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Review Article

A Critical Examination Of Synthetic Approaches And Pharmacological Profiles Of 1,2,4-Oxadiazole Derivatives

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ABSTRACT

Background:

The previous study about the 1,2,4-oxadiazole heterocyclic ring for its distinctive bio-isosteric characteristics and extraordinarily broad spectrum of biological activities have drawn a great deal of interest due to this feature, it is the innovative platform for developing new drugs. The synthesis of 1,2,4-oxadiazole derivatives involves several methods such as cyclization reactions, condensation reactions or modifications of existing scaffolds. Various synthetic routes are evaluated in terms of their efficiency, versatility, and scalability. In this study the various one pot synthesis reaction for 1,2,4-Oxadiazole derivatives. The simple condensation reaction between amidoximes and carboxylic acid esters to make 3,5-disubstituted 1,2,4-oxadiazoles in the presence of super base medium MOH/DMSO is described using the first reaction at room temperature in a single pot method. The some other reaction also studied. In that reaction different catalyst used and different condition for synthesis studied. A broad range of amidoximes and esters, including aryl, hetaryl, and alkyl ones, were examined. In addition to their anti-inflammatory and anticonvulsant properties, 1,2,4-oxadiazole compounds have anti-bacterial, antifungal, anticancer, antiviral, antidepressant, antiangiogenic, analgesic, anti-insomnia, anti-oedema, antiparasitic, and anti-Alzheimer properties in pharmacological activities. The review highlights recent advances in the synthesis and pharmacology of 1,2,4-oxadiazole derivatives and discusses potential future directions for research in this field.

INTRODUCTION

The 1,2,4-oxadiazole heterocycle was initially categorized as an azoxime or a Furo [ab1] diazole when it was first synthesized by Tiemann and Krüger in 1884[1]. Nearly eight decades after its discovery, the heterocycle attracted the attention

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of scientists when it was shown that it could be photochemically altered to generate other heterocyclic systems [2]. Early 1940s physiological function research on 1,2,4-oxadiazole derivatives led to the introduction of Oxolamine, the first-in-class commercial medication containing a 1,2,4-oxadiazole ring, as a cough suppressant [3]. Scientific interest in the utilization of 1,3,4-oxadiazoles has increased since 2000[4]. Conversely, 1,2,5-oxadiazole derivatives were primarily used as biologically active substances with cytotoxic qualities and as High Energy Density Materials (HEDMs) [5]. This isomer of oxadiazole is the least studied of all because of the instability and ring-opening of the 1,2,3-oxadiazole heterocycle, which causes the formation of substituted diazomethanes on [6]. The 1,2,4-oxadiazole heterocycle has been the subject of numerous studies over the past 40 years, which has produced a large number of compounds with a variety of biological effects, such as anti-inflammatory, anticancer, antiviral, antiangiogenic, antibacterial, antifungal, antidepressant, analgesic, anti-insomnia, anti-oedema, antiparasitic, and anti-Alzheimer anticonvulsant properties. Oxadiazoles are five-membered heterocyclic elements with one oxygen and two nitrogen atoms; they were formerly known as furadiazoles. Based on the location of the nitrogen atoms, oxadiazoles can be found in four different isomers: 1,2,3-, 1,2,4-, 1,2,5-, and 1,3,4-oxadiazole. [7

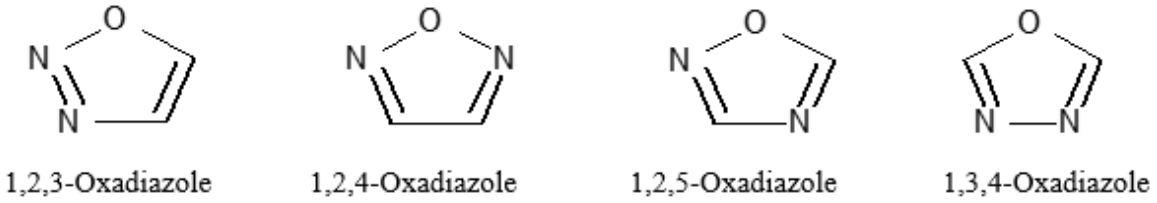


Fig. 1. chemical structure of oxadiazole isomers.

Currently, a small number of pharmaceuticals that are sold commercially contain the 1,2,4-oxadiazole nucleus. The drugs Prenoxdiazine, vasodilator Butalamine, nonbenzodiazepine anxiolytic medicine Fasiplon, antiviral Pleconaril, prescription Ataluren for Duchenne muscular dystrophy, and drug Proxazole for functional gastrointestinal disorders are among them. A severe psychiatric condition is major depressive disorder [8]. Nonetheless, the fundamental pathophysiological pathways responsible for depression remain incompletely characterized. The N-methyl-D-aspartate (NMDA) receptor complex functional antagonists are effective antidepressants in pre-clinical tests that is indicative of antidepressant activity; consequently, co-administration of NMDA antagonists with conventional antidepressants was found to have additive effects in the forced swimming test in rats, leading to the current theory that the NMDA receptor complex is a possible site of antidepressant action. Animal research on NOS inhibitors showed that they have characteristics similar to those of an antidepressant after it was discovered that nitric oxide (NO) synthase (NOS) activity was connected to the NMDA receptor complex. Subsequently, these molecules are tested to determine whether they can augment the antidepressant effects of prescription drugs. It has been demonstrated that 7-nitroindazole and NG-nitro-L-arginine augment the antidepressant effects of citalopram, fluoxetine, reboxetine, and imipramine. Thus, the NO-cGMP pathway is critical in mediating the behavioural effect in the forced swimming test. In a different investigation, the soluble guanylate cyclase (sGC) inhibitor [1H-[1,2,4] Oxadiazole[4,3-a] quinoxalin-1-one] (ODQ) reduced the duration of immobility in rats. [9]

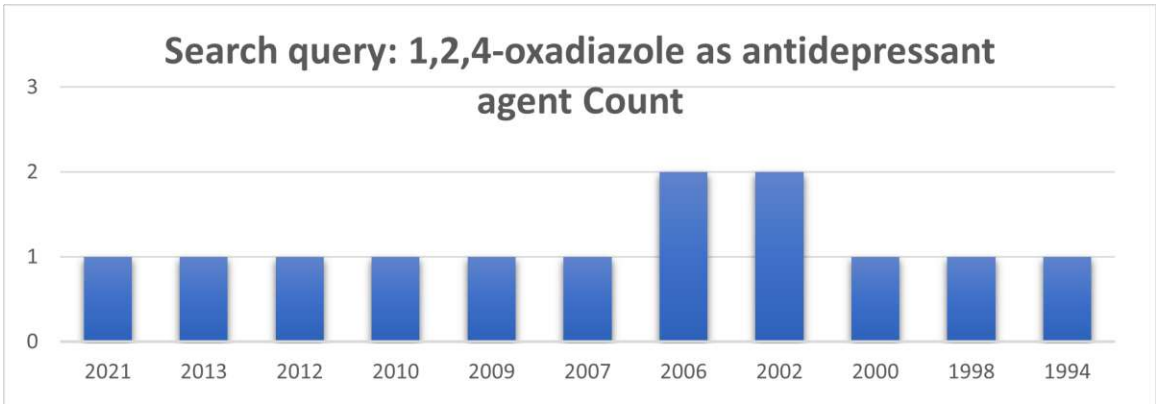
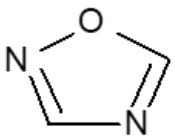


Fig. 2. Number of publications contain antidepressant activity of 1,2,4-oxadiazoles.

Physicochemical properties of 1,2,4-Oxadiazole:



1,2,4-Oxadiazole

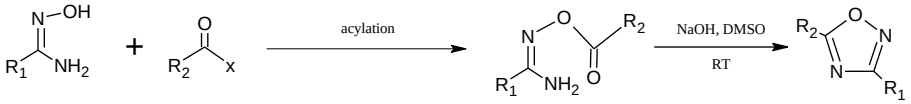
Molecular formula	: $C_2H_2ON_2$
Molecular weight	: 70.05 g/mol
IUPAC Name	: 1,2,4-oxadiazole
Solubility in water	: Soluble
Appearance	: White Crystalline Powder
Melting point	: 133°C
Log P	: -1.24

Fig. 3. structure of 1,2,4-oxadiazole

Synthesis:

Scheme 1:

In 2017, Baykov et al. published a study describing the first one-pot synthesis technique for the synthesis of 3,5-disubstituted-1,2,4-oxadiazoles at room temperature (RT). The process involved matching amidoximes with carboxylic acids, methyl or ethyl esters in the super basic medium NaOH/DMSO. [10]



Scheme 1. 1,2,4-oxadiazole analogue synthesis in the super base phase (X = methoxy or ethoxy, R1 = 4-methylphenyl, R2 = methyl or phenyl).

Scheme 2:

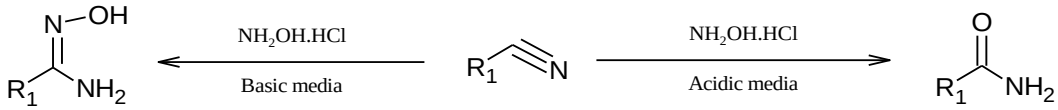
Zarei M. discussed a novel and intriguing one-pot process for producing 1,2,4-oxadiazoles that have undergone a 3,5-disubstitution. This process involves reacting the -COOH group with the Vilsmeier reagent and using the appropriate amidoximes and carboxylic acids. The benefits of establishing this method included good to exceptional yields (61–93%), a simple purification procedure, the utilization of easily obtainable starting ingredients, and a one-pot synthesis methodology. [11].

