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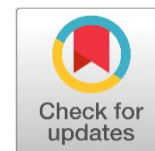
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Review Article:

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

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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.

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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).



Figure 1. Dioxolane chemical structures

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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).

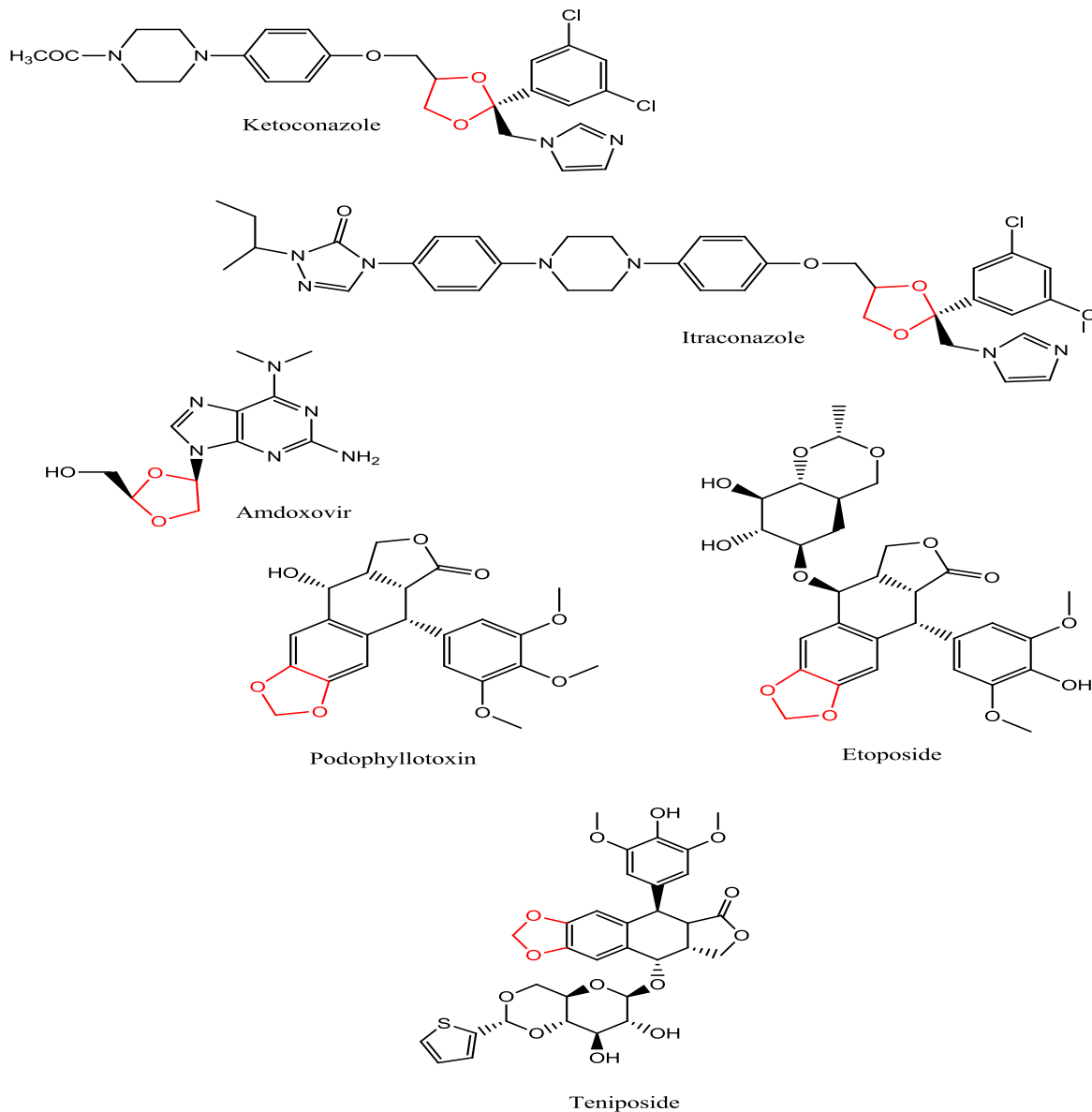


Figure 2. Drugs with a dioxolane scaffold in their chemical structures

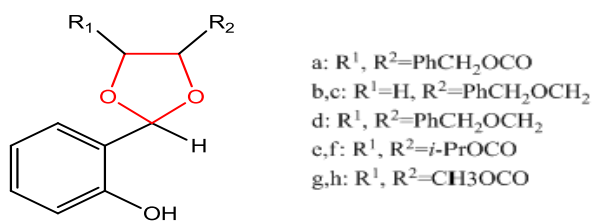


Figure 3. Compounds containing a 1,3-dioxolane scaffold prepared by Küçük et al.

Ovsyannikova and his colleagues synthesized a series of nine compounds containing a 1,3-dioxolane 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).

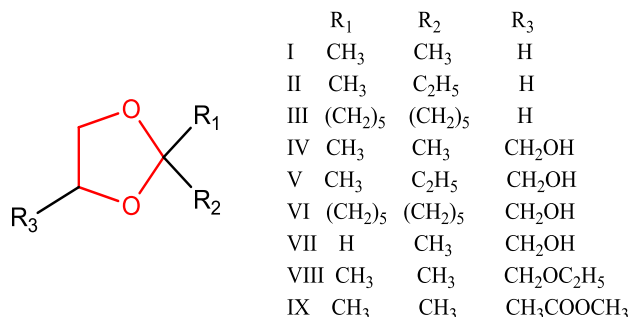


