SYNTHESIS OF NOVEL LIPOIC ACID DERIVATIVES

JUAN PABLO GONZÁLEZ-GUTIÉRREZ [a], S. MORIS [b] AND C. BARRIENTOS [b]*

[a]*Instituto de Ciencias Aplicadas, Facultad de Ingeniería, Universidad Autónoma de Chile, Chile.*
[b] *Centro de Investigación de Estudios Avanzados del Maule (CIEAM), Vicerrectoría de Investigación y Postgrado, Universidad Católica del Maule, Talca, Chile.*

ABSTRACT

Lipoic acid is a naturally occurring compound involved in biological processes with special reactivity due to its 1,2-dithiolane ring. The novel ALA derivatives were synthesized using the Steglich esterification in mild conditions and then concentrated and neutralized with yields of 45.1 to 81.2%.

Keywords: Steglich esterification; Lipoic derivatives.

1. INTRODUCTION

α-Lipoic acid (ALA) [5-[1,2]-dithiolan-3-yl-pentanoic acid] or thioctic acid is a natural compound with a five-member heterocycle, a dithiolane ring linked from a stereogenic center to an alkylic chain with a terminal carboxylic acid, obtaining two enantiomers R-(+)-α-lipoic acid with a natural occurrence and, S-(–)-α-lipoic acid with remarkable antioxidant activity[1], Figure 1.

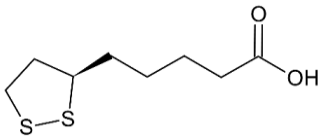

Figure 1. Chemical structure of α-Lipoic acid (ALA).

ALA is necessary for the proper generation of ATP from glucose via the citric acid cycle and is a cofactor of the enzymatic processes involved in mitochondrial decarboxylation in the Krebs cycle[2], (ALA) is present in living organisms in two forms: a reduced one (dihydrolipoic acid/DHLA) and an oxidized one (α-lipoic acid/ALA) which are in equilibrium in the homeostasis conditions[3,4]. DHLA is involved in the bio-synthesis of intracellular glutathione (GSH) and coenzyme Q_{10}[5,6]. Both forms (ALA/DHLA) constitute a redox system with the potential E°ALA/DHLA= -0.32 V[7], and due to this value, lipoic acid is considered a universal multifunctional antioxidant with various applications such as adjuvant in cancer treatment[7–10], Alzheimer disease[11], multiple sclerosis[12] and electrocatalytic electrocatalytic applications[13–15]. ALA is a vital modulator of several cellular metabolic processes, glutathione synthesis, glycine breakdown to CO_2 and NH_3, and oxidative decarboxylation of pyruvic acid to acetyl-CoA. Moreover, ALA plays a role in leucine, valine, and isoleucine metabolism and works as a cofactor in a multienzymatic complex of branched-chain alpha-ketoacid dehydrogenases[4,16]. Moreover, lipoic acid and its derivatives can be used to develop new polymeric materials, due to the 1,2-dithiolane ring, using the ring-opening polymerization mechanism, ROP, allowing the preparation of new polymeric materials by disulfide exchange propagation[17–20].

Because of the diverse applications of ALA, we present the synthesis of new ALA derivatives, Figure 2.

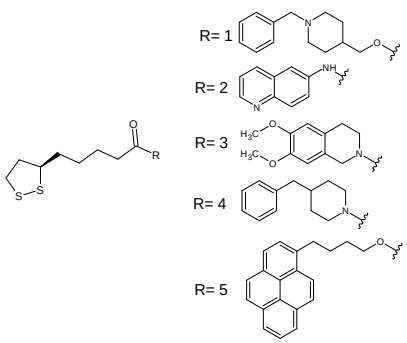

Figure 2. Chemical structure of compounds (**1-5**).

