RJC

RASĀYAN *J. Chem.*
Vol. 12 | No. 4 |2052 - 2057| October - December | 2019
ISSN: 0974-1496 | e-ISSN: 0976-0083 | CODEN: RJCABP
http://www.rasayanjournal.com
http://www.rasayanjournal.co.in

$Bi(OTf)_3$ PROMOTED MICROWAVE SYNTHESIS OF 2-ARYL, 5-SUBSTITUTED 1,3,4-OXADIAZOLES AND EVALUATION OF THEIR ANTICANCER ACTIVITY

Baby Ramana Mutchu[1], Siva Nagi Reddy Mule[1], Krishna Murthy Mannam[2] and Hari Babu Bollikolla[1,*]

[1]Department of Chemistry, Acharya Nagarjuna University,
Nagarjuna Nagar-522510, Guntur, AP, India
[2]Department of Chemistry, S.V.R.M.College, Nagaram, Guntur Dist., AP-India
*E-mail: dr.b.haribabu@gmail.com

ABSTRACT

Simplified production of 2-aryl,5-substituted-1,3,4-oxadiazoles was developed. A series of carboxylic acid hydrazides were reacted with aryl acid chloride in 10 mol% $Bi(OTf)_3$ in Dioxane under microwave at 120 ºC. This methodology was found successful for the generation of a sequence of 2-aryl,5-substituted-1,3,4-Oxadiazole derivatives in good yields (65-75 %). The as-prepared oxadiazoles were tested for their anticancer activity on HCT-116, MIA-PaCa2 and MDA-MB231 cell lines.

Keywords: 2-Aryl,5-disubstituted-1,3,4-oxadiazoles, 1,3,4-Oxadiazoles, Bismuth Triflate, Aryl Carboxylic Acid Hydrazide, Aryl Carboxylic Acid Chlorides.

INTRODUCTION

The heterocyclic compounds either cyclic or acyclic with one or more hetero atoms have significant importance in medicinal chemistry. Among various heterocyclics available, the chemistry of five-membered heterocycles was received a lot of magnitude due to their pronounced biological activities, for example substituted 1,3,4-oxadiazoles have been exploring for their broad spectra of biological actions such as antibacterial[1-3], antimycobacterial[4], antifungal[5,6], anti-inflammatory[7], anti-allergy[8,9], analgesic[10], anticonvulsant[11], antihypoglycemic[12], anticancer[13] and insecticidal properties.[14] Owing to this broad spectrum of biological performance 1,3,4-oxadiazoles has occupied outstanding position in the medicinal chemistry field. However, the need for potential anticancer compounds in the present day the synthetic methodologies and activity profile of these compounds should still need improvement.

A survey of literature revealed that most of the 1,3,4-oxadiazoles were generated by oxidative cyclization of acyl-hydrazones and cyclodehydration of semicarbazide derivatives. The reagents used for cyclo dehydration and oxidative cyclization are TMSNCS[15] Burgess Reagent[16], T3P®[17], TsCl[18], EDCI[19], cyanuric chloride[20], XtalFluor-E[21], Dess–Martin reagent[22], bis(trifluoroacetoxy)iodobenzene (BTI)[23], and PbO_2.[24] Even though there is wide generality in the methods there still some limitations, those are, high reaction times, harsh reagents, requirement of anhydrous solvents, inert atmosphere, much cost reagents, and stability of reagents. Recently, our group reported a method for synthesis of titled compounds with 2,5-disubstitution and chromene substitutions using 10-camphor sulphonic acid as a catalyst by cyclodehydration of carboxylic acid hydrazides and carboxylic acid chlorides with 75-92 % yield.[25] But this method needs heating the reaction mixture for about 16 h which is a time taking process. In our continued interest in the heterocyclic compounds[26-34], the authors desire to develop a more convenient and one-pot approach for the production of these useful heterocycles by means of some simple reagent.

In this communication, we tested the synthetic utility of bismuth triflate, to our knowledge, the synthesis of 1,3,4-oxadiazoles using this reagent, not reported so far. Bismuth triflate is a versatile catalyst in

http://dx.doi.org/10.31788/RJC.2019.1245237

CrossMark

organic synthesis as a catalyst in sulfonylation of Arenes[35], in one-pot multi-component reaction[36], and also as a reusable catalyst[37], and is been cheaper in operational cost. Encouraged by the effectiveness of the reagent it was envisaged to assimilate the substituted 1,3,4-oxadiazole moiety with the use of microwave irradiation. We report herein an efficient one-step procedure for 2-aryl,5-substituted 1,3,4-oxadiazoles by the reaction of arylcarboxylic acid chlorides with different acyl hydrazides in the catalytic amount of Bismuth triflate (10 mol %) under microwave irradiation.

