RESEARCH ARTICLE

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Comparative Study of Synthesis, Structural and Antioxidant Activity In Vitro of Some New Carboxylic α,α-diaminodiesters Derivatives

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ABSTRACT

Considering the richness of heterocyclic chemistry, and the diversity of applications it possesses, in the present work we were interested in preparing new polyfunctional α,α-diaminodiesters derived from glycine, via the N-alkylation reaction of methyl 2-azido-2-benzamidoacetate with a series of heterocyclic and non-heterocyclic carboxylic aminoesters, using different bases. The structures of the synthesized molecules were characterized by 1D and 2D NMR spectroscopy, mass spectrometry (MS-ESI) and elemental analysis. Two compounds from this series were isolated as single crystals and their chemical structures were determined by X-ray diffraction. The antioxidant effect of the synthesized compounds was tested in vitro using the free radical scavenging power (DPPH) and reducing power (FRAP) tests. The results show that the different extracts tested have a relatively high antioxidant power compared to the positive control considered, especially for the compound methyl 2-benzamido-2-(2-methoxy-2-oxo-1-phenylethyl)amino)acetate, which showed a very strong antiradical power and reducing power.

Keywords: N-alkylation, α,α-diaminodiesters, antioxidant activity, DPPH, FRAP.

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I. INTRODUCTION

Organic chemistry has been evolving for more than two centuries. It continues to generate enormous scientific interest and economic imperatives. Therefore, heterocyclic α-amino acids are of interest to researchers and industrialists, given their broad spectrum of action. Research in this area has grown significantly, and chemical and pharmacological studies of these substances have provided a better approach to the relationship between structure and activity.

Heterocycles are the largest and most diverse family of organic compounds [1]-[9]. Thus, heterocycles constitute the largest and most diverse family of organic compounds [1]-[9]. Heterocyclic amino acids play a predominant role in the synthesis of peptides and proteins [10]-[13], and so far they have aroused the interest of researchers, who study their structure-activity relationship thus allowing a better approach to understanding their mechanisms of action. The synthesis of new carboxylic amino acids and their esters has become a major interest for research teams around the world [14]-[21]. Their applications are in various fields: enzymology [22]-[25]; medicine and pharmacology [26]-[30]; industry [31] and asymmetric synthesis [32]-[34].

Finally, recently published works have revealed the interest of heterocyclic α-aminoesters derivatives as antioxidant agents [35], [36], which encouraged us to test the antioxidant effect of five products, which we synthesized in our laboratory, using the DDPH and Ferric Reducing Antioxidant Power (FRAP) tests.

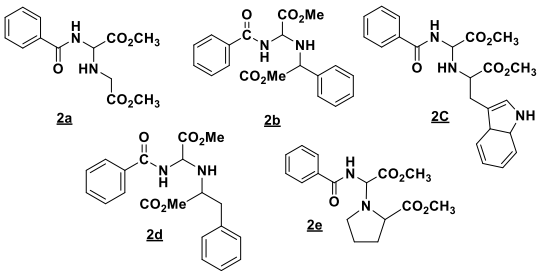
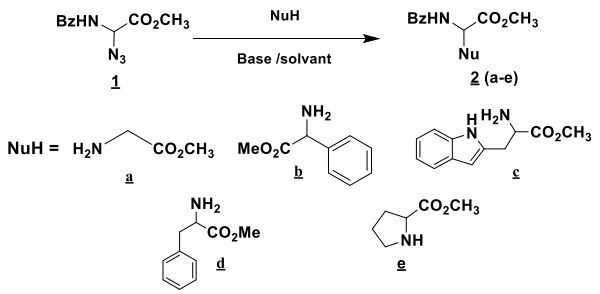


Fig. 1. Structures of the five synthesised molecules tested.

II. RESULTS AND DISCUSSION

A. Chemistry

The nucleophilic substitution reaction of methyl 2-azido-2-benzamidoacetate **1** with different derivatives of heterocyclic and non-heterocyclic aminoesters was promoted by the use of a base in dichloromethane or acetone as a solvent. The reaction is followed by CCM along the reaction time. The desired products were obtained with satisfactory yields ranging from 70 to 86% (Scheme 1 and Table I).



Scheme 1. Strategy for the synthesis of new carboxylic α,α–diaminoesters derivatives.

