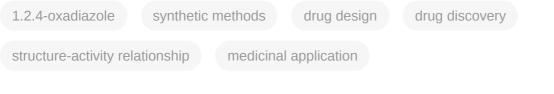# Novel 1,2,4-Oxadiazole Derivatives

Subjects: Pharmacology & Pharmacy

Contributor: Sebastian Demkowicz

Five-membered 1,2,4-oxadiazole heterocyclic ring has received considerable attention because of its unique bioisosteric properties and an unusually wide spectrum of biological activities. Thus, it is a perfect framework for the novel drug development. After a century since the 1,2,4-oxadiazole have been discovered, the uncommon potential attracted medicinal chemists' attention, leading to the discovery of a few presently accessible drugs containing 1,2,4-oxadiazole unit. It is worth noting that the interest in a 1,2,4-oxadiazoles' biological application has been doubled in the last fifteen years. Herein, after a concise historical introduction, we present a comprehensive overview of the recent achievements in the synthesis of 1,2,4-oxadiazole-based compounds and the major advances in their biological applications in the period of the last five years as well as brief remarks on prospects for further development.

1.2.4-oxadiazole   synthetic methods   drug design   drug discovery

structure-activity relationship   medicinal application

1. Introduction

Oxadiazoles are five-membered heterocyclic compounds containing one oxygen and two nitrogen atoms (historically, they were also known as furadiazoles). Depending on the position of nitrogen atoms, oxadiazoles may occur in the form of four different isomers: 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,2,5-oxadiazole and 1,3,4-oxadiazole (Figure 1). Amongst the isomers, the greatest interest is involved with 1,3,4-oxadiazoles. Their high importance is highlighted by a large number of applications in various scientific areas, e.g., pharmaceutical industry, drug discovery, scintillating materials as well as dyestuff industry [1]. It is also worth noting that compounds containing 1,3,4-oxadiazole unit exhibit a wide range of biological activities such as anticancer, antiparasitic, antifungal, antibacterial, antidepressant, anti-tubercular and anti-inflammatory [2][3][4][5].
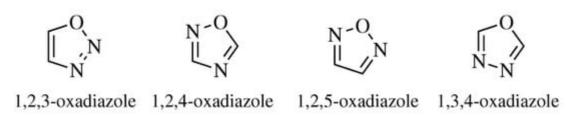

Figure 1. Chemical structures of oxadiazole isomers.

According to the *Web of Science* data the scientific attention of 1,3,4-oxadiazoles application is continuously rising since the year 2000 (Figure 2) [6]. On the other hand, 1,2,5-oxadiazole derivatives found application mainly as High Energy Density Materials (HEDMs) as well as biologically active compounds with cytotoxic properties [7][8][9]. Due to the instability and ring-opening of 1,2,3-oxadiazole heterocycle, resulting in substituted diazomethanes formation, this isomer of oxadiazole is least of all explored [10].
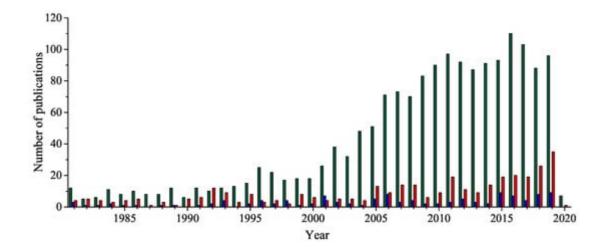

Figure 2. Number of publications containing the keywords: "1,2,4-oxadiazole" (red), "1,2,5-oxadiazole" (blue) and "1,3,4-oxadiazole" (green) in their title since 1980 [6].

2. Historical Remarks—1,2,4-Oxadiazole

The 1,2,4-oxadiazole heterocycle was synthesized for the very first time in 1884 by Tiemann and Krüger and was originally classified as azoxime or furo[*ab*1]diazole [11]. The heterocycle finally caught the attention of chemists almost 80 years after its discovery when photochemical rearrangement of it to the other heterocyclic systems was noted [12][13]. Biological activity studies of 1,2,4-oxadiazole derivatives started in the early 1940s and 20 years later First-In-Class commercial drug containing 1,2,4-oxadiazole ring—*Oxolamine* (Figure 3)—was described and introduced to the pharmaceutical market as a cough suppressant [14][15][16].

