Evaluation of antioxidant activity of selected new synthesized oxazolidin-2-one derivatives

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Abstract - Background: In order to envisage that the two bioactive molecules (pharmacophores) if linked together could generate novel molecular templates which are likely to exhibit interesting biological properties, gathering the two patterns in one molecule and combining their properties was our purpose and presents a new way to increase the efficiency of biologically active molecules. This field of research have gained too much interest as proven by large number of reviews and research articles published in the current years.
Objective: To the best of our knowledge, oxazolidinone derivatives are widely used as antipenetrant agents in a cosmetic and/or dermatologie composition but knowledge of their antioxidant properties is limited or even missing. Therefore, as a part of our ongoing studies toward the development of novel interesting biologically active agents, the evaluation of antioxidant activity of a series of ω-(oxathiolan-2-thion-5-yl)-α-oxazolidin-2-ones **(1-3)a-b** will be discussed in this study.

Key words: Biheterocycles, 2-oxazolidinones, oxathiolane-2-thione, PEG chain, antioxidant activity.

INTRODUCTION

Compounds that can incorporate different heterocyclic moieties endowed with various biological activities are a high priority in medical, pharmaceutical and therapeutic research today. [1,2] Indeed, in the last two decades, this research field is highly activated aiming to improve the pharmacological effect of bioactive structures by linking together according to structure-activity relationship and many synthetic strategies have already been reported in the literature. [3-5]

The process of oxidation, due to free radicals, is the cause of major concern for human health. In particular damages related to the skin have great relevance as major responsible for aging and related degenerative processes, among them, cancer, cataract, brain and cardiovascular diseases; [6-8] therefore, the dermo-pharmaceutics and cosmetology have a significant role in the prevention and attenuation the cutaneous aging through the study of substances with effective antioxidant activity, to be incorporated on cosmetic products for daily care.[9] Indeed, many antioxidants resulting from organic synthesis are developed and marketed with the intention to counteract the action of free radicals. [10]
2-oxazolidinones derivates have attracted greater attention as an important class of heterocyclic compounds in the field of drugs, pharmaceuticals, pesticides, cosmetics, and so on. [11,12] In particular, these compounds are widely used as antipenetrant agents in a cosmetic and/or dermatologie composition [13] but knowledge of their antioxidant properties is limited or even missing.

In order to enrich the wide spectrum of biological activities associated to oxazolidin-2-ones derivates, [14-16] we present, in this paper, the

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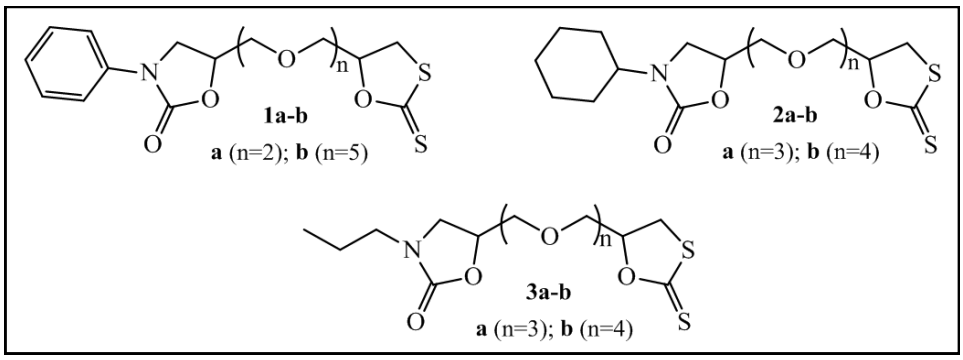

Figure 1: Chemical structure of evaluated compounds **(1-3) a-b**.

results of in vitro evaluation of antioxidant activities of various *N*-substitued oxazolidin-2-ones bridged by polyoxyethylene chain to a cyclic dithiocarbonate (Figure 1) by total antioxidant capacity (TAC), Ferric reducing power (FRP) and ferrous chelating (FIC) ability methods.