EXPERIMENTAL

Material and Methods

The melting points were determined on Meltemp equipment. TLC (E.Merck AL silica gel 60 F254) of Merck manufactures was used to check the purity of the samples. The chemicals and the reagents were of analytical grade and are of Merck brand. The substrates appropriate acid chlorides and carbo-hydrazides required for the preparation were obtained from commercial sources. After performing Thin-layer chromatography they were visualized in UV light. The experiments conducted on the microwave of Biotage, 300 Watt model. The Perkin Elmer FT-IR spectrometer was used for IR spectra. The ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ at 300 MHz/ 400MHz and 100 MHz respectively on Varian series (EM-360) instrument and the chemical shift values (δ) recorded ppm. The mass spectrums were obtained on Agilent 1100 series instrument.

General Procedure For The Synthesis Of 2,5-Substituted-1,3,4-Oxadiazoles (3a-m)

To the dioxane (4 mL) containing aryl carboxylic acid hydrazides **(1a-m)** (1.1 mmol) was added Bismuth triflate (10 mol%) and then *o*-toluoyl chloride **(2)** (1.1 mmol), the resulted mixture was heated under microwave at 120 ^{o}C for 15-20 min. After reaction completion, the mixture was evaporated under vacuum, added saturated Na_2CO_3 (10 mL), then extracted into dryether. The formed organic layer was dried over Na_2SO_4 and distilled in a vacuum to get the final 1,3,4-oxadiazole **(3a-m)** in 60-70 % without further purification. The products were characterized by all the spectral and compared with the literature data.[25]

Anticancer Activity[38]

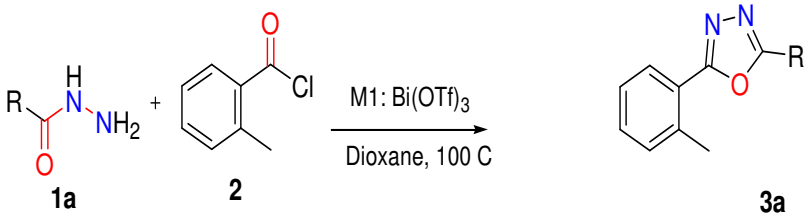
In order to test the compounds the selected cells were cultured (in DMEM), supplemented with 10% (v/v) FBS complete medium, CM, and 1% antibiotic as 10,000 units of penicillin, 10 mg streptomycin, and 25 g of amphotericin B/mL, solution of Sigma-Aldrich Company. The as-prepared cultures were fed 2 times a week and maintained with 80% humidity at 37 ◦C and incubated in an atmosphere of 5% CO_2. The cell viability was calculated by the colourimetric technique by MTT dye. Briefly, the cells were seed into 96-well plates (FB) at a density of 5×10^3 cells per well in 200 µL of CM and incubated by 24 h at 37 ◦C with 5% CO_2 as above. After that, the medium was removed and replaced with fresh CM and cells were incubated with the compounds at indicated conc.'s (0-200 µg/mL). Later, cells were incubated for another 72 h at 37 ◦C with 5% CO_2. To find out cell viability, MTT 10 mg/mL in PBS was added to every well and incubated for 4 h at 37 ◦C. Finally, 100 µL of 2-propanol/1 M HCl (19:1 v/v) was added to dissolve the formazan crystals. Further, the absorbance measurements were studied using a microplate spectrophotometer (BioTek Instruments, USA) at 595 nm.

RESULTS AND DISCUSSION

The authors mainly focused to develop a simplified methodology to produce 2-aryl,5-substituted 1,3,4-oxadiazole analogs with a variety of substitutions. Initially, the method was attempted with the reaction of aryl carboxylic acid chloride with various acyl hydrazides in the incidence of catalytic amounts of Bismuth triflate (M1, Scheme-1). The method was proceeded by heating of the reaction mixture containing equivalent moles aryl carboxylic acid chloride and acyl hydrazide with 10 mol % Bismuth triflate for a period of 4-6 h and the yields were found to be 70-80 %.

