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Review Article:

Advancements in the Synthesis and Biomedical Impacts of Molecules Incorporating 1,3-Dioxolane

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Abstract

Background: Numerous synthetic health-related products contain the 1,3-dioxolane ring (DOR) as a valuable constituent in their chemical structures. According to several structure-activity relationships, adding this heterocyclic ring to the compound's chemical framework could enhance various types of activities. These include anticancer, antifungal, antiviral, antibacterial, antioxidant, and anti-inflammatory effects**. Aim:** The current issue of negative drug reactions and resistance requires the creation of effective agents with new frameworks that can handle these pharmacological obstacles. In this review, the main focus is on new in-lab methods to make compounds that contain DOR and improve the biological effectiveness of medicines by using a new synthetic DOR's chemical structure. **Methods:** This review was conducted by the authors using a variety of databases, such as Web of Science, Google Scholar, PubMed, and Scopus, without specifying the publication dates. **Results:** The unique way that synthetic compounds with DOR are made and how well they work in medicine make experts want to do more research in this area. It is found by the investigators that the addition of this heterocyclic ring could enhance many biological activities for various bioactive agents. **Conclusion:** As indicated by a number of studies, the two oxygen atoms in the DOR backbone may enhance the studied ring's functionality. These atoms are believed to form hydrogen bonds with the active site. This improves the interactions between the ligand and the target, and consequently, the presence of this heterocyclic ring enhances biological activity.

1. Introduction

1,3-dioxolane ring (DOR) is a five-membered, fully saturated heterocyclic compound that incorporates two oxygen atoms, which are positioned on different sides of a methyl group. The oxygen atoms in the DOR give the molecule some polarity and make it possible for it to react, especially in processes that involve electrophilic addition or nucleophilic substitution. Additionally, the oxygen atoms add a degree of electron density that can affect how the molecule behaves in certain chemical conditions. Through the electron-donating effect, DOR can change how reactive attached functional groups. This makes them useful as building blocks in the production of organic compounds. This is especially true in reactions that create cyclic ethers, acetals, and polymers. Organic chemistry frequently uses the DOR as a protective group to hide reactive alcohols or aldehydes, especially in the synthesis of complex compounds as shown in as shown in **Figure 1** (1,2).

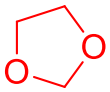

Figure 1. The chemical framework of DOR

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It is known that DOR is a crucial building block in the synthesis of a variety of medicinally active compounds, including adrenoreceptor antagonists, antiviral, antifungal, and anti-HIV compounds (3,4). Many structure-activity relationships have recommended the involvement of DOR in the various bioactive frameworks for future research and development (5,6). Some of the essential drugs utilized in healthcare applications that employ this ring system are depicted in **Figure 2** (7,8).

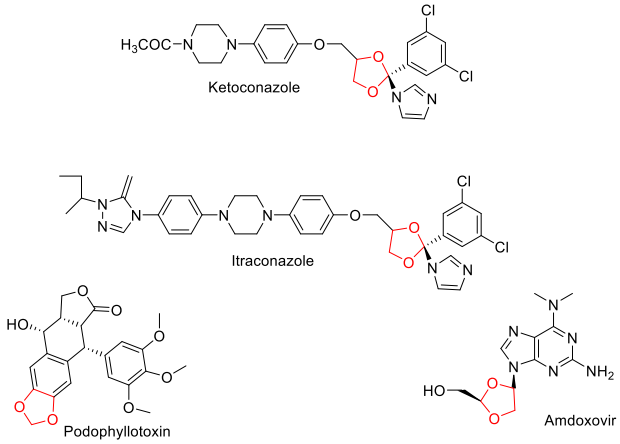
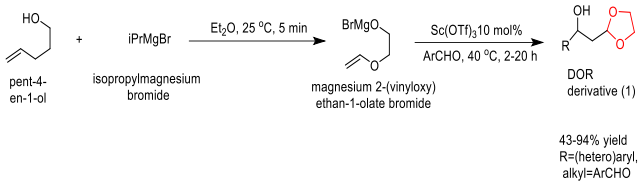


Figure 2. Chemical structures of DOR-incorporated drugs

1.2. Advancements in the synthesis of DOR-incorporating molecules

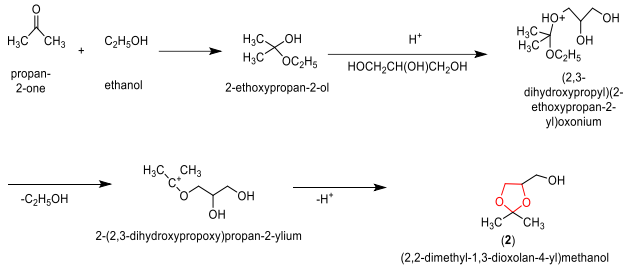
Organic chemical processes use DOR as a green solvent because it is not poisonous and efficiently recovers biodegradable compounds (9–11). It's a crucial compound in organic synthesis due to its ability to act as both a carbon source and a reagent for various transformations (12,13). DOR used with applications in biological contexts, polymer science, and biomedicinal activity. It serves as a versatile intermediate in the production of bio-based chemicals and pharmaceuticals, providing an eco-friendly alternative to more hazardous reagents (14,15). Its unique structure, featuring two ester groups, allows it to participate in reactions like esterification, transesterification, and carbon-carbon bond formation. These characteristics make it valuable in the synthesis of fine chemicals, additives, and catalysts, where high purity and selectivity are required (16,17).

Quinio *et al.* synthesized a variety of activated shielded aldol compounds by combining bromomagnesium 2-vinyloxy ethoxide with various aldehydes and 10 mol% Scandium trifluoro methane sulfonate, Lewis acid Sc(OTf). The Swern oxidation-CBS reaction turns an alcohol into a chiral alcohol with stereo-selectivity by combining Swern oxidation with Corey-Bakshi-Shibata reduction. This reaction may shorten the steps needed to make these aldols in a way that is selective for the enantiomers. As shown in Scheme 1 (18), the formation of DOR derivative (**1**) from 2-bromocyclohexanone leads to the production of a planned aldol product, which is the anti-diastereoisomer with 99% sterio-selectivity.



Scheme 1. Generation of DOR intermediate using $Sc(OTf)_3$ as a catalyst

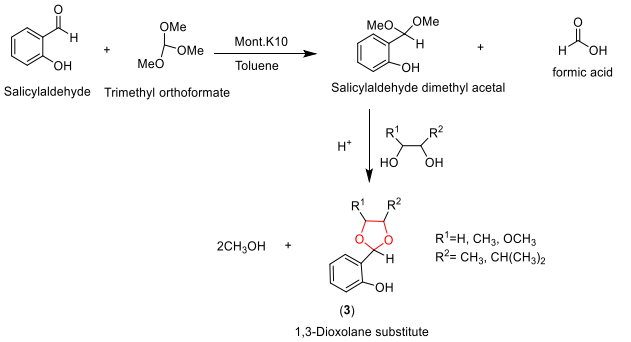
In their study, Vol'eva *et al.* made a DOR-incorporated compound called **2**, which is made by carbonyl compounds reacting with vicinal diols. When ethanol was added, the reaction went quickly and effectively, as seen in **Scheme 2**. A potential rationale could be that ethanol forms a hemiacetal, or adduct, with a carbonyl molecule, which serves as an active intermediate in the step of synthesis. In this case, ethanol helps the transketalyzation process happen without letting any water out, while glycerol ketalyzes aceton to make a cyclic product called a **2** (19).



