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Regioselective synthesis and biological activity of novel β,β'-diaminoalcohols

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Abstract: A highly effective and mild protocol for ring opening of epoxides with ethylenediamine in one step avoiding the use of expensive catalysts under solvent-free conditions is described. A variety of β,β'-diamino alcohols were obtained in high yields with excellent regiospecifity and in short reaction times. All the title compounds were screened for their antioxidant activity by β, β'-diaminoalcohols, hydroxyl radical, reducing power and ferrous ion chelating (FIC) methods and they showed promising antioxidant activity.

Keywords: β,β'-diaminoalcohols, epoxides, ethylenediamine, antioxidant activity.

INTRODUCTION

Epoxides are versatile intermediates in organic synthesis. For instance, their nucleophilic opening leads to a large number of 1,2-difunctionalized systems[1-6] and have been the subject of extensive studies[7-11]. The ring opening of epoxides with amines, is an important organic reaction for the preparation of β-amino alcohols, the products which act as key intermediates in organic chemistry and

in a range of various biologically active compounds, in addition to their use in pharmaceutical industries [11-18] and in the complexation of heavy metals[19-25].

Therefore, the development of new range of aminoalcohols and/or a new synthetic methodology remains a promising success in the field of chemistry and more particularly the β-blockers chemistry. In the course of our study on the ring opening of epoxides with nucleophilic, we have prepared a number of biologically active compounds and polydentate ligands exhibiting either a thioether or an oxathioether moiety as an additional donor function[26-28]. In continuation of our investigation on the use of oxirane We report herein the synthesis of a new series of symmetrically disubstituted β,β'-diaminoalcohols accessible from the reaction of ethylenediamine on a variety of epoxides in one step avoiding the use of expensive catalysts.

MATERIAL AND METHODS

Commercially available reagents and solvents were used without further purification. Acetonitrile was dried by distillation from sodium and stored over activated molecular sieves (4 A°). When necessary the reactions were performed in oven-dried glassware under dry nitrogen. Melting points were determined in open glass capillaries and are uncorrected. All the compounds were characterized by IR. ^{1}H and ^{13}C NMR were recorded on a 300 MHz AC Bruker spectrometer. High-resolution ESI-MS spectra were performed on a Thermo LTQ Orbitrap XL mass spectrometer. The spectra were recorded by infusion into the ESI source using MeOH as the solvent. NMR chemical shifts (δ) are reported in part per million (ppm) relative to the residual solvent peak (TMS). Column chromatography was performed on silica gel (70–230 mesh ASTM) using the reported eluents. Thin layer chromatography (TLC) was carried out on 5 x 20 cm plates with a layer thickness of 0.25 mm (Silica gel 60 F254). When necessary they were developed with KMnO4 and SiO2/I2.

General procedure for the synthesis of β,β'-diamino-alcohols: To a solution of epoxide (30 mmol) in ethanol (15 mL), a solution of ethylenediamine (15 mmol) in ethanol (10 mL) was added dropwise while stirring at room temperature for about 15 min. Stirring was continued at room temperature for 10 min. The progress of the reaction was monitored by TLC eluant: cyclohexane/acétate d'éthyle: 8/2). After completion of the reaction, the mixture was diluted with water (15 mL) and the product was extracted with diethyl ether (3x20 mL). The organic extracts were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude product was purified by column chromatoghraphy on silica gel (cycohexane/ ethyl acetate:8/2) to get pure compounds (**2a-h**).

1,1'-(Ethane-1,2-diylbis(azanediyl))bis(propan-2-ol)2a : White solid mp = 148°C^{1}H-NMR. (MeOD, 300 MHz): 1.15 (d, 3H, ^{3}J$_{HH}$ = 6,3Hz; CHC$\underline{H}_3$); 1.95 (bl, 1H, N$\underline{H}$) ; 2.72 (s, 2H, C$\underline{H}_2$NH), 2.48-2.60 (system ABX, 2H, C$\underline{H}_2$CH) ; 3.85 (m, 1H, C$\underline{H}$OH); 4.19 (bl, 1H, O$\underline{H}$) ; ^{13}C-NMR: 20.03(s, CHC$\underline{H}_3$); 53, 74 (s, C$\underline{H}_2$NH), 56, 50(s, NHC$\underline{H}_2$CH); 65, 67 (s, C$\underline{H}$OH).IR (neat): V$_{OH}$=3179 cm^{-1}; (OH), V$_{NH}$=2927 cm^{-1}HRMS for C$_8$H$_{20}$N$_2$O$_2$: Calcd.: 176.257; Found 176.249.

