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A Review on Biological Activities of 1,3,4-Oxadiazole and their Derivatives

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ABSTRACT

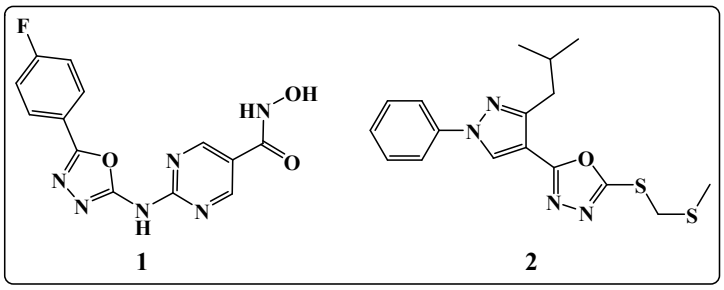
The 1,3,4-oxadiazole has been extensively studied in recent years due to its metabolic profile and ability to engage in hydrogen bonding with receptor sites. 1,3,4-Oxadiazoles and their derivatives show broad and potent activities such as anti-inflammatory, hypoglycemic, anxiolytic, antidepressant, anti-proliferative, antifungal, antibacterial and anti-tuberculosis, etc., but especially for treating cancer diseases. Substituted 1,3,4-oxadiazoles showed different mechanisms of action and participated in the discovery and development of anticancer drugs. The purpose of this review is to review the work reported on the biological activity of 1,3,4-oxadiazole derivatives since last decades.

Keywords: Anticancer, anticonvulsant, Oxadiazole.

Introduction

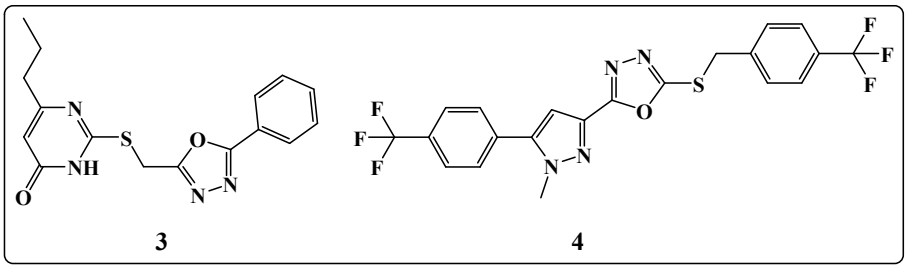
The 1,3,4-oxadiazole nucleus is present in various compounds with interesting medicinal properties, especially playing an important role in inducing anti-cancer activity. In recent years, 1,3,4-oxadiazole derivatives have attracted considerable attention due to their tumor suppressive properties associated with the inhibition of various growth factors such as enzymes and kinases, histone deacetylase, methionine aminopeptidase, thymidylate synthase, glycokinase, epidermal growth factor, vascular endothelial growth factor, and focal adhesion kinase etc. This review highlights the inhibitory activi0ty of 1,3,4-oxadiazole derivatives and their structure activity relationship to generate potential anticancer agents.

Rajak et al reported the synthesis of 2,5-disubstituted-1,3,4-oxadiazoles/ thiadiazole derivatives and evaluated for their anticancer activity against HCT-116 cell line by using MTT assay method.[1] The results of in vitro anticancer studies shows that compound **1** displayed maximum HDAC inhibitory activity with an IC_{50} = 0.017 µM against HDAC-1 and an IC_{50} = 0.28 µM in HCT-116 cell proliferation assay. In terms of potency, compound **1** showed almost similar results during in vivo anticancer studies against carcinoma cells in Swiss albino mice.



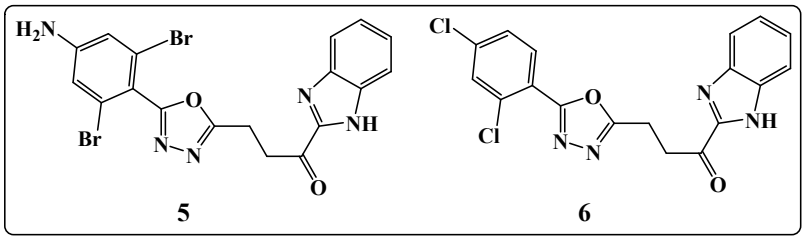
1 **2**

Abu-Zaid et al reported the anticancer activity of 1,3,4-oxadiazole-pyrazole hybrids against MCF-7 and HEPG2 cell lines.[2] Among them, the thioglycoside derivative **2** exhibited the highest cytotoxicity against MCF-7 and HEpG2 cell lines with IC_{50} values of 2.67 mg/mL and 4.62 mg/mL, respectively. Also none of the compounds showed toxicity at doses up to 500 $mg.kg^{-1}$ of animal body weight.



