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SYNTHESIS OF DERIVATIVES OF BETULINIC AND URSOLIC ACIDS ISOLATED FROM *COMBRETUM GLUTINOSIUM* PERR. EX DC (COMBRETACEAE) AND *MORINDA GEMINATA* DC (RUBIACEAE)

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ABSTRACT
Betulinic and ursolic acid isolated from the leaves of *Combretum glutinosium* Perr. Ex DC (Combretaceae) and *Morinda geminata* DC (Rubiaceae) have been used in fine chemistry. A coupling reaction with acid chlorides and/or HOBT has been successfully used for the synthesis of molecules derived from betulinic and ursolic acid. The semisynthesis of a set of small molecules derived from these promising compounds by pseudopeptide coupling is also reported. The obtained molecules were characterized by NMR and IR.

KEYWORDS: Betulinic acid, Ursolic acid, esterification.

INTRODUCTION

Combretum glutinosum Perr.Ex DC and *Morinda geminata DC* (Rubiaceae) are Senegalese traditional pharmacopoeia plants whose leaves are used in the treatment of various diseases. They are widely used therapeutically in Senegal, particularly in the Casamance region. This study of isolation[1,2] and characterization of secondary metabolites present in the leaves was undertaken with a view to understanding the therapeutic activity of these plants.

This part was motivated on the one hand by the desire to enhance and promote medicinal plants from Senegal, with a view to facilitating access for populations to traditionally improved medicines at lower cost and with fewer side effects, and on the other hand by the need to objectify or invalidate the traditional uses of Combretum glutinosum Perr. ex DC and *Morinda geminata* DC (Rubiaceae), plants of the Senegalese pharmacopoeia.

Betulonic acid, a triterpene compound isolated from plants used in traditional medicine, has been the subject of several studies. Terpenes isolated from the roots of several plant families have a wide range of biological activities, including antimicrobial and anti-plasmodial activity.[3] Studies have shown that a number of terpenes and terpene derivatives isolated from various sources, such as plants, kill *P. falciparum* parasites.[4-6] Betulinic acid derivatives with lupane skeleton are very interesting for the development of therapeutic agents respectively.[7] Betulonic acid has been isolated from Birch plants (butulaceae), Propolis Brazilian,[8] Ainsliaea acerifolia (compositae)[9] etc., which due to its bioactive interest has been the subject of several syntheses[9-10] from its derivative betulinol[11-12] or betulinic acid.[13-14] Other previous studies have shown that it has anti-prostate,[15] anti-HIV,[8] anti-cancer, antiviral, anti-inflammatory[9] activity.

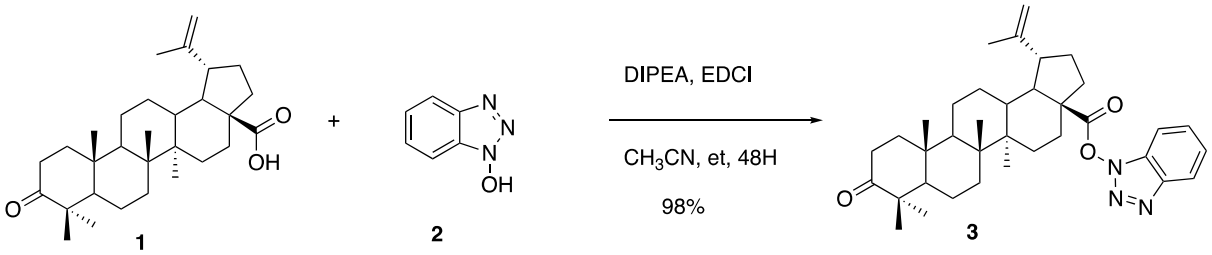
Ursolic acid is found naturally in many plants, such as apple peels, Sarraceniaceae, Plantaginaceae and Ericaceae.[16-19] It exists in the form of aglycone or glycosides in triterpene saponins.[19] Great interest has developed around ursolic acid due to its beneficial effects due in particular to its anti-inflammatory, anticancer and antioxidant properties.[20-23] Derivatives also obtained by reactions between 1,2-dibromoethane and ursolic acid showed a higher inhibitory concentration than ursolic acid.[24] In addition to being widely studied in organic chemistry, ursolic acid is a molecule of interest in the field of cosmetics. Indeed, it has interesting anti-inflammatory and antioxidant activity.[25-26] Ursolic acid inhibits elastase activity and stimulates collagen synthesis, which may help prevent degradation of the extracellular matrix of the dermis.[27-29]

In this manuscript, we report a new approach to pharmacomodulation through coupling reactions of natural molecules isolated from plants of the Senegalese pharmacopoeia. Therefore, we chose betulonic acid isolated from the leaf of *Combretum glutinosium*[1] and ursolic acid isolated from the leaves of *Morinda geminate*.[2] These will be coupled by cinnamic acids, cynnamoyl chlorides and other heterocycles.

MATERIALS AND METHODS

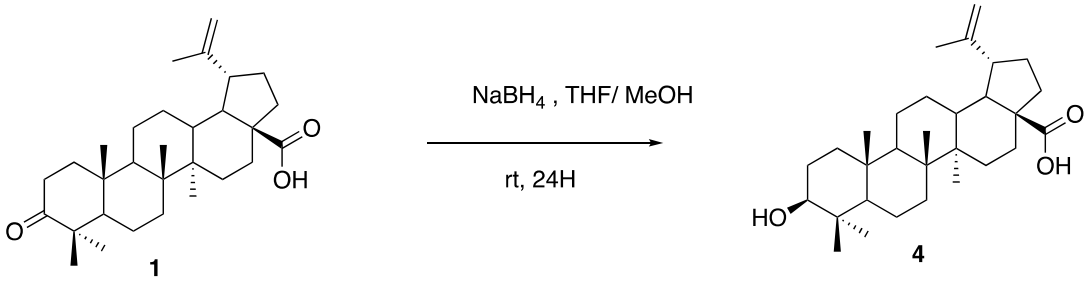
Methode and discussion of synthesis of the molecules studied

In this study we used betulinic and ursolic acid isolated in our Laboratory[1,2] as raw material. In order to synthesize derivatives of betulinic acid **1**, we carried out a coupling reaction between betulinic acid and Hydroxybenzotriazole (HOBT) **2** in the presence of EDCI in acetonitrile which provided compound **3** (98%) (Scheme 1). Molecule **3** was characterized based on the analysis of NMR spectra (^{1}H and ^{13}C).



