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Review article

Novel 1,3,4-Oxadiazole Hybrids with Antitumor and Anti-proliferative Potentials

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ABSTRACT

Cancer is a lethal illness, and research into the development of effective anti-cancer medications is ongoing at all hours of the day and night. This is where 1,3,4-oxadiazoles come into play, since they are privileged and authenticated compounds because of their anti-cancer capabilities. In the field of drug development, 1,3,4-oxadiazole entities are characteristic heterocyclic rings with dominant anti-cancer activities. As a result, the primary goal of this article is to review the synthesis and screening of new 1,3,4-oxadiazole powerful derivatives is to determine their anti-cancer, antitumor, and other potential applications in the creation of anti-neoplastic drugs. In this study, the focus is on the 1,3,4-oxadiazole hybrids as well as the most significant bioactivity and potentiality of these anti-cancer compounds. This review article will include references to significant current reviews in the material, as well as a relevant discussion on the general background of anti-cancer medications that include 1,3,4-oxadiazole hybrids.

Keywords: 1,3,4-Oxadiazole, Anti-cancer, Antitumor, Antiproliferative, Heterocycle, Activities

INTRODUCTION

Restorative science relies heavily on heterocycles. The heterocycles are explored first because of their crucial natural activity. The N=C=O heterocycle, 1,3,4-oxadiazole has a pleasant aroma. It comes in a variety of isomeric forms and comprises one oxygen molecule and two nitrogen molecules. The organic features of 1,3,4-oxadiazole subordinates are significant. Antimicrobial, mitigating, anti-cancer, cancer preventive agent, antiviral, and antidiabetic are just few of the many uses for this compound. Ataluren, an anti-cystic fibrosis treatment; Tiodazosin, and Nesapidil used as antihypertensive drugs; and Zabotentan, a last-ditch clinical trial therapy, are all examples of oxadiazole derivatives found in marketed pharmaceuticals. Additionally, 1,3,4-oxadiazole is used in material science. With a variety of actions, such as development factors, proteins, kinases, etc., 1,3,4-oxadiazole subordinates have demonstrated essential enemy of disease potential. 1,3,4-oxadiazoles have been shown to be effective in the fight against cancer in recent years, according to an audit article. Heterocycles, as well, are a major focus in the development of new materials and agricultural chemicals. When it comes to creating complex, individual sub-atomic platforms, however, the use of actual designed systems sometimes requires several steps and high energy consumption, or lacks repeatability and adaptability. Because of this, the need for more advanced economic norms for the specialized functionalization of various nitrogen-containing heterocyclic frameworks remains very pressing [1].

Chemoselective functionalization of 1,3,4-oxadiazoles, despite several instances, is undoubtedly less studied. Methods for C-C bond arrangement on the furoxan ring have recently been devised.

It is also unknown whether or not an appropriate heteroatom linker can help stabilize a desirable pharmacophore onto the 1,3,4-oxadiazole ring. Impediments to ring cleavage caused by direct nucleophilic substitution of alternative leaving groups at the 1,3,4-oxadiazole theme include the principal features of the two substrates and probable side reactions. Lately, the natural combination of 1,3,4-oxadiazolyl diazonium salts was offered as an aid in comparing or bringing together the (1,3,4-oxadiazolyl) azasydnone mixture. 1,3,4-oxadiazolyl diazonium salts have been proposed as ancestors of rarely open hydrazines, according to a couple [2]. However, even at the time, there was no instant way for determining the age of (furazanyl)-hydrazines. Because of the enlarged electron-inadequate character of the ring and its oxidative capacity, their furoxan analogues are also far away. That's why it's so appealing to develop the ability of 1,3,4-oxadiazolyl diazonium salts to directly attach pharmacologically relevant functionality to the 1,3,4-oxadiazole subunit. Using this process, the diazotization, reduction, and building of amino1,3,4-oxadiazoles unites hitherto elusive N-(1,3,4-oxadiazolyl)-hydrazones. Over the last decade, researchers have discovered a wide range of cancer-fighting and other ailments treating properties in 1,3,4-oxadiazoles, with a particular emphasis on the previous decade [3].

Figure 1: Structure of 1,3,4-oxadiazole

Understanding Cancer with Perspective of Biology

Neoplasia is a medical term that refers to "new development." According to the British oncologist R. A. Willis, a neoplasm is "an extraordinary mass of tissue whose growth outpaces and is ungraceful in comparison with that of the normal tissues and which persists in a same extravagant manner after the cessation of the stimuli that elicited the change." In the same way, in clinical practice, a tumor is usually referred to as a cancer, and the study of tumors is referred to as oncology (oncos = cancer, and logos = research of). In light of a neoplasm's expected clinical behavior, it is possible to divide it into two categories: those that are innocuous and those that are dangerous. Generally, a cancer is considered harmless when its minute and gross characteristics are viewed as moderately guiltless, implying that it will remain limited, that it will not spread to other locations, and that it will be amenable to nearby careful expulsion; the patient is expected to make it through. Malignant growths, which are derived from the Latin word meaning crab, are used to refer to all types of harmful tumors [4].