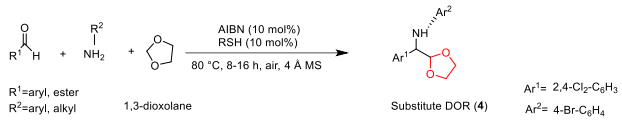
Scheme 2. Synthetic pathway of compound **2** as described by Vol'eva *et al.*

Kuçük *et al.* synthesized, as illustrated in **Scheme 3**, a new group of enantiomerically pure chiral and racemic DOR-incorporated compounds, were collectively coded **3**. The research team did this by reacting salicylaldehyde with diols and using montmorillonite K 10 as a catalyst. When the researchers added a small amount of trimethyl orthoformate, the reaction proceeded quickly and produced an excellent yield of about 99%. This is the first example of chiral acetalization, which begins with an aldehyde and proceeds to include aryl groups, aryls with a single substitution, and long chains of alkyls. The researchers investigated the stereochemistry of the synthesized compounds using a chiral HPLC system on a Chiralcel OD column (20).

Zeng *et al.* manufactured DOR-incorporated compounds collectively coded **4**, as illustrated in **Equation 1**, by the process of adding DOR to *in situ* produced imines, which has been described as a radical chain reaction. The chemistry was devoid of metal and redox, and cheap materials were transformed into shielded α-amino aldehydes with excellent-to-high outcomes applying a tiny amount of a radical precursor (azobisisobutyronitrile, AIBN). For the reaction to be successful, thiol and a small amount of atmospheric oxygen are essential, according to the monitoring researcher (21).

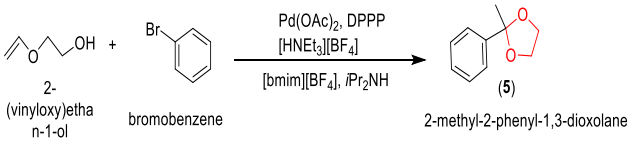


Scheme 3. Montmorillonite K10-catalyzed synthesis of the chiral DOR-incorporated compounds **3**



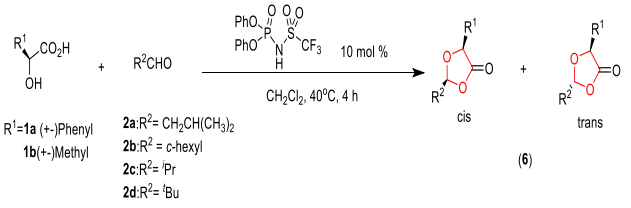
Equation 1. The radical chain reaction for creating DOR-incorporated compounds **4**

Xiao *et al.* created a DOR-incorporated compound coded **5** *via* the Heck coupling of electron-rich olefins with bromo- or chlorobenzene without the need for thallium acetate and silver triflate as halide scavengers. The reaction can be carried out in an imidazolium-based ionic liquid or a conventional molecular solvent when ammonium-based additives are added, and the product was generated in high yields and excellent region-selectivity, as shown in **Equation 2** (22).



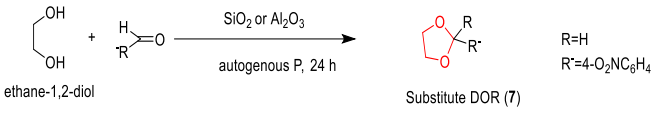
Equation 2. The synthetic pathway for creating DOR-incorporated compound **5**

As shown in **Equation 3**, Kuçük *et al.* used N-triflylphosphoramide, which is a good Brønsted acid catalyst, to make 2,5-disubstituted DOR-4-ones (**6**). Using this catalyst with various aldehydes resulted in the excellent sterio-selective production of optically pure and racemic mandelic and lactic acids. In this synthetic pathway, neither azeotropic distillation nor a dehydration agent were required (23).



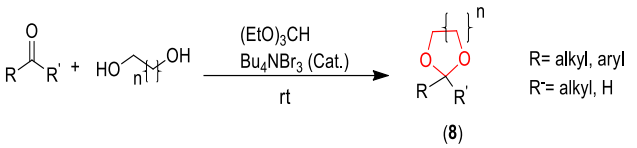
Equation 3. The general synthetic pathway for preparing DOR-incorporated compound **6**

Rohand *et al.* created DOR-incorporated compounds collectively coded **7**, as illustrated in **Equation 4**, by using SiO_2 or Al_2O_3 as a catalyst and pressure. In this creation, they condensed carbonyl compounds with 2-hydroxyethanol without the need for a solvent. Glycol interacts with 2-aminoethanol through the Brønsted acid catalyst (inorganic acid) or Lewis acidic catalyst (silica gel or alumina), forming a significant number of ionic bridges on the catalyst's surface (24).



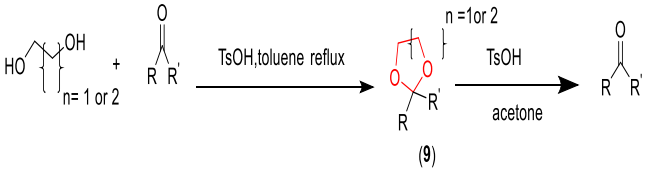
Equation 4. The general synthetic pathway for preparing DOR-incorporated compound **7**

Equation 5 illustrates the outcome of Gopinath *et al.*'s research on DOR-incorporated compounds, collectively referred to as **8**. Several carbonyl compounds can readily form acyclic and cyclic acetals in a mild reaction, with $(RO)_3CH$ and Bu_4N^+ Br_3 acting as catalysts in absolute alcohol. This method is superior to others in numerous ways, including its ability to selectively acetalize an aldehyde when a ketone is present, its capacity to create an acetal unevenly, its requirement for mild reaction conditions, its high efficiency, and its ease of separating the desired compounds (25).



Equation 5. The general pathway for creating DOR-incorporated compounds **8**

Equation 6 illustrates how a Bronsted or Lewis acid catalyst condenses 1,3-propanediol or 1,2-ethanediol with carbonyl molecules to generate DOR-incorporated compounds, collectively coded here as **9**. Since p-toluenesulfonic acid serves as a catalyst and is sensitive to moisture, the researchers routinely employ a Dean-Stark device to eliminate water from the refluxing toluene medium (26).



Equation 6. Synthesis of DOR-incorporated compounds **9**

1.3. Biomedical activities of DOR-incorporating molecules

1.3.1. Antioxidant activity

Antioxidant impact is one of the most important investigations currently receiving significant attention. Oxidative stress happens when there is an imbalance between pro-oxidants and antioxidants, causing redox pathways to break down and macromolecules to break down at the same time. This can cause a lot of health problems (27). The generation of excessively harmful free radicals or the body's inability to combat them could be the cause of the stress under study (28–30). Skeletal muscle dysfunction, cancer, cardiovascular disease, chronic hepatitis, chronic renal disease, and chronic pulmonary disorders are a few examples of these health issues (31,32). Moreover, cardiovascular conditions (atherosclerosis and hypertension), respiratory conditions (asthma), neurodegenerative diseases (Parkinson's disease, Alzheimer's disease, and multiple sclerosis), cataract development, and rheumatoid arthritis are included (33). DOR is a promising chemical moiety, so researchers are directed to create novel oxidative stress fighters by using it.