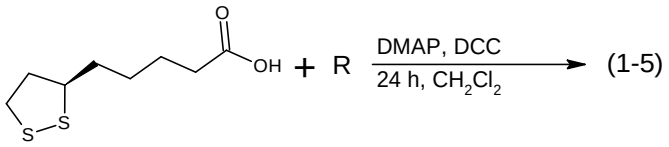

Figure 3. General scheme of synthesis of compounds (**1-5**).

2. EXPERIMENTAL SECTION

2.1 Materials

All the reagents and solvents used to synthesize these compounds were obtained commercially and used without further purification. The 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride, 6-aminoquinoline, (1-benzyl-4-piperidyl)methanol, and 4-benzylpiperidine were obtained from Ak Scientific Inc. (CA, USA) and, lipoic acid, acetone, diethyl ether, dichloromethane, methanol, ethyl acetate, 1-pyrenebutanol, 4-N,N-dimethylaminopyridine (DMAP) and dicyclohexylcarbodiimide (DCC) were obtained from Merck Millipore (Santiago, Chile).

2.2 Chemical characterization

Spectroscopic characterization ^{1}H-NMR and ^{13}C-NMR were recorded using a Bruker AMX 400 spectrometer at 400 MHz. Chemical shifts are reported relative to TMS (δ= 0.00) and coupling constants (J) are given in Hz. High-resolution mass spectra (HRMS) were recorded using a Bruker compact QTOF MS with direct injection. Reactions and product mixtures were routinely monitored by thin-layer chromatography (TLC) on silica gel pre-coated F_{254} Merck plates, and the compounds obtained were purified by column chromatography using ethyl acetate as the mobile phase.

2.3 Synthesis

General procedure

In a 100 mL round bottom flask, 0.576 g (2.794 mmol) of lipoic acid, 5% mol of DMAP, 0.576 g (2.794 mmol) DCC and 50 mL of CH_2Cl_2 were added with 2.794 mmol of the corresponding alcohol or amine. The reaction was carried out at room temperature, with a magnetic stir for 24 hours. Then, the formed solid was removed using vacuum filtered and washed with CH_2Cl_2 (2 x 20 mL). The Filtrate was concentrated in a rotary evaporator and then two portions of 20 mL of a solution of HCl 0.5 M were added, later two portions of 20 mL of Na_2CO_3 10% solution were added and finally washed with two portions of 30 mL of distilled water. Once the washing was completed, the organic phase was dried with Na_2SO_4 and concentrated at reduced pressure. Acetone was added to the reaction crude extracted in the previous stage and cooled for 24 hours for further precipitate formation.

3. RESULTS AND DISCUSSION

Due to the high sensitivity of lipoic acid to various reaction media for ester formation, all compounds (**1-5**) were synthesized using Steglich esterification[21–23]. All compounds were synthesised following the general procedure described above, Figure 3, with a yield between 45.1 – 81.2%. All

**Corresponding author email: cbarrientos@ucm.cl*

compounds were fully spectroscopically characterized by ^{1}H-NMR, ^{13}C-NMR, and HRMS, observing the following signs:

In ^{1}H-NMR, compound (**1**) presented an aromatic signal from the phenyl group with a δ ranging from 7.33 to 7.08 ppm, integrating five hydrogens. Additionally, a signal integrating for two hydrogens with a δ ranging from 3.45 to 3.39 ppm from the methylene part of the Ph-C**H$_2$**-N portion was observed, along with a signal integrating for one hydrogen with a δ ranging from 2.48 to 2.35 ppm. Compound (**2**) presented a signal integrating for one hydrogen at δ 8.70 ppm from the N-**H** amide, and an aromatic signal from quinoline with a δ ranging from 8.37 to 7.36 ppm. Compound (**3**) presented an aromatic signal at δ 6.58 ppm, integrating for two hydrogens from the 1,2,3,4-tetrahydroisoquinoline phenyl group, and a signal at δ 3.80 ppm, integrating for six hydrogens from the 1,2,3,4-tetrahydroisoquinoline methoxy group. Compound (**4**) presented an aromatic signal from the phenyl group with a δ ranging from 7.33 to 7.08 ppm, integrating five hydrogens. Additionally, this compound showed signals with δ ranging from 3.87 to 3.54 ppm, integrating for one hydrogen from the methylene of the alkyl chain of the piperidine group. Finally, compound (**5**) presented an aromatic signal with a δ ranging from 8.27 to 7.87 ppm, integrating nine hydrogens from pyrene. Additionally, a signal integrating two hydrogens at δ 4.16 ppm from the methylene group bonded to the oxygen of the ester group was observed. On the other hand, in ^{13}C-NMR, compounds (**1**-**5**) exhibited a signal in the range of δ 173.56 to 170.98 ppm, which corresponds to the carbonyl carbon of the amide or ester.

