Ann. For. Res. 66(2): 148-158, 2023
ISSN: 18448135, 20652445
ANNALS OF FOREST RESEARCH
www.e-afr.org

SYNTHESIS AND CHARACTERIZATION OF ALKALOID APORPHINE STEPHALAGINE AND ITS DERIVATIVES

Mohammed O. Hasan[1]
mohamedalarajy@gmail.com

Saadon Abdulla Aowda[2]
Sci.saadon.abdulla@uobabylon.edu.iq

Ahmed Kareem Obaid Aldulaimi[3]
ahmedaldulaimi1@gmail.com

Hala Shkyair Lihumis[2]
sc i.hala.shkair@uobabylon.edu.iq

Mohamed BOUAZIZ[1]
mohamedalarajy@gmail.com

1. Laboratory of Electrochemistry and Environment, ENIS, University of Sfax, Tunisia, BP 1175, Sfax, Tunisia
2. Department of Chemistry, College of Science, University of Babylon, Iraq
3. College of food sciences, Al-Qasim Green University, Babylon, Iraq

Abstract

Stephalagine was prepared by the reaction of chemical precursor via the formation of (2-(2-bromophenyl)-N-(2-(4-methoxybenzo[d][1,3]dioxol-5-yl)ethyl)acetamide,[**M1**]) and the formation of a heterocyclic compound (5-(2-bromobenzyl)-9-methoxy-7,8-dihydro-[1,3]dioxolo[4,5-g]isoquinoline, [**M2**]). Reduction of [**M2**] gave compound ((R)-5-(2-bromobenzyl)-9-methoxy-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinoline, [**M3**]) which undergo amidation with (chloro propyl acetate) to give (propyl (R)-2-(5-(2-bromobenzyl)-9-methoxy-7,8-dihydro-[1,3]dioxolo[4,5-g]isoquinolin-6(5H)-yl)acetate, [**M4**]). Which in turn was converted to (propyl (R)-2-(4-methoxy-5,6,7a,8-tetrahydro-7H-[1,3]dioxolo[4',5':4,5]benzo[1,2,3-de]benzo[g]quinolin-7-yl)acetate, [**M5**]) via intramoleculer cyclization. The reaction of [**M5**] with ($LiAlH_4Me$) gave the stephalegine [**M6**] in good yield. The intermediate compounds and the target molecules were identified by FT-IR spectra, ^{1}HNMR.
Keywords: Alkaloid Aporphine, Stephalagine, Annona Crassiflora fruit, anti-cancer.

Aim of the study

The compounds that were prepared in this study are present in nature in the fruits of the Annona Crassiflora fruit, where it is believed that they have great effectiveness in treating many common diseases such as obesity, and therefore they were prepared in the laboratory to be used in the manufacture of medicines to treat these diseases.

1. Introduction

In recent years, the importance of the natural products of the plants draw the attention of scientist and researchers to study their biological activates and to see the possibility of using them in the medical field. Researchers were focusing on the wild plants such as Annona Crassiflora fruit, which are widely cultivated in Latin America in the Savannah province of Brazil [1]. The studies have shown that the fruit of these trees contains different chemical compounds such as naturally occurring alkaloids, phenols and fibers that are of important biological activities [2].

In addition alkaloids are extracted from different plant parts such as roots, stems, seeds, peels, and fruits [3, 4], and sometimes they are extracted from special types of bacteria, fungi, animals like a poisonous frogs and some marine vertebrates [5, 6].

In general, alkaloids are considered a special class of heterocyclic amines, their chemical structures contains one nitrogen atom within a ring system, in addition to carbon and hydrogen [7]. Alkaloids may also contain oxygen and sulfur and rarely other elements such as chlorine, bromine, and phosphorus, so there are various forms of alkaloids [6,8].

Previous studies have shown that alkaloids of all kinds have wide medical uses, especially as analgesics for pain such as morphine [9], anti-cancers such as vinca alkaloids (vincristine) [10], anti-asthma such as ephedrine [11], Anti-Inflammatory [12], anti-malaria such as quinine [13], vasodilators such as vincamine, anti-diarrheal agents [14], anti-HIV [15], and as controlling compounds for high sugar and high blood pressure [16], antioxidative [17], in addition to their use as toxic pesticides and inhibitors of the pancreatic lipase enzyme such as Alkaloid Aporphine (stephalagine) [18]. In addition, alkaloids such as atropine, psilocin, nicotine, and cocaine are known as addictive and narcotic agents [19].

