Synthesis and *In Vitro* Anticancer Activity of Novel 1,3,4-Oxadiazole-Linked 1,2,3-Triazole/Isoxazole Hybrids

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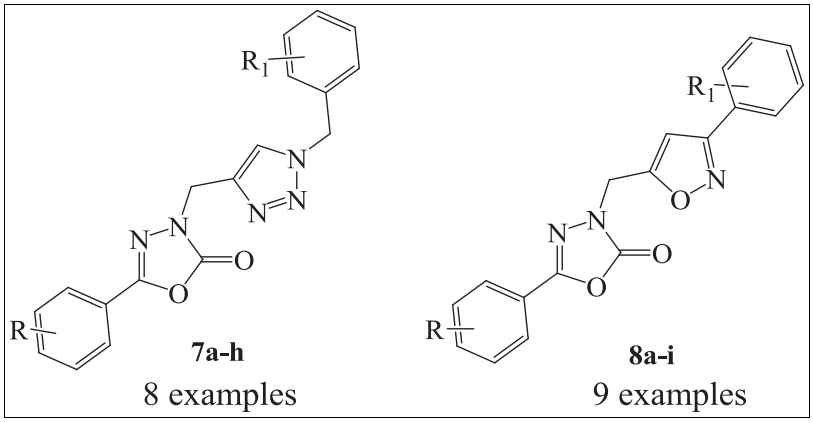

A series of new 1,3,4-oxadiazole-linked 1,2,3-triazole/isoxazole derivatives were designed and synthesized. All the synthesized compounds were screened for *in vitro* anticancer activity against four human cancer cells: HeLa (cervical), MDA-MB-231 (breast), DU-145 (prostate), and HEPG2 (liver). Among 17 compounds tested, **7a**, **7c**, and **7d** showed potent activity toward four cell lines.

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INTRODUCTION

Cancer is a life-threatening disease and is considered as the second most common cause of death worldwide after cardiovascular diseases. Despite significant progress that has been achieved in anticancer therapy, the development of new anticancer drugs represents a major challenge to medicinal chemist researchers. 1,3,4-Oxadiazoles are a very important class of heterocyclic compounds, and much attention has been paid to the chemistry and biological activities of this nucleus. Oxadiazoles are known to exhibit a wide range of biological activities, such as anticancer [1–5], antibacterial [6,7], antifungal [8,9], antidiabetic [10], antitubercular [11], and anti-inflammatory [12–14]. In addition, the triazole scaffold is an attractive moiety not only from a synthetic point of view but also in the context of biological and drug discovery applications [15–22] owing to its easy formation by click chemistry. On the other hand, isoxazoles are core components of many natural products [23–25], and their wide range of biological activities [26–30] makes them important anchors in the field of medicinal chemistry.

Individually, 1,3,4-oxadiazole and triazole/isoxazole moieties are of significant biological interest owing to their importance in drugs and pharmaceuticals (Fig. 1). To assess their combined biological impact, we designed and synthesized a new series of hybrid molecules containing 1,3,4-oxadiazole-linked triazole/isoxazole units in one core and subjected them to *in vitro* anticancer evaluation.

RESULTS AND DISCUSSION

Chemistry. As illustrated in Scheme 1, aryl acid hydrazides **3a**–**3d** were synthesized by the reaction of 85% hydrazine hydrate with esters **2a**–**2d**, which derived from substituted benzoic acids **1a**–**1d**, in methanol under reflux condition. Treatment of compounds **3a**–**3d** with ethyl chloroformate in toluene in the presence of potassium carbonate under reflux condition for 5 h gave ethyl 2-benzoylhydrazinecarboxylates **4a**–**4d**. The starting materials, 5-aryl-1,3,4-oxadiazol-2(3*H*)-ones (**5a**–**5d**) [31], were prepared in good yields by cyclization of

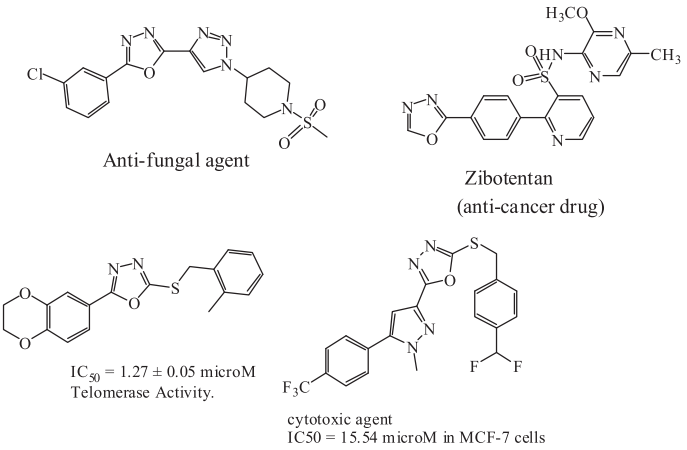
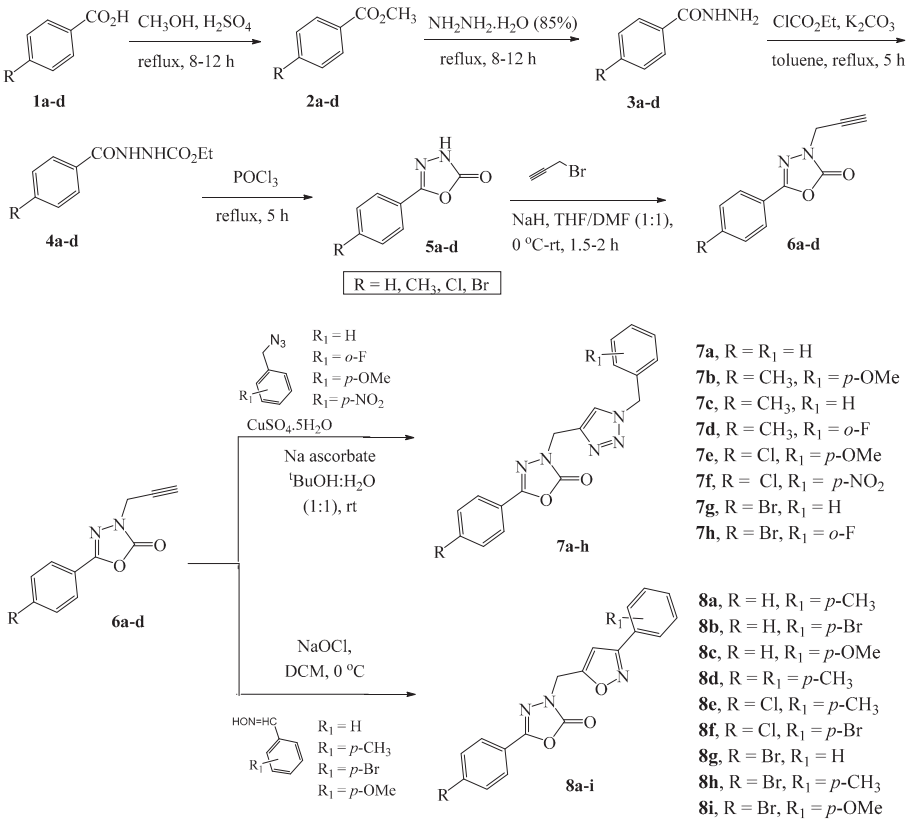