1,1'-(Ethane-1,2-diylbis(azanediyl))bis(butan-2-ol)2b: White solid mp = 155°C^{1}H NMR (300 MHz, MeOD) :0,97 (t, 6H,^{3}J$_{HH}$ = 7,5 Hz, ,2 CH$_2$C$\underline{H}_3$), 1,54 (m, 4H, C$\underline{H}_2$CH$_3$), 7,85 (bl, 2H, 2.N$\underline{H}$), 2, 76 (s, 4H, 2.C$\underline{H}_2$NH), 2.50 – 2,67 (ABX, 4H, 2.C$\underline{H}_2$CH), 3,59 (m, 2H, 2.C$\underline{H}$OH), 5,01 (bl, 2H, 2.O$\underline{H}$); ^{13}CNMR: 10, 11 (s, CH$_2$C$\underline{H}$3); 29, 25 (s, C$\underline{H}_2$CH$_3$); 72, 71 (s, C$\underline{H}$OH); 56, 19 (s, CHC$\underline{H}_2$NH); 49,85 (s, C$\underline{H}_2$NH); IR (neat):V$_{OH}$=3086cm^{-1}; V$_{NH}$=2935 cm^{-1}; HRMS for C$_{10}$H$_{24}$N$_2$O$_2$: Calcd.: 204,310; Found 204,309.

1,1'-(Ethane-1,2-diylbis(azanediyl))bis(hexan-2-ol) 2c: white solid mp 194 °C: ^{1}H NMR (400 MHz, Methanol-d_4); δ 0.95 (t, $^3J_{HH}$= 7.0 Hz, 3H,C$\underline{H}_3$).1,33-1,47(m,6H, C$\underline{H}_2$C$\underline{H}_2$C$\underline{H}_2$); 3,68 (m,1H,C$\underline{H}$OH); 2,50-2,67 (ABX, 2H,C$\underline{H}_2$NH); 2,76 (s, 2H, CH$_2$NH); 3,36 (bl,1H,OH) 3,17 (bl,1H,NH); ^{13}C NMR; 12,98, 22,39, 27,56, 34,86(4C, $\underline{C}$H$_3\underline{C}$H$_2\underline{C}$H$_2\underline{C}$H$_2$); 69,68 (1C,$\underline{C}$HOH); 55,13(1C, $\underline{C}$HCH$_2$NH); 47,99(1C, $\underline{C}$H$_2$NH.V$_{OH}$ =3089 cm^{-1} ; V$_{NH}$=2867 cm^{-1} ; HRMS for C$_{14}$H$_{32}$N$_2$O$_2$: Calcd.: 260.416; Found 260.412

3,3'-(Ethane-1,2-diylbis(azanediyl))bis(butan-2-ol)(methyl-methyl) 2d: white solid mp 180°C ^{1}H NMR (400 MHz, MeOD); 1,16 (d, 3H, $^3J_{HH}$ =6,5Hz ,C$\underline{H}_3$CHOH); 3,81(m,2H,C$\underline{H}$OH); 2,61 (m,2H,NHC$\underline{H}$CH$_3$); 1,05 (d,$^3J_{HH}$ = 6.6 Hz,NHCHC$\underline{H}_3$); 2.76(s,2H,C$\underline{H}_2$NH); 3,37 (bl, OH); 2,64 (bl,NH). ^{13}C NMR: 17,45($\underline{C}$H$_3$CH); 68,62 (CH$_3\underline{C}$H); 57,90 ($\underline{C}$HNH); 13,29 (NHCHC$\underline{H}_3$); 46,06($\underline{C}$H$_2$NH).V$_{OH}$ =3094 cm^{-1} ; V$_{NH}$=2881 cm^{-1} ; HRMS for C$_{10}$H$_{24}$N$_2$O$_2$: Calcd.: 204,310; Found 204,314

