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RESEARCH ARTICLE

Green and Efficient Microwave One-Pot Synthetic Approach to 2-*N*-Methylpiperazino-5-mercapto-substituted Aryl-1,3,4-oxadiazole Derivatives and Evaluation of their *In vitro* Antioxidant and Anti-inflammatory Activity

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Abstract: An efficient one pot sequential protocol has been developed for synthesis of 2-*N*-methyl-piperazino-5-mercapto-aryl substituted-1,3,4-oxadiazoles. Synthesized compounds were characterized by FTIR, ^{1}H NMR and elemental analysis. Antioxidant activity of methanol solutions of synthesized compounds was determined by reducing power assay and hydrogen peroxide scavenging activity at 700 nm and 250 nm respectively. The synthesized compounds were also screened for anti-inflammatory activity. Compound showed good anti-inflammatory and antioxidant activities.

Keywords: 1,3,4-Oxadiazole, Anti-inflammatory, Antioxidant, *N*-Methylpiperazine, Green synthesis

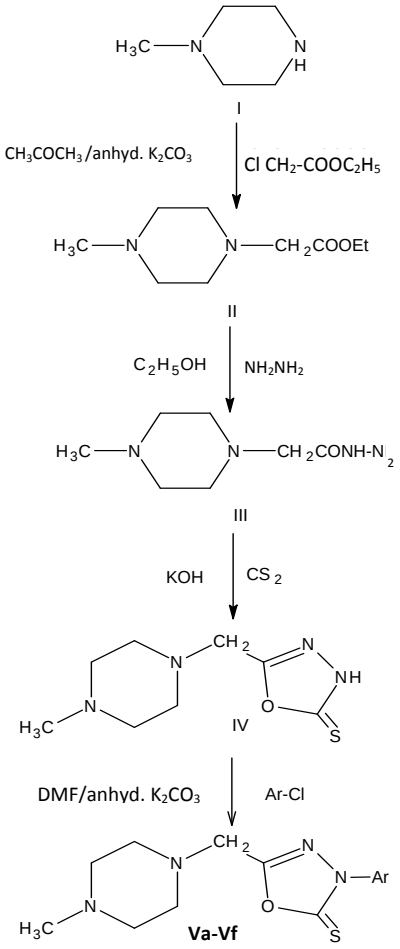
Introduction

Microwave assisted heating under controlled conditions has proved an efficient synthetic technique due to enhanced rates, higher selectivity, efficiency and higher yield[1,2]. A one-pot synthetic protocol has become one of the efficient approaches of synthesis because it avoids a lengthy separation and purification of the intermediates and hence increases chemical yield[3,4].

Some new pharmacologically important heterocyclic nucleus are reported to show remarkable antioxidant activity[5-7] and anti inflammatory activity[8,9]. Moreover 1,3,4-oxadiazole derivatives[10,11] and piperazine derivatives[12] have their own importance in drug discovery. In view of above findings 1,3,4-oxadiazole and piperazine moieties are incorporated together and evaluated for their anti-inflammatory and antioxidant activities.

Experimental

Melting points were determined in open capillary tubes in a 'Innco' electrical apparatus and are uncorrected (Table 1). FTIR was carried out on Schimadzu 8101 A. Spectrophotometer in KBr pellets and ^{1}H NMR was recorded on a DPX 300 MHz Brucker Spectrophotometer in DMSO with chemical shift in ppm (Table 2). MW irradiations were carried out in domestic Samsung microwave oven, model number 310 EMENO 22332. The synthesized products were frequently checked by thin layer chromatography (TLC). Absorbance for antioxidant activity was determined by ELICO SL 177 scanning mini spec.



Ar-Cl= Cl-$C_6H_4NO_2$(p), Cl-$C_6H_3NO_2$(o,p), Cl-$C_6H_4NO_2$(p), Cl-$C_6H_3NO_2$(m),NH_2(p), Cl-$C_6H_4NO_2$(p), Cl-$C_6H_3NH_2$(p), Cl-C_6H_4CHO(p), Cl-C_6H_3COOH(p)

Scheme 1

*One- pot synthesis of 2-N-methyl piperazino-5-mercapto-1,3,4-oxadiazole (**IV**)*