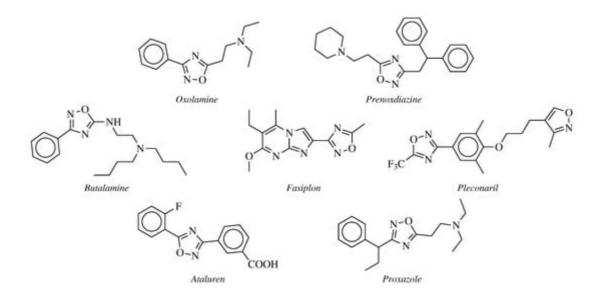**Figure 3.** Chemical structures of commercial drugs based on a 1,2,4-oxadiazole scaffold.

In the last 40 years, 1,2,4-oxadiazole heterocycle has been widely explored bringing a vast number of compounds exhibiting diverse biological activities such as anticancer, anti-inflammatory, anticonvulsant, antiviral, antibacterial, antifungal, antidepressant, antiangiogenic, analgesic, anti-insomnia, anti-oedema, antiparasitic, and anti-Alzheimer. It was proved that they also show inhibitory potency against Human Deacetylase Sirtuin 2 (HDSirt2), Carbonic Anhydrase (CA), Histone Deacetylase (HDAC), Rearranged during Transfection (RET) kinase, Penicillin-Binding Protein (PBP2a), efflux pump, cyclooxygenases (COX-1 and COX-2) and butyrylcholinesterase (BChE) as well as affinity to σ_1, σ_2, orexin, kappa opioid (KOR) and estradiol (ER) receptors (see sections below). Furthermore, 1,2,4-oxadiazole derivatives also found application as supramolecular liquid crystals and HEDMs [7][17][18][19]. Importantly, the heterocycle demonstrates bioisosteric equivalence with ester and amide moieties due to the possibility of creation specific interaction (e.g., hydrogen bonding). It is a particularly useful alternative when the instability of those groups is observed (e.g., when the hydrolysis may appear) [20][21]. Nowadays, there are a few commercially available drugs containing 1,2,4-oxadiazole nucleus such as *Oxolamine*, *Prenoxdiazine* (cough suppressant, Figure 3) *Butalamine* (vasodilator, Figure 3), *Fasiplon* (nonbenzodiazepine anxiolytic drug, Figure 3), *Pleconaril* (antiviral drug, Figure 3), *Ataluren* (Duchenne muscular dystrophy treatment drug, Figure 3) and *Proxazole* (a drug used for functional gastrointestinal disorders, Figure 3) [22][23][24]. It is worth noting that 1,2,4-oxadiazole ring, as the only one of all oxadiazole isomers, occurs in the structures of natural products. For example, in 2011 Carbone M. et al. isolated two indole alkaloids *Phidianidine A* and *Phidianidine B* (Figure 4) from sea slug Opisthobranch *Phidiana militaris* [25].
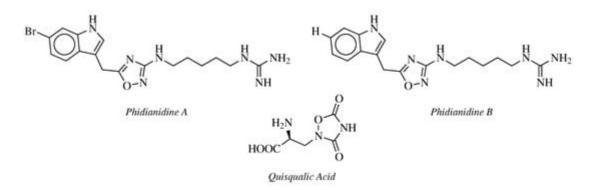

Figure 4. Chemical structures of naturally occurring 1,2,4-oxadiazole-containing compounds.

It was revealed that both Phidianidines exhibit in vitro cytotoxic activity against tumor and non-tumor mammalian cell lines (rat glial—C6, human cervical—HeLa, colon adenocarcinoma—CaCo-2, mouse embryo—3T3-L1 and rat heart myoblast—H9c2) as well as selective agonist properties against protein-tyrosine phosphatase 1B (PTP1B) and chemokine receptor type 4 (CXCR4) [26][27]. *Quisqualic acid* (Figure 4), obtained from seeds of *Quisqualis indica*, is another example of naturally occurring compound bearing 1,2,4-oxadiazole. This alanine-derivative exhibits affinity to metabotropic glutamate receptor type II and IV—attractive molecular targets for the treatment of stroke, epilepsy and neurodegenerative disorders [28][29].