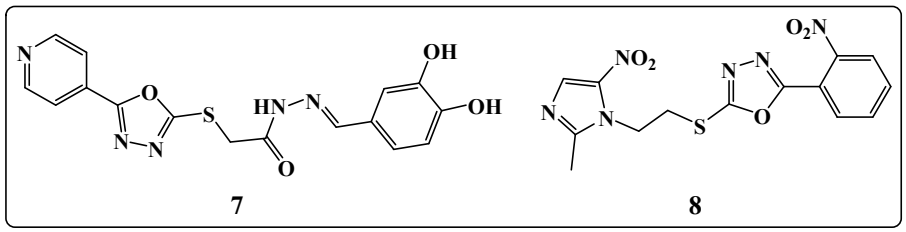
3 **4**

The synthesis of 1,2,4- and 1,3,4-Oxadiazoles and their systematic comparision in the AstraZeneca compound collection by *Bostrom et al*.[3] The results concluded that the less lipophilic 1,3,4-Oxadiazole compound **3** is sixteen times more soluble than the corresponding 1,2,4-Oxadiazole. *Puthiyapurayil et al* reported the synthesis of a novel series of 5-substituted-1,3,4-oxadiazole bearing *N*-methyl-4-(trifluoromethyl)phenyl pyrazole moiety linked 1,3,4-Oxadiazole derivatives and examined *in vitro* for their cytotoxicity against EAC, MCF-7 and A549 cancer cell lines by using MTT assay with Doxorubicin as standard drug.[4] Among them, the compound **4** showed most potent activity against MCF-7 with IC_{50} value of 15.54 µM as compared to Doxorubicin as standard drug.



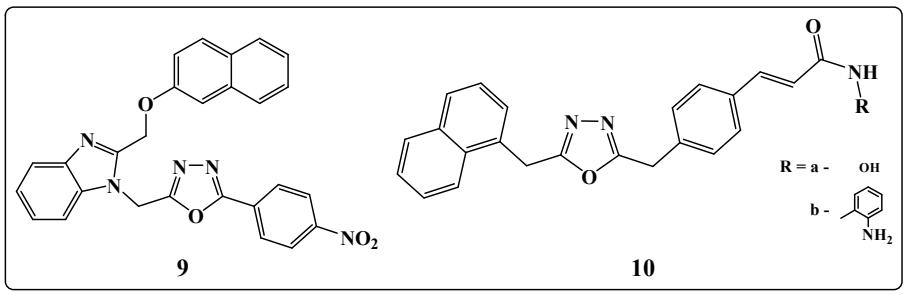
5 **6**

Husain et al reported the anticancer activity of hybrid oxadiazole-benzimidazole derivatives against a panel of 60 human cell lines.[5] Among the compounds tested, hybrid **5** exhibited remarkable growth inhibition (<32%) at a concentration of 10 µM. The compound showed good GI_{50} value in the range of 0.49-48.0 µM compared to all cell lines tested except HCT-15. All tested leukemia cancer cell lines were sensitive to **5** with GI_{50} value in the range of 2.89–4.94 µM. In case of non-small cell lung cancer, the compound showed the highest activity against HOP-92 cell line (GI_{50} = 0.499 µM, TGI=19.9 µM, LC50=>100 µM). The same group investigated the anticancer activity of oxadiazoles containing compounds similar to 1 with different substitutions.[6] Of these compounds, **6** displayed the highest activity at a concentration of 10 µM and was studied at various concentrations against a panel of 60 human cell lines. The compound showed the highest activity against breast cancer cell line (MDA-MB-468) with a GI_{50} value of 0.797 µM. The highest activity was observed against the non-small cell lung cancer HOP-92 cell line (GI_{50} = 1.77 µM).