Equimolar mixture of *N*-methylpiperazine and chloroethyl acetate was irradiated in a microwave oven in 10 mL acetone for 15 minutes in presence of 0.02 mole of anhydrous potassium carbonate. This resulted in formation of ethyl-*N*-methylpiperazino acetate(II). In the reaction mixture 0.012 mole of hydrazine hydrate was added gradually followed by addition of 10 mL absolute ethanol with continuous stirring and the resultant mixture was irradiated in microwave oven for 15 minutes. *N*-methylpiperazino acetyl hydrazide(III) was obtained by above process. 0.01 mole of *N*-mehtylpiperazino acetyl hydrazide and 0.02 mole of potassium hydroxide were dissolved in 10-12 mL of absolute ethanol. 0.015 mole CS_2 was added gradually with continuous stirring. The resultant solution thus obtained was irradiated for 15 minutes and then cooled, diluted with 100 mL water and filtered. The filtrate was acidified with acetic acid. The solid 2-*N*-methylpiperazino-5-mercapto-1,3,4-oxadiazole(IV) thus obtained was filtered, washed with water, dried and recrystallized using ethanol (Scheme 1).

2-N-Mehtylpiperazino methylene- 4-substituted aryl-5-mercapto-1,3,4-oxadiazoles (Va-Vf)

2-*N*-methylpiperazino methylene-5-mercapto-1,3,4-oxadiazole and 4-nitro chloro benzene were taken in equimolar ratio and irradiated under anhydrous conditions in 10 mL acetone and (0.02 g) anhydrous potassium carbonate for 15 minutes. Excess solvent was distilled off. On cooling a solid separated out which was filtered, dried and recrystallised from ethanol. The remaining compounds were synthesized in a similar manner.

Table 1. Analytical and elemental data of synthesized compounds

Compounds	MF (MW)	M.P, (%Yield)	% N Calcd, (Found)
IV	$C_8H_{14}N_4OS$ (214)	181 (72)	26.17 (26.19)
Va	$C_{14}H_{17}N_5O_3S$ (335)	188 (70)	20.89 (20.93)
Vb	$C_{14}H_{16}N_6O_5S$ (380)	208 (75)	22.11 (22.14)
Vc	$C_{14}H_{19}N_5OS$ (305)	190 (68)	24.00 (24.02)
Vd	$C_{14}H_{16}N_6O_5S$ (380)	208 (75)	22.95 (22.98)
Ve	$C_{15}H_{18}N_4O_2S$ (318)	218 (65)	17.61 (17.65)
Vf	$C_{15}H_{18}N_4O_3S$ (334)	226 (78)	16.77 (16.80)

Table 2. FTIR and ^{1}H NMR data of synthesized compounds

Compounds	IR	NMR
IV	3020 (C-N),1640 (C=N), 1280 (C=S), 3310 (NH)	2.14(s, 3H, CH_3), 2.64-2.68(m,8H, N-$(CH_2)_4$-N), 3.12(s,2H,-CH_2-), 9.10(s,1H, NH)
Va	3022 (C-N), 1645 (C=N) 1270 (C=S), 1525 (NO_2)	2.15(s, 3H, CH_3), 2.64-2.70(m,8H, N-$(CH_2)_4$-N), 3.14(s,2H,-CH_2-), 7.20-7.68(d, 4H, Ar-H)
Vb	2990 (C-N), 1648 (C=N), 1280 (C=S), 1530 (NO_2), 1522 (NO_2)	2.16(s, 3H, CH_3), 2.66-2.70(m,8H, N-$(CH_2)_4$-N), 3.08(s,2H,-CH_2-), 7.18-7.49(d, 3H, Ar-H)
Vc	2995 (C-N), 1635 (C=N), 1280 (C=S), 1530(NO_2), 3290(NH_2)	2.12(s, 3H, CH_3), 2.62-2.78(m,8H, N-$(CH_2)_4$-N), 3.12(s,2H,-CH_2-), 7.10-7.42(d, 3H, Ar-H), 9.12 (s,2H, NH_2)
Vd	3010 (C-N), 1642 (C=N), 1275 (C=S), 3310 (NH_2)	2.12(s, 3H, CH_3), 2.63-2.69(m,8H, N-$(CH_2)_4$-N), 3.10(s,2H,-CH_2-), 7.05-7.40(d, 4H, Ar-H), 9.15 (s,2H, NH_2)
Ve	2990 (C-N), 1645 (C=N) 1280 (C=S), 1710 (C=O)	2.14(s, 3H, CH_3), 2.62-2.67(m,8H, N-$(CH_2)_4$-N), 3.10(s,2H,-CH_2-), 7.14-7.44(d, 4H, Ar-H), 10.10 (s,1H, CHO)
Vf	3010 (C-N), 1645 (C=N), 1285 (C=S), 1690 (C=O), 3410(OH)	2.18(s, 3H, CH_3), 2.64-2.72(m,8H, N-$(CH_2)_4$-N), 3.14(s,2H,-CH_2-), 7.15-7.55(d, 4H, Ar-H), 12.10 (s,1H, OH)