One of the most important types of alkaloids used in medicine now is the stephalagine alkaloid, which is extracted from the peels of the fruits of the Annona crassiflora tree Stephalagine has great biological activities and medical effects as inflammatory pain relieving agent such as joint pain, in addition to inhibiting the pancreatic lipase enzyme (PL), which in turn works to break down fat, which helps in the treatment of obesity [20].

2. Material and Methods

2.1 Materials

All of the used chemicals are purchased from (commercial companies) (Purity 98%) and used without further purification.

2.2 Instruments and measurement

Characteristic infrared absorption frequencies ($\bar{\upsilon}_{max}$ cm^{-1}) were recorded in the range of (4000 - 400 cm^{-1}) using a (Bruker FT-IR) spectrophotometer. The ^{1}HNMR spectra were recorded on a (Bruker Avance III 500) spectrometer using tetramethylsilane (TMS) as internal reference, DMSO-d_{δ} as inert solvent and the chemical shifts δ are expressed in ppm unit with respect to TMS (δ = 0).

2.3 Synthesis

2.3.1 Synthesis of 2-bromophenylacetyl chloride.

A round-bottom flask (500 ml) equipped with a magnetic stirring bar was charged with a dry dichloromethane (300 ml) solution of 2-bromo phenyl acetic acid (38.3 gm, 0.18 mol) and triethylamine. Oxalyl chloride (23.4 gm, 0.185 mol) dissolved in dry dichloromethane (40 ml) was then slowly added dropwise to the reaction mixture. The reaction was allowed to proceed for 15 hours at ambient temperature while being stirred continuously. The solvent was then removed by applying reduced pressure to obtain the resulting 2-bromophenylacetyl chloride, which was used without any further purification.

2.3.2 Synthesis of N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-2-(2-bromophenyl)acetamide [M1]

A round-bottom flask (250 ml) was charged with a dry dichloromethane (125 ml) solution of 2-(benzo[d][1,3]dioxol-5-yl)ethan-1 amine (homopiperonylamine) (19.8 gm, 0.12 mol) and triethylamine (2 ml). Next, a freshly prepared solution of 2-bromophenylacetyl chloride (28 gm, 0.12 mol) in dry dichloromethane (70 ml) was added dropwise over a period of 20 minutes at 0 °C. The reaction mixture was stirred for 15 hours, then quenched by the addition of brine solution, and extracted with dichloromethane. The resulting solution was evaporated under reduced pressure to obtain the solid product, which was subsequently purified by crystallization from absolute ethanol.

2.3.3 Synthesis of 5-(2-bromobenzyl)-7,8-dihydro-[1,3]dioxolo[4,5-g]isoquinoline [M2]

A round-bottomed flask (250 ml) equipped with a condenser, dry calcium guard tube, and magnetic stirrer was used to prepare a solution of N-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-2-(2-bromophenyl) acetamide (27gm, 0.075 mol) in dry dichloromethane (125 ml). Phosphorus oxalyl chloride (10 gm, 0.078 mol) dissolved in dry dichloromethane (50 ml) was then added dropwise at 0 °C with continuous stirring. The reaction mixture was refluxed for 18 hours, after which the reaction was stopped, and the mixture was cooled to 0 °C and neutralized by the addition of 10% NaOH solution. The product was extracted using diethyl ether, and after evaporation of the ether, a solid product was obtained.

2.3.4 Synthesis of (R)-5-(2-bromobenzyl)-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinoline [M3]

A reaction mixture was prepared by dissolving 5-(2-bromobenzyl)-7,8-dihydro-[1,3]dioxolo[4,5-g]isoquinoline (15gm, 0.044 mol) and dimeric dicloro (p- cymene) ruthenium (ii) (4 gm, 0.0066 mol) with a trace amount of triethylamine in 60 ml of dimethylformamide (DMF). The mixture was stirred at 80 °C for 1 hour, and then a solution of 3,4-dihydroisoquinoline (5.8 gm, 0.044 mol) in 40 ml of DMF was added. The reaction mixture was cooled to 0 °C and a solution of formic acid (5.2 ml) and triethylamine (2.7 ml) was dropwise added. The reaction mixture was then worked up by adding saturated K_2CO_3, diluting with water and extracting the product using ethyl acetate. The organic layer was dried over anhydrous Na_2SO4 and the solvent was removed under reduced pressure.