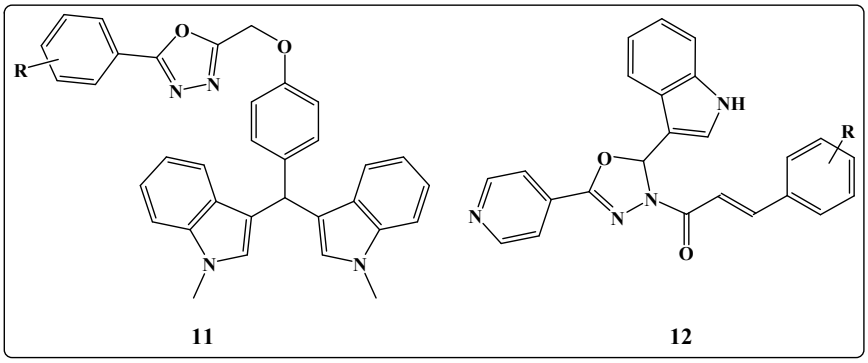
7 **8**

N-Benzylidene-2-(5-(pyridin-4-yl)-1,3,4-oxadiazol-2-yl)thio) acetohydrazide derivatives were synthesized as potential telomerase inhibitors.[7] Bioassay tests revealed that most of the compounds exhibited significant broad-spectrum anticancer activity against HEPG2, SW1116, MCF7 and BGC823 human cancer cells. Compound **7** showed the highest anticancer activity with an IC_{50} of 0.76–1.54 µM against the tested cancer cell lines and exhibited the most potent telomerase inhibitory activity with an IC_{50} of 1.18 ± 0.14 µM. *Du et al* reported a series of 1,3,4-oxadiazole thioether derivatives as effective inhibitors of thymidylate synthase (TS) enzyme.[8] The compound containing ortho-nitro phenyl group showed strong activity against HepG2 cell line with an IC_{50} value of 0.7±0.2 µM. That is, it showed better activity than positive controls such as 5-fluorouracil (IC_{50} = 22.8 ± 1.2 µM) and raltitrexed (IC50 = 1.3 ± 0.2 lM). Compound **8** exhibited moderate to potent inhibition of human TS with IC_{50} values in the range of 0.62–3.9 µM. The ortho-nitro substituted compound showed the highest activity (IC_{50} = 0.62 µM) as an inhibitor of human TS.



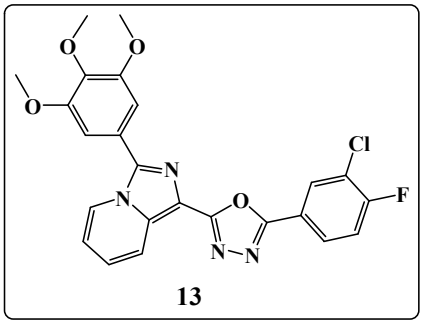
9 **10**

A series of oxadiazole-benzimidazole hybrids were synthesized and tested for antiproliferative activity against a panel of 60 cell lines.[9] Among them, compound **9** showed the significant activity with 72.85 growth percent and the cell line MDA-MB-468 (breast cancer) was found to be the most sensitive cell line (GP = 36.23). SAR experiments have shown that phenyl rings containing a nitro group in the para position promote anticancer activity. *Valente et al* described 1,3,4-oxadiazole-containing hydroxamates and 2-aminoanilides as histone deacetylase inhibitors and investigated their anticancer activity against human recombinant HDAC1, HDAC4 and HDAC6 with SAHA as the standard drug.[10] In human leukemia U937 cells, compound **10a** was more potent than SAHA in inducing apoptosis, and **10b** showed cell differentiation with potency similar to entinostat (MS-275).