MATERIALS AND METHODS

1. Chemistry

The 2-oxazolidinones derivates **(1-3)a-b** studied in the present work were synthesized according to the pathway reported in Figure 2 via one-pot reaction of lateral opening of diglycidyl ethers of polyoxyethylene developed in our laboratory.[17]
All compounds were characterized by infrared (IR), nuclear magnetic resonance (NMR) spectroscopy (^{1}H and ^{13}C) and HRMS. The IR spectra were performed on SHIMADZU JASCO FTIR 4000/6000 SERIES. The ^{1}H and ^{13}C NMR spectra were recorded on a BRUKER AC-300 at 300 and 75 MHz, respectively. All spectra were obtained using $CDCl_3$ as solvent and referenced to TMS. Chemical shifts of ^{1}H NMR spectra are reported in parts per million (ppm) on the δ scale from an internal standard of residual chloroform (7.27 ppm). Coupling constants were reported in hertz (Hz). Chemical shifts of ^{13}C NMR spectra were reported in ppm from the central peak of $CDCl_3$ (77.23 ppm) on the δ scale. The multiplicities of signals are indicated by the following abbreviation: s: singulet; d: doublet; t: triplet; m: multiplet. HRMS were obtained from FINIGAN MAT 95. Columns chromatography was performed using silica gel (Fluka 40-60 µm). Analytical TLC was performed using Silica Gel 60 F254 plates (Fluka 40-60 µm). All commercially available reagents were used without further purification. Anhydrous THF was distilled from sodium. All reactions were carried out under a protective atmosphere of dry nitrogen using oven-dried glassware unless otherwise stated.

2. General procedure:

One-pot Three Component Preparation of ω-(Oxathiolan-2-thione-5-yl)-α-Oxazolidin-2-ones Polyoxyethylene (1-3)a-b

To solution of oligoethylene glycols diglycidyl ether [18] (3 mmol) in 10 mL of anhydrous THF was added of lithium bromide (0.3 mmol, 0.026 g). After stirring the mixture at reflux for 0.5 h, a solution of isocyanate (3.3 mmol) in dry THF (5 mL) was added dropwise. After the consummation of totally amount of isocyanate monitored by TLC (Acetone/Ether: 80/20), the mixture was cooled at room temperature and 3.3 mmol of carbon disulfide was also added and then the reaction was left to stand at room temperature. After completion of the reaction, as indicated by TLC (Acetone/Ether: 60/40), the mixture was diluted with water (40 mL), and then extracted

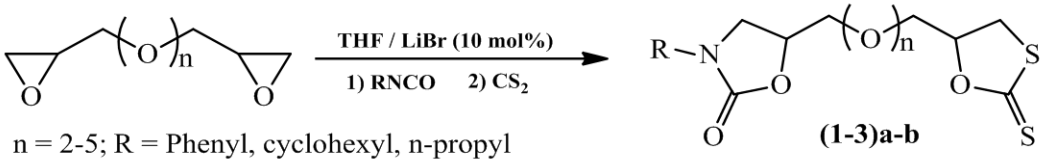

Figure 2: Synthetic strategy of biheterocyclic compounds **(1-3) a-b**.

with dichloromethane (4x40 mL). It was washed with water (2x30 mL) and dried on $MgSO_4$. The solvent was removed, and the residue was purified on column chromatography (eluent: Acetone/ Ether: 60/40) to obtain the ω-(Oxathiolan-2-thione-5-yl)-α-Oxazolidin-2-ones (**1-3)a-b** as viscous oils.

2. Spectral data for studied compounds (1-3)a-b

❖ ***5-(6-oxathiolan-2-thione-2,5-dioxahexan-5-yl) -3-phenyloxazolidin-2-one (1a):***

Colorless viscous oil, 235 mg, 60% yield. IR ($CHCl_3$): 1758 (C = O), 1420-1607 (C = C), 1140 (C = S) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 3.37-3.58 (m, 2H), 3.61-3.70 (m, 4H), 3.72-3.80 (m, 2H), 3.89-3.94(m, 2H), 4.03-4.09 (m, 2H), 4.72-4.80 (m, 1H), 5.05-5.19 (m, 1H), 7.09-7.14 (m, 1H, Harom), 7.33-7.38 (m, 2H, Harom), 7.52-7.55 (m, 2H, Harom).^{13}C NMR (75 MHz, $CDCl_3$) δ 35.9, 46.8, 69.7, 69.9, 70.61 (m, 2C), 71.4, 89.5, 118.1 (s, 2C), 123.9, 129.0 (s, 2C), 138.1, 154.6, 212.2. HRMS (ESI) calcd for $C_{16}H_{19}O_5NS_2Na$ $[M + Na]^+$ 392.0602, found: 392.0605.