2.3.5 Synthesis of propyl (R)-2-(5-(2-bromobenzyl)-7,8-dihydro-[1,3]dioxolo[4,5-g]isoquinolin-6(5H)-yl)acetate [M4]

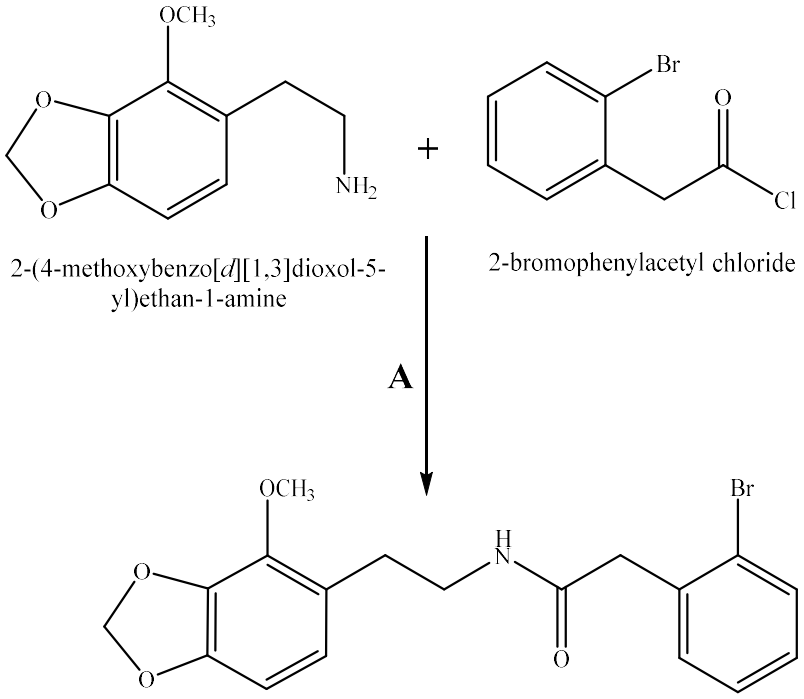
A solution of (R)-5-(2-bromobenzyl)-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinoline (11.5 gm, 0.033 mol) in dry dichloromethane (50 ml) with few drops of diisopropylethylamine and 4-(dimethylamino)pyridine was prepared. Amount of propyl chloroacetate (4.5 gm, 0.033 mol) in dry dichloromethane (25 ml) was slowly added to the prepared solution and the mixture was stirred for (15 hr) at 25°C. The reaction was quenched by the addition of saturated solution of ammonium chloride and the product was extracted by dichloromethane.

2.3.6 Synthesis of propyl (R)-2-(5,6,7a,8-tetrahydro-7H-[1,3]dioxolo[4',5':4,5]benzo[1,2,3-de]benzo[g]quinolin-7-yl)acetate [M5]

A solution of propyl (R)-2-(5-(2-bromobenzyl)-7,8-dihydro-[1,3]dioxolo[4,5-g]isoquinolin-6(5H)-yl)acetate (9.5 gm, 0.021 mol), potassium carbonate K_2CO_3 (2.9 gm, 0.021 mol) and palladium acetate, $Pd(OAc)_2$ (1.1gm,0.005 mol) in dimethylformamide (DMF) was prepared and contained in round - bottom flask supplied with magnetic stirrer. The reaction mixture was stirred for (17 h) at 130 °C then was cooled down and the solvent was removed under reduced pressure.

2.3.7 Synthesis of Stephalagine alkaloid [M6]

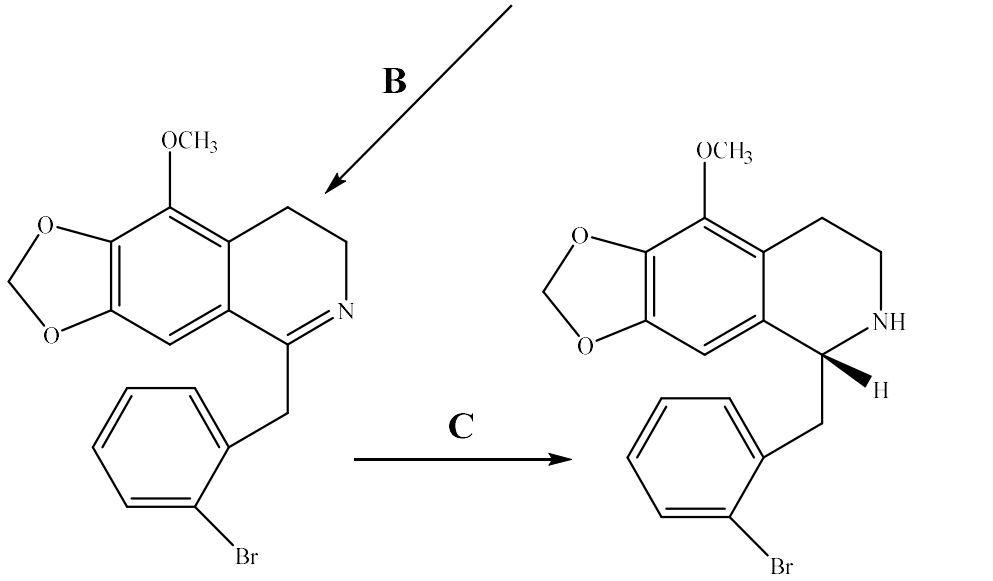
A reaction solution was prepared by dissolving propyl (R)-2-(5,6,7a,8-tetrahydro-7H-[1,3]dioxolo[4',5':4,5]benzo[1,2,3-de]benzo[g]quinolin-7-yl)acetate (4 gm, 0.011 mol) in dry tetrahydrofurane THF (60 ml), and contained in round - bottom flask (250 ml). The solution was cooled down to 0 °C, whereupon amount of Methyllithiumaluminum tetrahydride ($LiAlH_4Me$) (0.53 g, 0.014 mol) dissolved in dry THF (60 ml) was dropwisely added with continuous stirring. The mixture was allowed to worm up to room temperature and was stirred for (24 h), after wards, the mixture was slowly hydrolyzed with distilled water. The product was obtained by extraction with diethyl ether and dried over anhydrous magnesium sulphate, $MgSO_4$ after removed of diethyl ether with yield 80 %.