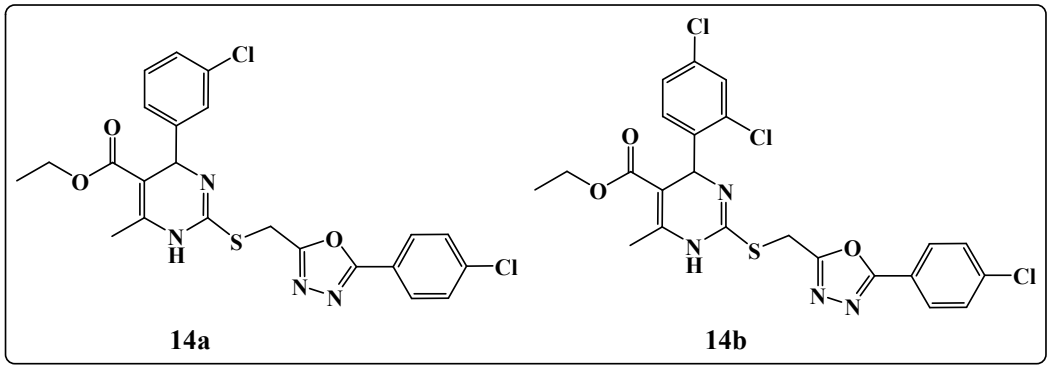
11 **12**

1,3,4-oxadiazole-linked bisindole derivatives **11** have been synthesized and evaluated for anticancer activity against four human cancer cell lines (MCF-7, KB, Colo-205, and A-549).[11] Four compounds with IC_{50} values range from 0.1 to 3.9 μM exhibited higher anticancer activity than etoposide with IC_{50} values range from 0.13–3.08 μM. *Desai et al* have synthesized a series of indole and pyridine based 1,3,4-oxadiazole derivatives **12** and evaluated them for in vitro antitubercular activity against Mycobacterium tuberculosis H37Ra (MTB) and Mycobacterium bovis BCG in both active and inactivated conditions.[12]



13

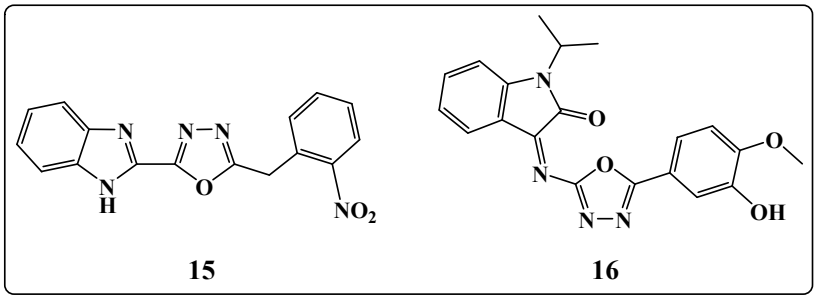
Subba Rao et al synthesized a series of imidazopyridinyl-1,3,4-oxadiazole conjugates and evaluated their cytotoxic activity.[13] Compound **13** showed remarkable activity against a panel of 60 human cancer cell lines with GI50 values ranging from 1.30 to 5.64 μM. This significant growth inhibition of met the single dose (10 μM) threshold criteria on all human cancer cell lines. Furthermore compound **13** displayed good antiproliferative activity against A549 cell line by inhibiting topoisomerase IIα and induced apoptosis.



14a **14b**

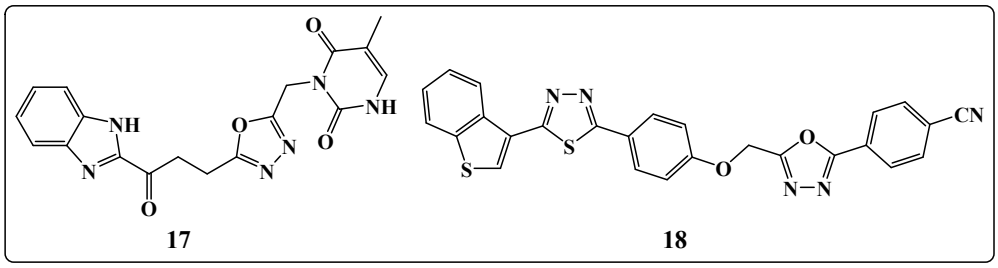
Ragab et al have designed and synthesized a series of 1,3,4-oxadiazole derivatives as monastrol analogues and were screened for their cytotoxic activity toward 60 cancer cell lines.[14] Seven compounds were further examined against the most sensitive cell lines, leukaemia HL-60 (TB) and MOLT-4 in which compound **14a** exhibited potent activity against HL-60 (B) with an IC_{50} value of 56 nm and compound **14b** exhibited excellent

cytotoxicity against MOLT-4 with an IC_{50} value of 80 nm. The activity of compounds **14a** and **14b** is more potent than that of the standard drug, monastrol.