Scheme 2:

The Vilsmeier reagent, which functions as an activator of carboxylic acid groups (R1, R2 = phenyl, 4-nitrophenyl, 4-chlorophenyl, 2-methoxyphenyl, methyl, 2-thiophenyl, and other chemicals), is used in the synthesis of 1,2,4-oxadiazoles.

Scheme 3:

Adib and colleagues report a significant improvement over previous methods with their one-pot, three-component reaction between nitriles, hydroxylamine, and aldehydes under solvent-free and microwave-irradiation conditions. However, the reaction requires aerial oxidation and a higher temperature (160°C) to be completed. Additionally, we were aware that acidic media would induce the nitrile to hydrolyse into the corresponding amide, negating the need for basic media in the hydroxylamine hydrochloride conversion of nitriles to amidoximes. Thus, nitrile can be used as the starting material in a one-pot synthesis of 1,2,4-oxadiazoles, but basic media are needed. [12].

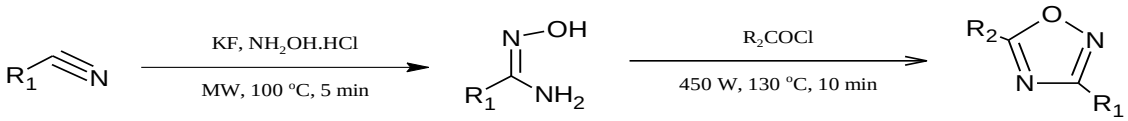


Scheme: 3

(R1 = 2-methoxyphenyl, methyl, 2-thiophenyl, 4-nitrophenyl, 4-chlorophenyl, 2-methoxyphenyl, and others).

Scheme 4:

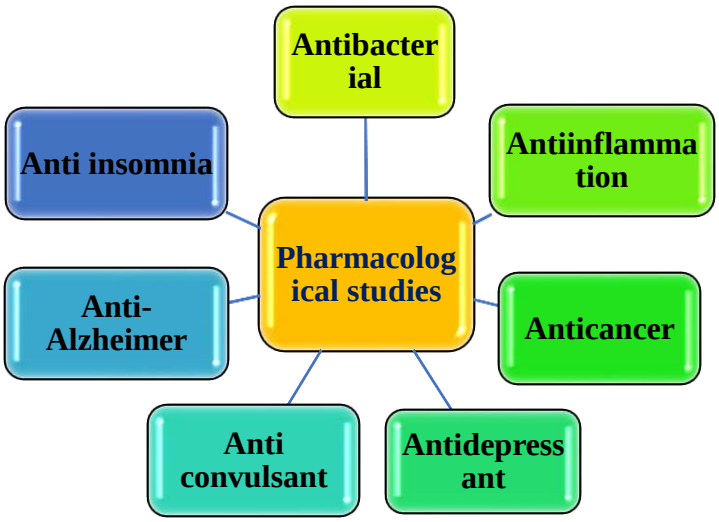
The microwave-assisted aryl-nitrile and hydroxylamine hydrochloride synthesis, which takes place in with the help of a catalyst (MgO, CH3COOH, or KF), is also described. Amidoxime and acyl chloride mix in a simple two-step process to form 1,2,4-oxadiazoles. [13].



Scheme: 4

(R1 = 2-methoxyphenyl, methyl, 2-thiophenyl, 4-nitrophenyl, 4-chlorophenyl, 2-methoxyphenyl, and others).

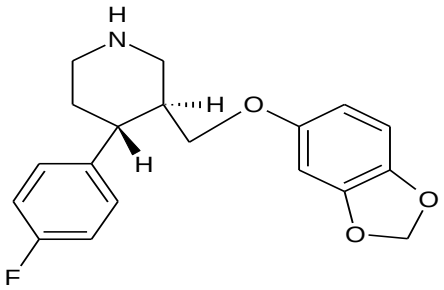
Pharmacological activity



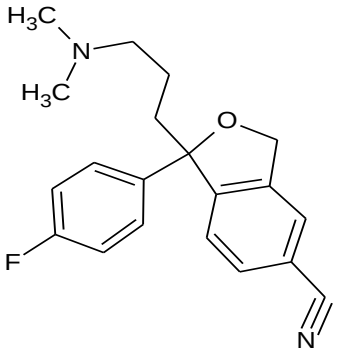
Antidepressant activity:

Depression is a diverse, multidimensional illness that presents with behavioral, physiological, and psychological symptoms. It is unable to replicate many of the depressive symptoms seen in humans, as listed in the Diagnostic and Statistical Manual of the American Psychiatric Association (DSM

IV), in mice. These symptoms include excessive guilt feelings and recurrent thoughts of suicide or death [14]. The forced swim test (FST), also known as Porsolt's test or the behavioral despair test, is by far the most well-known and often used of all the experimental techniques used in preclinical depression research. It is known that it mainly modifies monoamine neurotransmission, while its exact mechanism of action is yet unknown. A notable change in antidepressant medication screening occurred largely because of the FST's relative reliability across laboratories and its ability to detect the activity of a wide variety of clinically effective antidepressants [15]. The basis for both the TST and the FST is the observation that, in the face of an inevitably unpleasant environment, rodents (often mice, though gerbils and rats have also been utilized) make initial escape-oriented movements before adopting an immobile posture. Mice are uncontrollably suspended by their tails during the TST, but they are situated in a cylinder filled with water for the FST [16].A series of 3,4-dihydroquinolin-2(1H)-one derivatives was developed and synthesized by Deng et al., and these derivatives demonstrated good antidepressant efficacy. It is commonly known that oxadiazole compounds replaced with piperazine have inhibitory effects. This pharmacophore may therefore provide new lead molecules for the manufacture of antidepressants for illnesses that mimic depression. [17].



Paroxetine

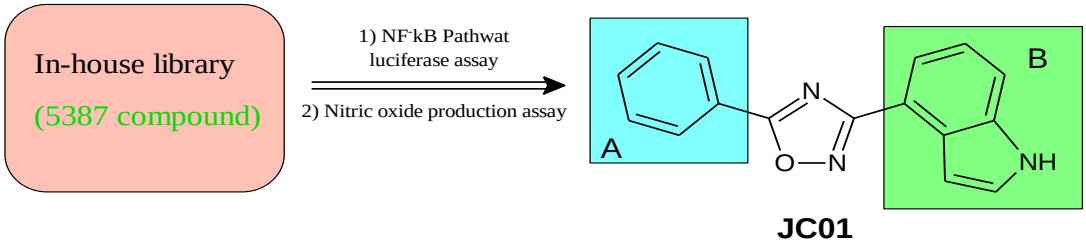


Citalopram

Fig. 4. chemical structure of paroxetine and citalopram

Anti-inflammatory activity:

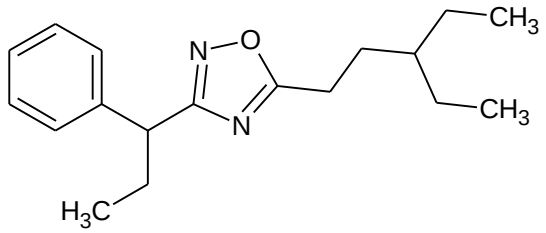
Essential characteristics of inflammation include redness, swelling, discomfort, heat, and malfunction. Inflammation is the body's defence reaction to dangerous stimuli including infections and irritants. Inflammation pathology is a complex process that the organism goes through to get rid of harmful stimuli and start the healing process of the tissues. An initial NF-κB inhibitor, 1,2,4-oxadiazole derivative JC01, was identified in order to find possible anti-inflammatory drugs that target the inhibition of NF-κB activation.



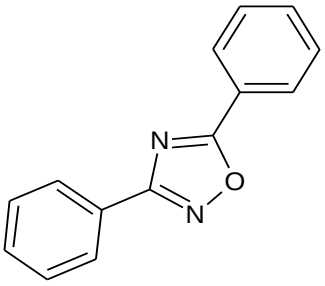
JC01

Uncontrolled inflammation can lead to the development of several conditions such as rheumatoid arthritis, osteoarthritis, diabetic neuropathy, tumour initiation and progression, and inflammatory bowel disease. The cyclooxygenases COX-1 and COX-2, which are

critical for the inflammatory response, are inhibited by the most widely used analgesics and anti-inflammatory medications, known as non-steroidal anti-inflammatory medicines (NSAIDs). Unlike COX-1, which is produced by the kidneys and gastrointestinal tract and whose suppression can have a range of unfavourable effects, COX-2 is directly produced during the inflammatory process, which is noteworthy from a medical standpoint The synthesis, in vitro assessment, and in vivo testing of 1,2,4-oxadiazoles combined with 2-mercapto-benzothiazoles as potent inflammatory agents have been reported by Yatam S. et al. Out of all the compounds developed, compound proved to be the most efficient and specific against COX-2[18].



Proxazole



3,5-Diphenyl-1,2,4-oxadiazole

Fig. 5. chemical structure of proxazole and 3,4-Diphenyl 1,2,4-oxadiaole.

As particular COX-2 inhibitors, a class of 1,2,4-oxadiazol-sulfonamide compounds was developed in 2018. Using an assay for carrageenan-induced rat paw edema, the produced compounds were assessed in vivo. Experiments with hot plates and tail immersion have also been conducted on rats. (Figure 5) In hot plate and tail immersion testing, the substance exhibited the greatest analgesic (5.7 to 14.3 and 4.5 to 8.0 s, respectively) and anti-inflammatory (55% reduction of acute inflammation, 3 hours after injection) effects at a single dose of 40 mg/kg. Sadly, aspirin (6.7 to 23.2 and 4.5 to 11.3 s in hot plate and tail immersion experiment, respectively, at dose of 10 mg/kg) and indomethacin (71% of reduction of inflammation, 3h) were reference compounds that showed higher activity than aspirin (figure 5). As a result, altering the activity's structure is required to make it better [19].