TABLE I: REACTION CONDITIONS FOR N-ALKYLATION

Comp.	Reaction time	Rdt. (%)	Physical aspect	Melting point (°C)	Base /Solvent/ (No. of Nu-H eq.)	Rf
2a	48h	80	Oil	-	DIEA/Acetone (1.2eq. of Nu-H)	0.62 (hexane/acetone, 1:1)
2b	16h	86	Solid white	126-128	NEt3/Dichloromethane (1.1eq. of Nu-H)	0.35 (hexane/acetate, 8:2).
2c	72h	86	Solid white	174-176	DIEA/Acetone (1.2eq. of Nu-H)	0,71 (CH_2Cl_2/acetate, 8:2)
2d	24h	70	Solid white	90-92	DIEA/Acetone (1.2eq. of Nu-H)	0,65 (hexane/acetate, 1:1)
2e	48h	75	Oil	-	DIEA/Acetone (1.2eq. of Nu-H)	0.69 (hexane/acetone, 3:2)

The N-benzoylated methyl 2-azido glycinate derivative **1** was prepared by the method of Steglich [37] and the procedure of Achamlale [38], [39] by the action of sodium azide with methyl α-bromo glycinate derivative.

The structures of the prepared compounds were established on the basis of ^{1}H and ^{13}C 1D NMR, ^{1}H-^{1}H and ^{1}H-^{13}C 2D homonuclear and heteronuclear NMR, Mass spectrometry, and Elemental analysis data. Two compounds from this series were isolated as single crystals and their chemical structures were determined by X-ray diffraction.

Thus, the compound (2R)-2-benzamido-2-{[(1R)-2-methoxy-2-oxo-1-phenylethyl]amino}methyl acetate **2b** with the empirical formula $C_{19}H_{20}N_2O_5$, crystallizes in the Orthorhombic system with the space group P212121 [40] (Fig. 2).

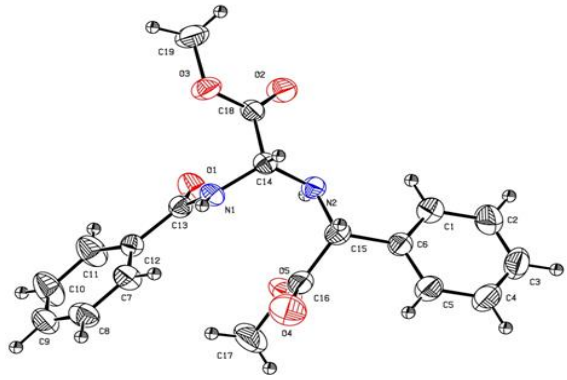


Fig.2. ORTEP view of compound 2b showing the atomic numbering scheme.

The methyl 2-((1-benzamido-2-methoxy-2-oxoethyl)amino) -3-(3a,7a-dihydro-1H-indol-3-yl)propanoate derivative **2c**, with the empirical formula $C_{22}H_{23}N_3O_2$, crystallizes in the Orthorhombic system with space group P212121[41].

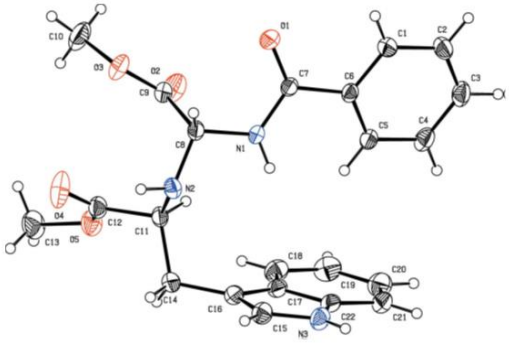


Fig.3. ORTEP view of compound **2c** showing the atomic numbering scheme.

B. Antioxidant Activity

Antioxidant activity defines the ability of an organism to protect itself against free radicals. The best-known antioxidants are ß-carotene (provitamin A), ascorbic acid (vitamin C), tocopherol (vitamin E), and phenolic compounds. Indeed, the antioxidant properties of most synthetic or naturally occurring antioxidants are attributed in part to the ability of these natural compounds to trap free radicals such as hydroxyl (OH•) and superoxides (O•) radicals. [42], [43].

1. Main methods for assessing antioxidant activity

There is a wide variety of physico-chemical methods to evaluate the antioxidant activity of natural extracts. Several methods are used to analyse the distinct steps of the oxidation process, such as the measurement of the weakening of the substrate, and/or the consumption of oxygen during oxidation; the formation of oxidation products, and the ability to trap free radicals in different phases.