Malignant development is a word that refers to a large collection of more than 100 various disorders that originate when deviations from normal physiological regulation produce intemperate expansion of atypical cells. Majority of the time, these clonal cells congregate and multiply, becoming malignancies that pack, assault, and eradicate ordinary tissue, weakening the body's essential parts and resulting in devastating consequences such as loss of personal pleasure and death. When used to a neoplasm, the term "harmful" implies that the sore has the ability to assault and destroy neighboring designs as well as spread to distant locations (metastasize) and cause passing. Not all malignant tumors aspire to take such a fatal course of action. The assignment detrimental has a red flag even if others are less strong and are dealt with properly [5].

A disease outbreak is the most common cause of mortality in economically developed countries, and it is the leading cause of death in agriculturally based countries. GLOBOCAN 2008 estimates that about 12.7 million malignant growth cases and 7.6 million malignant growth deaths occurred in 2008, with 56 percent of cases and 64 percent of deaths occurring in the economically developing countries. Among females, bosom illness is the most often diagnosed malignant growth and the most common cause of malignant growth passing. It accounts for 23 percent of all malignant growth cases and 14 percent of all malignant growth passings [6]. Cellular breakdown in the lungs is the most common illness location in men, accounting for 17 percent of all new malignant growth cases and 23 percent of all disease-related death cases. Despite the fact that the occurrence rates of malignant growth in the creating scene are a significant component of those observed in the created world in both genders, the overall illness mortality rates are remarkably similar [7]. Following a field investigation, it was discovered that adults aged 30-69 years account for 71 percent of disease-related deaths in India. Oral cancer (22.9 percent), stomach cancer (12.6 percent), and lung cancer (1T4 percent) are the three most common fatal illnesses in males, whereas malignant growths in the cervix (17.1 percent), stomach (14.1 percent), and bosom (10.2 percent) are the most common in women [8].

Significant advances have been made in the understanding of subatomic science and the hereditary characteristics of malignant growth cells, as well as the recognition of the infection as a fundamental example, which has opened up a new system for the development of innovative methodologies in disease treatment. The specific method utilized to treat malignant growth is dependent on the specific kind, location, and stage of the illness being treated. The treatment of malignant development may be accomplished via a variety of strategies, each with its own set of advantages. These include medical procedures, radiation therapy, immunologic therapy, and synthetic-based treatments, among others. The majority of the time, a combination of these tactics is used, with a substance component included in the majority of the most beneficial approaches

to illness treatment [9].

Despite the fact that malignant growth was recognized as an infection as far back as 1500 B.C., and despite the fact that natural treatments for disease were documented in numerous antiquated clinical works, the use of medications in malignant growth treatment had not been widely accepted until the 1930s, according to the American Cancer Society. Around a century ago, the use of androgens and estrogens in the treatment of bosom and prostatic tumors, as well as other types of neoplastic development, in conjunction with the adjustment of the hormonal state of malignant growth patients, was first introduced. Shortly after that, the discovery of anti-leukemic movement by the use of nitrogen mustards and folic acid analogs was made public. Up to this point, a few thousand synthetic chemicals as well as a variety of everyday products have been tested for their biological effects [10].

Despite the large number of readily available chemotherapeutic anti-neoplastic experts, the clinical demand for these specialists is still largely unmet. The primary reasons are as follows: the lack of selectivity in conventional medications, resulting in poisonousness; the metastatic spread, resulting in early growth implantation in organs other than the essential site; the heterogeneity of the infection, involving approximately 100 different types of disease; and the natural or procured protection from chemotherapy, resulting in multi-drug resistance after only a few beneficial cycles, for example [11].

It is always changing how we deal with illness therapy and the fundamental methods for doing so. The investigation of sub-atomic targets, hereditary remedies, controls of the invulnerable framework, stimulation of typical hematopoietic components, acceptance of separation in growth tissue, and hindrance of angiogenesis are currently being pursued in clinical conventions. For a variety of reasons, consistent with the novel aspects of anticipated inventive professionals, the significance of their restorative work in diverse types of sickness will most likely take many years to become clear. On the one hand, the atomic selectivity itself may necessitate a greater use of growth genotyping to guide drug selection, which may in any case address the issue of cancer hereditary instability. The atomic selectivity itself may necessitate a greater use of growth genotyping to guide drug selection [12].

Because a significant number of these sub-atomic objective-based medications are likely to have cytostatic rather than cytotoxic effects, the conventional clinical procedures for evaluating chemotherapeutic medications, which are based on cancer shrinkage at the most extreme endured portion, may not be appropriate, and other explicit proxy end-points should be considered [13]. It is the disheartening stage-III preliminary studies performed with a few network metallo proteinases inhibitors that has brought to light the fact that standard clinical preliminary endpoints are lacking for the assessment of sub-atomic designated cytostatic specialists. This is an important illustration that emerges from the dismal stage-III preliminary studies performed with a few network metalloproteinases inhibitors [14].

The 1,3,4-oxadiazole ring structure may be found in a variety of anti-cancer drugs, including Zibotentan, a well-known enemy of malignant development agent used in chemotherapy treatment that contains the 1,3,4-oxadiazole ring frameworks. It fills in as a bioisosteric substitute for amide, increases ester accumulation, and increases the lipophilic characteristic of the particle. A variety of organic properties have been discovered in 1,3,4-Oxadiazoles, including anti-cancer activity, histone deacetylase inhibitor, and MetAP2 inhibitor, as well as antimicrobial, calming, tubercular resistance, antidiabetic, antiproliferative, antidepressant, and anti-nervousness properties. It is possible to shape solid hydrogen holding particles in the human body to produce improved medication activity [15].

