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Diazole and triazole derivatives of castor oil extract: synthesis, hypoglycemic effect, antioxidant potential and antimicrobial activity

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SUMMARY: The ricinoleate triglyceride was extracted from castor-oil seeds grown in Algeria and isolated by catalytically methanolyse to methyl ricinoleate. Six diazole and triazole derivatives of ricinoleic acid were synthesized and characterized: 1,3,4-oxadiazole-5-thione (4); 1,3,4-thiadiazole-5-thione (5); 4-N-amino-1,2,4-triazole-5-thiol (7); 1,2,4-triazole-5-thione (9); 5-amino-1,3,4-oxadiazole (10) and 5-amino-1,3,4-thiadiazole (11). The antibacterial and antifungal screening data of synthesized compounds showed appreciable inhibition and among them, 5, 7 and 8 showed more inhibition on Gram positive *Enterococcus faecalis* than reference ampiciline; while compounds 1, 7, 8, 10 and 11 showed competitive antifungal effects compared to reference amphotericin B. In addition, all synthesized compounds (1-11) showed competitive antioxidant properties, particularly compounds 7 at 125, 250, 500 and 1000 µg/mL and compounds 4, 5 and 9 at a concentration of 1000 µg/mL. The intermediate compounds 1, 2 and 8 showed anti-α-amylase activity at various concentrations in the range of IC_{50} = (120.25 ± 1.17 - 130.42 ± 2.48). Oxadiazole 4 showed the best α-amylase inhibition by 78.5% at a concentration of 1000 µg/mL.

KEYWORDS: *Anti diabetic; Antimicrobial; Antioxidant; Castor oil; Extraction; Heterocycle*

RESUMEN: ***Diazoles y triazoles derivados del extracto de aceite de ricino: síntesis, efecto hipoglucémico, potencial antioxidante y actividad antimicrobiana.*** Los triglicéridos de ricinoleico se extrajeron de semillas de aceite de ricino cultivadas en Argelia y se sintetizó catalíticamente con metanolisis el ricinoleato de metilo. Seis derivados de diazoles y triazoles de ácido ricinoleico se han sintetizado y caracterizado: 1,3,4-oxadiazol-5-tiona (4), 1,3,4-tiadiazol-5-tiona (5), 4-N-amino-1,2,4-triazol-5-tiol (7), 1,2,4-triazol-5-tiona (9), 5-amino-1,3,4-oxadiazol (10) y 5-amino-1,3,4-tiadiazol (11). Los datos de detección antibacteriana y antifúngica de los compuestos sintetizados mostraron una inhibición apreciable, entre ellos, los compuestos 5, 7 y 8 mostraron más inhibición en *Enterococcus faecalis* Gram positivo que la ampicilina de referencia. Mientras que los compuestos 1, 7, 8, 10 y 11 mostraron una influencia antifúngica competitiva en comparación con la anfotericina de referencia B. Como todos los compuestos sintetizados (1-11) mostraron propiedades antioxidantes competitivas, particularmente los compuestos 7, a 125, 250, 500 y 1000 µg/mL también compuestos 4, 5 y 9 a una concentración de 1000 µg/mL. Los compuestos intermedios 1, 2 y 8 mostraron actividad anti-α-amilasa a diversas concentraciones en el rango de IC50 = (120.25 ± 1.17 - 130.42 ± 2.48). El oxadiazol 4 mostró la mejor inhibición de la α-amilasa en un 78.5% a una concentración de 1000 µg/mL.

PALABRAS CLAVE: *Aceite de ricino; Antidiabético; Antimicrobiano; Antioxidante; Extracción; Heterociclo*

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1. INTRODUCTION

Castor oil is a natural production of the castor plant (*Ricinus Communis*) (Mubofu, 2016). Castor oil plants are widespread throughout the globe, particularly in tropical regions such as India, the southeastern Mediterranean Basin of North Africa (Trochain, 1930), Los Angeles, California (Witchard, 1997) and elsewhere. Castor oil has many uses; for example, it remains of commercial importance as a non-freezing, antimicrobial, pressure-resistant lubricant for special purposes, either for latex or metals, or as a lubricating component in fuels (Imankulov, 2012). Castor oil has long been used on the skin to prevent dryness. Whether pure or processed, it is still a component of many cosmetics (Bianchi *et al.,* 2011*;* Rachapudi *et al.,* 2017).

The high percentage of ricinoleic acid residues in castor oil and their derivatives inhibit virus, bacteria or fungi (Ghosh *et al*., 2013). The literature has revealed several synthetic modifications and utilization of ricinoleic acid. These modifications vary between ethylenic bond (Godard *et al*., 2013) hydroxyl group (Thames *et al.,* 2006) and carboxylic acid group (Dutta *et al.,* 2011; Lavanya *et al.,* 2012).

Heterocyclic-fatty acid hybrids such as oxadiazole, thiadiazole and triazole derivatives of vegetable oils are a new class of fatty acid derivatives with a wide range of biological activities and significance in the field of medicinal chemistry. They possess a broad spectrum of therapeutic uses such as analgesic, antimicrobial, anti HIV activity, antitumor, antimalarial, anticancer, anticonvulsant, anti-diabetic, antioxidant (Cao *et al.,* 2014; Ahmad *et al.,* 2017).

This work is mainly concerned with the extraction of castor oil from seeds of the plant and the isolation of ricinoleic acid. The latter was subjected to synthetic modifications focused on the carboxylic group to ultimately give six diazole derivatives. The synthetic intermediates and final products were studied to determine the biological evaluation of their α-amylase inhibitory, antimicrobial and antioxidant activities.

2. MATERIALS AND METHODS

2.1. General

All reactions were monitored by TLC, silica gel F254, made by Merck, Germany. Melting points (ºC) were measured in open glass capillaries using a Branstead 9001 Electrothermal melting point apparatus and were not corrected. The UV visible electron spectroscopy was recorded on an Optisen View 4.2 spectrometer. The IR spectra were recorded using KBr disks in a GENESISIIFTIR spectrophotometer, in ν units of cm^{-1}. The ^{1}H and ^{13}C-NMR spectra (1D) were recorded on a Bruker AC 400 MHz spectrometer (University of Lyon 1, France) in DMSO-d_6 and referenced to TMS. Symbols δ were used for chemical sifts in ppm, s = singlet, d = doublet, dd = double doublet and m = multiplets. Mass spectra were obtained using a GC-MS CLARIS 500 (Laboratoire Régional de Police Scientifique d'Oran, Algeria). The microorganisms in this study were supplied and identified by the laboratory of microbiology by the university hospital of Oran1. The Mueller Hinton medium was supplied by (Difco).