Scheme 1: Synthesis of compound 3 derived from betulinic acid 1.

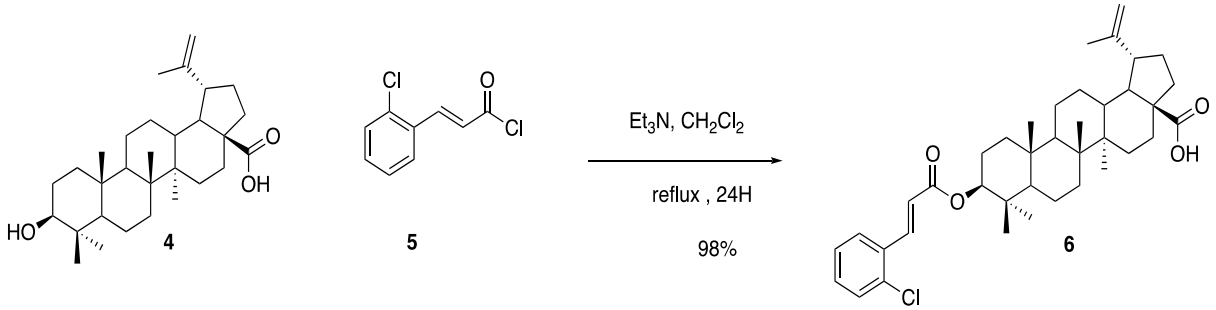
After this synthesis, we directed the modification to the ketone function of betulinic acid. Thus, the ketone function of betulinic acid was reduced by $NaBH_4$ in tetrahydropyran to provide betulinic acid **4** (94%) (Scheme 2). This reduction provides molecule **4** for pharmaco-modulation around the alcohol function.



Scheme 2: Synthesis of alcohol 4 derived from betulinic acid 1.

The resulting alcohol **4** was then further modulated by coupling reactions described below. Condensation of alcohol **4** with 2-chlorocinnamoyl **5** in the presence of triethylamine in dichloromethane afforded compound **6** (98%) (Scheme 3). Molecule **6** was characterized on the basis of NMR (^{1}H and ^{13}C) and IR spectrum analysis.

The ^{1}H proton spectrum shows the presence of two ethylenic CH at 6.48 and 8.73 ppm, a CH at the foot of the oxygen at 4.7ppm, and signals from the aromatic ring. On the IR spectrum (Fig. 1), we observe the vibration of a hydroxyl group of the acid at 3271 cm^{-1} by a broad band. At around 1682 cm^{-1}, there's an intense band corresponding to the CO of the acid and another at around 1621 cm^{-1} corresponding to the CO of a conjugated ester, justifying the formation of compound **6**.



Scheme 3: Synthesis of compound 6 derived from betulinic alcohol 4.

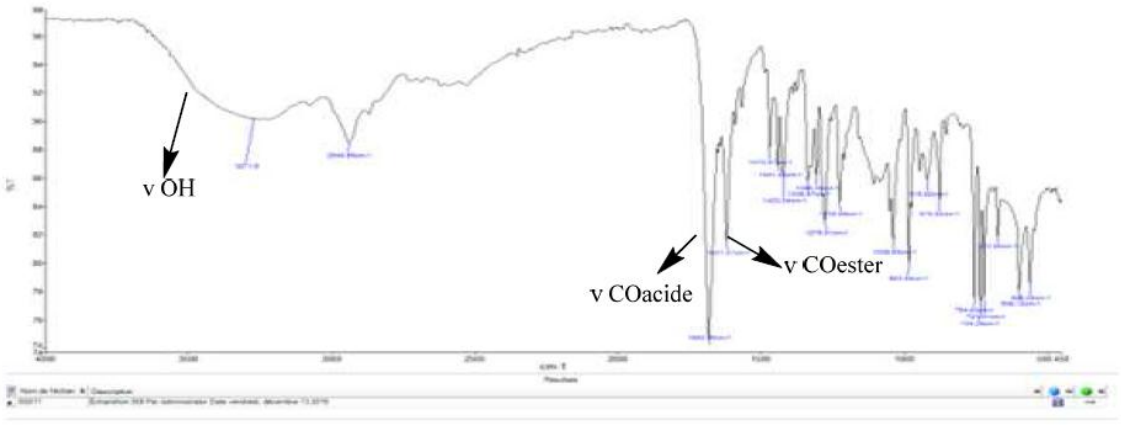
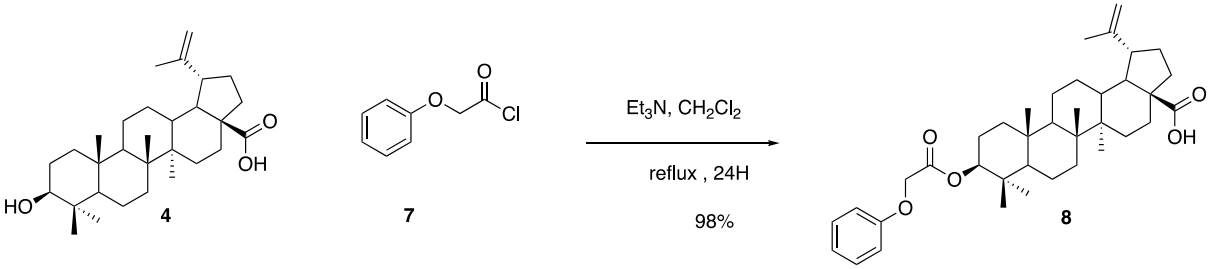


Fig. 1: IR spectrum of compound 6.

Condensation of betulonic alcohol **4** with phenoxyacetyl chloride **7** using triethylamine in dichloromethane led to compound **8** (94%) after purification on silica gel chromatography with cyclohexane/ethyl acetate (7/3) as eluent (Scheme 3). Compound **8** was characterized by NMR and IR. Analysis of the NMR spectrum shows the presence of two signals at 4.67 ppm and 4.75 ppm corresponding to the ethylenic CH_2 and the CH_2 respectively, linked to the phenoxy group. On this proton spectrum, at 4.75 ppm we observe a signal in the form of a quadruplet with a roof effect that is nothing other than an AB system justifying the $PhOCH_2CO_2X$ motif. The doublet at 4.6 ppm is the signal of the ethylenic group characteristic of the triterpene system of the lupane family. The carbon spectrum shows signals at 168.2 ppm characteristic of the CO of an ester, justifying the coupling between molecule **4** and **7**, and at 177.28 ppm characteristic of the CO of an acid. Hence the formation of molecule **8**. The IR spectrum shows a ν (C=O) vibration at 1727 cm^{-1} characteristic of a (CO acid) and a ν (CO) vibration at 1684 cm^{-1} characteristic of a CO ester.



