Research Article

Synthesis and Antioxidant Activity of 2-nonyl-5-aryl-1,3,4-oxadiazole Derivatives

Anu[1]*, Bhawna Sati[1], Sunil Kumar[2]
[1]Department of pharmacy, Banasthali Vidyapith, Banasthali, Rajasthan, India.
[2]Department of Chemical Engineering, JMIT, Radaur, Haryana, India.
***Corresponding author's E-mail:** anudhanda78@gmail.com

Accepted on: 07-09-2014; **Finalized on:** 31-10-2014.

ABSTRACT

2-nonyl-5-aryl-1,3,4-oxadiazole derivatives were synthesized by a multi-step reaction sequence. Structures of synthesized derivatives of oxadiazole were characterized and confirmed by IR and NMR. The synthesized compounds were screened for their *in vitro* antioxidant properties by DPPH method. The results of this investigation revealed that the synthesized compounds (3a, 3d and 3e) are potent antioxidant agents compared to standard.

Keywords: 1,3,4-oxadiazole derivatives, Antioxidant activity, DPPH, n-Capric acid.

INTRODUCTION

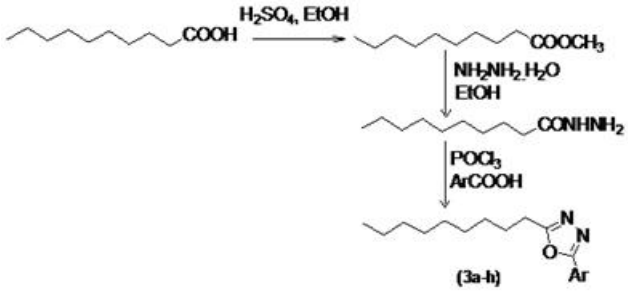
Oxidation is a chemical reaction characterized by transfer of an electron from electron rich to electron deficient entity. Antioxidant is a molecule that inhibits the oxidation of other molecules. Antioxidants are intimately involved in the prevention of cellular damage the common pathway for cancer, aging, and a variety of diseases. Antioxidants are widely used in dietary supplements and have been investigated for the prevention of diseases such as cancer, coronary heart disease and even altitude sickness.[1]

The wide occurrence of the heterocycles in bioactive natural products, pharmaceuticals, and agrochemicals[2,3] has made them as important synthetic targets. Several five-membered heterocyclic drugs possess diverse biological effects. Nitrogen and oxygen containing five membered azoles are important bioactive molecules, due to their wide array of pharmacological activities such as anti fungal[4], antimicrobial[5], anti-inflammatory, analgesic[6], hypolipidemic[7], anti tubercular[8], anti-convulsant[9] and cytotoxic agents[10] and anti oxidant[5,11-12] agent.

Literature survey revealed that attachment of different pharmacophores to 1,3,4-oxadiazole lead to qualitative as well as quantitative changes in the biological activity[13]. Prompted by the above findings we have studied antioxidant activity of synthesized 2-nonyl-5-aryl-1,3,4-oxadiazole derivatives by DPPH protocol.

MATERIALS AND METHODS

All the common solvents and chemicals were of LR grade and were procured from Central Drug House (CDH) Ltd, Merck India and Sigma Aldrich. The purity of the synthesized compounds was ascertained by by silica gel G coated TLC plate and the R_f values were determined. Melting points were determined by the capillary method. The infrared (IR) spectra were recorded on Perkin Elimer IR 4000-400 (ν_{max} in cm^{-1}) spectrophotometer and NMR spectra of synthesized compounds were recorded on Bruker Advance II 400 (400 MHz, ^1H NMR) instrument. Chemical shifts are reported as parts per million (ppm) using tetramethylsilane (TMS) as an internal standard.



Where Ar is 3a: C_6H_5, 3b: 4-ClC_6H_4, 3c: 4-$CH_3OC_6H_4$, 3d: 4-FC_6H_4, 3e: 3,4-$CH_3OC_6H_3$, 3f: 2-Cl-5-$NO_2C_6H_3$, 3g: 2,4-$ClC_6H_3CH_2$, 3h: 2-Cl $C_6H_4CH_2$.