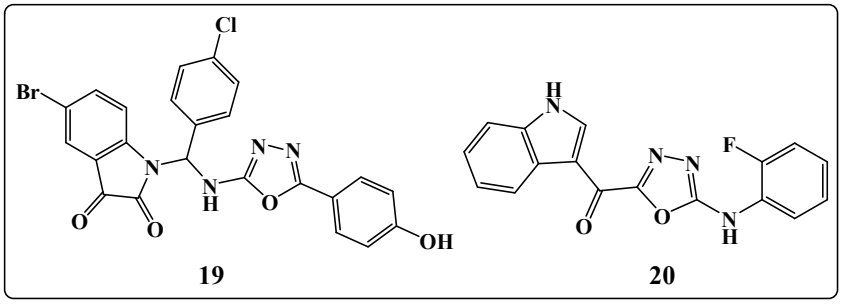
15 **16**

Hamdy and co-workers reported the synthesis of indole-based oxadiazole hybrids and evaluated their anticancer activity against Bcl-2-expressing human cancer cell lines.[15] Hybrid **15** showed significant IC_{50} values against Bcl-2-expressing human cancer cells (HeLa = 0.30 ± 0.04 μM; KG1A = 0.85 ± 0.08 μM; MDaMB-231 = 0.90 ± 0.02 μM). Compound **15** has Bcl-2 binding (ELISA assay) comparable to gossypol, an established natural product-based Bcl-2 inhibitor. *Javid et al* synthesized isotin based 1,3,4-oxadiazole, which showed potent thymidine phosphorylase inhibitory properties.[16] All hybrids exhibited better inhibition than the standard 7-dezaxanthin (IC_{50} = 38.68 ± 1.12 mM). Among the synthesized compounds, 3-hydroxy-4-methoxy phenyl (R) **16** showed excellent inhibitory properties with an IC50 value in the range of 4.70 ± 0.10–6.20 ± 0.10 mM. These results revealed that the phenyl ring containing the hydroxy group was responsible for the highest activity of the hybrid.



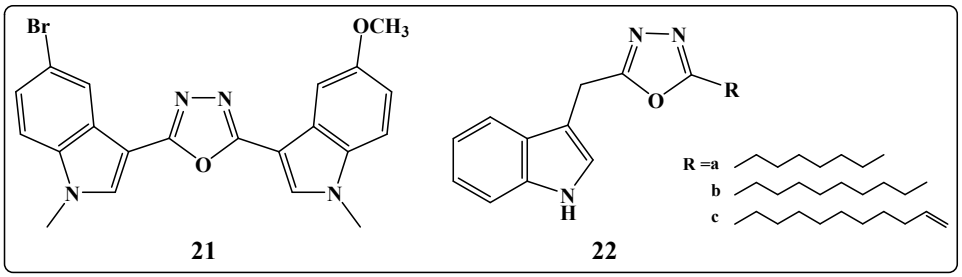
17 **18**

Benzimidazole fused oxadiazoles, an analogues of bendamustine, have been synthesized and cytotoxic activities of these analogues were carried out against full NCI 60 human cell lines.[17] Among all the tested compounds, **17** exhibited significant antiproliferative activity and was further screened at 10-fold dilutions of five different concentrations with GI_{50} values ranging from 0.09 to 16.2 μM and found superior for CNS cancer cell line SNB-75. *Spandana et al* reported the synthesis of a new series of 1,3,4-oxadiazole linked thiadiazole derivatives and screened them for their anticancer activity against A549, MCF-7, A375 and HT-29 cell lines using MTT assay with Combretastatin-A4 as standard drug.[18] Among them, compound **18** showed potent anticancer activity with moderate to high IC_{50} values against A549, MCF-7, A375 and HT-29 cell lines.

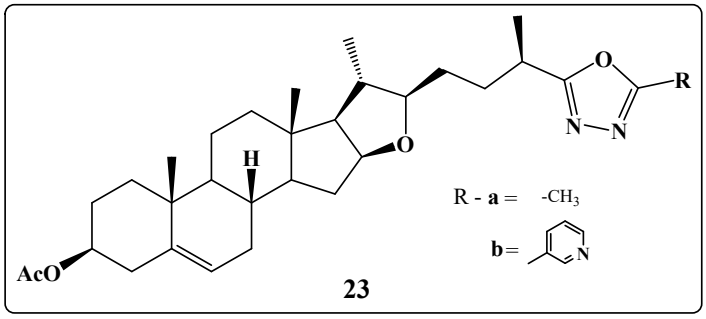


19 **20**

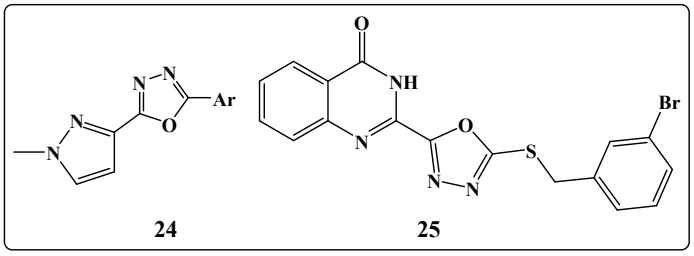
Twelve different (N-heterocycle) substituted 1,3,4-oxadiazoles were synthesized and their cytotoxic behavior was examined by MTT based assay by *Bhatt et al*.[19] Compound **19** displayed the best activity against two human cancer cell lines (IC50= 0.78 + 0.19 μM (HT29, IC50 = 0.26 + 0.15 μM (HepG2))) among all the synthesized compounds. *Naz et al* reported that 1,3,4-oxadiazole-based topsanthin analogs showed significant anticancer activity against an NCI panel of 60 human cancer cell lines in an in-vitro polymerization assay method.[20] Among the tested compounds, **20** showed better activity (IC_{50} = 2.42 mm) against MCF7 cell line compared to standard doxorubicin (IC_{50} = 6.31 mm). The compound inhibited tubulin polymerization with an IC_{50} of 3.89 mM (standard nocodazole IC_{50} = 2.49 mM), thereby inhibiting the motility of microtubules.