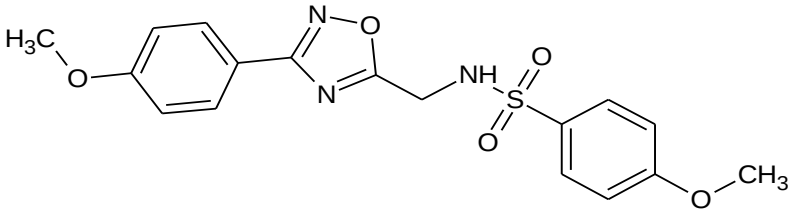


Fig. 6. chemical structure of 4-methoxy-N-{[3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl]} benzene sulfonamide.

Anticonvulsant activity:

Epilepsy is a neurological illness marked by frequent and unexpected convulsions that affects about 50 million people of all ages. Unfortunately, the cause of epilepsy is still unknown because congenital anomalies, brain traumas, tumors, strokes, and infections can all produce cases of the condition [20]. Mohammadi-Khanaposhtani M. and associates recently reported on a range of 1,2,4-oxadiazoles based on acridone and coumarin. In mice given maximal electroshock (MES) and pentylenetetrazole (PTZ) to produce

seizures, these compounds were evaluated as effective anticonvulsant medications. [21].

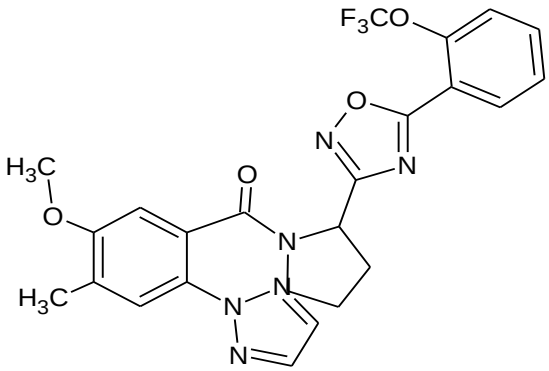
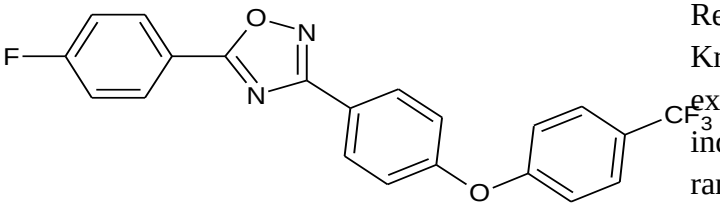


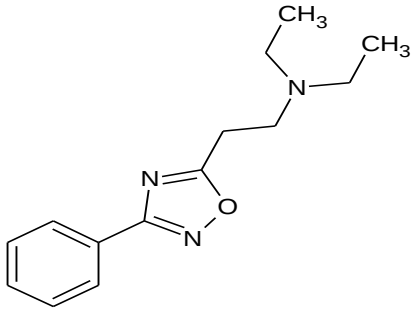
Fig. 7. chemical structure of (5-methoxy-4-methyl-2- [1, 2, 3] triazol-2-ylphenyl)- {(S)-2-[5-(2-trifluoromethoxyphenyl)- [1, 2, 4] oxadiazol-3-yl] pyrrolidin-1-yl} methanone

Antibacterial activity:

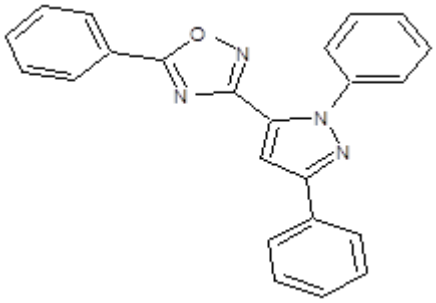
Antimicrobial resistance, or the capacity of certain bacteria to fend off the effects of antibiotics, poses a threat to public health and wastes limited medical resources when left unchecked. An alarming increase in potentially fatal infectious diseases is caused by multidrug-resistant Gram-positive and Gram-negative pathogen bacteria. The University of Notre Dame in the United States' O'Daniel P. I., et al. found in 2014 a novel class of non-lactam medications that could suppress PBP2a of Methicillin-Resistant Staphylococcus aureus (MRSA). They exerted great effort to create the novel antibiotic 1,2,4-oxadiazole. [22].



5-(4-fluorophenyl)-3- {4 - [4-(trifluoromethyl) phenoxy] phenyl}-1,2,4-oxadiazole



Oxalamine



3-(1,3-diphenyl-1H-pyrazol-5-yl)-5-phenyl-1,2,4-oxadiazole

Fig. 8. chemical structure of 5-(4-fluorophenyl)-3-{4 - [4-(trifluoromethyl) phenoxy] phenyl}-1,2,4-oxadiazole, Oxalamine and 3-(1,3-diphenyl-1H-pyrazol-5-yl)-5-phenyl-1,2,4-oxadiazole.

Utilizing the agar diffusion test, a novel class of 5-(1H-1,2,3-triazol-4-yl)-1,2,4-oxadiazole derivatives was synthesized and assessed as an antimicrobial agent against fungi (C. albicans) and bacteria (S. aureus, B. subtilis, and E. coli) as well as Gram-negative (P. vulgaris, P. aeruginosa). Recently, this investigation was conducted by Krolenko K. et al. The compound 1 (figure 8) exhibited superior biological activity over three independent series, with a grow inhibition zone ranging from 20 to 25 mm, in comparison to the reference compounds metronidazole and syntomycin, which are commonly used antibiotics. Even though 5-(1H-1,2,3-triazol-4-yl)-1,2,4-oxadiazole derivatives exhibit great promise, no additional research has been made public [23].

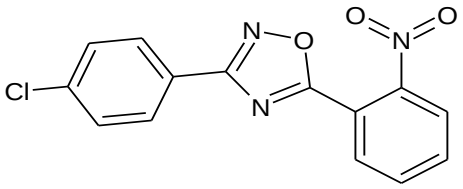


Fig. 10. chemical structure of 3-(4-chlorophenyl)-5-(2-nitrophenyl)-1,2,4-oxadiazole.

Recently, unique 1,2,4-oxadiazole-2-imidazole hybrids were generated as equivalents to a novel class of efflux pump inhibitors disclosed by Shetnev A. and Haynes K. M. and collaborators [26, 27]. Unfortunately, it was discovered that the amide moiety of the aforementioned efflux pump inhibitors was unstable during the in vivo test. This led to the hypothesis that increasing the hydrolysis resistance would require replacing the amide molecule with 1,2,4-oxadiazole. The antibacterial effects of novel compounds were evaluated against both Gram-positive and Gram-negative bacteria, including P. fluorescent and E. coli, as well as S. aureus and B. subtilis. The compound (figure 10) turned out to be the most potent derivative, with MIC values ranging from 8 to 16 g/mL (MIC values for pefloxacin, the reference molecule, ranged from 0.008 to 0.5).

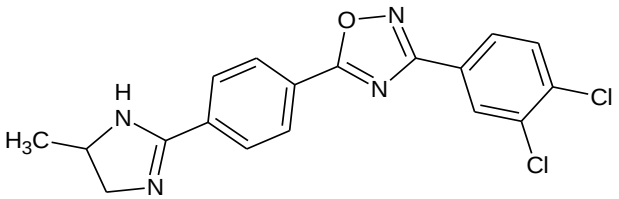
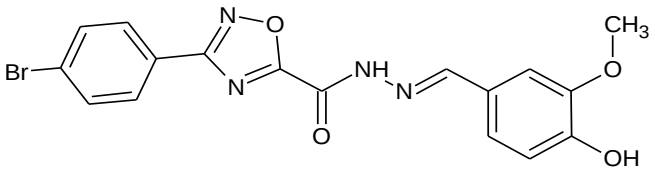


Fig. 11. chemical structure of 3-(3,4-Dicholophenyl)-5-[4-(5-methyl-4,5-dihydro-1H-imidazol-2-yl) phenyl]-1,2,4-oxadiazole.

Upare A. A. and associates presented in 2019 with inspiration drawn from the structure of cinnamic acid. [28] novel 1,2,4-oxadiazole compounds' synthesis and biological assessment as antitubercular medications. The addition of the 1,2,4-oxadiazole moiety to cinnamic acid makes sense in order to augment its antitubercular properties, as cinnamic acid and its derivatives have demonstrated good biological activity against Mycobacterium TB. [29]. A new class of powerful antimalarial medications, comprising derivatives of 1,2,4 oxadiazole-N-acylhydrazone joined together, was synthesized and its biological activity studied by Dos Santos Filho J. M. and colleagues in 2016. [30]. Based on biological screening against the blood-stage Plasmodium falciparum W2 strain, which is resistant to chloroquine, the chemical (figure 11) was the most effective derivative, able to reduce the development of microorganisms up to 72% at 10 g/mL. Furthermore, compounds of 1,2,4-oxadiazole-N -acylhydrazone have shown anti-Trypanosoma cruzi activity [31, 32].