❖ ***5-(15-oxathiolan-2-thione-2,5,8,11,14-penta oxapentadecan-5-yl)-3-phenyloxazolidin-2-one (1b):***

Colorless viscous oil, 450 mg, 86% yield. IR ($CHCl_3$): 1737 (C = O) 1453-1609 (C = C), 1115 (C = S) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 3.41-3.51 (m, 2H), 3.60-3.66 (m, 16H), 3.68-3.71 (m, 1H), 3.73-3.76 (m, 1H), 3.81-3.87 (m, 1H), 3.90-3.96(m, 1H), 4.02- 4.06 (m, 1H), 4.08-4.13(m, 2H), 4.74-4.81 (m, 1H), 5.22-5.29 (m, 1H), 7.09-7.14 (m, 1H, Harom), 7.33-7.38 (m, 2H, Harom), 7.53-7.55 (m, 2H, Harom).^{13}C NMR (75 MHz, $CDCl_3$) δ 35.9, 46.9, 69.8, 70.6 (m, 8C, CH2O), 71.08, 71.3, 89.4, 118.0 (s, 2C), 123.8 (s, 1C), 128.9 (s, 2C), 138.2, 154.6, 212.2. HRMS (ESI) calc. for $C_{22}H_{31}O_8NS_2Na$ $[M + Na]^+$ 524.1389, found: 524.1386.

❖ ***5-(6-oxathiolan-2-thione-2,5,8-trioxanonan-5-yl)-3-cyclohexyloxazolidin-2-one (2a):***

Colorless viscous oil, 282 mg, 64% yield. IR ($CHCl_3$): 1719 (C = O), 1121 (C = S cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.03-1.11 (m, 1H), 1.21-1.36(m, 5H), 1.50-1.68 (m, 5H), 3.34-3.40 (m, 1H), 3.50-3.56(m, 2H), 3.64-3.66 (m, 8H), 3.68-3.72 (m, 2H), 3.75-3.83 (m, 2H), 4.06-4.14 (m, 2H), 4.67-4.78 (m, 1H), 5.15-5.23 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.7, 25.4 (s, 2C), 29.6 (s, 2C), 33.3, 36.0, 49.8, 63.5; 69.8 (m, 6C), 70.5, 71.2, 89.3, 155.5, 212.1. HRMS (ESI) calc for $C_{18}H_{29}O_6NS_2Na$ $[M + Na]^+$ 442.1334, found: 442.1337.

❖ ***5-(12-oxathiolan-2-thione-2,5,8,11-tetraoxa dodecan-5-yl)-3-cyclohexyloxazolidin-2-one (2b):***

Colorless viscous oil, 345 mg, 71% yield. IR ($CHCl_3$): 1720 (C = O), 1120 (C = S) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.06-1.11(m, 1H), 1.25-1.42 (m, 5H), 1.64-1.79 (m, 5H), 3.36-3.39 (m, 1H), 3.53-3.59(m, 2H), 3.64-3.65 (m, 12H), 3.66-3.70 (m, 2H), 3.72-3.76 (m, 2H), 3.81-3.93 (m, 2H), 4.59-4.67 (m, 1H), 5.25-5.33 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.3, 30.0 (s, 2C), 30.3 (s, 2C), 36,0, 42,5, 52,3, 69.8, 70.5 (m, 6C), 71.1, 71,7, 89.4, 157.0, 212.2. HRMS (ESI) calc. for $C_{20}H_{33}O_7NS_2Na$ $[M + Na]^+$ 486,1596, found: 486.1593.

❖ ***5-(6-oxathiolan-2-thione-2,5,8-trioxanonan-5-yl)-3-propyloxazolidin-2-one (3a):***

Colorless viscous oil, 229 mg, 57% yield. IR ($CHCl_3$): 1748 (C = O), 1116 (C = S) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.82-0.87 (t, 3H), 1.41-1.49(m, 2H), 3.04-3.09 (t, 2H), 3.52-3.61(m, 2H), 3.63-3.64 (m, 8H), 3.65-3.68 (m, 2H), 3.78-3.82 (m, 2H), 4.14-4.17 (m, 2H), 4.76-4.80 (m, 1H), 5.15-5.23 (m, 1H).^{13}C NMR (75 MHz, $CDCl_3$) δ 11.2, 23.1, 36.1, 42.8, 63.7, 69.7; 69.8, 70.6 (m, 4C), 71.3, 89.2, 156.4, 212.0. HRMS (ESI) calc. for $C_{15}H_{25}O_6NS_2Na$ $[M + Na]^+$ 402.1021, found: 402,1023.