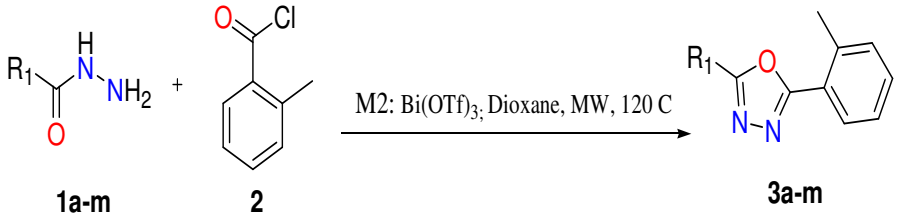
Further, to improve the reaction time we made an attempt for the one-pot synthesis under the microwave. In the process of evaluating the optimized methodology, 4-methoxy benzoyl hydrazide and *o*-toluoyl chloride were used to optimize the reaction condition of Scheme-2. Various solvents and temperatures

were tested for producing 2,5-disubstituted-1,3,4-oxadiazoles (M2, Scheme-2). Among the tested conditions Bismuth triflate with 10 mol % was found to be the best-optimized condition at 120 ºC under microwave heating for getting 2-aryl, 5-disubstituted-1,3,4-oxadiazoles with reasonably good yields (65-75 %).



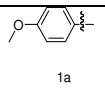
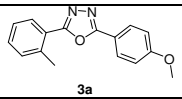
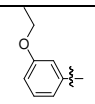
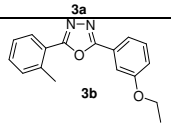
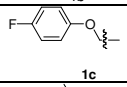
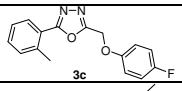
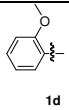
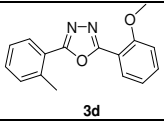
Scheme-1: Synthesis of 2-aryl,5-Substituted 1,3,4-Oxadiazoles

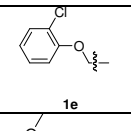
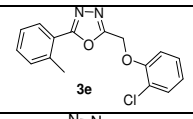
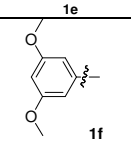
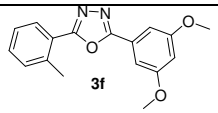
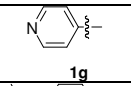
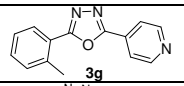
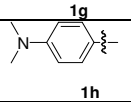
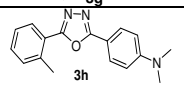
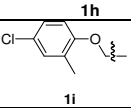
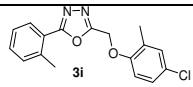
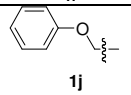
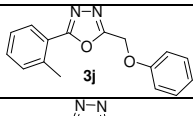
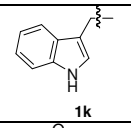
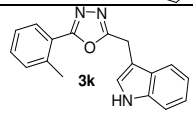
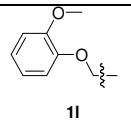
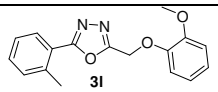
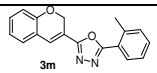
This protocol was found to be good in respect of not a requirement of anhydrous solvents or inert gas atmosphere and purification by chromatography. With these preliminary interpretations and advantages in hand, the authors wish to extend the method to a variety of carboxylic acid hydrazides. The reactions of **1a-m** (hydrazides) with *o*-toluoyl chloride **(2)** in the presence of 10 mol % Bismuth triflate under microwave irradiation produced 2,5-substituted-1,3,4-oxadiazoles (**3a-m**) with good yields (Table-1). As per table 1, carboxylic acid hydrazides with an electron-withdrawing or an e^--donating groups reacted efficiently. The *o,m,p*-substituted acid hydrazides reacted more efficiently with *o*-toluoyl chloride and resulted in the substituted-1,3,4-oxadiazoles in high yields. Further, we observed a good improvement of Bismuth triflate when compared to other methodologies, as the hydrazides having acid-sensitive ether linkages **(3e, 3h, 3i, 3j)** also reacted very well without failure. Moreover, the hydrazides having heterocyclic moiety **(3k, 3l)** were also reacted efficiently.



