RSC Advances

REVIEW

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Cite this: *RSC Adv.*, 2025, **15**, 32778

A two-decade overview of oxadiazole derivatives as promising anticancer agents

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Received 26th May 2025
Accepted 1st August 2025

DOI: 10.1039/d5ra03702f

rsc.li/rsc-advances

One of the most difficult illnesses that people today must deal with is cancer. It is distinguished by aberrant cell division and growth, which results in the development of tumors and lumps. The heterocyclic nucleus has drawn a lot of interest in the field of chemotherapeutics; moreover, it is essential in medicinal chemistry. Oxadiazole is a nitrogen–oxygen heterocyclic core with five members that exhibits remarkable anticancer properties. Inhibiting different enzymes and growth factors is the mechanism linked to tumor defeat. This review has covered research conducted over the past 20 years as well as their potential applications in drug development as antineoplastic agents, given the significance of oxadiazole and its derivatives in this global panic problem. This review aims to highlight the anticancer properties of 1,3,4-oxadiazole and its derivatives, 1,2,4-oxadiazole.

1 Introduction

The growth of abnormal cells that divide uncontrollably and have the ability to invade and destroy healthy body tissues is what defines cancer.[1] One of the most challenging public health issues facing humanity is cancer, which is characterized by high rates of morbidity and mortality.[1] Since cancer accounts for three out of ten premature non-communicable diseases (NCD)-related deaths globally (30.3% in individuals aged 30 to 69 years), it is primarily responsible for one in four deaths (22.8%).[2] Female breast cancer was the second most common type of cancer in 2022, accounting for 2 308 897 new cases with a death of roughly 665 684, while liver cancer was responsible for about 865 269 new cases with a death of roughly 757 948.[2] In 2023, about 1 958 310 new cancer cases, and about 609 820 deaths were recorded in USA for both males and females.[3]

Native Americans and Alaskans are more likely to develop hepatic cancers, whereas Europeans are more likely to develop female breast cancer.[4] Oxadiazoles are heterocyclic compounds with a five-membered ring that have two nitrogen atoms and one oxygen atom.[5] Oxadiazole can be made from furan by substituting two methane (–CH=) groups with two pyridine type nitrogen (–N=) groups. Oxadiazole has four structural isomers: 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,2,5-oxadiazole, and 1,3,4-oxadiazole. Its nucleus has a mesomeric effect, which makes it a relatively weak base.[5,6] In addition to other pharmacological effects, imidazole, benzothiazole, benzimidazole, 1,3,4-oxadiazole, and 1,2,4-oxadiazole derivatives have been reported to exhibit cytotoxic and anticancer bioactivity.[6–8] Commercially available oxadiazole-based medications include the well-known anticancer zibotentan **1**, butalamine **2**, ataluren **3**, oxolamine **4**, and proxazole **5**.[9] With eight oxadiazole-based drug molecules approved by the US FDA and more in clinical trials, oxadiazole has a promising future in the drug discovery process for chemotherapy.[10,11]

2 Material and methods

2.1 Data collection

Using electronic databases such as PubMed, Embase, and PsycINFO, a comprehensive literature search was carried out. "Oxadiazole nucleus", "chemotherapy", "therapeutic strategies", "cancer cell lines" and "cancer" were the search terms used. To reflect the latest advancements, articles released from January 2005 to January 2025 were included. Preclinical and clinical researchs were taken into account.

2.2 Study selection

Complete texts of articles that might be of interest were obtained and their eligibility was evaluated. Studies concentrating on oxadiazole-based compounds with acceptable activity against different types of cancer are eligible to be included.

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Exclusion criteria include articles written in languages other than English and studies that are not specifically about molecules based on oxadiazole moiety.

2.3 Data analysis

The extracted information was combined and subjected to a thematic analysis. The included studies' similarities and differences were noted. The main conclusions were outlined, emphasizing the benefits and drawbacks of various therapeutic modalities. Future directions and emerging trends were discussed.

2.4 Ethical considerations

Because this review article is based on the analysis and interpretation of previously published studies, ethical approval was not necessary.

2.5 Limitations

The quality and accessibility of the included studies place restrictions on the review. The review's focus is on oxadiazole-based compounds as anticancer agents; it ignores other topics like pathophysiological mechanisms or diagnostic techniques.

3 Results and discussion

Numerous derivative medications with an oxadiazole core have demonstrated clear cytotoxic and anticancer effects on various human cancer cell lines, including the following.

3.1 MCF-7 cell line

In 2021, several oxadiazole-based drugs were synthesized, including compound **1** (Fig. 1), which demonstrates anticancer activity against human breast cancer MCF-7 cell line, with an IC_{50} value of 5.897 ± 0.258 μM.[9] Compounds **2** and **3** (Fig. 1) exhibit potential as anticancer agents, with IC_{50} values against MCF-7 of 15.708 ± 0.659 and 15.063 ± 0.728 μM, respectively.[9] Substituting R_1 and R_2 in the original structure of the synthesized oxadiazole derivatives compounds **4(a–g)** (Fig. 1) with various substituents such as H, Cl, CH_3, OCH_3, CN, and F resulted in the synthesis of a series of oxadiazole-containing compounds, these compounds were evaluated for anticancer activity, yielding IC_{50} values ranging from 18.305 to 45.438 μM.[9]

In 2021, Alam *et al.* synthesized a series of naproxen 1,3,4-oxadiazole derivatives, compound **5** (Fig. 1) exhibits a cytotoxic effect against MCF-7, with an IC_{50} value of 2.13 μg mL^{-1}.[12] In the same year, Almalki *et al.* synthesized a series of 1,2,3-triazole-thymol-1,3,4-oxadiazole derivatives, compound **6** (Fig. 1) demonstrating the highest potency, this compound exhibited an antiproliferative effect against various human cell lines, with an IC_{50} value of approximately 1.1 μM against MCF-7.[13] In 2022, Kotla *et al.* synthesized a series of anticancer oxadiazole structures by substituting the R group in the structural formula depicted in compounds **7(a–e)** (Fig. 2).[14] Compound **7b** (Fig. 2) exhibits anticancer activity against various human cell lines with an IC_{50} of 0.31 μM for MCF-7.[14] Sreenivasulu *et al.*[15] synthesized two highly active oxadiazole-based drugs by substituting the R group in compounds **8(a and b)** (Fig. 2).

Compound **8a** (Fig. 2) exhibits cytotoxicity against various human carcinoma cell lines, with an IC_{50} of 1.8 μM against

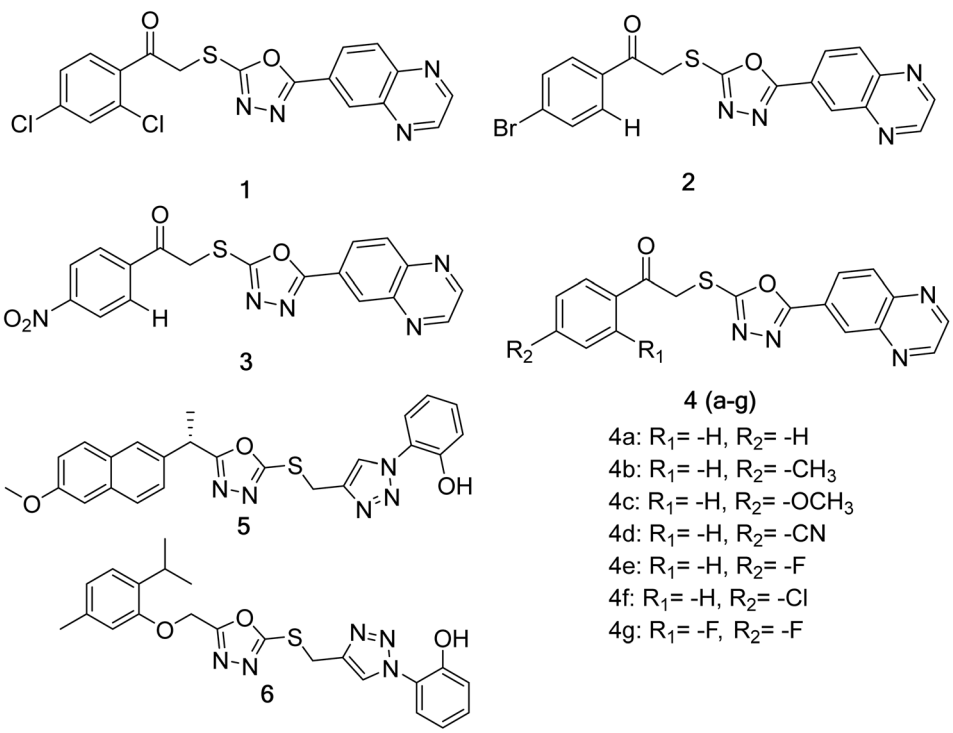

Fig. 1 Compounds (1–6).