3,3'-(Ethane-1,2-diylbis(azanediyl))bis(1-chloropropan-2-ol) 2e: White solid mp = 176°C ^{1}H NMR (300 MHz, MeOD) :3,50 - 3,67 (ABX, 4H, 2 ClC$\underline{H}_2$), 1, 56 (bl, 2H, 2.N$\underline{H}$), 2,86 (s, 4H, 2.C$\underline{H}_2$NH), 2, 70- 2, 89 (ABX, 4H, 2.C$\underline{H}_2$CH), 3, 94 (m, 2H, 2.C$\underline{H}$OH),3, 62 (b l, 2H, 2.O$\underline{H}$); ^{13}C NMR: 46,57 (s, $\underline{C}$H$_2$Cl); 47,51 (s, $\underline{C}$H$_2$NH); 51,60(s, NH $\underline{C}$H$_2$); 69,50 (s, $\underline{C}$HOH); IR (neat): V$_{OH}$ =3097 cm^{-1} ; V$_{NH}$=2874 cm^{-1}; HRMS for C$_8$H$_{18}$Cl$_2$N$_2$O$_2$: Calcd.: 245,146 Found 245,154

2,2'-(Ethane-1,2-diylbis(azanediyl))dicyclohexanol 2f: White solid mp = 160°C[1]H NMR (300 MHz, MeOD) :1,03– 2,04 (m, 16H, 8.C$\underline{H}_2$), 1,95 (bl, 2H, 2.N$\underline{H}$), 2,67 (s, 4H, 2.C$\underline{H}_2$NH), 2,30 (m, 2H, 2.C$\underline{H}$NH), 3, 28 (m, 2H, 2.C$\underline{H}$OH), 3, 61 (bl, 2H, 2.O$\underline{H}$) ; ^{13}C NMR: 24,22 (s, $\underline{C}$H$_2$); 24, 25 (s, $\underline{C}$H$_2$); 29, 57 (s, $\underline{C}$H$_2$); 33, 92 (s, $\underline{C}$H$_2$); 45,63 (s, $\underline{C}$H$_2$NH); 73,15 (s, $\underline{C}$HOH); 62,92 (s, $\underline{C}$HNH); IR (neat):V$_{OH}$ =3107 cm^{-1} ; V$_{NH}$=2898cm^{-1} ; HRMS for C$_{14}$H$_{28}$N$_2$O$_2$: Calcd.: 256.384; Found 256.396.

2,2'-(Ethane-1,2-diylbis(azanediyl))bis(1-phenylethanol) 2g: White solid mp = 190°C[1]H NMR (300 MHz, DMSO) :8,32 (bl, 2H, 2.N$\underline{H}$), 2,62 (s, 4H,2.C$\underline{H}_2$NH), 2,57 - 2,72 (ABX, 4H, 2.C$\underline{H}_2$CH), 4,06 (m, 2H, 2.C$\underline{H}$OH), 5, 25 (b l, 2H, 2.O$\underline{H}$), 7, 33 (m, 10$\underline{H}$, 2.Ph); ^{13}C NMR: 52,36(s, $\underline{C}$H$_2$NH); 56,52 (s, CH$\underline{C}$H$_2$NH); 71, 97 (s, OH$\underline{C}$H); 126,34 -127,19-128,53-138,45(4s, $\underline{C}$$_{ar}$); IR (neat):V$_{OH}$ =3079 cm^{-1} ; V$_{NH}$=2847 cm^{-1}; HRMS for C$_{18}$H$_{24}$N$_2$O$_2$: Calcd.: 300,395; Found 300,391
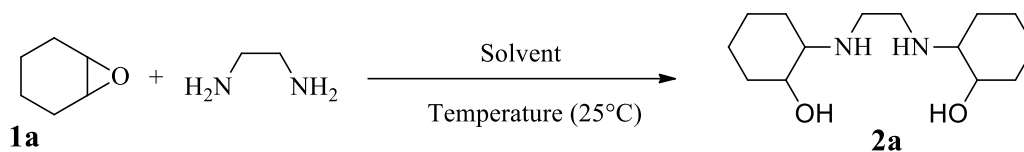
3,3'-(Ethane-1,2-diylbis(azanediyl))bis(1-phenoxypropan-2-ol) 2h: white solid mp 200°C: ^{1}H NMR (400 MHz, DMSO-d_6) δ; 3.87 (m, 1H, PhOC$\underline{H}_2$); 4,96 (m,1H, C$\underline{H}$OH); 2,57-2,67(ABX, 2H, OHCHC$\underline{H}_2$); 2,61(s,2H,C$\underline{H}_2$NH); 3,95(bl, 1H, OH); 5,76 (bl, 1H, NH); ^{13}C NMR (101 MHz, DMSO-d_6) δ ; 71,09 (1C, PhO$\underline{C}$H$_2$); 68,67 (1C,$\underline{C}$HOH); 52,96 (1C,CH$\underline{C}$H$_2$NH); 49,79 (1C,$\underline{C}$H$_2$NH); 114,91-120,87- 129,90-159,15 (4C , Phenyl)V$_{OH}$ =3092 cm^{-1} ; V$_{NH}$ =2860 cm^{-1} ; HRMS for C$_{20}$H$_{28}$N$_2$O$_2$: Calcd.: 360,447; Found 360,439.

