EA, Oğuztüzün S: Bioengineering functional copolymers. XX. synthesis of novel anticancer active poly(maleic anhydride-alt-2-vinyl-1,3-dioxolane) and its organoboron amide-ester branched derivatives. *Journal of Biological Chemistry* 2012; 40(2): 183-194.

44. Dung DTM, Dung PTP, Oanh DTK, Vu TK, Hahn H, Han BW. Exploration of novel 5'(7')-substituted-2'-oxospiro(1,3)dioxolane-2,3'-indoline-based N-hydroxypropenamides as histone deacetylase inhibitors and antitumor agents. *Arabian Journal of Chemistry* 2017; 10(4): 465-472.

45. Krove KL, Guo X, Liu S, Gao Z, Chu CK, Cheng Y. Anticancer activity of β-L-Dioxolane-cytidine, a novel nucleoside analogue with the unatural L Configuration. *Cancer Research* 1995; 55(14): 3008-3011.

46. Bongomin F, Gago S, Oladele R, Denning DW. Global and multi-national prevalence of fungal diseases-estimate precision. *Journal of Fungi* 2017; 3(4): 57-86.

47. Roomi AB, Widjaja G, Savitri D, Jalil AT, Mustafa YF, Thangavelu L, et al. SnO2:Au/Carbon Quantum Dots Nanocomposites: Synthesis, Characterization, and Antibacterial Activity. *Journal of Nanostructures* 2021; 11(3):514–23.

48. Jumintono J, Alkubaisy S, Yánez Silva D, Singh K, Turki Jalil A, Mutia Syarifah S, et al. Effect of cystamine on sperm and antioxidant parameters of ram semen stored at 4 °C for 50 hours. *Archives of Razi Institute* 2021; 76(4):981–9.

49. Al-abdeen SHZ, Mustafa YF. Synthesis and Biological Potentials of Novel Benzodipyrone- Based Derivatives. *Journal of Medicinal and Chemical Sciences* 2022; 5(6):1026–39.

50. Mustafa YF, Zain Al-Abdeen SH, Khalil RR, Mohammed ET. Novel functionalized phenyl acetate derivatives of benzo [e]-bispyrone fused hybrids: Synthesis and biological activities. *Results in Chemistry* 2023; 5:100942.

51. Mustafa YF, Bashir MK, Oglah MK. Original and innovative advances in the synthetic schemes of coumarin-based derivatives: A review. *Systematic Reviews in Pharmacy* 2020; 11(6):598–612.

52. Talismanov VS, Popkov SV, Zykova SS, Karmanova OG. Synthesis and pesticidal activity of some 4-Azolylmethyl-1,3-dioxolanes, based on cyclic ketones. *Research Journal of Pharmacy and Technology* 2021; 14(12): 6417-6422.

53. Pinet A, Cojean S, Nguyen LT, Vásquez-Ocmín P, Maciuk A, Loiseau PM, Pape PL, Figadère B, Ferrié L. Anti-protozoal and anti-fungal evaluation of 3,5-disubstituted 1,2-dioxolanes. *Bioorganic & Medicinal Chemistry Letters* 2021; 47: 128196-128202.

54. Delcourt A, Mathieu G, Baji H, Kimny T, Flammang M, Compagnon P. New polyazole derivatives from 2-(2,4-dichlorophenyl)-1,3-dioxolane. Antifungal activity. Structure-activity relationships. *Mycopathologi*, 1997; 137(1): 27–32.

55. Hoshi T, Yamada K, Yoshizawa Y, Oh K. Structure-activity relationship study for fungicidal activity of 1-(4-phenoxymethyl-2-phenyl-(1,3)dioxolan-2-ylmethyl)-1*H*-1,2,4-triazole derivatives against rice blast. *Journal of Plant Protection Research* 2015; 55 (4): 383-388.

56. Forman HJ, Zhang H. Targeting oxidative stress in disease: promise and limitations of antioxidant therapy. *Natural Reviews* 2021; 20(9): 689-709.