Figure 1. 1,3,4-Oxadiazole moiety containing pharmaceutical agents. IC_{50}, half maximal inhibitory concentration.

Scheme 1. Synthesis of oxadiazole–triazole/isoxazole hybrids.



compounds **4a**–**4d** under reflux conditions using $POCl_3$. Our study started with the reaction between 5-aryl-1,3,4-oxadiazol-2(3*H*)-ones (**5a**–**5d**) and propargyl bromide in the presence of NaH in tetrahydrofuran/dimethylformamide (1:1) to obtain the 5-aryl-3-(prop-2-ynyl)-1,3,4-oxadiazol-2(3*H*)-ones (**6a**–**6d**) [32]. In the second step, these *N*-propargylated compounds **6a**–**6d** were independently reacted with various azides using "click" chemistry and aldoximes, respectively giving novel 3-((1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl)-5-aryl-1,3,4-oxadiazol-2(3*H*)-one hybrids (**7a**–**7h**) and 5-aryl-3-((3-arylisoxazol-5-yl)methyl)-1,3,4-oxadiazol-2(3*H*)-one hybrids (**8a**–**8i**) in good yields (Scheme 1).

In this study, 17 derivatives, **7a**–**7h** and **8a**–**8i**, were synthesized and reported for the first time. All the synthesized compounds were characterized by ^{1}H-NMR, ^{13}C-NMR, and HRMS (the spectral data are included in the supporting information) data.

Biology. ***Antiproliferative activity.*** Meanwhile, *in vitro* antitumor activities of these compounds were evaluated against HeLa, MDA-MB-231, DU-145, and HEPG2 cells with the ultimate aim of developing novel potent antitumor agents.

Nocodazole and paclitaxel were employed as positive controls (Table 1). In general, antimitotic drugs are used as frontline therapies; hence, we choose these 2 antimitotic agents to compare the activities of the congeners.

On the basis of the GI_{50} values, we have predicted the structure–activity relationship of all the synthesized compounds (**7a**–**7h** and **8a**–**8i**), and we assumed that the compounds containing methyl-substituted aromatic groups present on the oxadiazole moiety such as **7a**, **7c**, and **7d** are potent toward the four human anticancer cells. Halogens present on the aromatic rings attached to the oxadiazole moiety affect the potentiality downwards.

As the bulkiness of the atoms (or) groups present on the benzylic group attached to the triazole moiety shows greater effects on the potentiality toward the cytotoxicity, it was observed that the smaller the atom (or) group, the greater was the potentiality in the case of **7a**, **7c**, and **7d**.

The congeners having an isoxazole link to the oxadiazole moiety showed moderate activity, which indicates that triazole-ring-linked congeners are more potent than the isoxazole-linked congeners. All these structure activity relationship (SAR) assumptions were deduced based on the preliminary GI_{50} results.

Immunoblot analysis of cellular cyclin B1 levels. As three compounds in this series showed significant cytotoxicity, we tested their effect on cellular cyclin B1. This is one of the essential regulatory proteins of mitosis, and a high level of cyclin B1 is an indicator for G2/M arrest. Thus, HeLa cells were treated with 5 μ*M* of compounds **7a**, **7c**, and **7d** for 24 h and subjected to an immunoblot for cyclin B1. We used nocodazole as a positive control and tubulin as a loading control. Interestingly, **7a**, **7c**, and **7d** showed a marked increase in cyclin B1 level comparable to nocodazole-treated cells (Fig. 2).

Immunoblot analysis of soluble versus insoluble (polymerized) tubulin in HeLa cells. To further examine whether these compounds disrupt microtubule dynamics, we checked the levels of soluble versus insoluble (polymerized) forms of tubulin. HeLa cells were treated with 5 μ*M* of compounds **7a**, **7c**, and **7d**. Nocodazole and dimethyl sulfoxide were used as positive and negative controls, respectively (Fig. 3).