RESULTS AND DISCUSSION

In order to optimize the reaction conditions, cyclohexene oxide (**1a**) (2 equiv) was taken as a representative epoxide and treated with ethylenediamine (1 equiv.) in the presence of various solvents at room temperature. The reactions were monitored by TLC and the optimum results are shown in **Table 1**. Under solvent-free conditions a satisfactory yield was obtained after 24 hours (**Table 1, entries 1).** In the presence of THF the reaction was slow and gave good yield (**Table 1, entry 2).**

Reactions in polar protic solvents such as H_2O; MeOH and EtOH gave good yields of the desired product and the best result was observed in EtOH(exellent yields, short reaction times).

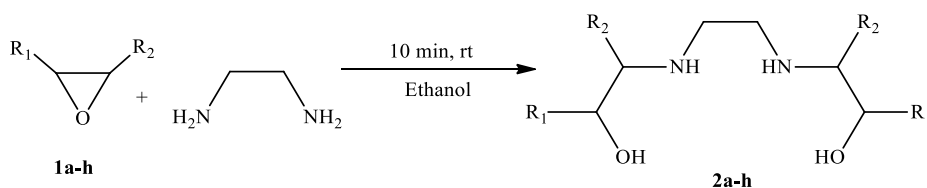**Table1**: Optimization of the reaction condition

Entry	solvent	Time,min[h]	Yields of (2a)*
1	Neat	[24]	64
2	THF	[48]	71
3	H_2O	[24]	65
4	MeOH	[2]	78
5	EtOH	10	90

*: Isolated yield of pure compound

This success has prompted us to extend the generality of the reaction to various epoxides **(Table 2, entries1-8).** A series of β, β'-diaminoalcohols **2a-h** were obtained in good yields (**Table 2**). Performing the reaction in ethanol as a solvent, affords significant advantages such as efficiency, good yields, short reaction times, easy work-up and environmental safety. As shown in **Table 2,** this reaction allows the preparation of β, β'-dihydroxy dithioethers in excellent yields. For the starting oxiranes **1a–h**, the epoxide ring was regiospecifically opened by nucleophilic attack on the terminal carbon atoms affording a secondary diol.
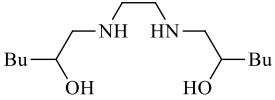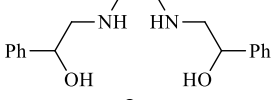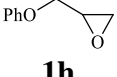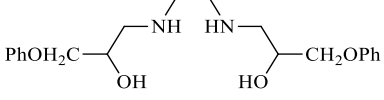
As compounds **2** are expected to be excellent agents endowed with antioxidant activity, we present in the following of our results of the study of the antioxidant activity of these compounds.

Table 2: Reaction of epoxides**1** with ethylenediamine.

$R_1, R_2 =$ Me,H(a); Et,H(b);n-Bu,H(c);Me,Me(d);CH$_2$Cl,H(e);(CH$_2$)$_4$(f);Ph,H(g);PhOCH$_2$,H(h)

Entry	epoxide	Product **2**	Time, min[h]	Yield (%)*
1			10	87

2	**1b** (Et epoxide)	**2b**	10	88
3	**1c** (Bu epoxide)	**2c**	10	89
4	**1d** (Me, Me epoxide)	**2d**	[1]	89
5	**1e** (Cl-CH₂ epoxide)	**2e**	10	83
6	**1f** (cyclohexene oxide)	**2f**	10	90
7	**1g** (Ph epoxide)	**2g**	15	77
8	**1h** (PhO-CH₂ epoxide)	**2h**	40	75

*: Isolated yield of pure compound

In vitro antioxidant activity: Oxidative stress, induced by oxygen radicals, is believed to be a primary factor in various degenerative diseases, such as cancer, atherosclerosis, gastric ulcer and other conditions Kumaran&Joel Karunakaran[29]. Many antioxidant compounds, naturally occurring from plant sources have been identified as a free radical or active oxygen scavengers[30]. Recently, interest has increased considerably in finding new synthetic antioxidants.