Scheme 1: Synthetic route for 2-nonyl-5-aryl-1,3,4-oxadiazole derivatives

Table 1: Characterization data of oxadiazole derivatives (3a-h)

Compound	Molecular formula	% yield	M.p. (°C)	R_f
3a	$C_{16}H_{22}N_2O$	84	24	0.7
3b	$C_{16}H_{21}ClN_2O$	86.6	42	0.76
3c	$C_{17}H_{24}N_2O_2$	98	39	0.67
3d	$C_{16}H_{21}FN_2O$	96	28	0.57
3e	$C_{18}H_{26}N_2O_3$	89	29	0.67
3f	$C_{16}H_{20}ClN_3O_3$	82	40	0.60
3g	$C_{17}H_{22}Cl_2N_2O$	80	45	0.57
3h	$C_{17}H_{23}ClN_2O$	85	50	0.61

Experimental

Procedure for synthesis of ester (1)

The esterification was carried out by using (0.1 Mol) of n-Capric acid in 32 ml of absolute ethanol and 1.1 ml of

H_2SO_4 and refluxed for 5-6 h. Mixture was poured into separating funnel containing diethyl ether and ether layer extracted, dried under vacuum and used for further reaction.

Procedure for synthesis of acid hydrazide (2)

A mixture of ester 1 (0.1 mol) and hydrazine hydrate 99% (0.11 mol) in 50 ml absolute ethanol was reflux for 5-6 h. The reaction mixture was cooled and left overnight. Solid obtained was collected and recrystallized from absolute ethanol.

Procedure for synthesis of (3a-h)

An equimolar amount of compound 2 and appropriate aromatic acids in 10 ml phosphorus oxychloride ($POCl_3$) was refluxed for 5 h. The reaction mixture was cooled to room temperature and poured onto crushed ice with continues stirring. The potassium hydroxide solution was added till the pH of the mixture raised to 8. The precipitates was collected by vacuum distillation, dried and recrystallized from absolute ethanol.

2-nonyl-5-phenyl-1,3,4-oxadiazole (3a)

IR (KBr), ν cm^{-1}: 2938 (C-H, Ar), 1596 (C=N), 1152 (C-O-C). ^{1}HNMR ($CDCl_3$) δ (ppm): 8.8 (m, 3H, Ar-H), 8.3 (m, 3H, Ar-H), 7.2-7.4 (s, 6H, CH_2), 4.5-4.7 (s, 2H, CH_2).

2-(4-chlorophenyl)-5-nonyl-1,3,4-oxadiazole (3b)

IR (KBr), ν cm^{-1}: 2926 (C-H, Ar), 1601 (C=N), 1104 (C-O-C), 720 (C-Cl). ^{1}HNMR ($CDCl_3$) δ (ppm): 7.2-7.5 (m, 3H, Ar-H), 8.05-8.4 (m, 4H, Ar-H), 4.55-4.75(s, 2H, CH_2).

2-(4-methoxyphenyl)-5-nonyl-1,3,4-oxadiazole (3c)

IR (KBr), ν cm^{-1}: 2935 (C-H, Ar), 1604 (C=N), 1103 (C-O-C), 1259, 1027 (-OCH_3). ^{1}HNMR ($CDCl_3$) δ (ppm): 6.9-7.03 (m, 3H, Ar-H), 7.2-7.4 (m, 4H, Ar-H), 4.5-4.7(s, 2H, CH_2), 3.8-3.9 (s, 3H, CH_3).

2-(4-fluorophenyl)-5-nonyl-1,3,4-oxadiazole (3d)

IR (KBr), ν cm^{-1}: 2925 (C-H, Ar), 1592 (C=N), 1091 (C-O-C), 1032 (C-F). ^{1}HNMR ($CDCl_3$) δ (ppm): 7.2-7.4 (m, 4H, Ar-H), 4.2-4.5 (s, 3H, CH_3), 3.4-3.7 (s, 3H, CH_3), 2.1-2.9 (s, 6H, CH_2), 1.2-1.8 (s, 8H, CH_2) 0.8-0.9 (s, 3H, CH_3).

2-(3,4-methoxyphenyl)-5-nonyl-1,3,4-oxadiazole (3e)

IR (KBr), ν cm^{-1}: 2929 (C-H, Ar), 1610 (C=N), 1179 (C-O-C), 1249, 1030 (-OCH_3). ^{1}HNMR ($CDCl_3$) δ (ppm): 6.8-7.3 (m, 5H, Ar-H), 3.7-3.8 (s, 2H, CH2), 2.9 (s, 2H, CH_2), 2.3 (s, 2H, CH_2), 2.1 (s, 2H, CH_2) 1.3-1.6 (s, 6H, CH_2), 1.2 (s, 2H, CH_2), 0.8 (s, 3H, CH_3).