2.2. Chemistry

2.2.1. Oil extraction

The castor oil (1) was extracted with a soxhlet extractor. Hexane (1L) and ground castor beans (200 g) were packed into a filter paper thimble. The extraction lasted 10 h. The crude oil was treated with hot water to remove gums, hydrates, phosphates and other impurities and then it was neutralized with 0.1N NaOH to remove free fatty acid and soap to give castor oil (1), (84 g, 40.2%) (Nakarmi *et al*., 2014). UV (λ_{max}) nm: 205; 210. IR (CCl_4), ν $cm^{-1:}$ 3452. 92(OH); 3008 (CH unsaturated); 2925, 2855 (alkyl groups); 1742.37(C = O). ^{1}H NMR (400 MHZ, DMSO d_6) δ (ppm): 5.37-5.34 (m, 6H, $CH_{alkenes}$); 5.19-5.14 (m, 1H, C-H_β); 4.34 (dd, 2H, C-Hα); 4.10 (dd, 2H, C-Hγ); 3.40(s, 3H, 3OH); 2.06 (m, 6H, $OCOCH_3$); 2.24-1.50 (m, 96H, CH paraffinic); 0.82 (m, 9H, CH_3 terminal). ^{13}C NMR (400 MHZ, DMSO d_6) δ ppm: 172.13; 132.1; 126.5; 79.1; 69.8; 68.9; 61.6; 39.9; 39.7; 39.4; 39.1; 38.8; 36.5; 35.1; 33.2; 31.4; 29.1; 29.0; 28.7; 28.6; 28.5; 26.3; 26.2; 22.10; 13.80.

2.2.2. Methyl ricinoleate (2). Transesterification reaction

The extracted oil (1) (25g; 0.028 mol) was kept in three necked round-bottom flasks and heated to 65 ˚C. NaOH /MeOH (2,5g /20 mL) were added with the aid of stirring and the mixture was heated for three hours (Akhabue et al., 2017). The reaction was monitored by TLC (cyclohexane /acetone 8/2). After sampling, the reaction was stopped by acidifying the mixture with concentrated HCl (37%) to neutralize the remaining alkali, and was allowed to stand for phase separation (for 24 h). The organic layer was left for phase separation 3 times and the collected fractions were dried on anhydrous $CaCl_2$ to give methyl ricinoleate (24.5g, 98%); R_F: 0.65 (cyclohexane /acetone 8/2). UV (λmax) nm: 204. IR (CCl_4), ν cm^{-1}: 3430.74(OH); 3008(C = C); (2928.38 and 2856) (alkyl groups); 3008(CH unsaturated); 1737.55(C = O). ^{1}H NMR (400 MHZ, DMSO d_6) δ (ppm): (5.42; 5.38; 5.27) (m, 1H, H_{10} and H_9); 4.38(t, 3H,O-CH_3); 4.01(t, 3H,O-CH_3); 3.40(s, 1H, OH); 2.23-1.14 (m, 32H, CH paraffinic); 0.84; 0.82 (t, 3H, CH_3 terminal). ^{13}C NMR (400 MHZ,

DMSO d_6) δ ppm: 175.0; 172.9; 130.8; 129.9; 127.8; 70.4; 60.0; 35.6; 34.2; 31.2; 29.6; 29.5; 28.6; 28.6; 27.5; 26.8; 22.9; 14.2. MS: Molecular formula $C_{18}H_{36}O_3$: 311, *m/z:* 311 (M+, 100 %).

2.2.3. Ricinoleic acid hydrazide

Methyl ricinoleate (2), (2.11 g; 0.01mol), ethanol (50 mL) and hydrazine hydrate 64% (12 mL) were refluxed for 10 h. Ethanol and hydrazine were evaporated under reduced pressure, white solid was produced, recrystallized from acetone/cyclohexane to give ricinoleic hydrazide (3), 2.2g, 90%). M.p. (80–85 °C); UV (λmax) nm: 205; 262. IR (KBr), ν cm^{-1}: 3323. 71 (OH, NH, NH_2); 3008 (HC = C); 2849.31 and 2918.73 (alkyl groups); 1636. 3 (N-C = O). ^{1}H NMR (400 MHZ, DMSO d_6) δ (ppm): 8.88 (s, 1H, NH); 5.39 (m, 1H, H_{10}); 5.37 (m, 1H, H_9); 3.34(s, 1H, OH); 4.37 (d, 2H, NH_2); 2.08-1.16 (m, 32H, CH paraffinic); 0.84 (t, 3H, CH_3 terminal). ^{13}C NMR (400MHZ, DMSO d_6) δ ppm: 172.3; 128.4; 69.7; 37.9; 37.6; 34.2; 31.2; 29.6; 29.4; 28.6; 25.6; 22.9; 21.9; 14.28. MS: Molecular formula $C_{18}H_{36}N_2O$: 312, *m/z:* 312 (M+, 100%).

2.2.4. 5-Ricinoleyl-1,3,4-oxadiazole-2-thione-thiol

Ricinoleic acid hydrazide (3), (1g; 0.0032 mol) in ethanol (80 mL) was added to CS_2 (30 mL) followed by (1.2 g) KOH, and the mixture was refluxed for 16 h until the release of H_2S had ceased. The mixture was then cooled and acidified with dilute HCl. The crude compound was recrystallized from chloroform to give 5-Ricinoleyl-1,3,4-oxadiazole-2-thione-thiol (4), (1.36 g, 70%), R_f: 0.64 (cyclohexane /acetone 7/3); m.p. (117–120), UV (λmax) nm: 205; 252. IR (KBr), ν cm^{-1}: 3418. 21 (OH); 3222. 47 (NH); (2957, 2868) (alkyl groups); 3046 (CH unsaturated); 2800 (S-H); 1594(C = N); 1423 (C = S); 1109 (COC). ^{1}H NMR (400 MHZ, DMSO d_6) σ (ppm): 14.38(s, 1H, SH); 5.75 (m, 1H, H_{10}); 5.85 (m, 1H, H_9); 3.42(s, 1H, OH); 3.33(s, 1H, OH); 2.69-1.21 (m, 32H, CH paraffinic); 0.84 (t, 3H, CH_3 terminal). ^{13}C NMR (400 MHZ, DMSO d_6) δ ppm: 180.7; 174.3; 164.7; 144.28; 130.21; 70.27; 39.9; 37.6; 31.1; 29.3; 26.7; 24.7; 24.4; 24.0; 22.5; 14.5. MS: Molecular formula $C_{19}H_{34}N_2O_2S$: 354, m/z 279 ($C_{19}H_{34}N$); m/z 297 ($C_{19}ON$), m/z 75 (CNOS) and m/z 59 (CNS).