❖ ***5-(12-oxathiolan-2-thion-2,5,8,11-tetraoxa-dodecan-5-yl)-3-propyloxazolidin-2-one(3b):***

Colorless viscous oil, 276 mg, 62% yield. IR ($CHCl_3$): 1723 (C = O), 1115 (C = S), cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.90-0.95 (t, 3H), 1.52-1.64 (m, 2H), 3.19-3.24 (t, 2H), 3.58-3.63 (m, 2H), 3.64-3.66 (m, 12H), 3.67-3.69 (m, 2H), 3.71-3.74 (m, 2H), 3.83-3.94 (m, 2H), 4.63-4.67 (m, 1H), 5.28-5.33 (m, 1H).^{13}C NMR (75 MHz, $CDCl_3$) δ 11.0, 22.17, 35.89, 42.11, 62.8, 69.7, 69.8; 70.5 (m, 6C), 71.6, 89.6, 157.8, 212.4. HRMS (ESI) calc. for $C_{17}H_{29}O_7NS_2Na$ $[M + Na]^+$ 446.5344, found: 446.5346.

BIOLOGICAL INVESTIGATION

All reagents were purchased from Sigma Aldrich, (St Louis, MI). Solvents were from Panreac (Barcelona, SP) and from Carlo Erba, Strada Rivoltana (Rodano, IT) and were of the highest analytical grade. All the tests, for the determination of antioxidant activity, were carried out in triplicate and the results averaged. Absorbance was recorded using an UV-Vis spectrophotometer (Jinway UV-Vis 6405).

1. Determination of Total Antioxidant Capacity (TAC)

Total antioxidant capacity assay is a spectroscopic method for the quantitative determination of antioxidant capacity, through the formation of Phosphomolybdenum complex. The assay is based on the reduction of Mo (VI) to Mo (V) by the sample and subsequent formation of a green phosphate Mo (V) complex at acidic pH. Total antioxidant capacity can be calculated by the method described by Prieto et al. **[19]** 0.1 mL of sample solution at different concentrations (0.001-1 mg/mL) was combined with 1 mL of reagent (0.6 M sulfuric acid, 28 mM sodium phosphate and 4 mM ammonium molybdate). The tube is capped and incubated in a boiling water bath at 95°C for 90 min. After cooling the sample to room temperature, the absorbance of the aqueous solution is measured at 695 nm against blank in UV spectrophotometer. A typical blank solution contained 1 mL of reagent solution and the appropriate volume of the same solvent used for the sample and it is incubated under same conditions as rest of the sample. For samples of unknown composition, antioxidant capacity can be expressed as: (%) = [(Atest - Acont)/Acont] *100, where Atest is the absorbance of the sample in the presence of the extract and Acont is the absorbance of the control. The result was expressed as IC_{50} which corresponds to the concentration of extract necessary to reduce 50% of phosphate Mo (V) complex. The results of these experiments are summarized in (Figure 3). It was found that compounds **1a** exhibited the highest TAC activity with an IC_{50} at 10.94 ± 0.0008 µg/mL followed by **1b** 11.78 ± 0.0006 µg/mL. The conversion of oxazolidin-2-one derivate **1** into derivate **2** decrease this ability only for **2a** with an IC_{50} at 18.77 ± 0.005 µg/mL but increase that of **2b** IC_{50} at 11.05 ± 0.0009 µg/mL. The transition into derivate **3** enhance the antioxidant activity for **3a** IC_{50} at 12.79 ± 0.0009 µg/mL but not for **3b** IC_{50} at 16.39 ± 0.004 µg/mL and compared with ascorbic acid (IC_{50} at 6.46 ± 0.001 µg/mL).