Figure 4. Compounds containing a 1,3-dioxolane scaffold prepared by Ovsyannikova et al

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, including *E. 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).

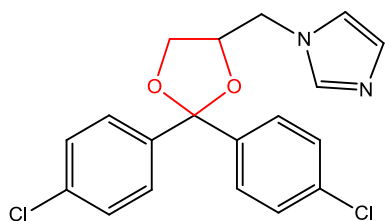


Figure 5. Compound 2c containing a 1,3-dioxolane scaffold prepared by Talismanov et al.

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).

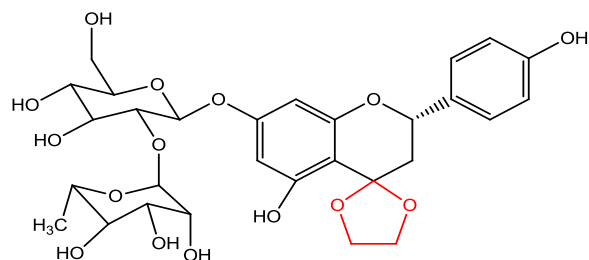


Figure 6. The naringin-based dioxolane derivative

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).

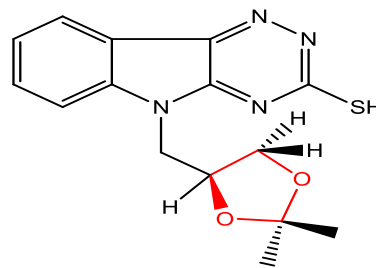


Figure 7. The most significant 1,3-Dioxolane-thiol conjugates prepared by Ramadan et al.

Begum and co-workers prepared a novel amide derivative of 1,3-dioxolane from tartaric acid (Figure 8) and investigated their antibacterial activities against *Enterobacter* spp., *Vibrio cholera*, and *Klebsiella* 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).

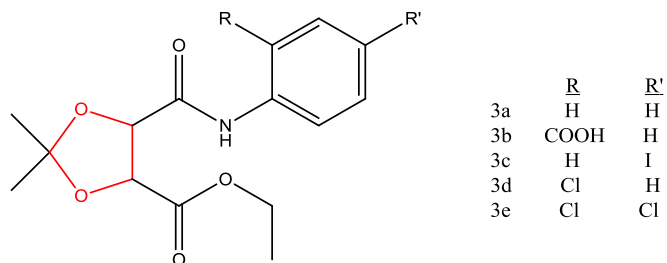


Figure 8. Amide derivatives (3a- of a 1,3-dioxolane prepared by Begum et al.