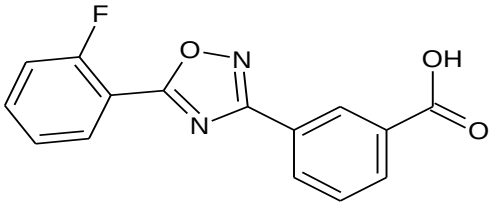
3-(4-bromophenyl)-*N*'-[(*E*)-(4-hydroxy-3-methoxyphenyl)methylidene]-1,2,4-oxadiazole-5-carbohydrazide

Fig. 12. chemical structure of 1,2,4-Oxadiazole derivative.

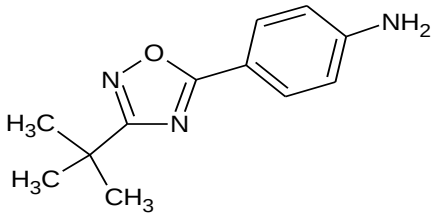
Anti-Cancer:

Every year, cancer affects over 20 million people globally and claims millions of lives. Regretfully, the incidence of new cases of cancer is rising, and by 2040, high-developed nations would have diagnosed almost 30 million people with the disease [33]. Thus, one of the most pressing needs of contemporary society and the challenge facing

modern medicine is the development of innovative cancer therapies or potent medications. Through biological research, several of the derivatives of 1,2,4-oxadiazoles have been proven to be efficacious anticancer drugs. Most significantly, a new family of apoptosis inducers was discovered, consisting of 1,2,4-oxadiazole derivatives that were replaced with 3,5-diaryl. Following that, investigations into the possible anticancer effects of 1,2,4-oxadiazole derivatives have commenced, resulting in the creation of an extensive chemical library's [34]. Maftei C. V. et al. recently reported the synthesis of 4-(3-(tert-butyl)-1,2,4-oxadiazol-5-yl)aniline, which has a mean IC50 value of approximately 92.4 M against a 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's 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). Crucially, the substance served as a precursor for the creation of other substances with stronger antiproliferative properties [35]. The biological efficacy of 1,2,4-oxadiazole-1,3,4-oxadiazole-fused derivatives against the cancer cell lines MCF-7, A549, and MDA MB-231 was investigated in a recent study by Polothi R. et al. The found compounds' anticancer effectiveness varied from good to exceptional [36].



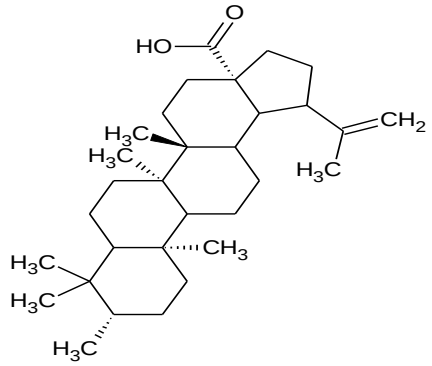
Ataluren



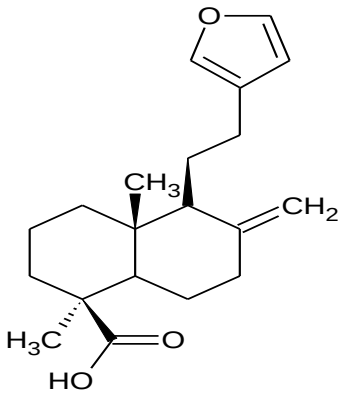
4-(3-tert-butyl-1,2,4-oxadiazol-5-yl) aniline

Fig. 13. chemical structure of Ataluren and 4-(3-tert-butyl-1,2,4-oxadiazol-5-yl) aniline.

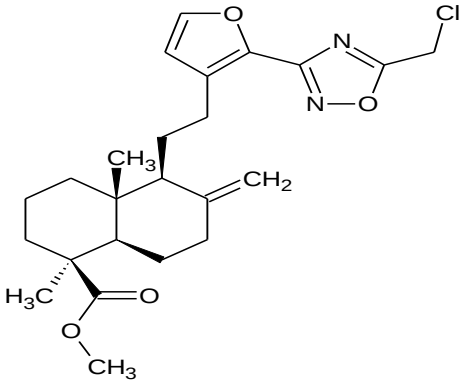
A study by Challa K., Krishna C., and associates, synthesized and evaluated C28-modified Betulinic Acid (Figure 13) against HeLa cell lines, human liver cancer (Hep G2), and human colon cancer (Colo 205). It included an ester or amide linker connecting the 1,2,4-oxadiazole ring [37]. A heterocycle substituted-1,2,4-oxadiazole was inserted at position C16 by Mironov et al. [38] to create a number of derivatives of Lambertianic acid (Figure 13). The obtained compounds underwent testing in relation to doxorubicin, a widely used anticancer drug used to treat acute lymphocytic leukemia, bladder cancer, breast cancer, and lymphoma [39, 40]. In human childhood and adult T acute lymphoblastic leukemia (CEM-13), MT-4, and human adult acute monocytic leukemia (U-937) cancer cell lines, compounds 2 and 3 (figure 13) showed higher biological activity than Lambertianic Acid alone, with IG50 values at sub-micromolar concentration, according to results obtained by Mironov et al. Notably, compound 2 and 3 demonstrated greater cytotoxic activity than doxorubicin.



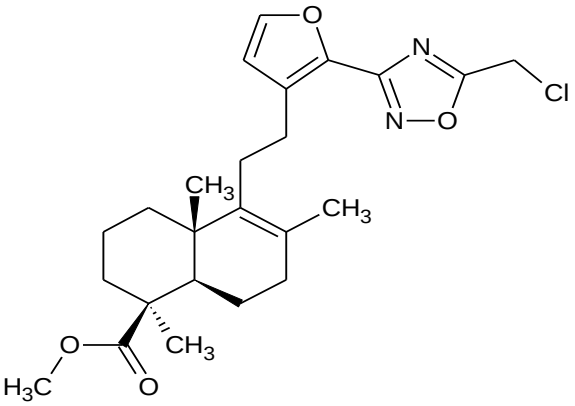
Betulinic acid



Lambertianic acid



Compound 2



compound 3

Fig. 14. chemical structure of Betulinic acid, Lambertianic acid, comp.2 and comp.3.

The research by Kucukoglu K. et al. examined a panel of eight cancer cell lines in vitro using a sequence of Schiff bases fused with 1,2,4-oxadiazole heterocycle. In comparison to 5-fluorouracil, a multi-acting medication used as a reference (CC50 = 214.3 M) for treating cancers of the colon, esophagus, stomach, breast, and pancreas (CC50 = 137.3, 79.0, and 140.3 _M, respectively), the results showed that compound (figure 14) was more biologically potent against the Ca9-22 cell line [41].

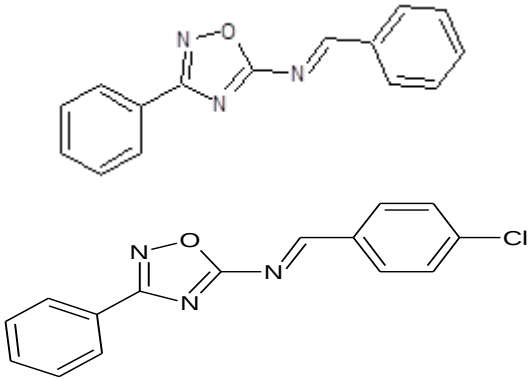
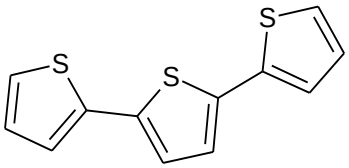


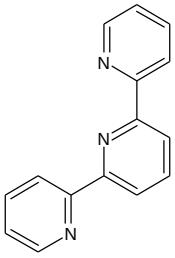
Fig. 15. chemical structure of 3-phenyl-N-[(E)-phenyl methylidene]- 1,2,4-oxadiazol-5-amine, N-[(E)-chlorophenyl) methylidene]-3-phenyl-1,2,4-oxadiazol-5-amine

Moniot S., Forgione M. studied a little over 40 novels containing substituted 3-aryl-5-alkyl-1,2,4-oxadiazole derivatives and discovered that they were selective inhibitors of NAD+ lysine deacetylase, or HDSirt2. Because of this, targeting HDSirt2 for the treatment of cancer, age-related illnesses, metabolic problems, and neurodegenerative diseases is an intriguing goal. [42].The biological activity of the resulting derivatives was assessed using a continuous assay with an a-tubulin-acetylLys40 peptide serving as the substrate. Avanzo R. E. and associates synthesized nine new diheterocyclic-ribose fused derivatives in 2017 using a 5-substituted-1,2,4-oxadiazole framework. Five-deoxy-5-S-(1,2,4-triazol-3-yl)-2,3-O-cyclopentylidene-D ribofuranoside derivatives may have modest antitumor properties, according to their earlier research. The ribose-derivative structure's anticancer activity was found to increase upon the addition of the 5-substituted-1,2,4-oxadiazole heterocycle. [43, 44]. Abd el Hameid M. K. has reported the discovery of 15 new 1,2,4-oxadiazole derivatives that are naturally occurring analogs of terthiopene, terpyridine, and prodigiosin. These substances have strong cytotoxic and pro-apoptotic effects against different types of

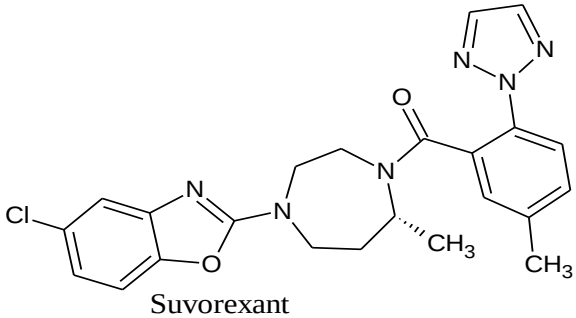
carcinoma. (Figure 15) [45]. When the obtained compounds were evaluated against the MCF-7 cancer cell line, the most effective ones were selected for further testing against the human colon cancer cell line, HCT-116. Compound 4 (figure 16) exhibited the highest activity against MCF-7 and HCT-116, according to the results, with IC50 values of 0.48, 0.78, 0.19 _M and 5.13, 1.54, 1.17 M, respectively.



