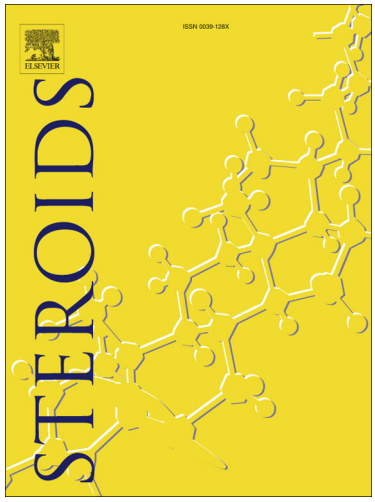

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PII: S0039-128X(16)30098-8
DOI: http://dx.doi.org/10.1016/j.steroids.2016.08.002
Reference: STE 8006

To appear in: *Steroids*

Received Date: 26 April 2016
Revised Date: 29 July 2016
Accepted Date: 2 August 2016

Please cite this article as: Khlebnicova, T.S., Piven, Y.A., Baranovsky, A.V., Lakhvich, F.A., Shishkina, S.V., Zicāne, D., Tetere, Z., Rāviņa, I., Kumpiņ š, V., Rijkure, I., Mieriņa, I., Peipiņ š, U., Turks, M., Synthesis of novel lupane triterpenoid-indazolone hybrids with oxime ester linkage, *Steroids* (2016), doi: http://dx.doi.org/10.1016/j.steroids.2016.08.002

Synthesis of novel lupane triterpenoid–indazolone hybrids with oxime ester linkage

Tatyana S. Khlebnicova [a], Yuri A. Piven [a], Alexander V. Baranovsky [a], Fedor A. Lakhvich [a], Svetlana V. Shishkina[b], Daina Zicāne [c], Zenta Tetere [c], Irisa Rāviņa [c], Viktors Kumpiņš [c], Inese Rijkure [c], Inese Mieriņa [c], Uldis Peipiņš [c], Māris Turks [c,*]

[a] *Institute of Bioorganic Chemistry, National Academy of Sciences of Belarus, Acad. Kuprevicha Str. 5/2, 220141 Minsk, Belarus*

[b] *Institute for Single Crystals, National Academy of Sciences of Ukraine, pr. Lenina 60, Kharkiv, 61001 Ukraine*

[c] *Institute of Technology of Organic Chemistry, Faculty of Materials Science and Applied Chemistry, Riga Technical University, P. Valdena Str. 3, Riga, LV-1048, Latvia. E-mail: maris_turks@ktf.rtu.lv*

Abstract

An efficient protocol for the synthesis of novel lupane triterpenoid-indazolone hybrids with oxime ester linkage has been developed from naturally accessible precursor betulin. For the first time a series of betulonic acid-indazolone hybrids have been synthesized *via* an acylation of corresponding 6,7-dihydro-1*H*-indazol-4(5*H*)-one oximes with betulonic acid chloride. Diastereoselective reduction of the obtained betulonic acid conjugates with $NaBH_4$ resulted in a formation of betulinic acid - indazolone hybrids in excellent yields. The configuration of the key compounds has been fully established by X-ray and 2D NMR analysis.

Key words

Triterpenoid-indazolone hybrids

Betulonic acid

Betulinic acid

Indazolone oximes

X-ray structure

1. Introduction

The hybridization of bioactive natural and unnatural compounds is one of the most promising for the design of new leading structures and the discovery of new and potent drugs in the field of medicinal chemistry [1–4]. Hybrid systems (sometimes also referred as conjugates) are defined as assembly of diverse molecular entities (in general two), natural or synthetic, to afford functional molecules, which intrinsically enhance or modulate the biological properties of individual components or, may exhibit new properties. The most widely applied definition of "hybrid molecule" defines a hybrid as a molecule that covalently connects two parent molecules that independently act at two distinct pharmacological target structures and the hybrid consequently is designed in a manner to maintain their activities at these two targets. In terms of drug design these two pharmacological actions are supposed to act in an overall synergistic manner concerning the disease to be targeted. This is why the hybrid approach gained special attention in recent times, since the complexity of several severe diseases, such as cancer and neurodegenerative disorders, can hardly be effectively targeted by one [5]. While tremendous efforts have been made over the past decades to improve the available therapeutic options, and a large number of potent chemotherapeutic anticancer agents have been identified and successfully used in clinical practice, cancer still remains a major cause of disease and death in most countries. Therefore, development of potent and specific anticancer agents is well-timed.

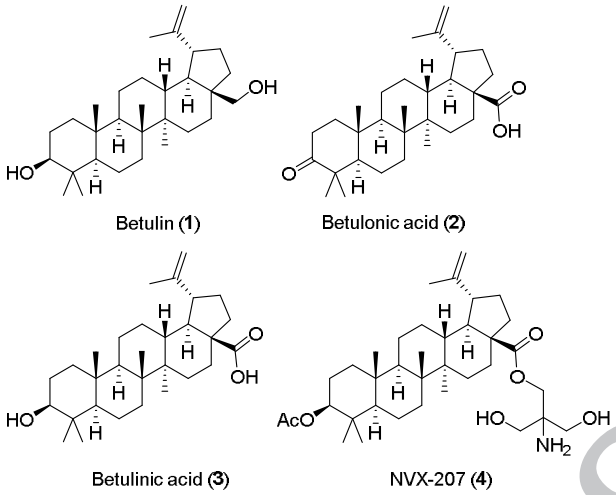
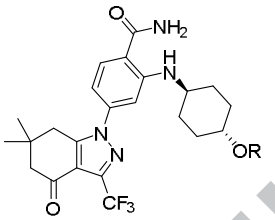


Fig. 1. Naturally occurring lupane triterpenoids **1–3** and an example of their semisynthetic derivative **4**.

Triterpenoids represent a varied class of natural products which constitute the major components of some medicinal plants [6–8]. Among these, some pentacyclic triterpene members have been exploited in recent past owing to their significant role in various biological activities [9,10]. Betulin, betulonic and betulinic acids (Fig.1), naturally occurring pentacyclic lupane triterpenoids, are common secondary metabolites of plants, primarily from Betula species (Betulaceae), that exhibits a variety of biological activities including an inhibition of human immunodeficiency virus (HIV), antibacterial, antimalarial, antiinflammatory, antitumor and other activities [11–14]. A large number of betulinic and betulonic acid derivatives have been developed to increase its therapeutic activity [15,16]. One well-tolerated betulinic acid derivative is NVX-207, which showed significant antitumor activity in clinical studies in canine cancer patients with treatment-resistant malignancies [17]. Some lupane triterpene hybrids with bioactive compounds showed interesting biological properties [18–21]. Previous studies suggested that an introduction of the nitrogen-containing heterocyclic rings to the pentacyclic triterpenoids can significantly improve the biological activities [15, 22–24].

On the other hand, indazole skeleton is an attractive structural scaffold in medicinal chemistry and various indazole derivatives have been described to possess useful levels of antiinflammatory, antipyretic, analgesic, antimicrobial, anticancer, sodium channel blocker, antitubercular, antiviral, antihypertensive, antiglaucoma, antioxidant, antidepressant, anxiolytic, neuroprotective and antidiabetic activities [25–28].



SNX2112: R = H
SNX5422: R = C(O)CH_2NH_2

Fig. 2. Inhibitors of heat-shock protein 90 (HSP90).

In particular, variously substituted tetrahydroindazolones were recently recognized as important anticancer drug candidates. Depending on structural peculiarities they were proved to act either as excellent inhibitors of heat-shock protein 90 [29,30] or regulators of the mitotic motor protein Eg5 [31]. The specific inhibition of the latter prevents uncontrollable division of malignant cells. Additionally, some of tetrahydroindazolone derivatives were shown to be active against various carcinomas [32] but at the same time being less toxic than other available antitumor drugs [33].

In the light of these facts, synthetic methodologies towards tetrahydroindazole analogs continue to develop [25]. Thus, we have recently developed an efficient one-step procedure for the synthesis of fluorine-containing 6,7-dihydro-1*H*-indazol-4(5*H*)-ones [34–37], which made these compounds accessible. We have also reported synthesis of triazolyl-substituted indazolones [38] and functionalized amino-

tetrahydroindazolones, including enantiomerically pure analogs and their conjugation with various carbohydrates [39–41].

The present work deals with synthesis of novel lupane triterpenoid-indazolone hybrids. Thus, in order to search for agents with potenial antitumor activity and selectivity, a series of lupane triterpene hybrids were synthesized by introducing variously substituted indazolone moieties at C28 position of betulonic and betulinic acid *via* oxime ester linkage. It should be noted that introduction of an oxime function into an appropriate skeleton is a reasonable approach to the preparation of potent cytotoxic agents and many oxime derivatives have exhibited potent inhibition activities against human tumors [42–44].

2. Experimental

2.1. General

^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on a Bruker AVANCE 500 spectrometer (500 MHz for ^{1}H, 125 MHz for ^{13}C and 470 MHz for ^{19}F) or Bruker AVANCE 300 spectrometer (300 MHz for ^{1}H and 75 MHz for ^{13}C). Chemical shift values are given in δ (ppm) relative to the residual solvent signals for δ_H 7.26 ppm ($CDCl_3$), 2.05 ppm (acetone-d_6), 7.16 ppm (C_6D_6) and δ_C 77.16 ppm ($CDCl_3$), 29.84 ppm (acetone-d_6), 128.06 ppm (C_6D_6). α,α,α-Trifluorotoluene was used as an external standard for ^{19}F NMR spectra; the chemical shifts were converted from α,α,α-trifluorotoluene to CCl_3F. COSY, HSQC, HMBC, and NOESY experiments were carried out with the use of the standard Bruker program package. Melting points were measured on Boetius apparatus and are uncorrected. IR spectra were recorded in KBr discs on a FT-IR Perkin Elmer Spectrum 100. High-resolution mass spectra (HRMS)

were recorded on a 6550 iFunnel Q-TOF LC/MS (Agilent Technologies) micromass spectrometer by electrospray ionization (ESI). Column chromatography was performed on 70–230 mesh silica gel. Reactions were monitored by thin layer chromatography (TLC) on pre-coated silica gel F_{254} plates with a UV indicator. Chemicals were purchased from Aldrich or Acros and used as received. Solvents were dried and freshly distilled according to common practice.

Betulonic acid (**2**) with technical product quality was obtained by reported procedure [45]. Indazolones 7**a–7n** were synthesized by a condensation of 2-acylcyclohexane-1,3-diones with phenyl hydrazines by described procedure [34–37]. The analytical data of indazolones 7**a–7f,7h,7i** were identical to those described in [34–37]. Indazolone oximes **8k,l** [46] and **8m,n** [33] were obtained according to previously published procedures.

2.2. Synthesis of the compounds

*Synthesis of betulonic acid (**2**) from its cyclohexylammonium salt*

5% Aqueous solution of phosphoric acid (185 mL) was added to a stirred suspension of cyclohexylammonium betulonate (**5**) (29.8 g, 0,053 mol, 98.7% purity by HPLC) in DCM (900 mL). The layers were separated and the DCM layer was successively washed with 5% aqueous solution of phosphoric acid (6 × 60 ml), water (7 × 120 ml; until pH 5 – 6) and brine (150 ml). The organic layer was dried over anh. Na_2SO_4, filtered and evaporated to provide betulonic acid with 97.8% purity by HPLC (23.7 g, 96% calculated on 100% cyclohexylammonium betulonate; or 88% calculated on the initial technical betulonic acid). Mp 245–247 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.55–1.18 (m, 15H, CH, CH_2), 1.06 (s, 3H, CH_3), 1.01 (s, 3H, CH_3), 0.99 (s, 3H, CH_3), 0.97 (s, 3H, CH_3), 0.92 (s, 3H CH_3), 1.76–1.58 (m, 2H, CH, CH_2) 1.69 (s, 3H,

CH_3), 2.07–1.84 (m, 3H, CH, CH_2), 2.34–2.15 (m, 2H, CH, CH_2), 2.56–2.34 (m, 2H, CH, CH_2), 3.07–2.94 (m, 1H, CH), 4.61 (brs, 1H, H_{vinyl}), 4.74 (brs, 1H, H_{vinyl}), 11.68–11.00 (brs, 1H, COOH). ^{1}H NMR data correspond to those reported in reference [47]. Elemental analysis, %: Found: C, 79.12; H, 10.29. $C_{30}H_{46}O_3$. Calcd: C, 79.25; H, 10.20.

*Cyclohexylammonium betulonate (**5**)*

A solution of cyclohexylamine (6.62 mL, 0.058 mol; 1 equiv.) in TBME (90 mL) was added to a vigorously stirred solution of technical betulonic acid [45] (92.8% purity by HPLC) (28.3 g, 0.058 mol; 1 equiv.) in TBME (260 mL) at room temperature. The resulting suspension was stirred for 40 min at room temperature, filtered and washed on the filter with TBME (5 × 20 mL). The precipitate consists of cyclohexylammonium betulonate with 96.1% purity by HPLC (31.3 g, 94%, calculated on 100% betulonic acid). The resulting technical salt was crystallized from a mixture of EtOAc/EtOH (400 mL : 400 mL) and the product (29.8 g, 89% calculated on 100% betulonic acid) with 98.7% purity by HPLC was obtained. Mp 208–210 °C. IR (KBr), ν_{max}: 2940 (CH), 2865 (CH), 2755–2610 (RN^+H_3), 2215, 1710 (CO), 1635, 1525, 1455, 1390, 1365, 1325, 880. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.92 (s, 3H, CH_3), 0.99 (s, 6H, $2CH_3$), 1.03 (s, 3H, CH_3), 1.08 (s, 3H, CH_3), 1.61–1.12 (m, 21H, CH, CH_2, $3CH_2$ from *c*-hexylamine), 1.84–1.62 (m, 4H, CH, CH_2), 1.70 (s, 3H, CH_3), 1.97–1.84 (m, 3H, CH, CH_2 from *c*-hexylamine), 2.10–1.99 (m, 2H, CH_2 from *c*-hexylamine), 2.29–2.18 (m, 1H, CH), 2.57–2.35 (m, 3H, CH, CH_2), 2.92–2.80 (m, 1H, CH or CH from *c*-hexylamine), 3.15–3.03 (m, 1H, CH or CH from *c*-hexylamine), 4.60 (brs, 1H, H_{vinyl}), 4.72 (brs, 1H, H_{vinyl}), 7.45–7.26 (brs, 3H, RN^+H_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.7, 16.15, 16.23, 19.4, 19.8, 21.2, 21.7, 24.9, 25.3,

25.8, 26.8, 30.0, 31.1, 33.1, 33.2, 33.9, 34.3, 37.0, 37.8, 38.5, 39.8, 40.8, 42.7, 47.4, 47.5, 49.4, 50.1, 50.5, 55.0, 56.9, 109.5, 151.6, 182.3, 218.4. Elemental analysis, %: Found: C, 77.68; H, 10.79; N, 2.45. $C_{36}H_{59}NO_3$. Calcd: C, 78.07; H, 10.74; N, 2.53.

