Heterocyclic Letters
Vol. 5 | No.4|653-660| Aug-Oct| 2015
ISSN : (print) 2231–3087 / (online) 2230-9632
CODEN: HLEEAI
http://heteroletters.org

SYNTHESIS, CHARACTERIZATION, AND ANTICANCER ACTIVITY OF 1,2,3-TRIAZOLE-DERIVED 1,3,4-OXADIAZOLE CONTAINING N-HETEROCYCLIC MOIETIES

Sirassu Narsimha,[a] Sudhakar Lavudya,[a] Althaf Hussain SK,[b] N Vasudeva Reddy*[a]

[a] *Department of Chemistry, Kakatiya University, Warangal, T S- 506 009, India*
[b]*Department of Biotechnology, Kakatiya University, Warangal, T S-506009, India*
vasujac3@gmail.com

ABSTRACT

1,4-Disubstituted 1,2,3-triazoles (**3a-3j**) have been synthesized by one pot [3+2] cycloaddition reaction of 2-(azidomethyl)-5-phenyl-1,3,4-oxadiazole(**1**) with propargyl bromide and N-heterocyclic compounds (**2a-j**), respectively. The compounds were evaluated for *in vitro* anticancer activity against two human cancer cell lines MCF-7 and HeLa. Cisplatin used as a standard drug. Compound **3h** has exhibited excellent activity against MCF-7 (IC_{50} 16.93 μM) than the standard drug Cisplatin. Compound **3j** against HeLa (15.97 μM) have also shown good activity. Remaining compounds have shown moderate to good anticancer activity against both cell lines.

KEYWORDS: 1,2,3-triazole; Oxadiazole: N-heterocyclic compounds; Anticancer activity.

INTRODUCTION

Cancer is a potential life-threatening disease characterized by the uncontrolled growth of abnormal cells. It is a major cause of health concern with an alarming increase in the number of patients throughout the world. It represents the second leading cause of human mortality after cardiovascular diseases.[I-III] Breast cancer is the most commonly diagnosed malignant tumor in women and accounting for approximately 23% of all female cancers and the second most lethal cancer in women worldwide today.[IV-VI] Nitrogen containing heterocyclic compounds play an important role in designing new structural entities of medicinal importance. Specifically, the 1, 2, 3-triazoles are an important class of heterocycles, which display very large spectrum of biological activities and are widely used as pharmaceuticals and agrochemicals.[VII-XII] This gives a great impetus to the search for potential pharmacologically active drugs carrying 1,2,3-triazole substituent. Oxadiazole ring system is an important heterocyclic group for medicinal chemistry. Many 1,3,4-Oxadiazoles have found medicinal applications, such as antimicrobial,[XIII] anti-inflammatory[XIV] analgesic[XV] antitumor[XVI] and anticonvulsant agents[XVII].

Multi-component reactions (MCRs) have emerged as an efficient and powerful tool in modern synthetic organic chemistry in which three or more different starting materials react to give a final product in a one-pot procedure. Several methods have been reported for the synthesis of 1, 2, 3-triazoles in one-pot procedure.[XVIII-XXI] In present study, continuation of our research[XXII] towards the designed new hybrid molecules through the combination of

three active structure units, namely, 1,2,3-triazole, 1,3,4-Oxadiazole, and N-heterocyclic compounds, in order to synthesize a novel series of 1,2,3-triazole derived oxadiazole containing the N-heterocyclic compounds and test their *in vitro* anticancer activity. Combining the activities of the triazole group, 1,3,4-Oxadiazole and the N-Heterocyclic group have designed and synthesized N-heterocyclics derived oxadiazole containing 1,2,3-triazoles as outlined in **Fig. 1.**