2-(4-methoxybenzo[*d*][1,3]dioxol-5-yl)ethan-1-amine

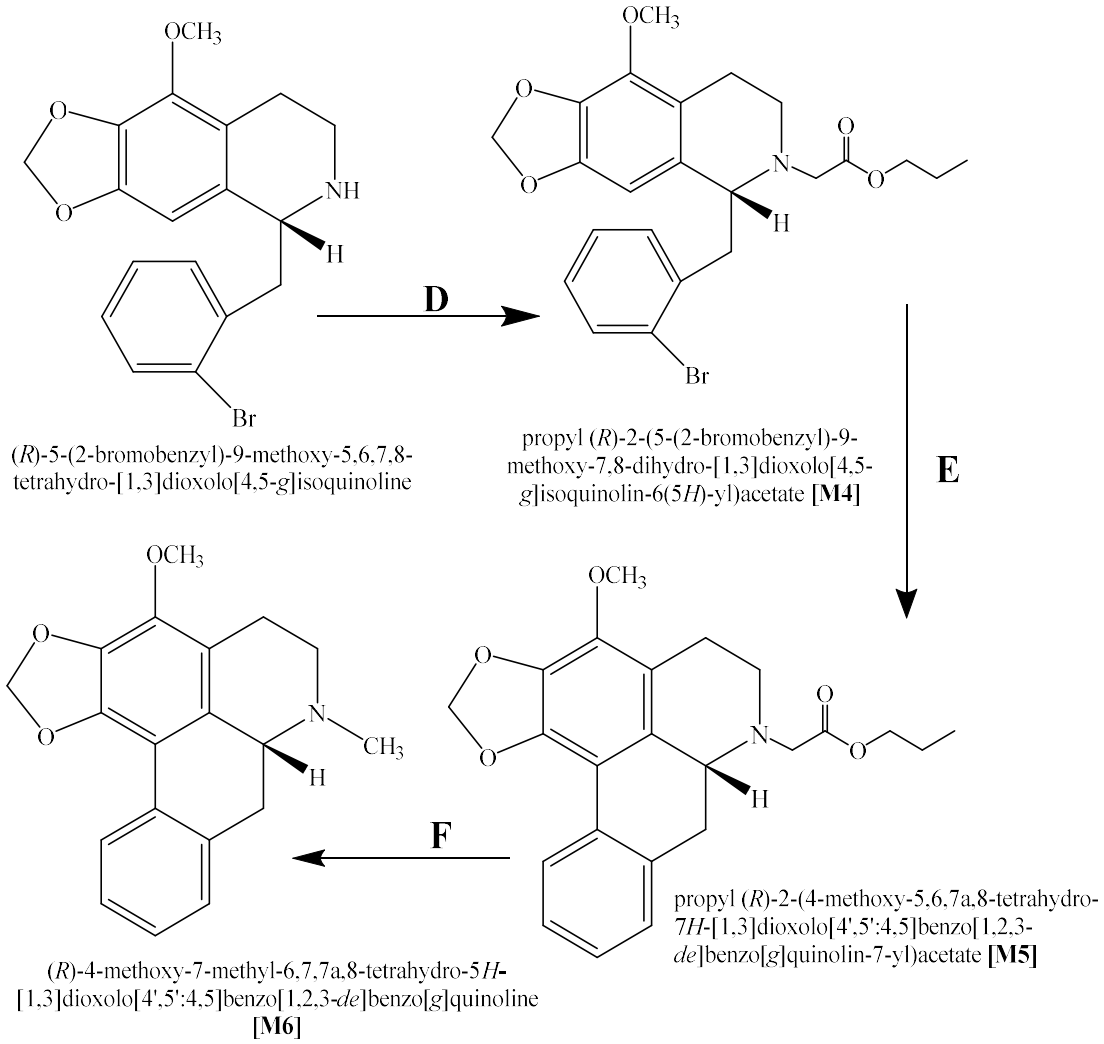
2-bromophenylacetyl chloride

2-(2-bromophenyl)-*N*-(2-(4-methoxybenzo[*d*][1,3]dioxol-5-yl)ethyl)acetamide [**M1**]