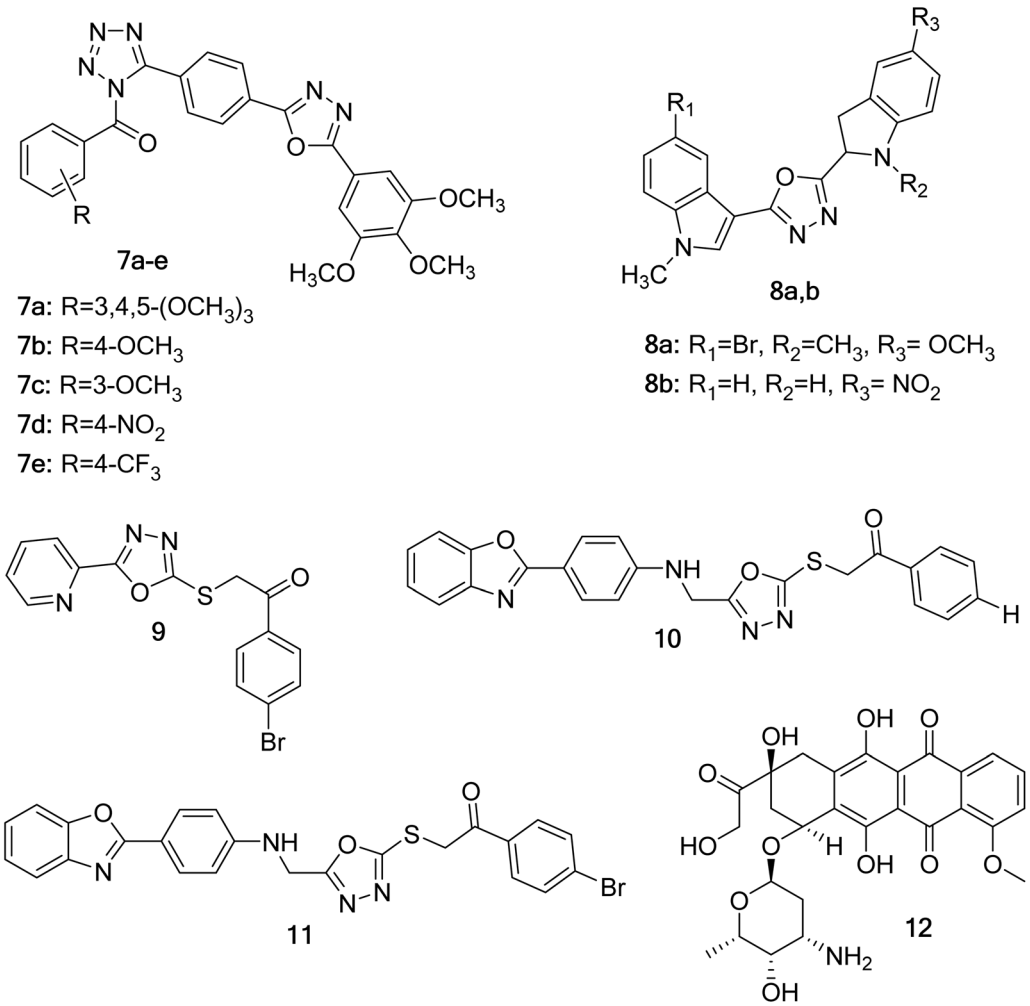

Fig. 2 Compounds (7–12).

MCF-7. In contrast, Compound **8b** (Fig. 2) demonstrates a cytotoxicity with an IC_{50} of 2.6 μM against MCF-7.[15] Abbas *et al.* created structures containing oxadiazole rings and assessed their anticancer activity against MCF-7 cells, compound **9** (Fig. 2) exhibited notable anti-tumor activity, evidenced by a GI_{50} value of 86.8 mg mL^{-1} against MCF-7 cells.[16] Omar *et al.* synthesized drugs derived from 1,3,4-oxadiazole in an *in vitro* study, the cytotoxicity results indicate that compounds **10** and **11** (Fig. 2) demonstrated greater inhibitory effects on MCF-7 cells better than Doxorubicin **12** (Fig. 2), with IC_{50} values of 1.76 ± 0.08 mM and 1.18 ± 0.04 mM, respectively.[17] El-Etrawy and Sherbiny performed two sequential studies that led to the synthesis of two compounds, compound **13** (Fig. 3), a thiouracil derivative, exhibits significant anticancer activity against the MCF-7 cell line, with an IC_{50} value of 3.80 microg per mL.[18]

Compound **14** (Fig. 3) demonstrated a significant cytotoxic effect on MCF-7, with an IC_{50} of 3.50 microg per mL. Doxorubicin **12** (Fig. 2), with an IC_{50} of 2.97 microg per mL, was served as a control in this study.[19] El-Mansouri *et al.* synthesized a series of 1,3,4-oxadiazole derivatives, and the cytotoxic activity of all synthesized compounds was evaluated *in vitro* against MCF-7, compound **15** (Fig. 3) demonstrates a significant growth inhibitory effect.[20] Mohan *et al.* detailed the synthesis of 1,2,4-oxadiazole-1,2,3-triazole-pyrazole derivatives and evaluated their anti-cancer activity against several cell lines, including MCF-7 cells. Compound **16** (Fig. 3) exhibited an IC_{50} of 0.081 ± 0.0012 mM in its anticancer action against MCF-7 cells.[21] Compounds **17** and **18** (Fig. 3) exhibited the highest levels of cytotoxicity, with IC_{50} values ranging from 0.88 to 8.37 μM against several cell lines, including MCF-7.[22] Furthermore, these compounds exhibited greater activity against MCF-7 cells compared to the reference, Doxorubicin **12** (Fig. 2).[22] Compound **19** (Fig. 4) has emerged as a potential agent against the MCF-7 cell line, exhibiting an IC_{50} of 5.704 ± 0.254 mm. A series of drugs derived from oxadiazole are synthesized by di-substitution as compounds **19–23** (Fig. 4). Among these, five structures exhibit significant anti-cancer effects, whereas the other structures demonstrate minimal anti-cancer activity against MCF-7.[8] Compounds **20** (Hoechst 33342), **21**, **22**, **23** (Fig. 4) and (Doxorubicin) **12** (Fig. 2) exhibit notable cellular toxicity in MCF-7 cells with IC_{50} values of 2.404 ± 0.118, 6.442 ± 0.287, 7.318 ± 0.352, 9.148 ± 0.391, and 10.525 ± 0.118 μM,

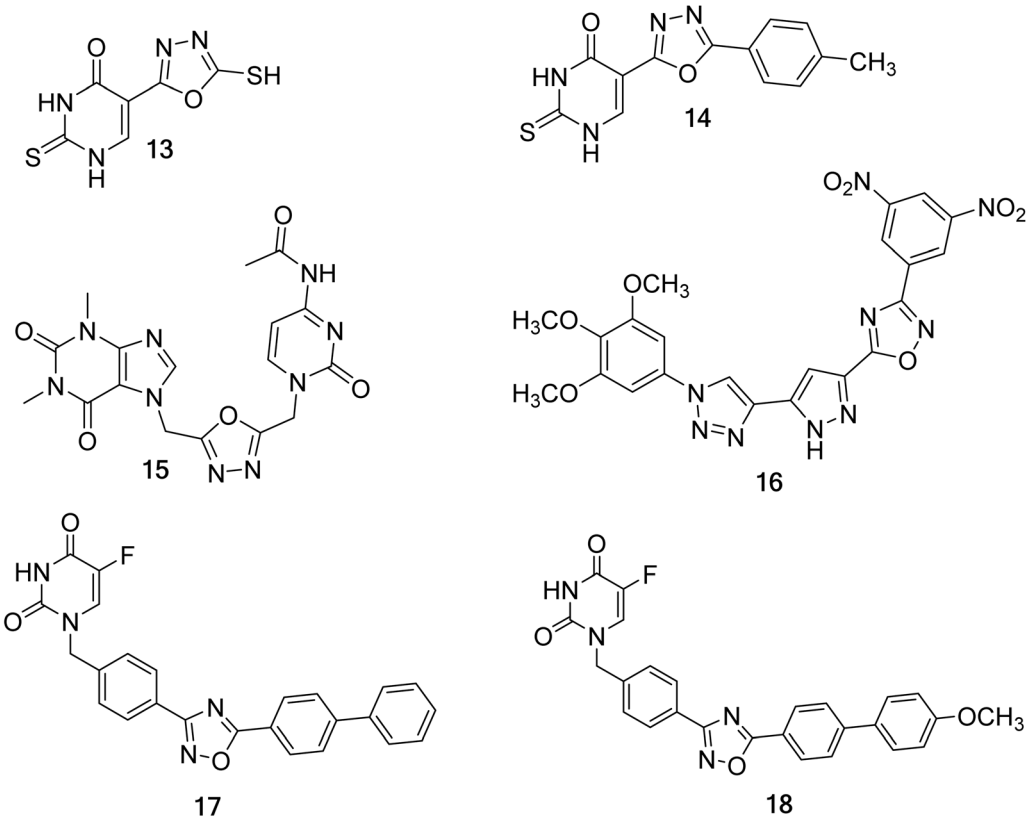

Fig. 3 (13–18).

respectively.[8] Moreover, the oxadiazole hybrid propanamide 24 (Fig. 4) served as a selective inhibitor of HDAC8.[11]

IC_{50} values against the breast cancer MDA-MB231 and MCF-7 cell lines decreased, demonstrating a dose-dependent effect alongside a reduction in the percentage of apoptotic cells and mitochondrial membrane potential.[11] A range of hybrid compounds integrating 1,3,4-oxadiazole and 1,3,4-thiadiazole with the Schiff base moiety were synthesized and evaluated *in*

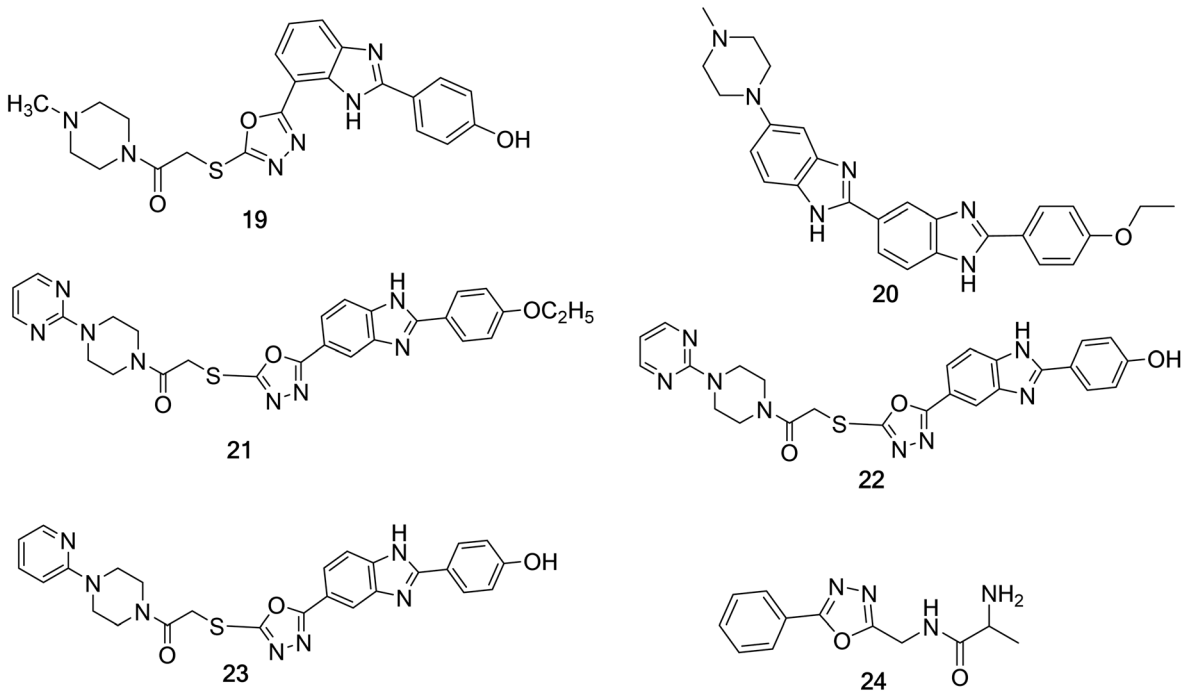

Fig. 4 Compounds (19–24).