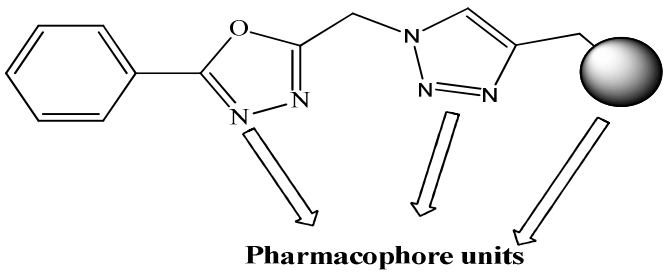


Figure 1: The designed bioactive scaffold has three variable parts

EXPERIMENTAL SECTION

GENERAL

Melting points were determined in open capillaries using Stuart SMP30 apparatus and are uncorrected. The progress of the reactions as well as purity of the compounds was monitored by thin layer chromatography with F254 silica-gel precoated sheets using hexane/ethyl acetate (7.5/2.5) as eluent. NMR spectra were recorded on Bruker 400 MHz spectrometer using $CDCl_3$ (^{1}H-NMR) as solvent and TMS as internal standard. Elemental analyses were performed on a Perkin-Elmer 240CHN analyser. FTIR spectra were recorded on a Bruker spectrometer; Mass spectra (ESI-MS spectrum) were recorded. Coupling constants (*J*) values are presented in Hertz and spin multiples are given as **s** (singlet), **d** (doublet), **t** (triplet), **dd** (doublet of doublet) and **m** (multiplet).

Synthesis of 2-(azidomethyl)-5-phenyl-1,3,4-oxadiazole (1): 2-(chloromethyl)-5-phenyl-1,3,4-oxadiazole (5g, 0.021 mol) and sodium azide (0.027mol) was added DMF and stirred at 80 ^{o}C for 6 h. After completion of reaction, the reaction mixture was poured onto crushed ice. The separated solid was filtered off, washed with water, and dried (4.3g, 83%). (^{1}H NMR, $CDCl_3$) δ 7.98 (m, 2H, Ar),7.68 (m, 3H, Ar),4.72 (s, 2H, CH2), ESI-MS m/z: 202 [M+H].

General procedure for (3a-3j): 2-(azidomethyl)-5-phenyl-1,3,4-oxadiazole (0.002 mol), propargyl bromide (0.0028 mol), N- heterocyclic compound (0.0021 mol) and Cs_2CO_3(0.005 mol) was added to THF (25 mL). 10 mol% of Cu (I) were added into the reaction mixture and stirred at room temperature for 8–10 h. After completion of reaction, the reaction mixture was diluted with ice-cold water (30 mL) and the product was extracted with ethyl acetate (3 x 20 mL). Combined organic layer was dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated under vacuum and the crude product obtained was purified by column chromatography (silica gel, eluent 25% ethyl acetate in petroleum ether).

2-((4-((1H-benzo[d]imidazol-1-yl)methyl)-1H-1,2,3-triazol-1-yl)methyl)-5-phenyl-1,3,4-oxadiazole(3a): White solid; mp 175-177 ^{o}C; IR(KBr, cm^{-1}) ν_{max} 3131, 3028, 2970, 1668, 1604, 1532, 1493; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 (s, N-*CH*=N, 1H), 8.02 (m, 2H), 7.94 (s, triazole-H,1H), 7.82 (m, 1H), 7.68 (m, 3H), 7.51 (m, 3H), 6.21(s, CH_2, 2H), 5.58 (s, CH_2, 2H), ESI-MS m/z: 358 [M+H]. Anal. Cal for $C_{19}H_{15}N_7O$; C, 63.86; H, 4.23; N, 27.44; found C, 63.88; H, 4.19; N, 27.41

2-((4-((1H-indol-1-yl)methyl)-1H-1,2,3-triazol-1-yl)methyl)-5-phenyl-1,3,4-oxadiazole(3b): White solid; mp 159-161 ^{o}C; IR(KBr, cm^{-1}) ν_{max} 3141, 3022, 2974, 1647, 1614, 1522, 1490 ; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (m, 2H), 7.89 (s, triazole-H,1H), 7.740 (m, 2H), 7.676 (m, 3H), 7.57 (m, 3H), 7.24(d, *J*= 8.0 Hz, 1H), 6.18(s, CH_2, 2H), 5.52 (s, CH_2, 2H), ESI-MS m/z: 357 [M+H]. Anal. Cal for $C_{20}H_{16}N_6O$; C, 67.40; H, 4.53; N, 23.58; found C, 67.47; H, 4.49; N, 23.52;