5-(2-bromobenzyl)-9-methoxy-7,8-dihydro-[1,3]dioxolo[4,5-*g*]isoquinoline **[M2]**

(*R*)-5-(2-bromobenzyl)-9-methoxy-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-*g*]isoquinoline [**M3**]



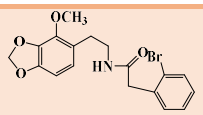
Scheme 1: Synthesis of Stephalagine alkaloid

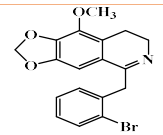
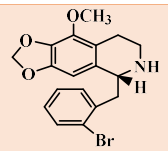
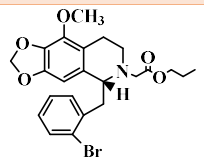
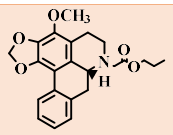
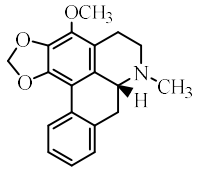
3. RESULTS and DISCUSSION

3.1 Characterization of Compounds [M1-M6]

The chemical structures of the synthesized compounds were characterized by their physical properties, shows table (1), FT-IR spectral absorption and ^{1}H NMR spectra.

Table (1): Physical properties of compounds (M1-M6).

Com. NO.	Molecular Structure	M.Wt	Color	M.p. °C	Yield%	Rf	(TLC) ethyl acetate : n-hexane
M1		392	Yellow	218-220	97	0.76	1:2

M2		374	Orange	284-286	93	0.77	1:2
M3		376	Light brown	280-281	64	0.65	1:1
M4		434	Black	206-207	74	0.7	1:2
M5		353	Dark Yellow	263-265	69	0.68	1:2
M6		309	Yellowish Orange	208-209	84	0.62	1:1

3.1.1 Characterization of Compound [M1]

FT-IR spectra (cm^{-1}): 3150 C-$H_{(arom.)}$,2998, 2883, C-$H_{(-OCH3)}$, 1688, -NH-C=O $_{(2^{\circ}\ amide)}$, 1470, C=C $_{(arom.)}$, 1230, 1087, C-O $_{(ether)}$, 650, C-Br

^{1}HNMR spectrum: 2.55(s,2H, =CH-CH_2), 3.38(2H,-CH_2-NH), 3.85(2H, CH_2-C=O), 3.85(s,3H,O-CH_3), 5.99(s,2H, O-CH_2-O) 6.75-6.96(m,5H, Aromatic protons), 8.23(s1H,NH, 2° Amide).

3.1.2 Characterization of Compound [M2]

FT-IR spectra (cm^{-1}): 3070 C-H $_{(arom.)}$, 2926 C-$H_{(-OCH3)}$, 1633 C=$N_{(imine)}$, 1525 C=C $_{(arom.)}$, 1227, 1010 C-O $_{(ether)}$, 670 C-Br.

^{1}HNMR spectrum: 2.87(s2H, =CH-CH_2) 3.61(s,2H, Ar-CH_2), 3.73(s,3H,O-CH_3), 3.85(s,2H,CH2-N), 6.03(s,2H, O-CH2-O) 6.79-7.6(m,5H, Aromatic protons).

3.1.3 Characterization of Compound [M3]

FT-IR spectra (cm^{-1}): 3300, N-$H_{(2^{\circ}\ amine)}$, 3090 C-$H_{(arom.)}$, 2943 C-$H_{(-OCH3)}$, 1604, C=C $_{(arom.)}$, 1395, C-N, 1247, 1074, C-O $_{(ether)}$, 640, C-Br.

^{1}HNMR spectrum: 1.80(s1H,NH), 2.83(s,2H, =CH-CH_2), 3.01(s,2H, Ar-CH_2), 3.18(s,2H, -CH_2-N), 3.51(s,3H,O-CH_3), 5.36(s,1H, -NH), 5.97(O-CH_2-O), 6.61-7.83(m,5H, Aromatic protons).