Vlahakis *et al.* produced several imidazole-DOR compounds that were evaluated as possible novel inhibitors of heme oxygenase (HO). These compounds, such as compound **10** in **Figure 3**, differ from metalloporphyrin HO inhibitors because they lack the aminothiophenol component of azalanstat. Replace this moiety in compound **10** with a hydrogen atom to make it methyl-terminated. The two-part structure of this compound core seems to be a big reason why they have strong inhibitory effects on the normal isozyme HO-2 and great specificity for the stress-induced HO-1 isozyme. The research group regards the compound under study as the most modern documented instance of isozyme-selective HO inhibition in its class (34).

Raskil'dina *et al.* made compounds **11** and **11a**, as illustrated in **Figure 3**, by an acid-catalyzed condensation of polyols and ketones. The research team determined the potential antioxidant effects of these compounds *in vitro* using various oxidative stress patterns. Recognize that the characteristics of these chemical compounds' framework significantly influence the appearance of their therapeutic properties. The chromatographic and NMR studies of the reaction showed encouraging results that increased the number of possible applications for the compounds under study as biologically effective antioxidants (35).

Namazifar *et al.* synthesized numerous compounds, including **12**, as depicted in **Figure 3**. It is a new antioxidant made up of phenolic and DOR functional groups and was fully described after being made using a simple method. This antioxidant compound's superior effectiveness and optimal thermal behavior permit it to break two oxidation chains at once and stop macromolecular degradation. More importantly, compared to commercial antioxidants such as butylated hydroxytoluene, the produced antioxidant compound **12** has the ability to significantly extend the induction period time, even at low concentrations. The chemical structure's hydroxyl, phenol, and ketal functional groups, along with the bulkier substituents in both orthopositions, are what make it work so well (36).

Sonmez *et al.* created a new collection of 21 spiro-isatin-containing Schiff bases. The research results demonstrated that compound **13**, as depicted in **Figure 3**, outperformed quercetin as an antioxidant in all tests. It had higher levels of DPPH (2,2-diphenyl-1-picrylhydrazyl) radical scavenging ability, CUPRAC (2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid)), and ABTS (2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid)). The SAR investigation showed that the type and location of the substituent on the phenyl ring might also affect how well compound **13** works as an antioxidant. The availability of hydroxyl groups and the size and location of halogens on the phenyl ring also significantly influence the antioxidant activity. The compound under study, with its well-known characteristics, can serve as a structural template for synthesizing agents with strong antioxidant activity. The imine groups in Schiff bases within the frameworks of the synthesized collection could form chelates with metal ions and exhibit strong affinity to transition metal ions, making these imines excellent ligands for the pro-oxidant metals (37).

Talisnanov *et al.* synthesized 1,2,4-triazole-containing compounds, including compound **14**, which is depicted in **Figure 3**, as novel radical scavengers. This compound demonstrated the strongest action, resulting in a roughly 50% decrease in the quantity of active radicals. When an aromatic ring joined to a hexylthiosulfonyl fragment and placed in the paraposition of the aryl ring, the compound under study demonstrated the strongest radical-scavenging activity. This research used trolox as a reference and measured the DPPH free radical scavenging capacity of compound **14** to assess its antiradical activity (38).

Numerous therapeutic and epidemiological studies have shown the widespread recognition of the crucial role of vitamins E and C in preventing diseases; however, because of their poor stability and bioavailability, these vitamins are hardly active (39). Manfredini *et al.* developed conjugates of these vitamins with the aim of enhancing their pharmacokinetic properties. Researchers have observed intriguing features for certain conjugates, with compound **15**, as shown in **Figure 3**, demonstrating the highest stability and antioxidant capabilities among them. The team also believes that this compound, capable of absorbing reactive oxygen species in both lipophilic and hydrophilic environments, can effectively shield an isolated rabbit heart from reperfusion-induced damage. Additionally, the compound under investigation exhibits an intriguing antioxidant effect when tested for its capacity to prevent the formation of malondialdehyde in rat liver microsomal membranes, particularly at a higher dose of 300 mM (40).

Nobre *et al.* use glycerol derivatives to make DOR compounds with the tellurium atom (Te). They do this in a

simple way by using PEG-400 as a solvent and sodium tetrahydridoborate as a base. Among the compounds created, the new technique produced a high yield of the novel compound **16**, as shown in **Figure 3**. The scientists tested the new compound's antioxidant power by doing tests on ferrous ions, superoxide dismutase-like activity, linoleic acid lipid peroxidation inhibition, NO and OH radical scavenging, DPPH, ABTS, and ferric reducing antioxidant power. When compared to solketal (2,2-dimethyl-1,3-dioxolane-4-methanol, a green solvent), the compound being studied was better at stopping lipid peroxidation and trapping free radicals. According to these results, compound **16** is a promising antioxidant, and the tellurium atom in its structure affects how active it is (41).

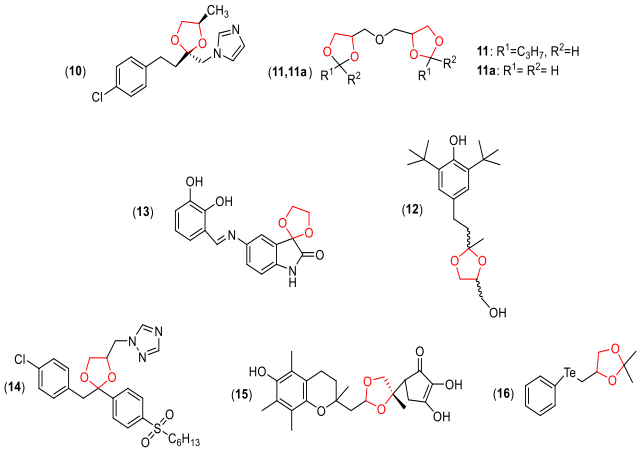


Figure 3. Chemical frameworks of DOR-incorporated compounds with antioxidant impact

1.3.2. Anticancer activity

The second most fatal illness globally is cancer. There are multiple reasons for it, spanning both outside influences and mutations in the genome (42–44). Researchers have focused on creating or researching novel cancer cures (45–47). In this context, DOR has been identified in many cytotoxic agents that may serve as potential anticancer candidates (48–50). One of the new groups of coumarin-fused DORs that Bashir *et al.* made through the Knoevenagel reaction is compound **17** shown in **Figure 4**. The chemical framework of this compound was determined by analyzing their FTIR, ^{1}H-NMR, and ^{13}C-NMR spectra. The compound under study was bioassayed to evaluate its ability to fight against the MCF-7 and SKG cancer cell lines. The IC_{50} values of DOR-incorporated compounds were lower than those lacking this heterocyclic ring. These results may show how important the DOR is for combating cancer cells in a number of ways, such as by blocking the telomerase enzyme and tubulin polymerization (51).