A new series of 2,5-bis(indolyl)-1,3,4-Oxadiazole analogues was synthesized and evaluated for their anticancer activities against Cervical (HeLa), Breast (MCF-7 & MDA-MB-231), Lung (A549) cancer cell lines by using Doxorubucin as standard drug with MTT reduction assay protocol.[21] Hybrid **21** showed promising activity against all cell lines (IC_{50} = 2.6 ± 0.89-6.34 ± 0.56 mm) except MDA-MB231. *Venepally et al* reported the synthesis of a series of novel indole and trimethoxyphenyl condensed 1,3,4-oxadiazoles and evaluated them for their cytotoxicity against A549, MCF-7 and HeLa cell lines.[22] Compounds **22a-c** exhibited potent inhibitory activity with IC_{50} values ranging from 8.26 to 11.36 µM.



In the search for new antimycobacterial drugs, a series of hybrid molecules with indole and oxadiazole motifs have been synthesized and screened for some promising activity against tubercular strains of *Mycobacterium tuberculosis* (ATCC 25177) and *Mycobacterium bovis* (ATCC 35734).[23] Compound inhibited *M. bovis* strain 100% in 10 µg/mL concentration, while compound 5m inhibited M. tuberculosis strain 90.4% in 30 µg/mL concentration. *Zhang et al* reported the synthesis of new diosgenin-linked 1,3,4-oxadiazole derivatives and evaluated for their cytotoxicity against four human cancer cell lines (Hep-G2, A549, MCF-7 and HCT-116) and normal human gastric epithelial cells using the MTT assay reduction method with Diosgenin and Mitomycin-C as standard drugs.[24] Among them, compounds **23a** and **23b** showed potent cytotoxicity against A549 cell line with IC_{50} values of 34.38 ± 1.22 µM and 33.55 ± 1.34 µM, respectively.



Metre et al have synthesized some novel 2-aryl-5-(1-aryl-1H-pyrazol-3-yl)-1,3,4-oxadiazoles **24** have been synthesized and the anti-tubercular activity was investigated against Mycobacterium tuberculosis H37Rv strain in which most of the compounds exhibited excellent activity at the 6.25 µg/ml concentrations.[25] *Li et al* designed and synthesized a series of 1,3,4-oxadiazole and 1,2,4-triazole linked quinazolinone derivatives and evaluated them for their in vitro antiproliferative activity against A549, HeLa, MCF-7 as well as L929.[26] Compound **25** showed a better growth inhibitory effect than 5-FU on A549, HeLa and MCF-7 cell lines with an IC50 value of 3.46 µM. Also all compounds showed lower cytotoxicity in L929 cells than the positive control drug 5-FU, so these compounds could become potential molecular templates for the discovery of new antitumor agents.

References:

1. Rajak, H.; Agarawal, A.; Parmar, P.; Thakur, B.S.; Veerasamy, R.; Sharma, P.C.; Khaya, M.D. 2,5-Disubstituted-1,3,4-oxadiazoles/thiadiazole as surface recognition moiety: Design and synthesis of novel hydroxamic acid based histone deacetylase inhibitors. *Bioorg. Med. Chem. Lett.* **2011;** *21,* 5735-5738.

2. Abu-Zaied, M.A.; El-Telbani, E.M.; Elgemeie, G.H.; Nawwar, G.A.M. Synthesis and in vitro anti-tumor activity of new oxadiazole thioglycosides, *Eur. J. Med. Chem.*, **2011**; *46,* 229-235.

3. Bostrom, J.; Hogner, A.; Llinas, A.; Wellner, E.; Plowright, A. T. Oxadiazoles in medicinal chemistry. *J. Med. Chem.,* **2012;** *55,* 1817-1830.