*2.2.1. 3-Cyclopropyl-6,6-dimethyl-1-phenyl-6,7-dihydro-1H-indazol-4(5H)-one (**7g**)*

The title compound was prepared in 59% yield according to [36] from 2-cyclopropanecarbonyl-5,5-dimethylcyclohexane-1,3-dione as a white solid. Mp 143–145 °C. IR (KBr) ν_{max}: 690, 715, 735, 755, 810, 890, 975, 1020, 1035, 1055, 1115, 1290, 1365, 1375, 1390, 1415, 1450, 1470, 1495, 1510, 1535, 1600, 1660, 2830–3085. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.97–1.01 (m, 2H, $CH_{2cyclopropyl}$), 1.05–1.08 (m, 2H, $CH_{2cyclopropyl}$), 1.09 (s, 6H, $2CH_3$), 2.40 (s, 2H, CH_2), 2.59–2.65 (m, 1H, $CH_{cyclopropyl}$) 2.74 (s, 2H, CH_2), 7.36–7.39 (m, 1H, H_{arom}), 7.43–7.48 (m, 4H, H_{arom}). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 8.5, 9.2, 28.5, 35.7, 37.4, 52.7, 117.1, 124.0, 128.0, 129.4, 138.9, 149.0, 155.8, 193.5. HRMS (ESI): m/z calcd for $C_{18}H_{20}N_2O$ $(M+H)^+$, 295.3788; found, 295.3797.

*2.2.2 6,6-Dimethyl-3-(furan-2-yl)-1-phenyl-6,7-dihydro-1H-indazol-4(5H)-one (**7j**)*

The title compound was prepared in 58% yield according to [36] from 2-furoyl-5,5-dimethylcyclohexane-1,3-dione as a white solid. Mp 180–182 °C. IR (KBr) ν_{max}: 690, 705, 755, 835, 885, 975, 990, 1020, 1025, 1060, 1080, 1165, 1225, 1285, 1305, 1370, 1390, 1410, 1425, 1460, 1475, 1500, 1510, 1525, 1600, 1660. 2865–3150. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.11 (s, 6H, $2CH_3$), 2.48 (s, 2H, CH_2), 2.80 (s, 2H, CH_2), 6.53 (dd, J = 3.4, 1.8 Hz, 1H, H_{furyl}), 7.42–7.45 (m, 1H, H_{furyl}), 7.49–7.55 (m, 5H, H_{arom}), 7.87 (d, J = 3.4 Hz, 1H, H_{furyl}). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 28.4, 35.4, 37.3, 53.0, 111.6, 114.0, 115.0, 124.6, 128.7, 129.5, 138.5,

142.5, 143.2, 146.8, 149.8, 191.8. HRMS (ESI): m/z calcd for $C_{19}H_{19}N_2O_2$ $(M+H)^+$, 307.1447; found, 307.1456.

*2.2.3. General procedure for the synthesis of oximes **8a–8j***

To a solution of indazolone **7a–7j** (1.0 mmol) in Py (5 ml), hydroxylamine hydrochloride (4.0 mmol, 0.28 g) was added. After refluxing for 3 h, the mixture was cooled to room temperature and poured into cold 18% hydrochloric acid (80 mL) and extracted with $CHCl_3$ (5 x 20 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated in vacuum to give oximes **8a–8j.** The analytical data of indazolone oximes **8a–8f** were identical to those described in [48].

*2.2.3.1. (E)-3-Cyclopropyl-6,6-dimethyl-1-phenyl-6,7-dihydro-1H-indazol-4(5H)-one oxime (**8g**)*

The title compound was prepared in 86% yield from indazolone **7g** as a white solid. Mp 191–194 °C. IR (KBr) ν_{max}: 685, 695, 730, 745, 755, 760, 795, 830, 885, 905, 925, 935, 945, 985, 1025, 1035, 1055, 1070, 1090, 1160, 1170, 1240, 1255, 1295, 1320, 1370, 1385, 1395, 1425, 1445, 1470, 1500, 1510, 1555, 1600, 1640, 2835–3080. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.96–1.04 (m, 4H, $2CH_{2cyclopropyl}$), 1.07 (s, 6H, $2CH_3$), 2.32–2.38 (m, 1H, $CH_{cyclopropyl}$), 2.63 (s, 2H, CH_2), 2.69 (s, 2H, CH_2), 7.31–7.34 (m, 1H, H_{arom}), 7.42–7.46 (m, 4H, H_{arom}). ^{13}C NMR (125 Hz, $CDCl_3$) δ: 8.1, 9.4, 28.6, 33.0, 36.4, 37.2, 112.4, 123.7, 127.3, 129.3, 139.3, 142.7, 152.1, 152.5. HRMS (ESI): m/z calcd for $C_{18}H_{22}N_3O$ $(M+H)^+$, 296.1763; found, 296.1774.

*2.2.3.2. (E)-3-Cyclopropyl-6,6-dimethyl-1-(4-fluorophenyl)-6,7-dihydro-1H-indazol-4(5H)-one oxime (**8h**)*

The title compound was prepared in 86% yield from indazolone **7h** as a white solid. Mp 232–234 °C. IR (KBr) ν_{max}: 675, 730, 745, 790, 810, 835, 890, 915, 930, 945, 985, 1035, 1050, 1075, 1100, 1155, 1215, 1235, 1295, 1365, 1385, 1400, 1420, 1450, 1515, 1555, 1610, 1640, 2870–3085. ^{1}H NMR (500 MHz, acetone-d_6) δ: 0.83–0.94 м (4H, $2CH_{2cyclopropyl}$), 1.04 (s, 6H, $2CH_3$), 2.55–2.61 (m, 3H, $CH_{cyclopropyl}$, CH_2), 2.70 (s, 2H, CH_2), 7.24–7.27 (m, 2H, H_{arom}), 7.53–7.55 (m, 2H, H_{arom}). ^{13}C NMR (125 MHz, acetone-d_6) δ: 9.2, 9.5, 28.6, 33.2, 36.6, 37.4, 113.8, 116.6 (d, J = 23 Hz), 125.8 (d, J = 9 Hz), 136.9, 142.4, 151.3, 152.6, 162.0 (d, J = 245 Hz). ^{19}F NMR (470 MHz, acetone-d_6) δ: –117.2 (1F). HRMS (ESI): m/z calcd for $C_{19}H_{20}FN_3O$ $(M+H)^+$, 314.1669; found, 314.1679.

*2.2.3.3. (E)-6,6-Dimethyl-3-(furan-2-yl)-1-phenyl-6,7-dihydro-1H-indazol-4(5H)-one oxime (**8i**)*

The title compound was prepared in 80% yield from indazolone **7i** as a white solid. Mp 200–202 °C. IR (KBr) ν_{max}: 685, 695, 725, 740, 765, 800, 825, 885, 905, 920, 935, 945, 985, 995, 1000, 1015, 1025, 1070, 1105, 1160, 1210, 1300, 1365, 1395, 1420, 1450, 1465, 1505, 1535, 1600, 1625, 2840-3070. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.06 (s, 6H, $2CH_3$), 2.65 (s, 2H, CH_2), 2.68 (s, 2H, CH_2), 6.48 (dd, J = 3.4, 1.8 Hz, 1H, H_{furyl}), 7.36–7.39 (m, 1H, H_{arom}), 7.44–7.53 (m, 5H, $4H_{arom}$, $1H_{furyl}$), 7.57 (brs, 1H, H_{arom}). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 28.4, 32.5, 36.4, 37.1, 110.0, 111.3, 112.2, 124.4, 128.1, 129.3, 138.8, 140.4, 142.8, 143.7, 147.7, 151.7. HRMS (ESI): m/z calcd for $C_{19}H_{20}N_3O_2$ $(M+H)^+$, 322.1556; found, 322.1565.

*2.2.3.4. (E)-6,6-Dimethyl-1-(4-fluorophenyl)-3-(furan-2-yl)-6,7-dihydro-1H-indazol-4(5H)-one oxime (**8j**)*

The title compound was prepared in 92% yield from indazolone **7j** as a white solid. Mp 214–216 °C. IR (KBr) ν_{max}: 680, 710, 720, 735, 755, 770, 795, 810, 830, 840, 845, 885, 900, 905, 915, 930, 945, 970, 990, 1020, 1065, 1110, 1160, 1225, 1370, 1395, 1420, 1445, 1465, 1485, 1515, 1625, 1670, 2875–3130. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.07 (s, 6H, $2CH_3$), 2.68 (s, 2H, CH_2), 2.75 (s, 2H, CH_2), 6.52 (dd, J = 3.4, 1.8 Hz, 1H, H_{furyl}), 7.13–7.17 (m, 2H, H_{arom}), 7.25–7.26 (m, 1H, H_{furyl}), 7.43–7.46 (m, 2H, H_{arom}), 7.91 (brs, 1H, H_{furyl}). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 28.2, 33.0, 36.7, 37.4, 106.5, 111.1, 111.9, 116.5 (d, J = 23 Hz), 126.3 (d, J = 9 Hz), 134.0, 140.6, 144.4, 146.0, 146.7, 152.5, 162.5 (d, J = 250 Hz). ^{19}F NMR (470 MHz, $CDCl_3$) δ: −111.5 (1F). HRMS (ESI): m/z calcd for $C_{19}H_{19}FN_3O_2$ $(M+H)^+$, 340.1461; found, 340.1473.

*2.2.4. General procedure for the synthesis of betulonic acid hybrids **9a–9n.***

To a solution of oximes **8a–8n** (1 mmol) in $CHCl_3$ (10 mL), pyridine (0.1 mL) and then dropwise a solution of betulonic acid chloride **6** [45] (1 mmol) in $CHCl_3$ (10 mL) were added. After refluxing for 20 h, the mixture was cooled to room temperature and treated with 10% hydrochloric acid (3 × 10 ml) and water (1 × 10 ml). The organic phase was dried ($MgSO_4$) and filtered. After removal of the solvent in vacuum, the residue was purified by silica gel column chromatography with petroleum ether/ethyl acetate as eluent to give the corresponding hybrids **9a–9n.**

*2.2.4.1. (E)-(6,6-Dimethyl-3-(trifluoromethyl)-1-phenyl-6,7-dihydro-1H-indazol-4(5H)-one O-(3-oxolup-20(29)-en-28-oyl) oxime (**9a**)*

The title compound was prepared in 48% yield from oxime **8a** as a white solid. Mp 200–204 °C. IR (KBr) ν_{max}: 695, 715, 765, 795, 830, 860, 885, 900, 920, 940,

985, 1010, 1025, 1055, 1080, 1115, 1145, 1170, 1205, 1245, 1290, 1320, 1350, 1375, 1400, 1455, 1505, 1545, 1600, 1610, 1640, 1705, 1750, 2875–3070. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.79–2.53 (m, 24H, CH, CH_2), 0.92 (s, 3H, CH_3), 0.98 (s, 3H, CH_3), 1.00 (s, 6H, $2CH_3$), 1.06 (s, 3H, CH_3), 1.09 (s, 3H, CH_3), 1.11 (s, 3H, CH_3), 1.71 (s, 3H, CH_3), 2.65 (d, J = 16.4 Hz, AB system, 1H, CH_2), 2.70 (d, J = 16.4 Hz, AB system, 1H, CH_2), 2.70 (s, 2H, CH_2), 3.12–3.18 (m, 1H, H19), 4.62 (brs, 1H, H_{vinyl}), 4.74 (brs, 1H, H_{vinyl}), 7.45–7.54 (m, 5H, H_{arom}). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.7, 15.9, 19.4, 19.6, 21.0, 21.4, 25.5, 26.5, 28.3, 28.5, 29.7, 30.5, 32.3, 33.1, 33.7, 34.1, 36.6, 36.9, 37.1, 38.2, 38.3, 39.6, 40.7, 42.5, 46.8, 47.3, 50.0, 50.1, 55.0, 56.5, 109.7, 110.7, 120.7 (q, J = 269 Hz) 124.2, 128.9, 129.5, 138.0, 138.9 q (J = 39 Hz), 145.2, 150.4, 154.7, 171.9, 218.2. ^{19}F NMR (470 MHz, $CDCl_3$) δ: −63.7 (3F). HRMS (ESI): m/z calcd for $C_{46}H_{60}F_3N_3NaO_3$ $(M+Na)^+$ 782.4484, found 782.4491.

*2.2.4.2. (E)-(6,6-Dimethyl-3-(perfluoroethyl)-1-phenyl-6,7-dihydro-1H-indazol-4(5H)-one O-(3-oxolup-20(29)-en-28-oyl) oxime (**9b**)*

The title compound was prepared in 38% yield from oxime **8b** as a white solid. Mp: 145–149 °C. IR (KBr) ν_{max}: 695, 735, 750, 770, 790, 820, 860, 895, 940, 965, 1025, 1055, 1080, 1095, 1120, 1155, 1190, 1220, 1290, 1315, 1335, 1375, 1390, 1400, 1450, 1460, 1505, 1540, 1600, 1620, 1640, 1705, 1755, 2870–3070. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.79–2.55 (m, 24H, CH, CH_2), 0.92 (s, 3H, CH_3), 0.97 (s, 3H, CH_3), 1.01 (s, 6H, $2CH_3$), 1.06 (s, 3H, CH_3), 1.09 (s, 3H, CH_3), 1.10 (s, 3H, CH_3), 1.71 (s, 3H, CH_3), 2.65 (d, J = 16.3 Hz, AB system, 1H, CH_2), 2.68 (d, J = 16.3 Hz, AB system, 1H, CH_2), 2.71 (s, 2H, CH_2), 3.12–3.18 (m, 1H, C19-H), 4.62 (brs, 1H, H_{vinyl}), 4.74 (brs, 1H, H_{vinyl}), 7.45–7.54 (m, 5H, H_{arom}). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.8, 16.0, 16.1, 19.6, 19.8, 21.2, 21.5, 25.7, 26.7, 28.4, 28.6, 29.9, 30.7, 32.5, 33.1,

33.8, 34.3, 36.9, 37.1, 37.2, 38.5, 39.8, 40.8, 42.6, 47.0, 47.5, 50.0, 50.1, 55.2, 56.7, 109.8, 110.9 (tq, *J* = 252 Hz, 39 Hz), 112.2, 119.3 (qt, *J* = 287 Hz, 37 Hz), 124.2, 129.0, 129.7, 138.1, 138.4 (t, *J* = 30 Hz), 145.2, 150.6, 154.8, 172.0, 218.3. ^{19}F NMR (470 MHz, $CDCl_3$) δ: −82.3 (3F), −110.7 (2F). HRMS (ESI): m/z calcd for $C_{47}H_{60}F_5N_3NaO_3$ $(M+Na)^+$, 832.4453, found 832.4443.