Terthiopene



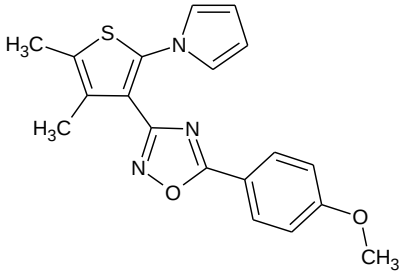
Terpyridine



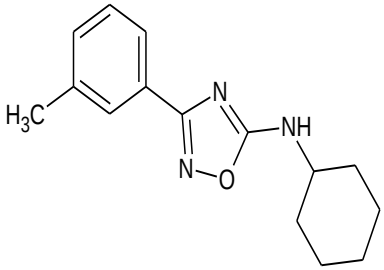
Suvorexant

Fig. 16. chemical structure of Terthiopene, Terpyridine and Suvorexant.

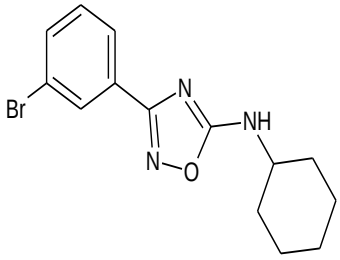
De Oliveira V. N. M. and associates from DCC synthesized a set of substituted N-cyclohexyl-3-aryl-1,2,4-oxadiazole-5-amines in 2018 under MWI and related arylamidoximes. The antitumor activity of these compounds was assessed in human prostate (PC-3), human astrocytoma (SNB-19), and human hCT-116 cancer cell lines. [46]. After additional testing against five cell lines, it was discovered that compounds 5 and 6 (figure 16) had the highest activity: mouse melanoma (B16F10), mouse adipose (L929), PC-3, SNB-19, and HCT-116. Pharmaceuticals2020, 13, 111 16 of 45 48.37 M. was the range where the IC50 values showed their activity. However, the levels of inhibition remained considerably lower than those of the reference compound, doxorubicin, suggesting that additional modifications to the chemical structure are required in order to improve the activity.



Compound 4



Compound 5

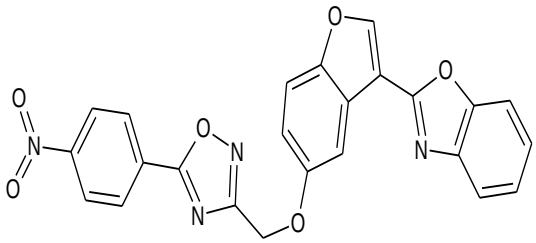


Compound 6

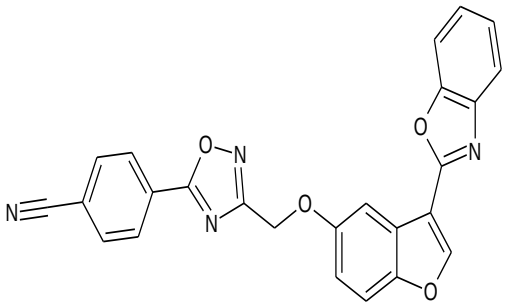
Fig. 17. chemical structure of comp.4, comp.5 and comp.6.

Ten novel compounds with a benzofuran group that are based on 1,2,4-oxadiazole derivatives were synthesized and biologically assessed in Pervaram S.'s study. The MTT assay was used to determine the antiproliferative potency of the obtained compounds with respect to the cancer cell lines A375, HT-29, and MCF-7. At sub-micromolar concentrations, compounds 7 and 8

(figure 17) showed encouraging cytotoxic activity when compared to the reference compound, combretastatin-A4. Remarkably, the substitution of halogen atoms for either EDG or EWG in the phenyl ring was linked to a notable decrease in biological activity. [47].



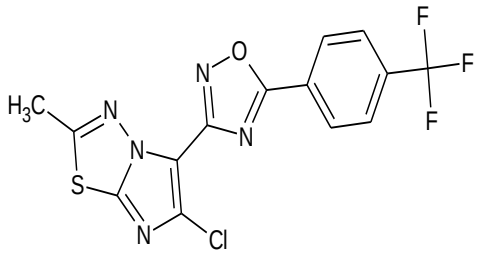
Compound 7



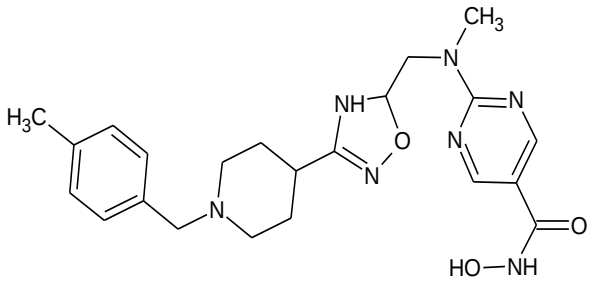
compound 8

Fig. 18. chemical structure of comp. 7 and comp. 8.

In a 2018 study, Chakrapani B. et al. synthesized and evaluated the cytotoxic potential of 1,2,4-oxadiazole-fused-imidazothiadiazole derivatives against the human cancer cell lines A375, MCF-7, and ACHN using doxorubicin as a reference compound. Figure 18 shows that of the isolated compounds, compound 9, exhibited strong antitumor activity, with IC50 values ranging from 0.11 to 1.47 _M against the previously mentioned cancer cell line. It is noteworthy that the reference compound exhibited similar or slightly decreased anticancer activity (IC50 values ranging from 0.79 to 5.51 _M).[48].



Compound 9



Compound 10

Fig. 19. chemical structure of comp. 9 and comp. 10.

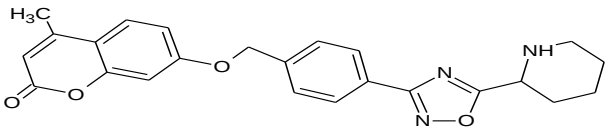
A unique class of substituted 1,2,4 oxadiazole-arylsulfonamides was found to be selective CA inhibitors in a recent study by Krasavin M. et al., with possible uses in cancer therapies. [49, 50] A comprehensive study (conducted by the same research team) examining various substituted heterocyclic compounds with sulfonamide moiety, such as 1,3 oxazole, isoxazole, imidazoline, and pyrazole, revealed that the biological activity and selectivity of 1,2,4-oxadiazol-5-yl-benzene sulphonamides were exceptionally high. [51]. The study by Yang F., Shan P., and colleagues has identified a new class of 1,2,4-oxadiazole derivatives based on hydroxamate as HDAC inhibitors. [52]. Four of the obtained compounds were tested for their inhibitory potential against HDAC-1 at a concentration of 20 nm, and their results were compared with that of supraanilohydroxamic acid, the reference compound. Suberanilohydroxamic acid (SAHA), also known as Vorinostat, received FDA approval in 2006 to treat cutaneous T cell lymphoma under the brand name Zolinza. [53]. With the IC50 values of 1.8, 3.6, and 3.0 nm, respectively, compound 10 (figure 18) demonstrated the strongest HDAC inhibitory activity among the synthesized derivatives, especially against HDAC-1, -2, and -3.

Anti-Alzheimer's Activity:

Alzheimer's disease (AD) is a chronic neurodegenerative illness that usually gets worse over time, resulting in behavioral issues,

disorientation, dementia, and language disorders. 3 to 9 years after diagnosis, the disease usually results in death. Notably, AD affects more than 40 million people globally and claims roughly 2 million lives each year. The etiology of AD is still poorly understood, despite the fact that the disease was first documented more than a century ago [54] Acetylcholine (ACh) is a neurotransmitter present in brain tissues that is hydrolysed by the enzymes acetylcholinesterase (AChE) and butyrylcholinoesteraze (BChE). Alzheimer's disease is characterized by a decrease in ACh concentration (AD) [55AChE inhibitors like galantamine, donepezil, and rivastigmine are now used to treat AD; however, they only slow the disease's progression or lessen its symptoms; the disease's progression cannot be stopped or altered. Therefore, it is crucial to develop novel, effective therapeutic strategies.

Recently, Zhang J. et al. synthesized and biologically assessed coumarin-1,2,4-oxadiazole-fused hybrids, which are selective AChE and BChE antagonists with strong neuroprotective activity. [56]. In a previous study, it was demonstrated that phenidianidine B modifications change the neurotoxic properties of the human neuroblastoma (SH-SY5Y) cancer cell line. [57]. The obtained 1,2,4-oxadiazole-coumarin derivatives were evaluated against BChE and AChE. All of the compounds tested had IC50 values between 89.7 and 45.6 M, which indicates moderate activity toward AChE. Out of all the BChE inhibitors, compound 11 (figure 19) showed the highest selectivity, with IC50 values of 8.2 and 77.6 M against BChE and AChE, respectively.



Compound 11

Fig. 20. chemical structure of compound 11.