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).

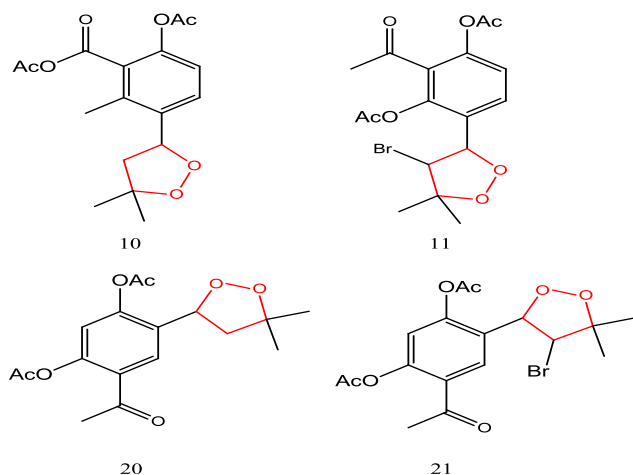


Figure 9. Acetophenones containing a 1,2-dioxolane scaffold prepared by Helesbeux et al

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).

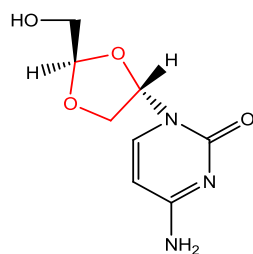
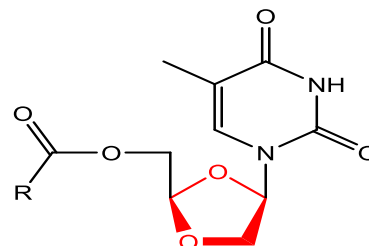


Figure 10. The active dioxolane-pyrimidine conjugate prepared by Kim et al.

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 = CH₃
2. R = C₄H₉
3. R = C₇H₁₅
4. R = C₁₁H₂₃
5. R = C₁₅H₃₁
6. R = (CH₃)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).

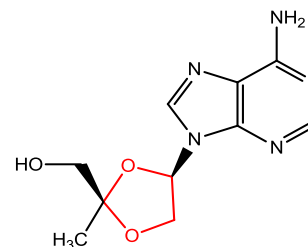


Figure 12. The dioxolane-nucleoside conjugate prepared by Franchini et al.

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).

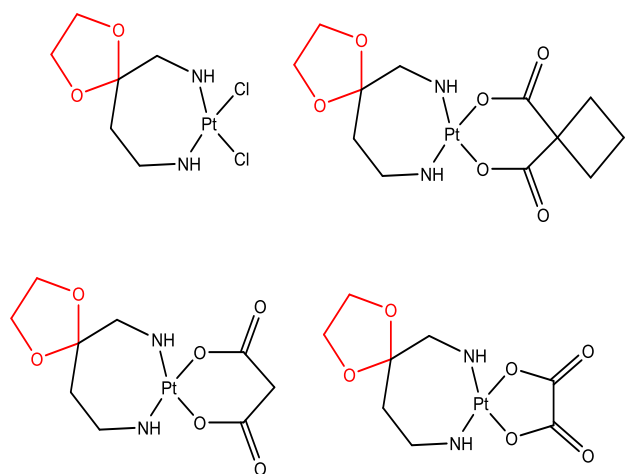


Figure 13. Novel platinum (II) complexes prepared by Kim *et al.*

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).

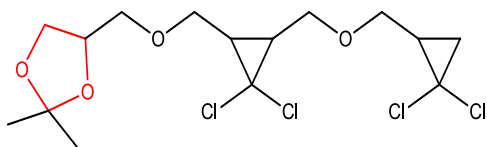


Figure 14. Cytotoxic active ether prepared by Dzhumaev *et al.*

Schmidt and his co-workers prepared novel 2,2-diphenyl-1,3-dioxolane and 4,5-diphenyl-1,3-dioxolane derivatives, 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 fragment. The *in vitro* investigations were made on human Caco-2 cells (colorectal adenocarcinoma), and the different isomers of the framework displayed 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 $39 \pm 4 \mu\text{M}$ for the HTC116 cell line and $17.17 \pm 2.93 \mu\text{M}$ for the MCF7 cell line. Doxorubicin was used as a control in this *in vitro* study (42).