2.2.5. 5-Ricinoleyl-1,3,4-thiadiazole-2-thione

The ricinoleic acid hydrazide (3), (1 g, 0.0032 mole) was mixed with KOH (0.5 g) dissolved in absolute ethanol. A solution of CS_2 (2.5 g) was added to the mixture with 15 mL of ethanol. The mixture was stirred for 1 h at room temperature and then refluxed for 24 hours. The final product was acidified with hydrochloric acid. The resulting solid residue was filtered and recrystallized from ethanol. The product was obtained in the form of yellowish crystals (5), (1.45g, 75%); R_F: 0.35 (cyclohexane /acetone 6/4); m.p. 97 °C. UV (λmax) nm: 205; 285. IR (CCl_4), ν cm^{-1}: 3308.29(OH,NH); 2980.45(C = C); (2921.63,2849.31) (alkyl groups); 1589.06(C = N); 1462.74(C = S). 1H NMR (400 MHZ, DMSO d6) δ (ppm): 5.42 (s, 1H, NH); 5.33 (m, 1H, H_{10}); 4. 75 (m, 1H, H_9); 3.33 (s, 1H, OH); 3.32 (s, 1H, OH); 2.24-1.16 (m, 32H, CH paraffinic); 0.84 (t, 3H, CH_3 terminal). 13C NMR (400 MHZ, DMSO d6) δ ppm: 174.9; 173.3; 130.8; 128.9; 70.0; 64.4; 60.3; 37.9; 34.3; 31.9; 29.5; 25.7; 24.9; 22.5; 14.5. MS: Molecular formula $C_{19}H_{34}N_2OS_2$: 364 m/z: 364 (M+, 100%).

2.2.6. 5-Ricinoleyl-4-amino-1, 2, 4-triazole-3-thiol

Ricinoleic acid hydrazide (3), (1g; 0.0032 mol) and KOH (1.5 g) in absolute ethanol (10 mL) were mixed together until the solution became clear. CS_2 (25 mL) was added. The solution was stirred for 10 h at room temperature, and then diethyl ether (20 mL) was added to form a precipitate ricinoyl-potassium thiocarbazinic acid (6). The intermediary product was mixed with (NH_2NH_2-H_2O) (4 mL). The solution was refluxed for 15 h until the color of the solution became clear green. After cooling to room temperature, ice water (10 mL) was added to the reaction mixture, which was then neutralized with 3N HCl to form a precipitate. The precipitate was isolated by filtration and purified by recrystallization from ethanol/water to afford the desired product in the form of yellow crystal: 5-Ricinoleyl-4-amino-1, 2, 4-triazole-3-thiol (7), 1.2g, 65%); R_f: 0.61 (cyclohexane /acetone: 6/4); Mp. (132˚C) UV (λ max) nm: 205; 240. IR (KBr), ν cm^{-1}: 3417.24 (OH); 3177 (NH_2); 2953, 2868 (alkyl groups); 2700 (SH); 1617 (C = N). ^{1}H NMR (400 MHZ, DMSO d_6) σ (ppm): 11.97 (s, 1H, SH); 4.22 (d, 2H, NH_2); 4.01 (d, 2H, NH_2); 5.75 (m, 1H, H_{10}); 5.39 (m, 1H, H_9); 3.34 (s, 1H, OH); 2.69-1.23 (m, 32H, CH paraffinic); 0.85 (t, 3H, CH_3 terminal). ^{13}C NMR (400 MHZ, DMSO d_6) δ ppm: 181.0; 174.3; 164,7; 128,2; 123,2; 70.0; 69.9; 60.3; 37.7; 31.9; 25.7; 22.5; 14.5. MS: Molecular formula $C_{19}H_{36}N_4OS$: 368; the pseudo-molecular peak [M + H] + with m / z 367.

2.2.7. N-Thiosemicarbazide ricinoleic

Ricinoleic acid hydrazide (3), 1g; 0.0032 mol) was dissolved in ethanol (20 mL) with stirring. Ammonium thiocyanate (0.58 g) and HCl (30%) were added, and the reaction mixture was refluxed for 6 h. Excess solvent was evaporated to almost dryness and recrystallized from methanol/petroleum ether to give N-Thiosemicarbazide ricinoleic (8), 0.97g, 65%) ; R_f : 0,45 (cyclohexane /acetone: 7/3) ; Mp (97 °C) ; UV (λmax) nm: 210; 265. IR (KBr) ν cm^{-1}: 3373.85 (OH); (3271.64, 3172.33, 3106.76) (NH and NH_2); (2851.24 and 2919.70)

(alkyl groups); 1699 (C = O); 1621 (C = O-N); 1492 (C = S). ^{1}H NMR (400 MHZ, DMSO d_6) σ (ppm): 8.87 (s, 1H, NH); 8.44 (s, 1H, NH); 4.32 (d,2H, NH_2); 5.36 (m, 1H, H_{10} and H_9); 3.33 (s, 1H, OH); 2.68-1.21 (m, 32H, CH paraffinic); 0.84 (t, 3H, CH_3 terminal). ^{13}C NMR (400 MHZ, DMSO d_6) δ ppm: 183.0; 178.4; 166.9; 164.7; 131.7; 127.5; 70.4; 69.9; 37.6; 29.3; 29.3; 28.6; 25.5; 25.4; 25.2; 14.5. MS: Molecular formula $C_{19}H_{37}N_3O_2S$: 371, m/z: 371 (M+, 100 %).

2.2.8. 5-Ricinoleyl-4H-1, 2, 4-triazole-3-thiol

N-Thiosemicarbazide ricinoleic (8), (1.0 g; 0.0024 mol) in ethanol (15 mL) was added to an alcoholic solution of 10% NaOH (20 mL), and the reaction mixture was refluxed for 12 h. The mixture was cooled and acidified with dilute HCl to pH (5–6). The crude compound was recrystallized from ethanol to give white needle-like crystals: 5-Ricinoleyl-4H-1,2,4-triazole-3-thiol (9), (0.75 g, 75%) ; m.p. (95 °C) ; R_f: 0.46 (cyclohexane /acetone: 6/4) ; UV (λmax) nm: 210. IR (KBr) ν cm^{-1}: 3433 (OH, NH); 3100(C = C); 2953 and 2868 (alkyl groups); 2722.05 (SH); 1636. 3 (C = N). ^{1}H NMR (400 MHZ, DMSO d_6) *σ* (ppm): 12.34(s, 1H, SH); 4.57 (s, 1H, NH); 5.75; 5.90 (m, 1H, H_{10} and H_9); 3.72(s, 1H, OH); 2.85-1.18 (m, 32H, CH paraffinic); 0.96 (t, 3H, CH_3 terminal). ^{13}C NMR (400 MHZ, DMSO d_6) *δ* ppm: 175.3; 174.7; 130.2; 125.2; 69.7; 39.9; 31.8; 29.9; 25.2; 24.9; 22.9; 14.5. MS: Molecular formula $C_{19}H_{35}N_3OS$: 353, The pseudo-molecular peak [M + H] + with m / z 354.