*2.2.4.3. (E)-(6,6-Dimethyl-3-(perfluoropropyl)-1-phenyl-6,7-dihydro-1H-indazol-4(5H)-one O-(3-oxolup-20(29)-en-28-oyl) oxime (**9c**)*

The title compound was prepared in 35% yield from oxime **7c** as a white solid. Mp 156−160 °C. IR (KBr) ν_{max}: 695, 715, 735, 750, 765, 820, 860, 890, 905, 935, 965, 980, 1010, 1020, 1055, 1085, 1115, 1190, 1205, 1230, 1260, 1290, 1315, 1355, 1375, 1390, 1400, 1455, 1500, 1540, 1600, 1620, 1640, 1705, 1755, 2870−3070. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.80−2.55 (m, 24H, CH, CH_2), 0.92 (s, 3H, CH_3), 0.97 (s, 3H, CH_3), 1.00 (s, 3H, CH_3), 1.01 (s, 3H, CH_3), 1.06 (s, 3H, CH_3), 1.08 (s, 3H, CH_3), 1.09 (s, 3H, CH_3), 1.71 (s, 3H, CH_3), 2.64 (d, *J* = 16.3 Hz, AB system, 1H, CH_2), 2.68 (d, *J* = 16.3 Hz, AB system, 1H, CH_2), 2.70 (s, 2H, CH_2), 3.10−3.16 (m, 1H, C19-H), 4.62 (brs, 1H, H_{vinyl}), 4.75 (brs, 1H, H_{vinyl}), 7.45−7.55 (m, 5H, H_{arom}). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.8, 15.8, 16.1, 19.6, 19.8, 21.2, 21.6, 25.8, 26.7, 28.4, 28.5, 29.8, 29.9, 30.8, 32.5, 33.0, 33.9, 34.3, 36.9, 37.1, 37.2, 38.5, 39.8, 40.8, 42.7, 47.0, 47.5, 50.0, 50.1, 55.2, 56.8, 109.3 (tm, *J* = 266 Hz), 109.8, 112.6, 112.9 (tt, *J* = 255 Hz, 32 Hz), 118.2 (qt, *J* = 289 Hz, 35 Hz), 124.4, 129.1, 129.7, 138.2, 138.4 (t, *J* = 30 Hz), 145.3, 150.6, 154.8, 172.0, 218.2. ^{19}F NMR (470 MHz, $CDCl_3$) δ: −80.3 (3F), −108.6 (2F), −125.1 (2F). HRMS (ESI): m/z calcd for $C_{48}H_{60}F_7N_3NaO_3$ $(M+Na)^+$ 882.4421, found, 882.4429.

*2.2.4.4. (E)-(6,6-Dimethyl-1-(4-fluorophenyl)-3-(trifluoromethyl)-6,7-dihydro-1H-indazol-4(5H)-one O-(3-oxolup-20(29)-en-28-oyl) oxime (**9d**)*

The title compound was prepared in 41% yield from oxime **8d** as a white solid. Mp: 271−275 °C. IR (KBr) ν_{max}: 700, 720, 740, 750, 765, 845, 885, 900, 940, 980, 1015, 1055, 1080, 1095, 1120, 1150, 1170, 1205, 1235, 1290, 1350, 1380, 1405, 1465, 1510, 1550, 1620, 1645, 1705, 1755, 2870−3070. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.79−2.52 (m, 24H, CH, CH_2), 0.92 (s, 3H, CH_3), 0.98 (s, 3H, CH_3), 1.00 (s, 6H, $2CH_3$), 1.06 (s, 3H, CH_3), 1.10 (s, 3H, CH_3), 1.11 (s, 3H, CH_3), 1.71 (s, 3H, CH_3), 2.65 (s, 2H, CH_2), 2.65 (d, J = 16.4 Hz, AB system, 1H, CH_2), 2.69 (d, J = 16.4 Hz, AB system, 1H, CH_2), 3.11−3.17 (m, 1H, C19-H), 4.62 (brs, 1H, H_{vinyl}), 4.74 (brs, 1H, H_{vinyl}), 7.19−7.24 (m, 2H, H_{arom}), 7.44−7.48 (m, 2H, H_{arom}). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.8, 16.1, 19.5, 19.8, 21.1, 21.5, 25.7, 26.7, 28.5, 28.6, 29.9, 30.7, 32.4, 33.2, 33.8, 34.3, 36.6, 37.0, 37.2, 38.3, 38.5, 39.8, 40.8, 42.6, 47.0, 47.5, 50.0, 50.1, 55.1, 56.7, 109.8, 110.9, 116.7 (d, J = 23 Hz), 120.8 (q, J = 270 Hz), 126.3 (d, J = 9 Hz), 134.2, 139.4, 139.4 (q, J = 39 Hz), 145.4, 150.5, 154.8, 162.6 (d, J = 260 Hz), 172.0, 218.3. ^{19}F NMR (470 MHz, $CDCl_3$) δ: −63.8 (3F), −111.7 (1F). HRMS (ESI): m/z calcd for $C_{46}H_{59}F_4N_3NaO_3$ $(M+Na)^+$ 800.4390, found 800.4399.

*2.2.4.5. (E)-(6,6-Dimethyl-1-(4-fluorophenyl)-3-(perfluoroethyl)-6,7-dihydro-1H-indazol-4(5H)-one O-(3-oxolup-20(29)-en-28-oyl) oxime (**9e**)*

The title compound was prepared in 38% yield from oxime **8e** as a white solid. Mp: 191−195 °C. IR (KBr) ν_{max}: 705, 735, 750, 845, 885, 895, 915, 940, 960, 985, 1015, 1055, 1080, 1095, 1120, 1140, 1155, 1185, 1220, 1290, 1320, 1335, 1380, 1420, 1460, 1520, 1550, 1620, 1640, 1705, 1755, 2870−3070. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.86−2.53 (m, 24H, CH, CH_2), 0.92 (s, 3H, CH_3), 0.97 (s, 3H, CH_3), 1.00

(s, 6H, $2CH_3$), 1.06 (s, 3H, CH_3), 1.09 (s, 3H, CH_3), 1.10 (s, 3H, CH_3), 1.70 (s, 3H, CH_3), 2.65 (d, J = 16.4 Hz, AB system, 1H, CH_2), 2.67 (s, 2H, CH_2), 2.69 (d, J = 16.4 Hz, AB system, 1H, CH_2), 3.11−3.17 (m, 1H, C19-H), 4.62 (brs, 1H, H_{vinyl}), 4.74 (brs, 1H, H_{vinyl}), 7.20−7.23 (m, 2H, H_{arom}) 7.44−7.47 (m, 2H, H_{arom}). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.8, 16.0, 16.1, 19.6, 19.8, 21.2, 21.5, 25.7, 26.7, 28.4, 28.6, 29.9, 30.7, 32.5, 33.1, 33.8, 34.3, 36.8, 37.1, 37.2, 38.4, 38.5, 39.8, 40.8, 42.6, 47.0, 47.5, 50.0, 50.1, 55.2, 56.7, 109.8, 110.7 (tq, J = 252 Hz, 39 Hz), 112.3, 116.7 (d, J = 23 Hz), 119.2 (qt, J = 287 Hz, 37 Hz), 126.2 (d, J = 9 Hz), 134.2, 138.5 (t, J = 31 Hz), 145.2, 150.5, 154.6, 162.6 (d, J = 250 Hz), 172.0, 218.4; ^{19}F NMR (470 MHz, $CDCl_3$) δ: −82.3 (3F), −110.8 (2F), −111.8 (1F). HRMS (ESI): m/z calcd for $C_{47}H_{59}F_6N_3NaO_3$ $(M+Na)^+$ 850,4358, found 850.4349.

*2.2.4.6. (E)-(6,6-Dimethyl-1-(4-fluorophenyl)-3-(perfluoropropyl)-6,7-dihydro-1H-indazol-4(5H)-one O-(3-oxolup-20(29)-en-28-oyl) oxime (**9f**)*

The title compound was prepared in 33% yield from oxime **8f** as a white solid. Mp: 131−135 °C. IR (KBr) ν_{max}: 665, 735, 750, 845, 890, 900, 920, 935, 965, 985, 1010, 1025, 1055, 1085, 1100, 1115, 1155, 1190, 1210, 1230, 1265, 1290, 1320, 1370, 1390, 1400, 1420, 1465, 1500, 1515, 1620, 1640, 1705, 1755, 2870−3070. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.80−2.53 (m, 24H, CH, CH_2), 0.93 (s, 3H, CH_3), 0.97 (s, 3H, CH_3), 1.01 (s, 3H, CH_3), 1.02 (s, 3H, CH_3), 1.06 (s, 3H, CH_3), 1.08 (s, 3H, CH_3), 1.10 (s, 3H, CH_3), 1.71 (s, 3H, CH_3), 2.62−2.70 (m, 4H, $2CH_2$), 3.10−3.15 (m, 1H, C19-H), 4.62 (brs, 1H, H_{vinyl}), 4.75 (brs, 1H, H_{vinyl}); 7.20−7.24 (m, 2H, H_{arom}), 7.45−7.48 (m, 2H, H_{arom}). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.9, 15.8, 16.1, 19.6, 19.8, 21.2, 21.6, 25.8, 26.8, 28.4, 28.6, 29.9, 30.8, 32.5, 33.0, 33.9, 34.3, 36.8, 37.1, 37.2, 38.6, 39.8, 40.8, 42.7, 47.0, 47.5, 50.0, 50.2, 55.3, 56.8, 109.3 (tm, J = 266 Hz),

109.8, 112.7, 112.9 (tt, *J* = 255 Hz, 32 Hz), 116.7 (d, *J* = 23 Hz), 118.2 (qt, *J* = 288, 34 Hz), 126.4 (d, *J* = 9 Hz), 134.3, 138.5 (t, *J* = 30 Hz), 145.3, 150.6, 154.7, 162.7 (d, *J* = 250 Hz), 172.0, 218.2. ^{19}F NMR (470 MHz, $CDCl_3$) δ: −80.3 (3F), −108.7 (2F), −111.7 (1F), −125.1 (2F). HRMS (ESI): m/z calcd for $C_{48}H_{59}F_8N_3NaO_3$ $(M+Na)^+$ 900.4326, found 900.4335.

*2.2.4.7. (E)-3-(Cyclopropyl)-6,6-dimethyl-1-phenyl-6,7-dihydro-1H-indazol-4(5H)-one O-(3-oxolup-20(29)-en-28-oyl) oxime (**9g**)*

The title compound was prepared in 75% yield from oxime **8g** as a white solid. Mp 130−134 °C. IR (KBr) ν_{max}: 695, 725, 760, 790, 820, 855, 890, 940, 985, 1025, 1035, 1055, 1095, 1105, 1135, 1170, 1255, 1295, 1320, 1350, 1370, 1385, 1405, 1450, 1510, 1545, 1600, 1645, 1705, 1750, 2870−3070. The NMR (500 MHz, $CDCl_3$) data were in Table 2. HRMS (ESI): m/z calcd for $C_{48}H_{65}N_3NaO_3$ $(M+Na)^+$ 754.4924, found, 754.4930.

*2.2.4.8. (E)-3-(Cyclopropyl)-6,6-dimethyl-1-(4-fluorophenyl)-6,7-dihydro-1H-indazol-4(5H)-one O-(3-oxo-lup-20(29)-en-28-oyl) oxime (**9h**)*

The title compound was prepared in 68% yield from oxime **8h** as a white solid. Mp 152−156 °C. IR (KBr) ν_{max}: 665, 725, 755, 840, 885, 940, 1015, 1035, 1055, 1080, 1100, 1135, 1155, 1170, 1225, 1295, 1320, 1370, 1380, 1385, 1400, 1420, 1460, 1505, 1520, 1610, 1640, 1705, 1750, 2875−3080. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.79−2.79 (m, 28H, CH, CH_2), 0.92 (s, 3H, CH_3), 0.99 (s, 3H, CH_3), 1.01 (s, 6H, $2CH_3$), 1.06 (s, 3H, CH_3), 1.08 (s, 3H, CH_3), 1.09 (s, 3H, CH_3), 1.71 (s, 3H, CH_3), 2.60 (s, 2H, CH_2), 2.65 (d, *J* = 16.5 Hz, AB system, 1H, CH_2), 2.68 (d, *J* = 16.5 Hz, AB system, 1H, CH_2), 2.73−2.81 (m, 1H, $CH_{cyclopropyl}$), 3.10−3.15 (m, 1H, C19-

H), 4.62 (brs, 1H, H_{vinyl}), 4.75 (brs, 1H, H_{vinyl}), 7.12–7.16 м (2H, H_{arom}), 7.38–7.40 (m, 2H, H H_{arom}). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 9.2, 9.7, 9.8, 14.8, 16.1, 16.3, 19.6, 19.8, 21.2, 21.6, 25.8, 26.8, 28.6, 28.8, 29.9, 30.8, 32.5, 33.4, 33.9, 34.3, 36.8, 37.1, 37.4, 38.6, 38.7, 39.8, 40.9, 42.7, 47.2, 47.5, 50.0, 50.1, 55.2, 56.8, 109.9, 111.4, 116.3 (d, J = 23 Hz), 125.6 (d, J = 8 Hz), 135.3, 143.6, 150.5, 154.1, 158.4, 161.8 (d, J = 247 Hz), 172.8, 218.2. ^{19}F NMR (470 MHz, $CDCl_3$) δ: – 113.9 (1F). HRMS (ESI): m/z calcd for $C_{48}H_{64}N_3NaO_3$ $(M+Na)^+$ 772.4829, found 772.4837.