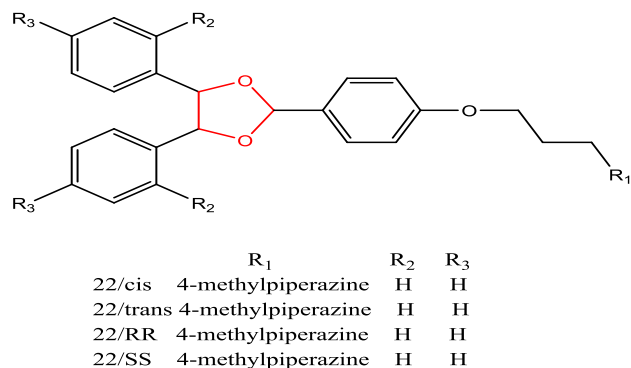


Figure 15. New 1,3-dioxolane derivatives as effective modulators to reduce MDR

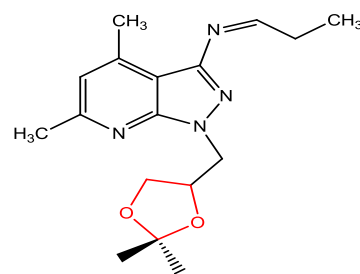


Figure 16. Pyrazolo-pyridine conjugated with 1,3-dioxolane prepared by Hawata *et al.*

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 $100 \mu\text{M/mL}$. Such a cytotoxic effect may be attributed to the formation of complex hydrogen bonds that influence the destruction of biomacromolecules in cancer cells (43).

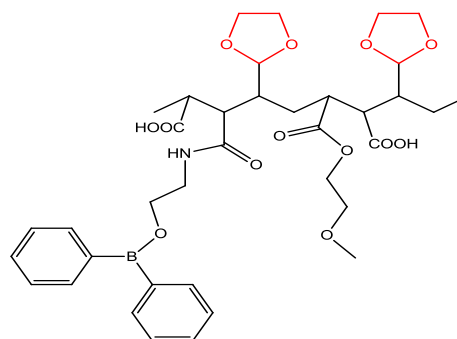


Figure 17. The organoboron amide-ester-carboxyl functionalized copolymers prepared by Kahraman *et al.*

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 a significant impact in the carcinogenesis. Results showed that these compounds possessed potent inhibitory activity, with an IC₅₀ for the compound displayed in **Figure 18** of 0.284 μM, which is comparable to the IC₅₀ 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).

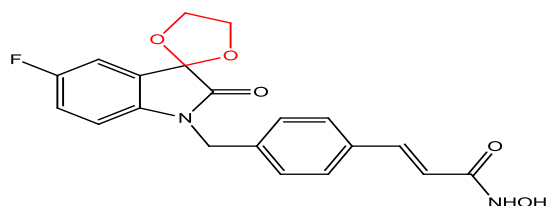


Figure 18. Compound with a 1,3-dioxolane-indoline system prepared by Dung *et al.*

All natural and synthetic nucleoside analogues are in the β-D-configuration; however, Grove and his co-workers prepared a novel unnatural nucleoside analogue that has 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 deoxycytidine deaminase enzyme (45).

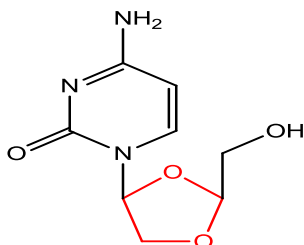


Figure 19. The β-L-dioxolane-cytidine prepared by Grove *et al.*

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 IC₅₀ of 0.125, 0.125, 0.5, and 4 μg/mL, respectively, compared to the IC₅₀ 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).