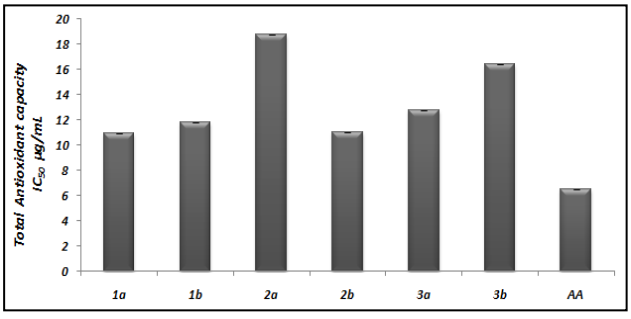

Figure 3: Total Antioxidant Capacity (TAC.) Tests were carried out in triplicate. Results are expressed at IC_{50} mg/mL as mean ± SEM.

2. Ferric reducing power (FRP)

It has been observed a direct correlation between antioxidant activity and reducing power of certain compounds. The reducing power of the extract was determined according to the method of Oyaizu **[20]** and compared with ascorbic acid. Substances which have a reducing potential, react with potassium ferricyanide (Fe^{3+}) to form potassium ferrocyanide (Fe^{2+}), which then reacts with ferric chloride to form ferric ferrous complex that has a maximum absorption at 700 nm. Experimentally, a methanolic solution of the extract (1 mL) at various concentrations (0.001-1 mg/mL) was mixed with phosphate buffer (0.2 M) and potassium ferricyanide (1%). The mixture was incubated at 50 °C for 20 min. Aliquots of trichloroacetic acid (10%) were added to the mixture, which was then centrifuged at 3000 rpm for 10 min. The upper layer (2.5 mL) was mixed with distilled water and a freshly prepared ferric chloride solution (0.1%). The absorbance was measured at 700 nm. Ascorbic acid was used as standard. A control sample was prepared without adding standard or extract.

Increased absorbance of the reaction mixture indicates increase in reducing power. The percent increase in reducing power was calculated using the following formula: Increase in reducing power (%) = [(Atest - Acont)/Acont] * 100, where Atest is the absorbance of the sample in the presence of the extract and Acont is the absorbance of the control. The result was expressed as IC_{50} which corresponds to the concentration of the extract necessary to reduce 50% of ferric ferrous complex.

In the case of tested compounds **1-3** (Figure 4), oxazolidin-2-one **1** showed the highest ferric reducing power with an IC_{50} at 1.40 ± 0.001 µg/mL for **1b** followed by **1a** with an IC_{50} at 1.63 ± 0.002 µg/mL when compared with other compounds. The remaining compounds exhibited FRP activity in the following order: **2b** (1.94 ± 0.002 µg/mL), **3b** (1.97 ± 0.001 µg/mL), **2a** (2.12 ± 0.002 µg/mL), **3a** (2.54 ± 0.001 µg/mL), and compared with ascorbic acid (IC50: 0.15 ± 0.0001 µg/mL).

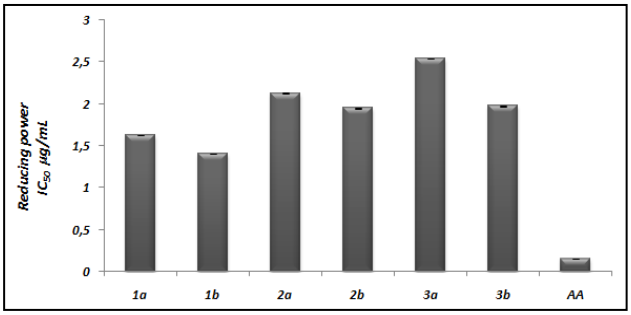

Figure 4: Ferric Reducing Power (FRP). Tests were carried out in triplicate. Results are expressed at IC_{50} mg/mL as mean ± SEM.

3. Ferrous ion chelating (FIC) activity

It was reported that chelating agents are effective as secondary antioxidants because they reduce the redox potential thereby stabilizing the oxidized form of the metal ion. [21]

The FIC ability of the extract was determined according to the method of Singh and Rajini. [22] A methanolic solution of the extract (1.0 mL) at various concentrations (0.001-1 mg/mL) was added to 1.0 mL of $FeSO_4$ (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 = [(Acont- Atest)/ Acont] * 100, where Acont is the absorbance of the control, and Atest is the absorbance of the sample in the presence of the extract. In the case of tested compounds **1-3** (Figure 5), derivative **1b** showed the highest FIC ability with IC_{50} at 0.183 ± 0.0004 mg/mL when compared with other compounds. The remaining compounds exhibited FIC activity