For high-resolution mass spectroscopy, molar masses found by this technique of all compounds were compared with that calculated theoretically.

Chemistry

(1-benzyl-4-piperidinyl)methyl 5-(1,2-dithiolan-3-yl)pentanoate (**1**).

Compound (**1**) was prepared as described in procedures **(A)**. Obtained as a dark yellow oil, yield 73.5%. ($C_{21}H_{31}NO_2S_2$): δ 7.33 – 7.08 (m, 5H), 3.97 – 3.83 (m, 2H), 3.49 – 3.39 (m, 2H), 3.19 – 3.04 (m, 1H), 2.90 – 2.80 (m, 2H), 2.72 (s, 1H), 2.48 – 2.35 (m, 1H), 2.31 – 2.21 (m, 2H), 1.98 – 1.85 (m, 3H), 1.66 – 1.57 (m, 6H), 1.47– 1.38 (m, 2H), 1.31– 1.16 (m, 3H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ 173.55, 138.43, 129.17, 128.17, 126.95, 68.79, 63.40, 56.34, 53.22, 40.22, 38.49, 35.34, 34.61, 34.08, 29.71, 28.95, 28.78, 24.74. HRMS m/z calcd. for $C_{21}H_{31}NO_2S_2$ (M+H), 394.1869; found, 394.1877.

4-(1,2-dithiolan-3-yl)-N-(quinolin-6-yl)butanamide (**2**).

Compound (**2**) was prepared as described in procedures **(B)**. Obtained as a dark yellow oil, yield 45.1%. ($C_{17}H_{20}N_2OS_2$): ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.70 (s, 1H), 8.37 (s, 1H), 8.31 (s, 1H), 7.97 (d, J = 8.4 Hz, 1H), 7.89 (d, J = 9.0 Hz, 1H), 7.50 (d, J = 9.0 Hz, 1H), 7.26 (dd, J = 8.6, 4.2 Hz, 1H), 3.42 (m, 1H), 3.01 (m, 2H), 2.40 – 2.22 (m, 4H), 1.80 – 1.62 (m, 4H), 1.38 (m, 2H), 1.18 – 1.02 (m, 2H), 0.73 (m, 2H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ 171.82, 149.22, 145.32, 136.20, 136.02, 129.83, 128.89, 123.41, 121.67, 116.18, 56.39, 40.24, 38.48, 34.67, 34.62, 28.88, 25.26. HRMS m/z calcd. for $C_{17}H_{20}N_2OS_2$ (M+H), 333.1090; found, 333.1099.

1-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)-4-(1,2-dithiolan-3-yl)butanone (**3**).

Compound (**3**) was prepared as described in procedures **(C)**. Obtained as a dark yellow oil, yield 81.2%. ($C_{19}H_{27}NO_3S_2$): ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.58 (s, 2H), 4.64 – 4.47 (m, 2H), 3.80 (s, 6H), 3.64 – 3.49 (m, 2H), 3.24 – 3.03 (m, 1H), 2.82 – 2.69 (m, 4H), 2.39 (m, 3H), 1.89 (m, 1H), 1.46 (m, 4H), 1.18 (m1H), 0.83 (m, 2H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ 171.58, 147.90, 147.68, 126.99, 125.83, 111.29, 109.45, 56.46, 56.09, 55.99, 43.90, 43.37, 40.25, 38.50, 34.78, 33.31, 29.11, 28.09, 24.96. HRMS m/z calcd. for $C_{19}H_{27}NO_3S_2$ (M+H), 382.1505; found, 382.10506.