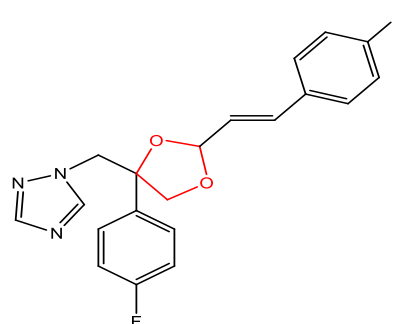


Figure 20. The structural backbone of the triazole-dioxolane conjugate prepared by Xiao-hui *et al.*

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 moieties with 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).

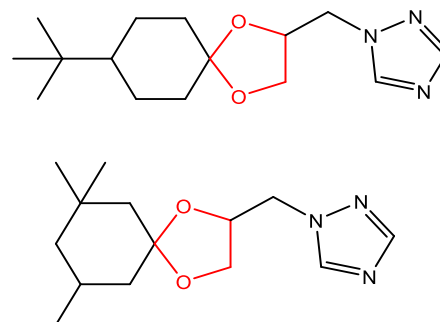


Figure 21. Triazole-1,3-dioxolane conjugates prepared by Talismanov *et al.*

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).

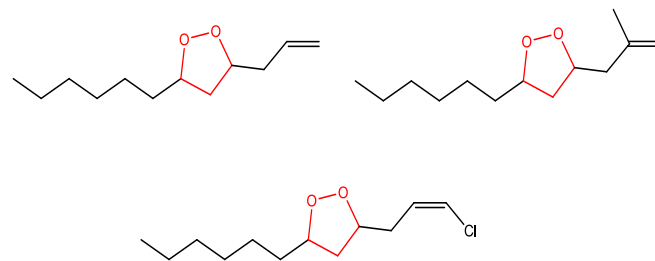


Figure 22. The 3,5-disubstituted 1,2-dioxolanes prepared by Pinet *et al.*

Delcourt and colleagues used 2-(2,4-dichlorophenyl)-1,3-dioxolane to prepare a new class of polyazole derivatives and examined their *in vitro* antifungal activities versus a series of pathogenic fungi that can attack animals 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).

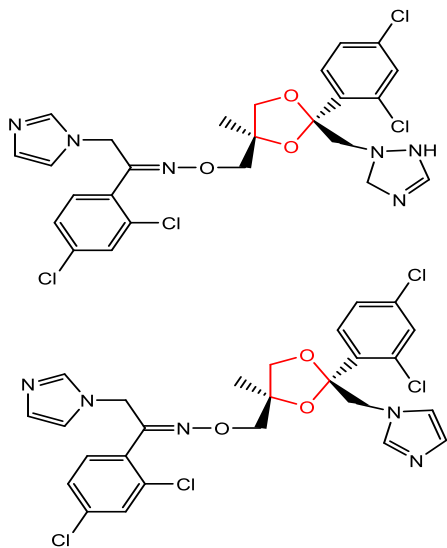


Figure 23. The 2-(2,4-dichlorophenyl)-1,3-dioxolane derivatives prepared by Delcourt *et al.*

In the agricultural field, Hoshi and colleagues synthesized a new series of 1,2,4-triazole derivatives and investigated their activity against *Magnaporthe oryzae*, 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).

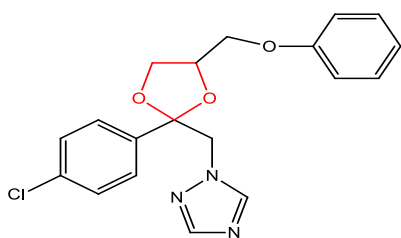


Figure 24. The active antifungal agent prepared by Hoshi *et al.*

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).

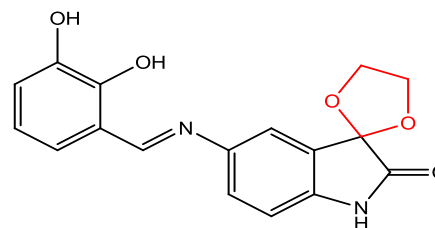


Figure 25. The most potent spiro-isatin-based Schiff base prepared by Sonmez *et al.*

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).