4. Puthiyapurayil, P.; Poojary, B.; Chikkanna, C.; Buridipad, S. K. Design, synthesis and biological evaluation of a novel series of 1,3,4-oxadiazole bearing N-methyl-4-(trifluoromethyl)phenyl pyrazole moiety as cytotoxic agents. *Eur. J. Med. Chem.,* **2012;** *53,* 203-210.

5. Husain, A.; Rashid, M.; Mishra, R.; Parveen, S.; Shin, D.-S.; Kumar, D. Benzimidazole bearing oxadiazole and triazolothiadiazoles nucleus: Design and synthesis as anticancer agents. *Bioorg. Med. Chem. Lett.*, **2012**; *22*, 5438-5444.

6. Rashid, M.; Husain, A.; Mishra, R. Synthesis of benzimidazoles bearing oxadiazole nucleus as anticancer agents. *Eur. J. Med. Chem.*, **2012**; *54*, 855-866.

7. Zhang, F.; Wang, X.L.; Shi, J.; Wang, S.F.; Yin, Y.; Yang, Y.S.; Zhang, W.M.; Zhu, H.L. Synthesis, molecular modeling and biological evaluation of *N*-benzylidene-2-((5-(pyridin-4-yl)-1,3,4-oxadiazol-2-yl)thio)acetohydrazide derivatives as potential anticancer agents. *Bioorg. Med. Chem.* **2014**; *22*, 468-477.

8. Du, Q.-R.; Li, D.-D.; Pi, Y.-Z.; Li, J.-R.; Sun, J.; Fang, F.; Zhong, W.-Q.; Gong, H.-B.; Zhu, H.-L. Novel 1,3,4-oxadiazole thioether derivatives targeting thymidylate synthase as dual anticancer/antimicrobial agents. *Bioorg. Med. Chem.*, **2013**; *21*, 2286-2297.

9. Salahuddin, M. Shaharyar, A. Mazumder, M.J. Ahsan, Ahsan, Synthesis, characterization and anticancer evaluation of 2-(naphthalen-1-ylmethyl/naphthalen2-yloxymethyl)-1-[5-(substituted phenyl)-[1,3,4]oxadiazol-2-ylmethyl]-*1H*-benzimidazole. *Arab. J. Chem.*, **2014**; *7*, 418-424.

10. Valente, S.; Trisciuoglio, D.; Luca, T. D.; Nebbioso, A.; Labella, D.; Lenoci, A.; Bigogno, C.; Dondio, G.; Miceli, M.; Brosch, G.; Bufalo, D. D.; Altucci, L.; Mai, A. 1,3,4-Oxadiazole-containing histone deacetylase inhibitors: anticancer activities in cancer cells. *J. Med. Chem.,* **2014,** *57,* 6259-6265.

11. Islavathu, H.; Sreenivasulu, R.; Jadav, S.S.; Jawed, M.; Rudraraju, A.; Raju, R. Synthesis and biological evaluation of 1, 3, 4-oxadiazole-linked bisindole derivatives as anti cancer agent. *Monatsheftefür Chemie Chemical*, **2015**; *146*, 1699-1705.

12. Desai, N.C.; Somani, H.; Trivedi, A.; Bhatt, K.; Nawale, L.; Khedkar, V.M.; Jha, P.C.; Sarkar, D. Synthesis, biological evaluation and molecular docking study of some novel indole and pyridine based 1,3,4-oxadiazole derivatives as potential antitubercular agents. *Bioorg. Med. Chem. Lett.*, **2016**; *26*, 1776-1783.

13. Subba Rao, A.V.; Vardhan M.V.P.S.V.; Subba Reddy N.V.; Reddy, T.S.; Shaik, S.P.; Bagul, C.; Kamal, A. Synthesis and biological evaluation of imidazopyridinyl-1,3,4-oxadiazole conjugates as apoptosis inducers and topoisomerase IIα inhibitors. *Bioorg. Chem.*, 69, 7-19.

14. Ragab, F.A.F.; Abou-Seri, S.M.; Abdel-Aziz, S.A.; Alfayomy, A. M.; Aboelmagd, M. Design, synthesis and anticancer activity of new monastrol analogues bearing 1,3,4-oxadiazole moiety. *Eur. J. Med. Chem.* **2017,** *138,* 140-151.