2.2.9. 5-Ricinoleyl-2-amino-1,3,4-oxadiazole

N-Thiosemicarbazide ricinoleic (8); (1.0 g, 0.0026 mol) was dissolved in an alcoholic solution of NaOH (5N) with the aid of stirring. The mixture was refluxed at 80 °C, during which an aqueous iodine solution (KI / I_2) was added gradually until the iodine color (pink-purple) persisted. Reflux was continued for 15h. Once the solution had cooled, it was filtered and then treated with a dilute sodium thiosulfate solution and finally washed with distilled water to give a straw-yellow solid which was recrystallized from ethanol to give 5-Ricinoleyl-2-amino-1,3,4-oxadiazole (10), (0.78g, 78%); m.p (128 °C); R_f : 0.56 (cyclohexane / acetone : 6/4) ; UV (λmax) nm: 210; 275. IR (KBr), ν cm^{-1}: 3389 (OH, NH_2); 2921.63 and 2850.27 (alkyl groups); 165.45 (O-C = N); 1119 (= C-O-C =). ^{1}H NMR (400 MHZ, DMSO d_6) *δ* (ppm): 5.54 (d, 2H, NH_2); 5.30 (m, 1H, H_{10}); 5.23 (m, 1H, H_9); 3.32(s, 1H, OH); 2.51-1.23 (m, 32H, CH paraffinic); 0.85 (t, 3H, CH_3 terminal). ^{13}C NMR (400 MHZ, DMSO d_6) *δ* ppm: 175.6; 174.9; 131.5; 125.5; 70.0; 37.3; 34.1; 31.9; 31.2; 29.3; 28.6; 25.6; 25.2; 22.6; 14.5. MS: Molecular formula $C_{19}H_{35}N_3O_2$: 337, m/z 253 ($C_{18}H_{33}O$); m/z 279 ($C_{19}H_{33}CN$); m/z 84 (C_2HON_3) and m/z 58 (CON_2H_2).

2.2.10. 5-Ricinoleyl-2-amino-1,3,4-thiadiazole 11.

N-Thiosemicarbazide ricinoleic (**8**, 1.0 g; 0.0024 mol) was added gradually under stirring to the cooled concentrated H_2SO_4 (30 mL) for 1 h. the reaction mixture was refluxed for 10 h in an oil bath. The precipitated solid was filtered, washed with water, dried and recrystallized with ethanol to give brown crystals (**11**, 0.40g, 40%); m.p. (110 °C); R_f: 0.43 (cyclohexane /acetone: 6/4) UV (λmax) nm: 210; 240. IR (KBr) ν cm^{-1}: 3444.24 (OH, NH_2); 2955.38(C = C-CH); (2920.66 and 2849.31) (alkyl groups); 1657.52 (S- C = N). ^{1}H NMR (400 MHZ, DMSO d_6) *σ* (ppm): 4.57 (d, 2H, NH_2); 5.38 (m, 1H, H_{10}); 5.57 (m, 1H, H_9); 3.37 (s, 1H, OH); 2.58-1.16 (m, 32H, CH paraffinic); 0.82 (t, 3H, CH_3 terminal). ^{13}C NMR (400 MHZ, DMSO d_6) *δ* ppm: 174.3; 173.3; 134.6; 128.5; 69.7; 61.0; 60.03; 37.0; 31.9; 29.4; 25.7; 25.2; 24.9; 22.9; 14.2. MS: Molecular formula $C_{19}H_{35}N_3OS$: 353, m/z 279 ($C_{19}H_{33}N$); m/z 227 ($C_{13}H_{21}NOS$); m/z 74 (CHN_2S); m/z 59 (CH_2N_2).

2.3. Biology

2.3.1. Antimicrobial activities

All the synthesized compounds were tested for their in vitro antimicrobial activity against the Gram positive bacteria *Staphylococcus aureus* (ATCC-25923), *Enterococcus faecalis* (ATCC-29212), *Bacillus cereus* (ATCC 21332), the Gram-negative bacteria *Pseudomonas aeruginosa* (ATCC-27853), *Escherichia coli* (ATCC-25922), *Klebsiella planticola (*ATCC-33531), *Salmonella, Proteus vulgarus (ATCC 29905)*, in the nutrient agar media and fungi *Candida albicans (*ATCC 10231), *Aspergillus niger* (ATCC 16404), *Trichosporon Sp,* Fusarium*, Penicillium Sp* and *Altenaria* in Sabouraud dextrose medium using the serial plate dilution method. The data for the minimum inhibitory concentrations (MIC) (10, 5, 2.5, 1.25, 0.625) µg/mL were determined for those compounds which demonstrated activity in the preliminary paper disk tests. The standard antibiotics ampicillin (10µg/disc) and amphotericin B (100µg/disc) were used as reference drugs for the antibacterial and antifungal activities, respectively.

2.3.2. Antioxidant activity (DPPH radical scavenging assay)

The DPPH solution was prepared in advance by dissolving 4 mg of DPPH in 100 mL of absolute methanol. 0.1 mL of each sample at different concentrations (65.5; 125; 250; 500; 1000) µg/mL were added to 3.9 mL of DPPH. Reference antioxidant solutions (ascorbic acid) were also prepared under the same conditions to serve as a positive control. The negative control consisted only of DPPH and methanol. The mixture was left in the dark for 30 min until discoloration. The

presence of the DPPH radicals gave a dark purple color to the solution and which was absorbed rapidly at 517 nm when reduced. The color became pale yellow. During the reaction, the layer of this radical became saturated on contact with an antioxidant, which explained the disappearance of its coloring. This discoloration highlighted the trapping power of the free radical by the tested product. The percentage of the anti-free radical activity was estimated according to the equation below (Vijayalaxmi *et al.,* 2015):

PI % = (Abs control - Abs product /Abs control) *100

PI: Percentage inhibition Abs control: Absorbance at the 517 nm wavelength of the negative control (DPPH + methanol).

2.3.3. α-Amylase inhibition activity

The α-amylase inhibitory activity of the synthetic compounds was determined using the chromogenic DNSA method with a few modifications (Adegboye *et al*., 2018). 300 µl of 0.02 M sodium phosphate buffer (pH 6.9) containing α-amylase solution (0.5 mg/mL) and 300 µl of sample at different concentrations (62.5; 125; 250; 500; 1000) µg/mL were incubated at 37 °C for 30 min. Afterwards, 300 µl of a 1% starch solution in 0.02 M sodium phosphate buffer were added to each tube at timed intervals. The reaction mixtures were then incubated at 37 °C for 15 min. The reaction was stopped with 0.5 mL of dinitrosalicylic acid (DNSA) color reagent. The reaction mixture was then diluted after adding 5 mL of distilled water, and absorbance was measured at 540 nm. The α-amylase inhibitory activity was calculated as follows:

Inhibition % = 1- (A_{samp} / A_{cont}) 100%).

Where A_{samp} and A_{cont} were defined as absorbance of the sample and the control, respectively.