1,3,4-Oxadiazoles as anti-cancer agents

1,3,4-Oxadiazole hybrids with five-membered heterocycles

1,3,4-Oxadiazole-imidazole hybrids

Hybrid oxadiazole benzimidazole compounds showed anti-cancer efficacy against a panel of 60 human cell lines, according to Asif *et al*. To our surprise, we found that hybrid **(1)** was able to limit growth by a whopping 32% at only 10 micrograms. HCT-15 colon cell line had a GI50 value more than 100, whereas all other cell lines examined had a GI50 value of 0.49-48.0 μM for the chemical. GI50 values were from 2.89-4.94 μM for all the examined leukaemia cancer cell lines for sensitivity. Compound GI50 = 0.499 nM, TGI = 19.9 nM, LC50 = >100 nM for HOP-92 cell-line and GI50 = 27.6 nM, TGI = >100 nM, LC50 >100 nM for A549/ATCC cell line in non-small cell lung cancer. Also, the GI50 value for the ovarian cancer subpanel was in the range of 2.60-29.4 μM. Additional cell lines evaluated were breast cancer, renal cancer, prostate cancer, melanoma cancer, and the CNS cancer subpanel. The chemical showed modest effectiveness against these other cell lines. When tested against various cell lines, the SAR (structure–activity relationship) showed that electron-withdrawing group (Bromo) on aromatic ring increased activity while electron-releasing group (–OH) decreased it. Cell lines with an unsubstituted phenyl ring were found to be 87.22 percent sensitive. The electron-withdrawing group on the aromatic ring linked to the oxadiazole ring was shown to have a considerable impact on the activity of the compound [16].

1,3,4-Oxadiazole-indole hybrids

Using the cancer cell lines HeLa, IMR-32, and MCF-7, Gudipati *et al*. discovered a series of 1,3,4-oxadiazole derivatives

with an indoline moiety. The compounds were then tested for anti-tumor activity. Compared to IMR-32 and MCF-7 cell lines, the HeLa cell line showed greater sensitivity to the investigated hybrids, as seen by the results. Compound **(2)** was more active against the HeLa cell line than cisplatin (IC_{50} = 14.08 µM). The hybrid has IC_{50} value of 13.48 µM for the IMR-32 cell line. Cisplatin was shown to be the most effective treatment for the MCF-7 cell line. For example, electron-withdrawing groups like F, Cl and Br were effective against all three cell lines in the SAR investigation [17].

1,3,4-Oxadiazole-pyrazole hybrids

1,3,4-oxadiazole-pyrazole hybrids showed anti-cancer efficacy against the MCF-7 and HEPG2 cell lines, according to Abu-Zaied *et al.* When tested against the MCF-7 and HEPG2 cell lines, thioglycoside derivative **(3)** showed the greatest level of cytotoxicity with IC_{50} values of 2.67 µg/mL and 4.62 µg/mL, respectively. Oxadiazole-thioglycoside hybrids with active sugars (IC_{50} 9-44.6 µg/mL) were more hazardous than those without active sugars (IC_{50} 9-43.6 µg/mL). In dosages up to 500 mg/kg of animal body weight, none of the tested substances displayed any toxicity. Active sugar moiety promotes activity, but the non-activated sugar oxadiazole rings diminish activity [18].

1,3,4-Oxadiazole-triazole hybrids

Inhibitors of the focal adhesion kinase (FAK) 1,3,4-oxadiazole derivatives with a triazole moiety were shown to have anti-cancer action by Zhang *et al.*Anti-cancer activity against the MCF-7 and HT29 cell lines was tested in all hybrids using the gold standard of cisplatin. Cisplatin had an IC_{50} of 11.20 µM, while hybrid had a lower IC_{50} of 5.68 µM, making it the most powerful cytotoxic agent against the MCF7 cell line. Compounds had a mild effect on the MCF7 cell line (IC_{50} = 8.25 µM-10.75 µM) as well. Cisplatin (IC_{50} = 15.83 µM) had the best activity against the HT29 cell line, with an IC_{50} value of 10.21 µM. When compared to cisplatin (8.6 µM), the FAK inhibitory activity of hybrid **(4)** was much higher (1.2 µM). Flow cytometry was used to investigate the hybrid's mode of action. As much as 1 µg/mL, 5 µg/mL, 10 µg/mL, and 20 µg/mL of the hybrid's anti-MCF7 activity were examined. There was an increase in apoptosis as measured by Annexin V-FITC/PI staining of 14.27 percent, 28.09 percent, 46.91 percent, and 61.29 percent at 1 µg/mL, 5 µg/mL, 10 µg/mL, and 20 µg/mL of the chemical. The best anti-cancer drug, which functions as FAK inhibitors, was revealed to be a hybrid. Researchers found that hybrids with electron-donating groups were less active than hybrids with electron-withdrawing groups. The order of electron-withdrawing groups in terms of potency was –F > –Cl > –Br > –NO2 > –CH3. As a result, the activity of electron-withdrawing groups was lowered in order ortho, meta, and para [19].