2-(2-chloro-5-nitrophenyl)-5-nonyl-1,3,4-oxadiazole (3f)

IR (KBr), ν cm^{-1}: 2925 (C-H, Ar), 1590 (C=N), 1150 (C-O-C) 1534, 1345 (C-NO_2), 739 (C-Cl). ^{1}HNMR ($CDCl_3$) δ (ppm): 8.0-8.35 (m, 3H, Ar-H), 4.2-4.4 (s, 3H, CH_3), 3.5-3.7 (s, 3H, CH_3), 2.1-2.8 (s, 6H, CH_2), 1.2-1.8 (s, 8H, CH_2) 0.8-0.9 (s, 3H, CH_3).

2-(2,4-dichlorobenzyl)-5-nonyl-1,3,4-oxadiazole (3g)

IR (KBr), ν cm^{-1}: 2940 (C-H, Ar), 1650(C=N), 1460 (C-H, CH_2), 1385 (C-H, CH_3), 1133 (C-O-C), 721 (C-Cl str). ^{1}HNMR ($CDCl_3$) δ (ppm): 7.21-7.40 (m, 3H, ArH), 4.4 (s, 2H, CH_2), 3.4 (s, 2H, CH_2), 2.9-3.0 (s, 2H, CH_2), 2.12 (s, 2H, CH_2), 1.81 (s, 2H, CH_2), 1.2-1.34 (t, 8H, CH_2), 0.8-0.9 (t, 3H, CH_3).

2-(2-chlorobenzyl)-5-nonyl-1,3,4-oxadiazole (3h)

IR (KBr), ν cm^{-1}: 2930 (C-H, Ar), 1645(C=N), 1455 (C-H, CH_2), 1383 (C-H, CH_3), 1130 (C-O-C), 719 (C-Cl). ^{1}HNMR ($CDCl_3$) δ (ppm): 7.10-7.40 (m, 4H, ArH), 4.5 (s, 2H, CH_2), 3.3 (s, 2H, CH_2), 2.8-3.0 (s, 2H, CH_2), 2.2 (s, 2H, CH_2), 1.71 (s, 2H, CH_2), 1.2-1.4 (t, 8H, CH_2), 0.8-0.9 (t, 3H, CH_3).

Antioxidant Activity

Antioxidant activity of synthesized compounds were carried out by DPPH method using ascorbic acid as standard reference and 3 µg/ml concentration of DPPH in methanol were used. The concentrations of dilution of synthesized compounds and standard drug was made in volumetric flask by using methanol. Five concentrations i.e. 100µg/ml, 200µg/ml, 300µg/ml, 400µg/ml, 500µg/ml was considered for antioxidant activity. Methanol (1 ml) with DPPH solution (1 ml) was used as blank. 1 ml of DPPH solution was mixed with 1 ml of sample solution and standard solution separately and mixture solutions were kept in dark for 30 min and optical density was measured at 517 nm and % inhibition was calculated using the formula given below:

$$\text{Percent inhibition of DPPH activity} = \frac{A - B}{A}$$

Where A = Absorbance of the blank

B = Absorbance of the sample

Table 2: Antioxidant activity of oxadiazole derivatives

Compound	% Inhibition				
	100 µg/ml	200 µg/ml	300 µg/ml	400 µg/ml	500 µg/ml
3a	87.12	87.73	88.51	87.80	88.14
3b	32.43	38.51	34.12	45.95	31.42
3c	35.81	45.94	39.18	42.56	41.55
3d	84.45	85.13	85.81	85.47	84.80
3e	85.81	86.79	86.48	87.06	86.75
3f	78.10	78.23	78.30	78.43	78.40
3g	50.11	51.13	50.30	51.20	52.13
3h	37.70	37.62	39.73	38.90	38.11
Ascorbic acid	86.82	87.53	88.17	88.10	89.52
Blank	0.296	0.296	0.296	0.296	0.296

RESULTS AND DISCUSSION

The reaction progress and purity of compounds were confirmed by TLC. The structures of the synthesized compounds (Scheme 1) were characterized

physiologically (Table 1) and by IR and ^{1}H NMR and found in good agreement with the spectral data.

The antioxidant activity of the synthesized compounds and the standard was assessed on the basis of the radical scavenging effect of the stable 1,1-diphenyl-2-picrylhydrazyl (DPPH) free radical activity. DPPH assay was carried out for compounds 3a-h at different concentrations from 100 to 500 µl/ml concentration. The compounds 3a, 3d and 3e showed excellent antioxidant activity in comparison to ascorbic acid where as 3b, 3c and 3h showed least free radical inhibition (Table 2).

