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

Oumaima Karai, Sara Hajib, Serigne Abdou Khadir Fall, Salaheddine Boukhssas, Khadim Dioukhane, Younas Aouine, Brahim Labriti, Hassane Faraj, and Anouar Alami

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 glycite, via the N-alkylation reaction of methyl 2-azido-2-benzamidoacetate with a series of heterocyclic and non-heterocyclic carboxylic aminooesters, 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)aminoacetate, which showed a very strong antiradical power and reducing power.

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

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Oumaima Karai
Engineering Laboratory of Organometallic, Molecular Materials and Environment, Faculty of Sciences Dhar El Mahraz, Sidi Mohammed Ben Abdellah University, Fez, Morocco.
(e-mail: oumaima.karai@usmba.ac.ma)

Sara Hajib
Engineering Laboratory of Organometallic, Molecular Materials and Environment, Faculty of Sciences Dhar El Mahraz, Sidi Mohammed Ben Abdellah University, Fez, Morocco.
(e-mail: sara.hajib@usmba.ac.ma)

Serigne Abdou Khadir Fall
Engineering Laboratory of Organometallic, Molecular Materials and Environment, Faculty of Sciences Dhar El Mahraz, Sidi Mohammed Ben Abdellah University, Fez, Morocco.
(e-mail: serigneabdoukhadir.fall@usmba.ac.ma)

Salaheddine Boukhssas
Engineering Laboratory of Organometallic, Molecular Materials and Environment, Faculty of Sciences Dhar El Mahraz, Sidi Mohammed Ben Abdellah University, Fez, Morocco.
(e-mail: salaheddine.boukhssas@usmba.ac.ma)

Khadim Dioukhane
Engineering Laboratory of Organometallic, Molecular Materials and Environment, Faculty of Sciences Dhar El Mahraz, Sidi Mohammed Ben Abdellah University, Fez, Morocco.
(e-mail: khdadm.dioukhane@usmba.ac.ma)

Younas Aouine
Team of Organic Chemistry and Valorization of Natural Substances, Faculty of Sciences, Ibn Zohr University, Agadir, Morocco.
(e-mail: y.aouine@uiz.ac.ma)

Brahim Labriti
Engineering Laboratory of Organometallic, Molecular Materials and Environment, Faculty of Sciences Dhar El Mahraz, Sidi Mohammed Ben Abdellah University, Fez, Morocco.
(e-mail: Brahim.Labriti@usmba.ac.ma)

Hassane Faraj
Engineering Laboratory of Organometallic, Molecular Materials and Environment, Faculty of Sciences Dhar El Mahraz, Sidi Mohammed Ben Abdellah University, Fez, Morocco.
(e-mail: hassansefaraj@usmba.ac.ma)

Anouar Alami*
Engineering Laboratory of Organometallic, Molecular Materials and Environment, Faculty of Sciences Dhar El Mahraz, Sidi Mohammed Ben Abdellah University, Fez, Morocco.
(e-mail: anouar.alami@usmba.ac.ma)

*Corresponding Author
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.

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 1H and 13C 1D NMR, 1H-1H and 1H-13C 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 C19H23N2O5, crystallizes in the Orthorhombic system with the space group P212121 [40] (Fig. 2).

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.](image1)

![Fig.1. Structures of the five synthesised molecules tested.](image2)

![Fig.2. ORTEP view of compound 2b showing the atomic numbering scheme.](image3)

![Fig.3. ORTEP view of compound 2c showing the atomic numbering scheme.](image4)
B. Antioxidant Activity

Antioxidant activity defines the ability of an organism to protect itself against free radicals. The best-known antioxidants are β-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 ethylenzothiazoline-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-picrylhydrazyl) 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 (FeSO4•7H2O) 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 O2-, which is rapidly dismutated into H2O2 at pH 7.4. The latter than interacts with Fe3+ to form the •OH radicals in the presence of ascorbic acid as a catalyst (Fenton reaction).

H2O2 + Fe3+-EDTA $\rightarrow$ •OH + OH- + Fe2+-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 the DPPH 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].
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.

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).

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

| 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(III) 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 13C) 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, 13C); 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 (CNRTST-Rabat). The Orteps of compounds 2b and 2e were obtained on a Bruker APEXII CCD detector diffractometer (CNRTST-Rabat).

A. Chemistry

1. N-alkylation reaction

To 11 mmoles of nucleophile (Nu-H), 50 ml of anhydrous solvent (dichloromethane or acetone) is added, the mixture is cooled to 0°C, then 22 mmoles 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 (NaHCO3), dried with Na2SO4 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-(1-methoxy-2-oxoethyl)amino)acetate 2a: Rdt.: 80 % (oil); Rd: 0.62 (hexane/acetone, 1:1). 1H-NMR (CDCl3, δ ppm): 3.15 (6, NH, N=C=CH2); 3.47-3.62 (dd, 2H, NH, CH2-C=); 3.55 (3, CH3); 3.73 (s, 1H, N=CH2-N); 3.68 (s, 3H, OCH3); 5.44 (4, d, NH-Bz, J = 7.84 Hz); 3.7-7.8 (m, 5H, H); 13C-NMR (CDCl3, δ ppm): 46.85 (1C, CH2-C); 51.87 et 52.74 (2C, OCH3); 64.81 (1C, N=CH2-N); 127.21-133.29 (6C, Carom); 167.49, 170.22 et 172.79 (3C, CO).