1,3,4-Oxadiazole-thiazole derivatives

1,3,4-oxadiazole compounds with various heterocyclic moieties (thiazole, pyrazole, coumarin, and naphthoxazines) were shown to be anti-cancer by Bondock *et al*. Thiazole-based hybrid **(5)** was the most effective against all cell lines (HepG2, WI-38, VERO, and MCF-7) examined. A similar 1,3,4-oxadiazole derivative lacking the heterocyclic moiety demonstrated excellent efficacy in the range of 21.2–39.2 µg/mL. Thiazolidin-5-one and naphtho[2,1-b][1,4]oxazine (IC_{50} = 145.6–410.6 µg/mL) were replaced with thiazolidin-5-one to lower the activity against all cell lines. Also, the hybrid showed a high level of resistance to DNA damage generated by the bleomycineiron complex, thereby reducing the synthesis of chromogen between the damaged DNA and thiobarbituric acid (TBA) [20].

1,3,4-Oxadiazole-thiazolidine-2,4-dione hybrids

1,3,4-oxadiazole-2,4-dione derivatives were tested for anti-cancer efficacy against the MCF-7 cell line by Asati and his colleagues. One of the investigated compounds had a GI_{50} value of 0.004 µM and shown significant action against the MCF-7 cell line. In contrast, certain hybrids exhibited modest activity (IC_{50} = 10.0 µM - 77.0 µM) with GI_{50} values. According to the SAR analysis, the phenyl ring was shown to be more active when it had more halogens than when it had less. When it came to the anti-proliferative action, electron-withdrawing groups (–Cl, –Br, I) from the phenyl ring outperformed electron-donating groups (2-CH_3). As a result, hybrids containing trichloro or trifluoro groups lacked strong action, indicating the phenyl ring's significance. The antitumor activity of the molecule containing an electron-donating amine group was modest [21].

1,3,4-Oxadiazole-thiadiazole hybrids

Fourteen 1,3,4-thiadiazole-modified 1,3,4-oxadiazole derivatives were examined for anti-cancer activity *in vitro* against the A549, SMMC7721, and MCF-7 cell lines. It was found that the cell line SMMC-7721 was very sensitive to hybrid **(7)** and the MCF-7 control cell line. The hybrid also had the highest IC_{50} values (4.11 µM) against the A549 cell line. While the identical electron-releasing groups (–CH_3 and OCH_3) were shown to increase activity against SMMC-7721 cells in the SAR analysis, they were found to inhibit activity when located at meta positions of the phenyl rings. At para position, OCH_3 and NO_2 considerably increased the antiproliferative activity, although F, Cl, and OCH_3 (at meta position) had no significant impact on the activity against the MCF-7 cell line. All other substituents increased cell proliferation, but unsubstituted and 4-nitro substituted phenyl rings had the strongest activity. The inclusion of both electron-withdrawing and electron-releasing groups enhanced the activity against SMMC-7721 and MCF-7 cell lines, according to these data. For the A549 cell line, the unsubstituted

phenyl ring was shown to be more effective than the substituted hybrids in increasing activity [22].

1,3,4-oxadiazole-pyrrole hybrids

1,3,4-oxadiazole derivatives with the pyrrolobenzodiazepine moiety were tested against a variety of cancer cell lines for their anti-cancer properties. The GI50 values of all hybrids ranged from 0.1 to 0.29 µM, which is a high level of anti-cancer activity. Cell viability assays were performed on the produced hybrids **(8)** to examine the anti-cancer efficacy of these drugs. In the A375 cell line, the hybrid caused apoptosis up to 36.66 percent (at 4 µM). Compared to the DC-81, which had 15.33 percent apoptotic cells, these hybrids caused apoptosis successfully. In addition, the number of cells in the A375 cells reduces in the G2/M phase. Western blot analysis was used to examine the influence of these hybrids on the p53, p21, and pRb dependent apoptosis pathway in A375 cells. The protein levels in compound increased significantly, contributing to the cell cycle being halted in the G1 phase. Pro-apoptotic proteins like Bax have been elevated in these hybrids, resulting in higher levels of the cytochrome c protein. The DNA repair enzyme is cleaved by caspase-3, which is activated by an elevated amount of cytochrome-c in the hybrid. Cell cycle arrest was confirmed by a substantial reduction in Cdk2 protein levels in the hybrid, which supports the G1/S transition blockage. The hybrid was shown to slow tumour development *in vivo* and to be non-toxic to test animals. All of these studies show that these hybrids have intriguing anti-cancer capabilities [23].