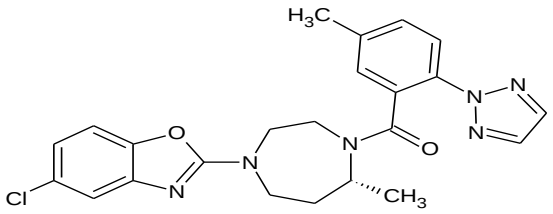
Anti-Allodynic Activity:

Neuropathic pain is a major problem on a global scale. Nowadays, opioids, anticonvulsants, and tricyclic antidepressants are used as treatments for chronic pain. But not all of them are effective, and when used repeatedly, some of them can have major adverse effects (such as potentially fatal addiction and abuse). Recently, sigma receptors (ϱ1 and ϱ2)—whose precise function is still unknown—were mistakenly identified as opioid receptors in the past, but they have been recognized as possible targets for the treatment of drug-resistant tumors and disorders of the central nervous system (CNS). [58]. In 2018, Cao X. et al. synthesized and evaluated a series of 3-phenyl-1,2,4-oxadiazole derivatives as potent anti-allodynic agents with affinity for the ϱ1 and ϱ2 receptors and minimal simultaneous activity against other central nervous system receptors. [59]. In accordance with their previous research, creating hybrid compounds using the pharmacophore of the six-membered heterocyclic rings of pyrimidine and pyridazinone in the 1,2,4-oxadiazole framework improved activity [60].

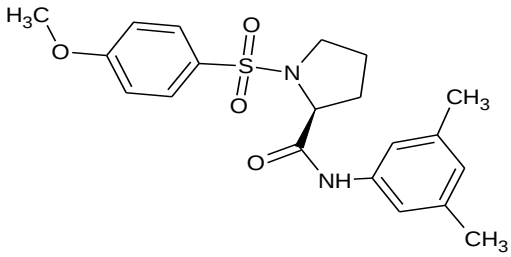
Anti-insomnia Activity:

An inadequate or unsatisfactory amount of sleep is known as insomnia. It is a health problem that typically manifests as a lack of sleep, difficulty concentrating, difficulty learning, mood swings, irritability, and occasionally even the development of heart disease, hypertension, dementia, or depression. Insomnia is thought to impact up to 70% of adults overall, making it a significant public health issue [61]. Orexin A and B neuropeptides were discovered in 1998, and since then, its antagonists, such as lemborexant and almorexant, have advanced to clinical trials [62]. The FDA approved Suvorexant (Figure 13) as the first Dual-Orexin Receptor Antagonist (DORA) in 2014. It is marketed as Belsomra and is used to treat insomnia [63]. There is still a need for more powerful substances with improved pharmacological profiles and safety though, as

common side effects include muscle weakness, sleepwalking, strange dreams, and somnolence the following morning [64]. In a recent study [65], Brotschi C. and Boss C. created novel 1,2,4-oxadiazole derivatives to be used as DORAs. This research is an extension of the long-term effort to develop a potent drug for the treatment of primary insomnia. Furthermore, phase I clinical trials were initiated for compound 12 (Figure 20), which was acquired by the aforementioned research group [66].



Suvorexant



Compound 12

Fig.21. chemical structure of Suvorexant and compound 12.

CONCLUSION:

The recent surge in interest surrounding the 1,2,4-oxadiazole heterocyclic ring stems from its unique bio-isosteric characteristics and broad spectrum of biological activities, making it an attractive platform for drug development. The synthesis of these derivatives involves diverse strategies, including cyclization reactions, condensation reactions, and modifications of existing scaffolds. Our study explored various synthetic routes, evaluating their efficiency, versatility, and scalability. Notably, one-pot synthesis reactions for 1,2,4-oxadiazole derivatives were investigated, with a focus on the condensation reaction between amidoximes and carboxylic acid esters using different catalysts and reaction conditions.

The results of our study demonstrate the feasibility of synthesizing a wide range of 1,2,4-oxadiazole derivatives, encompassing aryl, hetaryl, and alkyl substituents. These derivatives exhibit diverse pharmacological activities, including anti-inflammatory, anticonvulsant, antibacterial, antifungal, anticancer, antiviral, antidepressant, antiangiogenic, analgesic, anti-insomnia, anti-oedema, antiparasitic, and anti-Alzheimer properties. Such pharmacological diversity underscores the potential of 1,2,4-oxadiazole compounds as valuable candidates for drug discovery and development.

In conclusion, our findings contribute to a deeper understanding of the synthetic approaches and pharmacological profiles of 1,2,4-oxadiazole derivatives, paving the way for future research endeavors aimed at harnessing their therapeutic potential in various disease contexts.

ABBREVIATIONS:

AChE	Acetylcholinesterase
AD	Alzheimer Disease
AMF	Acute Myeloid Leukemia
BChE	Butyrylcholinoesterase
CNS	Central Nervous System
COX	Cyclooxygenase
DSM	Diagnostic and statistical manual
DOR	Delta-Opioid Receptor
DORA	Dual-Orexin Receptor Antagonist
EDC	1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide
EDG	Electron Donating Group
EWG	Electron Withdrawing Group
FDA	Food and Drug Administration
FST	Forced swim test
hCA	Human Carbonic Anhydrase
HDAC	Human Deacetylase
HDSirt2	Human Deacetylase Sirtuin 2
HEDMs	High Energy Density Materials
KOR	Kappa-Opioid Receptor
Me, Et& Ph	Methyl, Ethyl and Phenyl

MES	Maximal Electroshock
MOR	Mu-Opioid Receptor
MPTP	1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MRSA	Methicillin-Resistant
MWI	Microwave Irradiation
NAD+	Oxidized Nicotinamide Adenine Dinucleotide
NMDA	N-methyl-D-aspartate
NSAIDs	NON-Steroidal Anti-Inflammatory Drugs
NOS	Nitric oxide synthase
PTZ	Pentylenetetrazole
RT	Room Temperature
sGC	Soluble guanylate cylase
SAR	Structural-Activity Relationship
TST	Tail suspension test
TEA	Triethylamine

DECLARATION:

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All authors have read and approved the manuscript and give suggestions for correction.

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AVAILABILITY OF DATA AND MATERIALS:

The data that support the findings of this study are available from the corresponding
author, upon reasonable request.

CONSENT FOR PUBLICATION:

The authors declare no conflict of interest.

COMPETING INTERESTS:

The authors declare that they have no competing interests.

REFERENCE:

1. Tiemann, F.; Krüger, P. Ueber Amidoxime und Azoxime. Berichte Der Dtsch. Chem. Ges. 1884, 17, 1685–1698. [CrossRef]
2. Newman, H. Photochemistry of 3,5-diphenyl-1,2,4-oxadiazole II. Photolysis in protic media. Tetrahedron Lett. 1968, 9, 2421–2424. [CrossRef]
3. Newman, H. Photochemistry of 3,5-diphenyl-1,2,4-oxadiazole I. Photolysis in aprotic media. Tetrahedron Lett. 1968, 9, 2417–2420. [CrossRef]
4. Anderson, G.W.; Faith, H.E.; Marson, H.W.; Winnek, P.S.; Roblin, R.O. Studies in Chemotherapy. VI. Sulfanilamido Heterocycles. J. Am. Chem. Soc. 1942, 64, 2902–2905. [CrossRef]
5. Web of Science. Available online: http://www.webofknowledge.com./ (accessed on 16 December 2019)
6. Wei, H.; He, C.; Zhang, J.; Shreeve, J.M. Combination of 1,2,4-Oxadiazole and 1,2,5 Oxadiazole Moieties for the Generation of High-Performance Energetic Materials. Angew. Chem. 2015, 127, 9499–9503. [CrossRef]
7. Nguyen, M.T.; Hegarty, A.F.; Elguero, J. Can 1,2,3-Oxadiazole be Stable? Angew. Chem. Int. Ed. Engl. 1985, 24, 713–715. [CrossRef]
8. Salahuddin.; Mazumder, A.; Yar, M.S.; Mazumder, R.; Chakraborthy, G.S.; Ahsan, M.J.; Rahman, M.U. Updates on synthesis and biological activities of 1,3,4-oxadiazole: A review. Synth. Commun. 2017, 47, 1805–1847. [CrossRef]
9. Coupar, I.M.; Hedges, A.; Metcalfe, H.L.; Turner, P. Effect of aminophylline, butalamine and imolamine on human isolated smooth muscle. J. Pharm. Pharmacol. 1969, 21, 474–475. [CrossRef] [PubMed]
10. Bai F, Li X, Clay M, Lindstrom T, Skolnick P. Intra- and interstrain differences in models of “behavioral despair”. Pharmacol Biochem Behav 2001;70:187–92.
11. Baykov, S.; Sharonova, T.; Shetnev, A.; Rozhkov, S.; Kalinin, S.; Smirnov, A.V. The