3.1.4 Characterization of Compound [M4]

FT-IR spectra (cm^{-1}): 3090 C-$H_{(arom.)}$, 2945, 2883 C-$H_{(-OCH3)}$, 1732 -C=$O_{2(ester)}$, 1602, C=C $_{(arom.)}$, 1394, C-N, 1260, 1126, C-O $_{(ether)}$, 620, C-Br.

^{1}HNMR spectrum: 2.18(s,2H, -CH_2-), 2.83(s,2H, N-CH_2), 2.98(s,2H, =CH-CH_2), 3.01(s,2H, Ar-CH_2), 3.33(s,2H, N-CH_2-CO), 3.46(s,3H,O-CH_3), 5.36(s,1H, -CH-N), 5.97(O-CH_2-O), 7.02-7.98(m,5H, Aromatic protons).

3.1.5 Characterization of Compound [M5]

FT-IR spectra (cm^{-1}): 3060 C-$H_{(arom.)}$, 2950, 2885 C-$H_{(-OCH3)}$, 1735 -C=$O_{2(ester)}$, 1660, C=C $_{(arom.)}$, 1390, C-N, 1300, 1220, C-O $_{(ether)}$.

^{1}HNMR spectrum: 2.18(s,2H, -CH_2-), 2.83(s,2H, N-CH_2), 2.98(s,2H, =CH-CH_2), 3.02(s,2H, Ar-CH_2), 3.40(s,2H, N-CH_2-CO), 3.69(s,3H,O-CH_3), 3.79(s,2H, CO-O-CH_2-), 4.95(s, 1H, N-CH), 6.26(O-CH_2-O), 7.19-7.61(m,5H, Aromatic protons).

3.1.6 Characterization of Compound [M6]

FT-IR spectra (cm^{-1}): 3082 C-$H_{(arom.)}$, 2974, 2937, 2880 C-$H_{(alph.)}$,1606, 1540 C=C $_{(arom.)}$, 1394, 1338 C-N, 1265, 1075 C-O $_{(ether)}$.

^{1}HNMR spectrum: 2.25(s,3H, N-CH_3-), 2.55(s,2H, N-CH_2), 2.68(s,2H, =CH-CH_2), 3.02(s,2H, Ar-CH_2), 3.55(s,3H,O-CH_3), 3.79(s,2H, CO-O-CH_2-), 4.23(s, 1H, N-CH), 5.97(O-CH_2-O), 7.10-7.36(m,4H, Aromatic protons).

3.2 DISCUSSION

Compound [M1] was successfully prepared from (2-(4-methoxybenzo[d][1,3]dioxol-5-yl)ethan-1-amine) and (2-bromophenylacetyl chloride) and identified by FT-IR spectral that shows the disappearance of NH_2 group at 3420 Cm^{-1} and the appearance of O=CNH group at 1688 cm^{-1}, which is indicative of the formation of the amidic linkage. In addition the ^{1}HNMR spectrum gives significant chemical shift at 2.55($_S$,2H, =CH-CH_2), 3.38(2H,-CH_2-NH), 3.85(2H, CH_2-C=O), 3.85(s,3H,O-CH_3), 5.99($_S$,2H, O-CH_2-O) 6.75-6.96(m,5H, Aromatic protons), 8.23(s1H,NH, $_{2^\circ Amide}$). Which support formation of the [M1] Chemical structure. [M2] was prepared in good yield by the reaction of compound [M1] with phosphorous oxalyl chloride. The structure was confirmed by the FT-IR spectrum which shows the disappearance of the amidic group at 1688 cm and the appearance of the azomethine group -C=N- at 1633 Cm. The HNMR spectrum of the [M2] compound shows clear chemical shift at 2.87(s2H, =CH-CH_2) 3.61(s,2H, Ar-CH_2), 3.73(s,3H,O-CH_3), 3.85(s,2H,CH_2-N), 6.03(s,2H, O-CH_2-O) 6.79-7.6(m,5H, Aromatic protons). Which give good prove for the chemical structure of compound [M2]. The preparation of compound [M3] was achieved by the reaction of compound [M2] with dimeric dichloro (P-Cymene) ruthenium (ii). The structure of compound was assured the reduction of C=N at 1633 Cm^{-1} to give a secondary cyclic amino group at 3300 cm^{-1}. The ^{1}HNMR Spectrum shows the chemical shift of the different protons bonds at 1.80(s1H,NH), 2.83(s,2H, =CH-CH_2), 3.01(s,2H, Ar-CH_2), 3.18(s,2H, -CH_2-N), 3.51(s,3H,O-CH_3), 5.36(s,1H, -NH), 5.97(O-CH_2-O), 6.61-7.83(m,5H, Arom. protons) indicative of the formation of the compound. The reaction of [M3] with propyl chloroacetate gave compound [M4] in good yield. The FT-IR spectrum shows the formation of the ester group C-O at 1735 cm^{-1}. The ^{1}HNMR spectrum show proton chemical shifts at 2.18(s,2H, -CH_2-), 2.83(s,2H, N-CH_2), 2.98(s,2H, =CH-CH_2), 3.01(s,2H, Ar-CH_2), 3.33(s,2H, N-CH_2-CO), 3.46(s,3H,O-CH_3), 5.36(s,1H, -CH-N), 5.97(O-CH_2-O), 7.02-7.98(m,5H, Aromatic protons). The spectral data give good evidence for the formation of the compound. The compound [M5] was obtained from the intramoleculer cyclization of [M4] by using palladium acetate $Pd(OAc)_2$ in good yield. Its FT-IR spectrum shows the disappearance of C-Br at 620 cm^{-1}. The ^{1}HNMR spectrum of the compound