Scheme-2: Synthesis of 2, 5-Subsitutied-1, 3, 4-Oxadiazloes (3a-M)

Table-1: Synthesis Details and Anticancer Activities (IC_{50} (µg/mL)) Of 2-Aryl,5-Substituted- 1,3,4-Oxadiazoles

Entry	R_1	1,3,4-oxadiazole	*Yield (%)	HCT-116	MIA-PaCa2	MDA-MB231
1	 1a	 3a	74	81.1	70.0	76.6
2	 1b	 3b	71	68.2	57.1	72.5
3	 1c	 3c	71	63.3	65.2	84.1
4	 1d	 3d	62	>200	>200	>200

5	 1e	 3e	64	>200	>200	>200
6	 1f	 3f	67	138.9	117.5	122.2
7	 1g	 3g	70	98.7	81.0	77.2
8	 1h	 3h	60	73.2	71.4	85.0
9	 1i	 3i	62	66.7	95.2	90.0
10	 1j	 3j	65	156.3	141.6	148.0
11	 1k	 3k	63	>200	>200	>200
12	 1l	 3l	67	>200	>200	>200
13	 1m	 3m	71	80.6	94.5	105.6
		Doxorubicin		0.81	0.74	1.04

The synthesized 1,3,4-oxadiazole compounds were tested[38] on 3 cell lines such as HCT-116, MIA-PaCa2 and MDA-MB231 cell lines for their anticancer activity and the outcomes were presented in Table-1. Out of 13 oxadiazoles, seven compounds were found to possess reasonably good activity. The compound **3c** with *o*-tolyl, *p*-fluorophenoxy methyl substitution showed the highest activity (IC_{50}: 63.3 µg/mL) on the HCT116 cell line followed by **3i, 3b, 3h, 3m**, and **3g** compounds with IC_{50} ranging from 66-98.7 µg/mL**.** The compound **3a** with fluoro substitution showed the highest activity (IC_{50}: 57.1 µg/mL) against the MIA-PaCa2 cell line followed by **3c, 3a, 3h, 3g,** and **3i** compounds with IC_{50} ranging from 65-95.2 µg/mL. The compound **3b** was also found to possess the highest activity (72.5 µg/mL) on the MDA-MB231 cell line followed by **3a, 3g, 3c, 3h** and **3i** compounds with IC_{50} ranging from 76-85 µg/mL. Oxadiazole proved to be a potent anticancer drug on various human cancer cell lines, breast, lung, cervical, liver and skin cancer cell lines.[39] Earlier studies reported that 2,5,-disubstituted 1,3,4-oxadiazole exhibit more potent anticancer activity on various cell lines than the other isomers of oxadiazole.[40] Recently, a sequence of 2,5,-disubstituted 1,3,4-oxadiazole and thiadiazoles were also found to possess potential cytotoxicity.[41] In the present study, *o*-tolyl, *p*-fluorophenoxy methyl-substituted oxadiazole exhibited potent anti-proliferation activity against the tested cancer cell lines.

CONCLUSION

In conclusion, the authors have developed an efficient MW methodology to produce a variety 2-aryl,5-substituted 1,3,4-oxadiazoles by using a number of aryl carboxylic acid hydrazides and aryl acid chloride in the presence of the catalytic amount of Bismuth triflate. The more advantage of this technique is hydrazides containing acid-sensitive groups **(3e, 3h, 3i, 3j)** were also effectively converted to corresponding final products without any effect. The efficacy of this method was successfully established for the synthesis of new derivatives with various substrate moieties. The experimental procedure is very

simple, does not required anhydrous solvent, avoids the use of harsh reagents, inert gas atmosphere, and any purifications like chromatography.

ACKNOWLEDGMENT

The authors are highly thankful to Acharya Nagarjuna University for constant encouragement and Hetero Drugs labs, Hyderabad for grant support and technical help.