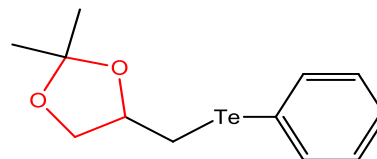


Figure 26. The 2,2-dimethyl-4-(phenyltellanylmethyl)-1,3-dioxolane prepared by Nobre *et al.*

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 this activity was attributed to the hexylthiosulfonyl substituent in the *para* position of the arene ring (67).

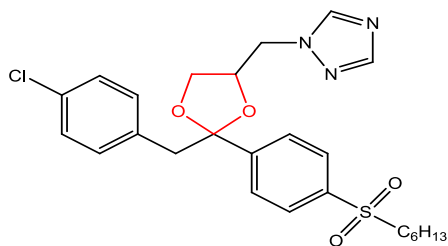


Figure 27. The active derivative prepared by Talismanovet al.

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 sesquiterpenoid products 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 displayed in **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).

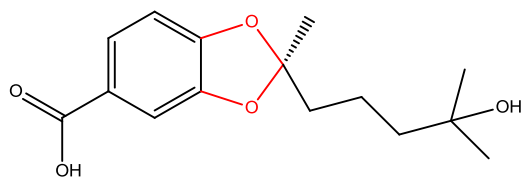


Figure 28. The novel seco-bisabolane skeleton with dioxolane ring isolated by Neu and his team

Guo and colleagues isolated and identified a novel sesquiterpenoid lindenane 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).

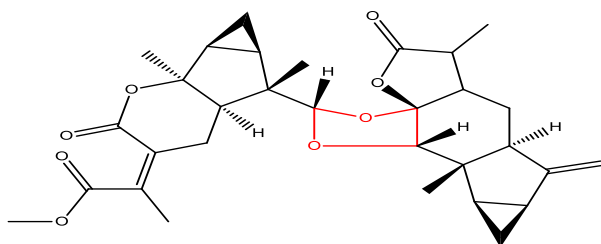


Figure 29. The novel sesquiterpenoid lindenane dimer with 1,3-dioxolane linkage

Hadjipavlou-Litina and colleagues synthesized and investigated the anti-inflammatory activity of a series of coumarins and coumarin-conjugates. The dioxolane-

coumarin 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 lipoxigenase enzyme (82).

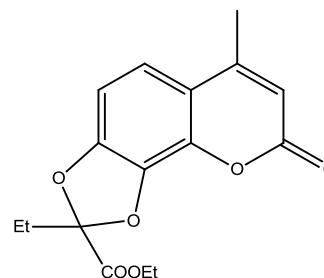


Figure 30. Dioxolane-coumarin conjugate prepared by Hadjipavlou-Litina et al.

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 dioxolane 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.

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تأثير اقتران حلقة الداياوكسولان على الفعالية البيولوجية: دراسة مقارنة

الخلاصة

المقدمة: تستلزم مشكلة الآثار الجانبية للأدوية تصميم وتوليف وتطوير عوامل علاجية جديدة ذات نشاط عالٍ مع آثار جانبية قليلة. وفقاً للعلاقة بين البنية والنشاط، تم العثور على جزء الداياوكسولين في العديد من العوامل العلاجية الطبيعية وتلعب دوراً مهماً في عملها الطبي. تمت دراسة اقترانات الداياوكسولين 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 الداياوكسولين في مختلف المجالات البيولوجية كسقالة واعدة حلقة غير متجانسة نشطة بيولوجياً. **الاستنتاج:** قد تكون الرابطة الهيدروجينية لذرات الأكسجين في هذه الحلقة الحلقة غير المتجانسة مع الموقع المستهدف مسؤولة عن تفاعلات هدف الترابط المحسن والنشاط الحيوي المحسن.

الكلمات المفتاحية: داياوكسولان، حلقة غير متجانسة، مضاد للبكتيريا، مضاد للفطريات، مضاد للفيروسات، سام للخلايا.