1.1. TEAC (Trolox Equivalent Antioxidant Capacity) method

This method was first described by Miller and Rice-Evans [44], then improved in 1999 by these authors [45]. In fact, it consists of the reduction of the coloured radical-cation (2,2'-azobis 3 ethylbenzothiazoline-6-sulphonic acid) better known under the name of ABTS•+. The development of its concentration at 734 nm is monitored during its reaction with the antioxidants. Antioxidant capacity is measured as the concentration (mM) of Trolox (a soluble vitamin E analogue) producing the same effect as the test sample on ABTS reduction [46]. The literature provides TEAC of some antioxidants (Vitamin C = 0.99 mM, β-carotene = 1.9 mM).

1.2. DPPH (1, 1-Diphenyl-2-picryhydrozyl) test

According to Rivero-Pérez and Brand-Williams [47], antioxidant capacity can also be measured using more stable free radicals. The **1,1-diphenyl-2-picrylhydrazyl** radical (DPPH) is a very stable free radical in the crystalline state and in solution, with a purple coloration. By this method, antioxidant activity is considered to be the ability of antioxidants to act as a trap for free radicals. They act by transferring a hydrogen atom, which leads to the disappearance of the DPPH radical during the reaction, and a change of colouring in the initial solution. The progression of the reaction is followed by spectrophotometry at 516 nm. The more easily a compound gives away its hydrogen atom, the more it is considered to be effective as an antioxidant. The percentage of the remaining DPPH is proportional to the concentration of the antioxidant. The concentration of the phenolic compound required to achieve a 50% loss of DPPH at equilibrium is known as IC50. The DPPH method has been used by many authors, due to its speed and reproducibility.

1.3. Ferric Reducing Antioxidant Power (FRAP)

The FRAP method developed by Benzie and Strain [48], corresponds to the reduction of a ferric tripyridyltriazine complex [(Fe(III)-TPTZ)2] to a ferrous tripyridyltriazine complex [(Fe(II)-TPTZ)2] by an antioxidant (AH), at a pH of 3.6, in order to maintain the solubility of iron. To ensure the linearity of the method and to calculate the results, a standard range is first performed with an aqueous solution of iron sulphate heptahydrate ($FeSO_4$-$7H_2O$) between 100 and 1000 µM. From the absorbance values read at 593 nm and measured at t = 0 min and at t = 4 min after mixing.

1.4. ORAC (Oxygen Radical Absorbance Capacity) method

It consists of a measurement of the protection exerted by a given substance or molecule against the oxidation of fluorescein by the radical derivatives of the thermolytic degradation of the AAPH radical. Unlike the DPPH test, which measures a reduction capacity, it is therefore strictly speaking a measure of antiradical power. The results are expressed in relation to the protection provided by a reference antioxidant, Trolox, and are reported per gram of product tested. When fluorescein is subjected to the oxidative action of a free radical, AAPH, we observe that its fluorescence response decreases over time (about 10 minutes). In the presence of an anti-free radical activity (compound, natural product, etc.) fluorescein is protected from stress and the duration of its fluorescence is increased. It is this increase that allows the antiradical power to be quantified via a calibration by Trolox.

1.5. Bleaching method for β-carotene

The bleaching test of detergent-carotene is used to evaluate the antioxidant activity of plant extracts, which consists in following the decoloration kinetics of detergent-carotene by the oxidation products of linoleic acid in the presence of an antioxidant. β-carotene is a lipophilic antioxidant that protects fatty acids from oxidation; the addition of a second antioxidant will preserve it [49]. The greater the effectiveness of an antioxidant, the slower the colour fading of β-carotene and vice versa [50], [51].

1.6. Hydroxyl radical scavenging (HRSA)

Following the Haber Weiss reaction [52], •OH is the highly reactive free radical formed in biological systems from superoxide anion and hydrogen peroxide in the presence of metal ions such as iron and copper. This radical has a free electron with a higher reduction potential (2310 mV) allowing it to act with lipids, proteins, polypeptides and DNA particularly thiamine and guanine [53]. In vitro, the ability to trap the hydroxyl radical by plant extracts is based on the Fenton reaction by measuring the generation of the •OH radical and its effect on the oxidation and degradation of biological molecules, such as DNA deoxyribose's. In this technique, the system involves the self-oxidation of the Fe2+–EDTA complex in an aqueous medium to form $O^{\bullet 2-}$, which is rapidly dismuted into H_2O_2 at pH 7.4. The latter than interacts with Fe^{2+} to form the •OH radicals in the presence of ascorbic acid as a catalyst (Fenton reaction).