After 24 h of treatment, cells were permeabilized to collect the soluble fraction, and the remaining cells were collected as the insoluble fraction and subjected to immunoblot analysis. This analysis revealed that these compounds showed potent inhibition of tubulin

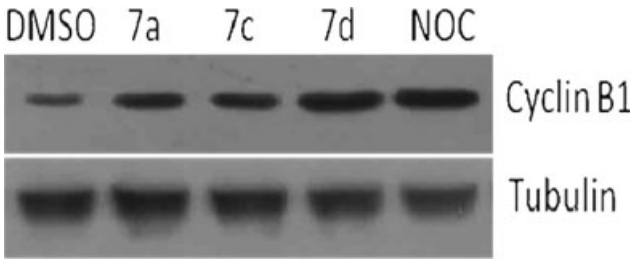


Figure 2. Western blot analysis of cyclin B1. DMSO, dimethyl sulfoxide; NOC, nocodazole.

Table 1

Growth inhibition of 50% (GI_{50})/μ*M* values of compounds triazole and isoxazole series, **7a**–**7h** and **8a**–**8i**.

Compound	HeLa	MDA-MB-231	DU-145	HEPG2
7a	**1.28 ± 0.3**	**1.75 ± 0.2**	**2.39 ± 0.4**	**1.84 ± 0.2**
7b	3.62 ± 1.1	6.4 ± 0.7	7.21 ± 0.8	4.25 ± 0.6
7c	**1.7 ± 0.25**	**2.14 ± 0.6**	**1.72 ± 0.04**	**1.78 ± 0.1**
7d	**0.82 ± 0.15**	**1.04 ± 0.2**	**0.96 ± 0.04**	**1.42 ± 0.25**
7e	4.25 ± 0.8	6.24 ± 0.04	8.82 ± 0.6	6.8 ± 0.05
7f	6.13 ± 0.7	6.92 ± 0.02	9.65 ± 0.8	8.26 ± 0.5
7g	8.23 ± 0.9	9.58 ± 1.2	8.24 ± 0.7	10.22 ± 0.6
7h	6.39 ± 0.5	8.11 ± 0.2	7.25 ± 1.1	5.16 ± 0.08
8a	7.29 ± 0.9	10.41 ± 1.2	6.47 ± 0.8	9.92 ± 0.6
8b	5.7 ± 0.9	8.8 ± 0.6	11.27 ± 1.4	6.01 ± 0.2
8c	8.16 ± 0.3	6.26 ± 0.7	9.43 ± 1.1	11.23 ± 1.2
8d	6.95 ± 0.6	8.12 ± 0.08	5.17 ± 0.2	8.27 ± 0.4
8e	7.82 ± 0.8	6.26 ± 0.9	7.55 ± 0.4	8.13 ± 1.1
8f	10.32 ± 1.1	9.13 ± 0.9	6.72 ± 0.45	7.34 ± 0,6
8g	6.2 ± 0.8	8.82 ± 1.2	7.51 ± 0.4	6.81 ± 0.8
8h	7.92 ± 0.7	6.34 ± 0.5	9.3 ± 1.2	9.29 ± 0.8
8i	8.37 ± 0.9	10.66 ± 1.1	9.18 ± 0.8	8.45 ± 0.9
Paclitaxel	0.034 ± 0.003	0.027 ± 0.002	<0.016 ± 0.004	0.05 ± 0.002
Nocodazole	0.021 ± 0.001	0.034 ± 0.003	0.023 ± 0.002	<0.011 ± 0.002

Potent towards the four human anti-cancer cells are shown in bold font.

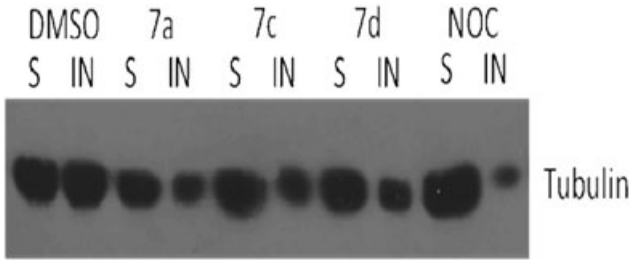


Figure 3. Western blot analysis of distribution of tubulin in soluble (S) versus insoluble (IN) fractions. DMSO, dimethyl sulfoxide; NOC, nocodazole.

polymerization and possessed increased levels of insoluble tubulin fraction similar to nocodazole-treated cells.

CONCLUSION

In the present study, a focused library of 1,3,4-oxadiazole-triazole/isoxazole moieties conjugated through a nitrogen linkage is synthesized and evaluated for their anticancer activity against four human cancer cell lines: HeLa, MDA-MB-231, DU-145, and HEPG2. Among them, **7a**, **7c**, and **7d** showed a potent anticancer activity against all the tested cancer cell lines and inhibited tubulin polymerization. Western blot analysis in the HeLa cell line showed that these lead compounds induced cyclin B1 protein level, which is a strong indicator of G2/M cell cycle arrest. These compounds also disrupted microtubule assembly and increased the amount of insoluble tubulin fractions of cells like other potent tubulin polymerization inhibitors such as nocodazole. These results demonstrate that the triazole and isoxazole series compounds are potent tubulin polymerization inhibitors, which can serve as a useful template for the generation of a related new class of molecules as potential anticancer drugs.

EXPERIMENTAL

Chemistry. Melting points were recorded on an Electrothermal melting point apparatus (Hyderabad, India) and are uncorrected. IR spectra were recorded on a Perkin-Elmer Fourier transform IR 240-C spectrophotometer (Hyderabad, India) using KBr optics. ^{1}H-NMR spectra were recorded on Bruker AV (Hyderabad, India) 300 MHz, $CDCl_3$, using tetramethylsilane as an internal standard. Electron spray ionization (ESI) and HRMS were recorded on a QSTARXL hybrid MS/MS system (Applied Biosystems, Hyderabad, India). All the reactions were monitored by thin-layer chromatography (TLC) on precoated silica gel 60 F_{254} (mesh); spots were visualized with UV light. Merck silica gel (180–200 mesh) was used for column chromatography.