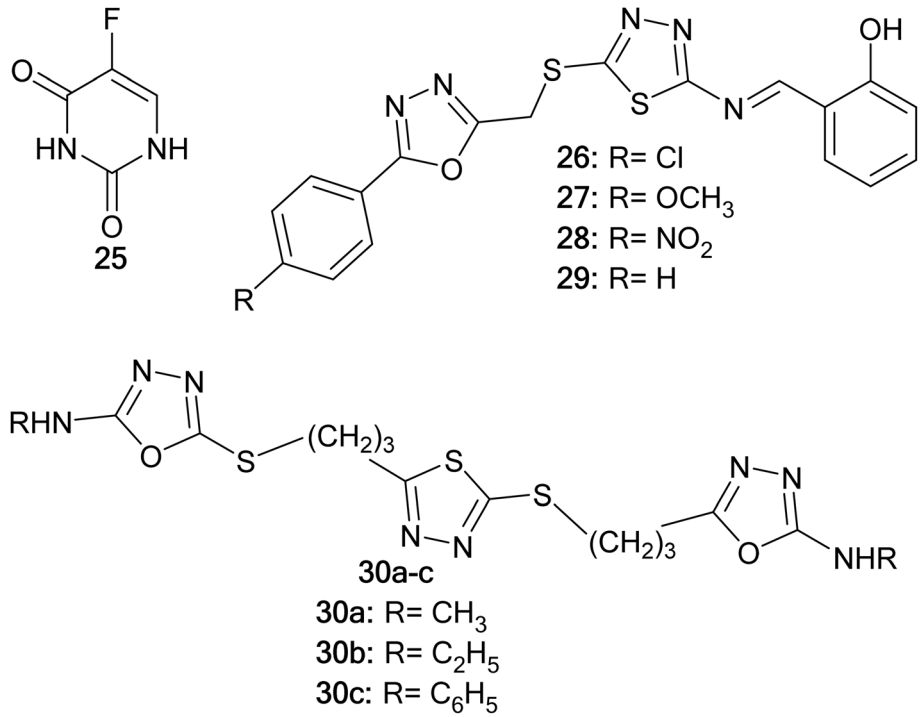

Fig. 5 Compounds (25–30).

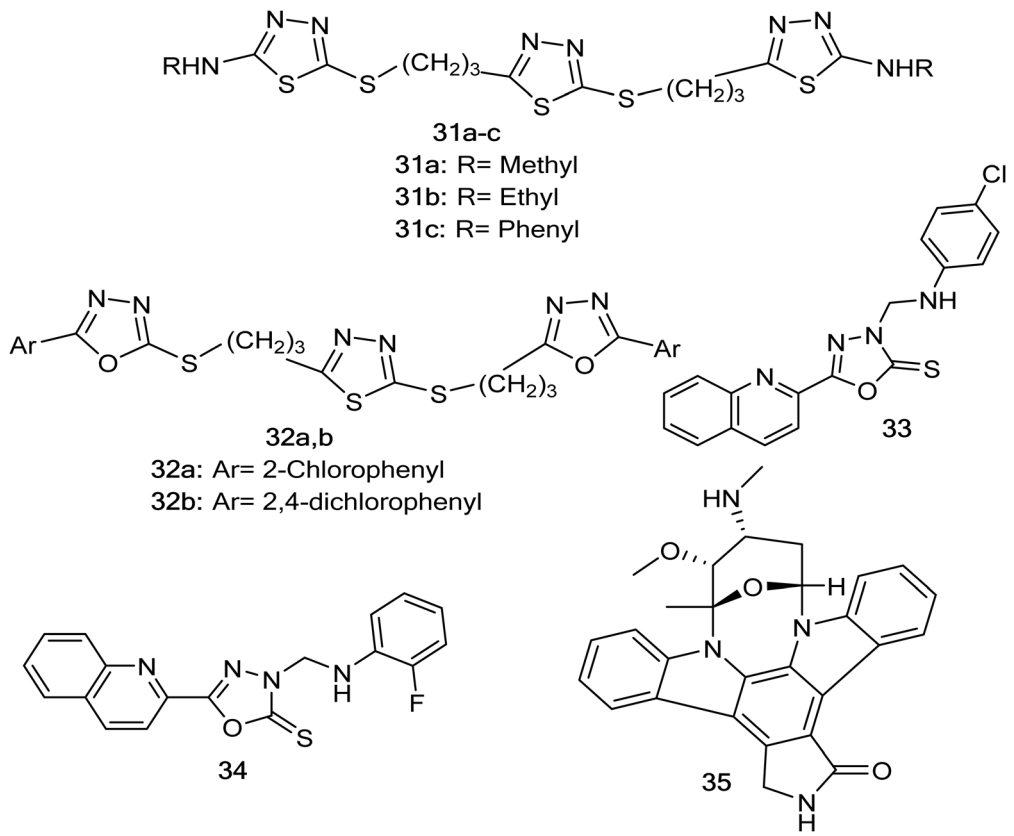

Fig. 6 Compounds (31–35).

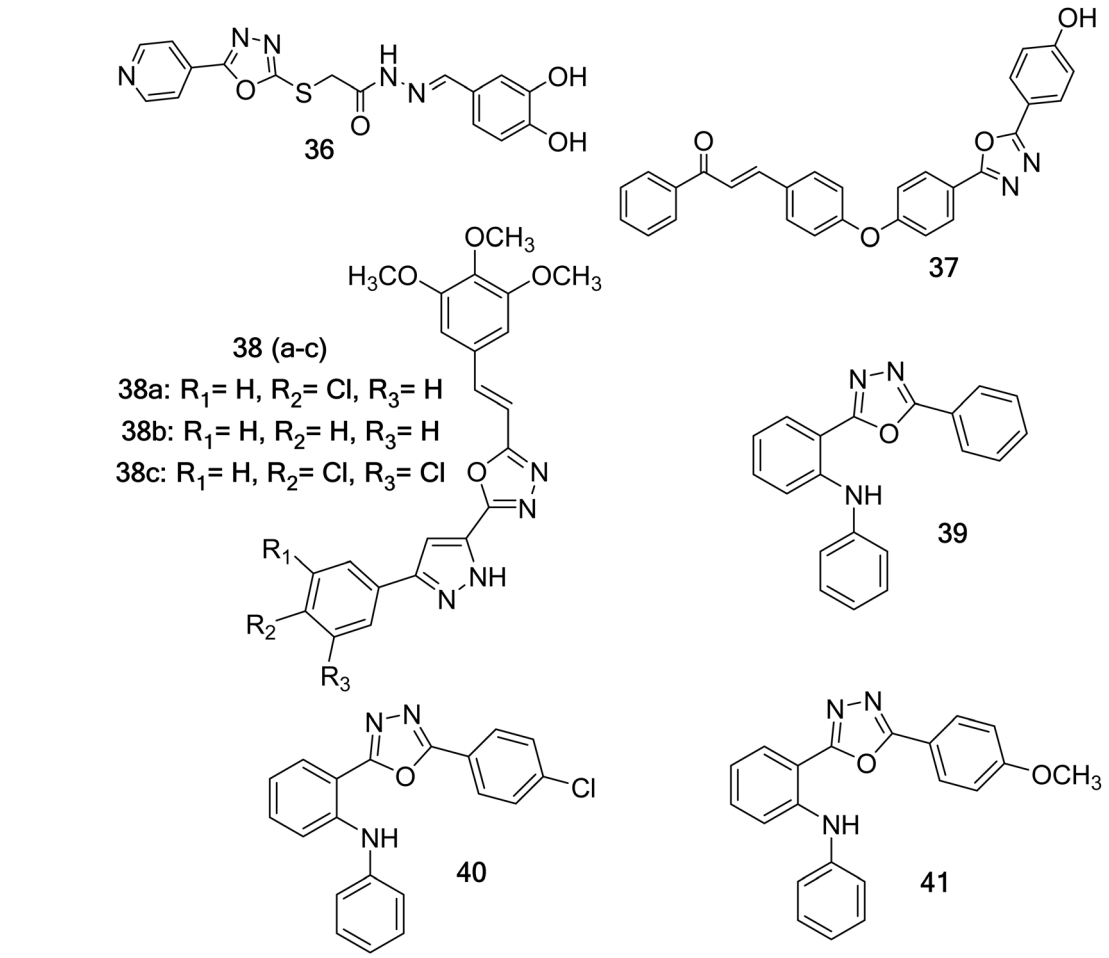

Fig. 7 Compounds (36–41).

vitro for anticancer efficacy against SMMC-7721, MCF-7, and A549 human cell lines utilizing the CCK-8 assay,[12] The findings indicated that certain chemicals exhibited greater efficacy against various cell lines compared to the positive control, 5-fluorouracil (compound **25**) (Fig. 5).