3. RESULTS AND DISCUSSION

3.1. Synthesis

The ricinoleiate triglyceride (1) was catalytically transesterified with methanol to give methyl ricinoleiate (2) in quantitative yield (Kumar *et al*., 2017) and converted to hydrazide (3) (Joshi *et al*., 2017), as summarized in Figure 1. Hydrazide (3) was subjected to synthetic modifications to reveal recinoleic diazoles and triazole derivatives: 1, 3,4-oxadiazole-5-thione (4), 1,3,4-thiadiazole-5-thione (5), 4-N-amino-1,2,4-triazole-5-thiol (7), 1,2,4-triazole-5-thiol (9), 5-amino- 1,3,4-oxadiazole (10), 5-amino-1,3,4-thiadiazole (11) and as summarized in

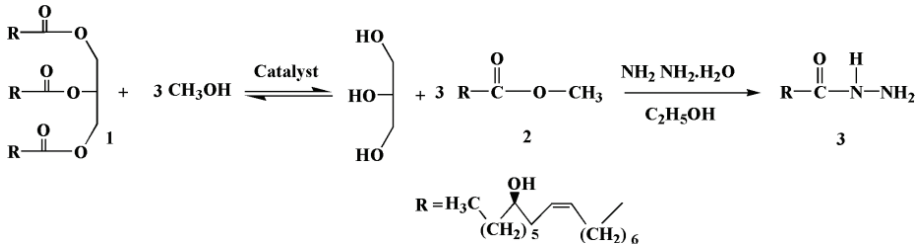

FIGURE 1. Conversion of ricinoleic triglyceride (1) to ricinoleic hydrazide (3).

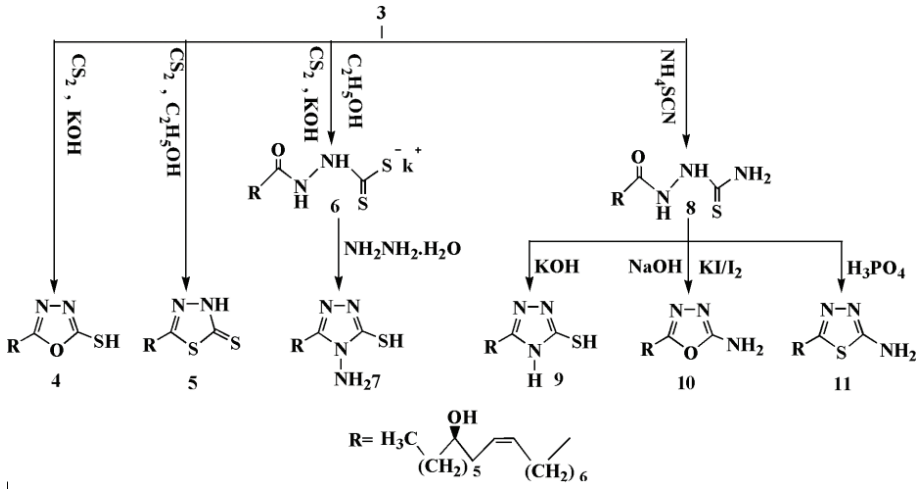

FIGURE 2. Synthetic pathways to diazole and triazole derivatives **(4), (5)**, (**7**), (**9**), (**10**) and (**11**) of ricinoleic

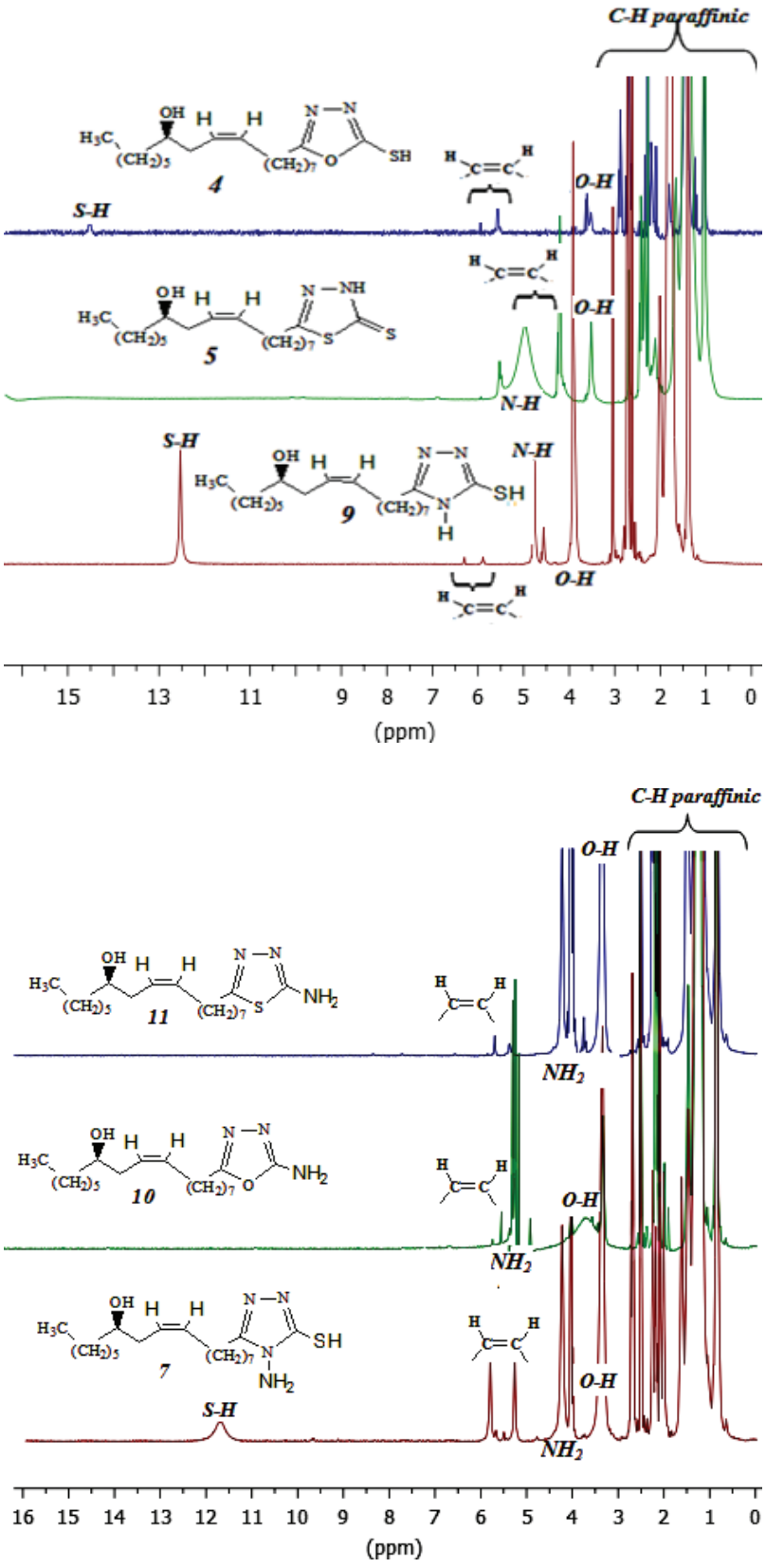

FIGURE 3. Characteristic signals in H[1]NMR of heterocyclic derivatives: 5-Ricinoleyl-1,3,4-oxadiazole-2-thione-thiol (4) , 5-Ricinoleyl-1,3,4-thiadiazole-2-thione (5), 5-Ricinoleyl-4-amino-1, 2, 4-triazole-3-thiol (7), 5-Ricinoleyl-4H-1,2,4-triazole-3-thiol (9), 5-Ricinoleyl-2-amino-1,3,4-oxadiazole (10), 5-Ricinoleyl-2-amino-1,3,4-thiadiazole (11).