General procedure for the synthesis of 5-aryl-1,3,4-oxadiazol-2(3*H*)-ones (5a–5d). The 5-aryl-1,3,4-oxadiazol-2(3*H*)-ones **(5a–5d)** were synthesized by a modified literature method as follows: $POCl_3$ (200 mL, mmol) was taken in a round-bottomed flask, and much ethyl 2-benzoylhydrazinecarboxylate (**4a–4d**) (mmol) was added to it at room temperature. After the addition is over, it was slowly heated to reflux for 5 h. $POCl_3$ was distilled, and then the reaction mass was poured into crushed ice and filtered, and the residue was purified by recrystallization from methanol to afford the corresponding products.

General procedure for the synthesis of 5-aryl-3-(prop-2-ynyl)-1,3,4-oxadiazol-2(3*H*)-ones (6a–6d). To a suspension of NaH (12.3 mmol, 2 equiv) in anhydrous tetrahydrofuran (20 mL) was added a solution of 5-aryl-1,3,4-oxadiazol-2(3*H*)-one (**5a–5d**) (6.17 mmol, 1 equiv) in anhydrous dimethylformamide (10 mL) in a dropwise manner at 0°C. After 30 min, propargyl bromide (9.87 mmol, 1.6 equiv) was added at 0°C and allowed to stir for 30 min at room temperature. After completion, followed by TLC, the mixture was quenched with ice H_2O (15 mL) and extracted with ethyl acetate (2 × 50 mL). The combined organic layer was dried over anhydrous Na_2SO_4, concentrated, and purified by silica gel column chromatography (hexane : ethyl acetate, 9:1) to afford the pure *O*-propargylated compounds **6a–6d**.

5-Phenyl-3-(prop-2-yn-1-yl)-1,3,4-oxadiazol-2(3H)-one (6a). Colorless solid; yield 98%; mp 60–62°C; IR (KBr): 2969, 1782, 1670, 1351, 740 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.89–7.85 (m, 2H), 7.55–7.45 (m, 3H), 4.61 (d, J = 2.6 Hz, 2H), 2.42 (t, J = 2.4 Hz, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 153.7, 152.7, 131.8, 128.9 (2C), 125.8 (2C), 123.5, 75.7, 73.8, 35.7; HRMS (ESI) for $C_{11}H_9N_2O_2$ $[M + H]^+$, found 201.0668, Calcd 201.0664.

3-(Prop-2-yn-1-yl)-5-(p-tolyl)-1,3,4-oxadiazol-2(3H)-one (6b). Colorless solid; yield 96%; mp 76–77°C; IR (KBr): 2965, 1782, 1608, 1350, 741 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.75 (d, J = 8.3 Hz, 2H), 7.28 (d, J = 7.9 Hz, 2H), 4.59 (d, J = 2.6 Hz, 2H), 2.42–2.40 (m, 4H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 153.9, 152.8, 142.4, 129.6 (2C), 125.7 (2C), 120.7, 75.8, 73.7, 35.6, 21.6; HRMS (ESI) for $C_{12}H_{11}N_2O_2$ $[M + H]^+$, found 215.0828, Calcd 215.0820.

5-(4-Chlorophenyl)-3-(prop-2-yn-1-yl)-1,3,4-oxadiazol-2(3H)-one (6c). Colorless solid; yield 98%; mp 62–64°C; IR (KBr): 3092, 2923, 1781, 1384, 837 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.80 (d, J = 8.8 Hz, 2H), 7.46 (d, J = 8.8 Hz, 2H), 4.60 (d, J = 2.4 Hz, 2H), 2.42 (t, J = 2.4 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 152.9, 152.5, 138.1, 129.4 (2C), 127.1 (2C), 122.0, 75.6, 73.9,

35.8; HRMS (ESI) for $C_{11}H_8ClN_2O_2$ $[M + H]^+$, found 235.0279, Calcd 234.0274.

5-(4-Bromophenyl)-3-(prop-2-yn-1-yl)-1,3,4-oxadiazol-2(3H)-one (6d). Colorless solid; yield 96%; mp 70–72°C; IR (KBr): 2969, 2926, 1779, 820 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.73 (d, J = 8.7 Hz, 2H), 7.63 (d, J = 8.6 Hz, 2H), 4.60 (d, J = 2.6 Hz, 2H), 2.42 (t, J = 2.6 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 153.0, 152.5, 132.3 (2C), 127.2 (2C), 126.5, 122.4, 75.6, 73.9, 35.8; HRMS (ESI) for $C_{11}H_8BrN_2O_2$ $[M + H]^+$, found 278.9779, Calcd 278.6769.

General procedure for the synthesis of 3-[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]-5-aryl-1,3,4-oxadiazol-2(3*H*)-ones (7a–7h). To a mixture of (azidomethyl)-benzenes (0.55 mmol) were added propargyl compounds (**6a**–**6d**) (0.5 mmol) in *t*BuOH : H_2O (1:1, 15 mL), $CuSO_4{\cdot}5H_2O$ (0.1 mmol), and sodium ascorbate (0.47 mmol) at room temperature. The mixture was stirred for 2 h at the same temperature. The mixture was poured into ice water (10 mL) with stirring. The solution was extracted with ethyl acetate (3 × 20 mL), washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography (petroleum ether : ethyl acetate, 5:5) to afford the pyrazolotriazole hybrid compounds (**7a**–**7h**).