REFERENCES

1. B.S. Holla, R. Gonsalves, S. Shenoy, *Eur. J. Med. Chem.*, **35**, 267 (2000), **DOI:** 10.1016/S0223-5234(00)00154-9.
2. G. Sahin, E. Palaska, M. MelikeEkizoglu, *Ozalp, IlFarmaco.*, **57**, 539 (2002), **DOI:** 10.1016/S0014-827X(02)01245-4.
3. S. Sgarad, M. Ganesh, G. Sunil; G. Charnsingh, *Bioorg. Med. Chem. Lett.*, **20**, 7200 (2010), **DOI:** 10.1016/j.bmcl.2010.10.111.
4. F. Macaev, G. Rusu, S. Pogrebnoi, A. Gudima, E. Stingaci, L. Vlad, N. Shvets, F. Kandemirli, A. Dimoglo, R. Reynolds, *Bioorg. Med. Chem,* **13**, 4842 (2005), **DOI:** 10.1016/j.bmc.2005.05.011.
5. X. J. Zou, L. H. Lai, G. Y. Jin, Z. X. Zhang, *J. Agric. Food Chem*, **50**, 3757 (2002), **DOI:** 10.1021/jf0201677.
6. V. Padmavathi, G. Dinneswara Reddy, S. Nagi Reddy, K. Mahesh, *Eur. J. Med. Chem.*, **46**, 1367 (2011), **DOI:** 10.1016/j.ejmech.2011.01.063
7. E. Palaska, G. Sahin, P. Kelicen, N. T. Durlu; G. Altinok., *II Farmaco*, **57**, 101 (2002), **DOI:** 10.1016/S0014-827X(01)01176-4.
8. G. Dinneswara Reddy, S-J Park, H. M. Cho, T-J Kim, M. E. Lee.; *J. Med. Chem.*, **55**, 6438 (2012), **DOI:**10.1021/jm300421h.
9. G. Dinneswara Reddy, S-J Park, M-W Lee, T-J Kim, M. E. Lee, *Eur. J. Med. Chem.*, **62**, 84(2013), **DOI:** 10.1016/**j**.ejmech.2012.12.035
10. M. Amir, K. Shikha, *Eur. J. Med. Chem*, **39**, 535 (2004), **DOI:**10.1016/j.ejmech.2004.02.008.
11. A. Almasirad, A. Sayyed, M. Tabatabai, A. Faizi, N. Kebriaeezadeh, A. Mehrabi, A. Dalvandi, Shafiee, *Bioorg. Med. Chem. Lett.,* **14**, 6057 (2014), **DOI:**10.1016/j.bmcl.2004.09.072.
12. K.S. Bhat, M.S. Karthikeyan, B.S. Holla, N.S. Shetty, *Indian J. Chem., Sec. B.*, **43B**, 1765 (2004)
13. M. I. Husain, A. Kumar, R.C. Srivastava, *Curr. Sci*, **55**, 644 (1986).
14. X. Zheng, Z. Li, Y. Wang, W. Chen, O. Huang, C. Liu, C. Song, *J. Fluor. Chem.,* **123**, 163 (2003).
15. G. Dinneswara Reddy, H Mo Cho, Myong Euy Lee., *RSC Advances,* **3(21)**, 7684(2013), **DOI:** 10.1039/C3RA41044G.
16. C. Li, D. Hamilton, Dickson; *Tetrahedron Lett.*, **50**, 6435 (2009), **DOI:** 10.1016/j.tetlet.2009.08.084.
17. J.K. Augustine, V. Vairaperumal, S. Narasimhan, P. Alagarsamy, A. Radhakrishnan; *Tetrahedron.* **65**, 9989 (l2009)
18. P. Stabile, A. Lamonica, A. Ribecai, D. Castoldi, G. Guercio, O. Curcuruto, *Tetrahedron Lett.,* **51**, 4801 (2010).
19. L. Eugene, P. Chekler, M. Hassan, Z. Elokdah, J. Butera, *Tetrahedron Lett.,* **49**, 6709 (2008)
20. O. Cyrous, O. Kangani, B. W. Day., *Tetrahedron Lett.*, **50**, 5332(2009).
21. P. Marie-France, A. Laetitia, H. Jean-Denys, P. Jean-Francois, *Org. Biomol. Chem.*, **10**, 988 (2012), **DOI:** 10.1039/C1OB06512B.
22. C. Dobrota, C. Codrut, P. Chivescu, I. Dumitru, M. Matache, I. Baciu, L. Laviniaruta, T*etrahedron Lett.,* **50**, 1886 (2009).
23. Z. Shang, J. Reiner, J. Chang, K. Zhao, *Tetrahedron Lett.,* **46**, 2701 (2005)
24. C. Kuo-Chen, W. Fung Fuh, H.Chih-Hao, H. Yu-Ying, C. Po-Wei, L.Yang-Ming, L. Shao-Kai Lin, *J. Heterocyclic Chem.*, **46**, 111 (2009)
25. M. Siva Nagi Reddy, B. Sailaja Kumari, V. Ganapathi, G. Dinneswara Reddy and B. Hari Babu, *RSC Adv*., **4(102)**, 58397 (2014), **DOI:**10.1039/C4RA11218K.
26. B. S. N. Murthhy, K. A. Emmanuel, K. Surendra Babu and B. Hari Babu, *Journal of Organometallic Chemistry*, **866**, 177 (2018), **DOI:** 10.1016/j.jorganchem.2018.04.027.