Scheme 4: Synthesis of compound 8 derived from betulinic alcohol 4.

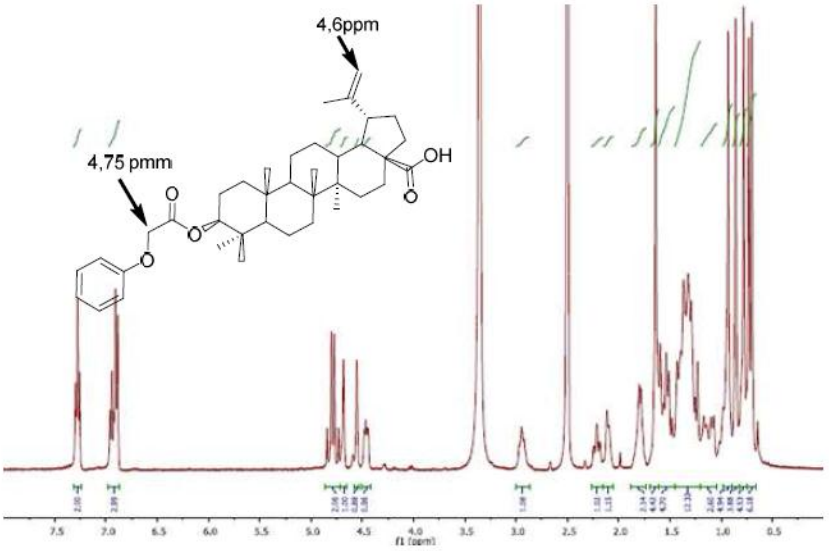
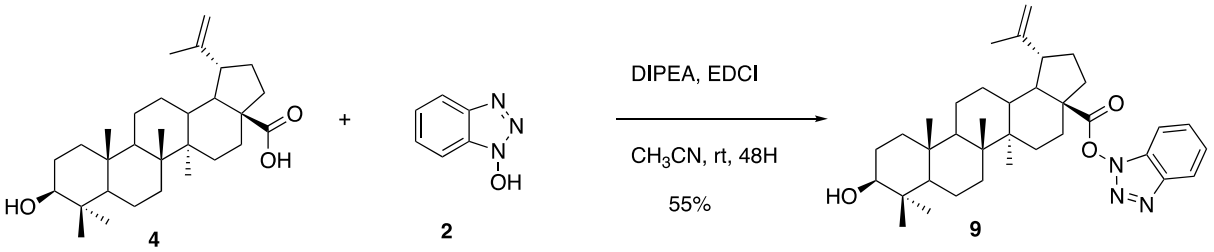


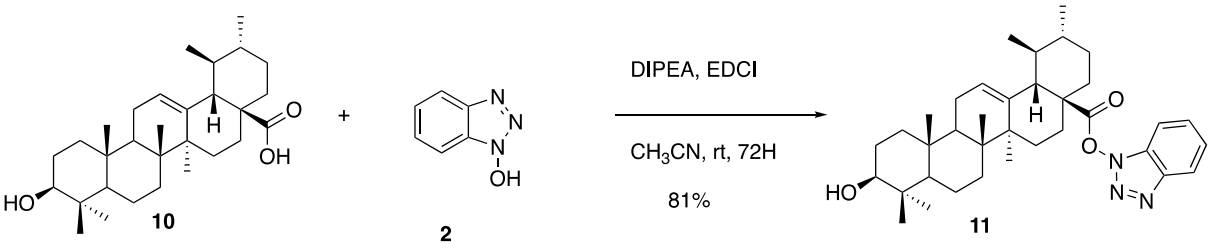
Fig. 2: Proton spectrum of compound 8.

Coupling of betulinic alcohol **4** with HOBT **2** using EDCI and DIPEA as coupling agent in THF at room temperature led to compound **9** (55%) after purification by silica gel chromatography with the eluent Cyclohexane/Ethyl acetate (7/3).



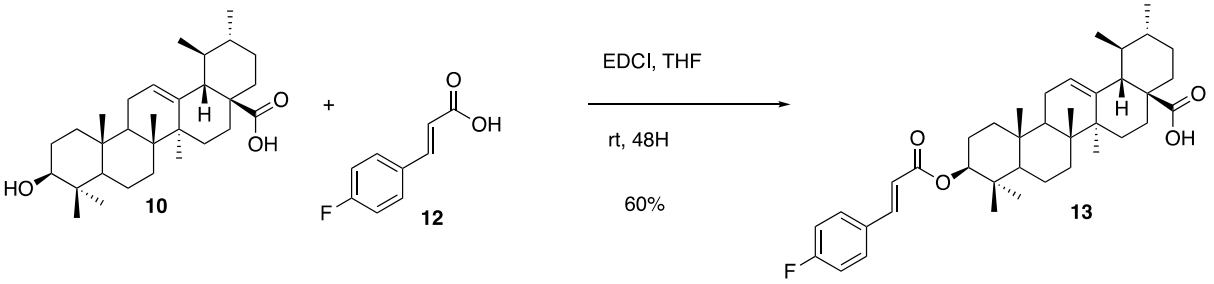
Scheme 5: Synthesis of compound 9 derived from betulinic alcohol 4.

Ursolic acid is also of great interest for its cytotoxic, hypoglycemic, analgesic and chemopreventive potential.[22-28] It's with this in mind that, we have been interested in the synthesis of ursolic acid derivatives in order to couple them with other molecules and explore this synergy. The coupling reaction between ursolic acid **10** and HOBT **2** in the presence of EDCI and Et_3N in THF (Tetrahydrofuran) at room temperature afforded compound **11** (81%) (Scheme 5). Compound formation was confirmed on the basis of NMR and IR spectrum analysis.



Scheme 6: Synthesis of compound 11 derived from ursolic acid 10.

The coupling reaction of ursolic acid with 4-fluoro cinnamic acid **12** using EDCI and triethylamine in THF (Tetrahydrofuran) afforded compound **13** (60%) (Scheme 6).



Scheme 7: Synthesis of compound 13 derived from ursolic acid 10.