Antioxidant activity

All the synthesized compounds were screened for antioxidant potential *in vitro* by reducing power activity and hydrogen peroxide-scavenging activity.

Reducing power activity by $FeCl_3$

Reducing power (RP) of synthesized compounds was determined (Figure 1) according to the method of Oyaizu[13]. Different aliquots of the test sample and ascorbic acid as standard for comparison at concentration of 50 µg/mL, 100 µg/mL, 150 µg/mL, 200 µg/mL and 250 µg/mL were taken in different test tubes. 2.5 mL Phosphate buffer (pH 6.6) and 2.5 mL of 1% $K_3Fe(CN)_6$ were added in each test tube. Test solutions were kept for 20 minutes at 50 ^{0}C in water bath. After 20 minutes 2.5 mL 10% trichloro acetic acid was added in each test solution. An aliquot of 2.5 mL was withdrawn from each test solution and in it 2.5 mL distilled water and 1.0 mL $FeCl_3$ (0.1%) were added. A blank was also prepared without adding the test compound.

Each experiment was carried out in triplicate and mean value was calculated. Finally the antioxidant activity was evaluated by determining the absorbance at 700 nm after 10 minutes.

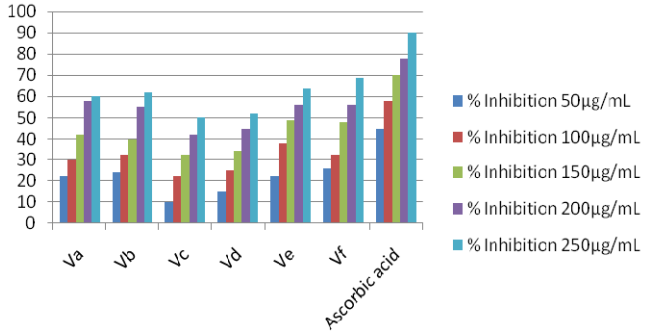


Figure 1. Antioxidant activity by reducing power assay

Hydrogen peroxide scavenging activity

The hydrogen peroxide scavenging activity was determined by the method of Gerald *et al*[14]. The synthesized compounds were dissolved in 3.4 mL of 0.1 M phosphate buffer (7.4 p H) and mixed with 600 µL of 43 mM solution of hydrogen peroxide. The absorbance value at 230 nm of the test samples were recorded at 10 minutes intervals between 0 to 40 minutes. BHT was used as standard for comparison (Figure 2).

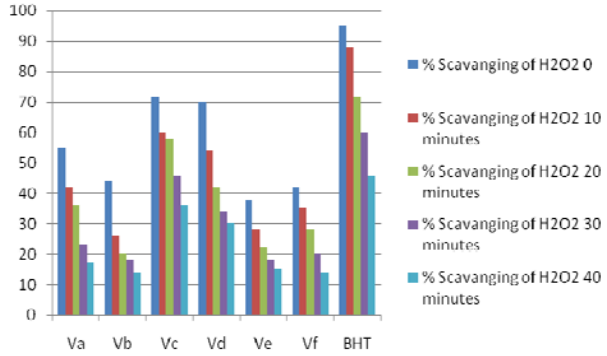


Figure 2. Antioxidant activity by hydrogen peroxide scavenging activity

Anti inflammatory activity

The synthesized compounds were screened for *in vitro* anti-inflammatory activity by method of Elias *et al*[8]. Synthesized compounds were dissolved in DMF and diluted with phosphate buffer (0.2 M, pH 7.4) to got solution of 1 mg/mL 0.8 mg/mL 0.6 mg/mL 0.4 mg/mL 0.2 mg/mL concentration. Test solution (1 mL) containing different concentrations of compounds was mixed with 1 mL of 1mg/mL albumin solution in phosphate buffer and incubated at 27 ^{0}C for 15 minutes. Denaturation was induced by keeping the reaction mixture at 60 ^{0}C in water bath for 15 minutes. After cooling, the transmittance of the turbid suspension was measured at 660 nm. The percentage inhibition of denaturation was calculated with reference to control where no drug was added and Ibuprofen was used as standard for comparison. The percentage inhibition of denaturation was calculated by using following formula.