3. Anticancer Agents

Every year cancer impacts about 20 million people all over the world resulting in deaths counting in millions (Figure 5). Unfortunately, a number of new cancer cases is still rising and almost 30 million people will be diagnosed with carcinoma by 2040 in high-developed countries [30]. For that reason, finding new cancer treatments or effective drugs is one of the greatest needs of the current community and a challenge for modern medicine. Biological evaluation of 1,2,4-oxadiazoles revealed that some of their derivatives are potent anticancer agents. The greatest breakthrough came with the discovery of 3,5-diarylsubstituted derivatives of 1,2,4-oxadiazole as a new series of apoptosis inducers [31]. Since then, exploration of the anticancer activity of 1,2,4-oxadiazole derivatives has been started resulting in a creation of a wide library of compounds [32][33].
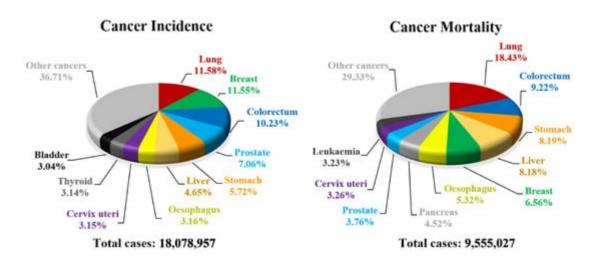

Figure 5. Estimated number of cancer incidences and cancer-related deaths in 2018.

Recently, Maftei C. V. et al. reported the synthesis of 4-(3-(*tert*-butyl)-1,2,4-oxadiazol-5-yl)aniline (**1**, Figure 6), which exhibits moderate activity with a mean IC_{50} value of approximately 92.4 µM against panel of 11 cancer cell lines (human colon adenocarcinoma—CXF HT-29, human gastric carcinoma—GXF 251, human lung adenocarcinoma—LXFA 629, human non-small cell lung carcinoma—LXFL 529, breast cancer-derived from athymic mice' lung metastatic site—MAXF 401, human melanoma—MEXF 462, human ovarian adenocarcinoma—OVXF 899, human pancreatic cancer—PAXF 1657, human pleuramesothelioma cancer—PXF 1752, human renal cancer—RXF 486, human uterus carcinoma—UXF 1138). Importantly, compound **1** became a precursor for synthesis of novel compounds with greater antiproliferative activities [34].
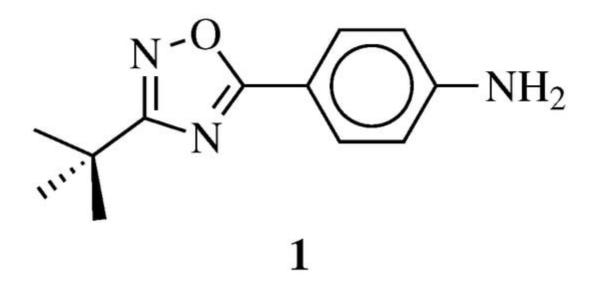
Figure 6. Chemical structure of 4-(3-(*tert*-butyl)-1,2,4-oxadiazol-5-yl)aniline **1**.

Further modification of **1** led to the discovery of its derivative **2** (Table 1) exhibiting significantly greater antitumor activity evaluated against a panel of 12 human tumor cell lines (CXF HT-29, GXF 251, LXFA 629, LXFL 529, MAXF 401, MEXF 462, OVXF 899, PAXF 1657, human prostate cancer—PRXF 22Rv1, PXF 1752, RXF 486 and UXF 1138), especially toward OVXF 899 and PXF 1752 cell lines with the IC_{50} values of 2.76 and 9.27 µM, respectively. Moreover, compound **2** showed high selectivity against renal cancer cell line with the IC_{50} = 1.143 µM [35]. In addition, the same research team reported new gold(I) complexes with 1,2,4-oxadiazole-containing *N*-heterocyclic carbene ligands. Obtained results clearly revealed impressive potency of imidazolium salts. The most active derivative **3** (Table 1) showed extremely low IC_{50} values from 0.003 to 0.595 µM against the same panel of 12 cancer cell lines with highest activity in an in vitro assays with LXFA 629 and MAXF 401 cells (IC_{50} = 0.003 µM for both of them) [36]. Thus, **3** seems to be an ideal candidate for further evaluation. More advanced in vivo studies may reveal some additional features, although no information has been published up to date.

Table 1. 1,2,4-oxadiazole derivatives with antitumor activity.