Experimental Details of the synthesis of Molecules

Experimental section

^1H and ^{13}C NMR spectra were recorded at room temperature on a BRUKER UltraShield 500 spectrometer and tetramethylsilane (TMS) was used as internal reference. ^1H analyses were obtained at 300 MHz and ^{13}C analyses at 125 MHz. Chemical shifts δppm are expressed in parts per million relatives to TMS (δppm= 0.00). Different deuterated solvents were used depending on the solubility of the products. For ^1H spectra, the abbreviations s, d, t, q, dd and m refer to signals in singlet, doublet, triplet, quadruplet, split doublet and multiplet form. Coupling constants J are expressed in Hertz (Hz). The infrared spectra have been recorded on a spectrometer Perkin-Elmer 842 (reference: polystyrene).

Reactions were monitored by Macherey-Nagel Polygram Sil G/ UV254 silica gel thin-layer chromatography (TLC), and products were detected under ultraviolet illumination at 254 nm. Product purification by column chromatography was carried out on silica gel (Merck Kieselgel 60).

1H-benzo[d][1,2,3]triazol-1-yl (1R,3aS,5aR,5bR,11aR)-5a,5b,8,8,11a-pentamethyl-9-oxo-1-(prop-1-en-2-yl)icosahydro-3aH-cyclopenta[a]chrysene-3a-carboxylate (***3***)

Betulinic acid (0.456 g, 0.798 mmol), EDCI.HCl (1.810 mmol, 0.347 g), Hydroxybenzotriazole (HOBT.H_2O)

(4.163 mmol, 0.562 g) and DIPEA (0.8 ml) are successively added to a 50 mL flask containing acetonitrile (5 mL). The reaction was kept under stirring for 48 h under nitrogen pressure at room temperature. After 48 h stirring, the reaction is treated with 80 mL 10% hydrochloric acid and 80 mL ethyl acetate, then the aqueous phase is washed once with 50 mL ethyl acetate. The organic phases are combined and washed successively with 80 mL saturated $NaHCO_3$, 80 mL saturated NaCl and 80 mL water. The organic phases are reunited and dried with $MgSO_4$, then concentrated in vacuo. The residue was purified by silica gel chromatography in petroleum ether/ethyl acetate eluent (8/2). It was concentrated by steam rota to give compound **3** (0.447g; 98%).

(1R,3aS,5aR,5bR,9S,11aR)-9-hydroxy-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)icosahydro-3aH-cyclopenta[a]chrysene-3a-carboxylic acid (***4***)
In a 100 mL flask containing 2.5 mL methanol and 2.5 mL THF, 200 mg (0.440 mmol) betulinic acid **1** and 66.54 mg (1.760 mmol) $NaBH_4$ were introduced. After 24 h stirring at room temperature under nitrogen, 10 mL of 10% HCl and 10 mL of ethyl acetate were added. The aqueous phase is washed with 3×3 mL ethyl acetate. The organic phases are combined, dried over $MgSO_4$ and concentrated under reduced pressure to give compound **4** (0.188 g; 94%) after purification on silica gel with cyclohexane/ethyl acetate eluent (Cycl/AcOEt (7/3)).

(1R,3aS,5aR,5bR,9S,11aR)-9-(((E)-3-(2-chlorophenyl)acryloyl)oxy)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)icosahydro-3aH-cyclopenta[a]chrysene-3a-carboxylic acid (***6***)
In a 100 mL flask containing dichloromethane (3 mL) are successively added 0.15 g (0.330 mmol) of betulinic acid and 0.130 g (0.660 mmol) of 2-chlorocynnamoyl chloride in the presence of triethylamine (0.5 mL). The reaction is followed under argon stirring at reflux overnight. At the end of the reaction, 10 mL of water and 10 mL of ethyl acetate are added. The aqueous phase is extracted with 3×5 mL ethyl acetate. The organic phases were combined, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was crystallized in hexane to give a white powder **6** weighing 0.2 g (98%).

(1R,3aS,5aR,5bR,9S,11aR)-5a,5b,8,8,11a-pentamethyl-9-(2-phenoxyacetoxy)-1-(prop-1-en-2-yl)icosahydro-3aH-cyclopenta[a]chrysene-3a-carboxylic acid (***8***)
0.15 g (0.330 mmol) of betulinic acid and 0.110 g (0.660 mmol) of phenoxy chloride are successively added in the presence of triethylamine (0.5 mL) in a 100 mL flask containing dichloromethane (3 mL). After stirring under nitrogen at reflux overnight, 10 mL of water and 10 mL of ethyl acetate are added. The aqueous phase is extracted with 3×5 mL ethyl acetate. The organic phases were combined, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel chromatography with the eluent Cycl/AcOEt (9/1) to give a white powder 8 (94%).

1H-benzo[d][1,2,3]triazol-1-yl (1R,3aS,5aR,5bR,9S,11aR)-9-hydroxy-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)icosahydro-3aH-cyclopenta[a]chrysene-3a-carboxylate (***9***)
In a 50 mL flask, 150 mg (0.26 mmol) betulinic acid, Hydroxybenzotriazole $HOBT.H_2O$ (0.598 mmol, 0.081 g) in the presence of DIPEA (0.5 mL) and EDCI.HCl (0.590 mmol, 0.113 g) are added successively in THF. The reaction is stirred under argon at room temperature for 48 h. After 48 h of stirring, 10 mL ethyl acetate and 5 mL water are added to the reaction medium; the organic phase is recovered and the aqueous phase washed with 3×5 mL ethyl acetate. The organic phases are combined and dried over $MgSO_4$, then evaporated. The residue is purified by silica gel chromatography (Cycl/AcOEt 3/7 and 5/5). The product is obtained as a white powder **9** (825 mg, 55%).

1H-benzo[d][1,2,3]triazol-1-yl(1S,2R,4aS,6aS,6bR,10S,12aR,14bS)-10-hydroxy-1,2,6a,6b,9,9,12a-heptamethyl-1,3,4,5,6,6a,6b,7,8,8a,9,10,11,12,12a,12b,13,14b-octadecahydropicene-4a(2H)-carboxylate (***11***)
In a 50 mL flask, 100 mg (0.218 mmol) ursolic acid and 29.577 mg (0.218 mmol) Hydroxybenzotriazole (HOBT), 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide. HCl (EDCI.HCl) (0.495 mmol, 0.095 g) and triethylamine (0.5 mL) are successively introduced into tetrahydrofuran (THF). After 72 h stirring under nitrogen at room temperature, 10 mL AcOEt and 10 mL distilled water are added. The organic phase is recollected and the aqueous phase extracted with 2 mL AcOEt. The organic phases are combined and dried over $MgSO_4$. After evaporation, the residue was purified (Cycl/AcOEt (7/3)). The product obtained from this reaction is a green powder **11**, with a yield of 81.21%.