*2.2.4.9. (E)-6,6-Dimethyl-3-(furan-2-yl)-1-phenyl-6,7-dihydro-1H-indazol-4(5H)-one O-(3-oxolup-20(29)-en-28-oyl) oxime (**9i**)*

The title compound was prepared in 76% yield from oxime **8i** as a white solid. Mp 175–179 °C. IR (KBr) ν_{max}: 695, 715, 745, 765, 855, 885, 910, 940, 995, 1025, 1055, 1085, 1095, 1100, 1135, 1165, 1225, 1260, 1290, 1315, 1370, 1390, 1430, 1455, 1505, 1535, 1600, 1620, 1640, 1705, 1750, 2870–3145. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.86–2.52 (m, 24H, CH, CH_2), 0.92 (s, 3H, CH_3), 0.99 (s, 3H, CH_3), 1.00 (s, 3H, CH_3), 1.02 (s, 3H, CH_3), 1.06 (s, 3H, CH_3), 1.10 (s, 3H, CH_3), 1.11 (s, 3H, CH_3), 1.72 (s, 3H, CH_3), 2.72 (s, 2H, CH_2), 2.73 (d, J = 16.4 Hz, AB system, 1H, CH_2), 2.76 (d, J = 16.4 Hz, AB system, 1H, CH_2), 3.11–3.16 (m, 1H, C19-H), 4.64 (brs, 1H, H_{vinyl}), 4.77 (brs, 1H, H_{vinyl}), 6.60 (dd, J = 3.5 Hz, 1.7 Hz, 1H, H_{furyl}), 7.40–7.43 (m, 1H, H_{arom}), 7.48–7.54 (m, 5H, 4H_{arom}, 1H_{furyl}), 8.30 (d, J = 3.5 Hz, 1H, H_{furyl}). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.8, 16.1, 16.1, 19.5, 19.8, 21.2, 21.6, 25.7, 26.7, 28.5, 28.6, 29.9, 30.8, 32.7, 33.0, 33.8, 34.3, 36.9, 37.0, 37.4, 38.6, 38.9, 39.8, 40.8, 42.7, 47.1, 47.5, 49.8, 50.1, 55.1, 56.8, 109.0, 109.9, 112.0, 114.4, 124.5, 128.3, 129.4, 138.7, 141.3, 142.7, 144.4, 147.4, 150.5, 156.6, 172.8, 218.3. HRMS (ESI): m/z calcd for $C_{49}H_{63}N_3NaO_4$ $(M+Na)^+$, 780.4716, found 780.4724.

*2.2.4.10. (E)-6,6-Dimethyl-1-(4-fluorophenyl)-3-(furan-2-yl)-6,7-dihydro-1H-indazol-4(5H)-one O-(3-oxolup-20(29)-en-28-oyl) oxime (**9j**)*

The title compound was prepared in 64% yield from oxime **8j** as a white solid. Mp: 175−179 °C. IR (KBr) ν_{max}: 700, 745, 830, 840, 885, 900, 910, 920, 940, 995, 1050, 1080, 1095, 1110, 1135, 1165, 1225, 1290, 1320, 1370, 1390, 1420, 1460, 1510, 1520, 1620, 1640, 1705, 1750, 2875−3135. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.86−2.52 (m, 24H, CH, CH_2), 0.92 (s, 3H, CH_3), 0.98 (s, 3H, CH_3), 1.00 (s, 3H, CH_3), 1.02 (s, 3H, CH_3), 1.06 (s, 3H, CH_3), 1.10 (s, 3H, CH_3), 1.12 (s, 3H, CH_3), 1.72 (s, 3H, CH_3), 2.67 (s, 2H, CH_2), 2.72 (d, J = 16.3 Hz, AB system, 1H, CH_2), 2.76 (d, J = 16.3 Hz, AB system, 1H, CH_2), 3.11−3.16 (m, 1H, C19-H), 4.64 (brs, 1H, H_{vinyl}), 4.77 (brs, 1H, H_{vinyl}), 6.60 (dd, J = 3.5 Hz, 1.8 Hz, 1H, H_{furyl}), 7.17−7.21 (m, 2H, H_{arom}), 7.49−7.52 (m, 3H, $2H_{arom}$, $1H_{furyl}$), 8.30 (dd, J = 3.5, 0.5 Hz, 1H, H_{furyl}). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.8, 16.1, 16.1, 19.5, 19.8, 21.2, 21.6, 25.7, 26.7, 28.5, 28.6, 29.9, 30.8, 32.7, 33.0, 33.8, 34.3, 36.8, 37.1, 37.4, 38.6, 38.8, 39.8, 40.8, 42.7, 47.1, 47.5, 49.9, 50.1, 55.1, 56.8, 109.0, 109.9, 112.1, 114.5, 116.4 (d, J = 23 Hz), 126.5 (d, J = 9 Hz), 134.9, 141.4, 142.8, 144.5, 147.3, 150.4, 156.4, 162.2 (d, J = 249 Hz), 172.8, 218.2. ^{19}F NMR (470 MHz, $CDCl_3$) δ: −112.7 (1F); HRMS (ESI): m/z calcd for $C_{49}H_{62}FN_3NaO_4$ $(M+Na)^+$ 798,4622, found 798.4629.

*2.2.4.11. 6,6-Dimethyl-1-phenyl-6,7-dihydro-1H-indazol-4(5H)-one O-(3-oxolup-20(29)-en-28-oyl) oxime (**9k**)*

The title compound was prepared as a 80:20 mixture of *Z*/*E* isomers according (NMR data) in 83% yield from oxime **8k** as a white solid. Mp: 170−171 °C. IR (KBr) ν_{max}: 3465, 2955 (CH), 2870 (CH), 1755 (COOR), 1705 (CO), 1630, 1600, 1505,

1455, 1105, 1075, 1055, 895, 840, 760, 695. The NMR (500 MHz, $CDCl_3$) data are provided in Table 2. HRMS (ESI): m/z calcd for $C_{45}H_{62}N_4O_3$ $(M+H)^+$ 692.4786, found 798.4629. 692.4782.

*2.2.4.12. (E)-3,6,6-Trimethyl-1-phenyl-6,7-dihydro-1H-indazol-4(5H)-one O-(3-oxolup-20(29)-en-28-oyl) oxime (**9l**)*

The title compound was prepared in 63% yield from oxime **8l** as a white solid. Mp: 142−144 °C. IR (KBr) ν_{max}: 3440, 2955 (CH), 2870 (CH), 1750 (COOR), 1705 (CO), 1600, 1510, 1460, 1105, 1060, 895, 760, 695. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.93 (s, 3H, CH_3), 1.01 (s, 3H, CH_3), 1.02 (s, 6H, C6′-Ha, C6′-Hb), 1.10 (s, 3H, CH_3), 1.09 (s, 3H, CH_3), 1.08 (s, 3H, CH_3), 1.60-1.21 (m, 15H, CH, CH_2), 1.77−1.68 (m, 1H, CH), 1.73 (s, 3H, CH_3), 1.98−1.85 (m, 2H, CH/CH_2), 2.14−2.03 (m, 2H, CH/CH_2), 2.52−2.31 (m, 4H, CH, CH_2), 2.63 (s, 3H, C3′-C$\underline{H_3}$), 2.66 (s, 2H, C5′/7′), 2.69 (s, 2H, C5′/7′), 3.14 (td, J = 11.7 Hz, J = 5.4 Hz, 1H, CH), 4.64 (brs, 1H, H_{vinyl}), 4.76 (brs, 1H, H_{vinyl}), 7.42−7.34 (m, 1H, H_{arom}), 7.53−7.43 (m, 4H, H_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.8, 14.9, 15.3, 16.1, 16.2, 19.5, 19.8, 21.2, 21.6, 22.2, 24.6, 24.9, 25.7, 26.7, 29.9, 30.7, 32.3, 33.8, 34.3, 37.1, 37.3, 38.5, 39.8, 40.8, 42.6, 47.0, 47.5, 49.98, 50.10, 55.2, 56.6, 110.1, 113.4, 115.5, 121.3, 138.7, 146.4, 147.7, 149.3, 150.6, 153.0, 159.5, 172.8, 218.2. HRMS (ESI): m/z calcd for $C_{46}H_{64}N_3O_3$ $(M+H)^+$ 706.4942, found 706.4926.

*2.2.4.13. 3-Methyl-1-pyrid-2-yl-6,7-dihydro-1H-indazol-4(5H)-one O-(3-oxolup-20(29)-en-28-oyl) oxime (**9m**)*

The title compound was prepared in 25% yield from oxime **8m** as a white solid. Mp: 142−144 °C. IR (KBr) ν_{max}: 3425, 2945 (CH), 2870 (CH), 1750 (COOR),

1705 (CO), 1590, 1470, 1445, 1390, 1135−1085, 880, 780, 700. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.92 (s, 3H, CH_3), 1.00 (s, 9H, $3CH_3$), 1.06 (s, 3H), 1.10−0.89 (m, 2H, CH/CH_2), 1.56−1.23 (m, 15H, CH, CH_2), 1.81−1.65 (m, 1H, CH), 1.70 (s, 3H, C30-H), 2.10−1.85 (m, 5H, CH, CH_2), 2.53−2.31 (m, 4H, C5′-H, CH/CH_2), 2.61 (s, 3H, C3′-C$\underline{H_3}$), 2.89−2.68 (m, 2H, C6′-H), 3.13 (td, *J* = 11.2 Hz, *J* = 4.3 Hz, 1H, CH), 3.33 (t, *J* = 6.0 Hz, 1H, C7′-H), 4.61 (bs, 1H, H_{vinyl}), 4.75 (bs, 1H, H_{vinyl}), 7.20−7.14 (m, 1H, H_{arom}), 7.80 (td, 1H, *J* = 8.1 Hz, *J* = 1.8 Hz, H_{arom}), 7.92 (d, *J* = 8.1 Hz, 1H, H_{arom}), 8.40 (d, *J* = 3.8 Hz, 1H, H_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.8, 15.3, 16.1, 16.2, 19.5, 19.8, 21.2, 21.6, 22.2, 24.6, 24.9, 25.7, 26.7, 29.9, 30.7, 32.3, 33.8, 34.3, 37.1, 37.3, 38.4, 39.8, 40.8, 42.3, 47.0, 47.5, 50.0, 50.1, 55.2, 56.6, 110.1, 113.4, 115.5, 121.3, 138.7, 146.4, 147.7, 149.3, 150.6, 152.9, 159.5, 172.8, 218.4. HRMS (ESI): m/z calcd for $C_{43}H_{59}N_4O_3$ $(M+H)^+$ 679.4582, found: 679.4580.

*2.2.4.14. 6,6-Dimethyl-1-pyrid-2-yl-6,7-dihydro-1H-indazol-4(5H)-one O-(3-oxolup-20(29)-en-28-oyl) oxime (**9n**)*

The title compound was prepared in 45% yield from oxime **8n** as a white solid. Mp: 139-141 °C. IR (KBr) ν_{max}: 3440, 2955 (CH), 2870 (CH), 1760 (COOR), 1705 (CO), 1635, 1590, 1475, 1445, 1400, 1385, 1105, 1075, 1055, 915, 885, 840, 780, 720. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.92 (s, 3H, CH_3), 1.00 (s, 6H, C6′-Ha, C6′-Hb), 1.01 (s, 3H, CH_3), 1.05 (s, 3H, CH_3), 1.12 (s, 3H, CH_3), 1.14 (s, 3H, CH_3), 1.16−0.81 (m, 1H, CH), 1.47−1.23 (m, 12H, CH, CH_2), 1.72−1.55 (m, 3H, CH, CH_2), 1.70 (s, 3H, C30-H), 2.30−1.74 (m, 5H, CH, CH_2), 2.58−2.41 (m, 3H, CH, CH_2) 2.53 (s, 2H, C5′-H), 3.11 (td, 1H, *J* = 11.3 Hz, *J* = 5.1 Hz, CH), 3.21 (s, 2H, C7′-H), 4.62 (brs, 1H, H_{vinyl}), 4.76 (bs, 1H, H_{vinyl}), 7.29−7.23 (m, 1H, $H_{pyridyl}$ (overlaping with $CHCl_3$)), 7.86 (td, *J* = 8.1 Hz, *J* = 1.7 Hz, 1H, $H_{pyridyl}$), 7.95 (d, *J* = 8.1 Hz, 1H,

$H_{pyridyl}$), 8.34 (s, 1H, C3′-H), 8.47 (d, *J* = 4.3 Hz, 1H, $H_{pyridyl}$). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.8, 16.1, 16.2, 19.5, 19.8, 21.2, 21.8, 25.7, 26.7, 28.1, 28.3, 29.9, 30.6, 32.4, 33.6, 33.8, 34.3, 37.1, 37.3, 37.9, 39.4, 39.8, 40.8, 42.4, 42.7, 46.5, 47.5, 50.17, 50.19, 55.2, 55.3, 109.9, 112.2, 115.8, 122.1, 138.9, 142.0, 145.9, 147.9, 150.5, 152.9, 153.5, 172.9, 218.4. HRMS (ESI): m/z calcd for $C_{44}H_{61}N_4O_3$ $(M+H)^+$ 693.4738, found 693.4752.

*2.2.5. Synthesis of hybrids **9m,n** by condensation with EDCI*

A mixture of betulonic acid **2** (0.45 g, 1 mmol), selected oxime **8m** or **8n** (1 mmol), 1-ethyl-3-(3-dimethylamino-propyl)carbodiimide hydrochloride (EDCI) (0.38 g, 2 mmol) and DMAP (catalytic amount) in dichloromethane (15 mL) was stirred for 20 h at room temperature, followed by addition of water (20 mL). The resulting layers were separated and the aqueous phase was extracted with dichloromethane (3 × 5 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. The solid residue was purified by column chromatography on silica gel (eluent – Hex:EtOAc 9:1 and 6:1).

*2.2.6. General procedure for the synthesis of betulinic acid hybrids **10a–10j.***

To a solution of betulonic acid hybrids **9a–9j** (1.0 mmol) in isopropanol (20 mL), $NaBH_4$ (4.0 mmol) was added. After mixing for 18 h at room temperature, the solvent was removed in vacuum, cooled (0^oC) 3% hydrochloric acid (20 ml) was added to the residue and extracted with $CHCl_3$ (5 × 10 ml). The combined organic phase was dried ($MgSO_4$) and filtered. A removal of the solvent in vacuum led to the corresponding hybrids **10a–10j.**

*2.2.6.1. (E)-(6,6-Dimethyl-3-(trifluoromethyl)-1-phenyl-6,7-dihydro-1H-indazol-4(5H)-one O-[(3β)-3-hydroxylup-20(29)-en-28-oyl] oxime (**10a**)*

The title compound was prepared in 95% yield from hybrid **9a** as a white solid. Mp 171−175 °C. IR (KBr) ν_{max}: 695, 715, 765, 795, 830, 860, 885, 900, 940, 980, 1015, 1025, 1055, 1085, 1095, 1120, 1150, 1170, 1205, 1290, 1320, 1350, 1375, 1390, 1400, 1450, 1470, 1505, 1545, 1600, 1620, 1645, 1755, 2875−3075. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.67−2.46 (m, 24H, CH, CH_2), 0.73 (s, 3H, CH_3), 0.80 (s, 3H, CH_3), 0.93 (s, 3H, CH_3), 0.95 (s, 3H, CH_3), 0.99 (s, 3H, CH_3), 1.08 (s, 3H, CH_3), 1.10 (s, 3H, CH_3), 1.69 (s, 3H, CH_3), 2.65 (d, J = 16.4 Hz, AB system, 1H, CH_2), 2.69 (d, J = 16.4 Hz, AB system, 1H, CH_2), 2.69 (s, 2H, CH_2), 3.11−3.20 (m, 2H, C3-H, C19-H), 4.61 (brs, 1H, H_{vinyl}), 4.73 (brs, 1H, H_{vinyl}), 7.44−7.53 (m, 5H, H_{arom}). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.9, 15.5, 16.3, 18.4, 19.5, 21.0, 25.7, 27.5, 28.1, 28.5, 28.6, 29.9, 30.7, 32.5, 33.2, 34.5, 36.7, 37.2, 37.3, 38.4, 38.5, 38.9, 39.0, 40.9, 42.6, 47.0, 50.1, 50.7, 55.5, 56.8, 79.1, 109.8, 110.9, 120.9 (q, J = 270 Hz), 124.3, 129.0, 129.7 138.1, 139.3 (q, J = 39 Hz), 145.3, 150.6, 154.9, 172.1. ^{19}F NMR (470 MHz, $CDCl_3$) δ: −114.0 (3F). HRMS (ESI): m/z calcd for $C_{46}H_{62}F_3N_3NaO_3$ $(M+Na)^+$ 784.4641; found 784.4650.