57. Sonmez F, Gunesli Z, Kurt BZ, Gazioglu I, Avci D, Kucukislamoglu M. Synthesis, antioxidant activity and SAR study of novel spiro‐isatin‐based Schif bases. *Molecular Diversity* 2019; 23(4): 829-844.

58. Jebir RM, Mustafa YF. Watermelon Allsweet : A promising natural source of bioactive products. *Journal of Medicinal and Chemical Sciences* 2022; 5(5):652–66.

59. Kasim SM, Abdulaziz NT, Mustafa YF. Synthesis and biomedical activities of coumarins derived from natural phenolic acids. *Journal of Medicinal and Chemical Sciences* 2022; 5(4):546–60.

60. Khalil RR, Mohammed ET, Mustafa YF. Various promising biological effects of Cranberry extract : A review. *Clinical Schizophrenia and Related Psychoses* 2021; 15(S6):1–9.

61. Khalil RR, Mohammed ET, Mustafa YF. Evaluation of in vitro antioxidant and antidiabetic properties of Cydonia Oblonga seeds ' extracts. *Journal of Medicinal and Chemical Sciences* 2022; 5(6):1048–58.

62. Mustafa YF, Kasim SM, Al-Dabbagh BM, Al-Shakarchi W. Synthesis, characterization and biological evaluation of new azo-coumarinic derivatives. *Applied Nanoscience (Switzerland)* 2023; 13:1095–1102.

63. Jasim SF, Mustafa YF. Synthesis , ADME Study , and antimicrobial evaluation of novel naphthalene-based derivatives. *Journal of Medicinal and Chemical Sciences* 2022;5(5):793–807.

64. Mustafa YF, Al-omari NA. Design , Synthesis and Kinetic Study of Coumarin-Based Mutual Prodrug of 5-Fluorouracil and Dichloroacetic acid. *Iraqi J Pharm Sci* 2016;25(1):6–16.

65. Nobre PC, Borges EL, Silva CM, Casaril AM, Martinez DM, Lenardão EJ, Alves D, Savegnago L, Perin G. Organochalcogen compounds from glycerol: Synthesis of new antioxidants. *Bioorganic & Medicinal Chemistry* 2014; 22 (21): 6242-6249.

66. Talisnanov VS, Popkov SV, Zykova SS, Karmanova OG. Synthesis and evaluation of antiradical activity of 1,2,4-triazole derivatives substituted by cyclic ketals. *Journal of Pharmaceutical Sciences and Research* 2018; 10(5): 1267-1271.

67. Higgins AJ, Lees P. The acute inflammatory process, arachidonic acid metabolism and the mode of action of anti-inflammatory drugs. *Equine Veterinary Journal* 1984; 16 (3): 163-175.

68. Jasim SF, Mustafa YF. A Review of Classical and Advanced Methodologies for Benzocoumarin Synthesis. *Journal of Medicinal and Chemical Sciences* 2022; 5(5):676–94.

69. Ismael RN, Mustafa YF, Al-Qazaz HK. Citrullus lanatus, a Potential Source of Medicinal Products: A Review. *Journal of Medicinal and Chemical Sciences*. 2022; 5:607–18.

70. Mohammed ET, Khalil RR, Mustafa YF. Phytochemical Analysis and Antimicrobial Evaluation of Quince Seeds' Extracts. *Journal of Medicinal and Chemical Sciences* 2022; 5(6):968–79.

71. Jasim SF, Mustafa YF. Synthesis and antidiabetic assessment of new coumarin- disubstituted benzene conjugates: An in silico-in virto study. *Journal of Medicinal and Chemical Sciences* 2022; 5(6):887–99.

72. Waheed SA, Mustafaa YF. Novel naphthalene-derived coumarin composites: synthesis, antibacterial, and antifungal activity assessments. *Eurasian Chemical Communications* 2022; 4(8):709–24.