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°.
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-[[1(R)-2-methoxy-2-oxo-1-phenylethyl]amino]acetate 2b has the most significant reducing power followed by 2c, 2d, 2a and 2e, respectively.

It should be noted that the DPPH test performed on 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,ω-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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Oumainia Karai was born in Fez, Morocco, in 1990. She obtained her Bachelor’s and master’s degree in chemistry at Sidi Mohammed Ben Abdellah University Faculty of Sciences and technologies, Fez, Morocco, in 2011 and 2013. She is a doctor in organic chemistry since 2020 from Sidi Mohammed Ben Abdellah University Faculty of Sciences Dhar El Mahraz, Fez, Morocco. Her research interests include Synthesis and spectroscopic study of new compounds derived from heterocyclic and non-heterocyclic carboxylic α,α-diaminodiesters, and on the study of their biological and antioxidant activities. Her research has been the subject of several publications (indexed journals, and conferences).

Sara Hajib was born in February 1990 in Fez, Morocco, where she completed her primary, secondary, and university education. The latter were capped respectively by obtaining a Bachelor’s in chemical analysis techniques and quality control and a Master's degree in the chemistry of bioactive molecules at the Faculty of Sciences and Technologies of Fez in 2015. Currently, she is pursuing her Ph.D. degree at Sidi Mohammed Ben Abdellah University Faculty of Sciences Dhar El Mahraz, Fez, Morocco.
Serigne Abdou Khadir Fall was born in Bamby, Senegal, on 07/31/1988. He is a PhD student in organic chemistry at the Faculty of Sciences, Dhar El Mahraz - Fez, Morocco. His research focused on the synthesis and study of bioactive molecules. Indeed, after obtaining his baccalaureate in 2009, he continued his studies in chemistry where he holds a bachelor's degree in industrial analytical chemistry in 2013, followed by a Master's in the analytical chemistry of environmental technologies in 2015.

Salaheddine Boukhssas was born in Fez, Morocco, in 1992. He received his higher education degree in Chemistry and a Master's Degree in Organic Chemistry from Sidi Mohamed Ben Abdellah University, Faculty of Sciences DM of Fez, Morocco, respectively in 2014 and 2016. Then, he started a Ph.D. degree in the field of heterocyclic chemistry in the organic chemistry laboratory and he began his career as an assistant teacher in the same Faculty. In 2019, He has engaged in the field of education as a professor of Physical Sciences and Chemistry at Ijabra High school in Taounate City, Morocco.

Khadiim Dioukhane was born in Senegal where he obtained his baccalaureate degree in 2010 before coming to Morocco for university studies. He obtained his License in "Technology Food" at the Faculty of Sciences and Technologies of Sultan Moulay Slimane University of Béni Mellal, Morocco, in 2013. He obtained his Master degree in Structural Chemistry from the Faculty of Sciences of Sidi Mohamed Ben Abdellah University in Fez, Morocco, in 2015. Currently, he is pursuing for his doctoral studies in organic chemistry at the same faculty, where he focused on the synthesis, characterization, electrochemical and biological studies of certain mono and biheterocyclic compounds.

Younas Aouine was born in Ait-Seghrouchen of Taza, Morocco, in 1979. He received his higher education diploma in Chemistry from the Sidi Mohamed Ben Abdellah University of Fez, Morocco, in 2003. He obtained his advanced degree (D.E.S.A) and Ph.D. degree in Organic and Heterocyclic Chemistry from the same university, in 2005 and 2015, respectively. Since 2006, he has been working as a researcher in organic chemistry laboratory (LCO) with Professors at Faculty of Sciences DM, University of Fez. In 2008, he joined the Ministry of Education as a professor of Physical Sciences and Chemistry in Imzouren High School, Al Hoceima in northern Morocco. Since 2018, he joined the Department of Chemistry of the Ibn Zohr University, Agadir, as an assistant professor. His teaching has been devoted to organic and heterocyclic chemistry courses. His current research is focalized firstly on synthesis and characterization of new heterocyclic α-amino acids and their precursors and on the other hand on the study of their biological and electrochemical activities.

Anouar Alami was born in Fez, Morocco, in 1966. He studied Chemistry at Montpellier II University, France and he obtained his Ph.D. degree in 1991. He then joined the department of chemistry at the Faculty of Sciences Dhar El Marhaz, Sidi Mohamed Ben Abdellah University (Fez, Morocco) in 1993. His current research is focused on the synthesis and characterization of new heterocyclic α-amino acids and their precursors and on the other hand on the study of their biological and electrochemical activities. He has taken part in conferences and communications in national and international congresses and has published the results of research (+70 publications and communications) in several international journals.

Brahim Labriti was born in Tiflet, Morocco, in 1962. He studied the Chemistry at the Faculty of Sciences Dhar El Mehraz, Sidi Mohammed Ben Abdellah University in Fez - Morocco, where he obtained his Ph.D. degree in 1994. He then joined the department of chemistry at the same Faculty in 1996 as an assistant professor. He is a member of the amino acids and peptides team in the organic chemistry laboratory. His current research is concentrated on the synthesis and characterization of new tetrazolic α-aminoo acids and their precursors and on the study of their biological and electrochemical activities.