shows the significant proton chemical shifts at 2.18(s,2H, -CH_2-), 2.83(s,2H, N-CH_2), 2.98(s,2H, =CH-CH_2), 3.02(s,2H, Ar-CH_2), 3.40(s,2H, N-CH_2-CO), 3.69(s,3H,O-CH_3), 3.79(s,2H, CO-O-CH_2-), 4.95(s, 1H, N-CH), 6.26(O-CH_2-O), 7.19-7.61(m,5H, Aromatic protons). Supporting the suggested structure of the compound. The target compound stephalagine [M6] was obtained from the reduction of compound [M5] by using methyl lithium aluminium tetrahydride as strong reducing agent. The FT-IR spectrum of the compounds shows the disappearance of the ester group at 1735 cm^{-1}. The ^{1}HNMR spectrum shows the proton chemical shifts at 2.25(s,3H, N-CH_3-), 2.55(s,2H, N-CH_2), 2.68(s,2H, =CH-CH_2), 3.02(s,2H, Ar-CH_2), 3.55(s,3H,O-CH_3), 3.79(s,2H, CO-O-CH_2-), 4.23(s, 1H, N-CH), 5.97(O-CH_2-O), 7.10-7.36(m,4H, Aromatic protons) the spectral data gave adequate evidence for the formation of the compound.

4. Conclusion

New organic compounds were prepared and identified from some raw materials to be similar to the substances found in Annona Crassiflora fruit, by accessing the proven results in this research, as they were diagnosed by the methods used in the identification of organic compounds in the latest devices.

References

[1] Formagio, A.S., Vieira, M.C., Volobuff, C.R., Silva, M.S., Matos, A.I., Cardoso, C.A.,Foglio, M.A., Carvalho, J.E., In vitro biological screening of the anticholinesterase and antiproliferative activities of medicinal plants belonging to Annonaceae. Braz. J. Med. Biol. Res, 2015. 48, 308–315. https://doi.org/10.1590%2F1414-431X20144127.

[2] Arruda, H.S., and Pastore, G.M. Araticum (Annona crassiflora Mart.) as a source of nutrients and bioactive compounds for food and non-food purposes: A comprehensive review. Food Research International, 2019.123, 450-480. https://doi.org/10.1016/j.foodres.2019.05.011

[3] Justino, A.B., Pereira, M.N., Vilela, D.D., Peixoto, L.G., Martins, M.M., Teixeira, R.R., Miranda, N.C., da Silva, N.M., de Sousa, R.M.F., de Oliveira, A., Espindola, F.S., Peel of araticum fruit (Annona crassiflora Mart.) as a source of antioxidant compounds with -amylase, -glucosidase and glycation inhibitory activities. Bioorg. Chem, 2016. 69, 167–182. https://doi.org/10.1016/j.bioorg.2016.11.001.

[4] Aguilar-Hernández. G., Zepeda-Vallejo L.G., García-Magaña. M.D., Vivar-Vera. M.D.A., Pérez-Larios. A., Girón-Pérez M. I., Coria-Tellez A. V., Aguayo C. -R, Montalvo-González .E., Extraction of Alkaloids Using Ultrasound from Pulp and By-Products of Soursop Fruit (Annona muricata L.). *Appl. Sci.* **2020**, *10*(14), 4869; https://doi.org/10.3390/app10144869.

[5] Roberts, M. F., Wink, M, Alkaloids: Biochemistry, Ecology, and Medicinal Applications. Boston: Springer US, 1st ed. 1998

[6] Kittakoop, P., Mahido, C., Ruchirawat. S., Alkaloids as Important Scaffolds in Therapeutic Drugs for the Treatments of Cancer, Tuberculosis, and Smoking Cessation. Current Topics in Medicinal Chemistry, 2014. 14, 239-252. https://doi.org/10.2174/1568026613666131216105049.