2-((4-((1H-pyrrolo[2,3-b]pyridin-1-yl)methyl)-1H-1,2,3-triazol-1-yl)methyl)-5-phenyl-1,3,4-oxadiazole(3c): White solid; mp 164-166 ^{o}C; IR(KBr, cm^{-1}) ν_{max} 3130, 3020, 2938, 1642, 1600, 1512, 1487; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (m, 2H), 7.87 (s, triazole-H,1H), 7.84 (m, 2H), 7.69 (m, 3H), 7.56 (m, 3H), 6.24(s, CH_2, 2H), 5.55 (s, CH_2, 2H); ESI-MS m/z: 358 [M+H]. Anal. Cal for $C_{19}H_{15}N_7O$; C, 63.86; H, 4.23; N, 27.44; found C, 63.89; H, 4.20; N, 27.40;

2-((4-((1H-imidazol-1-yl)methyl)-1H-1,2,3-triazol-1-yl)methyl)-5-phenyl-1,3,4-oxadiazole (3d): White solid; mp 140-142 ^{o}C; IR(KBr, cm^{-1}) ν_{max} 3098, 3037, 2964, 1660, 1601, 1551, 1490; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (m, 2H), 7.89 (s, 1H, *triazole-**H***), 7.66 (m, 4H), 7.44 (d, *J*= 8.0 Hz, 1H), 7.262 (d, *J*= 8.0 Hz, 1H), 6.27(s, CH_2, 2H), 5.58 (s, CH_2, 2H); ESI-MS m/z: 308 [M+H]. Anal. Cal for $C_{15}H_{13}N_7O$; C, 58.63; H, 4.26; N, 31.90; found C, 58.61; H, 4.29; N, 31.94;

2-((4-((1H-pyrazol-1-yl)methyl)-1H-1,2,3-triazol-1-yl)methyl)-5-phenyl-1,3,4-oxadiazole (3e): White solid; mp 137-139 ^{o}C; IR(KBr, cm^{-1}) ν_{max} 3130, 3018, 2974, 1670, 1615, 1535, 1492; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (m, 2H), 7.85 (s, 1H, *triazole-**H***), 7.64 (m, 3H),7.58 (m, 2H), 6.57 (m, 1H), 6.17(s, CH_2, 2H), 5.52 (s, CH_2, 2H); ESI-MS m/z: 308 [M+H]. Anal. Cal for $C_{15}H_{13}N_7O$; C, 58.63; H, 4.26; N, 31.90; found C, 58.60; H, 4.28; N, 31.93.

4-((1-((5-phenyl-1,3,4-oxadiazol-2-yl)methyl)-1H-1,2,3-triazol-4-yl)methyl)morpholine(3f): White solid; mp 129-131 ^{o}C; IR(KBr, cm^{-1}) ν_{max} 3102, 3022, 2974, 1673, 1597, 1527, 1490; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (m, 2H), 7.82 (s, 1H, *triazole-**H***), 7.77 (m, 3H), 6.11(s, CH_2, 2H), 5.54 (s, CH_2, 2H), 3.87 (m, 2H), 3.82 (m, 2H), 3.69 (m, 2H), 3.60 (m, 2H); ESI-MS m/z: 327 [M+H]. Anal. Cal for $C_{16}H_{18}N_6O_2$; C, 58.88; H, 5.56; N, 25.75; found C, 58.93; H, 5.59; N, 25.71.

2-phenyl-5-((4-(thiomorpholinomethyl)-1H-1,2,3-triazol-1-yl)methyl)-1,3,4-oxadiazole(3g): White solid; mp 134-136 ^{o}C; IR(KBr, cm^{-1}) ν_{max} 3137, 3021, 2977, 1643, 1592, 1518, 1487; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 (m, 2H), 7.91 (s, 1H, *triazole-**H***), 7.84 (m, 3H), 6.14(s, CH_2, 2H); 5.58 (s, CH_2, 2H), 3.78 (m, 2H), 3.71 (m, 2H), 2.83 (m, 2H), 2.72 (m, 2H); ESI-MS m/z: 343 [M+H]. Anal. Cal for $C_{16}H_{18}N_6OS$; C, 56.12; H, 5.30; N, 24.54; found C, 56.11; H, 5.35; N, 24.51.