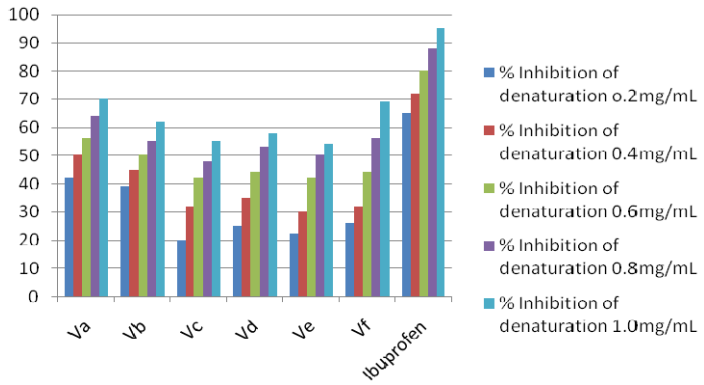


Figure 3. Anti inflammatory activity by inhibition of denaturation of albumin

Results and Discussion

The antioxidant activity in terms of reducing power shows that as the concentration of the test compounds increases there is increase in the reducing power of these derivatives. Among the six derivatives synthesized, maximum reducing potential was observed in compounds **Ve** and **Vf**. However less activity was observed compared to ascorbic acid.

The antioxidant activity in terms of hydrogen peroxide scavenging potential shows that oxidation power of the synthesized compounds decreases with increase in time. However, maximum hydrogen peroxide scavenging values were observed for compound **Vc** and **Vd**. Moreover, anti-inflammatory data reveal that maximum percentage inhibition of denaturation of albumin was observed in the case of **Va** and **Vf** while other derivative showed moderate inhibition in comparison of standard ibuprofen.

Conclusion

Microwave assisted synthesis can be used to reduce the time and increase the yield of reaction. The bioactivity results revealed that synthesized *N*-methylpiperazino substituted-1,3,4-oxadiazoles may be used in exploring new antioxidant and anti-inflammatory lead drugs.

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References

1. Adnani M, Ashour D H, Ali K F, Mohsen A M, *Asian J Chem*., 2012, **24(12)**, 5592-5596.
2. Pradeep P, Deohate and Berad B N, *J Indian Chem Soc.*, 2014, **91**, 1361-1364.
3. Bahrami K, Khodaei M M and Kavianinia I, *Synthesis*, 2007, 417-427.
4. Huq C A M A and Sivakumar S, *J Indian Chem Soc.*, 2014, **91(2)**, 313-318.
5. Hossain M M, Muhib M H, Mia M R, Kumar S and Wadud S A, *Bangladesh Med Res Counc Bull.*, 2012, **38(2)**, 47-50.
6. Kotaiah Y, Harikrishna N, Nagaraju K and Rao C V, *European J Med Chem.*, 2012, **58**, 340–345; DOI:10.1016/j.ejmech.2012.10.007

7. Singhal M, Paul A, Singh H P, Dubey S K and Songara R K, *Int J Pharm Sci Drug Res.*, 2011, **3(2)**, 150-154.
8. Elias G and Rao M N A, *Indian J Exp Biol*., 1988, **26**, 540-542.
9. Shaaban M R, Saleh T S, Mayhoub A S, Mansour A and Faraq A M, *Bioorg Med Chem.*, 2008, **16(12)**, 6344-6352; DOI:10.1016/j.bmc.2008.05.011
10. Bhardwaj N, Saraf S K, Sharma P and Kumar P, *J Chem.*, 2009, **6(4)**, 1133-1138; DOI:10.1155/2009/698023
11. Joshi N K, Kundariya D S and Pasrmar J M, *Int J Chem Tech Res.*, 2012, **4(4)**, 1503-1508.
12. Sah P and Gharu C P, *Indian J Res.*, 2013, **2(3)**, 15-17.
13. Oyaizu M, *Japan J Nut.*, 1986, **44**, 307–315.
14. Gerald M Rosen and Elmer J Rauckman, *Meth Enzym.*, 1984, **105**, 198-209; DOI:10.1016/S0076-6879(84)05026-6