1-(4-benzyl-1-piperidinyl)-5-(1,2-dithiolan-3-yl)pentanone (**4**).

Compound (**4**) was prepared as described in procedures **(D)**. Obtained as a dark yellow oil, yield 54.2%. ($C_{20}H_{29}NOS_2$): ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.02 (m, 5H), 3.94 – 3.83 (m, 1H), 3.77 (d, *J* = 13.6 Hz, 1H), 3.71 – 3.60 (m, 1H), 3.60 – 3.49 (m, 1H), 3.19 – 3.02 (m, 2H), 2.81 – 2.67 (m, 1H), 2.55 – 2.47 (m, 2H), 2.47 – 2.34 (m, 3H), 2.04 – 1.85 (m, 4H), 1.73 – 1.63 (m, 2H), 1.48 – 1.41 (m, 4H), 1.27 – 1.07 (m, 1H), 0.88 – 0.68 (m, 1H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ 170.98, 139.95, 129.08, 128.30, 126.05, 56.42, 42.98, 40.25, 38.50, 38.27, 34.70, 32.77, 30.96, 28.88, 26.34, 25.50, 25.35, 24.74. HRMS m/z calcd. for $C_{20}H_{29}NOS_2$ (M+H), 364.1763; found, 364.1772.

4-(pyren-1-yl)butyl 5-(1,2-dithiolan-3-yl)pentanoate (**5**).

Compound (**5**) was prepared as described in procedures **(E)**. Obtained as a dark yellow oil, yield 64.0%. ($C_{28}H_{30}O_2S_2$): ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.27 (dd, *J* = 9.2, 1.8 Hz, 1H), 8.17 (dd, *J* = 7.8, 4.5 Hz, 2H), 8.15 – 8.07 (m, 2H), 8.07 – 7.94 (m, 3H), 7.87 (dd, *J* = 7.9, 1.7 Hz, 1H), 4.16 (m, 2H), 3.51 (m, 1H), 3.39 (t, *J* = 7.7 Hz, 2H), 3.18 – 3.01 (m, 2H), 2.45 – 2.23 (m, 3H), 1.95 (m, 1H), 1.84 – 1.79 (m, 2H), 1.71 – 1.54 (m, 6H), 1.49 – 1.37 (m, 2H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ 173.56, 136.34, 131.45, 130.90, 129.89, 128.63, 127.52, 127.30, 127.25, 126.66, 125.85, 125.13, 125.04, 124.93, 124.83, 124.74, 123.30, 64.19, 56.32, 40.17, 38.45, 34.58, 34.12, 33.06, 28.75, 28.68, 28.15, 24.73. HRMS m/z calcd. for $C_{28}H_{30}O_2S_2$ (M-H), 461.1603; found, 461.1632.

CONCLUSIONS

Considering the high sensitivity of ALA to the reaction medium, Steglich esterification is a good option to be used to prepare ALA derivatives. All compounds were obtained and fully characterized by ^{1}H-NMR, ^{13}C-NMR, and HRMS.

ACKNOWLEDGMENTS

This work was supported by FONDECYT-Iniciación 11220164.

INTEREST CONFLICT

We declare no interest conflict in this work.