[7] Bhambhani S., Kondhare K.R., Giri., P A. Diversity in Chemical Structures and Biological Properties of Plant Alkaloids. Molecules. 2021. 26(11): 3374. https://doi:10.3390/molecules26113374.

[8] Ain, Q-U., Khan, H., Mubarak, MS., Pervaiz, A. Plant Alkaloids as Antiplatelet Agent: Drugs of the Future in the Light of Recent Developments. Front. Pharmacol, 2016. 7, 292. https://doi:10.3389/fphar.2016.00292

[9] Kupnicka, p., Kojder, K., Metryka, E., Kapczuk, P., Jeżewski, D., Gutowska, I., Goschorska, M., Chlubek, D., Bosiacka, I., B., Morphine-element interactions – The influence of selected chemical elements on neural pathways associated with addiction**,** Journal of Trace Elements in Medicine and Biology**,** 2020. 60,126495. https://doi.org/10.1016/j.jtemb.2020.126495

[10] Dhyani P., Quispe C., Sharma E., Bahukhand A., Sati P, Attri. D. C., Szopa A., Sharifi-Rad J., Docea A.O., Mardare I., Calina. D., Cho W.C . Anticancer potential of alkaloids: a key emphasis to colchicine, vinblastine, vincristine, vindesine, vinorelbine and vincamine. Cancer Cell International, 2022. 22, 206. https://doi.org/10.1186/s12935-022-02624-9.

[11] Dousari. A. S., Satarzadeh. N, Amirheidari. B., Forootanfar H, Medicinal and Therapeutic Properties of Ephedra. Revista Brasileira de Farmacognosia, 2022. 32, 883-899. https://doi.org/10.1007/s43450-022-00304-3.

[12] Souza C. R. M., Wallace P. Bezerra, and Janeusa T. Souto. Marine Alkaloids with Anti-Inflammatory Activity: Current Knowledge and Future Perspectives. 2020. 18, 147. https://doi.org/10.3390/md18030147 .

[13] Obonyo C.O, Ogutu. B. R. Quinine plus clindamycin vs artemether-lumefantrine for treatment of uncomplicated falciparum malaria in western Kenya. Malaria Journal. 2022, 21, 198. https://doi.org/10.1186/s12936-022-04222-6.

[14] Omar, F., Tareq, A. M., Alqahtani, A. M., Dhama, K., Sayeed, M. A., Emran, T. B., Simal-Gandara, J, Roles of Alkaloids from Medicinal Plants in the Management of Diabetes Mellitus. Molecules. 2021. *26*(8), https://doi.org/10.3390/molecules26082297.

[15] Zhang H., Zhang, C., Han, Y., Wainberg M. A., Yue, J., New Securinega alkaloids with anti-HIV activity from Flueggea virosa, RSC Adv, 2015. https://doi.org/10.1039/C5RA22191A.

[16] Adhikari, B., Roles of Alkaloids from Medicinal Plants in the Management of Diabetes Mellitus, Journal of Chemistry, 2021. 2691525. https://doi.org/10.1155/2021/2691525

[17] Bernardes, A. C. F. P. F., Araújo, M. C. D. M., Barros, C. H., Soares, R. D. D. A., Costa, D. C., Guimaraes, D. A. S., Sesquiterpene lactones from Lychnophora species: Antinociceptive, Journal of Ethnopharmacology, 2021. https://doi.org/10.1016/j.jep.2020.113738.

[18] Wang, F.-X.; Zhu, N.; Zhou, F.; Lin, D.-X. Natural Aporphine Alkaloids with Potential to Impact Metabolic Syndrome, Molecules, 2021. 26, 6117. https://doi.org/10.3390/

[19] Kathrin Laura Kohnen-Johannsen and Oliver Kayser, Tropane Alkaloids: Chemistry, Pharmacology, Biosynthesis and Production. Molecules. 2019. 24, 796; https://doi:10.3390/molecules24040796.

[20] Pereira. M . Nunes., Justino A. B., Martins. M. M., Peixoto. L. G., Vilela D. D., Santos P.S., Teixeira T. L., da Silva C. V., Goulart L. R., Pivatto M., Espindola F. S., Stephalagine, an alkaloid

with pancreatic lipase inhibitory activity isolated from the fruit peel of Annona crassiflora Mart., Industrial Crops and Products. 2017. 97, 324-329. https://doi.org/10.1016/j.indcrop.2016.12.038.