4-((1-((5-phenyl-1,3,4-oxadiazol-2-yl)methyl)-1H-1,2,3-triazol-4-yl)methyl)thiomorpholine 1,1-dioxide(3h): White solid; mp 154-156 ^{o}C; IR(KBr, cm^{-1}) ν_{max} 3128, 3027, 2874, 1658, 1594, 1532, 1494; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 (m, 2H), 7.91 (s, 1H, *triazole-**H***), 7.84 (m, 3H), 6.14 (s, CH_2, 2H), 5.58 (s, CH_2, 2H), 4.07 (m, 2H), 3.97 (m, 2H), 3.32 (m, 2H), 3.28 (m, 2H); ESI-MS m/z: 375 [M+H]. Anal. Cal for $C_{16}H_{18}N_6O_3S$; C, 51.33; H, 4.85; N, 22.45; found C, 51.30; H, 4.88; N, 22.41.

4-((1-((5-phenyl-1,3,4-oxadiazol-2-yl)methyl)-1H-1,2,3-triazol-4-yl)methyl)morpholine-3-carbonitrile(3i): White solid; mp 131-133 ^{o}C; IR(KBr, cm^{-1}) ν_{max} 3134, 3018, 2965, 2220,1671, 1610, 1525, 1490; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08 (m, 2H), 7.82 (s, 1H, *triazole-**H***), 7.71 (d, J= 8.0 Hz, 1H), 7.66 (m, 2H), 6.16 (s, CH_2, 2H), 5.53 (s, CH_2, 2H), 4.53 (m, 1H), 4.30 (m, 1H), 3.89 (m, 1H), 3.73 (m, 1H), 3.62 (m, 3H); ESI-MS m/z: 352 [M+H]. Anal. Cal for $C_{17}H_{17}N_7O_2$; C, 58.11; H, 4.88; N, 27.90; found C, 58.14; H, 4.93; N, 27.86.

3-((1-((5-phenyl-1,3,4-oxadiazol-2-yl)methyl)-1H-1,2,3-triazol-4-yl)methyl)benzo[d]oxazol-2(3H)-one(3j): White solid; mp 141-143 ^{o}C; IR(KBr, cm^{-1}) ν_{max} 3130, 3022, 2968, 1756, 1658, 1614, 1530, 1493; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (m, 2H), 7.89 (s, 1H, *triazole-**H***), 7.76(m, 3H), 7.62 (d, *J* = 4.5 Hz, 1H), 7.24 (m, 2H), 7.35 (d, *J* = 6.3 Hz, 1H), 6.11(s, CH_2, 2H); 5.52 (s, CH_2, 2H); ESI-MS m/z: 375 [M+H]. Anal. Cal for $C_{19}H_{14}N_6O_3$; C, 60.96; H, 3.77; N, 22.45; found C, 60.91; H, 3.73; N, 22.41.

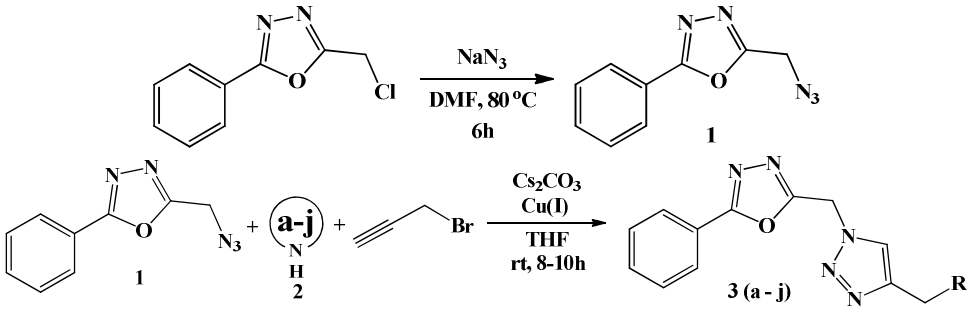
ANTI CANCER ACTIVITY

All the synthesized compounds were evaluated for their in vitro anticancer activity against three different human cancer cell lines i.e. breast cancer cell line (MCF-7) and cervical carcinoma cell line (HeLa). Cell viability in the presence of the test samples were measured by the MTT-microcultured tetrazolium assay. This assay is a quantitative colorimetric method for determination of cell viability. The assessed parameter is the metabolic activity of viable cells. Metabolically active cells reduce pale yellow tetrazolium salt (MTT) to a dark blue water-insoluble formazan, which can be directly quantified after solubilization with DMSO. The absorbance of the formazan directly correlates with the number of viable cells. MCF-7 andHeLa cells were plated into a 96-well plate at a density of 1x10^4 cells/well. Cells were grown overnight in the full medium and then switched to the low serum media. DMSO was used as control. After 48 h of treatment with different concentrations of test compounds, the cells were incubated with MTT (2.5 mg/mL) in the CO_2 chamber for 2 h. The medium was then removed and 100 µL of DMSO was added into each well to dissolve formazan crystals. After thoroughly mixing, the plates were read at 570 nm for optical density which is directly correlated with cell quantity. The results were represented as percentage of viability. All the experiments were carried out in triplicates. The IC_{50} values were calculated from the percentage of cell viability and compared with the reference drug Cisplatin