3-((1-Benzyl-1H-1,2,3-triazol-4-yl)methyl)-5-phenyl-1,3,4-oxadiazol-2(3H)-one (7a). Colorless solid; yield 89%; mp 160–162°C; IR (KBr): 3141, 2925, 1773, 1610, 830 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.83–7.78 (m, 2H), 7.57 (s, 1H), 7.52–7.41 (m, 3H), 7.40–7.34 (m, 3H), 7.30–7.25 (m, 2H), 5.52 (s, 2H), 5.09 (s, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 152.9, 152.7, 141.7, 134.2, 132.2 (2C), 129.1(2C), 128.9, 128.1(2C), 127.1 (2C), 126.3, 122.7, 122.5, 54.3, 41.5; HRMS (ESI) for $C_{18}H_{15}N_5O_2Na$ $[M + Na]^+$, found 356.1148, Calcd 356.1118.

3-((1-(4-Methoxybenzyl)-1H-1,2,3-triazol-4-yl)methyl)-5-(p-tolyl)-1,3,4-oxadiazol-2(3H)-one (7b). Colorless solid; yield 83%; mp 147–149°C; IR (KBr): 3108, 2922, 1776, 1615, 1252, 823 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.68 (d, J = 8.2 Hz, 2H), 7.52 (s, 1H), 7.27–7.21 (m, 4H), 6.81 (d, J = 8.6 Hz, 2H), 5.45 (s, 2H), 5.06 (s, 2H), 3.80 (s, 3H), 2.39 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 159.9, 153.6, 153.2, 142.2, 129.7 (2c), 129.6 (3c), 126.2, 125.6 (2c), 122.5, 120.8, 114 (2c), 55.2, 53.8, 41.4, 21.6; HRMS (ESI) for $C_{20}H_{20}N_5O_3$ $[M + H]^+$, found 378.1575, Calcd 378.1566.

3-((1-Benzyl-1H-1,2,3-triazol-4-yl)methyl)-5-(p-tolyl)-1,3,4-oxadiazol-2(3H)-one (7c). Colorless solid; yield 80%; mp 167–169°C; IR (KBr): 3132, 2995, 1770, 1609, 1347, 747 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.69 (d, J = 8.3 Hz, 2H), 7.58 (brs, 1H), 7.40–7.34 (m, 4H), 7.29–7.21 (m, 3H), 5.52 (s, 2H), 5.08 (s, 2H), 2.39 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 153.6, 153.2, 142.2, 134.2, 129.6 (3C), 129.1 (2C), 128.8, 128.1 (2C), 125.6 (2C), 122.7, 120.8, 54.2, 41.4, 21.6; HRMS (ESI) for $C_{19}H_{17}N_5O_2$ Na $[M + Na]^+$, found 370.1298, Calcd 370.1274.

3-((1-(2-Fluorobenzyl)-1H-1,2,3-triazol-4-yl)methyl)-5-(p-tolyl)-1,3,4-oxadiazol-2(3H)-one (7d). Colorless solid; yield 76%; mp 176–178°C; IR (KBr): 3071, 2985, 1772, 1615, 1343, 766 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.68 (t, J = 8.2 Hz, 3H), 7.38–7.27 (m, 2H), 7.24(d, J = 8.1 Hz, 2H) 7.17–7.09 (m, 2H), 5.58 (s, 2H), 5.09 (s, 2H), 2.39 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 160.5 (d, $J_{C\text{-}F}$ = 247.9 Hz), 153.6, 153.2, 142.2, 142.0, 131.0 (d, $J_{C\text{-}F}$ = 8.1 Hz) 130.6 (d, $J_{C\text{-}F}$ = 2.9 Hz), 129.6 (2c), 125.7 (2c), 124.8 (d, $J_{C\text{-}F}$ = 2.9 Hz), 122.9, 121.5 (d, $J_{C\text{-}F}$ = 14.5 Hz), 120.8, 115.8 (d, $J_{C\text{-}F}$ = 20.5 Hz), 47.7 (d, $J_{C\text{-}F}$ = 3.7 Hz), 41.4, 21.6; HRMS (ESI) for $C_{19}H_{17}FN_5O_2$ $[M + H]^+$, found 366.1375, Calcd 366.1366.

5-(4-Chlorophenyl)-3-((1-(4-methoxybenzyl)-1H-1,2,3-triazol-4-yl)methyl)-1,3,4-oxadiazol-2(3H)-one (7e). Colorless solid; yield 88%; mp 178–180°C; IR (KBr): 3073, 1780, 1613, 1492, 1095, 836 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.74 (d, J = 8.7 Hz, 2H), 7. 53 (s, 1H), 7.43 (d, J = 8.7 Hz, 2H), 7.27–7.21 (m, 2H), 6.89 (d, J = 8.7 Hz, 2H), 5.46 (s, 2H), 5.07 (s, 2H), 3.81 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): 160.0, 152.9, 152.6, 141.6, 137.8, 129.7 (2C), 129.3 (2C), 126.9 (2C), 126.1, 122.5, 122.1, 114.5 (2C), 55.3, 53.9, 41.5; HRMS (ESI) for $C_{19}H_{16}ClN_5O_3Na$ $[M + Na]^+$, found 420.0866, Calcd 420.0839.