27. B. S. N. Murthhy, P. Naresh, M. Baby Ramana and B. Hari Babu, *New Journal of Chemistry*, **42(2)**, 918 (2018), **DOI:** 10.1039/C7NJ03527F.
28. T. Vijaya Durga, B. Hari Babu, M. Siva Nagi Reddy, B. Sailaja Kumari, and A. Vasu Babu, *Letters in Organic Chemistry*, **15(7)**, 569 (2018), **DOI:** 10.2174/1570178614666170811121704.
29. N. Ramesh, M. Ganagadhara Rao, A. Vasu BAbu, P. Nagababu, V. Umamaheswara Rao and B. Hari Babu, *Res. Chem. Intermed,* **43(7)**, 4145 (2017), **DOI:** 10.1007/s00044-016-1630-y.
30. M. Siva Nagi Reddy, N. Sharmila, J. N. Kolla, J. Suender Singh, J. Venkataesan, B. Lourdu Rani, B. Hari Babu, *Medicinal Chemistry Research*, **25(11)**, 2534 (2016), **DOI:** 10.1007/s00044-016-1668-x.
31. N. Ramesh, M. Gangadhara Rao, V. Ravi, V. Umamaheswara Rao and B.Hari Babu, *Med Chem Res.*, **25(9)**, 1945 (2016), **DOI:** 10.1007/s00044-016-1630-y.
32. B. Hari Babu, K.Vijay, K. Bala Murali Krishna, N. Sharmila and M. Baby Ramana, *J. Chem. Sci*, **28(9)**, 1475 (2016), **DOI:** 10.1007/s12039-016-1130-0.
33. K. Bala Murali Krishna, B. Lourdu Rani, P. Naresh, and B. Hari Babu, *Org. Commun.*, **11(1)**, 62 (2018), **DOI:** 10.25135/acg.oc.40.18.02.066.
34. O. Surendranatha Reddy, Ch.VenkataSuryanarayana, K.J.P.Narayana, V. Anuradha and B. Hari Babu, *Med. Chem. Res.*, **24(5)**, 1777 (2015), **DOI:** 10.1007/s00044-014-1276-6.
35. S. Répichet, Ch. Le Roux, P. Hernandez, J. Dubac; *J. Org. Chem.*, **64(17)**, 6479 (1999).
36. Md. Abd El Aleem. Ali. Ali.El-Remaily, *Chinese Journal of Catalysis*, **36**, 1124 (2015), **DOI:** 10.1016/S1872-2067(14)60308-9.
37. S. Pourshahrestani, I. Mohammadpoor-Baltork, M. Moghadam, S. Tangestaninejad, A.R. Khosropour, V. Mirkhani, *Journal of the Iranian Chemical Society*, **12**, 573 (2015), **DOI:** 10.1007/s13738-014-0514-7.
38. DA. Scudiero, RH. Shoemaker, KD. Paull, A. Monks, S. Tierney, TH. Nofziger, MJ. Currens, D. Seniff, MR. Boyd, *Cancer Res.*, **48(17)**, 4827 (1988).
39. S. Dash, BA. Kumar, J. Singh, BC. Maiti, TK. Maity T K, *Med Chem Res.*, **20**, 1206 (2011), **DOI:** 10.1007/s00044-010-9455-6.
40. J. Sun, H. Zhu, ZM. Yang, H. Zhu, *Eur J Med Chem.*, **60**, 23, (2013), **DOI:** 10.1016/j.ejmech.2012.11.039.
41. M. Baby Ramana, K. Vijay, O. Surendranatha Reddy, B. S. N. Murthy, and B. Hari Babu, *Chemistry Africa*, (2018), **DOI:** 10.1007/s42250-018-00034-x.

[RJC-5237/2019]