RESULTS AND DISCUSSION

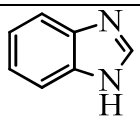
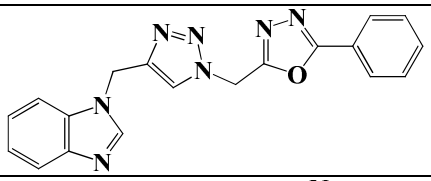
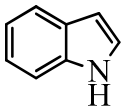
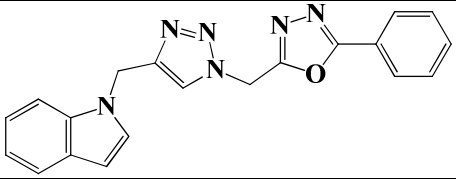
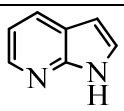
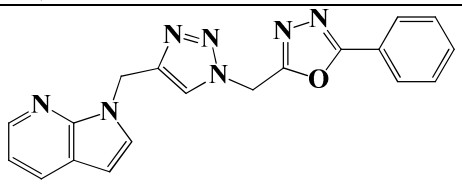
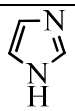
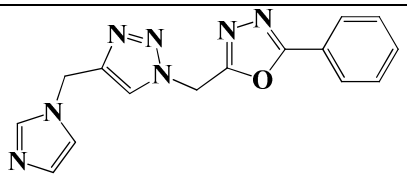
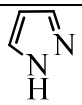
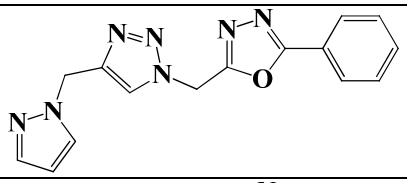
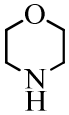
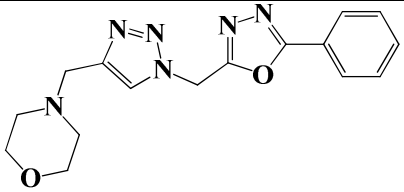
CHEMISTRY

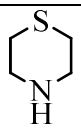
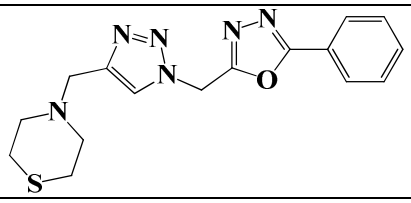
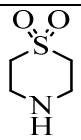
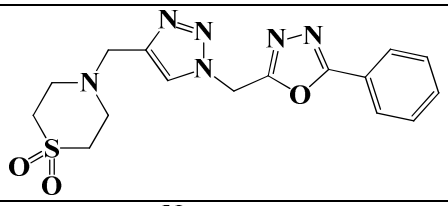
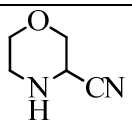
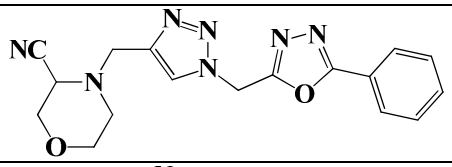
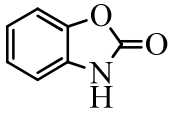
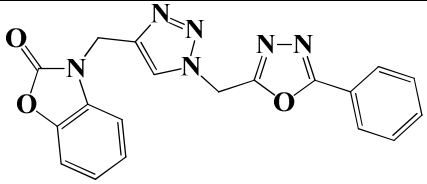
1,4-Disubstituted 1,2,3-triazoles were prepared in good yield according to literature procedure[XXIII]. The 1,3-dipolar cycloaddition of 2-(azidomethyl)-5-phenyl-1,3,4-oxadiazole (**1**) with propargyl bromide and N-heterocyclic compounds (**2a-j**) in presence of Cs_2CO_3 in THF at room temperature yielded 1,4-disubstituted 1,2,3-triazoles (**Table 1**). 2-(azidomethyl)-5-phenyl-1,3,4-oxadiazole(1) was obtained by using nucleophilic substitution reaction of 2-(chloromethyl)-5-phenyl-1,3,4-oxadiazole with sodiumazide. The synthetic pathway was outlined in **Scheme 1**.