The antioxidant capacities of compounds (2a-h) were evaluated, in vitro, by 1,1-diphenyl-2-picrylhydrazyl (DPPH), reducing power, ferrous ion chelating (FIC), and degradation desoxyribose methods, using ascorbic acid as standard.

DPPH radical scavenging activity: The free radical scavenging activity of the compounds (2a- h) with the same concentration (1mg/ml) was expressed in terms of percentage scavenging using the stable radical 2,2 diphenyl 2 picrylhydrazyl hydrate (DPPH) described by Barcaetal[31]. Briefly, solution of DPPH in methanol was prepared (0,035mg/ml) and stock solution of various compounds (1mg/mL). 3ml of DPPH solution was mixed with 1 mL of compounds. The samples were kept in the dark for 30 minutes at room temperature.

The absorbance was measured at 517 nm. All the tests were run in triplicate and expressed as the mean ± standard deviation (SD). Ascorbic acid was used as standard or positive control, parallel to the test

compound and in the absence of the test compound/standard used as the negative control. The capability to scavenge the DPPH radical was calculated using the following equation.

% inhibition of DPPH radical= [(Abs cont−Abs test) /Abs cont] × 100

Where Abs cont = absorbance of the control (reacting mixture without the test sample) and, Abs test sample = absorbance of reacting mixture with the test sample.

Our data presented in **Figure 1** showed that the compounds (2b, 2c and 2e**)** have the highest capacity of scavenging of DPPH radicals with inhibition% of DPPH radicals of 60.06±0.33%, 58.25±0.28%, and 57.43±1.25%, respectively compared to ascorbic acid (AA) 86±0.7%.
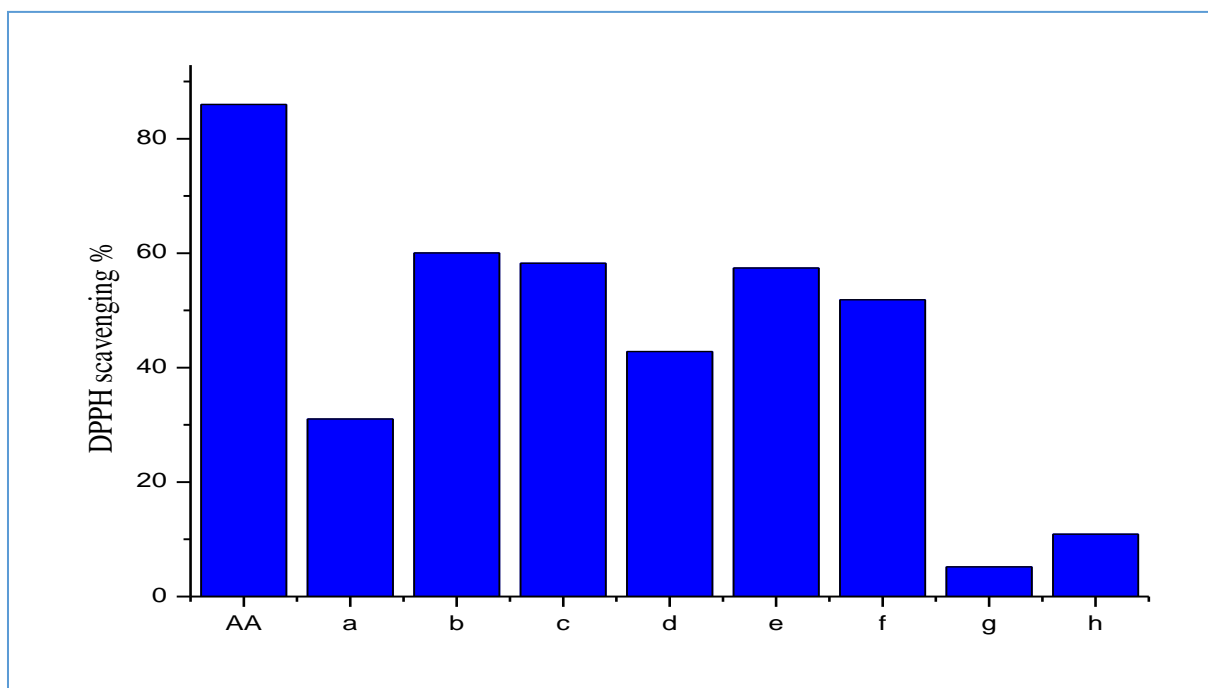

Figure 1: DPPH Radical Scavenging Activity of compounds (2a-h) tested compounds and ascorbic acid (AA) is a standard.