$$H_2O_2 + Fe^{2+}\text{-EDTA} \longrightarrow \bullet OH + OH^- + Fe^{3+}\text{-EDTA}$$

2. Scavenging power of the DPPH- radical

The antioxidant activity of the synthesized products compared with ascorbic acid, used as a positive control, was determined by the DPPH method. This activity was evaluated using a visible UV spectrophotometer by monitoring the reduction of this radical, which is accompanied by its transition from the violet colour (DPPH•) to the yellow colour (DPPH-H), which can be measured at 515 nm [54].

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TABLE II: IC50 VALUES OF THE CRUDE EXTRACTS AND THE CONTROL, DETERMINED BY THE DPPH TEST

Retrieved from	IC50 (mg/ml)
Methyl 2-benzamido-2-((2-methoxy-2-oxoethyl)amino)propanoate **2a**	0,49
Methyl (2R)-2-benzamido-2-{[(1R)-2-methoxy-2-oxo- 1-phenylethyl]amino}acetate **2b**	0,19
methyl 2-((1-benzamido-2-methoxy-2-oxoethyl)amino)-3-(3a,7a-dihydro-1H-indol-3-yl)propanoate **2c**	0,74
Methyl 2-((1-benzamido-2-methoxy-2-oxoethyl)amino)-3-phenylpropanoate **2d**	0,92
Methyl 1-(1-benzamido-2-methoxy-2-oxoethyl) pyrrolidine-2-carboxylate **2e**	1,18
Ascorbic acid	0,083

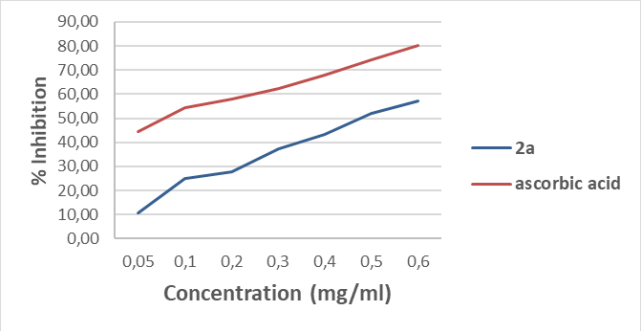

Fig.4. Antioxidant activity of extract **2a** compared to ascorbic acid.

Among the five extracts tested, extract **2b** is an effective antioxidant compared to the other extracts. Nevertheless, the power of the reference antioxidant remains higher than that of the studied extracts. In the light of the results obtained, we can conclude that the various extracts tested have a significant antioxidant power compared to the positive control considered.

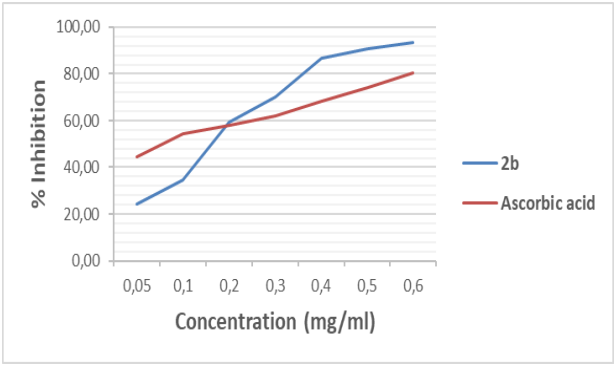

Fig.5. Antioxidant activity of extract **2b** compared to ascorbic acid.

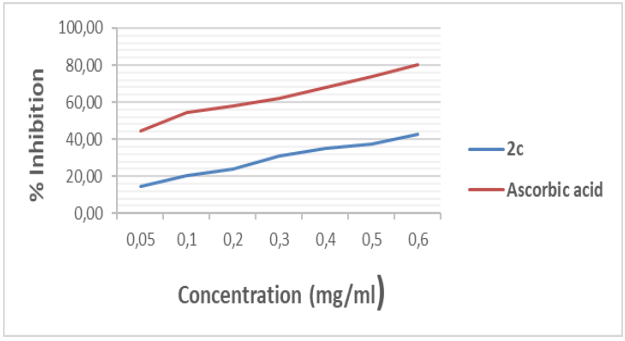

Fig.6. Antioxidant activity of extract **2c** compared to ascorbic acid.