1,3,4-Oxadiazole-podophyllotoxin hybrids

On a panel of cancer cell lines, a novel class of anti-cancer 1,3,4-oxadiazole derivatives with podophyllotoxin moiety was tested. HepG2 and HeLa cell lines (IC_{50} = 1.51 µM and 2.68 µM, respectively) were more sensitive to **(9)** than podophyllotoxin (IC_{50} = 17.94 µM and 18.82 µM, respectively) among the investigated substances. Compared to industry standards like podophyllotoxin, etoposide, and 5-FU, the hybrid exhibited superior selectivity against the Vero and L929 cell lines. Another aspect of anti-tumor activity that was examined by the investigators was that of free hydroxyl groups. A demethylated hybrid exhibited less anti-cancer activity than the, which suggested that free–OH groups do not have an impact on activity. HepG2 cells' cell cycle was stopped in S-phase by the hybrid, according to a Flow cytometry study. The western blot approach was used to investigate the compound's mechanism of action. DNA topoisomerase II expression was effectively suppressed by **(9)**, which subsequently hindered cell growth. An alkyl group (–CH3) or oxadiazole ring substituents had a good influence on anti-cancer profile, according to the SAR, but aromatic ring substituents had an adverse effect on activity. Using free –OH groups instead of methoxy substitutes lowered the activity against the cell lines examined [24-25].

1,3,4-Oxadiazole-carbolines hybrids

There were seven cancer cell lines (MCF-7, NCI-ADR/RES, NCI-H460; OVCAR-03; PC-3; UACC62) that Savariz *et al*. tested a variety of 1,3,4 oxadiazole derivatives with carbolines moiety. For comparison, doxorubicin had a GI_{50} value between 0.05 µM and 0.13 µM, whereas the hybrid **(10)** was the most active, with values between 0.67 µM and 3.20 µM. Anti-cancer activity was enhanced by N-dimethyl groups at the para-position of the phenyl ring, while the nitro and the hydroxyl groups were found to have a detrimental effect. Similar to the positive control, N-substituted oxadiazole showed no action. According to the results of the fluorescence quenching experiment and the competition test, **(10)** had a substantial intercalative binding contact with the ctDNA [26].

1,3,4-Oxadiazole-purine hybrids

A novel family of oxadiazole derivatives bearing purine ring **(11)** was produced and evaluated for anti-cancer efficacy against Huh7 (human liver cancer) cell line. The most active molecule was determined to have a cell viability of 53.58 at a concentration of 100 µg/mL to have a 4-chloro-phenyl ring hybrid. A para-chloro substituent on the phenyl ring was shown to be the most active molecule, whereas chloro substitutions on the ortho and meta positions of the ring were found to be the least effective. The investigated cell lines did not interact in an intriguing way with the fluoro substituent present (cell viability = 130.86).

1,3,4-Oxadiazole-diosgenin hybrids

Twelve diosgenin compounds with a 1,3,4-oxadiazole ring were tested for anti-cancer efficacy by Zhang *et al*. Tomitomycin C's IC_{50} was 20.37 µM to >100 µM for all hybrids, indicating mild to moderate activity by comparison. Compounds having large aromatic rings were shown to be less active than the methyl-substituted molecule in the SAR study. Because of their free –OH group, deacetylated oxadiazole derivatives **(12)** outperformed acetylated derivatives in terms of cancer cell growth inhibition [27].