General Structure	Substituents	The Most Active Derivatives	Activity	Ref.
	R_1 = H, NH_2 and other (see Ref.); R_2 = H or phenyl.		IC_{50} values of 2.76 and 9.27 µM against OVXF 899 and PXF 1752 cancer cell lines, respectively.	[35]
	X = Cl or Br; R_1 = methyl, benzyl, 2-pyridinyl or anthracen-9-ylmethyl.		IC_{50} values of 3 nM against LXFA 629 and MAXF 401 cancer cell lines, respectively.	[36]

General Structure	Substituents	The Most Active Derivatives	Activity	Ref.
	X = O or NH; **R₁** = phenyl, benzyl, 2-chlorophenyl, 4-fluorophenyl, 2-mehylphenyl, 4-bromophenyl, 4-methylphenyl, 4-methoxyphenyl, 4-pyridinyl, 2-methoxyphenyl, 2-benzyloxyphenyl or 3-pyridinyl.		IC$_{50}$ values between 26.1–34.3 µM against Colo 205, Hep G2 and Hela cell lines.	[37] [38]
	R₁ = methyl, chloromethyl or phenyl.		GI$_{50}$ values of 0.08 (**5a**) and 0.34 (**5b**) µM against CEM-13 cell line.	[39]
	R₁ = H, Br, Cl, F, methoxy or NH$_2$.		CC$_{50}$ values of 137.3, 79.0 and 140.3 µM against Ca9-22 cell line, respectively.	[40]
	R₁ = H, 2-chloro, 3-chloro, 4-chloro, 4-nitro, 4-methyl, 4-methoxy, 4-trifluoromethyl, 2-bromo, 3-bromo, 4-bromo or 4-fluoro; **R₂** = N(CH$_3$)$_2$, N(C$_2$H$_5$)$_2$, pyrrolidine-1-yl, azepan-1-yl, morpholin-1-yl, thiomorpholine-1-yl, N-methylpiperazin-1-yl, N-phenylpiperazin-1-yl, 3-bromopropan-1-yl or 3-chloropropan-1-yl.		80% of death of NB4, K562 and MDA-MB-231 cancer cell lines at 25 (**7a**) and 10 (**7b**) µM.	[41]
	R₁ = H or NH$_2$; **R₂** = isopropylidene or cyclopentylidene; **R₃** = 4-nitrophenyl, 4-chlorophenyl or 3,4,5-trimethylphenyl.		GI$_{50}$ of 4.5 µM against WiDr cancer cell line.	[42]
	R₁ = CH$_3$ or —(CH$_2$)$_4$—; **R₂** = H, Cl, Br, methyl or methoxy.		IC$_{50}$ values of 0.48 (**9a**), 0.78 (**9b**), 0.19 (**9c**) µM against MCF-7 cancer cell line.	[43]
	R₁ = H, 3-methyl, 4-methyl, 3-bromo, 4-methoxy, 4-trifluoromethyl, 4-chloro, 4-bromo or 4-fluoro.		IC$_{50}$ values between 13.6–48.37 µM against HCT-116, PC-3, SNB-19, B16F10, L929 cell lines.	[44]
	R₁ = H, 3,4,5-trimethoxy, 4-methoxy, 4-chloro, 4-bromo, 4-fluoro, 4-trifluoromethyl, 4-nitro, 4-cyano or 4-methyl.		IC$_{50}$ values in a range from 0.11 to 2.09 µM against MCF-7, A375 and HT-29 cancer cell lines.	[45]