Compound **26** (Fig. 5), exhibited the highest potency against SMMC-7721 cells, with an IC_{50} value of 2.84 μM.[23] Compounds **27** and **28** exhibited significant anticancer activity against MCF-7 cells, with IC_{50} values of 4.56 μM and 4.25 μM, respectively[23] (Fig. 5). The unsubstituted phenyl compound **29** (Fig. 5) and the 4-nitro-substituted Compound **28** (Fig. 5) demonstrated significant efficacy against A549 cells, with IC_{50} values of 4.11 μM and 4.13 μM, respectively.[23] The pharmacological findings demonstrate that substituents on the phenyl ring of 1,3,4-oxadiazole play a significant role in altering antiproliferative effects across various tumor cell lines.[23]

In 2015, various oxadiazole derivatives were examined for their antiproliferative effects in four distinct human cancer cell lines: MCF-7, T47D, Caco-2 and HeLa cells.[24] Every chemical showed comparatively high activity against the cell lines under investigation. While converting the methyl and phenyl groups in compound **30a,c** (Fig. 5) and compound **31a,c** (Fig. 6) into ethyl groups **30b** (Figure 5) and **31b** (Fig. 6) significantly increased the cytotoxic activity with LD_{50} values ranging from 376 ng per microL to 438 ng per microL, there was no difference in activity associated with replacing oxadiazole with thiadiazole.[24,25] This suggests a steric factor mediating either transport or molecular interaction of these compounds with cellular targets. Additionally, compound **32b** (Fig. 6), which has twice the activity (LD_{50} = 356–398), was created by adding one additional Cl atom to structure **32a** (Fig. 6) (LD_{50} = 648–690).[24]

Sun *et al.* (2013) identified and examined 1,3,4-oxadiazole compounds containing quinoline groups, the study involved testing three distinct cancer cell lines: HepG2, (SGC-7901), and MCF-7.[26] Compounds **33** and **34** (Fig. 6) exhibited antiproliferative effects with IC_{50} values of 7.1 and 6.8 μM, respectively against MCF-7 which are greatly higher than 5-fluorouracil **25** (Fig. 5). The telomerase inhibitory activity exhibited by them was significantly greater than that of the reference Staurosporine **35** (Fig. 6).[26] In 2014, Zhang *et al.* examined the inhibitory effects of pyridine 1,3,4-oxadiazole analogues on telomerase activity.[27] Among the derivatives obtained, compound **36** (Fig. 7) demonstrated the most potent anti-cancer activity against four distinct cancer cell lines: liver cancer HePG2, MCF-7, SW1116, and BGC823, surpassing the efficacy of the reference compound, 5-fluorouracil **25** (Fig. 5).[27]

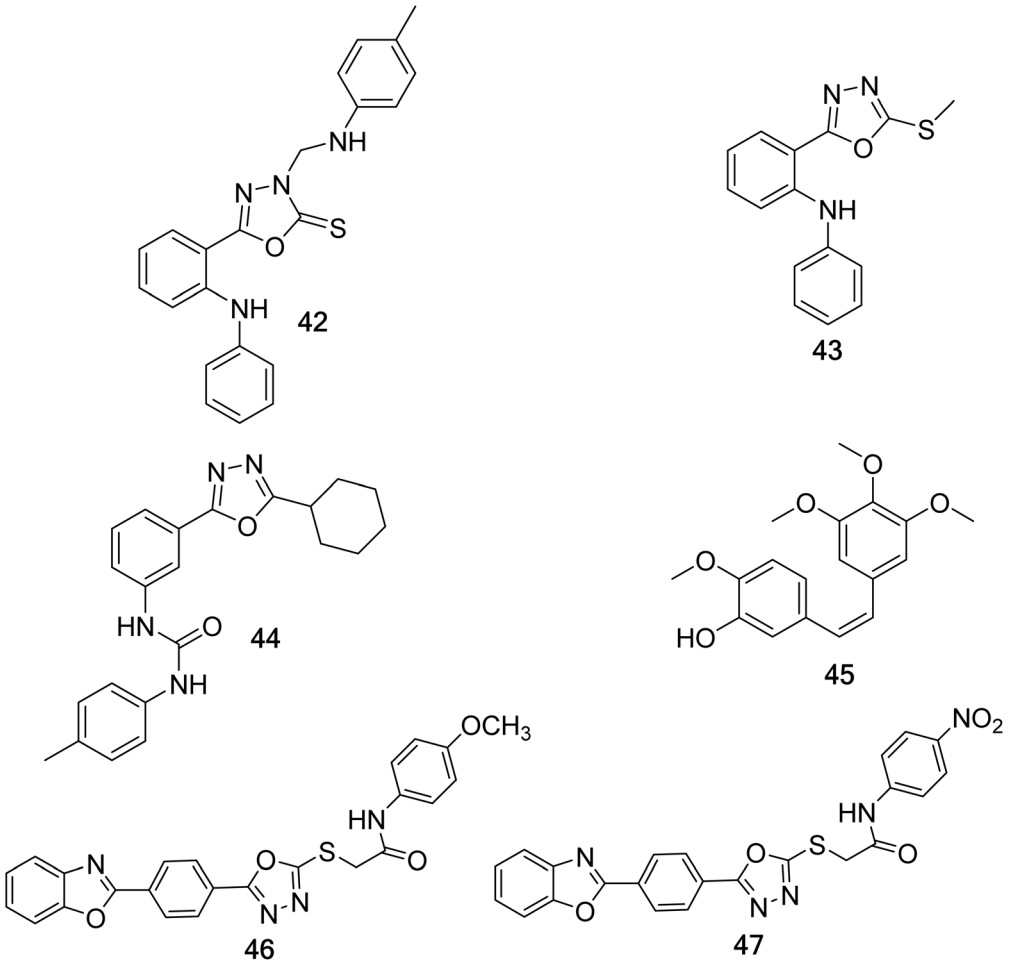

Fig. 8 Compounds (42–47).

Compound **36** (Fig. 7) exhibited significant inhibitory potential against telomerase enzyme, exceeding that of the comparator medication, Staurosporine **35** (Fig. 6).[27] Thasneem *et al.* developed a series of chalcone-linked oxadiazole derivatives by synthesizing various substituted chalcones with substituted oxadiazole. These derivatives were evaluated for anticancer activity against MCF-7 cell line using the MTT assay, compound **37** (Fig. 7) exhibits significant activity, with an IC_{50} of 6.8 μM.[28]

Kamal *et al.* developed a restricted library of hybrids containing oxadiazole to evaluate their antineoplastic activity *in vitro* on several human cell lines, including IMR32, HeLa, MCF-7, and A549. Three produced hybrids, **38a**, **38b**, and **38c** (Fig. 7), demonstrated significant cytotoxicity against the specified human cell types and inhibited tubulin polymerization.[29] A molecular docking study was performed to elucidate the mechanisms by which effective derivatives interact with the active colchicine site. IC_{50} values for cytotoxicity range from 1.5 to 11.2 μM, while values for tubulin polymerization inhibition are 1.3, 3.9, and 2.4 μM.[29]

Rahman presented findings on the anticancer activity and QSAR studies of a series of 2,5-disubstituted-1,3,4-oxadiazole, 2-substitutedthio-5-substituted-1,3,4-oxadiazole, and Mannich bases of 5-substituted-1,3,4-oxadiazole-2(3*H*)-thione featuring a diphenylamine moiety.[30] The Sulfo-Rodamine B (SRB) assay was employed to evaluate the antiproliferative activity of all synthesized compounds against MCF-7 and HT29 cancer cell lines.[30]

Compared to the MCF-7 cell line, all tested drugs exhibit significant antiproliferative effects on human colon cancer HT29 cells. Compounds (**39–43**) (Fig. 7 and 8) exhibited significant cytotoxicity (IC_{50} 1.3–2.0 μM) towards the HT29 cell line. QSAR analysis indicates that the steric bulk of a molecule's structure and conformation is a critical factor in anticancer efficacy.[30]

A series of 2,5-disubstituted-1,3,4-oxadiazoles featuring amide, urea, and sulphonamide functionalities has been reported.[31] 15 Compounds were synthesized and evaluated for anticancer activity, among them compound **44** (Fig. 8) has been identified as an effective anticancer agent.[31] The structure–activity relationship (SAR) of synthesized compounds indicated that the presence of a urea moiety with an electron-donating group enhances cytotoxicity. Additionally, the incorporation of substituted benzene sulphonamide into the 1,3,4-oxadiazole ring increased cytotoxicity against the MCF-7 cell line.

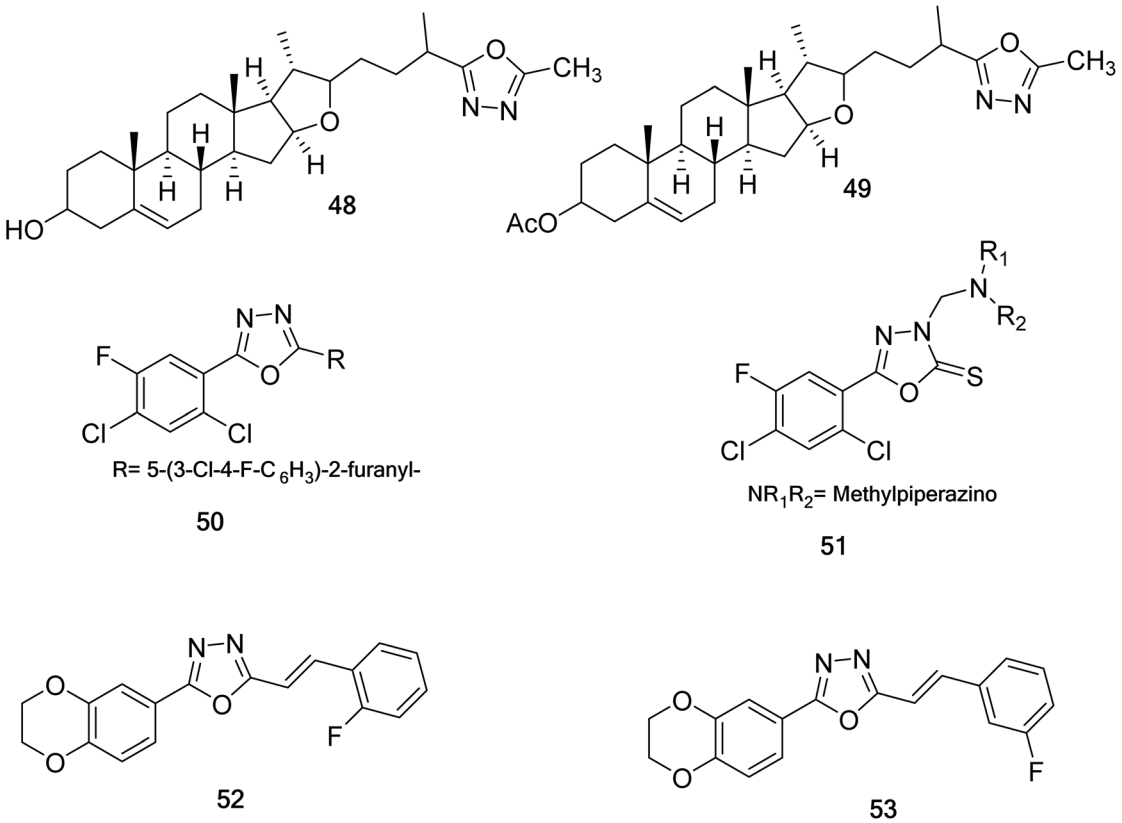

Fig. 9 Compounds (48–53).