(1S,2R,4aS,6aS,6bR,10S,12aR,14bS)-10-(((E)-3-(4-fluorophenyl)acryloyl)oxy)-1,2,6a,6b,9,9,12a-heptamethyl-1,3,4,5,6,6a,6b,7,8,8a,9,10,11,12,12a,12b,13,14b-octadecahydropicene-4a(2H)-carboxylic acid (***13***)
150 mg (0.328 mmol) of ursolic acid, 54.570 mg (0.3284 mmol) of 4-fluoro cinnamic acid, DIPEA (0.5 mL) and EDCI.HCl (0.143 g, 0.745 mmol) in acetonitrile (5 mL) are successively added in a 100 mL flask. After 48 h stirring under nitrogen at room temperature, 10 mL ethyl acetate and 5 mL water are added to the reaction medium. The organic phase is recollected and the aqueous phase washed with 3×5 mL AcOEt. The organic phases were combined and dried over $MgSO_4$, then evaporated in vacuo and the residue purified on gel chromatography (Cycl/AcOEt (7/3)), yielding compound **13** (90 mg, 60%).

RESULTATS AND DISCUSSION

Charactérisation of Sunthetic Molecules

1H-benzo[d][1,2,3]triazol-1-yl (1R,3aS,5aR,5bR,11aR)-5a,5b,8,8,11a-pentamethyl-9-oxo-1-(prop-1-en-2-yl)icosahydro-3aH-cyclopenta[a]chrysene-3a-

carboxylate (***3***)
IR (Cm^{-1}): 1850 cm^{-1} ν (CO), 1680 cm^{-1} ν (CO ester), 1660 cm^{-1} ν (C=C).
^{1}H-NMR ($CDCl_3$, 500 MHz) δ(ppm): 4.75 (d, 2H, CH_2); 7.50 (m, 4H, CH_{Ar},); 0.50-1.50 (m ,15H, $5CH_3$); 3.75 (s, 1H, CH,); 3 (dt, J=6.45, 7.8Hz, 1H, CH); 2.23 (dt, J=6.45, 7.8Hz, 1H, CH,); 1.63 (dd,1H, J=6.45, 6.50Hz, CH); 2.65 (m, 2H, CH_2).

^{13}C-NMR ($CDCl_3$, 125 MHz) δ(ppm): 14.80 (CH_3); 16.10 (CH_3); 17.3 (CH_3); 19.10 (CH_3); 19.22 (CH_3); 19.50 (CH_2); 21.45 (CH_2); 25.05 (CH_2); 26.75 (CH_3); 29.80 (CH_2); 30.08 (CH_2); 30.11 (CH_2); 30.65 (CH_2); 31.50 (C); 33.8 (CH_2); 34.20 (C); 36.83 (CH_2); 39.10 (CH_2); 46.98 (C); 47.4 (C); 50.01 (CH); 50.15 (CH); 52.03 (C); 53.15 (CH); 55.12 (CH); 55.33 (CH); 108.02 (CH_{Ar}), 110.91 (=CH_2); 120.85 (CH_{Ar}); 124.83 (CH_{Ar}); 128.84 (CH_{Ar}); 129.03 (C_{Ar}); 149.32 (C); 143.75 (C_{Ar}); 171.91 (CO); 218.15 (CO).

(1R,3aS,5aR,5bR,9S,11aR)-9-hydroxy-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)icosahydro-3aH-cyclopenta[a]chrysene-3a-carboxylic acid (***4***)
IR (Cm^{-1}): 3373 cm^{-1} ν (OH alcohol/acid), 1701 cm^{-1} ν (CO acid), 1665 cm^{-1} ν (C=C).
^{1}H-NMR ($CDCl_3$, 500 MHz) δ(ppm): 0.75 (m, 6 H, 3 CH_2); 0.81 (m, 4 H, $2CH_2$); 0.86 (s, 3H, CH_3); 0.92 (m, 4 H, $2CH_2$); 1.12 (m, 2H, 2CH); 1.32 (s, 12 H, $4CH_3$); 1.51 (m, 4H, $2CH_2$); 1.60 (m, 3H, CH_3); 1.80 (m, 2H, CH_2); 2.15 (d, J=6.45, 1H, CH); 3.34 (t, J=7.45, 1H, CH).

^{13}C-NMR ($CDCl_3$, 125 MHz) δ(ppm): 14.83 (CH_3); 15.50 ($2CH_3$); 16.27 (CH_3); 18.43 (CH_2); 19.50 (CH_3); 20.98 (CH_2); 25.63 (CH_2); 26.34 (CH_2); 27.51 (CH_2); 28.12 (CH_3); 29.82 (CH_2); 30.68 (CH_2); 32.27 (CH_2); 34.45 (CH_2); 37.33 (CH_2); 38.84 (2C); 39.04 (C); 40.83 (C); 47.02 (CH); 49.37 (CH); 50.67 (CH); 52.25 (CH); 55.47 (CH); 56.80 (C); 80.65 (CH-O); 110.92 (=CH_2); 142.83 (C); 170.98 (CO).

(1R,3aS,5aR,5bR,9S,11aR)-9-(((E)-3-(2-chlorophenyl)acryloyl)oxy)-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)icosahydro-3aH-cyclopenta[a]chrysene-3a-carboxylic acid (***6***)
IR (Cm^{-1}): 3271 cm^{-1} ν (OH acid), 1682 cm^{-1} ν (CO acid), 1621 cm^{-1} ν (CO ester conjugated).
^{1}H-NMR ($CDCl_3$, 500 MHz) δ(ppm): 0.75 (m, 6 H, $3CH_2$); 0.81 (m, 4H, $2CH_2$); 0.86 (m, 3H, CH_3); 0.92 (m, 4H, $2CH_2$); 1.12 (m, 2H, 2CH); 1.32 (m, 12H, $4CH_3$); 1.51 (m, 4 H, $2CH_2$); 1.65 (m, 3H, CH_3); 1.80 (m, 2H, CH_2); 2.15 (d, 1H, J=6.45 Hz, CH); 2.25 (t, J=6.75Hz, 1H, CH); 2.92 (m, 1H, CH); 4.94 (t, J=6.85Hz, 1H, O-CH); 4.67-4.70 (2 s, 2H, CH_2); 6.48 (d, J=7.5Hz, 1H, CH); 6.92 (m, 3H, $3CH_{Ar}$); 7.27 (m, 2H, $2CH_{Ar}$); 8.73 (m, 1 H, CH).