General Structure	Substituents	The Most Active Derivatives	Activity	Ref.
	R₁ = H, 3,4,5-trimethoxy, 4-methoxy, 4-chloro, 4-bromo, 4-fluoro, 4-trifluoromethyl, 4-nitro, 4-cyano or 4-methyl.	12a R₁ = 4-NO₂ 12b R₁ = 4-CN 12c R₁ = 3,4,5-OCH₃ 12d R₁ = 4-CF₃	IC_{50} values between 0.011–1.89 µM against A549, MCF-7, A375 and HT-29 cancer cell lines.	[46]
	R₁ = H, 3,4,5-trimethoxy, 4-methoxy, 4-chloro, 4-bromo, 4-fluoro, 4-trifluoromethyl, 4-nitro, 3-nitro or 4-methyl.	13a R₁ = 3,4,5-OCH₃ 13b R₁ = 4-CF₃ 13a-b	IC_{50} values in a range of 0.11–1.47 µM against A375, MCF-7 and ACHN cancer cell lines.	[47]
	R₁ = H, 3,4,5-trimethoxy, 4-methoxy, 4-chloro, 4-bromo, 4-fluoro, 4-trifluoromethyl, 4-nitro, 4-cyano or 4-methyl.	14a R₁ = 4-NO₂ 14b R₁ = 4-CN 14c R₁ = 3,4,5-OCH₃ 14d R₁ = 4-CF₃ 14a-d	IC_{50} values between 0.12–2.78 µM against MCF-7, A549 and A375 cancer cell lines.	[48]
	R₁ = methyl, phenyl, 4-fluorophenyl, benzyl or 4-methoxbenzyl; **R₂** = phenyl, 9-phenanthryl or 4-pyridinyl; **R₃** = 4-nitrophenyl, 4-chlorophenyl, 4-trifluoromethylphenyl or 4-fluorophenyl.	15	IC_{50} value of 10.38 µM toward MCF-7 cancer cell line.	[49]
	R₁ = methyl, phenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-t-butylphenyl, 4-methylphenyl, 2-methoxyphenyl, 3-methoxyphenyl, cyclopropyl, 2-pyridinyl, 3-pyridinyl, 4-pyridinyl, 2-thienyl, 3-thienyl, 4-cyanophenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-chlorophenyl or 3,4-dichlorophenyl; **Ar₁** = p-phenylene, m-phenylene, p-methoxyphenylene or 2,4-thienyl.	16a 16b	K_i value of 89 pm and 0.75 nm (hCA IX and hCA II, respectively) for **16a** in CO_2 hydration stopped-flow biochemical assay. **16b** showed high selectivity toward PANC-1 cancer cell line.	[50] [51]
	R₁ = H, F, Cl, Br or methoxy; **R₂** = H, F or Br.	17a R₁ = Cl R₂ = Br 17b R₁ = OCH₃ R₂ = Br 17a-b	IC_{50} values of 0.65 (**17a**) and 2.41 µM (**17b**) against MCF-7 cancer cell line.	[52]
	R₁ = H, 3,4,5-trimethoxy, 4-methoxy, 4-chloro, 4-bromo, 4-fluoro, 4-nitro, 3-nitro, 4-cyano or 4-trifluoromethyl.	18a R₁ = 3,4,5-OCH₃ 18b R₁ = 3-NO₂ 18c R₁ = 4-NO₂ 18a-c	IC_{50} values in a range of 0.45–2.11 µM against MCF-7, A549, MDA-MB-231 cancer cell lines.	[53]
	X, Y = N, O or O, N; **n** = 5 or 6; **R₁** = H, 2-methyl, 4-methyl, 4-methoxy, 2-fluoro, 3-fluoro, 4-fluoro, 4-bromo or 4-nitro.	20a R₁ = H 20b R₁ = 3-F 20c R₁ = 3-Cl 20a-c	IC_{50} values of 8.2, 10.5, 12.1 nM (**20a**, **20b**, **20c**, respectively) toward HDAC-1.	[54] [55]

General Structure	Substituents	The Most Active Derivatives	Activity	Ref.
	R_1 = H, 4-methyl, 3-methyl, 2-fluoro, 4-fluoro, 2,4-difluoro, 2-chloro, 4-cyano, 4-trifluoromethyl or 2-chloro-4-fluoro.	21	IC_{50} values of 1.8, 3.6 and 3.0 nM against HDAC-1, -2 and -3, respectively.	[56]
	R_1 = 3-pyridinyl, 4-pyridinyl, 4-methoxy-3-pyridinyl, 5-(2-methoxyethoxy)-3-pyridinyl, 5-morpholin-3-pyridinyl or 5-(1-methyl-1*H*-pyrazol-3-yl)-3-pyridinyl.	22	IC_{50} value of 7.3 nM against RET enzyme in ELISA assay.	[57]

Betulinic Acid

Lambertianic Acid

Figure 7. Chemical structure of *Betulinic Acid* and *Lambertianic Acid*.

Mironov et al. carried out a synthesis of several derivatives of *Lambertianic acid* (Figure 7) by the introduction of substituted-1,2,4-oxadiazole heterocycle at the C16 position [39]. Obtained compounds were tested in comparison with doxorubicin—widely used anticancer agent in the treatment of breast, bladder carcinomas, lymphoma, and acute lymphocytic leukemia [59][60]. Obtained outcomes by Mironov et al. revealed that **5a**–**b** (Table 1) exhibited more favorable biological activity than *Lambertianic Acid* itself with the GI_{50} values at sub-micromolar concentration against human childhood and adult T acute lymphoblastic leukemia (CEM-13), MT-4, and human adult acute monocytic leukemia (U-937) cancer cell lines. It is worth noting that **5a**–**b** demonstrated greater cytotoxic activity than doxorubicin. Additional biological studies indicated that activities of **5a**–**b** against human breast adenocarcinoma—MCF-7, MDA-MB-231 and human melanoma—MEL-8 cancer cell lines were slightly lower than the reference compound. Interestingly, flow cytometry assay revealed that the above-mentioned compounds are potent inducers of apoptosis in MCF-7, MDA-MB-231 and MEL-8 cell lines and are acting in a dose-dependent manner.