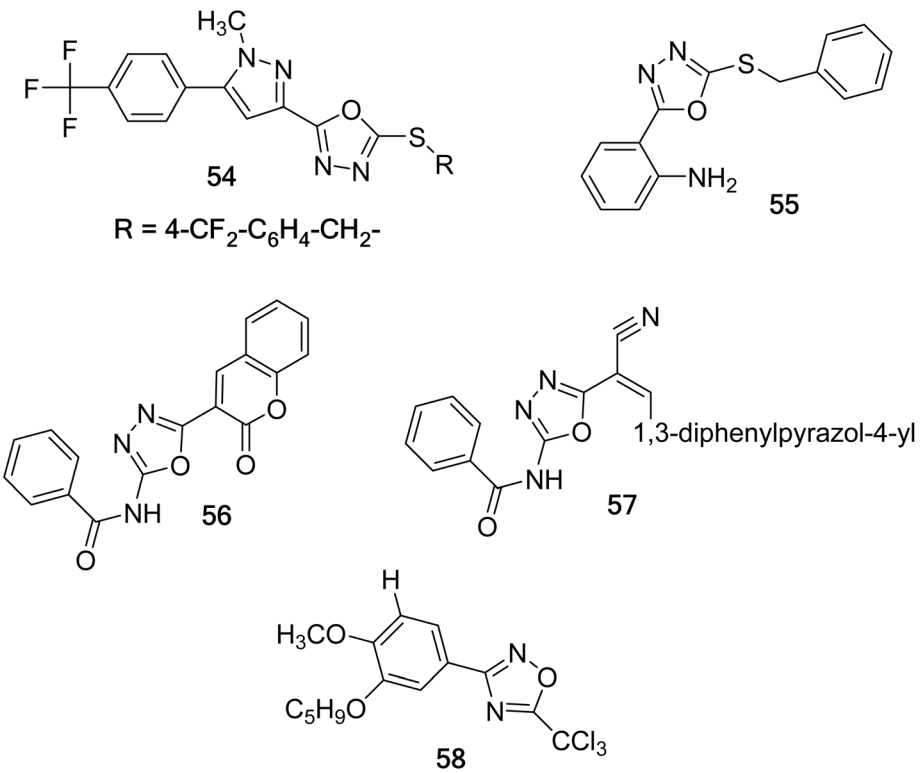

Fig. 10 Compounds (53–59).

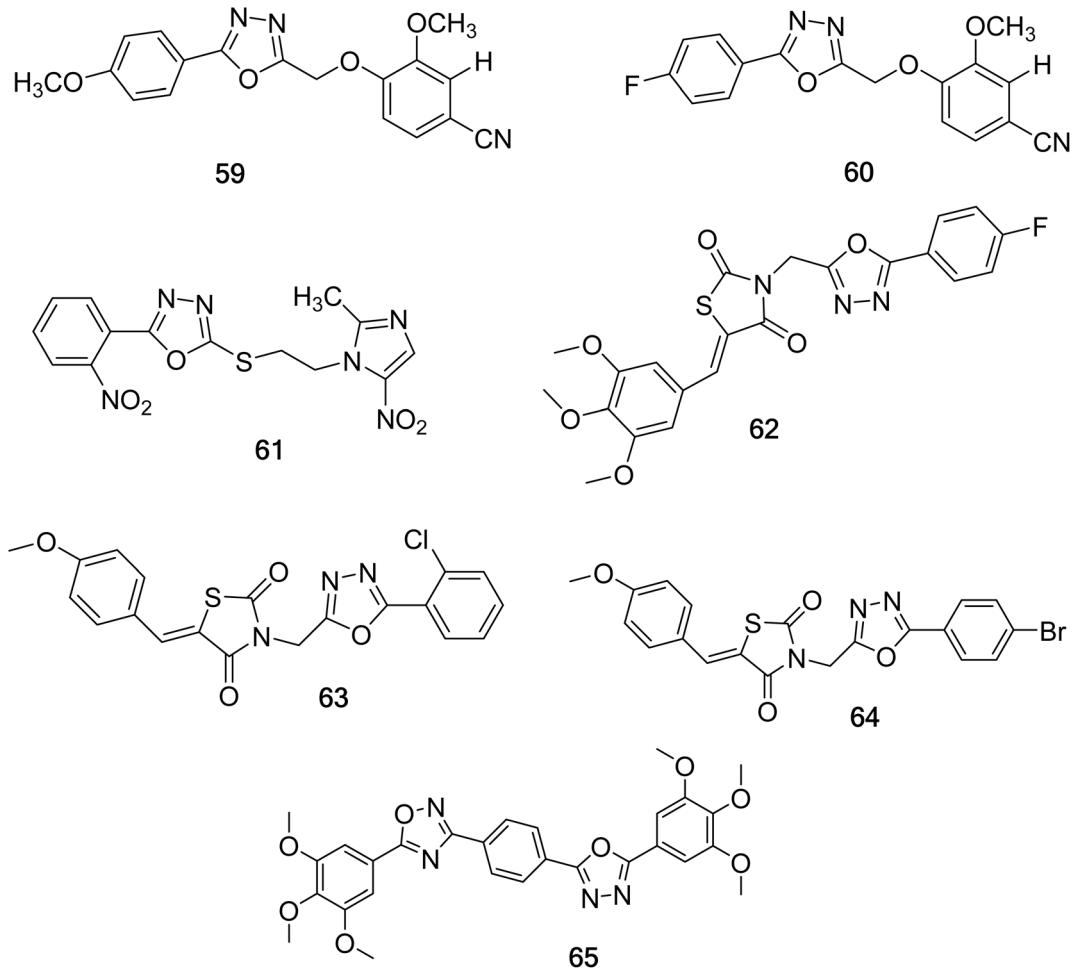

Fig. 11 Compounds (60–65).

Conversely, the attachment of a substituted benzamide unit to 1,3,4-oxadiazole derivatives diminished cytotoxicity against both the MCF-7 and HeLa cell lines.[31] Selvaraj *et al.* demonstrated that the incorporation of electron-donating groups at the *p*-position of urea and sulphonamide units containing 1,3,4-oxadiazole rings enhanced anticancer activity.[31] Subramanyam *et al.* synthesized ten 1,3,4-oxadiazole-2-benzothiazole derivatives featuring five aryl substitutions.[32] Ravinaik *et al.* synthesized a series of amide 1,3,4-oxadiazole linked benzoxazole derivatives, with their structures validated by spectral data.[33] The synthesized compounds were evaluated against four human cancer cell lines: A549, MCF-7, A375, and HT-29, using Combretastatin-A4 **45** (Fig. 8) as a control medication.[33] Compound **46** and **47** (Fig. 8) exhibited superior anticancer activity against the HT-29 cancer cell line when compared to the standard medication, with IC_{50} values of 0.018 and 0.093 μM, respectively.[33]

Zhang and colleagues synthesized a series of oxadiazole rings integrated into a steroid framework.[34] Two of these compounds **48** and **49** (Fig. 9) exhibited anti-proliferative effects on four cell lines (HepG2, MCF-7, A549, and HCT-116).[34]

Bhat *et al.* synthesized oxadiazole derivatives, compounds **50** and **51** (Fig. 9), demonstrated notable efficacy against the breast cancer MCF-7 cell line.[35]

Sun *et al.* synthesized 1,3,4-oxadiazole possessing 1,4-benzodioxan moiety. Most of the synthesized derivatives were evidenced to have powerful antitumor activities and low toxicities. Amongst them, compounds **52** and **53** (Fig. 9) displayed the greatest anticancer activities against Human Umbilical Vein Endothelial cells.[36]

Puthiyapurayil *et al.* synthesized various oxadiazole compounds incorporating the *N*-methyl-4-(CF_3) phenyl pyrazole moiety.[37] One compound exhibited the highest cytotoxic activity with MIC value of 15.54 mm in MCF-7 cells, identified as compound **54** (Fig. 10).[37] Liu *et al.* developed a series of 2-(benzylthio)-5-aryloxadiazoles, one of these derivatives (compound **55**) demonstrated significant anti-tumor effects in tests conducted on cell lines including MCF-7, A549, and B16-F10.[38] Gefitinib was utilized as the reference drug for comparison.[38]

Bondock *et al.* presented various heterocyclic structures associated with oxadiazole. Five compounds demonstrated significant efficacy against HepG2, WI 38, MCF-7, and VERO at

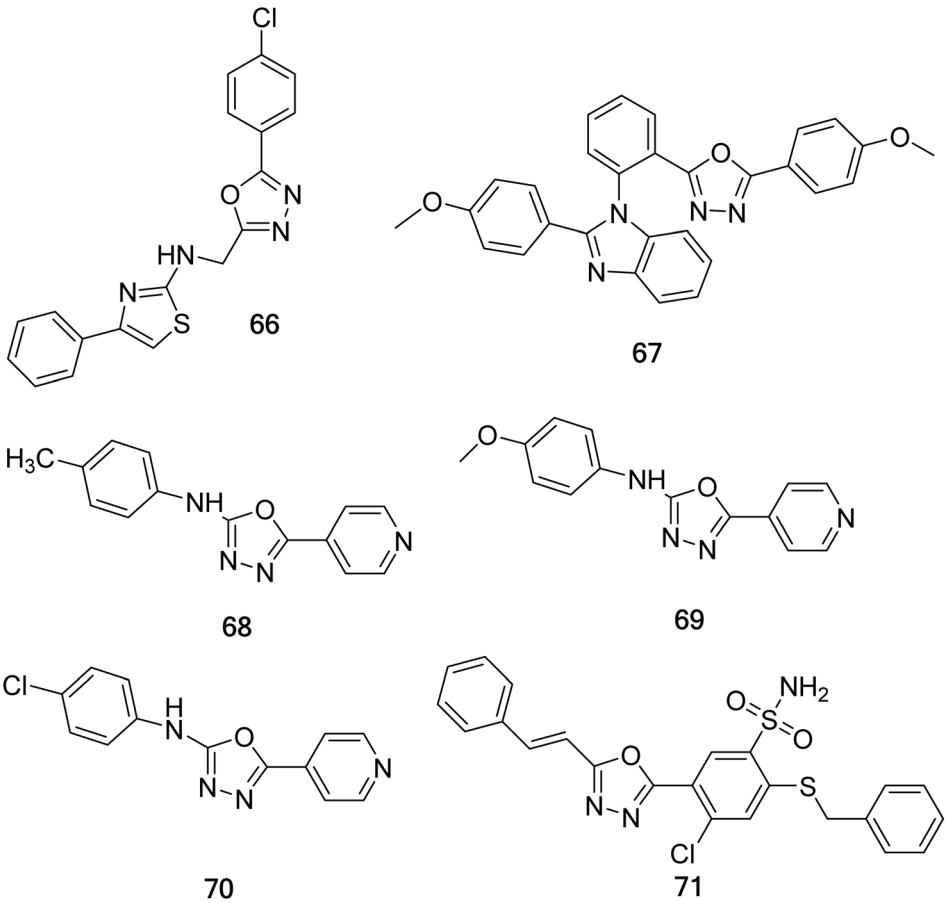

Fig. 12 (66–71).