figure 2. The first set of heterocyle derivatives 4, 5 and 7 were achieved by refluxing hydrazide 3 with CS_2 and aqueous KOH to give 2-ricinoleyl-1,3,4-oxadiazole-5-thiol (4) (Taieb Brahimi *et al.,* 2017). While using the excess CS_2 it yielded 2-ricinoleyl-1,3,4-thiadiazole-5-thione (5) (Gad El-Karim *et al*., 2013). However, heating hydrazide (3) with CS_2 in alcoholic KOH resulted in the crude ricinoleic potassium thiocarbazinic acid (6), which without separation and further analysis was refluxed with hydrazine hydrate to give 5-ricinoleyl-4- amino-1,2,4-triazole-3-thiol (7)

The second set of heterocycles (9-1)1 was prepared from N-thiosemicarbazide ricinoleic (8), which had already been prepared by treating hydrazide (3) with ammonium thiocyanide. 5-Ricinoleyl-4H-1,2,4-triazole-3-thiol (9) was obtained by the cyclization of 8 with KOH (Belkhadem *et al*., 2017); while 2-amino oxadiazole (10) was isolated

Table 1. Antibacterial activity of castor oil (1) and its synthesized derivatives (2-11).

	Gram-positive bacteria				Gram-negative bacteria			
	S.a.	**E.f.**	**B.c.**	**P.a.**	**E.c.**	**K.P.**	**Sal.**	**P.v.**
Compound	**Zone of inhibition in mm and MIC (minimum inhibitory concentration) in µg/mL**							
1	-	-	7 (100)	7 (25)	7 (25)	8 (50)	10 (6.5)	10 (25)
2	-	-	7 (50)	7 (25)	8 (25)	7 (50)	12 (25)	10 (25)
3	-	-	-	-	10 (25)	10 (25)	15 (25)	-
4	14 (6.25)	7 (50)	-	7 (100)	10 (12.5)	10 (25)	15 (12.5)	8 (25)
5	10 (6.25)	12 (25)	-	-	8 (25)	10 (25)	10 (6.25)	8 (25)
7	7 (25)	9 (50)	7 (25)	7 (25)	-	10 (25)	10 (25)	-
8	25 (100)	7 (100)	7 (50)	8 (25)	10 (6.25)	8 (50)	10 (6.25)	10 (100)
9	7 (25)	7 (50)	-	7 (50)	7 (25)	10 (25)	7 (50)	8 (25)
10	7 (50)	7 (12.5)	7 (50)	7 (50)	-	8 (25)	10 (25)	-
11	8 (50)	8 (50)	7 (100)	7 (100)	-	10 (25)	10 (25)	-
Amp	25	8	32	15	20	32	18	22

The figures in the table show the zone of inhibition (mm) and the corresponding MIC (µg/mL) values in brackets.
Amp: Ampicillin (10 µg/ disc).
S.a. (Staphylococcus aureus), E.f. (Enterococcus faecalis), B.c. (Bacillus cereus), P.a. (Pseudomonas aeruginosa), E.c. (Escherichia coli), K.P. (Klebsiella planticola), Sal. (Salmonella), P.v. (Proteus vulgarus).

Table 2. Antifungal activity of castor oil (1) and its synthesized derivatives (2-11) at 100 µg/mL.

	Fungi					
	Mold			Yeast		
Compound	**Candida albicans**	**Trichosporon Sp**	**Aspergillus niger**	**Fusarium**	**Penicillium Sp**	**Altenaria**
1	-	-	+++	-	-	+++
2	-	-	++	-	-	+++
3	++	++	-	+	+++	-
4	++	++	-	-	-	+
5	++	++	-	-	-	+
7	+++	-	-	-	-	++
8	-	+++	-	+++	+++	-
9	-	-	-	-	-	+
10	++	+++	-	+++	-	+++
11	-	++	-	+++	-	+++
Ref	+++	++	+++	+	+++	+++

Key to the inhibition zones activities: Highly active = (21-30 mm) +++; Moderately active = (16-20 mm) ++; Slightly active = (10-15 mm) +; Inactive = (< 10mm) -
Ref: amphotericin B (100 µg/disc.).