^{13}C-NMR ($CDCl_3$, 125 MHz) δ(ppm): 14.83 (CH_3); 15.50 ($2CH_3$), 16.15 (CH_2); 16.27 (CH_3); 18.43 (CH_2); 19.50 (CH_3); 20.98 (CH_2); 25.63 (CH_2); 27.51 (CH_2); 28.12 (CH_3); 29.82 (CH_2); 30.68 (CH_2); 32.27 (CH_2); 34.45 (CH_2); 37.33 (CH_2); 38.84 (2C); 39 (C); 40.83 (C); 42.57 (CH); 47.02 (CH); 49.37 (CH); 50.67; (CH); 55.47 (CH); 56.50 (C); 79.19 (CH-O); 109.86 (=CH_2); 119.86 (=CH-); 127.35 (CH_{Ar}); 127.95 (CH_{Ar}); 130.40 (CH_{Ar}); 131.62 (CH_{Ar}); 132.45 (C-Cl); 135.35 (C); 140.91 (=CH-); 142.83 (C); 150.56 (CO); 170.98 (CO).

(1R,3aS,5aR,5bR,9S,11aR)-5a,5b,8,8,11a-pentamethyl-9-(2-phenoxyacetoxy)-1-(prop-1-en-2-yl)icosahydro-3aH-cyclopenta[a]chrysene-3a-carboxylic acid (***8***)
IR (Cm^{-1}): 1727 cm^{-1} ν(C=O acid), 1684 cm^{-1} ν (CO ester).
^{1}H-NMR ($CDCl_3$, 500 MHz) δ(ppm): 0.70 (m, 6H, $3CH_2$); 0.81 (m, 4H, $2CH_2$); 0.86 (m, 3H, CH_3); 0.92 (m, 4H, $2CH_2$); 1.12 (m, 2H, 2CH); 1.32 (m, 12H, $4CH_3$); 1.50 (m, 4H, $2CH_2$); 1.61 (m, 3H, CH_3); 1.82 (m, 2H, CH_2); 2.10 (d, 1H, CH); 2.20 (t, 1 H, CH); 2.92 (m, 1 H, CH); 4.94 (t, J=6.86, 1 H, O-CH); 4.67-4.70 (s, 2H, CH_2); 4.75 (s, 2H, O-CH_2); 6.92 (m, 3H, $3CH_{Ar}$); 7.27 (m, 2H, $2CH_{Ar}$); 12.10 (s,1H, OH).

^{13}C-NMR ($CDCl_3$, 125 MHz) δ(ppm): 14.38 (CH_3); 15.70 ($2CH_3$); 15.88 (CH_2); 16.26 (CH_3); 17.70 ($2CH_3$); 18.96 (CH_2); 25.06 (CH_2); 27.52 ($2CH_2$); 29.23 (CH_2); 30.10 (CH_2); 33.72 (2 CH_2); 36.35 (CH_2); 36.62 (2C); 37.45 (C); 37.58 (C); 42.05 (CH); 46.64 (CH); 48.53 (CH); 49.62 (CH); 54.53 (CH); 55.43 (C); 64.54 (O-CH_2); 81.06 (O-CH); 109.71 (=CH_2); 114.37 (2 CH_{Ar}); 121.14 (CH_{Ar}); 129.50 ($2CH_{Ar}$); 150.34 (CH); 157.63 (C_{Ar}); 168.70 (CO); 177.28 (CO).

1H-benzo[d][1,2,3]triazol-1-yl (1R,3aS,5aR,5bR,9S,11aR)-9-hydroxy-5a,5b,8,8,11a-pentamethyl-1-(prop-1-en-2-yl)icosahydro-3aH-cyclopenta[a]chrysene-3a-carboxylate (***9***)
IR (Cm^{-1}): 3405 cm^{-1} ν (OH alcohol), 1684 cm^{-1} ν (CO ester), 1645 cm^{-1} ν (C=C).
^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm): 0.78 (s, 6H, $2CH_3$); 0.86 (s, 9H, $3CH_3$); 1.01 (m, 8H, CH_2); 1.93 (m, 2H, CH_2); 2.07 (m, 2H, CH_2); 3.33 (s, 2H, 2CH); 4.10 (d, H, OH); 4.64 (s, H, HC=); 4.79 (s, H, CH=); 7.55 (d, J= 7.80Hz, 2H, $2CH_{Ar}$); 7.71 (d, J=7.8Hz, 2H, $2CH_{Ar}$).

^{13}C-NMR (125 MHz, $CDCl_3$) δ (ppm): 14.23 (CH_3); 14.39 (CH_3); 15.40 (CH_3); 18.04 (CH_3); 18.21 (CH_2); 20.57 (CH_2); 25.46 (CH_2); 26.62 (CH_2); 27.27 ($2CH_3$); 29.89 (CH_2); 30.88 (CH_2); 34.28 (CH_2); 36.11 (CH_2); 38.49 ($2CH_2$); 38.89 (CH); 40.37 (2C); 42.07 (2C); 49.65 (CH); 50.59 (CH); 55.44 (CH); 57.12 (CH et C); 78.35 (HO-CH); 108.10 (CH_{Ar}); 109.67 (H_2C=); 119.57 (CH_{Ar}); 125.17 (CH_{Ar}); 128.81 (CH_{Ar}); 143.33 ($2C_{Ar}$); 149.65 (C); 171.90 (CO).

1H-benzo[d][1,2,3]triazol-1-yl(1S,2R,4aS,6aS,6bR,10S,12aR,14bS)-10-hydroxy-1,2,6a,6b,9,9,12a-heptamethyl-1,3,4,5,6,6a,6b,7,8,8a,9,10,11,12,12a,12b,13,14b-octadecahydropicene-4a(2H)-carboxylate (***11***)
IR (Cm^{-1}): 3405 cm-1 ν (OH alcohol), 1684 cm^{-1} ν (CO ester), 1645 cm^{-1} ν (C=C).