5-(4-Chlorophenyl)-3-((1-(4-nitrobenzyl)-1H-1,2,3-triazol-4-yl)methyl)-1,3,4-oxadiazol-2(3H)-one (7f). Pale yellow solid; yield 80%; mp 150–151°C; IR (KBr): 3086, 2922, 1774, 1521, 1345, 729 cm^{-1}; ^{1}H-NMR (4500 MHz, $CDCl_3$): δ 8.23 (d, J = 8.6 Hz, 2H), 7. 75 (d, J = 8.6 Hz, 2H), 7.66 (s, 1H), 7.47–7.40 (m, 4H), 5.64 (s, 2H), 5.12 (s, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 152.9, 152.7, 148.1, 142.3, 141.1, 138.0, 129.3 (2C), 128.6 (2C), 126.9 (2C), 124.3 (2C), 123.0, 121.9, 53.2, 41.5; HRMS (ESI) for $C_{18}H_{14}ClN_6O_4$ $[M + H]^+$, found 413.0787, Calcd 413.0765.

3-((1-Benzyl-1H-1,2,3-triazol-4-yl)methyl)-5-(4-bromophenyl)-1,3,4-oxadiazol-2(3H)-one (7g). Pale yellow solid; yield 82%; mp 197–198°C; IR (KBr): 3276, 2930, 1776, 1608, 1402, 836 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.69 (d, J = 8.9, 2.1 Hz, 2H), 7. 59 (d, J = 8.8, 2.1 Hz, 2H), 7.56 (s, 1H), 7.40–7.35 (m, 3H), 7.30–7.26 (m, 2H), 5.52 (s, 2H), 5.08 (s, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 153.5, 153.2, 141.9, 133.8, 133.2, 131.6, 130.5, 130.4, 128.9 (2c), 128.2, 125.7 (2c), 123.6, 123.5, 123.1, 53.9, 41.5; HRMS (ESI) for $C_{18}H_{15}BrN_5O_2$ $[M + H]^+$, found 412.0213, Calcd 412.0209.

5-(4-Bromophenyl)-3-((1-(2-fluorobenzyl)-1H-1,2,3-triazol-4-yl)methyl)-1,3,4-oxadiazol-2(3H)-one (7h). Pale yellow solid; yield 75%; mp 174–176°C; IR (KBr): 3130, 2985, 1765, 1380, 823 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.69–7.65 (m, 3H), 7.60–7.57 (m, 2H), 7.40–7.34 (m,

1H), 7.31–7.26 (m, 1H), 7.17–7.09 (m, 2H), 5.59 (s, 2H), 5.09 (s, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 161.7 (d, J_{C-F} = 247.3 Hz), 152.9, 152.7, 141.7, 132.2 (2c), 131.0 (d, J_{C-F} = 8.1 Hz), 130.6 (d, J_{C-F} = 2.9 Hz), 127.1 (2c), 126.3, 124.8 (d, J_{C-F} = 3.7 Hz), 122.9, 122.5, 121.5 (d, J_{C-F} = 14.7 Hz), 115.8 (d, J_{C-F} = 20.5 Hz), 47.8(d, J_{C-F} = 4.4 Hz), 41.5; HRMS (ESI) for $C_{18}H_{14}BrFN_5O_2$ $[M + H]^+$, found 432.0344, Calcd 432.0314.

General procedure for the synthesis of 5-aryl-3-((3-phenylisoxazol-5-yl)methyl)-1,3,4-oxadiazol-2(3*H*)-ones (8a–8i). Propargylated compounds (**6a–6d**) (0.5 mmol) and triethylamine (0.5 mmol) were taken in dichloromethane (5 mL), and the resulting mixture was cooled to 0°C. Aqueous sodium hypochlorite (11%, 10 mL) of 10 mL was added over 30 min at 0°C, followed by aryl aldehyde oximes (1.0 mmol), and the reaction mixture was maintained at room temperature. After completion of the reaction monitored by TLC, the reaction mixture was concentrated under vacuum and extracted with ethyl acetate. The organic layers were separated and dried over anhydrous sodium sulfate. The resulting crude product was washed with *n*-hexane to obtain pyrazoloisoxazole hybrid products (**8a–8i**).

5-Phenyl-3-((3-(p-tolyl)isoxazol-5-yl)methyl)-1,3,4-oxadiazol-2(3H)-one (8a). White solid; yield 71%; mp 115–117°C; IR (KBr): 3140, 2995, 1785, 1573, 1397, 830 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.87–7.83 (m, 2H), 7.54–7.45 (m, 5H), 7.34–7.24 (m, 2H), 6.53 (s, 1H), 5.17 (s, 2H), 2.47 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.7, 163.3, 153.9, 153.0, 136.9, 131.9, 131.1, 129.6, 129.4, 129.0 (2c), 128.9, 125.9, 125.8 (2c), 123.4, 104.4, 41.3, 21.1; HRMS (ESI) for $C_{19}H_{15}N_3O_3Na$ $[M + Na]^+$, found 356.1035, Calcd 356.1006.

3-((3-(4-Bromophenyl)isoxazol-5-yl)methyl)-5-phenyl-1,3,4-oxadiazol-2(3H)-one (8b). Colorless solid; yield 80%; mp 155–157°C; IR (KBr): 3066, 2927, 1794, 1613, 1291, 897 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.85 (d, *J* = 6.9 Hz, 1H), 7.78 (d, *J* = 7.1 Hz, 1H), 7.67 (d, *J* = 8.4 Hz, 1H), 7.58 (d, *J* = 8.5 Hz, 1H), 7.56–7.43 (m, 5H) 6.64 (s, 1H), 5.16 (s, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 166.0, 161.8, 154.0, 153.0, 132.2 (2C), 132.0, 129.0 (2C), 128.7, 128.3 (2C), 126.9, 125.8 (2C), 123.3, 101.7, 41.3; HRMS (ESI) for $C_{18}H_{13}BrN_3O_3$ $[M + H]^+$, found 398.0170, Calcd 399.0140.