1,3,4-Oxadiazole hybrids with six-membered heterocycles

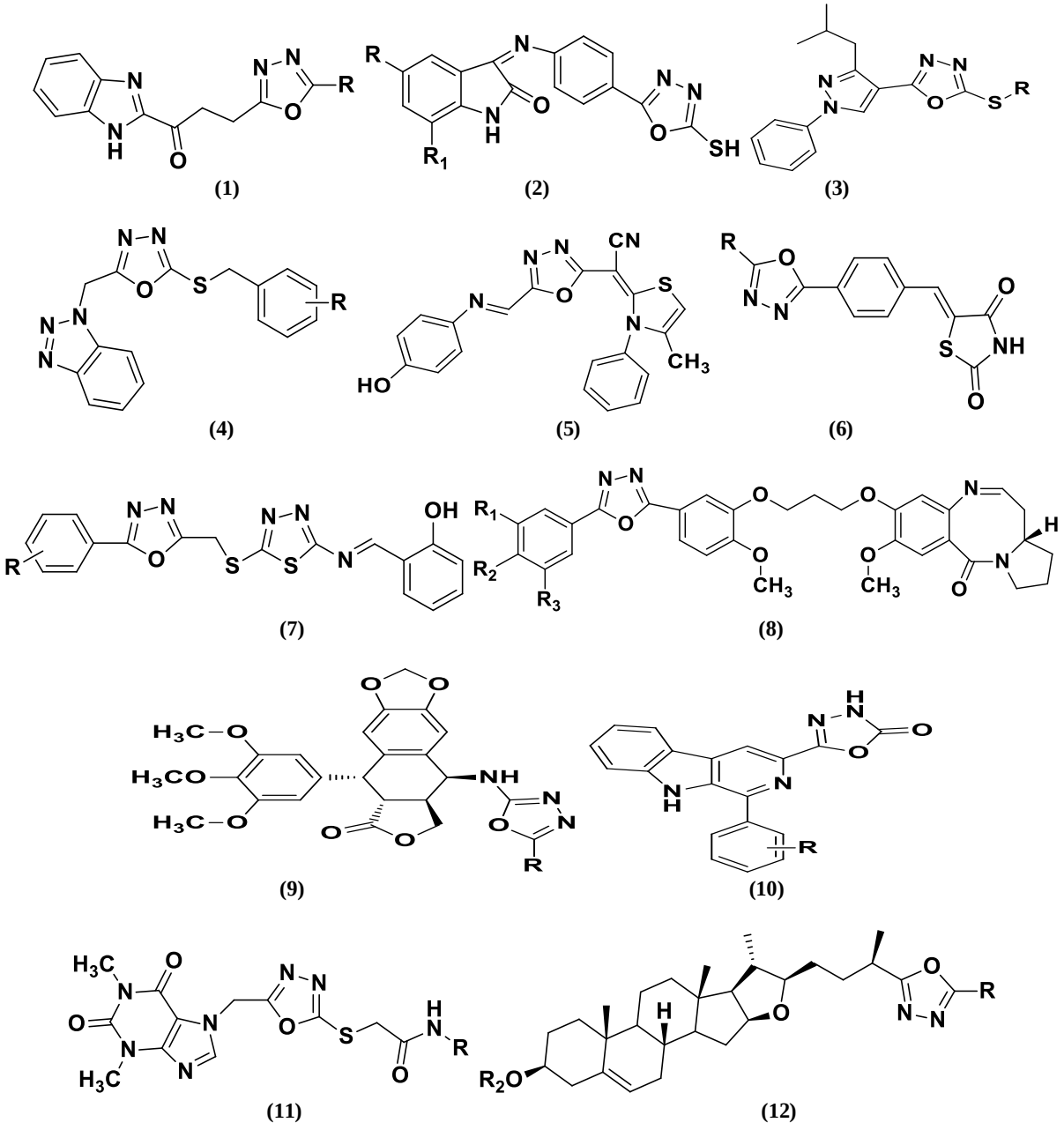
1,3,4-Oxadiazole-pyridine hybrids

New 1,3,4-oxadiazole compounds were tested against SGC-7901 to see whether they have anti-cancer properties (gastric cell). Only the **(13)** hybrid had IC_{50} values of 1.61 µg/mL and was more active than the positive control (5-Fluorouracil). The ability of the hybrids to suppress telomerase was examined. Ethidium bromide was found to be ineffective in comparison to the hybrid (IC_{50} = 2.5 µM), whereas the hybrid was shown to be much more effective. The SAR analysis found that electron-donating groups in the phenyl ring's para position increased activity, whereas the identical groups in the ortho position lowered activity. This is consistent with previous findings. Similarly, halogen atoms with para-substituted halogens

rather than ortho-substituted halogens exhibited more activity.

Anti-cancer activity was unaffected by substituting the para position of the phenyl ring with hydroxyl, but a hybrid with a 2-OH and 4-OCH_3 substituent was determined to be the most active. The 1-naphthyl group in the hybrid was more active than the pyridine, furan, and thiophene moiety in the other hybrids. As a result, anti-cancer activity is influenced by changes to the phenyl ring's aromatic ring [28-29].

Figure 2 (A): Novel 1,3,4-Oxadiazole hybrids with five-membered heterocycles.



1,3,4-Oxadiazole-quinoline hybrids

HepG2, SGC-7901, and MCF-7 cell lines were tested by Sun and colleagues for anti-cancer activity of 1,3,4-oxadiazoles containing a quinolone moiety. With IC_{50} values ranging from 1.2 nM to 20.7 μM, the fluoro substituted hybrids demonstrated the most potency against all three cell lines. For all cell lines investigated, the para-chloro substituted hybrid **(14)** had IC_{50} values of 0.8 to 7.6 μM. The hybridalso has an impressive IC_{50} value of 0.9 μM for telomerase inhibition. The anti-cancer activity of the compounds was increased by hybrids containing halogens, according to the results of the SAR research. Fluorine-substituted hybrids had potency in the order ortho > meta > para, while chloro-substituted hybrids had potency ortho > meta > para. The least active halogens were bromine-substituted hybrids [30].

1,3,4-Oxadiazole-1,4-benzodioxane hybrids

A series of 1,4-benzodioxane moiety carrying 1,3,4-oxadiazole derivatives, synthesized by Zhang *et al.*, was shown to be very effective against cancer. Cancer cell lines (HEPG2, HeLa, SW1116, and BGC823) were most sensitive to hybrids, with IC_{50} values ranging from 7.21 to 25.87 μM. With an IC_{50} value of 7.21

μM, hybrid **(15)** was shown to be effective against the HEPG2 cell line. In addition, the hybrid showed superior telomerase inhibitory action than staurosporine (IC_{50} = 8.32 μM). It was found that the order of potency for *ortho* and *para*-substituted halogens was as follows: –I > –Br > –Cl > –F, respectively. The potency of hybrids with electron-donating methyl groups ranged from *ortho* to *meta* to *para* in the sequence of potency [31-32].

1,3,4-Oxadiazole-piperazine hybrids

Hybrids of 1,3,4-oxadiazole and piperazine **(16)** have been shown to suppress HIF-1. One of the most potent inhibitors of HIF-1, with an IC_{50} value of 38.1 μM, was a hybrid oxadiazole with a meta-bromo and ortho-chloro group. However, the IC_{50} values for these other chemicals ranged from 46.1 μM to 70.2 μM. It was shown that other hybrids in the series were less active, with an IC_{50} of more than 100 μM. There was no significant anti-cancer activity in any of the hybrids evaluated against HCT116 cell lines (IC_{50} = >100 μM) compared to ursolic acid (IC_{50} = 23.8 μM), despite all of the compounds being tested for cytotoxicity. Unsubstituted phenyl rings were shown to be more active than substituted phenyl rings in the SAR research. Meta-bromo substituted hybrids were more active than ortho-bromo substitutes in halogens, while ortho substituents were more active than para-substituents in chloro substituted hybrids. Substitutions that provide electrons (–CH_3 and –OCH_3) reduce hybrids' anti-cancer activity [33].