first one-pot ambient-temperature synthesis of 1,2,4-oxadiazoles from amidoximes and carboxylic acid esters. Tetrahedron 2017, 73, 945–951. [CrossRef]
12. Zarei, M. A Mild and Efficient One-Pot Preparation of 1,2,4-Oxadiazoles from Nitriles and Carboxylic Acids Using Vilsmeier Reagent. ChemistrySelect 2018, 3, 11273–11276. [CrossRef]
13. Rostamizadeh, S.; Ghaieni, H.R.; Aryan, R.; Amani, A.M. Clean one-pot synthesis of 1,2,4-oxadiazoles under solvent-free conditions using microwave irradiation and potassium fluoride as catalyst and solid support. Tetrahedron 2010, 66, 494–497. [CrossRef]
14. Kaboudin, B.; Saadati, F. Magnesia-supported hydroxylamine hydrochloride in the presence of sodium carbonate as an efficient reagent for the synthesis of 1,2,4-oxadiazoles from nitriles. Tetrahedron Lett. 2007, 48, 2829–2832. [CrossRef]
15. Jones, I., Blackshaw, J.K., 2000. An evolutionary approach to psychiatry. Aust N Z J Psychiatry 34, 8–13.
16. Cryan, J.F., Markou, A., Lucki, I., 2002a. Assessing antidepressant activity in rodents: recent developments and future needs. Trends Pharmacol Sci 23, 238–245.
17. Thierry, B., Steru, L., Simon, P., Porsolt, R.D., 1986. The tail suspension test: ethical considerations. Psychopharmacology (Berl) 90, 284–285.
18. Rostamizadeh, S.; Ghaieni, H.R.; Aryan, R.; Amani, A.M. Clean one-pot synthesis of 1,2,4-oxadiazoles under solvent-free conditions using microwave irradiation and potassium fluoride as catalyst and solid support. Tetrahedron 2010, 66, 494–497.
19. Yatam, S.; Gundla, R.; Jadav, S.S.; reddy Pedavenkatagari, N.; Chimakurthy, J.; Rani B, N.; Kedam, T. Focused library design and synthesis of 2-mercapto benzothiazole linked 1,2,4-oxadiazoles as COX-2/5-LOX inhibitors. J. Mol. Struct. 2018, 1159, 193–204. [CrossRef]
20. Vijaya Bhargavi, M.; Shashikala, P.; Sumakanth, M.; Krishna, C. Synthesis, Molecular Docking, Analgesic, and Anti-Inflammatory Activities of New 1,2,4-Oxadiazolo-Sulfonamides. Russ. J. Gen. Chem. 2018, 88, 804–811. [CrossRef]
21. Goldberg, E.M.; Coulter, D.A. Mechanisms of epileptogenesis: A convergence on neural circuit dysfunction. Nat. Rev. Neurosci. 2013, 14, 337–349. [CrossRef] [PubMed]
22. Mohammadi-Khanaposhtani, M.; Shabani, M.; Faizi, M.; Aghaei, I.; Jahani, R.; Sharafi, Z.; Shamsaei Zafarghandi, N.; Mahdavi, M.; Akbarzadeh, T.; Emami, S.; et al. Design, synthesis, pharmacological evaluation, and docking study of new acridone-based 1,2,4-oxadiazoles as potential anticonvulsant agents. Eur. J. Med. Chem. 2016, 112, 91–98. [CrossRef] [PubMed]
23. O'Daniel, P.I.; Peng, Z.; Pi, H.; Testero, S.A.; Ding, D.; Spink, E.; Leemans, E.; Boudreau, M.A.; Yamaguchi, T.;Schroeder, V.A.; et al. Discovery of a New Class of Non-b-lactam Inhibitors of Penicillin-Binding Proteins with Gram-Positive Antibacterial Activity. J. Am. Chem. Soc. 2014, 136, 3664–3672. [CrossRef]
24. Krolenko, K.Y.; Vlasov, S.V.; Zhuravel, I.A. Synthesis and antimicrobial activity of 5-(1H-1,2,3-triazol-4-yl)-1,2,4-oxadiazole derivatives. Chem. Heterocycl. Compd. 2016, 52, 823–830. [CrossRef]
25. Cunha, F.; Nogueira, J.; de Aguiar, A. Synthesis and Antibacterial Evaluation of 3,5-Diaryl-1,2,4-oxadiazole Derivatives. J. Braz. Chem. Soc. 2018, 29, 2405–2416. [CrossRef]
26. Rozenski, J.; De Ranter, C.J.; Verplanken, H. Quantitative Structure-Activity Relationships

for Antimicrobial Nitroheterocyclic Drugs. Quant. Struct.-Act. Relatsh. 1995, 14, 134–141. [CrossRef]
27. Shetnev, A.; Baykov, S.; Kalinin, S.; Belova, A.; Sharoyko, V.; Rozhkov, A.; Zelenkov, L.; Tarasenko, M.; Sadykov, E.; Korsakov, M.; et al. 1,2,4-Oxadiazole/2-Imidazoline Hybrids: Multi-target-directed Compounds for the Treatment of Infectious Diseases and Cancer. Int. J. Mol. Sci. 2019, 20, 1699. [CrossRef] [PubMed]
28. Haynes, K.M.; Abdali, N.; Jhawar, V.; Zgurskaya, H.I.; Parks, J.M.; Green, A.T.; Baudry, J.; Rybenkov, V.V.; Smith, J.C.; Walker, J.K. Identification and Structure–Activity Relationships of Novel Compounds that Potentiate the Activities of Antibiotics in Escherichia coli. J. Med. Chem. 2017, 60, 6205–6219. [CrossRef] [PubMed]Int. J. Mol. Sci. 2019, 20, 1699. [CrossRef] [PubMed]
29. Atmaram Upare, A.; Gadekar, P.K.; Sivaramakrishnan, H.; Naik, N.; Khedkar, V.M.; Sarkar, D.; Choudhari, A.; Mohana Roopan, S. Design, synthesis and biological evaluation of (E)-5-styryl-1,2,4-oxadiazoles as anti-tubercular agents. Bioorg. Chem. 2019, 86, 507–512. [CrossRef]
30. Cardona, P.J. Understanding Tuberculosis—New Approaches to Fighting against Drug Resistance; InTech: London, UK, 2012. [CrossRef]
31. dos Santos Filho, J.M.; de Queiroz e Silva, D.M.A.; Macedo, T.S.; Teixeira, H.M.P.; Moreira, D.R.M.; Challal, S.; Wolfender, J.L.; Queiroz, E.F.; Soares, M.B.P. Conjugation of N-acylhydrazone and 1,2,4-oxadiazole leads to the identification of active antimalarial agents. Bioorg. Med. Chem. 2016, 24, 5693–5701. [CrossRef]
32. dos Santos Filho, J.M.; Leite, A.C.L.; de Oliveira, B.G.; Moreira, D.R.M.; Lima, M.S.; Soares, M.B.P.; Leite, L.F.C. Design, synthesis and cruzain docking of 3-(4-substituted-aryl)-1,2,4-oxadiazole-N-acylhydrazones as anti-Trypanosoma cruzi agents. Bioorg. Med. Chem. 2009, 17, 6682–6691. [CrossRef] [PubMed]
33. Dos Santos Filho, J.M.; Moreira, D.R.M.; de Simone, C.A.; Ferreira, R.S.; McKerrow, J.H.; Meira, C.S.; Guimarães, E.T.; Soares, M.B.P. Optimization of anti-Trypanosoma cruzi oxadiazoles leads to identification of compounds with efficacy in infected mice. Bioorg. Med. Chem. 2012, 20, 6423–6433. [CrossRef] [PubMed]
34. Bray, F.; Ferlay, J.; Soerjomataram, I.; Siegel, R.L.; Torre, L.A.; Jemal, A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J. Clin. 2018, 68, 394–424. [CrossRef]
35. Pace, A.; Buscemi, S.; Piccionello, A.P.; Pibiri, I. Recent Advances in the Chemistry of 1,2,4-Oxadiazoles. In Advances in Heterocyclic Chemistry; Academic Press Inc.: Cambridge, MA, USA, 2015; Volume 116, pp. 85–136. [CrossRef]
36. Maftei, C.V.; Fodor, E.; Jones, P.G.; Franz, M.H.; Kelter, G.; Fiebig, H.; Neda, I. Synthesis and characterization of novel bioactive 1,2,4-oxadiazole natural product analogs bearing the N-phenylmaleimide and N-phenylsuccinimide moieties. Beilstein J. Org. Chem. 2013, 9, 2202–2215. [CrossRef] [PubMed]
37. Cao, X.; Yao, Z.; Dou, F.; Zhang, Y.; Qiu, Y.; Zhao, S.; Xu, X.; Liu, X.; Liu, B.; Chen, Y.; et al. Synthesis and Biological Evaluation of Sigma-1 (σ1) Receptor Ligands Based on Phenyl-1,2,4-oxadiazole Derivatives. Chem. Biodivers. 2019, 16, e1800599.
38. Krishna, C.; Bhargavi, M.V.; Krupadanam, G.L.D. Design, Synthesis, and Cytotoxicity of Semisynthetic Betulinic Acid-1,2,4-

Oxadiazole Amide Derivatives. Russ. J. Gen. Chem. 2018, 88, 312–318. [CrossRef]