Scheme 1: Synthetic route of 1,4-disubstituted 1,2,3-triazoles derivatives

Table 1: Synthesis of 1,4-disubstituted 1,2,3-triazoles using different N-propargyl Heterocycli compounds **(3a-j)**.

S.No	R(2a-j)	Product (3a-j)	Time	Yield(%)
1			**8**	**68**
2			**8**	**64**
3			**8**	**60**
4			**8**	**72**
5			**8**	**66**
6			**10**	**54**

7			**10**	**56**
8			**10**	**50**
9			**10**	**48**
10			**9**	**70**

ANTICANCER ACTIVITY

In vitro anticancer activity was carried out against cancer cell lines MCF-7 and HeLa. Cisplatin was used as a reference drug (IC_{50} **11.44 & 7.28** μM). Cell viability in the presence of the test samples were measured by the MTT-microcultured tetrazolium assay.[XXIV-XXV] The response parameter calculated was the IC_{50} value, which corresponds to the concentration required for 50% inhibition of cell viability (**Table 2**).

Activity results (**Table 2**) revealed that, the compound derived from thiomorpholine 1,1-dioxide group containing triazole ring, that is, **3j** has exhibited excellent activity against HeLa (IC_{50} **15.97** μM) than the standard drug Cisplatin (**fig 2**). Compound **3a** exhibited good activity against both cell lines MCF-7 & HeLa (IC_{50} **20.21** & **19.97** μM) and compound **3h** shows good activity against MCF-7 (IC_{50} **16.93** μM) (**Fig 2**). Remaining compounds have exhibited promising activity with IC_{50} values ranging from MCF-7 (**21.35** to **69.09** μM) and HeLa (**23.82** to **58.63** μM).

Table 2: Inhibition values (IC_{50}) of (**3a-3j**) on human tumor cell lines MCF-7 and HeLa.

Compound	**MCF-7**	**HeLa**
3a	20.21	19.97
3b	54.95	34.05
3c	29.42	23.82
3d	30.29	43.55
3e	51.88	35.24
3f	63.34	36.46
3g	69.09	58.63
3h	16.93	51.00
3i	>200	25.41
3j	21.35	15.97
Cisplatin	**11.44**	**7.28**

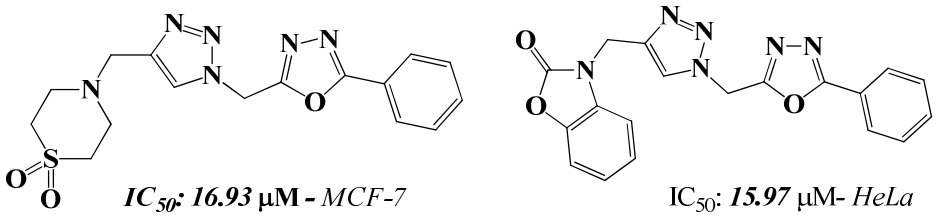


Figure 2: Anticancer candidates containing triazole- oxadiazole and N-heterocycle scaffolds.

CONCLUSION

1,2,3-triazole compounds (**3a-3j**) have been synthesized and evaluated for their *in vitro* anticancer activity against human cancer cell lines MCF-7 and HeLa. All compounds showed good anticancer activity. Compound **3j** was found potent activity against HeLa the IC_{50} value **15.97** μM respectively, as compared to standard drug cisplatin (IC_{50}, **7.28** μM). The synthesized compounds may serve as a lead compounds for the design and development of new anticancer agents.

ACKNOWLEDGEMENT: The author Narsimha is thankful to Council of Scientific and Industrial Research, Government of India, New Delhi, for the Award of senior research Fellowship.