15. Hamdy, R.; Ziedan, N.I.; Ali, S.; Bordoni, C.; El-Sadek, M.; Lashin, E.; Brancale, A.; Jones, A.T.; Westwell, A.D. Synthesis and evaluation of 5-(1*H*-indol-3-yl)-*N*-aryl-1,3,4-oxadiazol-2-amines as Bcl-2 inhibitory anticancer agents. *Bioorg. Med. Chem. Lett.*, 2017; *27*, 1037-1040.

16. Javid, M.T.; Rahim, F.; Taha, M.; Nawaz, M.; Wadood, A.; Ali, M.; Mosaddik, A.; Shah, S.A.A.; Farooq, R.K. Synthesis, SAR elucidations and molecular docking study of newly designed isatin based oxadiazole analogs as potent inhibitors of thymidine phosphorylase. *Bioorg. Chem.*, 2018; 79, 323-333.

17. Rashid, M.; Husain, A.; Mishra, R.; Karim, S.; Khan, S.; Ahmad, M.; Al-wabel, N.; Husain, A.; Ahmad, A.; Khan, S.A. Design and synthesis of benzimidazoles containing substituted oxadiazole, thiadiazole and triazolo-thiadiazines as a source of new anticancer agents. *Arab. J. Chem.*, **2019**; *12*, 3202-3224.

18. Spandana, Z.; Sreenivasulu,R.; Rekha, T.M.; Rao, M.V.B. Novel 1,3,4-oxadiazole fused thiadiazole derivatives: synthesis and study of anticancer activities. *Lett. Drug Des. Discov.* **2019**, *16*, 656-662.

19. Bhatt, P.; Sen, A.; Jha, A. Design and ultrasound assisted synthesis of novel 1,3,4-oxadiazole drugs for anti-cancer activity, *Chemistry Select*, **2020**; *5*, 3347-3354.

20. Naaz, F.; Ahmad, F.; Lone, B.A.; Pokharel, Y.R.; Fuloria, N.K.; Fuloria, S.; Ravichandran, M.; Pattabhiraman, L.; Shafi, S.; Yar, M.S. Design and synthesis of newer 1,3,4-oxadiazole and 1,2,4-triazole based Topsentin analogues as antiproliferative agent targeting tubulin. *Bioorg. Chem.*, **2020**; *95*, 103519.

21. Sreenivasulu, R.; Tej, M.B.; Jadav, S.S.; Sujitha, P.; Kumar, C.G.; Raju, R.R. Synthesis, anticancer evaluation and molecular docking studies of 2,5-bis(indolyl)-1,3,4-oxadiazoles, nortopsentin analogues. *J. Mol. Struct.* **2020**, *1208*, 127875.

22. Venepally, V.; Routhu, S.R.; Kumar, C.G.; Jala, R.C.R. Synthesis, cytotoxic evaluation of novel 2-((1H-indol-3-yl)methyl)-5-alkyl-1,3,4-oxadiazole and 2-alkyl-5-(3,4,5-trimethoxyphenyl)-1,3,4-oxadiazole derivatives. *Indian J. Chem.*, **2020**; *59B*, 465-473.

23. Desai, N.C.; Somani, H.C.; Mehta, H.K.; Jadeja, D.J.; Khasiya, A.G.; Khedkar, V.M. Microwave-assisted organic synthesis, antimycobacterial activity, structure-activity relationship and molecular docking studies of some novel indole-oxadiazole hybrids. *SAR and QSAR in Environ. Res.*, **2022**; *33*, 89-109.

24. Zhang, J.; Wang, X.; Yang, J.; Guo, L.; Wang, X.; Song, B.; Dong, W.; Wang, W. Novel diosgenin derivatives containing 1,3,4-oxadiazole/thiadiazole moieties as potential antitumor agents: Design, synthesis and cytotoxic evaluation. *Eur. J. Med. Chem.* **2020**, *186,* 111897.

25. Metre, T.V.; Joshi, S.D.; Kodasi, B.; Bayannavar, P.K.; Nesaragi, A.R.; Madar, S.F.; Mavazzan, A.R.; Kamble, R.R. L-proline catalyzed ring transformation of 5-substituted tetrazole to 1,3,4-oxadiazoles as anti-tubercular agents, *Synth. Commun.*, **2022**; *52*, 1500-1516.

26. Li, Z.; Men, Y.; Gao, S.; Cui, P.; Wang, H.; Chen, B. Design, synthesis, and antiproliferative investigation of novel quinazolinones incorporating 1,3,4-oxadiazole and 1,2,4-triazole thioether moieties. *Phosphorus, Sulfur, and Silicon and the Related Elements*, **2024**; *199*, 45-53.