CONCLUSION

The antioxidant activity of synthesized compounds revealed that oxadiazoles containing 4-fluorophenyl and 3,4-dimthoxyphenyl group at C-5 position of 1,3,4-oxadiazole ring have better result as compared to the standard drug and can be selected for further studies.

REFERENCES

1. Swaran JS, Flora, Structural, chemical and biological aspects of antioxidants for strategies against metal and metalloid exposure, Oxid Med Cell Longev, 2(4), 2009, 191-206.
2. He DH, Zhu YC, Yang ZR, Xihu, A, Synthesis and characterization of novel stilbene derivatives with 1,3,4-Oxadiazole unit, J Chinese Chem Soc, 56, 2009, 268-270.
3. Tully WR, Gardner CR, Gillespie RJ, Westwood R, 2-(Oxadiazolyl)- and 2-(thiazolyl)imidazo[1,2-a]pyrimidines as agonists and inverse agonists at benzodiazepine receptors, J Med Chem, 34, 1991, 2060-2067.
4. Prakash O, Kumar M, Kumar R, Sharma Ch, Aneja KR, Hypervalent iodine(III) mediated synthesis of novel unsymmetrical 2,5-disubstituted 1,3,4-oxadiazoles as antibacterial and antifungal agents, Eur J Med Chem, 45, 2010, 4252-4257.
5. Malhotra M, Rawal RK, Malhotra D, Dhingra R, Deep A, Sharma PC, Synthesis, characterization and pharmacological evaluation of (Z)-2-(5-(biphenyl-4-yl)-3-(1-(imino)ethyl)-2,3-dihydro-1,3,4-oxadiazol-2-yl)phenol derivatives as potent antimicrobial and antioxidant agents, Arab J Chem, 2013, DOI: 10.1016/j.arabjc.2013.01.005.
6. Akhter M, Husain A, Azad B, Ajmal M, Aroylpropionic acid based 2,5 disubstituted-1,3,4-oxadiazoles: Synthesis and their anti-inflammatory and analgesic activities, Eur J Med Chem, 44, 2009, 2372-2378.
7. Jayashankar B, Rai KML, Baskaran N, Sathish HSS, Synthesis and pharmacological evaluation of 1,3,4-oxadiazole bearing bis(heterocycle) derivatives as anti-inflammatory and analgesic agents, Eur J Med Chem, 44, 2009, 3898-3902.
8. Kumar GVS, Rajendraprasad Y, Mallikarjuna BP, Chandrashekar SM, Kistayya C, Synthesis of some novel 2-substituted-5-[isopropylthiazole] clubbed 1,2,4-triazole and 1,3,4-oxadiazoles as potential antimicrobial and antitubercular agents, Eur J Med Chem, 45, 2010, 2063-2074.
9. Bhat MA, Al-Omar MA, Siddiqui N, Synthesis, anticonvulsant and neurotoxicity of some novel 1,3,4-oxadiazole derivatives of phthalimide, Der Pharma Chemica, 2(2), 2010, 1-10.
10. Padmavathi V, Reddy GS, Padmaja A, Kondaiah P, Ali-Shazia, Synthesis, antimicrobial and cytotoxic activities of 1,3,4-oxadiazoles, 1,3,4-thiadiazoles and 1,2,4-triazoles, Eur J Med Chem, 44, 2009, 2106-2112.
11. Musad AE, Ali-Saeed BRM, Vishwanath BS, Rai KML, Synthesis and evaluation of antioxidant and antibacterial activities of new substituted bis(1,3,4-oxadiazoles), 3,5-bis(substituted) pyrazoles and isoxazoles, Bio Org Med Chem Lett, 21, 2011, 3536-3540.
12. Liang Ma, Xiao Y, Li C, Zheng-Lu X, Dong-Dong L, Yan-Ting W, Hai-Tian M, Hai-Liang Z, Ming-Hua W, Yong-Hao Y, Synthesis and antioxidant activity of novel Mannich base of 1,3,4-oxadiazole derivatives possessing 1,4-benzodioxan, Bioorg Med Chem, 2013, DOI: http://dx.doi.org/10.1016/j.bmc.2013.08.002.
13. Mitropoulou TN, Tzanakakis GN, kletsas D, Kalofonos HP, Karamanos NK, Letrozole as a potent inhibitor of cell proliferation and Expression of metalloproteinases (mmp-2 and mmp-9) by human epithelial breast cancer cells, Int J Cancer, 104, 2003, 155-160.

Source of Support: Nil, **Conflict of Interest:** None.