*2.2.6.2. (E)-(6,6-Dimethyl-3-(perfluoroethyl)-1-phenyl-6,7-dihydro-1H-indazol-4(5H)-one O-[(3β)-3-hydroxylup-20(29)-en-28-oyl] oxime (**10b**)*

The title compound was prepared in 97% yield from hybrid **9b** as a white solid. Mp 142−146 °C. IR (KBr) ν_{max}: 695, 725, 735, 750, 765, 795, 820, 860, 895, 945, 960, 980, 1010, 1025, 1055, 1085, 1100, 1120, 1155, 1190, 1220, 1290, 1315, 1330, 1375, 1390, 1400, 1450, 1465, 1500, 1543, 1600, 1620, 1645, 1755,

2875−3070. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.67−2.37 (m, 24H, CH, CH_2), 0.74 (s, 3H, CH_3), 0.81 (s, 3H, CH_3), 0.93 (s, 3H, CH_3), 0.96 (s, 3H, CH_3), 1.00 (s, 3H, CH_3), 1.09 (s, 3H, CH_3), 1.10 (s, 3H, CH_3), 1.71 (s, 3H, CH_3), 2.66 (d, J = 16.4 Hz, AB system, 1H, CH_2), 2.70 (d, J = 16.4 Hz, AB system, 1H, CH_2), 2.70 (s, 2H, CH_2), 3.12−3.20 (m, 2H, C3-H, C19-H), 4.61 (brs, 1H, H_{vinyl}), 4.74 (brs, 1H, H_{vinyl}), 7.45−7.54 (m, 5H, H_{arom}). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.9, 15.5, 16.2, 16.3, 18.5, 19.6, 21.1, 25.8, 27.6, 28.1, 28.4, 28.6, 30.0, 30.8, 32.6, 33.1, 34.6, 36.9, 37.3, 37.4, 38.5, 38.6, 38.9, 39.0, 40.9, 42.6, 47.1, 50.1, 50.8, 55.5, 56.8, 79.2, 109.8, 110.9 (tq, J = 252 Hz, 39 Hz), 112.3, 119.3 (qt, J = 287 Hz, 37 Hz), 124.3, 129.0, 129.7, 138.2, 138.4 (t, J = 30 Hz), 145.2, 150.6, 154.8, 172.1. ^{19}F NMR (470 MHz, $CDCl_3$) δ: −82.0 (3F), −110.3 (2F). HRMS (ESI): m/z calcd for $C_{47}H_{62}F_5N_3NaO_3$ $(M+Na)^+$ 834.4609; found, 834.4616.

*4.1.6.3. (E)-(6,6-Dimethyl-3-(perfluoropropyl)-1-phenyl-6,7-dihydro-1H-indazol-4(5H)-one O-[(3β)-3-hydroxylup-20(29)-en-28-oyl] oxime (**10c**)*

The title compound was prepared in 97% yield from hybrid **9c** as a white solid. Mp: 199−204 °C. IR (KBr) ν_{max}: 660, 675, 695, 715, 735, 750, 765, 820, 860, 890, 920, 935, 985, 1010, 1020, 1055, 1085, 1110, 1190, 1210, 1230, 1320, 1355, 1375, 1390, 1400, 1450, 1465, 1500, 1545, 1600, 1620, 1645, 1755, 2870−3070. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.67−2.36 (m, 24H, CH, CH_2), 0.75 (s, 3H, CH_3), 0.82 (s, 3H, CH_3), 0.93 (s, 3H, CH_3), 0.96 (s, 3H, CH_3), 1.00 (s, 3H, CH_3), 1.08 (s, 3H, CH_3), 1.09 (s, 3H, CH_3), 1.71 (s, 3H, CH_3), 2.65 (d, J = 16.3 Hz, AB system, 1H, CH_2), 2.68 (d, J = 16.3 Hz, AB system, 1H, CH_2), 2.70 (s, 2H, CH_2), 3.10−3.20 (m, 2H, C3-H, C19-H), 4.62 (brs, 1H, H_{vinyl}), 4.75 (brs, 1H, H_{vinyl}), 7.45−7.54 (m, 5H, H_{arom}). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 15.0, 15.5, 16.3, 18.5, 19.6, 21.1, 25.8, 27.6, 28.1, 28.4,

28.5, 29.9, 30.8, 32.6, 33.0, 34.6, 37.0, 37.3, 37.4, 38.5, 38.6, 38.9, 39.0, 40.9, 42.6, 47.1, 50.1, 50.8, 55.6, 56.8, 79.2, 109.3 (tm, J = 266 Hz), 109.8, 112.6, 112.9 (tt, J = 255 Hz, 32 Hz), 118.2 (qt, J = 289 Hz, 35 Hz), 124.4, 129.0, 129.7, 138.2, 138.5 (t, J = 30 Hz), 145.3, 150.7, 154.8, 172.0. ^{19}F NMR (470 MHz, $CDCl_3$) δ: −80.3 (3F), −108.6 (2F), −125.1 (2F). HRMS (ESI): m/z calcd for $C_{48}H_{62}F_7N_3NaO_3$ $(M+Na)^+$ 884.4577; found, 884.4588.

*2.2.6.4. (E)-6,6-Dimethyl-1-(4-fluorophenyl)-3-(trifluoromethyl)-6,7-dihydro-1H-indazol-4(5H)-one O-[(3β)-3-hydroxylup-20(29)-en-28-oyl] oxime (**10d**)*

The title compound was prepared in 96% yield from hybrid **9d** as a white solid. Mp > 245 °C (decomp.). IR (KBr) ν_{max}: 700, 720, 740, 765, 845, 885, 895, 940, 985, 1010, 1035, 1055, 1085, 1095, 1120, 1150, 1170, 1205, 1235, 1290, 1350, 1375, 1390, 1405, 1420, 1455, 1465, 1510, 1550, 1620, 1645, 1755, 2875−3075. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.67−2.36 (m, 24H, CH, CH_2), 0.74 (s, 3H, CH_3), 0.80 (s, 3H, CH_3), 0.93 (s, 3H, CH_3), 0.95 (s, 3H, CH_3), 0.99 (s, 3H, CH_3), 1.09 (s, 3H, CH_3), 1.10 (s, 3H, CH_3), 1.70 (s, 3H, CH_3), 2.62 (d, J = 16.3 Hz, AB system, 1H, CH_2), 2.65 c (2H, CH_2), 2.69 (d, J = 16.3 Hz, AB system, 1H, CH_2), 3.11−3.20 (m, 2H, C3-H, C19-H), 4.61 (brs, 1H, H_{vinyl}), 4.73 (brs, 1H, H_{vinyl}), 7.19−7.22 (m, 2H, H_{arom}), 7.44−7.47 (m, 2H, H_{arom}). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.9, 15.5, 16.3, 18.4, 19.5, 21.0, 25.7, 27.5, 28.1, 28.5, 28.6, 29.9, 30.7, 32.5, 33.2, 34.5, 36.7, 37.2, 37.3, 38.4, 38.5, 38.9, 39.0, 40.9, 42.6, 47.0, 50.1, 50.7, 55.5, 56.8, 79.1, 109.8, 110.9, 120.9 (q, J = 270 Hz), 124.3, 129.0, 129.7 138.1, 139.3 (q, J = 39 Hz), 145.3, 150.6, 154.9, 162.6 (d, J = 250 Hz), 172.1. ^{19}F NMR (470 MHz, $CDCl_3$) δ: −114.0 (3F). HRMS (ESI): m/z calcd for $C_{46}H_{61}F_4N_3NaO_3$ $(M+Na)^+$ 802.4547; found 802.4540.

*2.2.6.5. (E)-6,6-Dimethyl-1-(4-fluorophenyl)-3-(perfluoroethyl)-6,7-dihydro-1H-indazol-4(5H)-one O-[(3β)-3-hydroxylup-20(29)-en-28-oyl] oxime (**10e**)*

The title compound was prepared in 95% yield from hybrid **9e** as a white solid. Mp: > 210 °C (decomp.). IR (KBr) ν_{max}: 705, 720, 735, 750, 765, 790, 830, 845, 885, 900, 945, 960, 985, 1010, 1035, 1055, 1085, 1100, 1120, 1150, 1190, 1225, 1285, 1315, 1335, 1380, 1390, 1400, 1420, 1450, 1465, 1500, 1515, 1545, 1620, 1645, 1755, 2875−3075. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.67−2.37 (m, 24H, CH, CH_2), 0.75 (s, 3H, CH_3), 0.81 (s, 3H, CH_3), 0.93 (s, 3H, CH_3), 0.96 (s, 3H, CH_3), 1.00 (s, 3H, CH_3), 1.09 (s, 3H, CH_3), 1.10 (s, 3H, CH_3), 1.71 (s, 3H, CH_3), 2.65 (d, J = 16.2 Hz, AB system, 1H, CH_2), 2.66 (s, 2H, CH_2), 2.70 (d, J = 16.4 Hz, AB system, 1H, CH_2), 3.12−3.20 (m, 2H, C3-H, C19-H), 4.62 (brs, 1H, H_{vinyl}), 4.74 (brs, 1H, H_{vinyl}), 7.20−7.24 (m, 2H, H_{arom}). 7.45−7.54 (m, 2H, H_{arom}). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 15.0, 15.5, 16.2, 16.3, 18.5, 19.6, 21.1, 25.8, 27.6, 28.2, 28.5, 28.6, 30.0, 30.8, 32.6, 33.1, 34.6, 36.8, 37.3, 37.4, 38.5, 38.6, 38.9, 39.0, 40.9, 42.6, 47.1, 50.1, 50.8, 55.6, 56.8, 79.2, 109.8, 110.9 (tq, J = 252 Hz, 39 Hz), 111.0, 116.7 (d, J = 23 Hz), 119.3 (qt, J = 287 Hz, 37 Hz), 126.3 (d, J = 23 Hz), 134.2, 138.4 (t, J = 30 Hz), 145.3, 150.6, 154.6, 162.6 (d, J = 250 Hz), 172.1. ^{19}F NMR (470 MHz, $CDCl_3$) δ: −82.0 (3F), −110.4 (2F), −111.5 (1F). HRMS (ESI): m/z calcd for $C_{47}H_{61}F_6N_3NaO_3$ $(M+Na)^+$ 852.4515; found 852.4527.

*2.2.6.6. (E)-6,6-Dimethyl-1-(4-fluorophenyl)-3-(perfluoropropyl)-6,7-dihydro-1H-indazol-4(5H)-one O-[(3β)-3-hydroxylup-20(29)-en-28-oyl] oxime (**10f**)*

The title compound was prepared in 95% yield from hybrid **9f** as a white solid. Mp: > 210 °C (decomp.). IR (KBr) ν_{max}: 700, 710, 735, 750, 765, 830, 845, 920, 935, 985, 1015, 1025, 1055, 1085, 1095, 1115, 1125, 1155, 1190, 1210, 1230, 1285, 1350,

1375, 1390, 1400, 1420, 1455, 1465, 1500, 1515, 1620, 1645, 1755, 2870–3080. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.66–2.36 (m, 24H, CH, CH_2), 0.75 (s, 3H, CH_3), 0.81 (s, 3H, CH_3), 0.92 (s, 3H, CH_3), 0.96 (s, 3H, CH_3), 0.99 (s, 3H, CH_3), 1.08 (s, 3H, CH_3), 1.09 (s, 3H, CH_3), 1.71 (s, 3H, CH_3), 2.65 (d, J = 16.3 Hz, AB system, 1H, CH_2), 2.66 (s, 2H, CH_2), 2.68 (d, J = 16.3 Hz, AB system, 1H, CH_2), 3.10–3.20 (m, 2H, C3-H, C19-H), 4.62 (brs, 1H, H_{vinyl}), 4.74 (brs, 1H, H_{vinyl}), 7.20–7.24 (m, 2H, H_{arom}). 7.44–7.48 (m, 2H, H_{arom}). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 15.0, 15.5, 16.3, 18.5, 19.6, 21.1, 25.8, 27.6, 28.1, 28.4, 28.5, 30.0, 30.8, 32.6, 33.0, 34.6, 36.8, 37.3, 37.4, 38.5, 38.9, 39.0, 40.9, 42.6, 47.0, 50.0, 50.8, 55.5, 56.8, 79.2, 109.3 (tm, J = 266 Hz), 109.8, 112.7, 112.9 (tt, J = 255 Hz, 32 Hz), 116.7 (d, J = 23 Hz), 118.2 (qt, J = 289 Hz, 35 Hz), 126.4 (d, J = 9 Hz), 134.3, 138.5 (t, J = 30 Hz), 145.4, 150.6, 154.6, 162.6 (d, J = 250 Hz), 172.0. ^{19}F NMR (470 MHz, $CDCl_3$) δ: −80.0 (3F), −108.3 (2F), −111.4 (1F), −124.8 (2F). HRMS (ESI): m/z calcd for $C_{48}H_{61}F_8N_3NaO_3$ $(M+Na)^+$ 902.4483 found, 902.4492.