MIC concentrations between 10 and 1000 μg mL^{-1}, particularly compounds **56** and **57** (Fig. 10) displayed 32.6 and 37.4 μg mL^{-1} against MCF-7, respectively.[39]

Kumar *et al.* proposed a series of 1,2,4-oxadiazole derivatives.[40] The trichloromethyl analogs exhibited the highest efficacy among the derivatives in this series, showing notable activity against PC3, DU145, LnCaP, MCF-7, MDA-MB-231, PaCa2, and DUP145, specially compound **58** (Fig. 10).[40]

Lakshmithendral *et al.* synthesized 2-(phenoxymethyl)-5-phenyl-1,3,4-oxadiazoles.[41] Two analogs demonstrated moderate to strong anti-breast cancer activity in the MDA-MB-453 and MCF-7 cell lines, specifically compounds **59** and **60** (Fig. 10 and 11).[41] Du *et al.* identified 1,3,4-oxadiazole-thioether derivatives as inhibitors of the thymidylate synthase enzyme, demonstrating their potential as anti-cancer agents. Compound **61** (Fig. 11) demonstrated the highest efficacy, exhibiting IC_{50} values of 0.7 μM, 18.3 μM, and 30.0 μM against HepG2, MCF-7, and SGC-7901 cancer cell lines, respectively.[42]

Derivatives of 1,3,4-oxadiazole and thiazolidine-2,4-dione, particularly compound **62** (Fig. 11) exhibited notable cytotoxic activity, with IC_{50} values between 0.81 and 11.9 μM against A549, A375, MCF-7, and HT-29 cancer cell lines.[43,44] Alzhrani *et al.* reported on hybrids of 1,3,4-oxadiazole and thiazolidinedione, specifically compound **63** and **64** (Fig. 11), which demonstrated cytotoxicity with IC_{50} values of 7.74 and 7.87, respectively, against the MCF-7 cell line through the inhibition of the thymidylate synthase enzyme.[44]

Compound **65** (Fig. 11), which contains both 1,3,4-oxadiazole and 1,2,4-oxadiazole structures, demonstrated significant anticancer activity with IC_{50} values ranging from 0.34 to 2.45 μM against MCF-7, A549, and MDA-MB-231 cancer cell lines through the inhibition of EGFR (epidermal growth factor receptor).[45] Jisha *et al.* synthesized compound **66** (Fig. 12), demonstrating significant cytotoxicity against DLA and MCF-7 with LD_{50} values of 136 μg mL^{-1} and 132 μg mL^{-1}, respectively.[46]

Kapoor and Dhiman synthesized compound **67** (Fig. 12), which exhibited notable cytotoxic effects against MCF-7 cells.[47] Abdo and Kamel reported a series of compounds **68**, **69** and **70** (Fig. 12), which exhibited cytotoxic effects between 0.725 and 3.274 μM across six human cancer cell lines: NUGC, DLD1, HA22T, HEPG2, HONE1, and MCF-7 cells.[48] Slawinski *et al.* synthesized compound **71** (Fig. 12) that has demonstrated promising anti-cancer activity against HCT-116, MCF-7, and HeLa cancer cell lines, with an IC_{50} value between 11 and 29 μM.[49] The ibuprofen derivative (compound **72**) (Fig. 13), was reported by Alderawy *et al.*,[50] and exhibited significant cytotoxicity, attaining 85.1% inhibition of MCF-7 cells. Malojirao *et al.* synthesized compound **73** (Fig. 13), as a potent cytotoxic agent, demonstrating IC_{50} values ranging from 4.8 to 5.1 μM against

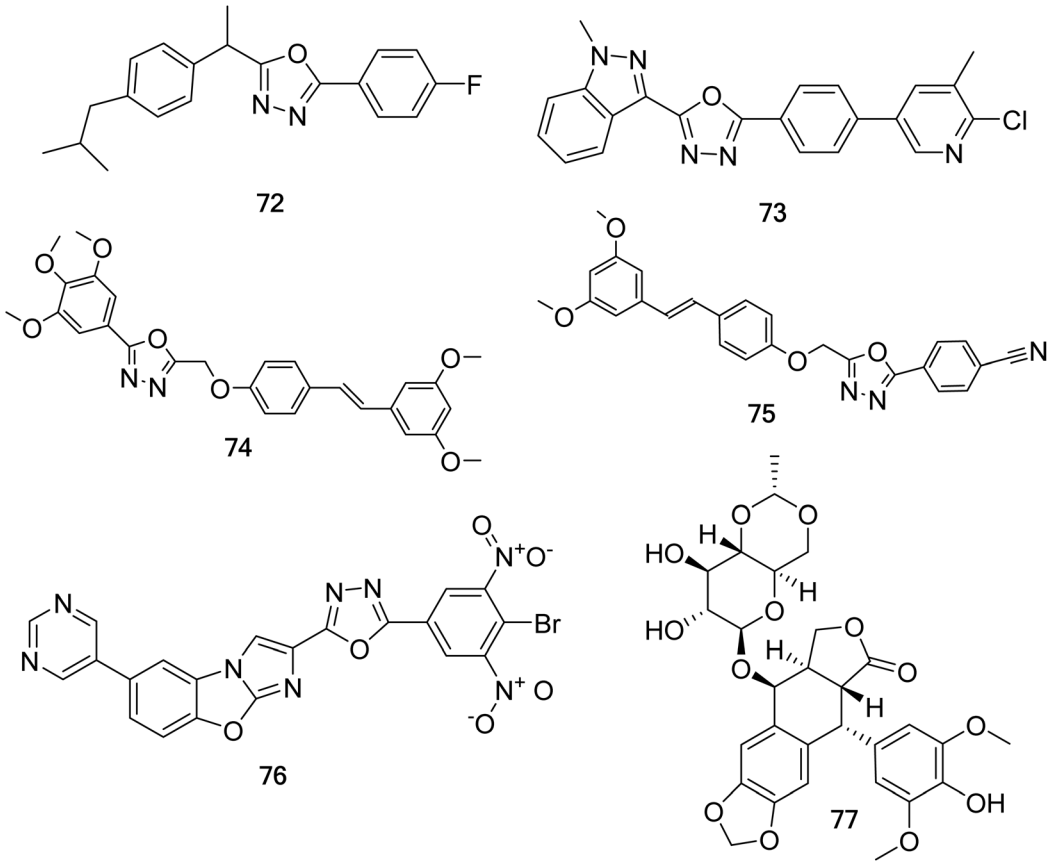

Fig. 13 Compounds (72–77).

A549, MCF-7, A375, HepG2, Huh-7, ACHN, A498, and LLC cells.[51] Moreover, derivatives of benzopyran 1,3,4-oxadiazole, developed by Kumar *et al.*, demonstrated significant anti-cancer effects on the MCF-7 cell line.[52] Derivatives of resveratrol-linked 1,3,4-oxadiazole, specifically compounds **74** and **75** (Fig. 13), demonstrated improved anti-cancer efficacy, with IC_{50} values of

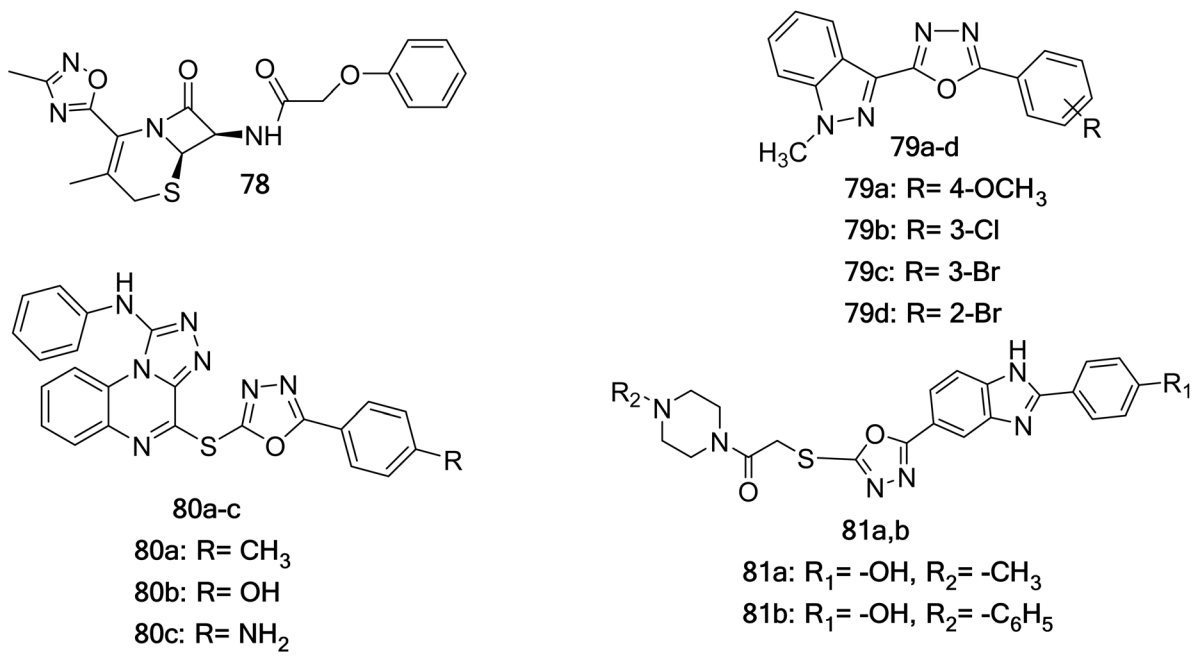

Fig. 14 Compounds (78–81).