In the study of Kucukoglu K. et al. a series of Schiff bases fused with 1,2,4-oxadiazole heterocycle has been synthesized and evaluated in vitro against a panel of 8 cancer cell lines [40]. Results revealed that **6a**–**c** (Table 1) exhibited higher biological potency (CC_{50} = 137.3, 79.0 and 140.3 μM, respectively) against Ca9-22 cell line than 5-fluorouracil (a multi-acting agent used in the treatment of colon, esophageal, stomach, breast and pancreatic cancers) applied as a reference (CC_{50} = 214.3 μM). On the other hand, the cytotoxic potency of obtained compounds occurred to be far weaker than doxorubicin. For this reason, modifications of chemical structure including a different substitution of terminal aromatic rings or an introduction of additional pharmacophores are worth of consideration to improve biological activity.

Moniot S., Forgione M. et al. reported a study of about 40 novel substituted 3-aryl-5-alkyl-1,2,4-oxadiazole derivatives as selective inhibitors of HDSirt2—NAD^+ lysine deacetylase—an attractive target for treating neurodegenerative disorders, metabolic dysfunctions, age-related diseases and cancer [41]. The biological activity

of obtained derivatives was assessed in a continuous assay using an α-tubulin-acetylLys40 peptide as a substrate. Based on the detailed structure-activity relationship (SAR) studies, compounds **7a** and **7b** ([Table 1](#)) emerged as the most potent HDSirt2 inhibitors when tested against human leukemia cell lines (U-937, NB4, HL-60, and K562) and MDA-MB-231 cell line. Analog **7a** was able to induce apoptotic death in over 80% of NB4, K562 and MDA-MB-231 cancer cell at the concentration of 25 μM. Moreover, **7b** achieved the same effect at 10 μM. According to the western blot analyses, the involvement of HDSirt2 inhibition for apoptotic death induction has been confirmed. In addition, the crystal structure of 1,2,4-oxadiazole derivatives in complex with HDSirt2 revealed yet unexplored subcavity, which may be extremely useful for further inhibitors development [41].

In 2017, Avanzo R. E. and coworkers synthesized 9 novel diheterocyclic-ribose fused derivatives containing 5-substituted-1,2,4-oxadiazole framework. Their previous study suggested that 5-deoxy-5-*S*-(1,2,4-triazol-3-yl)-2,3-*O*-cyclopentylidene-β-D-ribofuranoside derivatives are moderate antitumor agents. It turned out that the introduction of 5-substituted-1,2,4-oxadiazole heterocycle into the ribose-derivative structure improved anticancer activity [42][61]. Obtained compounds were tested against human lung (A549), SW1573, HeLa, human breast (HBL-100), T-47D, and human colon (WiDr) cancer cell lines. Among them, compound **8** ([Table 1](#)) showed the highest antiproliferative potency and selectivity against WiDr with the GI_{50} value of 4.5 μM. It was noticed that the presence of electron withdrawing group (EWG) at the *para* position of the aromatic ring occurred to be crucial to ensure high biological activity.

Recently, Abd el hameid M. K. reported 15 novel 1,2,4-oxadiazole derivatives as analogs of *Terthiopene*, *Terpyridine*, and *Prodigiosin* ([Figure 8](#))—naturally occurring compounds with potent cytotoxic and pro-apoptotic properties against various types of carcinoma [43]. Obtained compounds were preliminary evaluated against MCF-7 cancer cell line and the most potent were selected for further evaluation toward human colon cancer—HCT-116 cell line. Obtained results revealed that **9a**–**c** ([Table 1](#)) exhibited the highest activity with the IC_{50} values of 0.48, 0.78, 0.19 μM and 5.13, 1.54, 1.17 μM against MCF-7 and HCT-116, respectively. In addition, their biological activities were comparable or greater than reference *Prodigiosin* (the IC_{50} values of 1.93 and 2.84 μM against MCF-7 and HCT-116 cell line, respectively). Interestingly, flow cytometry analysis revealed that the above-mentioned compounds were able to arrest cell proliferation at G1 phase in MCF-7 cells and were triggering apoptosis via increasing of caspase3/7 activity, thus are suitable for further development as potent anticancer agents.
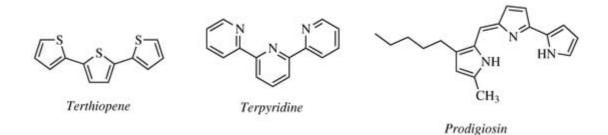

Figure 8. Chemical structure of *Terthiopene*, *Terpyridine*, and *Prodigiosin*.