*2.2.6.7. (E)-3-(Cyclopropyl)-6,6-dimethyl-1-phenyl-dihydro-1H-indazol-4(5H)-one O-[(3β)-3-hydroxylup-20(29)-en-28-oyl] oxime (**10g**)*

The title compound was prepared in 95% yield from hybrid **9g** as a white solid. Mp 169–173 °C. IR (KBr) ν_{max}:): 675, 695, 735, 790, 820, 855, 885, 895, 910, 942, 975, 980, 1010, 1025, 1035, 1055, 1085, 1100, 1105, 1130, 1160, 1170, 1190, 1250, 1295, 1320, 1370, 1375, 1390, 1405, 1450, 1465, 1510, 1545, 1600, 1620, 1645, 1745, 2870–3070. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.67–2.38 (m, 28H, CH, CH_2), 0.75 (s, 3H, CH_3), 0.81 (s, 3H, CH_3), 0.95 (s, 3H, CH_3), 0.96 (s, 3H, CH_3), 1.00 (s, 6H, $2CH_3$), 1.08 (s, 3H, CH_3), 1.09 (s, 3H, CH_3), 1.71 (s, 3H, CH_3), 2.65 (s, 2H, CH_2), 2.65 (d, J = 16.5 Hz, AB system, 1H, CH_2), 2.69 (d, J = 16.5 Hz, AB system,

1H, CH_2), 2.75−2.80 (m, 1H, $CH_{cyclopropyl}$) 3.10−3.20 (m, 2H, C3-H, C19-H), 4.62 (brs, 1H, H_{vinyl}), 4.74 (brs, 1H, H_{vinyl}), 7.33−7.47 (m, 5H, H_{arom}). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 9.2, 9.8, 9.9, 14.9, 15.5, 16.3, 16.5, 18.5, 19.5, 21.1, 25.7, 27.6, 28.1, 28.6, 28.7, 29.9, 30.8, 32.6, 33.3, 34.6, 36.9, 37.3, 37.5, 38.6, 38.8, 38.9, 39.0, 40.9, 42.6, 47.2, 50.0, 50.7, 55.5, 56.9, 79.2, 109.8, 111.4, 123.8, 127.6, 129.4, 139.0, 143.6, 150.6, 154.0, 158.4, 172.9. HRMS (ESI): m/z calcd for $C_{48}H_{67}N_3NaO_3$ $(M+Na)^+$ 756.5080, found 756.5091.

*4.1.6.8. (E)-3-(Cyclopropyl)-6,6-dimethyl-1-(4-fluorophenyl)-dihydro-1H-indazol-4(5H)-one O-[(3β)-3-hydroxylup-20(29)-en-28-oyl] oxime (**10h**)*

The title compound was prepared in 96% yield from hybrid **9h** as a white solid. Mp 182-186 °C. IR (KBr) ν_{max}: 665, 725, 755, 840, 890, 940, 985, 1110, 1035, 1054, 1100, 1295, 1320, 1370, 1380, 1390, 1400, 1420, 1455, 1465, 1520, 1605, 1615, 1645, 1745, 2870−3070. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.66−2.37 (m, 28H, CH, CH_2), 0.74 (s, 3H, CH_3), 0.80 (s, 3H, CH_3), 0.94 (s, 3H, CH_3), 0.95 (s, 3H, CH_3), 1.00 (s, 6H, $2CH_3$), 1.07 (s, 3H, CH_3), 1.08 (s, 3H, CH_3), 1.70 (s, 3H, CH_3), 2.60 (s, 2H, CH_2), 2.64 (d, J = 16.4 Hz, AB system, 1H, CH_2), 2.68 (d, J = 16.4 Hz, AB system, 1H, CH_2), 2.73−2.79 (m, 1H, $CH_{cyclopropyl}$) 3.09−3.19 (m, 2H, C3-H, C19-H), 4.61 (brs, 1H, H_{vinyl}), 4.74 (brs, 1H, H_{vinyl}), 7.12−7.15 (m, 2H, H_{arom}), 7.37−7.40 (m, 2H, H_{arom}). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 9.2, 9.7, 9.8, 14.9, 15.5, 16.3, 16.5, 18.4, 19.5, 21.1, 25.7, 27.5, 28.1, 28.6, 28.7, 29.9, 30.8, 32.6, 33.3, 34.6, 36.8, 37.3, 37.4, 38.6, 38.7, 38.9, 39.0, 40.9, 42.6, 47.2, 50.0, 50.7, 55.5, 56.8, 79.1, 109.8, 111.4, 116.2 (d, J = 23 Hz), 125.6 (d, J = 8 Hz), 135.2, 143.6, 150.6, 154.0, 158.3, 161.7 (d, J = 248 Hz), 172.8. ^{19}F NMR (470 MHz, $CDCl_3$) δ: −113.8 (1F). HRMS (ESI): m/z calcd for $C_{48}H_{66}FN_3NaO_3$ $(M+Na)^+$ 774.4986, found 774.4972.

*2.2.6.9. (E)-6,6-Dimethyl-1-phenyl-3-(furan-2-yl)-dihydro-1H-indazol-4(5H)-one O-[(3β)-3-hydroxy-lup-20(29)-en-28-oyl] oxime (**10i**)*

The title compound was prepared in 96% yield from hybrid **9i** as a white solid. Mp: 196−200 °C; IR (KBr) ν_{max}: 675, 700, 720, 745, 765, 795, 820, 830, 855, 995, 1025, 1035, 1050, 1060, 1085, 1100, 1135, 1165, 1225, 1240, 1315, 1370, 1390, 1435, 1455, 1470, 1485, 1505, 1540, 1600, 1625, 1640, 1750, 2870−3070. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.67−2.40 (m, 24H, CH, CH_2), 0.74 (s, 3H, CH_3), 0.81 (s, 3H, CH_3), 0.95 (s, 3H, CH_3), 1.01 (s, 3H, CH_3), 1.01 (s, 3H, CH_3), 1.10 (s, 3H, CH_3), 1.11 (s, 3H, CH_3), 1.72 (s, 3H, CH_3), 2.71 (s, 2H, CH_2), 2.73 (d, J = 16.4 Hz, AB system, 1H, CH_2), 2.76 (d, J = 16.4 Hz, AB system, 1H, CH_2), 3.11−3.19 (m, 2H, C3-H, C19-H), 4.63 (brs, 1H, H_{vinyl}), 4.77 (brs, 1H, H_{vinyl}), 6.60 (dd, J = 3.5, 1.7 Hz, 1H, H_{furyl}), 7.40−7.43 (m, 1H, H_{arom}), 7.48−7.54 (m, 5H, $4H_{arom}$, $1H_{furyl}$), 8.30 (d, J = 3.5 Hz, 1H, H_{furyl}). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.9, 15.5, 16.2, 16.3, 18.4, 19.6, 21.1, 25.8, 27.5, 28.1, 28.5, 28.6, 29.9, 30.8, 32.8, 33.0, 34.5, 37.0, 37.4, 37.5, 38.6, 38.8, 38.9, 39.0, 40.9, 42.7, 47.2, 49.9, 50.7, 55.5, 56.9, 79.1, 109.0, 109.9, 112.1, 114.4, 124.6, 128.3, 129.4, 138.8, 141.4, 142.7, 144.4, 147.4, 150.6, 156.5, 172.9. HRMS (ESI): m/z calcd for $C_{49}H_{65}N_3NaO_4$ $(M+Na)^+$ 782.4873, found 782.4882.

*2.2.6.10. (E)-6,6-Dimethyl-1-(4-fluorophenyl)-3-(furan-2-yl)-dihydro-1H-indazol-4(5H)-one O-[(3β)-3-hydroxylup-20(29)-en-28-oyl] oxime (**10j**)*

The title compound was prepared in 94% yield from hybrid **9j** as a white solid. Mp 192−196 °C. IR (KBr) ν_{max}: 705, 730, 745, 765, 830, 840, 885, 895, 905, 920, 940, 985, 995, 1010, 1035, 1055, 1085, 1100, 1110, 1130, 1165, 1185, 1230, 1290, 1320, 1375, 1390, 1415, 1455, 1465, 1485, 1510, 1515, 1620, 1640, 1750,

2870−2135. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.67−2.40 (m, 24H, CH, CH_2), 0.74 (s, 3H, CH_3), 0.81 (s, 3H, CH_3), 0.95 (s, 3H, CH_3), 0.96 (s, 3H, CH_3), 1.01 (s, 3H, CH_3), 1.10 (s, 3H, CH_3), 1.12 (s, 3H, CH_3), 1.72 (s, 3H, CH_3), 2.67 (s, 2H, CH_2), 2.72 (d, J = 16.3 Hz, AB system, 1H, CH_2), 2.76 (d, J = 16.3 Hz, AB system, 1H, CH_2), 3.10−3.20 (m, 2H, C3-H, C19-H), 4.64 (brs, 1H, H_{vinyl}), 4.77 (brs, 1H, H_{vinyl}), 6.61 (dd, J = 3.5, 1.7 Hz, 1H, H_{furyl}), 7.17−7.21 (m, 2H, H_{arom}), 7.49−7.52 (m, 3H, $2H_{arom}$, $1H_{furyl}$), 8.30 (d, J = 3.5 Hz, 1H, H_{furyl}). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.9, 15.5, 16.2, 16.3, 18.4, 19.6, 21.1, 25.7, 27.5, 28.1, 28.5, 28.6, 29.9, 30.8, 32.8, 33.0, 34.5, 36.8, 37.4, 37.5, 38.6, 38.9, 39.0, 40.9, 42.7, 47.2, 49.9, 50.7, 55.5, 56.9, 79.1, 109.1, 109.9, 112.1, 114.6, 116.4 (d, J = 23 Hz), 126.5 (d, J = 9 Hz), 134.9, 141.4, 142.8, 144.5, 147.3, 150.5, 156.4, 162.2 (d, J = 249 Hz), 172.9. ^{19}F NMR (470 MHz, $CDCl_3$) δ: −112.7 (1F). HRMS (ESI): m/z calcd for $C_{49}H_{64}FN_3NaO_4$ $(M+Na)^+$ 800.4779, found 800.4783.

*2.2.7. (E)-3-Cyclopropyl-6,6-dimethyl-1-phenyl-1,5,6,7-tetrahydro-4H-indazol-4-one O-ethyl oxime (**11**)*

To a solution of oxime **8g** (0.15 mmol, 0.05 g) in 5 ml of DMF, sodium hydroxide (0.3 mmol, 0.012 g) was added and the mixture was stirred at room temperature for 30 min. Then ethyl iodide (0.3 mmol, 0.048 g, 0.025 ml) was added, the reaction mixture was stirred for 24 h, treated with 50 ml of 3% aqueous HCl and extracted with ether (3 x 15 ml). The combined organic phase was dried ($MgSO_4$) and filtered. After removal of the solvent in vacuum, the residue was purified by silica gel column chromatography with petroleum/ethyl acetate as eluent to give the *O*-ethyl oxime **11** in 75% yield as white solid. Mp 127−129 °C. IR (KBr) ν_{max}: 670, 680, 695, 725, 740, 765, 790, 810, 830, 875, 910, 940, 980, 1030, 1035, 1045, 1065, 1090,

1120, 1250, 1290, 1355, 1365,.1385, 1400, 1420, 1450, 1470, 1500, 1510, 1540, 1600, 1610, 2840−3085. The NMR (500 MHz, acetone-d_6) data are provided in Table 2. HRMS (ESI): m/z calcd for $C_{20}H_{25}N_3NaO$ $(M+Na)^+$ 346.1895, found 346.1886.

2.2.8. General methods for synthesis of model oxime acetates ***12-14****.*

General method I for preparation of model *O*-acetyl oximes: a mixture in a ratio of oxime (0.25 g), acetic anhydride (5.0 mL) and pyridine (10.0 mL) was stirred at room temperature, followed by addition of water until the precipitate is formed. The resulting mixture was stirred, filtered and washed with water. The obtained solid was dried in the air.

General method II for preparation of model *O*-acetyl oximes is equal to the method described in chapter 2.2.4., but differs by the use of AcCl instead betulonic acid chloride (**6**): acetylchloride (0.1 mL, 1.4 mmol) in chloroform (10 mL) was added to cold oxime (1 mmol) and Py (0.1 mL) in chloroform (10 mL) and refluxed for 12 h. The solution was washed with 10% hydrochloric acid (3×10 mL) and water (10 mL), dried over $MgSO_4$, filtered and evaporated. Hexane was added to the remaining oil and the mixture was evaporated to dryness. The obtained solid residue was dissolved in methanol and water was added. The formed white precipitate was filtered and dried in air.

*2.2.8.1. (E)-3,6,6-Trimethyl-1-phenyl-1,5,6,7-tetrahydro-4H-indazol-4-one O-acetyl oxime (****12****)*

The title compound was prepared in 99% (method I) or 70% (method II) yield from oxime **8l** as white solid. Mp 173−175 °C. IR (KBr) ν_{max}: 3105−2835 (CH), 1765 (COOR), 1625, 1610, 1600, 1505, 1420, 1370, 1205, 1005, 930, 920, 880, 765, 695.

^{1}H NMR (300 MHz, C_6D_6, 60°C) δ: 0.69 (s, 6H, C6-(C<u>H</u>$_3$)$_2$), 1.97 (s, 3H, CH_3 from Ac), 2.22 (s, 2H, C7-H), 2.44 (s, 2H, C5-H), 2.77 (s, 3H, C3-C<u>H</u>$_3$), 7.00 (t, *J* = 8.2 Hz, 1H, H_{arom}), 7.13 (t, *J* = 8.2 Hz, 2H, H_{arom}), 7.40 (d, *J* = 8.2 Hz, 2H, H_{arom}). ^{13}C NMR (75 MHz, C_6D_6, 60°C) δ: 15.0, 19.6, 28.1, 33.1, 37.2, 38.1, 112.1, 123.5, 127.1, 129.3, 140.1, 143.6, 148.2, 157.5, 168.9. HRMS (ESI): m/z calcd for $C_{18}H_{21}N_3O_2$ $(M+H)^+$: 312.1707, found 312.1698.

*2.2.8.2. 6,6-Dimethyl-1-phenyl-1,5,6,7-tetrahydro-4H-indazol-4-one O-acetyl oxime (**13**)*

The title compounds were prepared as a 60:40 mixture of *Z*/*E* isomers (NMR data) in 90% (method I) or 69% (method II) yield from oxime **8k** as white solid. Mp 113–131 °C. IR (KBr) ν_{max}: 3065–2830 (CH), 1765 (COOR), 1610, 1550, 1510, 1495, 1205, 995, 930, 885, 845, 765, 700. NMR data for (*Z*)-**13** (major isomer): ^{1}H NMR (300 MHz, C_6D_6) δ: 0.622 (s, 6H, C6-(C<u>H</u>$_3$)$_2$), 1.79 (s, 3H, CH_3 from Ac), 2.14 (s, 2H, C7-H), 2.25 (s, 2H, C5-H), 7.03–6.95 (m, 1H, H_{arom}), 7.09 (t, *J* = 7.3 Hz, 2H, H_{arom}), 7.40–7.33 (m, 2H, H_{arom}), 8.66 (s, 1H, C3-H). ^{13}C NMR (75 MHz, C_6D_6) δ: 19.4, 27.3, 33.1, 37.4, 42.1, 111.8, 124.0, 127.4, 129.4, 139.7, 142.5, 143.7, 153.3, 167.7. NMR data for (*E*)-**13** (minor isomer): ^{1}H NMR (300 MHz, C_6D_6) δ: 0.619 (s, 6H, C6-(C<u>H</u>$_3$)$_2$), 1.93 (s, 3H, CH_3 from Ac), 2.13 (s, 2H, C7-H), 2.40 (s, 2H, C5-H), 7.03-6.95 (m, 1H, H_{arom}), 7.09 (t, *J* = 7.3 Hz, 2H, H_{arom}), 7.40–7.33 (m, 2H, H_{arom}), 8.34 (s, 1H, C3-H). ^{13}C NMR (75 MHz, C_6D_6) δ: 19.6, 28.0, 33.6, 36.7, 37.7, 114.0, 123.4, 127.4, 129.3, 137.1, 139.8, 142.9, 156.0, 168.7. HRMS (ESI): m/z calcd for $C_{17}H_{19}N_3O_2$ $(M+H)^+$ 298.1550. $C_{17}H_{19}N_3O_2$, found 298.1534.