Both naturally occurring nucleosides and all anticancer nucleoside analogue drugs exist in the beta-D configuration. Grove *et al.* produce compound **18**, as shown in **Figure 4**, which is the first L-nucleoside analogue to demonstrate cytotoxic properties. Cells metabolized compound **18** into its mono-, di-, and triphosphate forms, then integrated them into DNA. The change to monophosphate, which is similar to cytosine arabinoside, was made easier by cellular deoxycytidine kinase, which is important for cytotoxicity. In contrast to cytosine arabinoside, compound **18** was resistant to degradation by deoxycytidine deaminase. Due to its inhibition of hepatocellular and prostate tumor growth, which are typically challenging to treat, the compound under study presents as a promising candidate for further evaluation. What the researchers found is that the chiral specificities of cellular enzymes vary a lot. This suggests that harnessing these differences could lead to the development of more effective drugs to combat viruses and cancer (52).

Dzhumaev *et al.* created a novel series of ethers involving compound **19**, as illustrated in **Figure 4**. The anticancer efficacy of this compound was assessed *in vitro* against various tumor cell lines, including the human normal cell line HEK293 (immortalized embryonic kidney cells), human lung adenocarcinoma A549, and human mammary gland duct cancer MCF-7. In terms of the test results, the compound being studied had the strongest anticancer effects. This was because it had more gym-dichloropropane fragments and DOR, which changed the viability of cancer cells (53).

Compound **20**, a unique bioengineering of alternating copolymers and their organoboron derivatives, was developed by Kahraman *et al.* *In vitro* studies showed that this compound was much more effective against HeLa cervical cancer cells when doses were higher than 100 µM. This meant that compound **20**, as shown in **Figure 4**, was more cytotoxic to the cancer cells under investigation. The researchers assert that this activity has led to intricate hydrogen bonding that influences the breaking down of biological molecules in this cell type (54).

To improve the ability of aryl-2*H*-pyrazole derivatives to stop telomerase, Luo *et al.* created a new compound **21** moiety (55). An assay that measured how well this compound blocked telomerase showed its highest IC_{50} value, measuring 0.9 µM. The compound being studied effectively stopped the growth of the human gastric cancer cell line SGC-7901 and the human melanoma cell line B16-F10. This was demonstrated by IC_{50} values of 18.07 and 5.34 µM, respectively. Docking modeling showed that compound **21**, as shown in **Figure 4**, had a strong binding affinity for the active site of telomerase. This stopped telomerase from doing its job. The research group came up with a 3D-QSAR method to make pharmacophore identification better. This made it possible to make new drugs that are more effective at blocking telomerase (56).

Researchers have extensively studied flavonoids as polyphenolic compounds exhibiting medicinal and curative effects (57). However, the lack of adequate bioavailability has prevented the formulation of most flavonoids as clinical-

used pharmaceuticals (58). Jin *et al.* describe a way to make flavonoids, like compound **22**, more useful by adding ethyl-2,3-butadienoate allenes. These phytochemicals are changed when ethyl-2,3-butadienoate allenes are added. This creates C(sp^2)-O bonds and selectively alkenylates hydroxyl groups in certain areas. The researchers also evaluated the anti-cancer efficacy of modified compound **22**. The findings indicated that this compound demonstrated superior *in vitro* inhibitory efficacy against various cancer cell lines compared to its parent. The initial investigations into the structure-activity relationship revealed that the addition of DOR to compound **22**, as illustrated in **Figure 4**, significantly enhanced its cytotoxicity against the majority of tested cancer cell lines. The results of this research may aid in the development or late-stage adaptation of complex flavonoids as potential anti-cancer drug candidates (59).

Schmidt and coworkers made compounds that collectively coded **23** as part of their research and looked at how they could work as powerful regulators to weaken the multi-drug resistance of certain tumors. This regulation is thought to be mediated by interacting with P-glycoprotein, which is the main cause of this resistance. **Figure 4** illustrates the compounds under study, which possess various lipophilic linker structures and chargeable basic groups, facilitating the interaction with their target. Also, compared to other congeners, these ones showed the strongest ability to stop the growth of human Caco-2 cells (colorectal adenocarcinoma) (60).

The platinum-based anticancer agents cisplatin, carboplatin, and oxaliplatin exemplify a remarkable accomplishment in translational science (61). Kim and collaborators' fundamental research findings led to the identification of platinum complexes as DNA-binding agents that induce cell cycle interruption. Test how well the complexes combat cisplatin-resistant murine L1210 leukemia cells and three human gastric cancer cell lines (SNU-6, SNU-1, and SNU-5) in a lab setting compared to cisplatin and carboplatin. The results showed that complexes that collectively coded **24** as shown in **Figure 4** were much more effective than the controls against the four cancer cell lines that were tested (62).

Dung *et al.* made indoline derivatives and tested how well they worked at stopping histone deacetylase 2 in three types of human cancer cells: SW620 (colon cancer), PC3 (prostate cancer), and AsPC-1 (pancreatic cancer). Investigators selected this enzyme for the initial biological assessment due to its significant role in the progression of various cancer types. The findings revealed that compound **25**, shown in **Figure 4**, has DOR built into its molecular structure and has strong binding and inhibiting activity against the enzyme that was tested. Its IC_{50} value is 0.284 µM, which is almost the same as the standard drug vorinostat's (IC_{50} = 0.265 µM) (63).

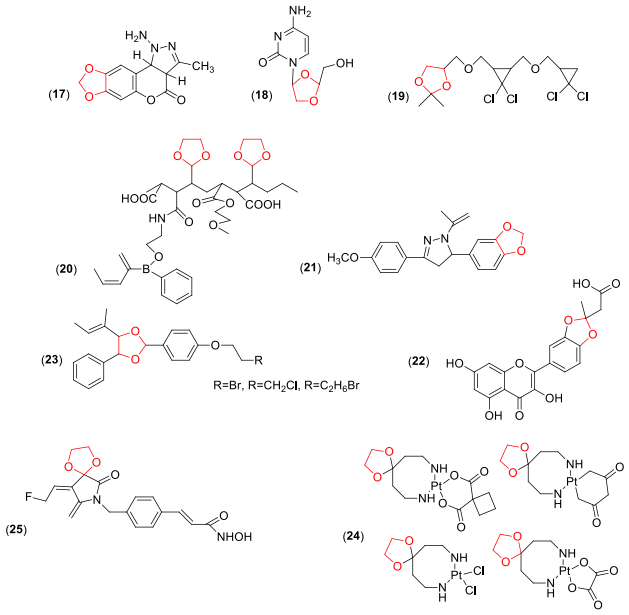


Figure 4. Chemical structures of DOR-incorporated compounds with anticancer activity

1.3.3. Anti-inflammatory activity

The expulsion of pro-inflammatory substances from the cell in response to an endogenous or exogenous stimulus induces inflammation. Each of them is termed an inflammatory mediator and serves as a sword with two sides offering benefits as well as drawbacks (64–66). The primary mediators involved are prostaglandins, leukotrienes, histamine, bradykinin, and, more recently, platelet-activating factor and interleukin-1 (67–69). This forces the search for natural and synthetic anti-inflammatory medications that can selectively inhibit mediator generation (70–72).

One of the efforts focuses on incorporating DOR into new chemical compounds to produce anti-inflammatory effects. This was achieved by Fylaktakidou and coworkers when they created compound **26**, as shown in **Figure 5**. This compound demonstrates a notable anti-inflammatory *in vivo* effect at a concentration of 0.01 mmol/kg, yielding a protection percentage of 57%, compared to 47% for indomethacin at the same concentration. The two tested compounds, **26** and reference, were evaluated using carrageenan-induced rat paw edema to assess their capacity to inhibit proteolysis and β-glucuronidase, as well as their impact on the ferrous ion-stimulated peroxidation of linoleic acid. The results showed that **26** had a strong anti-inflammatory effect (55–57%). The higher effectiveness was due to greatly decreasing the activity of the enzyme lipoxygenase 5 (73).