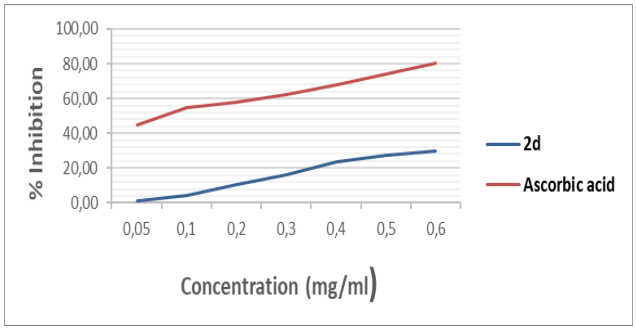

Fig.7. Antioxidant activity of **2d** extract compared to ascorbic acid.

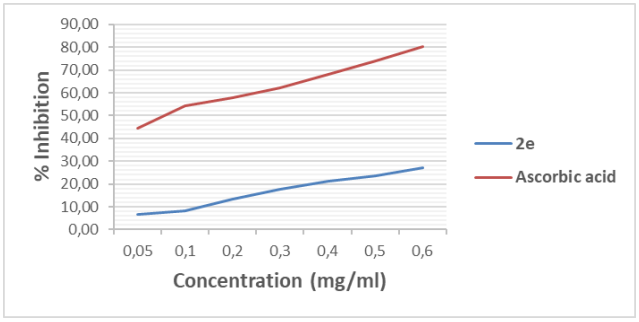

Fig.8. Antioxidant activity of extract **2e** compared to ascorbic acid.

3. *Reducing power (FRAP)*

For the FRAP method, the revelation of reducing power is based on the shift from the yellow colour of potassium ferrocyanide to a greenish blue colour whose intensity depends on the reducing power of each sample. The latter depends mainly on the quantity of reducer present in the tested medium. This translates into an increase in absorbance measured at 700 nm [55]. The results show that the reductive power of synthetic extracts is based on their concentrations used. It is noted that the reductive power of the tested extracts remains lower than that of the reference antioxidant (ascorbic acid).

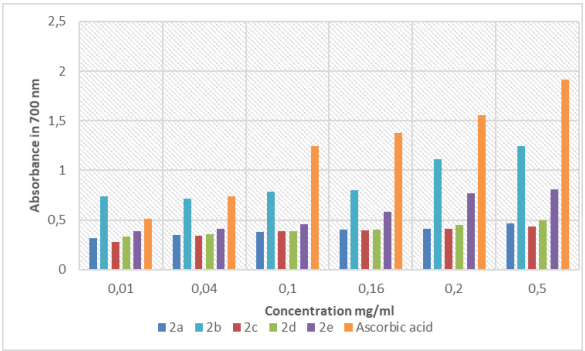

Fig. 9. Reducing power of synthetic extracts compared to ascorbic acid.

The lower the IC50 value, the greater the antioxidant activity of a compound. The results obtained are grouped in the table given below:

TABLE III. IC50 VALUES (MG/ML) OF CRUDE AND CONTROL EXTRACTS DETERMINED

Retrieved from	IC50 (mg/ml)
2a	176,41
2b	43,66
2c	194,55
2d	155,88
2e	54,6
Ascorbic acid	18,78

The results show that the compounds tested are electron donors and are able to reduce Fe^{3+} ions linearly as a function of concentration. These results are compared with the standard antioxidant (ascorbic acid). At concentrations ranging from 0.01 to 0.5 mg/ml, extract **2b** has the most significant reducing power, followed by extracts **2e**, **2d**, **2a** and **2c**, respectively.

III. Materials and Methods

All solvents were purified following the standard techniques and commercial reagents were purchased from Sigma-Aldrich (St. Louis, MO, USA). Melting point was determined with an Electrothermal melting point apparatus and was uncorrected. NMR spectra (^1H and ^{13}C) were recorded on a Bruker AM 300 spectrometer (operating at 300.13 MHz for 1H, at 75.47 MHz for 13C) (Bruker Analytische Messtechnik GmbH, Rheinstetten, Germany). NMR data are listed in ppm and are reported relative to tetramethylsilane (^1H, ^{13}C); residual solvent peaks being used as internal standard. All reactions were followed by TLC. TLC analyses were carried out on 0.25 mm thick precoated silica gel plates (Merck Fertigplatten Kieselgel 60F254) and spots were visualized under UV light or by exposure to vaporized iodine. Mass spectra were recorded on a PolarisQ Ion Trap GC/MSn Mass Spectrometer (CNRST-Rabat). The Orteps of compounds **2b** and **2c** were obtained on a Bruker APEXII CCD detector diffractometer (CNRST-Rabat).