Degradation of deoxyribose (Fenton's reaction): This assay was determined with desoxyribose degradation method described by Halliwell and Gutteridge [32].The ability of the compounds **(**2a-h) at the same concentration (1mg/mL) to prevent the formation of hydroxyl radicals' results in decomposition of desoxyribose known as the Fenton's reaction. Briefly, reaction mixture containing a methanolic solution of compounds (1mg/mL), 120 µL 20 mM deoxyribose, 400 µL 0.1 M phosphate buffer, 40 µL 20 mM hydrogen peroxide and 40 µL 500 µM FeSO4, and the volume was made to 800 µL with distilled water. The reaction mixture was incubated at 37 ∘C for 30 min, and the reaction was quenched by the addition of 0.5 mL of 2.8% TCA (trichloroacetic acid), this was followed by the addition of 0.4 mL of 0.6% TBA solution. The tubes were subsequently incubated in boiling water for 20 min. The absorbance was measured at 532 nm with a spectrophotometer.

OH radical scavenging ability percentage (%) = [(Abs cont−Abs test) /Abs cont] × 100

Where Abs cont = absorbance of the control (reacting mixture without the test sample) and,

Abs test sample = absorbance of reacting mixture with the test sample.

The results are summarized in **Figure 2**, all compounds scavenge OH• produced in Fe^{2+}/H_2O_2 induced decomposition of deoxyribose in Fenton reaction. The OH• scavenging ability of compounds (2a-f) is 73.63% ± 0.87, 62.77 % ± 1.39, 61.12 % ± 1.21, 70.12 % ± 0.96, 62.02% ± 1.84 and 63.12% ±0.92, respectively compared to 79,84%± 0,53 observed for ascorbic acid at the same concentration (1mg/mL).
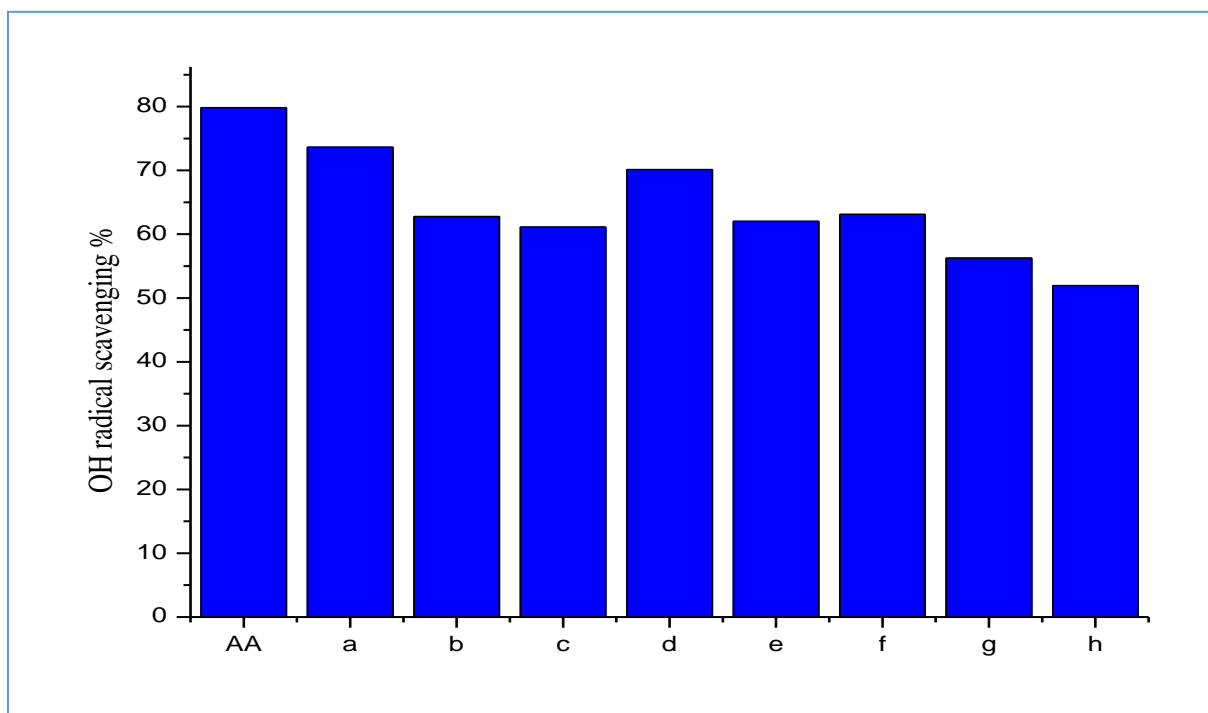

Figure 2: OH radical scavenging ability of tested compounds **(2a- h)** and ascorbic acid (AA).