Non-COX2-selective NSAIDs can't connect with the less water-loving (hydrophobic) channel because they have a carboxylic group on them. This indicates that they do not bind to the COX2 enzyme as effectively as specific COX2

inhibitors (74–76). Hameedi *et al.* investigated the production of compounds, collectively referred to as compound **27**, using a unique benzodioxole framework, with a focus on ketoester and acetic acid derivatives as shown in **Figure 5**. The compounds **27a**-**27d** demonstrated superior efficacy against COX2 relative to COX1, in comparison to ketoprofen, which served as a reference standard. The researchers thought that the different levels of activity were due to the fact that 1,2-methylenedioxybenzene had a larger molecular size than the phenyl moiety of ketoprofen (77).

Li *et al.* created DOR-containing racemic compounds, collectively coded as **28** as shown in **Figure 5**. The DOR scaffold is crucial to the molecular components of these specific enantiomers, potentially influencing their functions and characteristics. The research group (78) provides evidence that suggests the DOR scaffold may be responsible for the compound's exceptional anti-inflammatory properties.

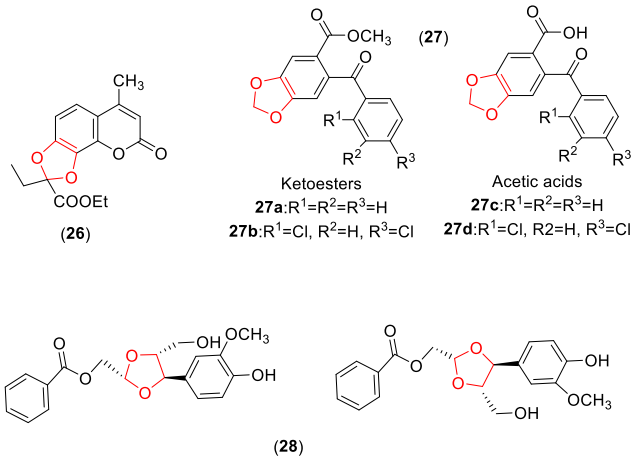


Figure 5. Chemical structures of DOR-incorporated compounds with anti-inflammatory impact

1.3.4. Antidiabetic activity

Diabetes mellitus is a disease of metabolic dysregulation, most notably abnormal glucose metabolism, accompanied by characteristic long-term complications (79–81). The complications that are specific to diabetes include retinopathy, nephropathy, and neuropathy (82–84). Considering the growing incidence of disease, resistance to existing medications, and their negative side effects, the investigation of novel compounds with antidiabetic effects has become necessary (85–87).

Kumar *et al.* synthesized two different forms of cytopiloyne, a polyacetylenic glucoside that might help fight diabetes. In this synthesis, they created compound **29**, as depicted in **Figure 6**, starting with DOR. They then used neighboring-group participation and anomeric stereocontrol to connect compound **29** to the glucoside group during glycosylation. This step was crucial for guaranteeing the accurate stereochemistry of the product. To make the alkyne-alkyne bond, a new method called palladium/silver-catalyzed cross-coupling was used. This is a big step forward in chemical synthesis. The investigators assert that additional research may examine the antidiabetic characteristics of the prepared products and their DOR intermediates, potentially elucidating their biological activity and therapeutic applications (88).

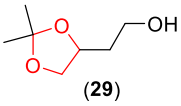


Figure 6. Chemical structure of DOR-incorporated intermediate with antidiabetic activity

1.3.5. Anticonvulsant activity

Guilherme *et al.* generated numerous indandione-derived compounds, including compound **30** as show in **Figure 7**. The pentobarbital-induced sleep assay showed that this compound makes sleep last longer and has a strong hypnotic effect by turning on the α-opioid receptor. Further tests using the elevated plus maze assay revealed that the compound under investigation possesses anti-anxiety properties, most likely *via* the same opioid receptors. The research results indicated that compound **30** is a potential therapeutic candidate for pain management. Furthermore, the researchers proposed that this compound could serve as a viable option for further exploration in the advancement of dual-action anticonvulsant agents (89).

Nikol'skaya *et al.* created compound **31**, aiming for a muscarine-like action. By utilizing mice for the investigation, this compound demonstrated a general depressive impact and can activate the dopaminergic and central adrenergic systems, which may indicate an attachment to antidepressants. Crucially, compound **31**, as demonstrated in **Figure 7**, also exhibits a central m-cholinergic action, suggesting more research. Examining the ways in which this m-cholinergic pathway affects their stimulatory activity may broaden the spectrum of antidepressant effects and provide useful therapeutic insight (90).

The central nervous system is concentrating on the 5-HT1A receptor (5-HT1AR) for the treatment of distress and neurological disorders (91). A group of DOR-based 2-heteroaryl-phenoxyethylamines, including compound **32**, were made from a set of heterobiaryl analogs of the lead compound. The researchers looked at structure-activity relationships and structure attraction at the 5-HT1AR and created compound **32** by exchanging one of the phenyl rings in the basic moiety with an electron-deficient pyridine, as shown in **Figure 7**. This compound was demonstrated to be a remarkably potent and selective 5-HT1AR agonist, exhibiting tenfold potency compared to the lead compound. Among the other synthesized compounds, the compound under study is the most stimulating. The passive diffusion of the MDCKII-MDR1 monolayer, which simulates the blood-

brain barrier, facilitated *in vitro* penetration and demonstrated promising neuroprotective effects (92).

According to Rajopadhye *et al.*, they made a lot of compounds with DOR in them. Their anticonvulsant screening results show that compound **33**, shown in **Figure 7**, is a new and very effective anticonvulsant. X-ray studies could potentially reveal a comprehensive model that encompasses the spatial structure of anti-maximal electroshock-induced seizures and the non-spiro phenacyloindoles, which exhibit anticonvulsant activity. The compound under study, which was submitted for screening, nearly demonstrated the ability to prevent mice from experiencing seizures induced by electrical and chemical stimuli (93).

Utech *et al.* synthesized various 4-(aminoalkyl) substituted DOR to create compound **34**, which is shown in **Figure 7**. The lead structure permits various substitutions, resulting in a variety of compounds with unique characteristics. This diversity is crucial for identifying effective antagonists for the targeted receptors. Medical chemistry frequently investigates DOR derivatives for potential applications. The presence of DOR in the structure of compound **34** might make it better at attaching to N-methyl-D-aspartate and π receptors, which is what the research is mostly about. This indicates that DOR may influence the therapeutic effects of the compound under study (94)**.**

In the study by Rehman *et al.*, a lot of progress has been made in making new compounds, which are coded here as **35** and could work against very late antigen 4 (VLA4). This antagonism is crucial for treating various inflammation-mediated diseases (95). The study shows that a DOR can effectively replace the proline ring, which is common in VLA4 antagonists, without affecting or possibly improving its ability to bind to the receptor being studied. This makes the DOR a useful bioisostere. Three of the synthesized compounds, as displayed in **Figure 7**—(**35a-c**)—showed strong binding affinities. This suggests that certain structural features, like the 2,6-dichlorophenyl substituent, are crucial for receptor interaction. The structure-activity relationships consistently showed that ortho-substituents on the phenylalanine group led to higher binding affinities. This shows how important steric and hydrophobic interactions are in binding to receptors. Furthermore, compounds **35b** and **35c** demonstrated promising metabolic stability in human liver microsomes, an essential factor for therapeutic development (96).