A. Chemistry

1. N-alkylation reaction

To 11mmoles of nucleophile (**Nu-H**), 50 ml of anhydrous solvent (dichloromethane or acetone) is added, the mixture is cooled to 0 °C, then 22mmoles of base (triethylamine, DIEA) is added, followed by 10 mmoles of N-protected methyl α-azidoglycinate **1**. The mixture is stirred for one hour at 0°C and then at room temperature. The reaction is monitored by TLC along the reaction time. The solvent is evaporated under reduced pressure. The residue obtained is quenched with a 15% citric acid solution and extracted with methylene chloride. The organic phase is washed with a saturated solution of sodium hydrogen carbonate (**$NaHCO_3$**), dried with Na_2SO_4 and the solvent is evaporated. The residue obtained is either chromatographed on a silica gel column (eluent: ethyl acetate/hexane) or recrystallized in ether.

*Methyl 2-benzamido-2-((2-methoxy-2-oxoethyl)amino)acetate **2a**:* Rdt.: 80 % (oil) ; Rf = 0,62 (hexane/acetone, 1:1). **^{1}H-NMR** ($CDCl_3$, δ ppm): 3.15 (e, ^{1}H, N**H**-CH_2-); 3.47-3.62 (dd,2H, NH-C**H_2**-, J_1 = 5.6 Hz,J_2= 6.4 Hz); 3.55 (s, 3H, OC**H_3**); 3.73 (s, 1H, N-C**H**-N); 3.68 (s, 3H, OC**H_3**); 5.44 (d, 1H, N**H**-Bz, *J* = 7.84 Hz); 7.3-7.8 (m, 5Harom).**^{13}C-NMR** ($CDCl_3$, δ ppm): 46.85 (1C,**C**H_2-C); 51.87 et 52.74 (2C, O**C**H_3); 64.81 (1C, N-**C**H-N); 127.21-133.29 (6C, **C**arom); 167.49, 170.22 et 172.79 (3C,**C**O).

*Methyl (2R)-2-benzamido-2-{[(1R)-2-methoxy-2-oxo-1-phenyl ethyl]amino}acetate **2b*** [56]

Methyl 2-((1-benzamido-2-methoxy-2-oxoethyl)amino)-3-(3a,7a-dihydro-1H-indol-3-yl)propanoate **2c** [57].

*Methyl 2-((1-benzamido-2-methoxy-2-oxoethyl)amino)-3-phenyl propanoate **2d***: **Rdt.** : 70 % (solid white) ; **F**= 90-92°. C**^{1}H-NMR** ($CDCl_3$, δ ppm): 2.73 (e, 1H, N**H**-CH-CH_2-Ph); 2.94-3.07 (m, 2H, -C**H_2**-Ph);3.48 (s, 3H, OC**H_3**);3.8 (s, 4H, -C**H**-CH_2-Ph + OC**H_3**); 5.51-5.53 (d, 1H, N-C**H**-N, *J* = 8.15 Hz); 6.72-6.74 (d, 1H, N**H**Bz, *J* = 8.14 Hz); 7.17-7.76 (m, 10H, 10H_{arom}). **^{13}C-NMR** ($CDCl_3$, δ ppm): 39.77 (1C, -CH_2-Ph); 51.90 et 52.77 (2C, OCH_3);59.61 (1C, -C**H**-CH_2-Ph); 64.47 (1C, N-C**H**-N); 126.86-136.61 (10C, C_{arom}); 166.86, 170.02 et 175.54(3C, C**O**).**MS** *m/z* (%) =**370,15**. $C_{20}H_{22}N_2O_5$ (%), **Calculated values**: C, 64.85; H, 5.99; N, 7.56; **Values found** (%): C64.82, H 6.02, N 7.58.