Reducing propriety: The reducing power of new compounds (2a-h) was assayed according to the method of Pulido *et al*.[33]. Briefly, a methanolic solution of compounds (1 mL) at same concentration (1mg/mL) was mixed with 2.5 mL of phosphate buffer (0.2 M) and 2.5 mL of 1% potassium ferricyanide and incubated at 50°C for 20 min. To this mixture, 2.5 mL of 10% trichloroacetic acid was added and the mixture was centrifuged at 3000 rpm for 20 min. The upper layer (2.5 mL) was mixed with 2.5 mL of deionized water and 0.5 mL of 0.1% Ferric chloride and the same treatment was performed to a standard ascorbic acid solution and the absorbance taken at 700 nm.

The reducing property was measured using the following equation:

Reducing power %= [(Abs cont−Abs test) /Abs cont] × 100

Where Abs cont = absorbance of the control (reacting mixture without the test sample) and, Abs test sample = absorbance of reacting mixture with the test sample.

Figure 3 shows the reducing propriety of different compounds at the same concentration and compared to ascorbic acid as a standard. The compound (2a) has a highest percentage of reducing power 77.32±0.75 %, which is comparable to that of ascorbic acid 78.73±0.82 %.

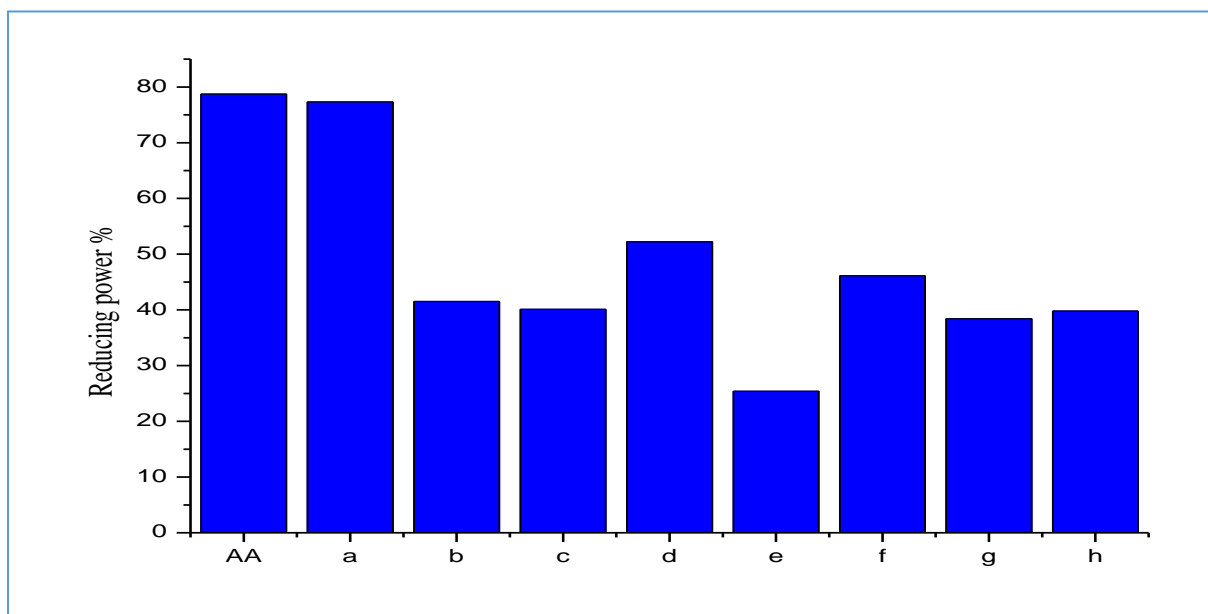**Figure 3:** Reducing power assay (**2a- h**: tested Compounds, AA: ascorbic acid)

Ferrous Ion Chelating (FIC) Ability: The FIC ability of new compounds (2a-h) was determined according to the method of Singh and Rajini [34]. A methanolic solution of compounds (1.0 mL) at same concentrations (1 mg/mL) was added to 1.0 mL of FeSO4 (0.1 mM) and 1.0 mL of ferrozine (0.25 mM). The tubes were shaken well and left to stand for 10 min. The absorbance was measured at 562 nm. The ability of each sample to chelate ferrous ions was calculated relative to the control consisting of only iron ferrozine, using the following formula:

% FIC = [(Abs cont– Abs test) / Abs cont] x 100

Where Abs cont is the absorbance of the control, and Abs test is the absorbance of the sample in the presence of test compound.