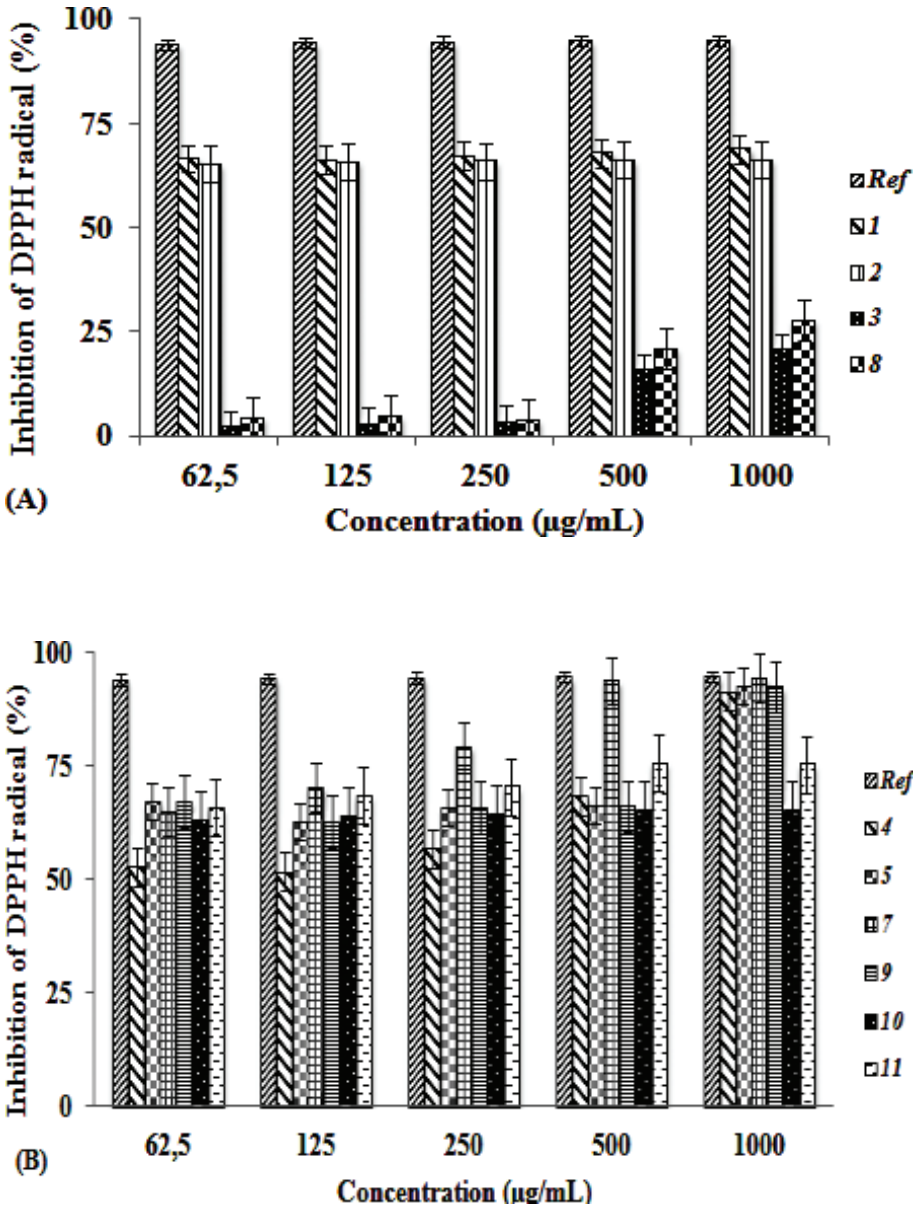

FIGURE 4. DPPH scavenging effect (%) of castor oil and its synthesized derivatives at different concentrations of: (A) Intermediate compounds: Castor oil (1) , Methyl ricinoleate (2) , Ricinoleic acid hydrazide (3) , N-Thiosemicarbazide ricinoleic (8) and ascorbic acid as reference. (B) Heterocyclic synthetic products: 5-Ricinoleyl-1,3,4-oxadiazole-2-thione-thiol (4), 5-Ricinoleyl-1,3,4-thiadiazole-2-thione (5), 5-Ricinoleyl-4-amino-1, 2, 4-triazole-3-thiol (7), 5-Ricinoleyl-4H-1,2,4-triazole-3-thiol (9), 5-Ricinoleyl-2-amino-1,3,4-oxadiazole (10), 5-Ricinoleyl-2-amino-1,3,4-thiadiazole (11) and Ascorbic acid as reference. Each point shows the average value of three replicates ± SD.

after treating 8 with NaOH in the presence of I_2/KI. 2-Amino thiadiazole (11) was collected after reacting (8) with H_3PO_4. The structural determination of all synthetic compounds 2-11 was confirmed spectroscopically by IR, UV, ^{1}H- NMR, ^{13}C-NMR and MS (see Figure 3). All compounds 1-11 became available, and a study of their antimicrobial, antioxidant and hypoglycemic activities was carried out.

3.2. Pharmacological screening

3.2.1. Antimicrobial activities

The results for antimicrobial activities are summarized in Tables 1 and 2.

The gram-positive bacteria under consideration showed zones of inhibition inferior to those observed by the Gram-negative bacteria. In general, the first

TABLE 3. IC_{50} values for castor oil 1 and its synthesized derivatives (2-11) with references of DPPH scavenging and α amylase inhibitory activity.

Compound	DPPH Scavenging Activity (IC50 (µg/mL)	Antiradical Power (1/ IC50)	α-amylase inhibitory activity (IC50 (µg/mL))
1	32,16 ± 0.58	0,031	130.42 ± 2.48
2	44,45 ± 0.45	0,022	120.25 ± 1.17
3	ND	ND	400.64 ± 2.75
4	56,74 ± 0.32	0,019	325.90 ± 2.75
5	58,24 ± 0.30	0,020	552.80 ± 3.15
7	50,15 ± 0.41	0,018	736.00 ± 5.66
8	ND	ND	125.00 ± 1.75
9	57,49 ± 0.35	0,017	920.56 ± 8.15
10	48,46 ± 0.28	0,001	ND
11	52,48 ± 0.38	0,001	ND
Ascorbic acid †	33,67 ± 0.45	0,030	-
Acarbose ‡	-	-	85.65 ± 1.09

Each point shows the average value of three replicates ± SD
*ND (*Not detected). † (reference of antioxidant activity); ‡ (reference of anti diabetic activity).
DPPH (2, 2-diphenyl-1- picrylhydrazyl radical); IC_{50} (Inhibitory concentration 50).

site of action of the products tested on bacterial cells was the plasma membrane. This was directly related to the amphiphilic nature of the tested products which facilitated their insertion between the membrane phospholipids and ensured their solubilization in the lipid bilayer (Soliman *et al.,* 2015). The good activity was attributed to the presence of pharmacologically active groups NH-CS-NH, C = O and C = S attached to the heterocyclic nuclei (triazoles, oxadiazoles and thiadiazoles). The presence of amine functions (NH_2) provided the tested molecules a higher activity on mushrooms than those of other products.

3.2.2. Antioxidant activity

From a methodological point of view, the free radical test, 2,2-diphenyl-1- picrylhydrazyl radical (DPPH) is recommended for compounds containing the SH, NH and OH (Barbuceanu *et al*., 2014) groups and was carried out at ambient temperature. This made it possible to eliminate any risk of thermal degradation of labile molecules (Li *et al.,* 2018). This test consisted of the reduction of an alcoholic solution of the radical species $DPPH^{\bullet}$ in the presence of a hydrogen donor antioxidant (AH), which resulted in the formation of a non-radical form of DPPH-H. Based on the experimental results (see Figure 4), the starting ricinoleic triglyceride (1), ester (2) and diazoles (4, 5, 7, 9, 10 and 11) showed high activity at different concentrations. Indeed, the structure-activity relationship of the heterocycle showed that the scavenging activity of the radicals increased with the presence of the hydrogen donor groups (-NH_2, -NH, -SH, -OH). The conjugation between the free radicals of the hetero atoms (Nitrogen, Oxygen, Sulfur) and the π electrons of the aromatic ring represented an additional factor to increase the stability of the radical structure.

IC_{50} (Inhibitory concentration 50), also referred to as EC_{50} (Efficient Concentration 50), is the concentration of the test sample needed to reduce 50% of the DPPH radical. The IC_{50} are calculated graphically by percent inhibition as a function of different concentrations of the tested product. From the value shown in Table 3, we noted a strong antiradical power for castor oil, which resulted in a fairly low IC_{50}, comparable to that of the standard compound ascorbic acid.