*Methyl 1-(1-benzamido-2-methoxy-2-oxoethyl) pyrrolidine-2-carboxylate **2e**:* **Rdt.:** 75 % (oil); **^{1}H-NMR** ($CDCl_3$, δ ppm): 1.26-1.38 (m, 2H, -CH_2-C**H_2**-CH-); 1.79-1.88 (m, 2H, -CH_2-C**H_2**-CH_2-); 2.84-3.05 (m, 2H, NH-C**H_2**-CH_2-); 3.80 (s, 3H, OC**H_3**);3.86 (s, 3H, OC**H_3**); 4.21-4.24 (dd, 1H, -CH_2-C**H**-, J_1 = 3.60 Hz, J_2 = 5.85 Hz); 5.69-5.71(d, 1H, N-C**H**-N, *J* = 6.0 Hz); 5.84 (d, 1H, N**H**-Bz, *J* = 6.0 Hz); 7.44-7.87 (m, 5Harom). **^{13}C-NMR** ($CDCl_3$, δ ppm): 23.04 (1C, -CH_2-C**H_2**-CH_2-); 29.70 (1C, -CH_2-C**H_2**-CH-); 52.13 (1C, -C**H_2**-CH_2-CH_2-); 52.29 et 53.01 (2C, OC**H_3**); 66.43 (1C, -CH_2-CH_2-C**H**-); 68.16 (1C, N-C**H**-N); 127.22-133.23 (6C, Carom); 168.01, 170.14 et 174.49 (3C, C**O**).

B. Antioxidant Power

1. Measurement of the DPPH-radical scavenging capacity

The protocol followed in this analysis is that described by Huang et al. [58]. First, we prepare the parent solution of DPPH at a concentration of 60 µmole, so we put 2.4 mg of DPPH in 100 ml of methanol. After stabilization of this solution, take 3.8 ml and add to 200 µl of the extract already prepared, and mix with a vortex. After 30 min of incubation in darkness and at room temperature, the optical density (DO) reading is performed at 515 nm. A vitamin C concentration range (L-ascorbic acid) was prepared for comparison in the analysis of the results. All tests were performed in triplicate.

2. Reducing power (FRAP)

The reductive power of the samples was determined using the Benzie principle [59]. The protocol adopted was as follows: 250 µl of pre-prepared sample extract is added to a mixture of 250 µl of a phosphate buffer solution (200 mM, pH 6,6), and 250 µl of 1% potassium ferricyanure (p/v). The set was incubated in a 50 °C water bath for 20 minutes, then 250 µl 10% trichloroacetic acid (w/v) was added to the mixture. Then we centrifuge at 10000 ppm for 10 min. 1 ml of the supernatant is recovered, 1 ml of distilled water is added and 0,1 ml of ferric chloride solution (0,1%, w/v). The absorbance of the reaction medium is read at 700nm against a similar white, replacing the extract with distilled water, which allows to calibrate the device. Positive control is represented by a solution of a standard antioxidant: Ascorbic acid, the absorbance of which is measured under the same conditions as the samples.

IV. Conclusion

Based on the structural model of methyl α-azidoglycinate, we synthesized a new heterocyclic and non-heterocyclic systems based on the N-alkylation reaction of methyl 2-azido-2-benzamidoacetate with a series of carboxylic aminoesters. The synthesised compounds were tested in vitro

for their antioxidant activity using the radical scavenging power (DPPH), and reducing power (FRAP) tests. The results reveal that the tested compounds are electron donors and are able to reduce Fe3+ ions in a linear concentration-dependent manner. These results are compared with the standard antioxidant (ascorbic acid). At concentrations ranging from 0.01 to 0.5mg/ml, Methyl (2R)-2-benzamido-2-{[(1R)-2-methoxy-2-oxo-1-phenylethyl]amino}acetate **2b** has the most significant reducing power followed by **2e**, **2d**, **2a** and **2c**, respectively.

It should be noted that the DPPH test performed on aminoesters synthesized by Galeshshahi et al. [60], showed that all tested extracts exhibited significant antioxidant activity, with IC50 values ranging from 3,9-33,6 % compared with the reference antioxidant butylated hydroxytoluene or 2,6-di-tert-butyl-4-methylphenol (BHT), which had a value of 1,1 %.

While our synthesized products, carboxylic α,α-diaminodiesters had IC50 values ranging from 0.19-1.18% compared with the reference antioxidant which had a value of 0.018%. As a result, both results show that the antioxidant activity of this family of molecules, despite its importance, is still less important than that of the reference antioxidant.

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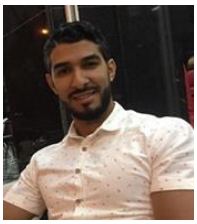

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