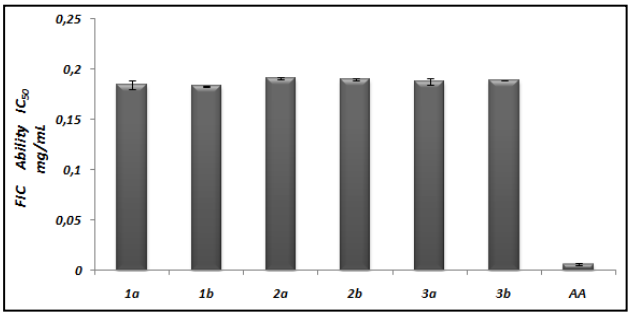

Figure 5: Ferrous Ion Chelating (FIC) activity. Tests were carried out in triplicate. Results are expressed at IC_{50} mg/mL as mean ± SEM.

in the following order: **1a** (0.184 ± 0.004 mg/mL), **3a** (0.187 ± 0.003 mg/mL), **3b** (0.188 ± 0.0004 mg/mL), **2b** (0.19 ± 0.0006 mg/mL), **2a** (0.191 ± 0.0008 mg/mL), and compared with ascorbic acid (IC50: 0.0057 ± 0.001 mg/mL).

4. Statistical analysis

Results are expressed as the mean ± standard error of the mean (SEM). Statistical differences were evaluated by one-way analysis of variance (ANOVA). All analyses were performed using STATISTICA version 5.00 (Stat Soft- France, Tulsa, OK, USA) for Windows, p value < 0.05 was considered significant.

DISCUSSION

In recent years many bioactive compounds have been linked to various 2-oxazolidinone derivates witch increase its biological potential. [23] Considering the biological significance of oxazolidin-2-one and oxathiolan-2-thione moiety, [24-26] a novel hybrid molecules obtained by connecting them via a polyoxyethylene chain were designed previously and herein we focused our effort to evaluate their antioxidant activities.

According to the results obtained, compounds **(1-3)a-b** exhibited significant in vitro antioxidant activity compared to the standard ascorbic acid. Compounds **(1-3)a-b** showed the highest antioxidant activity in TAC and FIC abilities. This can be attributed to the well known tendency of keto function to reduce free radical levels and to inhibit the production of reactive oxygen species (ROS). [27] Furthermore, the sulfur groups present in these molecules could contribute to this activity. Indeed, it has been reported that molecules with ammonium structure exhibit potent radical scavenging activity which increases with the increase of the positive charge density on nitrogen atoms. [28]

The conversion of compounds **1** into compound **2** decreases the total antioxidant activity and ferrous reducing power only with **a**. This can be attributed to structure of compounds that having two or more carbon substituent in the length PEG chain, showed moderate abilities; while when compounds were translated into compound **3** having an undersized length PEG chain, correct slightly this disruptions. The presence of electron donating methyl groups in compound **3** might be the cause for lesser activity associated with the compounds.[29] Structure activity relationship

studies show that, the highest antioxidant activity was obtained with substituent having highest lipophilicity, lowest electron withdrawing power and highest polarisability. Among the compounds highest antioxidant activity was observed with substituent oxazolidin-2-one **1** possessing highest lipophilicity. [30] As well as, the effect of length PEG chain and the effect of linked aryl group to the nitrogen atom.

Furthermore, compounds (**1-3)a-b** showed a low affinity for bivalent cations, FIC ability, in comparison with ascorbic acid. It is important to mention here that metal chelating capacity is significant as it contributes to reduce the concentration of the catalyzing transition metals in lipid peroxidation. [31] The data obtained reveal that all test compounds demonstrate an effective capacity for iron binding, suggesting that their action as antioxidants could be related to their iron-binding capacity. With regard to the mechanism of antioxidant activity of compounds **1**, one can speculate that this compound, as iron reducer and chelator; exert a secondary antioxidant effect by chelating Fe^{2+} ions necessary for the formation of hydroxyl radicals in the Fenton reaction. [**32**]

CONCLUSION

Gathering two patterns in the same molecule and combining their properties present a new way to increase the efficiency of biologically active molecules. From this study, it is clear that 3,5-disubstitued oxazolidin-2-one if connected to 1,3-oxathiolane-2-thione moiety with polyoxyethylene chain exhibited significant in vitro antioxidant activity compared to the standard ascorbic acid. These results give additional support that 2-oxazolidinones derivates are furthermore source of biologically important compounds for medicinal and biomedical research.

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