REFERENCES

I. P. B. Bach, J. R. Jett, U. Pastorino, M. S. Tockman, S. J. Swensen, C. B. Begg, JAMA.297, 953 (2007).
II. J. B. Gibbs, Science. 287, 1969 (2000).
III. L. Arve, T. Voigt, H. Waldmann, QSAR Comb. Sci. 25, 449 (2006).
IV. T. Sorlie, Eur. J. Cancer. 40, 2667 (2004).
V. F. Labrie, C. Labrie, A. Belanger, J. Simard, S. Gauthier, V. Luu-The, Y. Merand, V. Giguere, B. Candas, S. Luo, C. Martel, S. M. Singh, M. Fournier, A. Coquet, V. Richard,R. Charbonneau, G. Charpenet, A. Tremblay, G. Tremblay, L. Cusan, R. Veilleux, J.Steroid Biochem. Mol. Biol.69,51 (1999).
VI. R. Siegel, E. Ward, O. Brawley, A. Jemal, CA Cancer J. Clin.61, 212 (2011).
VII. L. S. Kallander, Q. Lu, W. Chen, T. Tomaszek, G. Yang, D. Tew, T. D. Meek, G. A. Hofmann, C. K. Schulz-Pritchard, W. W. Smith, C. A. Janson, M. D. Ryan, G. F. Zhang,K. O. Johanson, R. B. Kirkpatrick, T. F. Ho, P. W. Fisher, M. R. Mattern, R. K. Johnson,M.J. Hansbury, J. D. Winkler, K. W. Ward, D. F. Veber, S. K. Thompson, J. Med. Chem.48, 5644 (2005).
VIII. P. W. Baures, Org. Lett. 1, 249 (1999).
IX. A. C. Tome, Sci. Synth. 2004, 13, 415– 601;
X. S. G. Agalave, S. R. Maujan, V. S. Pore, Chem. Asian J. 2011, 6, 2696– 2718;
XI. J. O. F. Melo, C. L. Donnici, R. Augusti, M. T. P. Lopes, A. G. Mikhailovskii, Heterocycl. Commun. 2003, 9, 235–238;
XII. A. Lauria, R. Delisi, F. Mingoia, A. Terenzi, A. Martorana, G. Barone, A. M. Almerico, Eur. J. Org. Chem. 2014, 3289–3306.
XIII. G. V. Suresh Kumar, Y. Rajendraprasad, B. P. Mallikarjuna, S. M. Chandrashekar, C. Kistayya, Eur. J. Med. Chem.45, 2063 (2010).
XIV. K. Manjunatha, B. Poojary, P. L. Lobo, J. Fernandes, N. S. Kumari, Eur. J. Med. Chem.45,5225(2010).
XV. A. Husain, A. Ahmad, M. M. Alam, M. Ajmal, P. Ahuja, Eur. J. Med. Chem. 44, 3798

(2009).
XVI. L. Lee, L. M. Robb, M. Lee, R. Davis, H. Mackay, S. Chavda, B. Babu, E. L. O'Brien, A. L. Risinger, S. L. Mooberry, M. Lee, J. Med. Chem. 53, 325 (2010).
XVII. A. Zarghi, S. A. Tabatabai, M. Faizi, A. Ahadian, P. Navabi, V. Zanganeh, A. Shafiee, Bioorg. Chem. Lett. 15, 1863(2005).
XVIII. A. Prasad,W. Dehaen,V. V. Fokin, E. V.Der Eycken, Org. Lett. 6, 4223 (2004).
XIX. A. Lutz, K. P.Harish, D. Landsberg, R. Vicente, Org. Lett. 10, 3081(2008).
XX. L. Wen-Tai , W. Wan-Hsun, C.-H. Tang, R. Tai, S.-T. Chen, ACS Comb. Sci.13, 72 (2011).
XXI. A. K. Feldman, B. Colasson, V. V. Fokin, Org. Lett. 6, 3897 (2004).
XXII. S. Narsimha, T. Ranjith Kumar, N. Satheesh Kumar, S. Yakoob, N. Vasudeva Reddy, Med. Chem. Res. 23, 5321(2014).
XXIII. Z.-Y. Yan, Y.-B. Zhao, M.-J. Fan, W.-M. Liu, Y.-M. Liang, Tetrahedron. 61, 9331 (2005).
XXIV. F. Denizot, R.Lang, J. Immunol. Methods. 89, 271 (1986).
XXV. S. Myadaraboina, M. Alla, V. Saddanapu, V. R. Bommena, A. Addlagatta, Eur. J. Med.Chem. 45, 5208 (2010).

Received on August 23, 2015