4. Antimicrobial Agents

So far literature have listed over 1400 different species of microbials (including bacteria, viruses, protozoa, fungi and helminthes) able to elicit illnesses in human body which very often leads to death. Surprisingly, only 20 of them (mainly bacteria) are responsible for approximately two thirds of the fatal cases [62]. Estimated deaths from infections is continuously falling, from 16 million in 1990 to approximately 15 million to forecasting 13 million in 2050 in high-developed countries. However, people are still suffering an enormous burden dint of pneumonia, HIV/AIDS, tuberculosis, malaria, diarrhea and many other diseases [63][64]. In light of the numerous pandemic threats in European countries and the world, including the recent infections with the SARS-CoV-2 virus causing COVID-19, discovering new, effective antibacterial/antiviral drugs and the development of modern therapies are two challenges of paramount importance.

In 2014 O'Daniel P. I., Mobashery S., and Chang M. et al. from the University of Notre Dame in the United States put a great effort into the development of 1,2,4-oxadiazole as new antibiotics and discovered a new class of non-β-lactam drugs that were able to inhibit PBP2a of Methicillin-Resistant *Staphylococcus aureus* (MRSA) [65]. Detailed computer screening allowed to select 29 compounds from 1.2 million compounds (ZINC database), which were tested for their antibacterial activity against ESKAPE pathogens and agent **23** (Table 2) emerged as the most promising. Its further evaluation brought an enormous number of derivatives and led to the discovery of **24** (Table 2), which exhibited superior antibacterial activity against Vancomycin-Resistant *S*. *aureus* (VRSA), Vancomycin-Resistant *Enterococcus faecium* (VRE) as well as MRSA with the MIC values ranging from 1 to 2 µg/mL. Moreover, rapid-time kill kinetics studies revealed that **24** was able to cause instant cell death of VRE and Daptomycin-non-Susceptible isolates at 4 mg/L in 1 h resulting in better outcomes than reference compound—daptomycin [66]. Further modifications of **24** and very detailed SAR analysis allowed to obtain a wide library of its analogs (counting in hundreds of derivatives) and resulting in discovery of 5-(1*H*-indol-5-yl)-3-(4-(4-(trifluoromethyl)phenoxy)phenyl)-1,2,4-oxadiazole (also called as **ND-421**, Table 2). **ND-421** exhibited longer half-time, a high volume of distribution, low clearance, excellent bioavailability, 3 times longer postantibiotic effect than linezolid without inoculum effect with unaltered biological activity [67][68][69]. Additionally, in vitro studies against *S. aureus*, which exhibits two- and four-fold increased resistance, revealed first-time-reported, unique resistance mechanism to 1,2,4-oxadiazoles in MRSA. Moreover, those pathogen mutants did not show increased resistance to ampicillin, imipenem, linezolid, and vancomycin antibiotics (which are last drug-based defense against MRSA and VRSA) which made **ND-421** a perfect alternative drug for refractory microorganisms [70]. It is also worth pointing out that **ND-421** showed high synergy with other β-lactams (oxacillin, piperacillin, imipenem, meropenem and cefepime) unlike to non-β-lactam antibiotics (vancomycin, linezolid, gentamicin, doxycycline and azithromycin). Recently, the same research team performed additional in vitro studies of **ND-421** against 210 different MRSA and VRE, which exhibited the MIC_{50} values of 4 µg/mL in all examined strains. Moreover value of MIC_{50} were consistently lowered when studied compound was used in combination with oxacillin [71][72]. In summary, 1,2,4-oxadiazoles **23**, **24** and **ND-421** are extremely potent and very promising non-β-lactam bactericidal antibiotics against Gram-positive multi-resistant bacteria suitable for further in vivo evaluation and clinical studies, although no information has been published up to date.

Table 2. 1,2,4-oxadiazole derivatives and their antimicrobial activity.