*2.2.8.3. 6,6-Dimethyl-1-pyrid-2-yl-1,5,6,7-tetrahydro-4H-indazol-4-one O-acetyl oxime (**14**)*

The title compounds were prepared as a 60:40 mixture of *Z*/*E* isomers (NMR data) in 81% yield (method I) from oxime **8n** as white solid. Mp 95–97 °C. IR (KBr) ν_{max}: 3435–2870 (CH), 1765–1755 (COOR), 1635, 1590, 1470, 1445 1400, 1365, 1240, 1205, 1160, 1010, 995, 925, 885, 785, 720. ^{1}H NMR (300 MHz, C_6D_6) for (*Z*)-14 (major isomer) δ: 0.78 (s, 6H, C6-$(CH_3)_2$), 1.79 (s, 3H, CH_3 from Ac), 2.22 (s, 2H, C5-H), 3.09/3.08 (s, 2H, C7-H [for both isomers]), 6.54–6.45 (m, 1H, Py), 7.12–7.01 (m, 1H, Py), 8.12–7.99 (m, 2H, Py), 8.64 (s, 1H, C3-H). ^{1}H NMR (300 MHz, C_6D_6) for (*E*)-14 (major isomer) δ: 0.78 (s, 6H, C6-$(CH_3)_2$), 1.89 (s, 3H, CH_3 from Ac), 2.38 (s, 2H, C5-H), 3.09/3.08 (s, 2H, C7-H [for both isomers]), 6.54–6.45 (m, 1H, Py), 7.12–7.01 (m, 1H, Py), 8.12–7.99 (m, 2H, Py), 8.31 (s, 1H, C3-H).

^{13}C NMR (75 MHz, C_6D_6) for a mixture of (*Z*)-14 and (*E*)-14 δ: 19.5/19.4, 28.4, 32.7, 37.6, 39.0, 114.6, 115.8/115.2, 121.5/121.2, 137.7, 138.5/138.4, 145.6/144.8, 147.5/147.4, 153.8/153.7, 156.3, 168.4/167.8. HRMS (ESI): m/z calcd for $C_{16}H_{18}N_4O_2$ $[M+H]^+$ 299.1503, found 299.1495.

2.3. X-Ray analysis

*2.3.1. X-ray analysis of lupane triterpenoid-indazolone hybrid **9l***

The colourless crystals of lupane triterpenoid-indazolone hybrid **9l** ($C_{46}H_{63}O_3N_3$) are orthorhombic. At 293 K a = 9.1315(5), b = 15.370(1), c = 29.963(2) Å, V = 4205.3(5) Å^3, M_r = 705.99, Z = 4, space group $P2_12_12_1$, d_{calc}= 1.115 g/cm^3, μ(MoK_α) = 0.069 mm^{-1}, F(000) = 1536. Intensities of 27937 reflections (12250 independent, R_{int}=0.091) were measured on the «Xcalibur-3» diffractometer (graphite monochromated MoK_α radiation, CCD detector, ω-scaning, $2\Theta_{max}$ = 60°). The

structure was solved by direct method using SHELXTL package [49]. Positions of the hydrogen atoms were located from electron density difference maps and refined using "riding" model with $U_{iso} = nU_{eq}$ of the carrier atom (n = 1.5 for methyl groups and n = 1.2 for other hydrogen atoms). Full-matrix least-squares refinement against F^2 in anisotropic approximation for non-hydrogen atoms using 12202 reflections was converged to $wR_2 = 0.144$ ($R_1 = 0.069$ for 4515 reflections with $F>4\sigma(F)$, S = 0.858). The final atomic coordinates, and crystallographic data for molecule **9l** have been deposited to the Cambridge Crystallographic Data Centre, 12 Union Road, CB2 1EZ, UK (fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk) and are available on request quoting the deposition number CCDC 1474459.

*2.3.2. X-ray analysis of model compound (E)-**12**.*

The colourless crystals of model compound (*E*)-**12** ($C_{18}H_{21}N_3O_2$) are monoclinic. At 190 K a = 12.0216(5), b = 8.6746(3), c = 15.8382(9) Å, β = 100.216(2)°, V = 1625.5(1) Å^3, M_r = 311.38, Z = 4, space group $P2_1/n$, d_{calc}= 1.272 g/cm^3, $\mu(MoK_\alpha)$ = 0.085 mm^{-1}, F(000) = 664. Intensities of 3669 unique reflections (R_{int}=0.043) were measured on the Nonius KappaCCD diffractometer (graphite monochromated MoK_α radiation, $2\Theta_{max}$ = 54.84°) equipped with low temperature Oxford Cryosystems Cryostream Plus device. The structure was solved by direct method using SIR 2011 [50] and refined by SHELXL [49] as implemented in the program package WinGX [51]. Positions of the hydrogen atoms were calculated geometrically and refined using "riding" model with $U_{iso} = 1.5U_{eq}$ of the carrier atom with C – H = 0.93 – 0.96 Å. Full-matrix least-squares refinement against F^2 in anisotropic approximation for non-hydrogen atoms using 3669 reflections converged to $wR_2 = 0.1276$ ($R_1 = 0.0524$ for 2514 reflections with $F>4\sigma(F)$, S = 1.024). The final atomic coordinates, and

crystallographic data for molecule (*E*)-**12** have been deposited to the Cambridge Crystallographic Data Centre, 12 Union Road, CB2 1EZ, UK (fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk) and are available on request quoting the deposition number CCDC 1472066.

3. Results and discussion

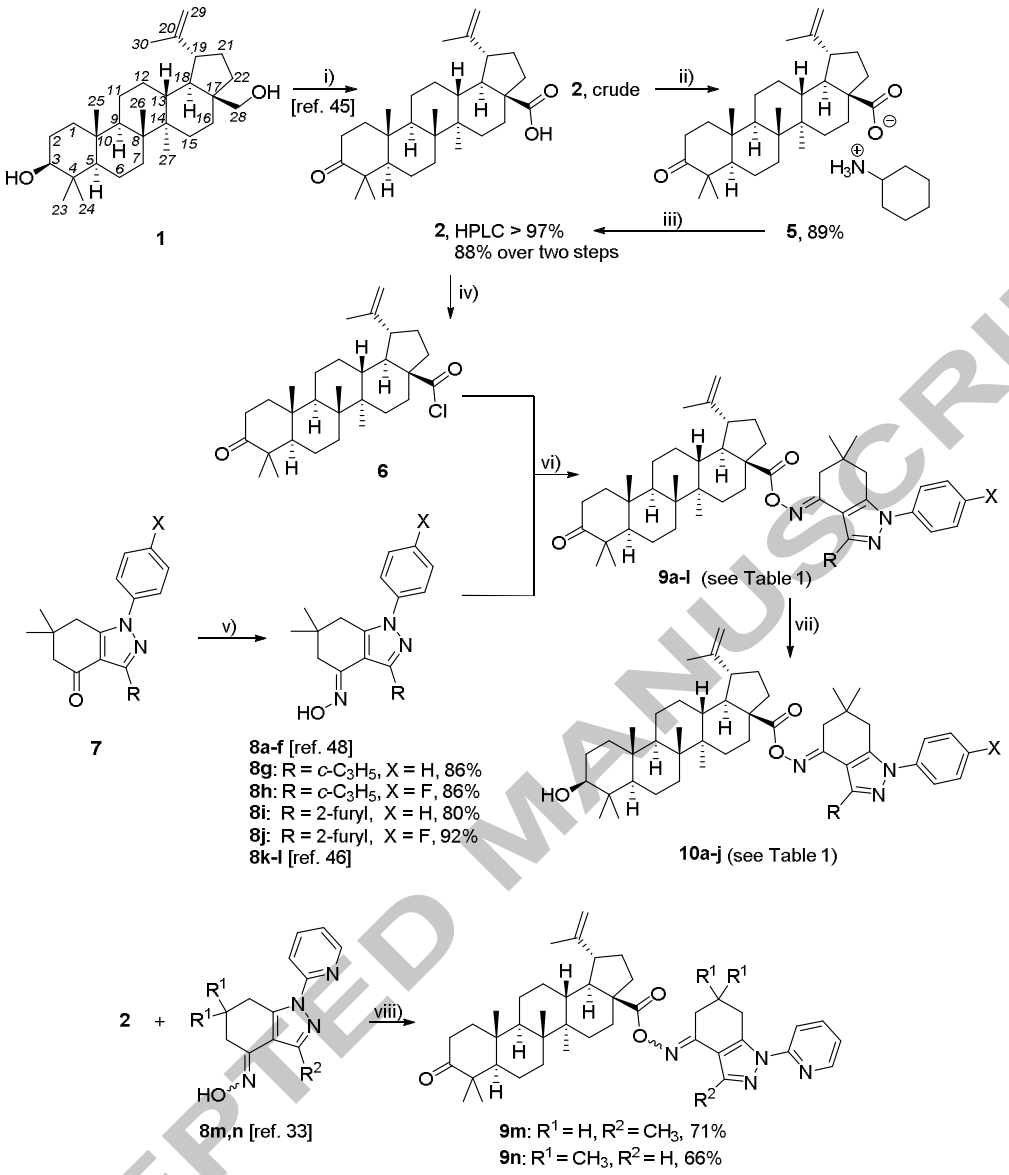
The synthetic strategy to prepare the lupane triterpenoid-indazolone hybrids is depicted in Scheme 1. It required an access to betulonic acid (**2**) and its chloride **6**.

We started our investigations with development of preparative procedure for purification of betulonic acid. The latter was obtained by standard Jones oxidation [45] and as such required purification either by preparative chromatography [52,53] or *via* crystallization of I group metal salts [45,54]. We have discovered that superior to the previously reported purification methods is formation and crystallization of cyclohexylammonium salt **5**. Thus, simple treatment of betulonic acid of technical quality with cyclohexylamine gave excellent isolated yield of salt **5** which is easy to handle. After purification procedure salt **5** is transformed into acid **2** by straightforward treatment with H_3PO_4. The described procedure was implemented on multigram quantities, it can be easy scalable and provided product **2** with HPLC purity > 97%.

Next, the purified betulonic acid **2** was transformed into the corresponding chloride **6** according to the previously reported procedure [45] and immediately coupled to the selected oxime. The respective indazolone-derived oximes **8a–n** were prepared by refluxing the corresponding keto compounds **7** with 4-fold excess of hydroxylamine hydrochloride in pyridine as described by us earlier [48]. Then with both key-components in hand one-pot procedure (**2→6→9**) leading to the target conjugates **9a-**

n was achieved. In a typical experiment a mixture consisting of a selected 6,7-dihydro-1*H*-indazol-4(5*H*)-one oxime **8**, betulonic acid chloride **6** and pyridine in $CHCl_3$ was refluxed for 5 h. The acylated products **9a-n** were obtained in average to good yields after purification by silica gel column chromatography (Table 1). Alternatively, hybrids of type **9** can be obtained by a direct condensation of acid **2** with an oxime in the presence of 1-ethyl-3-(3-dimethylamino-propyl)carbodiimide hydrochloride and catalytic amount of 4-(dimethylamino)pyridine. Following the latter procedure products **9m** and **9n** were obtained in 71% and 66% isolated yields, respectively.

In order to obtain betulinic acid derivatives with free HO-group at C3, the 3-keto products **9a-j** were diastereoselectively reduced to the expected alcohols with $NaBH_4$ in dry isopropanol. This provided betulinic acid–indazolone hybrids **10a-j** in excellent yields. The lupane skeleton ensured the hydride attack exclusively from the α-face and solely the 3β-configured hybrids **10** possessing an equatorially orientated hydroxyl group were obtained.



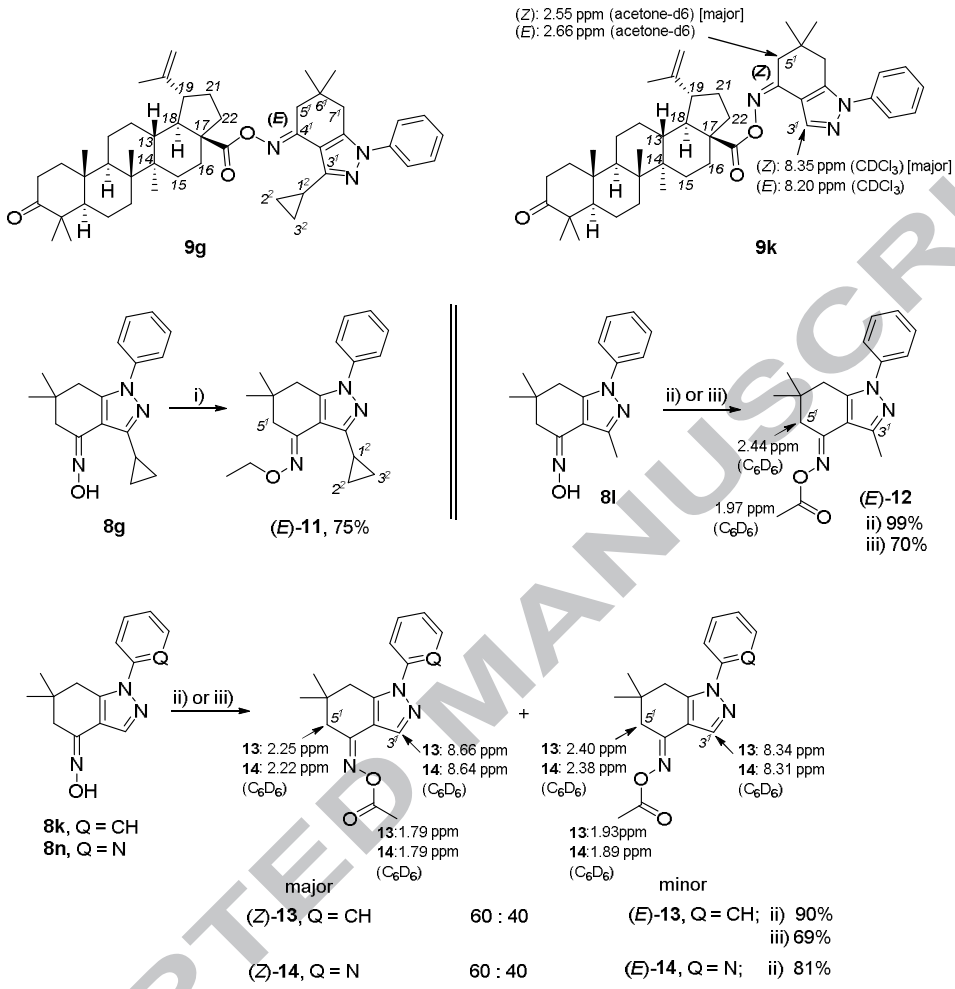
Scheme 1. Synthetic route for the preparation of target hybrids **9** and **10**. Reagents and conditions: i) Jones oxidation; ii) c-Hex-NH_2; iii) H_3PO_4; iv) $(COCl)_2$; v) $NH_2OH{\cdot}HCl$, Py, reflux, 3 h; vi) Py, $CHCl_3$, reflux, 20 h; (vii) $NaBH_4$, isopropanol, 24 h; (viii) EDCI, DMAP, CH_2Cl_2, 20 h.