^{1}H-NMR (600 MHz, $CDCl_3$) δ (ppm): 0.75 (s, 3H, CH_3); 0.97 (m, 7H, $2CH_3$, CH); 1.01 (s, 6H, $2CH_3$); 1.20 (s, 3H, CH_3); 1.34 (s, 3H, CH_3); 1.45 (s, H, CH); 1.67 (m, 14H, $6CH_2$, 2CH); 2.10 (m, 6H, $3CH_2$); 2.99 (d, J=6.48Hz, H, CH); 3.35 (s, H, CH-O); 5.30 (s, 1H, OH); 6.51 (s, H,=CH); 7.37 (m, 2H, $2CH_{Ar}$); 7.55 (m, 1H, CH_{Ar}); 8.56 (m, 1H, CH_{Ar}).

^{13}C-NMR (150 MHz, $CDCl_3$) δ (ppm): 15.78 (CH_3); 17.04 (CH_3); 17.67 (CH_2); 18.10 (CH_3); 18.43 (CH_3); 21.19 (CH_3); 23.52 (CH_3); 27.10 (CH_2); 27.36 (CH_3); 28.29 (CH_2); 28.53 (CH_2); 30.64 (CH_2); 31.90 (CH_2); 33.35 (CH_2); 36.84 (CH_2); 37.11 (C); 37.15 (C); 38.84 (CH_2); 38.86 (CH); 39.19 (CH); 41.01 (C); 42.30 (C); 42.70 (C); 47.68 (CH); 53.19 (CH); 55.40 (CH); 79.15 (CH-O); 120.64 (CH_{Ar}); 124.76 (CH_{Ar}); 125.23 (=CH-); 127.26 (CH_{Ar}); 128.63 (CH_{Ar}); 136.96 (C_{Ar}); 141.60 (C); 142.24 (C_{Ar}); 173.75 (CO).

(**1S,2R,4aS,6aS,6bR,10S,12aR,14bS)-10-(((E)-3-(4-fluorophenyl)acryloyl)oxy)-1,2,6a,6b,9,9,12a-heptamethyl-1,3,4,5,6,6a,6b,7,8,8a,9,10,11,12,12a,12b,13,14b-octadecahydropicene-4a(2H)-carboxylic acid* (13)***

IR (Cm^{-1}): 3396 cm^{-1} ν (OH acid), 1725 cm^{-1} ν (CO acid), 1684 cm^{-1} ν (CO ester), 1645 cm^{-1} ν (C=C).

^{1}H-NMR ($CDCl_3$, 500 MHz) δ (ppm): 0.76 (m, 6H, $3CH_2$); 0.81 (m, 4H, $2CH_2$); 0.86 (m, 3H, CH_3); 0.92 (m, 4H, $2CH_2$); 1.12 (m, 2H, 2CH); 1.32 (m, 12H, CH_3); 1.55 (m, 4H, $2CH_2$); 1.62 (m, 3H, CH_3); 1.85 (m, 2H, CH_2); 2.10 (d, J=6.45Hz, 1H, CH); 3.34 (t, J=7.80Hz, , 1H, CH); 3.25 (m, 1H, CH), 7.10-7.60 (m, 4H, CH_{Ar}); 7.71 (d, 1H, CH); 6.75 (d, 1H, CH).

^{13}C-NMR ($CDCl_3$, 125 MHz) δ(ppm): 14.83 (CH_3); 15.50 ($2CH_3$), 16.15 (CH_2); 16.27 (CH_3); 18.43 (CH_2); 19.50 (CH_3); 20.98 (CH_2); 21.80 (CH_3); 25.63 (CH_2); 27.51 (CH_2); 28.12 (CH_3); 29.82 (CH_2); 30.68 (CH_2); 32.27 (CH_2); 37.33 (CH_2); 38.84 (2C); 39.15 (C); 40.83 (C); 42.57 (CH); 43.83 (C); 47.02 (CH); 49.37 (CH); 50.67 (CH); 55.47 (CH); 82.47 (CH-O); 116.01 (=CH-); 117.23 ($2CH_{Ar}$); 129.66 (=CH-); 129.77 ($2CH_{Ar}$); 131.60 (C); 143.33 (=CH-); 144.24 (C); 161.69 (C-F); 165.71 (CO); 173.75 (CO).

CONCLUSION

In this study, we developed pharmaco-modulation syntheses of natural molecules derived from betulinic and ursolic acids, isolated from the leaves of *Combretum glutinosium* and *Morinda geminata*, plants in the Senegalese pharmacopoeia, in order to enhance their value in medicinal chemistry through bioactive activity tests. The synergy of two molecules could play a crucial role in activity compared with the natural unimolecular molecule. The prospect of a bioactive study is currently underway at the Laboratory.

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REFERENCES

1. N'Diaye, D., Mbaye, M. D., Gassama, A. and Lavaud, C. "Structural determination of triterpenoids isolated from leaves *Combretum glutinosum* Perr. Ex DC (Combretaceae)," *Int. J. Biol. Chem. Sci.*, 2017; *11*: 488–498.
2. Sambou**,** O., Gassama, A., Karé, M., Gambe, D., Rivard, M., Martens, T. and Lachaise, I. "Antimicrobial anthraquinones and triterpenoid isolated from *Morinda geminata* DC (Rubiaceae)," *Mediterr. J. Chem.*, 2017; *6*: 191–195.
3. Kerharo, J. and Adam, J. G. " La Pharmacopée sénégalaise traditionnelle. Plantes médicinales et toxiques " *J. Agric. Trop. Bot. Appl.*, 1974; *21*: 76–77.
4. Boolamou, B., Lapo, A., Camara, K., Assane, M., Bassene, E. and Samb, A. "Activité anti-inflammatoire du décocté aqueux des écorces de racines de *Morinda geminata* DC (Rubiaceae)," *Int. J. Biol. Chem. Sci.*, 2015; *8*: 1871.
5. Portet, B., Fabre, N., Roumy, V., Gornitzka, H., Bourdy, G., Chevalley, S., Sauvain, M., Valentin, A. and Moulis, C. "Activity-guided isolation of antiplasmodial dihydrochalcones and flavanones from Piper hostmannianum var. berbicense," *Phytochemistry*, 2007; *68*: 1312–1320.
6. Riel, M. A., Kyle, D. E. and Milhous, W. K. "Efficacy of scopadulcic acid A against *Plasmodium falciparum* in *vitro*," *J. Nat. Prod*, 2002; *65*: 614–615.
7. Benoit-Vical, F., Imbert, C., Bonfils, J. P. and Sauvaire, Y. "Antiplasmodial and antifungal activities of iridal, a plant triterpenoid," *Phytochemistry*, 2003; *62:* 747–751.
8. Ziegler, H. L., Jengen, T. H., Cristensen, J., Stark, D., Hagerstrand, H., Sittie, A. A., Olsen, C. E., Staalso, T., Ekpe, P. and Jaroszewski, J.W. "Possible artefacts in the in *vitro* determination of antimalarial activity of natural products that incorporate into lipid bilayer: Apparent antiplasmodial activity of dehydroabietinol, a constituent of Hyptis suaveolens," *Planta Med.*, 2002; *68*: 547–549.
9. Suksamrarn, A., Tanachatchairatana, T. and Kanokmedhakul, S. "Antiplasmodial triterpenes from twigs of Gardenia saxatilis, "*J. Ethnopharmacol*, 2003; *88*: 275–277.
10. Ito, J., Chang, F. R., Wang, H. K., Park, Y. K., Ikegaki, M., Kilgore, N. and Lee, K. H. "Anti-AIDS agents. 48. Anti-HIV activity of moronic acid derivatives and the new melliferone-related triterpenoid isolated from Brazilian propolis," *J. Nat. Prod*, 2001; *64*: 1278–1281.
11. Sanz, C. U. and R. L. K. Z. C., Min, C.Y. "Effects of Mouth-rinse with Sesame Oil On Chemotherapy-Induced Oral Mucositis In Patients with Hematologic Cancer," *Arch. Pharmacal Res*, 2006; *29*: 63.
12. Van Loc, T., Van Sung, T., Kamperdick, C. and Adam, G. "Synthesis of Amino Acid Conjugates and