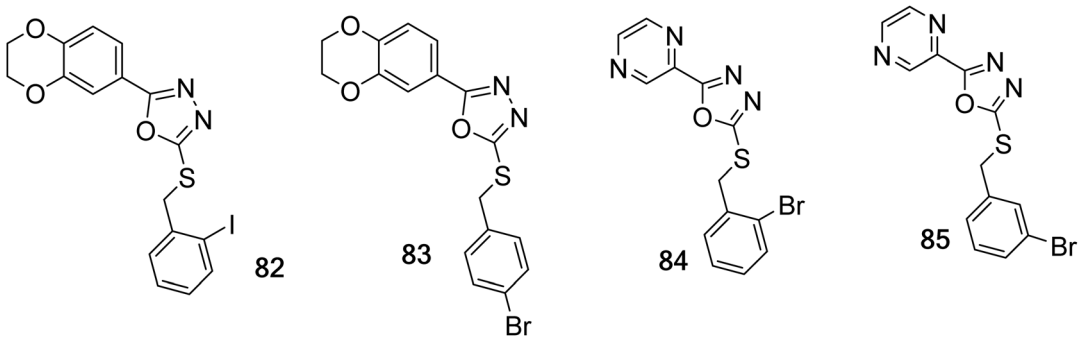

Fig. 15 Compounds (82–85).

0.11 μM to 1.56 μM and 0.45 μM to 1.98 μM, respectively, in comparison to the standard drug Adriamycin (Doxorubicin) 12 (Fig. 2) which exhibited IC_{50} values ranging from 2.10 μM to 3.41 μM against MCF-7, A549, and MDA-MB-231 cells.[53] Innovative pyrimidine-oxazole based 1,3,4-oxadiazole hybrids, compound **76** (Fig. 13), demonstrated significant anti-cancer activity with IC_{50} values ranging from 0.011 μM to 19.4 μM. In comparison, the reference drug etoposide compound 77 (Fig. 13) exhibited IC_{50} values from 0.13 μM to 3.08 μM against MCF-7, A549, Colo-205, and A2780 cell lines.[54]

3.2 HepG2 CELL LINE

Gold *et al.* (2016) developed a cephalosporin analogue that exhibits a significant activity against the human liver cancer HepG2 cell line, with an LD_{50} greater than 100 g mol^{-1} for compound **78** (Fig. 14).[55]

Compound **5** (Fig. 1) demonstrates notable cytotoxicity against the HepG2 cell line, exhibiting an IC_{50} value of 1.63 μM, among the series of naproxen 1,3,4-oxadiazole derivatives developed by Alam *et al.*.[12] Compound **6** (Fig. 1), a drug synthesized by Almalki *et al.* that combines 1,2,3-triazole with thymol-1,3,4-oxadiazole, exhibits a proliferation inhibitory effect against HepG2 hepatic cancer with an IC_{50} of 1.4 μM. This efficacy surpasses that of the established drugs Doxorubicin **12** (Fig. 2) and 5-fluorouracil **25** (Fig. 5), which have IC_{50} values of 1.8 μM and 28.65 μM, respectively, against HepG2.[13]

A series of indazole tethered oxadiazole compounds were synthesized by Dukanya *et al.*, compounds **79a**, **79b**, **79c**, and **79d** (Fig. 14) exhibited anticancer activity against human liver cancer HepG2, with IC_{50} values of 19.5, 21.4, 24.5, and 22.3 μM, respectively.[56] *In vitro* studies demonstrated that compound **79a** inhibited the proliferation of HepG2 cells through the suppression of SIRT2 expression.[56] The anticancer activity of compounds **80a**, **80b**, and **80c** (Fig. 14) were evaluated on HepG2 by Kaneko *et al.* The group of derived 1,2,4-triazole[4,3-a] quinoxaline-1,3,4-oxadiazole molecules exhibits IC_{50} values against HepG2 of (5.35 ± 0.22), (4.86 ± 0.25), and (3.84 ± 0.13 μM), respectively.[57] Compounds **81a** and **81b** (Fig. 14) exhibited cytotoxic activity against HepG2, measured at 5.695 ± 0.283 μM and 21.86 ± 0.991 μM, respectively, superior to Doxorubicin compound **12** (Fig. 2).[8]

Compounds **82** and **83** (Fig. 15) exhibited notable anticancer efficacy with IC_{50} values of 7.21 μM and 8.54 μM, respectively, against HepG2.[58] Additionally, compounds **84** and **85** (Fig. 15) demonstrate IC_{50} values of 4.22 μM and 5.79 μM, respectively, surpassing the positive control Staurosporine **36** (Fig. 7) (IC_{50} = 6.73 μM).[59] Sun *et al.* synthesized a series of 1,3,4-oxadiazole-based candidates, including compounds **33** and **34** (Fig. 6), which exhibited higher HepG2 antiproliferative activity than 5-fluorouracil **25** (Fig. 5), with IC_{50} values of 0.8 ± 0.2 and 1.2 ± 0.2 μM, respectively (5-fluorouracil IC_{50} = 21.9 ± 1.4 μM).[26]

Yang *et al.* developed a series of 1,2,4-oxadiazole-based drug derivatives, including compounds **86** and **87** (Fig. 16), which exhibit IC_{50} values of 1.07 μM and 1.03 μM against HepG2, respectively.[60]

Bhat *et al.* synthesized compound **88** (Fig. 17) that demonstrated significant cytotoxic effects, with an IC_{50} value of 0.26 μM against the HepG2 cell line, through the inhibition of EGFR and cyclin-dependant kinase CDK2 activity.[61] Compound **89** (Fig. 17) exhibited promising anticancer activity against the

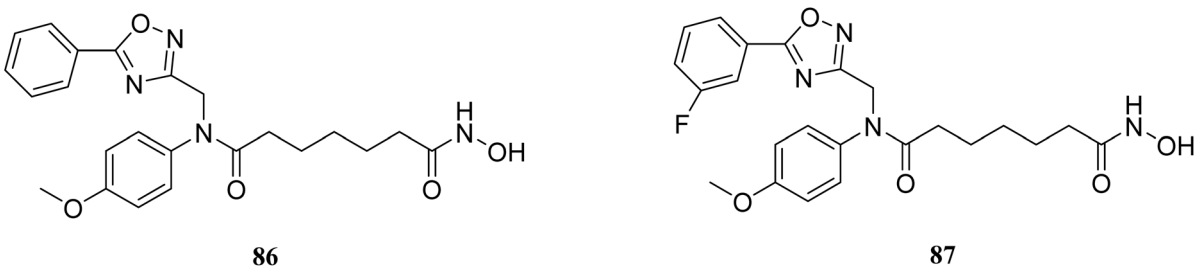

Fig. 16 Compounds (86 and 87).

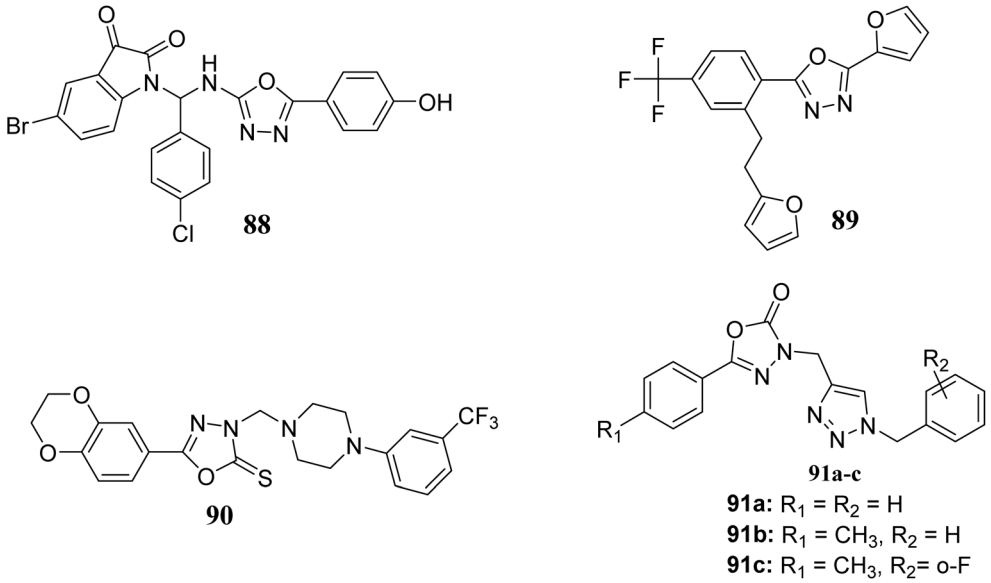

Fig. 17 Compounds (88–91).