REFERENCES

1. C. Bellini, F. Mancin, E. Papini, R. Tavano, *Antioxidants*. **13** (2024).
2. A.K. Tripathi, A.K. Ray, S.K. Mishra, S.M. Bishen, H. Mishra, A. Khurana, *Rev. Bras. Farmacogn*. **33** (2023).
3. A. Gruzman, A. Hidmi, J. Katzhendler, A. Haj-Yehie, S. Sasson, *Bioorg. Med. Chem*. **12** (2004).
4. M. Turkowicz, I. Jastrzebska, M. Hryniewicka, U. Kotowska, D. Gudalewska, J. Karpińska, *Food Chem*. **309** (2020).
5. V.E. Kagan, E.A. Serbinova, G.M. Koynova, S.A. Kitanova, V.A. Tyurin, T.S. Stoytchev, P.J. Quinn, L. Packer, *Free Radic. Biol. Med*. **9** (1990).
6. H. Xie, X. Yang, Y. Cao, X. Long, H. Shang, Z. Jia, *CNS Neurosci. Ther*. **28** (2022).
7. S. Yan, J. Lu, B. Chen, L. Yuan, L. Chen, L. Ju, W. Cai, J. Wu, *Antioxidants*. **13** (2024).
8. T. Aiba, Y. Kono, T. Etoh, Y. Kawano, Y. Oshima, M. Inomata, *Cancer Sci*. **114** (2023).
9. M. Attia, E.A. Essa, R.M. Zaki, A.A. Elkordy, *Antioxidants*. **9** (2020).
10. I. V Ozhogin, P. V Zolotukhin, V. V Tkachev, A.D. Pugachev, A.S. Kozlenko, A.A. Belanova, S.M. Aldoshin, B.S. Lukyanov, *Russ. Chem. Bull*. **70** (2021).
11. D. Kaur, T. Behl, A. Sehgal, S. Singh, N. Sharma, S. Chigurupati, A. Alhowail, A. Abdeen, S.F. Ibrahim, C. Vargas-De-La-Cruz, M. Sachdeva, S. Bhatia, A. Al-Harrasi, S. Bungau, *Life Sci*. **284** (2021).
12. D. Kong, A.A. Saqer, M. Carpinelli de Jesus, N. Khan, A. Jones, J.T. Blanchfield, M.T. Smith, C.M. Williams, *Bioorg. Med. Chem*. **69** (2022).
13. A.C.F. Santos, R.C.S. Luz, F.S. Damos, A.E.G. Santana, D.G. Pessoa, M. Navarro, M.O.F. Goulart, *J. Solid State Electrochem*. **24** (2020).
14. B.B. Petković, M. Ognjanović, B. Antić, V. Viktorovich Avdin, D.D. Manojlović, S. Vranješ Đurić, D.M. Stanković, *Electroanalysis*. **33** (2021).
15. Y. Qian, L. Zhang, Y. Tian, *Anal. Chem.* **94** (2022).
16. S. Lechner, R.R. Steimbach, L. Wang, M.L. Deline, Y.-C. Chang, T. Fromme, M. Klingenspor, P. Matthias, A.K. Miller, G. Médard, B. Kuster, *Nat. Commun*. **14** (2023).
17. I.O. Levkovskyi, S. Mochizuki, A. Zheng, X. Zhang, F. Zhang, *Nano TransMed*. **2** (2023).
18. Q. Yu, Z. Fang, S. Luan, L. Wang, H. Shi, *J. Mater. Chem. B*. **12** (2024).
19. J. Gao, Q. Zhang, B. Wu, X. Gao, Z. Liu, H. Yang, J. Yuan, J. Huang, *Small*. **19** (2023).
20. A. Ghosh, K. Kozlowski, T.W.J. Steele, *Polymers (Basel)*. **15** (2023).
21. R.M. Annuur, D. Triana, T. Ernawati, Y. Murai, M. Aswad, M. Hashimoto, Z.P. Tachrim, *Molecules*. **29** (2024).
22. D. Olender, M. Józkowiak, H. Piotrowska-Kempisty, K. Sowa-Kasprzak, L. Zaprutko, I. Muszalska-Kolos, E. Baranowska-Wójcik, D. Szwajgier, Pharmaceuticals. **16** (2023).
23. E. Popa, A.A. Andelescu, V. Badea, P. Svera (m. Ianăși), E.I. Szerb, *Molbank*. **2024** (2024).