3.2.3. Hypoglycemic effect (α-amylase inhibition)

The digestive enzyme (α-amylase) was responsible for hydrolyzing dietary starch (maltose), which broke down into glucose prior to absorption. The inhibition of α-amylase led to a reduction in post prandial hyperglycemia under diabetic conditions (Yilmazer-Musa *et al*., 2012; Menteşe *et al.,* 2014). α-Amylase activity can be measured in-vitro by the hydrolysis of starch in the presence of the α-amylases enzyme. The α-amylase inhibitory activity was determined by using dinitro salicylic acid (DNSA). Triglyceride (1), its corresponding ester (2), synthetic products 3-11

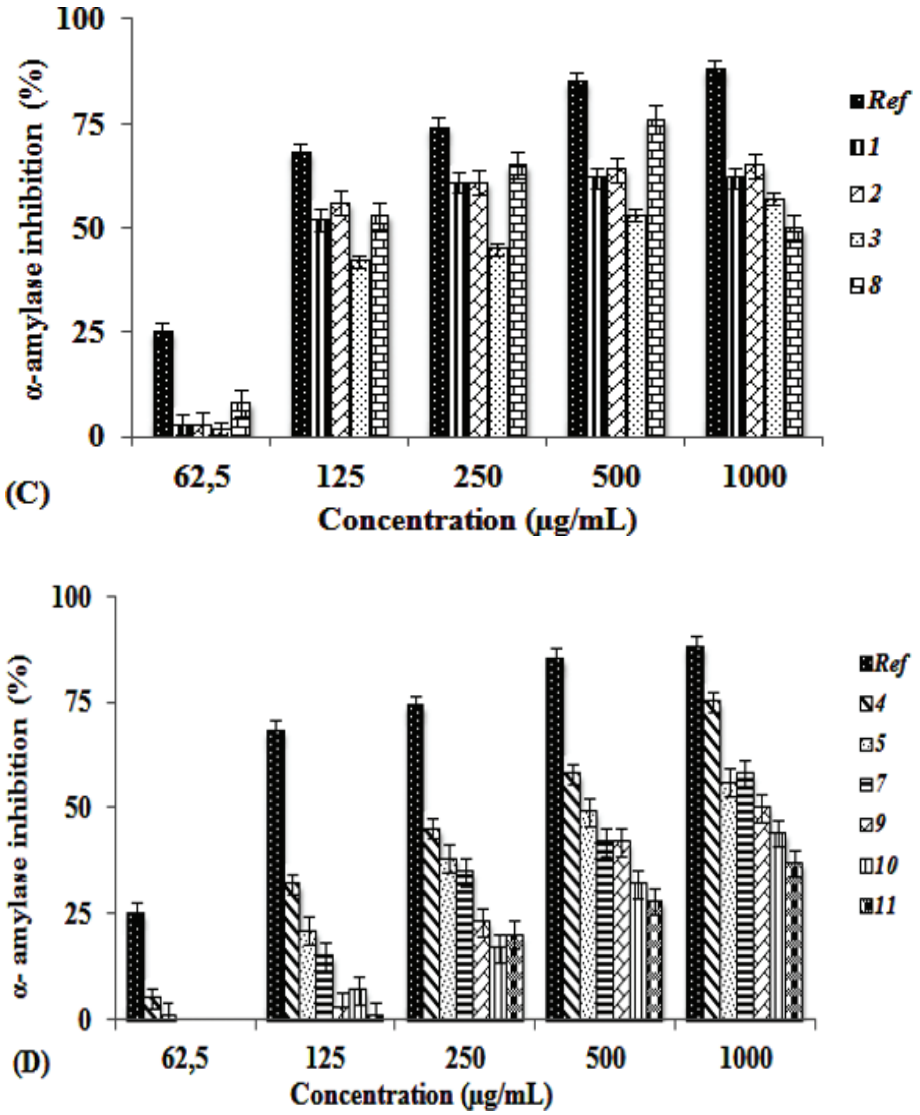

FIGURE 5. Percentage of α- amylase inhibition versus different concentration of:
(C) Intermediate products: Castor oil (1) , Methyl ricinoleate (2), Ricinoleic acid hydrazide (3) , N-Thiosemicarbazide ricinoleic (8) and Acarbose as reference. (D) Heterocyclic synthetic products: 5-Ricinoleyl-1,3,4-oxadiazole-2-thione-thiol (4) , 5-Ricinoleyl-1,3,4-thiadiazole-2-thione (5), 5-Ricinoleyl-4-amino-1, 2, 4-triazole-3-thiol (7), 5-Ricinoleyl-4H-1,2,4-triazole-3-thiol (9), 5-Ricinoleyl-2-amino-1,3,4-oxadiazole (10), 5-Ricinoleyl-2-amino-1,3,4-thiadiazole (11) and Acarbose as reference. Each point shows the average value of three replicates ± SD.

(except 6) and acarbose, as control, were evaluated for in vitro α-amylase and showed a wide range of inhibitory activity (Figure 5**)**. At a lower IC_{50} concentration (µg/mL), the above mentioned compounds were grouped into three inhibitory groups: Group A, consisting of compounds (1), (2) and (8), which exhibited an inhibition at the lowest corresponding concentrations (130.42 ± 2.48, 120.25 ± 1.17 and 125.00 ± 1.75) µg/mL (see Table 3).

Group B, comprised of compounds (3) and (4), which showed inhibition at moderately higher concentrations (400.64 ± 2.75, 325.90 ± 2.75) µg/mL. Group C consisted of compounds (5), (7), and (9) at corresponded to the highest concentrations (552.80 ± 3.15, 736.00 ± 5.66, 920.56 ± 8.15) µg/mL. Among the synthetic compounds (4), (5), (7), (9), (10) and (11), no significant inhibitory effect was detected for the heterocycles (10) and (11). Oxadiazole 4 showed the best α-amylase inhibition.

4. CONCLUSIONS

The oil extract (1) (ricinoleate triglyceride) reacted over 40% from original castor oil and was closest to highest percentage reported in the literature (45%)

(Nakarmi *et al*., 2014). The synthetic compounds showed better biological effects on Gram-negative bacteria. The presence of amine functions (NH_2) of the tested molecules provided all synthesized compounds with higher activity on mushrooms. All synthesized compounds showed high antioxidant activity. The compounds with the greatest anti-radical activity were noted as: Castor oil (1) > Ester (2) > Amino-oxadiazole (10) > Amino-triazole (7) > Amino-thiadiazole (11) > oxadiazole (4) > triazole (9) > thiadiazole (11). The intermediate and diazole derivatives 1-11 were evaluated for in vitro α-amylase inhibitory activity and showed good to moderate inhibitory activity compared to standard acarbose. The synthesized compounds can be ranked in descending order of their anti-diabetic activity as follows: Acarbose > Ester (2) > Castor oil (1) > thiosemicarbazide (8) > hydrazide (3) > oxadiazole (4) > thiadiazole (5) > Amino-triazole (7) > triazole (9) > Amino-oxadiazole (10) > Amino-thiadiazole (11).

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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