The ability of different compounds (2a-h) with same concentration (1mg/mg) to chelate ferrous ion is also reported in **Figure 4**. Our data showed that the compound (2a) is a good chelator of ferrous ion as compared to the ascorbic acid even for the same concentration, compound 2a (FIC%=61.77±0.78%) and ascorbic acid (FIC%=65.1±1.57%).
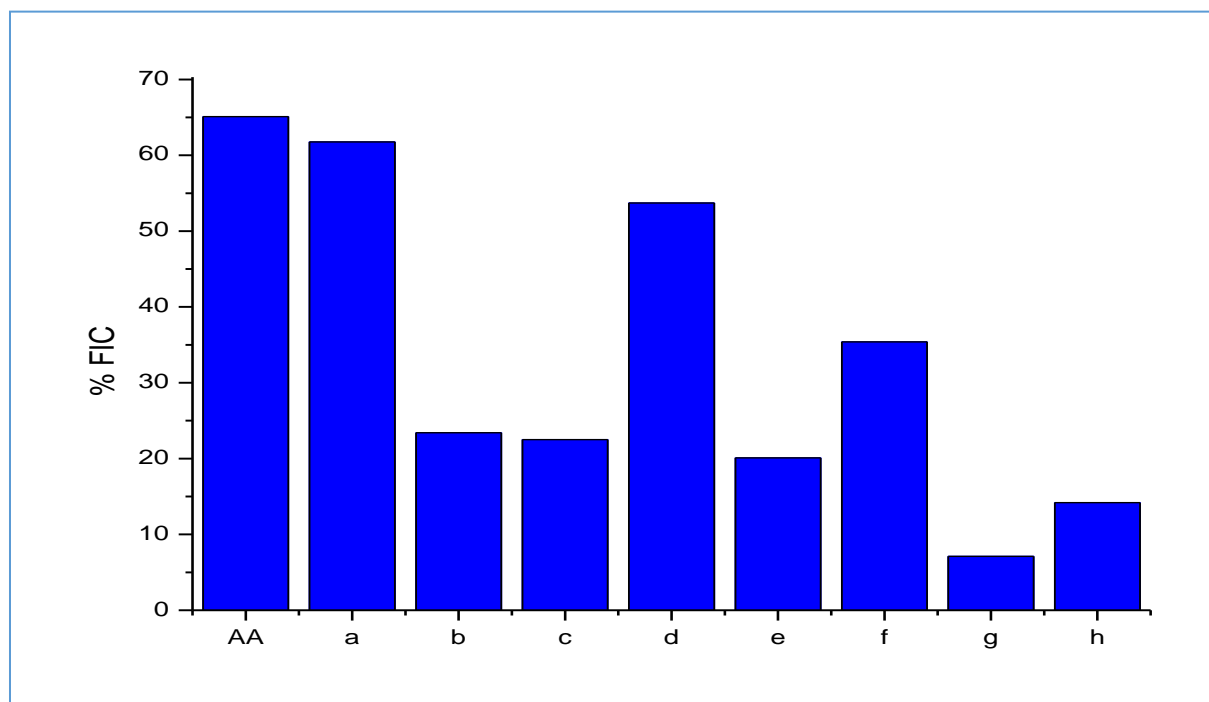
Figure 4: Ferrous ion chelating (FIC) ability (**2a- h**: tested compounds, AA: ascorbic acid).

CONCLUSION

In conclusion, we successfully developed a simple and clean procedure for the synthesis of β,β'-diaminoalcohols, in ethanol as solvent. This synthesis has the advantages of efficiency, generality, and good yields and avoids the use of expensive catalysts and hazardous solvents. Also, these products seem to be very beneficial through their promising biological activities. According to previous results, some compounds showed the ability of chelating the ferrous ion, capacity of reducing of iron and the ability to chelate the hydroxyl radicals.

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