Further Derivatives of 3α-Hydroxylup-20 (29) ene-23,28-dioic acid," *J. für Prakt. Chemie*, 2000; *342*: 63–71.
13. Melnikova, N., Burlova, I., Kiseleva, T., Klabukova, I., Gulenova, M., Kislitsin, A., Vasin, V. and Tanaseichuk, B. "A practical synthesis of betulinic acid using selective oxidation of betulin on aluminium solid support," *Molecules*, 2012; *17*: 11849–11863.
14. Lee, C. K. "A new norlupene from the leaves of Melaleuca leucadendron," *J. Nat. Prod*, 1998; *61*: 375–376.
15. Chen, I. H., Du, Y. C., Lu, M, C., Lin, A. S., Hsieh, P. W., Wu, C. C., Li Chen, S., Fu Yen, H., R.Chang, F. and Wu, Y. C. "Lupane-type triterpenoids from Microtropis fokienensis and Perrottetia arisanensis and the apoptotic effect of 28-hydroxy-3-oxo-lup-20(29)-en-30-al," *J. Nat. Prod*, 2008; *71*: 1352–1357.
16. Ikeda, Y., Murakami, A. and Ohigashi, H. "Ursolic acid: An anti- And pro-inflammatory triterpenoid," *Mol. Nutr. Food Res.*, 2008; *52*: 26–42.
17. Csuk, R. and Siewert, B. "A convenient separation of ursolic and oleanolic acid," *Tetrahedron Lett*, 2011; *52*: 6616–6618.
18. Frighetto, R. T. S., Welendorf, R. M., Nigro, E. N., Frighetto, N. and Siani, A. C. "Isolation of ursolic acid from apple peels by high speed counter-current chromatography," *Food Chem*, 2008; *106*: 767–771.
19. Morrison, S. A., Li, H., Webster, D., Johnson, J. A. and Gray, C. A. "Antimycobacterial triterpenes from the Canadian medicinal plant Sarracenia purpurea," *J. Ethnopharmacol*, 2016; *188*: 200–203.
20. Ringbom, T., Segura, L., Noreen, Y., Perera, P. and Bohlin, L. "Ursolic acid from Plantago major, a selective inhibitor of cyclooxygenase-2 catalyzed prostaglandin biosynthesis," *J. Nat. Prod.*, 1998; *61*: 1212–1215.
21. Jie, L. "Pharmacology of oleanolic acid and ursolic acid," *J. Ethnopharmacol*, 1995; *49*: 57–68.
22. Yin, R., Li, T., Tian, J., Xi, P. and Liu, R. H. " Ursolic acid, a potential antica compound for breast cancer therapy " *Accepted Manuscript*," 2018; 58: 1-30.
23. Dufour, D., Pichette, A., Mshvildadze, V., Bradette-Hebert, M. E., Lavoie, S., Longtin, A., Laprise, C. and Legault, J. "Antioxidant, anti-inflammatory and anticancer activities of methanolic extracts from Ledum groenlandicum Retzius," *J. Ethnopharmacol*, 2007; *111*: 22–28.
24. Innocente, A. M., Silva, G. N. S., Cruz, L. N., Moraes, M. S., Nakabashi, M., Sonnet, P., Gosmann, G., Garcia, C. R. S. and Gnoatto, S. C. B. "Synthesis and antiplasmodial activity of betulinic acid and ursolic acid analogues," *Molecules*, 2012; *17*: 12003–12014.
25. Ma, C. M., Cai, S. Q., Cui, J. R., Wang, R. Q., Tu, P. F., Hattori, M. and Daneshtalab, M. "The cytotoxic activity of ursolic acid derivatives," *Eur. J. Med. Chem.*, 2005; *40*: 582–589.
26. Khwaza, V., Oyedeji, O. O. and Aderibigbe, B. A. "Ursolic acid-based derivatives as potential anti-cancer agents: An update," *Int. J. Mol. Sci.*, 2020; *21*: 1–27.
27. Srinivasan, R., Aruna, A., Lee, J. S., Kim, M., Shivakumar, M. S. and Natarajan, D. "Antioxidant and Antiproliferative Potential of Bioactive Molecules Ursolic Acid and Thujone Isolated from Memecylon edule and Elaeagnus indica and Their Inhibitory Effect on Topoisomerase II by Molecular Docking Approach," *Biomed Res. Int*, 2020; *20*: 12.
28. Liang, Y., Niu, Q.-Q., Zhao, Y.-H. "Pharmacological research progress of ursolic acid for thetreatmentofliver diseases", *Tradit Med Res*, 2021; *6:* 1–12.
29. Murakami, S., Takashimaa, H., Sato-Watanabea, M., Chonana, S., Yamamotoa, K., Saitoha, M., Saitoa, S., Yoshimuraa, H., Sugawaraa, K., Yangb, J., Gaob, N., and Zhang, X. "Ursolic acid, an antagonist for transforming growth factor (TGF)-β1," *FEBS Lett*, 2004; *566*: 55–59.