HepG2 cell line in comparison to 5-fluorouracil **25** (Fig. 5).[62] Compound **90** (Fig. 18) exhibits the highest efficacy in inhibiting the growth of liver cancer cells (HepG2) relative to the reference, 5-fluorouracil (compound **25**) (Fig. 5).[62]

Madhavilatha *et al.* furnished a derivative of 1,2,3-triazole or isoxazole linked to 1,3,4-oxadiazole, as a potential anticancer agents. These derivatives were evaluated for their antineoplastic properties *in vitro* against four human cell lines: HeLa, MDA-MB-231, DU-145, and HEPG2, representing cervical, breast, prostate, and liver cancers, respectively.[63]

Compounds **91a–c** (Fig. 17) disrupts the cell cycle at the G2/M phase and acts as an inhibitor of tubulin polymerization.[63,64]

Compounds **91a**, **91b**, and **91c** (Fig. 17) exhibited notable anticancer activity. The growth inhibition (GI_{50}) values for the respective cell lines in μM were 1.28, 1.75, 2.39, and 1.84 for **91a**; 1.7, 2.14, 1.72, and 1.78 for **91b**; and 0.82, 1.04, 0.96, and 1.42 for **91c**, respectively.[63]

The anti-cancer properties of 1,3,4-oxadiazole-thioether derivatives were assessed using three distinct cell lines: HepG2 for liver cancer, SGC-7901 for stomach cancer, and MCF-7 for breast cancer. Compound **61** (Fig. 11) exhibits the most significant activity against liver cancer cells, demonstrating an effect 30 times greater than that of the reference drug, 5-fluorouracil **25** (Fig. 5).[42,65]

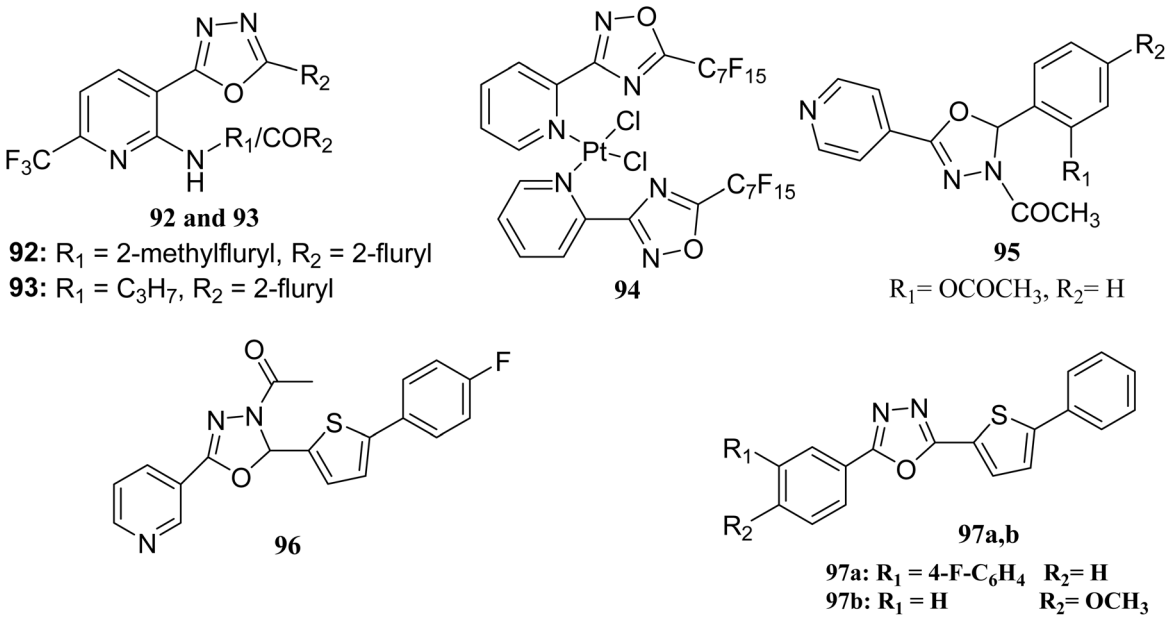

Fig. 18 Compounds (92–97).

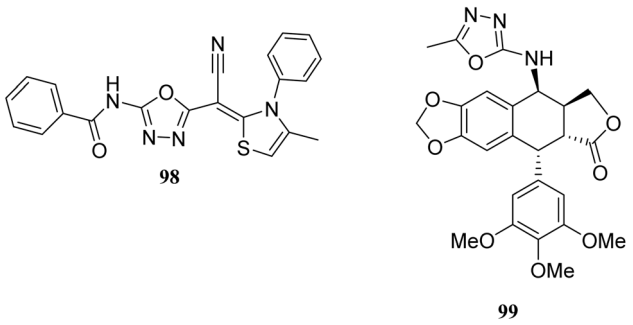

Fig. 19 Compounds (**98** and **99**).

Kumar *et al.* identified and synthesized derivatives of 1,3,4-oxadiazole based on pyridine.[66] An evaluation was conducted on various cancer cell lines, including HeLa, DU145, HepG2, and MBA-MB-231, representing cervical, prostate, liver, and breast cancers, respectively. Compounds **92** and **93** (Fig. 18), demonstrated the highest efficacy as anticancer agents, showing cytotoxicity at concentrations below 15 μM. The IC_{50} values for the compounds against the specified cell lines were 9.8, 8.2, 9.5, and 8.7 μM for compound **92**, and 12.8, 10.1, 11.6, and 9.9 μM for compound **93**, respectively.[66] Rubino *et al.* reported Compound **94** (Fig. 18) and assessed it against several human cell lines, including MCF-7, HepG2 and HCT116. Compound **94** demonstrates the most potent antitumor effect by inducing cell death, with IC_{50} values of 20.2, 4.0, and 1.1 μM, respectively, by utilizing the MTT method.[67] Sankhe *et al.* prepared and screened seven derivatives containing oxadiazole for their cytotoxic properties.[68] The study was conducted on the HepG2 and the MCF-7 cell lines. Among the seven drug candidates, compound **95** (Fig. 18) exhibited the highest proliferative inhibition activity, with an IC_{50} value of 52.71 μM on HepG2.[68] Kumar *et al.* developed a collection of oxadiazole-based compounds using a convergent synthetic approach. The anticancer properties of these compounds were assessed through *in vitro* assays conducted on HeLa, Caco-2, HepG2, and MCF-7 cell lines. Compound **96** (Fig. 18) exhibited notable potency with an IC_{50} of 8.6 μM, similar to the reference drug 5-fluorouracil **25** (Fig. 5) in the breast cancer cell line.[69] Adimule *et al.* examined the synthesis of analogs featuring oxadiazole and thiophene, which were then assessed for their anticancer efficacy against the Caco-2, PANC-1, and HepG2 cell lines, in comparison to the standard drug 5-fluorouracil **25** (Fig. 5). The results demonstrated that compound **97a** (Fig. 18) displayed considerable cytotoxicity, closely aligning with the standard, against the Caco-2 cell line, with an IC_{50} value of 5.3 μM. Compound **97b** showed moderate cytotoxicity against HepG2 with IC_{50} of 28.4 μM.[70]

Bondock *et al.* developed a small library of analogs derived from the oxadiazole structure, which were assessed for anticancer activity through *in vitro* methods among them, compound **98** (Fig. 19), demonstrated the highest efficacy against multiple human tumor cell lines, including HepG2, VERO, and WI-38. The IC_{50} values for this compound are 12.4 μM, 17.3 μM, and 15.8 μM, respectively.[39] Ren *et al.* conducted an evaluation of designed and synthesized derivatives of 1,3,4-oxadiazole-2-amino-podophyllotoxin as potential antitumor agents, utilizing the MTT assay.[71] Compound **99** (Fig. 19), exhibited notable antiproliferative activity in the HepG2 cell line, evidenced by an IC_{50} value of 1.29 μM. Compound **99** (Fig. 19) was found to inhibit the expression of the gene and protein for DNA topoisomerase IIb, causing S-phase arrest and ultimately resulting in apoptosis of tumor cells.[71]

Compounds **100** and **101** (Fig. 20) exhibited relative cytotoxicity against HepG2 cells, with IC_{50} values of 2.6 and 5.8 μM, respectively, in comparison to the reference drug 5-Fluorouracil **25** (Fig. 5).[72]

4 Conclusion

An overview of the research on possible medication candidates with various oxadiazole ring isomers that exhibit tolerable biological activity. Utilizing the nucleus is a crucial strategy in the development and synthesis of anticancer drugs since its presence has a clear direct impact on biological activity. The literature has demonstrated the use of oxadiazole as a scaffold for the synthesis of various agents, and various mechanisms have also been demonstrated to account for the various mechanisms of action that arise when this scaffold is used. Lastly, the use of oxadiazole derivatives is a very effective and promising strategy for the synthesis and design of upcoming anticancer drugs.

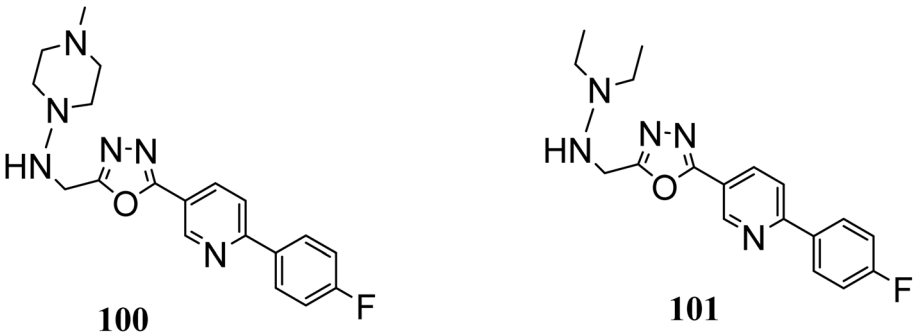

Fig. 20 Compounds (**100** and **101**).

Abbreviations

A2780	human ovarian cancer cell line
A375	human melanoma cell line
A431	human epidermoid cancer cell line
A549	adenocarcinomic human alveolar basal epithelial cells
B16-F10	melanoma cell line
BGC823	human papillomavirus-related endocervical adenocarcinoma
Caco-2	human epithelial colorectal adenocarcinoma
CCK-8	cell counting kit-8
CDK2	cyclin dependant kinase 2
FDA	food and drug administration
GI50	growth inhibition 50%
HDAC8	histone deacetylase 8
HeLa	human epithelial cancer
HepG2	hepatoblastoma
HT-29	adherent epithelial cell line
IC50	half maximal inhibitory concentration
IMR32	human neuroblastoma cell line
LD_{50}	lethal dose 50%
MCF-7	michigan cancer foundation-7
MDA-MB-231	M D anderson – metastatic breast – 231 human breast cancer cell line
MTT	colorimetric assay to measure cell survival
NCD	non communicable disease
QSAR	quantitative structure–activity relationship
SGC-7901	stomach cancer
SMMC-7721	human hepatocellular carcinoma
SW1116	colorectal cancer
SW1116	colorectal cancer
T47D	human ductal breast epithelial tumor

Conflicts of interest

The authors declare no conflict of interest.

Data availability

No data was used for the research described in this review article.

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