73. Jebir RM, Mustafa YF. Novel coumarins isolated from the seeds of Citrullus lanatus as potential antimicrobial agents. *Eurasian Chemical Communications* 2022; 4(8):692–708.

74. Jasim SF, Mustafa YF. New fused-coumarin composites: Synthesis, anticancer and antioxidant potentials evaluation. *Eurasian Chemical Communications* 2022; 4(7):607–19.

75. Waheed SA, Mustafa YF. Synthesis and evaluation of new coumarins as antitumor and antioxidant applicants. *Journal of Medicinal and Chemical Sciences* 2022; 5(5):808–19.

76. Al-hatim RR, Al-alnabi DIB, Al-younis ZK, Al-shawi SG, Singh K, Abdelbasset WK, et al. Extraction of tea polyphenols based on orthogonal test method and its application in food preservation. *Food Science and Technology* 2022; 42:e70321.

77. Jebir RM, Mustafa YF. Natural products catalog of allsweet watermelon seeds and evaluation of their novel coumarins as antimicrobial candidates. *Journal of Medicinal and Chemical Sciences* 2022; 5(5):831–47.

78. Waheed SA, Mustafa YF. The in vitro effects of new albocarbon-based coumarins on blood glucose-controlling enzymes. *Journal of Medicinal and Chemical Sciences* 2022; 5(6):954–67.

79. Hammoodi SH, Ismael SS, Mustafa YF. Mutual prodrugs for colon targeting: A review. *Eurasian Chemical Communications* 2022;4(12):1251–65.

80. Niu S, Yang L, Zhang G, Chen T, Hong B, Pei S, Shao Z. Phenolic bisabolane and cuparenesesquiterpenoids with anti-inflammatory activities from the deep-sea-derived Aspergillus sydowii MCCC 3A00324 fungus. *Bioorganic Chemistry* 2020; 105: 104420-104432.

81. Guo Y, Tang G, Li Z, Lin S, Yin S. Chlojapolactone A, An unprecedented 1,3-Dioxolane linked-lindenane sesquiterpenoid dimer from chloranthus japonicas. *Communication* 2013; 5: 103047-103051.

82. Hadjipavlou-Litina DJ, Litinas KE, Kontogiorgis C. The Anti-inflammatory Effect of Coumarin and its Derivatives. *Anti-Inflammatory & Anti-Allergy Agents in Medicinal Chemistry* 2007; 6: 293-306.

تأثير اقتران حلقة الدايوكسولان على الفعالية البايولوجية: دراسة مقارنة

الخلاصة

المقدمة: تستلزم مشكلة الآثار الجانبية للأدوية تصميم وتوليف وتطوير عوامل علاجية جديدة ذات نشاط عالٍ مع آثار جانبية قليلة. وفقًا للعلاقة بين البنية والنشاط ، تم العثور على جزء الديوكسولين في العديد من العوامل العلاجية الطبيعية وتلعب دورًا مهمًا في عملها الطبي. تمت دراسة اقترانات الديوكسولين الاصطناعية في مجموعة متنوعة من المجالات البيولوجية ، بما في ذلك السمية الخلوية والنشاط المضاد للبكتيريا والفطريات والفيروسات ومضادات الأكسدة ومضادات الالتهابات ، وقد أظهرت فاعلية مميزة تشجع على مزيد من البحث في هذا الوضع. **الهدف**: يسلط هذا الاستعراض الضوء على أحدث الدراسات حول اقتران حلقة الديوكسولين في مختلف المجالات البيولوجية كسقالة واعدة حلقية غير متجانسة نشطة بيولوجيًا. **الاستنتاج**: قد تكون الرابطة الهيدروجينية لذرات الأكسجين في هذه الحلقة الحلقية غير المتجانسة مع الموقع المستهدف مسؤولة عن تفاعلات هدف الترابط المحسن والنشاط الحيوي المحسن.

الكلمات المفتاحية: ديوكسولان ، حلقية غير متجانسة ، مضاد للبكتيريا ، مضاد للفطريات ، مضاد للفيروسات ، سام للخلايا.