1,3,4-Oxadiazole-monastrol hybrids

According to Ragab and associates, 1,3,4-oxadiazole-monastrol derivatives **(17)** demonstrated antitumor activity in a panel of 60 cell lines. Growth inhibition was seen in leukaemia cell lines (HL-60(TB) and MOLT-4). In order to determine the inhibitory concentration (IC_{50}) of these hybrids, monastrol was utilised as a positive control. It was found that monastrol, which had the lowest IC_{50} value of 0.147 μM and 0.215 μM for HL-60(TB) and MOLT-4, respectively, was sensitive to hybrids. When it comes to the MOLT-4 cell line, hybrid has an IC_{50} of 0.086 μM. Similar IC_{50} values of 0.103 μM were discovered for the most active cell line, the HL-60(TB) line of researches. Hybrids prevented cells from entering the G2/M phase of the cell cycle, which led to cell death, according to a study of cell cycles. While monastrol (0.294 μM) only showed 6.26 percent of V-FITC positive apoptotic HL-60(TB) cells in hybrid, the percentage of V-FITC positive apoptotic hybrid cells was 19.3 times higher (23.76 percent). It was shown that hybrid had an even greater effect on V-FITC positive apoptotic MOLT-4 cells than monastrol (which increased the percentage by 7.60 percent), rising by 16.37 percent. Hybrids with meta-chloro and 2,4-dichloro substituted phenyl rings showed improved antiproliferative activity in the SAR study [34-35].

1,3,4-Oxadiazole-coumarin hybrids

1,3,4-oxadiazole derivatives with coumarin moiety showed antitumor activity against HePG-2 and MCF-7 cell lines in a study by Morsy *et al*. For HePG-2 and MCF-7 cell lines, hybrid **(18)** had the highest IC_{50} values of 13.6μM, 1.06μM, and 1.38 μM, respectively, showing the greatest activity. According to the results of the SAR analysis, adding a methyl group to the R position and fluoro substituents to the R1 position increases the potency of the compounds [36].

1,3,4-Oxadiazole-morpholine hybrids

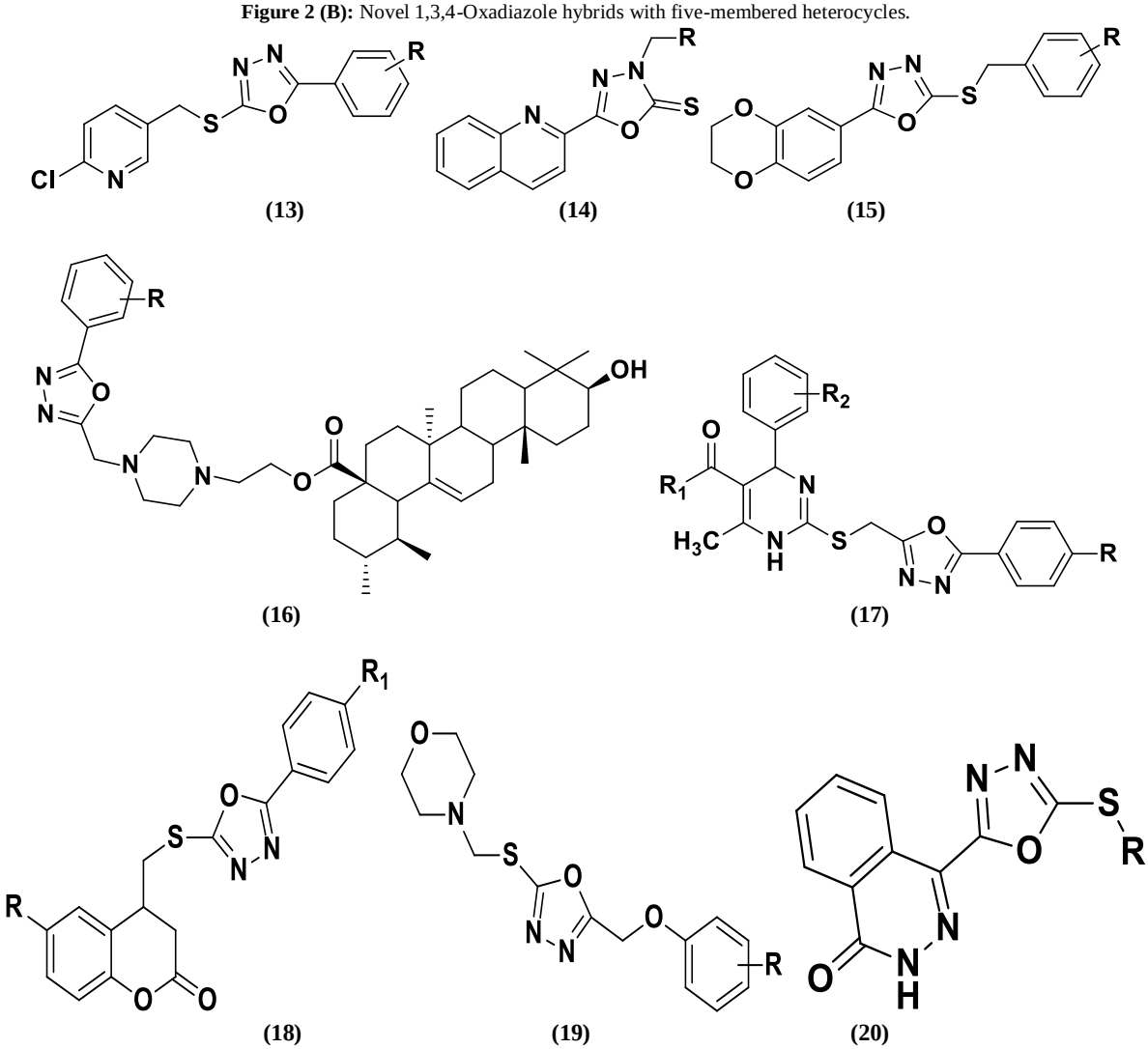
Dalton's Lymphoma Ascites (DLA) tumour cells were treated *in vitro* and *in vivo* using 1,3,4-oxadiazole derivatives possessing the morpholine moiety, according to Al-Ghorbani *et al*. Hybrid containing para-chloro substituents (n = 1) displayed the greatest cytotoxicity against DLA tumour cells, with an IC_{50} value of around 8.4 μM. The antitumor efficacy of **(19)** was examined *in vivo* using a DLA tumour model and a dose of 75 mg/kg body weight administered intraperitoneally (i.p.). The tumours in the spleen and liver of mice with control tumours were found to be abnormally growing. Compared to normal mice, tumor-bearing animals treated with **(17)** had a comparable size liver and spleen after treatment with the hybrid. Hematological and serum profiles were virtually identical to those of the non-tumor-bearing treatment group when **(17)** was administered to normal, non-tumor-bearing animals. The hybrid's ability to fight DLA tumour cells while having no side effects makes it a viable therapy option. Researchers found that chloro substituents with a single CH_2 group were more active than chloro substituents with three CH2 groups. The anti-cancer profile diminished with increasing aliphatic chain length [37-38].