3-((3-(4-Methoxyphenyl)isoxazol-5-yl)methyl)-5-phenyl-1,3,4-oxadiazol-2(3H)-one (8c). Colorless solid; yield 68%; mp 139–141°C; IR (KBr): 3129, 2956, 1771, 1616, 1392, 834, 696 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.87–7.83 (m, 2H), 7.73(d, *J* = 8.8 Hz, 2H), 7.53–7.44 (m, 3H), 6.96 (d, *J* = 8.8 Hz, 2H), 6.59 (s, 1H), 5.13 (s, 2H), 3.85 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): 165.4, 162.3, 161.1, 153.9, 153.0, 131.9, 128.9 (2c), 128.2 (2c), 125.8 (2c), 123.4, 120.9, 114.3 (2c), 101.6, 55.3, 41.5; HRMS (ESI) for $C_{19}H_{16}N_3O_4$ $[M + H]^+$, found 350.1151, Calcd 350.1140.

5-(p-Tolyl)-3-((3-(p-tolyl)isoxazol-5-yl)methyl)-1,3,4-oxadiazol-2(3H)-one (8d). Colorless solid; yield 72%; mp 113–115°C; IR (KBr): 3127, 2824, 1761, 1611, 1345, 824 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.74 (d, *J* = 8.3 Hz, 2H), 7.50–7.46 (m, 1H), 7.37–7.23 (m, 5H), 6.52 (s, 1H), 5.18 (s, 2H), 2.47 (s, 3H), 2.41 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 164.8, 163.3, 154.1, 153.0, 142.5, 136.8, 131.0, 129.7 (2c), 129.6, 129.4, 128.1, 125.9, 125.7 (2c), 120.5, 104.3, 41.3, 21.6, 21.1; HRMS (ESI) for $C_{20}H_{17}N_3O_3Na$ $[M + Na]^+$, found 370.1194, Calcd 370.1162.

5-(4-Chlorophenyl)-3-((3-(p-tolyl)isoxazol-5-yl)methyl)-1,3,4-oxadiazol-2(3H)-one (8e). White solid; yield 78%; mp 154–156°C; IR (KBr): 3127, 2966, 1773, 1614, 1392, 834 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.78 (d, *J* = 8.5 Hz, 2H), 7.49–7.43 (m, 3H), 7.36–7.23 (m, 3H), 6.53 (s, 1H), 5.16 (s, 2H), 2.47 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 164.5, 163.3, 153.1, 152.8, 138.2, 136.9, 131.0, 129.6, 129.3 (3c), 128.1, 127.0 (2c), 125.9, 121.8, 104.4, 41.3, 21.1; HRMS (ESI) for $C_{19}H_{14}ClN_3O_3Na$ $[M + Na]^+$, found 390.0643, Calcd 390.0621.

3-((3-(4-Bromophenyl)isoxazol-5-yl)methyl)-5-(4-chlorophenyl)-1,3,4-oxadiazol-2(3H)-one (8f). Pale yellow solid; yield 67%; mp 119–121°C; IR (KBr): 3117, 2956, 1775, 1602, 1362, 829, 764 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.81–7.76 (m, 2H), 7.67(d, *J* = 8.5 Hz, 2H), 7.59(d, *J* = 8.5 Hz, 2H), 7.49–7.42 (m, 2H), 6.64 (s, 1H), 5.15 (s, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): 165.8, 161.8, 153.2, 152.8, 138.3, 132.2 (2c), 129.4 (2c), 129.3, 128.3 (2c), 127.1 (2c), 124.6, 121.8, 101.8, 41.3; HRMS (ESI) for $C_{18}H_{12}BrClN_3O_3$ $[M + H]^+$, found 431.9762, Calcd431.9750.

5-(4-Bromophenyl)-3-((3-phenylisoxazol-5-yl)methyl)-1,3,4-oxadiazol-2(3H)-one (8g). Pale yellow solid; yield 82%; mp 122–124°C; IR (KBr): 3276, 2930, 1776, 1608, 1402, 836 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): 7.83–7.66 (m, 4H), 7.64–7.57 (m, 3H), 7.46–7.40 (m, 2H), 6.65 (s, 1H), 5.14 (s, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 165.4, 162.7, 153.1, 152.9, 132.3 (2c), 130.2, 128.9 (2c), 128.4, 127.1 (2c), 126.7 (2C), 126.4, 122.4, 101.9, 41.3; HRMS (ESI) for $C_{18}H_{13}BrN_3O_3$ $[M + H]^+$, found 398.0130, Calcd 398.0140.

5-(4-Bromophenyl)-3-((3-(p-tolyl)isoxazol-5-yl)methyl)-1,3,4-oxadiazol-2(3H)-one (8h). Pale yellow solid; yield 76%; mp 169–171°C; IR (KBr): 3139, 2984, 1779, 1659, 1291, 820 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.71 (d, *J* = 8.5 Hz, 2H), 7.62 (d, *J* = 8.5 Hz, 2H), 7.48 (d, *J* = 7.6 Hz, 1H), 7.37–7.22 (m, 3H), 6.53 (s, 1H), 5.16 (s, 2H), 2.47 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 164.4, 163.3, 153.1, 152.7, 136.8, 132.3 (2c), 131.1, 129.6, 129.3, 128.0, 127.1 (2c), 126.6, 125.9, 122.2, 104.4, 41.3, 21.1; HRMS (ESI) for

$C_{19}H_{15}BrN_3O_3$ [M + H]$^+$, found 412.0299, Calcd 412.0296.