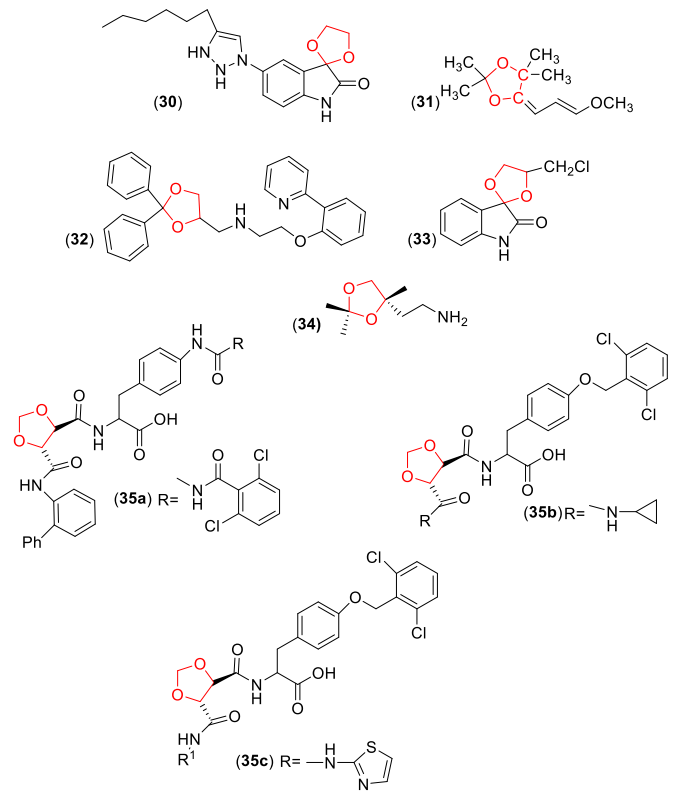
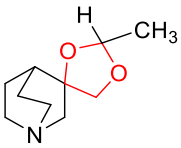


Figure 7. Chemical structures of DOR-incorporated compounds with anticonvulsant activity

1.3.6. Anti-Alzheimer activity

Nordval *et al.* developed a series of tetrahydrofuran analogues of compound **36** as shown in **Figure 8**, finding that its trans configuration exhibited more selectivity and activity than cis in removing [3*H*]-quinuclidinyl benzilate from muscarinic receptors in guinea pig organs. To find out what role each oxygen atom plays in compound **36**'s effectiveness and selectivity, it binds to the muscarinic acetylcholine receptor as a partial agonist, which means it activates the receptor but not as much as full agonists do. So, the compound under study possesses the capacity to boost cholinergic signaling in the brain, presenting a promising approach for mitigating symptoms related to Alzheimer's disease (97).



(**36**)

Figure 8. The chemical structure of DOR-incorporated compound with anti-Alzheimer's disease impact

1.3.7. Anticoagulant activity

Khanapure *et al.* have developed and created a series of unique compounds known collectively here as **37**, which act on COX-1 and COX-2 but exhibit high potency and selectivity as COX-2 inhibitors. Researchers have found that adding a one-carbon spacer group between the central benzo-DOR and the cycloalkyl or aryl substituent makes compound **37** more flexible and helps the COX-2 inhibitors work better. As illustrated in **Figure 9**, the addition of fluorine to the metaposition of a phenyl ring transforms compound **37** into a potent and selective COX-2 inhibitor, thereby enhancing its blood-thinning properties through its action on COX-1 (98).

Murashkina *et al.* used a base to help different isatins react with 3-hydroxyprop-1-yn-1-yl phosphonates. Researchers found that t-BuOLi could interact with several types of aryl-substituted and N-functionalized isatins. This resulted in the creation of numerous products that effectively and selectively interacted with specific stereotypes. When tested for their ability to kill cells, N-benzylated spirodioxolanes showed the best results with the HuTu 80 cell line. On the other hand, compound **38** as shown in **Figure 9** demonstrated anticoagulant activity surpassing that of acetylsalicylic acid (99,100).

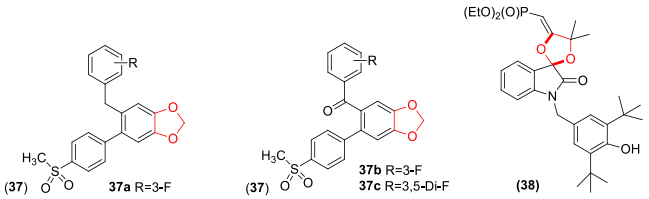


Figure 9. Chemical structures of DOR-incorporated compounds with anticoagulant impact

1.3.8. Antibacterial activity

Over the past 20 years, a wide range of microorganisms have developed resistance to antibiotics (101,102). Researchers have linked this to varying habits regarding the development of pathogens (103,104). The variations that lead to antibiotic resistance are most likely caused by natural mutations that alter biochemistry in the bacterial cell rather than by drug-induced changes (105,106). Whether they are developing novel medications or using DOR in scaffolding, researchers are diligently working to lessen the current effects of this issue on humans (107,108).

The work of Talismanov *et al.* produces compound **39**, which can be seen in **Figure 10**. It is made by rearranging aryl ketones with 3-chloro-1,2-propanediol and then alkylating them. This compound has been shown to have an antibacterial effect similar to ciprofloxacin against Gram-positive bacteria like *Staphylococcus aureus*, *Bacillus subtilis*, and *Enterococcus faecalis*. To make the desired compound, the structure had to be changed by adding several bulky and lipophilic substituents, such as chloro-, cyclohexyl-, and tertbutyl- (109).

Ovsyannikova *et al.* made compound **40** as shown in **Figure 10**, which is made up of cyclic ketals and acetals, and showed that it could kill both Gram-positive and Gram-negative bacteria. This action, which may be linked to this compound's antiradical activity and is dependent on its hydrophilic-hydrophobic balance, provides specific structural parameter variation for the synthesis of a novel active moiety. The strong antimicrobial properties of the compound under study enable its use as an antiseptic for sterilizing tools and work surfaces (110).

Dösler *et al.* examined the potential antimicrobial and antibiofilm properties of the DOR-incorporated compounds, collectively coded as **41** as shown in **Figure 10**, against a variety of pathogen microorganisms. The antifungal properties against *Candida albicans* and the antibacterial properties against *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Enterococcus faecalis*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Proteus mirabilis* were examined *in vitro*. The results demonstrated the compound type's potential antibacterial and anti-biofilm effects (111).

Küçük *et al.* used a large amount of montmorillonite K 10 as a catalyst to react salicylaldehyde with diols that were readily available in the market. This created a group of new enantiomerically pure and racemic compounds, which are shown in **Figure 10** as **42**. The reaction happened quickly and in high yield percentages. Spectroscopic evaluation and elemental analysis determined the structures of the recently synthesized compounds. On the other hand, microbiological testing showed that compounds **42a** and **42b** were very good at killing *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Enterococcus faecalis*, and *Pseudomonas aeruginosa* bacteria. They were also very good at killing *Candida albicans* fungus (20).