1,3,4-Oxadiazole-phthalazinone hybrids

1,3,4-oxadiazole derivative containing phthalazinone moiety **(20)** was tested against two cancer cell lines (HepG2 and MCF-7) and one normal cell line (WI-38). The positive controls had IC_{50} values of 4.5 μM and 4.2 μM, while hybrids had IC50 values ranging from 4.5–8.4 μM against cancer cell lines. The toxicity research revealed that hybrids had IC_{50} values of 74.9 μM and 72.4 μM for normal cell lines, respectively, and were not harmful. It was determined how the hybrids worked by observing how they affected the expression of key genes (p53, caspase 3, cdk1, and txnrd1). A threefold rise in caspase 3 and a fourfold increase in p53 expression were seen in the hybrid. Similar to the caspase 3 and p53 genes, the HepG2 cells were treated, however the hybrids did not exhibit any impact on cdk1. The cdk1 gene's expression was significantly suppressed by hybrid as well. The txnrd1 gene was unaffected by any of the hybrids. Apoptosis is indicated by an increase in p53 and caspase-3 expressions. There are several reasons why cell death occurs, but one of the most common is the depletion of cdk1 and Txnrd1. The p38 mitogen-activated protein kinase concentration was reduced by 84percentin hybrids, respectively. These hybrids reduced

the concentration of topoisomerase-II by 84 percent. Free –NH and –SH groups were shown to increase activity through hydrogen bond formation with DNA's nucleic bases, according to the SAR results. The chloroacetyl-modified oxadiazole ring was more active than the alkyl and aryl-modified oxadiazole rings. In addition, hybrids with a nitro and methoxy substituted phenyl ring increased the anti-cancer effect [39-40].

Figure 2 (B): Novel 1,3,4-Oxadiazole hybrids with five-membered heterocycles.



CONCLUSION

In order for oxadiazole derivatives to have therapeutic potential, they must be able to form efficient binding contacts with various receptors or enzymes in biological systems, triggering a wide range of biological activities in the process. It is hoped that this study would bring fresh insights into the rational design of possible oxadiazole-based therapeutic drugs that are less toxic and have enhanced pharmacokinetic features. With the 1,3,4-oxadiazole connected tetrafluoro substituted benzene ring, a potent anti-cancer property has been identified, suggesting that further study on these kinds of compounds may be carried out in order to increase the anti-cancer properties. Currently underway research on the anti-cancer activity of the oxadiazole ring structure has been summarized in this article. Only the most effective anti-cancer combinations from the family of drugs were included, keeping the article's core focus in mind. All of the information offered in this article was gathered via ongoing dissemination in highly accepted global diaries of restorative and pharmaceutical research. Scientists working on anti-cancer treatments who are interested in restorative physics may find the major components useful [17,24,41-42].

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