39. Mironov, M.E.; Pokrovsky, M.A.; Kharitonov, Y.V.; Shakirov, M.M.; Pokrovsky, A.G.; Shults, E.E. Furanolabdanoid-based 1,2,4-oxadiazoles: Synthesis and cytotoxic activity. ChemistrySelect 2016, 1, 417–424. [CrossRef]
40. Guest, J.F.; Panca, M.; Sladkevicius, E.; Gough, N.; Linch, M. Cost Effectiveness of First-Line Treatment with Doxorubicin/Ifosfamide Compared to Trabectedin Monotherapy in the Management of Advanced Soft Tissue Sarcoma in Italy, Spain, and Sweden. Sarcoma 2013, 2013, 1–19. [CrossRef]
41. Carvalho, C.; Santos, R.; Cardoso, S.; Correia, S.; Oliveira, P.; Santos, M.; Moreira, P. Doxorubicin: The Good, the Bad and the Ugly Effect. Curr. Med. Chem. 2009, 16, 3267–3285. [CrossRef]
42. Kucukoglu, K.; Tugrak, M.; Demirtas, A.; Sakagami, H.; Gul, H.I. Synthesis and Cytotoxic Activity of (4-Substituted-benzylidene) -(3-Phenyl-1,2,4-Oxadiazol-5-YL) Methylamines. Pharm. Chem. J. 2016, 50, 234–238. [CrossRef]
43. Moniot, S.; Forgione, M.; Lucidi, A.; Hailu, G.S.; Nebbioso, A.; Carafa, V.; Baratta, F.; Altucci, L.; Giacché, N.; Passeri, D.; et al. Development of 1,2,4-Oxadiazoles as Potent and Selective Inhibitors of the Human Deacetylase Sirtuin 2: Structure–Activity Relationship, X-ray Crystal Structure, and Anticancer Activity. J. Med. Chem. 2017, 60, 2344–2360. [CrossRef] [PubMed]
44. Avanzo, R.E.; Padrón, J.M.; D'Accorso, N.B.; Fascio, M.L. Synthesis and in vitro antiproliferative activities of (5-aryl-1,2,4-oxadiazole-3-yl) methyl D-ribofuranosides. Bioorg. Med. Chem. Lett. 2017, 27, 3674–3677.[CrossRef] [PubMed]
45. Avanzo, R.E.; Anesini, C.; Fascio, M.L.; Errea, M.I.; D'Accorso, N.B. 1,2,4-Triazole D-ribose derivatives: Design, synthesis and antitumoral evaluation. Eur. J. Med. Chem. 2012, 47, 104–110. [CrossRef]
46. Abd el hameid, M.K.; Mohammed, M.R. Design, synthesis, and cytotoxicity screening of 5-aryl-3-(2-(pyrrolyl) thiophenyl)-1, 2, 4-oxadiazoles as potential antitumor molecules on breast cancer MCF-7 cells. Bioorg. Chem. 2019, 86, 609–623. [CrossRef]
47. de Oliveira, V.N.M.; dos Santos, F.G.; Ferreira, V.P.G.; Araújo, H.M.; do Ó Pessoa, C.; Nicolete, R.; de Oliveira, R.N. Focused microwave irradiation-assisted synthesis of N-cyclohexyl-1,2,4-oxadiazole derivatives with antitumor activity. Synth. Commun. 2018, 48, 2522–2532. [CrossRef]
48. Pervaram, S.; Ashok, D.; Sarasija, M.; Reddy, C.V.R.; Sridhar, G. Synthesis and Anticancer Activity of 1,2,4-Oxadiazole Fused Benzofuran Derivatives. Russ. J. Gen. Chem. 2018, 88, 1219–1223. [CrossRef]
49. Chakrapani, B.; Ramesh, V.; Pourna Chander Rao, G.; Ramachandran, D.; Madhukar Reddy, T.; Kalyan Chakravarthy, A.; Sridhar, G. Synthesis and Anticancer Evaluation of 1,2,4-Oxadiazole Linked Imidazothiadiazole Derivatives. Russ. J. Gen. Chem. 2018, 88, 1020–1024. [CrossRef]
50. Krasavin, M.; Shetnev, A.; Sharonova, T.; Baykov, S.; Tuccinardi, T.; Kalinin, S.; Angeli, A.; Supuran, C.T. Heterocyclic periphery in the design of carbonic anhydrase inhibitors: 1,2,4-Oxadiazol-5-yl benzenesulfonamides as potent and selective inhibitors of cytosolic hCA II and membrane-bound hCA IX isoforms. Bioorg. Chem. 2018, 76, 88–97. [CrossRef]

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51. Krasavin, M.; Shetnev, A.; Sharonova, T.; Baykov, S.; Kalinin, S.; Nocentini, A.; Sharoyko, V.; Poli, G.; Tuccinardi, T.; Presnukhina, S.; et al. Continued exploration of 1,2,4-oxadiazole periphery for carbonic anhydrase-targeting primary arene sulfonamides: Discovery of subnanomolar inhibitors of membrane-bound hCA IX isoform that selectively kill cancer cells in hypoxic environment. Eur. J. Med. Chem. 2019, 164, 92–105. [CrossRef] [PubMed]
52. Krasavin, M.; Korsakov, M.; Dorogov, M.; Tuccinardi, T.; Dedeoglu, N.; Supuran, C.T. Probing the 'bipolar' nature of the carbonic anhydrase active site: Aromatic sulfonamides containing 1,3-oxazol-5-yl moiety as picomolar inhibitors of cytosolic CA I and CA II isoforms. Eur. J. Med. Chem. 2015, 101, 334–347. [CrossRef] [PubMed]
53. Yang, F.; Shan, P.; Zhao, N.; Ge, D.; Zhu, K.; Jiang, C.s.; Li, P.; Zhang, H. Development of hydroxamate-based histone deacetylase inhibitors containing 1,2,4-oxadiazole moiety core with antitumor activities. Bioorg. Med. Chem. Lett. 2019, 29, 15–21. [CrossRef] [PubMed]
54. Yang, Z.; Shen, M.; Tang, M.; Zhang, W.; Cui, X.; Zhang, Z.; Pei, H.; Li, Y.; Hu, M.; Bai, P.; Chen, L. Discovery of 1,2,4-oxadiazole-Containing hydroxamic acid derivatives as histone deacetylase inhibitors potential application in cancer therapy. Eur. J. Med. Chem. 2019, 178, 116–130. [CrossRef]
55. Querfurth, H.W.; LaFerla, F.M. Alzheimer's Disease. N. Engl. J. Med. 2010, 362, 329–344. [CrossRef]
56. Sterling, J.; Herzig, Y.; Goren, T.; Finkelstein, N.; Lerner, D.; Goldenberg, W.; Miskolczi, I.; Molnar, S.; Rantal, F.; Tamas, T.; et al. Novel Dual Inhibitors of AChE and MAO Derived from Hydroxy Aminoindan and Phenethylamine as Potential Treatment for Alzheimer's Disease. J. Med. Chem. 2002, 45, 5260–5279. [CrossRef]
57. Zhang, J.; Li, J.C.; Song, J.L.; Cheng, Z.Q.; Sun, J.Z.; Jiang, C.S. Synthesis and evaluation of coumarin/1,2,4-oxadiazole hybrids as selective BChE inhibitors with neuroprotective activity. J. Asian Nat. Prod. Res. 2019, 21, 1090–1103. [CrossRef]
58. Jiang, C.S.; Fu, Y.; Zhang, L.; Gong, J.X.; Wang, Z.Z.; Xiao, W.; Zhang, H.Y.; Guo, Y.W. Synthesis and biological evaluation of novel marine-derived indole-based 1,2,4-oxadiazoles derivatives as multifunctional neuroprotective agents. Bioorg. Med. Chem. Lett. 2015, 25, 216–220. [CrossRef]
59. Huang, Y.S.; Lu, H.L.; Zhang, L.J.; Wu, Z. Sigma-2 Receptor Ligands and Their Perspectives in Cancer Diagnosis and Therapy. Med. Res. Rev. 2014, 34, 532–566. [CrossRef]
60. Cao, X.; Yao, Z.; Dou, F.; Zhang, Y.; Qiu, Y.; Zhao, S.; Xu, X.; Liu, X.; Liu, B.; Chen, Y.; et al. Synthesis and Biological Evaluation of Sigma-1 (s1) Receptor Ligands Based on Phenyl-1,2,4-oxadiazole Derivatives. Chem. Biodivers. 2019, 16, e1800599. [CrossRef] [PubMed]
61. Ge, L.; Guyatt, G.; Tian, J.; Pan, B.; Chang, Y.; Chen, Y.; Li, H.; Zhang, J.; Li, Y.; Ling, J.; et al. Insomnia and risk of mortality from all-cause, cardiovascular disease, and cancer: Systematic review and meta-analysis of prospective cohort studies. Sleep Med. Rev. 2019, 48, 101215. [CrossRef]
62. de Lecea, L.; Kilduff, T.S.; Peyron, C.; Gao, X.B.; Foye, P.E.; Danielson, P.E.; Fukuhara, C.; Battenberg, E.L.F.; Gautvik, V.T.; Bartlett, F.S.; et al. The hypocretins: Hypothalamus-specific peptides with

neuroexcitatory activity. Proc. Natl. Acad. Sci. USA 1998, 95, 322–327. [CrossRef]

63. Dubey, A.; Handu, S.; Mediratta, P. Suvorexant: The first orexin receptor antagonist to treat insomnia. J. Pharmacol. Pharmacother. 2015, 6, 118. [CrossRef] [PubMed]
64. Jacobson, L.H.; Callander, G.E.; Hoyer, D. Suvorexant for the treatment of insomnia. Expert Rev. Clin. Pharmacol. 2014, 7, 711–730. [CrossRef] [PubMed]
65. Brotschi, C.; Roch, C.; Gatfield, J.; Treiber, A.; Williams, J.T.; Sifferlen, T.; Heidmann, B.; Jenck, F.; Bolli, M.H.; Boss, C. Oxadiazole Derivatives as Dual Orexin Receptor Antagonists: Synthesis, Structure–Activity Relationships, and Sleep-Promoting Properties in Rats. ChemMedChem 2019, 14, 1257–1270. [CrossRef]
66. Boss, C.; Roch-Brisbare, C.; Steiner, M.A.; Treiber, A.; Dietrich, H.; Jenck, F.; von Raumer, M.; Sifferlen, T.; Brotschi, C.; Heidmann, B.; et al. Structure-Activity Relationship, Biological, and Pharmacological Characterization of the Proline Sulfonamide ACT-462206: A Potent, Brain-Penetrant Dual Orexin 1/Orexin 2 Receptor Antagonist. ChemMedChem 2014, 9, 2486–2496. [CrossRef

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