Begum *et al.* created a new plural based on DOR coded shown in **Figure 10** as **43** and looked into its derivatives as possible antibacterial agents against *Klebsiela pneumonia*, *Vibrio cholera*, and *Enterobacter aerogenes*. When compared to standard chloramphenicol, the prepared derivatives **43a** and **43b** demonstrated superior antibacterial activity against the bacteria under investigation. Moreover, mono-halogenated derivatives showed excellent results, although they were not as strong as those of *ortho-para*-disubstituted halogen derivatives. This fact demonstrated the significance of the halophenyl motif in the development of effective antibacterial agents (112,113).

The heterocyclic framework of naringin served as the basis for the chemical framework of the newly created compound **44** shown in **Figure 10**. Researchers led by Jodeh used the microbroth-diluting method to test this DOR-based substance and found that it is very good at killing both Gram-positive bacteria (like *Staphylococcus aureus*) and

Gram-negative bacteria (like *Escherichia coli* and *Pseudomonas aeruginosa*) (114).

Shahini *et al.* developed a number of compounds, collectively referred to shown in **Figure 10** as **45**, that contained silver. Researchers established their chemical frameworks using a variety of photometric techniques. The compounds **45a** and **45b** demonstrated the greatest effectiveness in eliminating bacteria, effectively halting the growth of Gram-negative strains of *Acinetobacter baumannii*, *Peudomonus aeruginosa*, *Klebsiella pneumoniae*, and *Escherichia coli*. Also, the same effect was observed concerning the Gram-positive strain of *Staphylococcus aurous*. This investigation used vancomycin and colistin as golden references (115).

During their research, Ramadan and colleagues created a number of sterioselective products, including compound **46**, as seen in **Figure 10**. In the agar well-diffusion method, imipenem was used as a control drug to see how well the compound killed *Escherichia coli*, *Pseudomonas aeruginosa*, and *Staphylococcus aurous* bacteria. The results showed that the target compound had very strong anti-*Staphylococcus aurous* activity, but it had no effect at all on the Gram-negative bacteria that were tested. Using clotrimazole as a reference, the compounds' modest efficacy against *Candida albicans* was discovered (116).

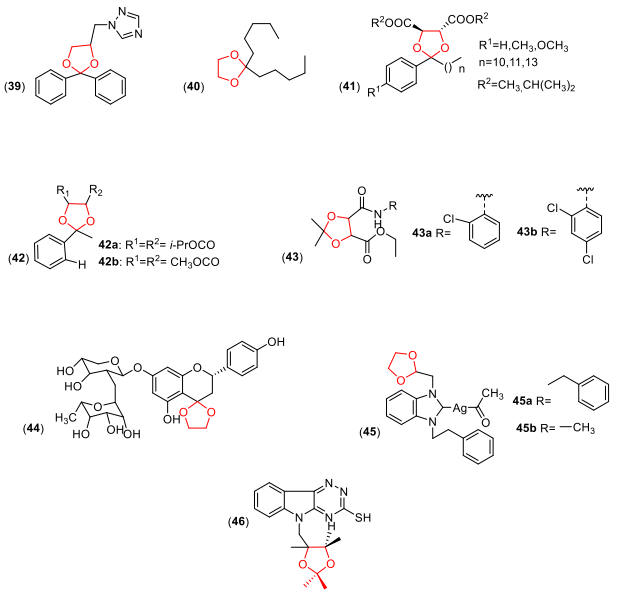


Figure 10. Chemical structures of DOR-incorporated compounds with antibacterial activity

1.3.9. Antifungal and antiparasitic activity

Fungal diseases continue to be serious and unrecognized causes of illness and death globally, despite progress in medicine and interventions to improve the quality of life for patients at risk of fungal diseases; HIV-related incidence is declining, but cancer, sepsis, immunosuppressive disorders, and influenza diagnoses are increasing (117–119). Immunocompromised patients require improved prevention and management to control morbidity and mortality (120–122). In many respects, human fungal diseases are fundamentally different from infectious diseases. Since fungi are eukaryotic pathogens, they are remarkably similar to their host cells, which hinders the creation of antifungal drugs (123–125). Therefore, it has become essential to use the DOR scaffold to produce novel antifungals or boost their efficacy.

Talismanov et al. studied the characteristics of compound **47** under cultivation to prevent infections by *Lactarius salmonicolor*, *Candida albicans*, and harmful fungi such as *Fusarium oxysporum* and *Fusarium moniliforme*. The researcher proposed the potential identification of compound **47** as shown in **Figure 11** as an effective antimycotic and antifungal. Therefore, the design of compound **47** focuses on modifying the aryl group's structure with various bulky and lipophilic substituents, and an initial logP computation is performed using both mathematical and experimental methods. Also modified the structures by replacing aryl substituents with benzyl ones, aiming to explore the influence of structural flexibility on pharmacological effectiveness (126).

The rise in metronidazole-resistant infections has led to a search for alternative medications for the treatment of trichomoniasis (127). In this context, Lopes *et al.* detailed their creation and testing of a DOR-containing tellurium derivative, known as compound **48** and depicted in **Figure 11**, against *Trichomonas vaginalis*. The researchers tested six different concentrations of this compound against the ATCC 30236 isolate of this parasite in a lab setting. At a final concentration of 90 mM and an IC_{50} of 60 mM, compound **48** killed all the *Trichomonas vaginalis* trophozoites tested. The trophozoite kinetic growth curve showed that the compound under study killed all the parasites after 24 hours and slowed their growth by 22% at a concentration of 90 mM after 12 hours of exposure. These findings supported the assumption that the compound **48** is a valuable prospect for the management of this parasitic infection. (128).

For finding new antifungal drugs to treat rice blast (*Pyricularia orizae*), Hoshi *et al.* tested the antifungal effects of DOR-containing compounds including **49** **Figure 11**. The researchers employed several tests for *in vitro* mycelial growth inhibition to ascertain this activity. The results revealed that the compound under study exhibited the strongest antifungal activity among the tested compounds. Also, at 100 µM, it stopped the growth of fungus by about 94.0 ± 3.8%. (129).

Delcourt *et al.* developed the antimycotic properties of compounds **50** and **51**, as shown in **Figure 11**. However, the researchers only tested the compounds' *in vitro* activity against filamentous fungi. They specifically targeted *Aspergillus fumigatus* and *Scedosporium apiospermum*, which are known to cause long-lasting fungal infections. Apart from *Candida albicans*, *Candida neoformans*, and

Candida glabrata, the yeasts displayed mixed susceptibilities. These compounds with an oxime group and four chlorine atoms were the most active. The structure-activity relationship reported suggests that these structural features could improve the investigated scaffold's antifungal properties (130).

A group of scientists led by Begum made a number of aliphatic ester-aromatic amid-linked DOR derivatives and tested how well they killed *Aspergillus niger*, *Helminthosporium sativum*, and *Fusarium solani*. When compared to standard terbinafine, all prepared derivatives demonstrated excellent activity against tested fungal strains. Researchers discovered that compound **52** **Figure 11** with a parasubstituted phenyl ring was the most effective antifungal candidate(112).