5-(4-Bromophenyl)-3-((3-(4-methoxyphenyl)isoxazol-5-yl) methyl)-1,3,4-oxadiazol-2(3H)-one (8i). Pale yellow solid; yield 70%; mp 162–164°C; IR (KBr): 3101, 2924, 1761, 1510, 1345, 824 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.76–7.66 (m, 4H), 7.60 (d, *J* = 8.8 Hz, 2H), 6.95 (d, *J* = 8.8 Hz, 2H), 6.60 (s, 1H), 5.13 (s, 2H), 3.84 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 165.1, 162.3, 161.1, 153.1, 152.7, 132.3 (2c), 129.9, 128.6, 128.2 (2c), 127.1 (2c), 122.2, 114.3 (2c), 101.7, 55.3, 41.3; HRMS (ESI) for $C_{19}H_{15}BrN_3O_4$ [M + H]$^+$, found 428.0239, Calcd 428.0245.

BIOLOGY

Materials and methods: cell cultures, maintenance, and antiproliferative evaluation. The cell lines MDA-MB-231, HEPG2, DU-145, and HeLa (breast, liver, prostate, and cervical, respectively), which were used in this study, were procured from the American Type Culture Collection, United States, were grown in Dulbecco's modified Eagle's medium (containing 10% fetal bovine serum) under a humidified atmosphere of 5% CO_2 at 37°C. The compounds triazole and isoxazole series were evaluated for their *in vitro* antiproliferative activity in these four different human cancer cell lines. A protocol of 48 h of continuous drug exposure was employed, and a sulforhodamine B (SRB) cell proliferation assay was performed to estimate cell viability or growth. Cells were trypsinized when subconfluent from 60-mm dishes and plated in 96-well plates in 100-μL aliquots at plating densities depending on the doubling time of the respective cell lines. The 96-well plates were incubated at 37°C, 5% CO_2, 95% air, and 100% relative humidity. After 24 h, experimental compounds were added and incubated for 48 h with different doses (0.01, 0.1, 1, 10, and 100 μ*M*). After 48 h of incubation, cell monolayers were fixed by the addition of 10% (wt/vol) cold trichloroacetic acid and incubated at 4°C for 1 h, after which they were washed with tap water and allowed to air dry. Cells were then stained with 0.057% SRB dissolved in 1% acetic acid at room temperature for 30 min. Unbound SRB was washed two to three times with 1% acetic acid and again allowed to air dry. The protein-bound dye representing surviving cells was dissolved in 10 m*M* Tris solution for Optical Density (OD) determination at 510 nm using a microplate reader (Enspire, Perkin-Elmer). With the seven absorbance measurements [time zero (*Tz*), growth control (*C*), and the five dose-treated cells (*Ti*)], the percentage of growth was calculated at each of the drug concentration levels. Percentage growth inhibition was calculated as follows:

$$[(Ti - Tz)/(C - Tz)] \times 100$$

for concentrations for which $Ti \geq Tz$ and

$$[(Ti - Tz)/Tz] \times 100$$

for concentrations for which $Ti < Tz$.

The dose–response parameter, GI_{50}, was calculated for each experimental drug. GI_{50} was calculated from $[(Ti - Tz)/(C - Tz)] \times 100 = 50$, which is the drug concentration resulting in a 50% reduction in net protein increase (as measured by SRB assay) in control cells during the drug treatment.

Western blot analysis of cyclin B1 and soluble versus insoluble (polymerized) tubulin. HeLa cells were plated in six-well plates at 2×10^5 cells per well in Dulbecco's modified Eagle's medium with 10% fetal bovine serum. Cells were treated with 5 μ*M* of compounds **7a**, **7c**, and **7d** for 24 h. After treatment, cells were washed twice with phosphate-buffered saline and lysed with 200 μL of 1× Laemmli sample buffer (180 m*M* of Tris-HCl pH 6.8, 6% sodium dodecyl sulfate, 15% glycerol, 7.5% *b*-mercaptoethanol, and 0.01% bromophenol blue). Then samples were heated at 98°C for 5 min. An equal amount of samples was run on a 10% sodium dodecyl sulfate–polyacrylamide gel and was transferred to a nitrocellulose membrane using semidry transfer at 60 mA for 70 min. Then the blot was probed with the primary rabbit anti-cyclin-B1 antibody at 1:1000 μL (Sigma, Hyderabad, India) and horseradish-peroxidase-coupled goat antirabbit secondary antibody at 1:5000 (Sigma) dilution. Mouse anti-α-tubulin antibody 1:5000 (Sigma) was probed as a loading control. Bands were visualized by using radiographic film (Kodak, Hyderabad, India). For soluble versus insoluble tubulin, HeLa cells were seeded in six-well plates at 2×10^5 cells per well in a complete growth medium (Dulbecco's modified Eagle's medium) and treated with 5 μ*M* of compounds **7a**, **7c**, and **7d** for 24 h. After that, cells were washed with phosphate-buffered saline, and soluble and insoluble tubulin fractions were collected. For collection of soluble tubulin fraction, cells were permeabilized with 300 μL of Triton lysis buffer [80 m*M* Pipes-KOH (pH 6.8), 1 m*M* of $MgCl_2$, 1 m*M* of egtazic acid, 0.2% Triton X-100, 10% glycerol, 0.1% protease inhibitor cocktail (Sigma)] and incubated for 2 min at room temperature. After incubation, lysis buffer was gently removed, mixed with 150 μL of 3× Laemmli sample buffer and stored as soluble fraction. To collect insoluble fraction, 300 μL of 1× Laemmli sample buffer was added to the remaining cells in each well. The samples were boiled at 98°C for 5 min. Then the protein samples were separated in a 10% sodium dodecyl sulfate–polyacrylamide gel, transferred, then probed with mouse anti-α-tubulin diluted 1:5000 μL (Sigma) and with goat antimouse secondary

antibody coupled with horseradish peroxidase diluted 1:5000 μL (Sigma), and analyzed similarly to cyclin B1.

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SUPPORTING INFORMATION

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