General Structure	Substituents	The Most Active Derivatives	Activity	Ref.
	R$_1$ = H, OH, OCH$_3$, NH$_2$, NHAc, NH$_3$Cl, NHMs, NH-nBu, NH-tBu, NHCOPh, NH-iPr, PO$_3$H$_2$, PO(OEt)$_2$, SO$_2$NH$_2$, CONH$_2$, COOH, COOCH$_3$ F, Cl, Br, I, NO$_2$, ethynyl or CN; **Ar$_1$** = phenyl, benzyl, 2-pyrole, 3-pyridyl, 4-pyridyl, 5-indole, 3-pyrrazole, 2-imidazole and many others (see Ref.); **Ar$_2$, Ar$_3$** = p-phenylene, 6-indole, 2-pyridyl, 6-chromene, carbazole, N-phenylpiperazine, N-phenylmorpholine and many others (see Ref.); **X** = NH, CH$_2$, O, CO, NBn, SO or SO$_2$.		MIC$_{50}$ values <4 μg/mL against over 210 diverse, MRSA and VRE strains.	[65] [67] [68] [72]
	X = NH or none; **R$_1$** = H, 3-chloro-4-fluorophenyl, 2-chlorophenyl, 2-ethyl, 4-ethyl, 5-bromo-2-fluorophenyl or 2-methylpyridin-5-yl.		Grown inhibition zone within 20–25 mm against *S. aureus*, *B. subtilis*, *E. coli*, *P. vulgaris*, *P. aeruginosa*, *C. albicans*.	[73]
	R$_1$ = H, 2-chloro or 3-chloro; **X** = CH or N; **R$_2$** = H, 2-nitro, 2-chloro, 3-bromo, 2-chloro-5-nitro, 2-bromo, 3-nitro, 2-iodo, 3,5-dinitro, 4-nitro or 2-hydroxy.		MIC value of 60 μM against *E. coli*.	[74]

General Structure	Substituents	The Most Active Derivatives	Activity	Ref.
	R₁ = H, F, Cl, Br, I, methyl, ethyl, methoxy or *i*Pr; **R₂** = H, methyl, methoxy, *i*Pr, F, Cl, Br or I; **R₃** = H, F, Cl, Br, nitro, *i*Pr, OBn, methoxy, ethoxy or CN.		MIC value of 64 μg/mL against *S. epidermidis*.	[75]
	R₁ = H or methyl; **Ar₁** = *p*-phenylene or *m*-phenylene; **R₂** = methyl, cyclopropyl, 2-thienyl, 2-chlorophenyl, 3-chlorophenyl, 3,4-dichlorophenyl, 4-ethylphenyl, 4-*t*-butylphenyl, 4-methylphenyl, 3,4,-dimethylphenyl and many others (see Ref.).		MIC values in a range 8–16 μg/mL toward *S. aureus*, *B. subtilis*, *E. coli*, *P. fluorescent*.	[76]
	R₁ = phenyl, 4-mehtoxyphenyl, 4-chlorophenyl, 3-methylthienyl or 2-pyridinyl; **R₂**, **R₃** = H, methyl, phenyl, 4-chlorophenyl, 4-methoxyphenyl, 3,4,-dimethoxyphenyl or 2,3-dimethoxyphenyl.		MIC value of 0.68 mM against *S. aureus*.	[77]
	R₁ = phenyl, 4-methylphenyl, 4-methoxyphenyl, 4-methylthiophenyl, 2-chlorophenyl, 4-chlorophenyl, 2-3-dichlorophenyl, 3,4-dichlorophenyl, 4-fluorophenyl, 4-bromophenyl, 4-hydroksyphenyl, 2-		IC₅₀ value of 0.045 μg/mL against *M. tuberculosis* (H37Ra).	[78]

General Structure	Substituents	The Most Active Derivatives	Activity	Ref.
	bromo-4-fluorophenyl, 4-cyanophenyl, 4-pyridinyl, 1-napthyl and others (see Ref.).			
	R_1 = 4-pyridyl, 3-pyridinyl or 3,5-difluorophenyl; R_2 = 3,5-dimethoxyphenyl, 3,5-difluorophenyl, 3-cyanophenyl, 2,3-dimethylphenyl, cyclopentyl or 4-izopropylphenyl.		MIC value of 0.5 µg/mL against *M. tuberculosis* (H37Ra).	[79]
	R_1 = H, F, Cl, Br, methyl, nitro, methoxy or hydroxy; R_2 = 4-hydroksy-3-methoxyphenyl, 2-styryl, ferrocene or 5-benzo[1,3]dioxole.		IC$_{50}$ value of 0.02 µM against *P. falciparum*. In vivo studies failed—none in vivo activity.	[80]
	R_1 = Me, Et, cyclopropyl, *i*Pr, CF$_3$, *i*Bu or CH$_2$OCH$_3$; Ar$_1$ = *p*-phenylene, *p*-2-methylphenylene, *p*-2,6-dimethylphenylene, 2,5-pyridinyl or 3-methylbenzothiophene		IC$_{50}$ values of 66.0, 22.0 and 3.7 nM against hRV-B14, hRV-A21 and hRV-A71, respectively.	[81]

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