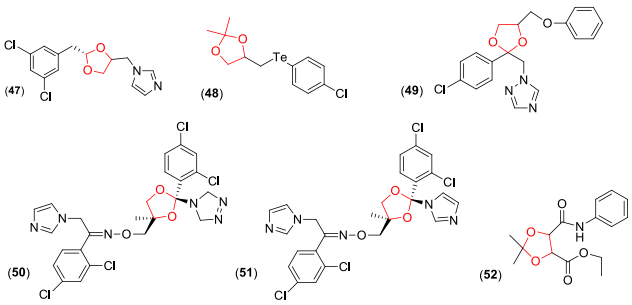


Figure 11. Chemical structures of DOR-incorporated compounds with antifungal/antiparasitic impact

1.3.10. Antiviral activity

The ongoing COVID-19 pandemic serves as an indicator that viruses pose a continual threat to international health. A lack of information regarding the interactions between viruses, like the SARS-CoV-2 virus, and the human host currently limits effective therapeutic intervention (131–133). Therefore, it is still essential to prepare analogs of nucleosides for antiviral, antibacterial, and antitumor chemotherapy (134–136).

Zhang *et al.* produced a number of new compounds, including the one denoted here as **53**, using the DOR framework as shown in **Figure 12**. The significance of 3C-like protease, also known as main protease, for viral replication makes it an attractive target for treating human rhinovirus infections. The compound being looked at had an IC_{50} value of 2.50 ± 0.7 mM against human rhinovirus-3C protease, which means it might be able to stop this enzyme from working. This finding demonstrates that the molecular structure of **53** is a perfect framework for developing novel anti-rhinoviral opportunities(137).

The compound **54** shown here in **Figure 12** is what's made when 2,6-diaminopurine-riboside-5′-diphosphate prodrugs like amdoxovir are deaminated in the lab and in living things. In their study, Narayanasamy *et al.* used molecular modeling to find out what role DOR plays in keeping the link between the nucleoside triphosphate and the mutant HIV-1 reverse transcriptase strong. This was due to the potent *in vitro* anti-HIV effectiveness of a 2,6-diaminopurine dioxolanyl nucleoside and its deaminated metabolite against both drug-resistant strains and the wild-type HIV. According to the results, compound **54**'s ethylamino group at position 6 makes it 17 times more potent than its predecessor molecule. (138). In order to maximize the drug-reverse transcriptase interactions, Franchini *et al.* prepared numerous derivatives based on the latter work. Out of all the derivatives under study, Compound **55** **Figure 12** demonstrated the best *in vitro-in silico* results. This suggests that this compound may be a better anti-HIV candidate than its parent compound, **54** (139).

Compound **56** is one of the numerous purine-based products that Bondada *et al.* developed using a phosphoramidate-based prodrug approach. This compound **Figure 12** was 300 times more effective against the hepatitis B virus and 3,600 times more effective against HIV-1 than the original nucleoside that matched it. The improved production of adenosine-DOR triphosphate inside cells made some of the desired properties of the target compound clearer. Five normal cell lines were not hurt by it, and it had broad-spectrum antiviral activity at submicromolar levels (IC_{50} against HIV = 0.086 µM and IC_{50} against hepatitis B virus = 0.8 µM) (140).

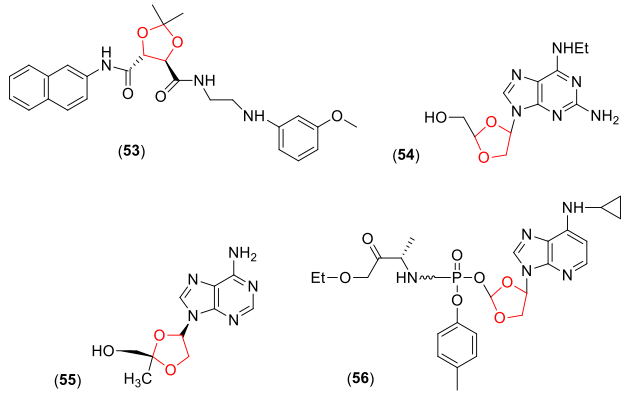


Figure 12. Chemical structures of DOR-incorporated compounds with antiviral activity

3. Conclusion

The reviewed research on DOR synthesis has highlighted the improved ligand-target interactions. Because they can create hydrogen bonds with the target site, the oxygen atoms in the heterocyclic ring under investigation are responsible for this improvement. This relationship style may have a number of benefits, such as minimizing adverse effects, lowering the frequency and amount of dosages, and lowering the risk of resistance. This could lead to an advancement in patient adherence and the desired biologic performance. Numerous scientific studies, spanning a range of pharmacological areas, frequently synthesize the heterocyclic ring under study using different chemical units. The authors underline that DOR is an important topic that needs further investigation in order to create new medicinal agents.

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التطورات في تركيب الجزيئات التي تحتوي على 1،3-ديوكسولان وتأثيراتها الطبية الحيوية

الخلاصة

المقدمة: تحتوي العديد من المنتجات الصناعية المتعلقة بالصحة على حلقة 1،3-ديوكسولان (DOR) كمكون قيم في هياكلها الكيميائية. وفقًا للعديد من علاقات البنية والنشاط، فإن إضافة هذه الحلقة غير المتجانسة إلى الإطار الكيميائي للمركب يمكن أن يعزز أنواعًا مختلفة من الأنشطة. وتشمل هذه التأثيرات المضادة للسرطان ومضادة للفطريات ومضادة للفيروسات ومضادة للبكتيريا ومضادة للأكسدة ومضادة للالتهابات. الهدف: تتطلب المشكلة الحالية المتمثلة في التفاعلات الدوائية السلبية والمقاومة إنشاء عوامل فعالة بأطر جديدة يمكنها التعامل مع هذه العقبات الدوائية. في هذه المراجعة، ينصب التركيز الرئيسي على طرق جديدة في المختبر لصنع مركبات تحتوي على DOR وتحسين الفعالية البيولوجية للأدوية باستخدام بنية كيميائية جديدة لـ DOR اصطناعية. الطرق: أجرى المؤلفون هذه المراجعة باستخدام مجموعة متنوعة من قواعد البيانات، مثل Web of Science وGoogle Scholar وPubMed وScopus، دون تحديد تواريخ النشر. النتائج: الطريقة الفريدة التي يتم بها تصنيع المركبات الاصطناعية مع DOR ومدى نجاحها في الطب تجعل الخبراء يرغبون في إجراء المزيد من الأبحاث في هذا المجال. وجد الباحثون أن إضافة هذه الحلقة غير المتجانسة يمكن أن تعزز العديد من الأنشطة البيولوجية لمختلف العوامل النشطة بيولوجيًا. الاستنتاج: وفقًا لعدد من الدراسات، فإن ذرتي الأكسجين في العمود الفقري DR قد تعززان وظيفة الحلقة المدروسة. يُعتقد أن هذه الذرات تشكل روابط هيدروجينية مع الموقع النشط. هذا يحسن التفاعلات بين الربيطة والهدف، وبالتالي، فإن وجود هذه الحلقة غير المتجانسة يعزز النشاط البيولوجي.

الكلمات المفتاحية: 1،3-دايوكسولان، مضاد للبكتيريا، مضاد للسرطان، مضاد للأكسدة، النشاط الحيوي، مركبات حلقية غير متجانسة.