Table 1.
Synthesis of betulonic acid−indazolone (**9a–l**) and betulinic acid− indazolone (**10a–j**) hybrids.

Entry	R	X	Yield of **9a–l**	Yield of **10a–j**
1	CF_3	H	**9a**, 48%	**10a**, 95%
2	C_2F_5	H	**9b**, 38%	**10b**, 97%
3	C_3F_7	H	**9c**, 35%	**10c**, 97%
4	CF_3	F	**9d**, 41%	**10d**, 96%
5	C_2F_5	F	**9e**, 38%	**10e**, 95%
6	C_3F_7	F	**9f**, 33%	**10f**, 95%
7	*c*-C_3H_5	H	**9g**, 75%	**10g**, 95%
8	*c*-C_3H_5	F	**9h**, 68%	**10h**, 96%
9	2-furyl	H	**9i**, 76%	**10i**, 96%
10	2-furyl	F	**9j**, 64%	**10j**, 94%
11	H	H	**9k**, 83%	-
12	CH_3	H	**9l**, 63%	-

With the desired oxime esters **9** and **10** in hand, we raised the question about their *E*/*Z*-configuration. It is interesting to note that all compounds **9a–j,l,m** containing R-substituent at C3′ of indazolone moiety larger than hydrogen atom were isolated as single diastereoisomers. A lack of possibility for simple spectral comparison between two isomers and intensive signal overlapping in the aliphatic regions of ^{1}H-NMR spectra made the deciphering of the structures rather difficult (Table 2). In this context we were delighted to observe the formation of diastereomeric mixtures in the case of products **9k,n** which bear C3′ unsubstituted indazolone moiety. This opened a possibility to compare chemical shifts and nuclear Overhauser effects (nOe's) between the isomers and to assign the structures. We have

also prepared model compounds **11–14** for which the aliphatic region in their ^{1}H-NMR spectra is depleted from the triterpenoid signals (Scheme 2).



Scheme 2. Synthesis and structure elucidation of model compounds **11–14** for (*E*)/(*Z*)-geometry assignment of hybrids **10g,k**. Reagents and conditions: (i) NaOH, EtI, DMF, 24 h; (ii) Ac_2O, Py, 12 h; (iii) AcCl, Py, $CHCl_3$, reflux, 12 h.

O-Alkylated oxime (*E*)-**11** was prepared with intention to obtain a compound which contains spacially near CH-system applicable for nOe analysis. It was obtained in 75% isolated yield by an *O*-alkylation of **8g** with 2 equivalents of ethyl iodide in the presence of 2 equivalents of NaOH in DMF.

NOESY data of compounds (*E*)-**9g** and (*E*)-**11** support the *anti*-configuration of the oxime group, yet these data can be considered as ambiguous. For instance,

relatively weak nOe effect between the ethyl group and H-5 was observed for compound (*E*)-**11**. On the other hand, a very weak NOESY cross-peak was found between the protons of cyclopropyl and ethyl groups as well. The latter fact can be explained with free rotation of the ethyl substituent assuming that the (*E*)-**11** configuration assignment is correct. Some interesting cross-peaks are in the spectrum of conjugate (*E*)-**9g**. Protons at C13, C19 and C22 interact with H-5 of cyclohexane ring, but interactions are weak due to big distance between protons. In overall, the NOESY data for (*E*)-**9g** are in favor of *anti*-configuration taking in account the absence of cross-peaks of the cyclopropane and phenyl rings with the lupane fragment.

Alternatively, oxime acetates **12–14** can be regarded as the simplest models for the aforementioned oxime esters with betulonic acid. The introduced methyl group from acetate can serve for the required nOe analysis. Compounds **12–14** were prepared in good isolated yields by treating the selected oximes with either acetic anhydride or acetyl chloride. The latter method fully imitates the conditions applied in synthesis of conjugates **9a-n** (oxime + RC(O)Cl + Py + $CHCl_3$) although provides lower yields than that using Ac_2O. As discussed above, the compound possessing methyl substituent at C3′ was isolated as pure (*E*)-**12** isomer. On contrary, oximes **13** and **14** were produced as inseparable mixtures of *E*/*Z*-isomers with slight preference for (*Z*)-form. Also in the case of compounds **12–14** the expected nOe's were relatively weak. Nevertheless, the molecular structure of (*E*)-**12** was unambiguously established by its single crystal X-ray analysis (Figure 3).

Further it was found that the (*E*)- and (*Z*)-isomers of oxime acetates reveal distinct ^{1}H-NMR pattern with characteristic differences for chemical shifts of protons at C3′, C5′ and acetyl group (compounds **12–14**, Scheme 2). One can assume that in C3′-H for

(*Z*)-**13/14** and C5′-H for (*E*)-**13/14** are deshielded due to the magnetic anisotropy cone of carbonyl group. Additionally, acetate H_3C-group is somewhat shielded in (*Z*)-**13/14** most probably due to the influence of the heteroaromatic system. Most importantly, the chemical shifts observed for (*E*)-**13** and (*E*)-**14** are consistent with those of (*E*)-**12**, even if the latter contains C3′-CH_3 group.

A certain similarity with (*E*)-**9g** is observed in the NOESY spectrum of compound **9k** which is a mixture of 2 isomers. The C5′-H proton of the major isomer of **9k** has cross-peaks with many protons of the lupane fragment. However, C3′-H proton has interactions with protons at C22, C19 and C16 which is in contradiction with the (*E*)-**9g** data. Moreover, the signals of the cyclohexane ring of compound **9k** are different from those of (*E*)-**11** and (*E*)-**9g**. At the same time, the ^{1}H and ^{13}C shifts of the minor isomer cyclohexane ring coincide with those of (*E*)-**11** and (*E*)-**9g**. Therefore, the major isomer of **9k** should have opposite configuration of the oxime group, i.e. 3′-unsubstituted indazolones give (*Z*)-oximes predominantly. The same conclusion can be reached from chemical shift analysis of major and minor isomers of **9k**. Similarly to differences between (*Z*)/(*E*)-**13/14** also in this case C5′-H in (*E*)-**9k** should be deshielded in comparison with (*Z*)-**9k** and C3′-H in (*Z*)-**9k** should be deshielded in comparison with (*E*)-**9k**.

Finally, after several efforts single crystals of suitable quality were obtained from compound **9l** which belongs to the majority of hybrid molecules and bears C3′-methyl group at indazole moiety. Its X-ray analysis (Figure 4) unambiguously revealed the presence of (*E*)-oxime ester linkage and thus proved the conclusions that were previously derived from the NMR analysis. Comparison of X-ray structures of compounds (*E*)-**12** and **9l** revealed that in both of them the indazole fragments are virtually superimposable and the partially saturated cycle adopts a sofa conformation.

Some decrease of conjugation was observed between oxime bond and ester carbonyl group due to rotation around N-O bond in the hybrid molecule **9l** as to compare to the model compound (*E*)-**12**. Thus, the N-O-C=O torsion angles in molecules (*E*)-**12** and **9l** are -10.7° and -17.5(5)°, respectively. It is interesting to note that the mean planes of triterpenoid fragment and indazolone fragment (with exception of methyl groups and hydrogen atoms) form dihedral angle about 68°.

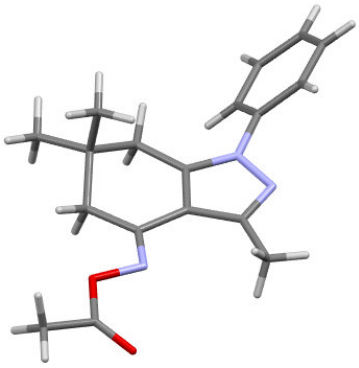


Fig. 3. X-ray structure of model compound (*E*)-**12**. Crystallographic data for oxime ester (*E*)-**12** have been deposited with the Cambridge Crystallographic Data Center as a supplementary publication No. CCDC 1472066.

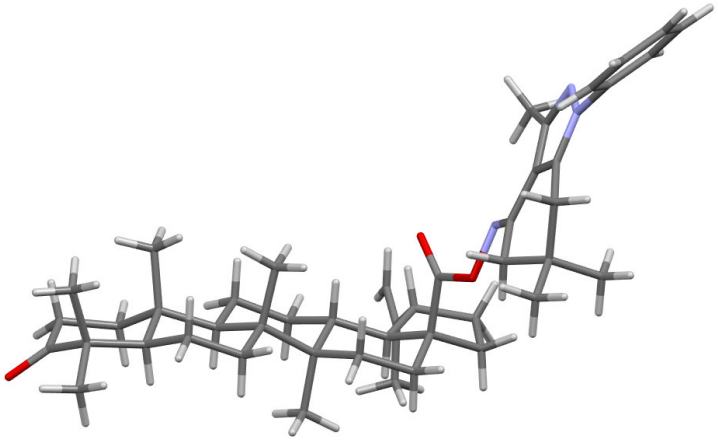


Fig. 4. X-ray structure of lupane triterpenoid-indazolone hybrid **9l**. Crystallographic data for compound **9l** have been deposited with the Cambridge Crystallographic Data Center as a supplementary publication No. CCDC 1474459.

Table 2
^{1}H (500 MHz) and ^{13}C (125 MHz) NMR data for compounds **9g, 9k** (in $CDCl_3$) and **11** (in acetone-d_6)

Position	(*E*)-9g		(*Z*)-9k (major)		(*E*)-9k minor[c]		(*E*)-11	
	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H
1	39.8	1.39, 1.91	39.8	1.38, 1.91	nd[a]	nd[a]	-	
2	34.3	2.41, 2.48	34.3	2.40, 2.48	nd[a]	1.44, 1.99	-	
3	218.3	-	218.4	-	nd[a]	-	-	
4	47.5	-	47.8	-	nd[a]	-	-	
5	55.1	1.31	55.1	1.31	nd[a]	-	-	
6	19.8	1.45 (2)	19.8	1.44 (2)	nd[a]	nd[a]	-	
7	33.9	1.43 (2)	33.8	1.41 (2)	nd[a]	nd[a]	-	
8[b]	40.8	-	40.8	-	nd[a]	-	-	
9	50.1	1.38	50.2	1.38	50.1	1.35	-	
10	37.1	-	37.0	-	nd[a]	-	-	
11	21.6	1,31, 1.45	21.6	1.32, 1.44	nd[a]	nd[a]	-	
12	25.7	1.08, 1.77	25.7	1.04, 1.78	nd[a]	nd[a]	-	
13	38.6	2.37	37.9	2.56	38.6	2.37	-	
14[b]	42.7	-	42.6	-	42.7	-	-	
15	29.9	1.26, 1.59	29.9	1.27, 1.56	29.8	1.25, 1.60	-	
16	32.5	1.51, 2.38	32.4	1.63, 2.46	nd[a]	nd[a]	-	
17	56.8	-	56.2	-	56.8	-	-	
18	49.9	1.68	50.2	1.67	49.9	1.70	-	
19	47.1	3.12	46.5	3.11	47.1	3.10	-	
20	150.6	-	150.5	-	150.4	-	-	
21	30.7	1.44, 2.07	30.6	1.42, 2.02	30.7	1.44, 1.99	-	
22	37.4	1.53, 2.07	37.3	1.55, 2.18	37.4	1.61, 2.06	-	
23	26.7	1.06	26.7	1.06	nd[a]	nd[a]	-	
24	21.2	1.00	21.1	1.01	nd[a]	nd[a]	-	
25	16.1	0.92	16.1	0.92	16.1	0.92	-	
26	16.3	0.99	16.2	1.00	16.3	0.99	-	
27	14.8	1.01	14.8	1.02	14.8	1.00	-	
28	172.8	-	173.0	-	nd[a]	-	-	
29	109.9	4.62, 4.75	109.9	4.62, 4.76	110.0	4.62, 4.75	-	
30	19.5	1.71	19.5	1.70	nd[a]	nd[a]	-	
3′	153.9	-	141.7	8.35	137.2	8.20	152.7	-
3′a	111.4	-	111.1	-	113.1	-	113.4	-
4′	158.5	-	153.3	-	157.4	-	151.4	-
5′	38.8	2.67 (2)	42.4	2.55 (2)	38.7	2.66 (2)	37.3	2.60
6′	33.3	-	34.1	-	33.7	-	33.3	2.75
6′-$\underline{Me}_2$	28.7	1.07, 1.08	27.8, 28.1	1.07, 1.10	28.7 (2)	1.09 (2)	28.5	1.07
7′	37.0	2.66 (2)	37.6	2.70 (2)	nd[a]	2.73 (2)	37.5	2.75
7′a	143.5	-	144.2	-	143.2	-	142.6	-
iPh	139.1	-	138.8	-	138.9	-	140.5	-
mPh	129.6 (2)	7.45	129.5	7.51	129.5	7.51	129.9	7.51
pPh	127.5	7.34	128.4	7.43	128.0	7.39	127.6	7.38
oPh	123.7 (2)	7.42	124.0	7.49	123.5	7.49	123.7	7.53
2″, 3″	9.68, 9.77	1.03, 1.06	-	-	-	-	9.1 (2)	0.94, 0.97
1″	9.22	2.77	-	-	-	-	9.6	2.68
$CH_3\underline{CH}_2$	-		-	-	-	-	69.6	4.16
$\underline{CH}_3CH_2$	-		-	-	-	-	15.1	1.31

[a] nd: not detected
[b] Interchangeable
[c] The assignment of minor isomer signals were executed only in part because of overlapping with the signals of the major isomer.

4. Conclusions

In summary, we have developed synthesis of novel lupane triterpenoid-indazolone hybrids containing oxime ester linkage. The synthetic pathway includes oxidation of naturally occuring betulin to betulonic acid, purification of the latter *via* its cyclohexylammonium salt, transformation of betulonic acid into betulonoyl chloride and its coupling with the corresponding 6,7-dihydro-1*H*-indazol-4(5*H*)-one oximes. Reduction of oxime esters of betulonic acid **9** with $NaBH_4$ in dry isopropanol occurred with full diastereoselectivity at C3 and led to the formation of betulinic acid-indazolone hybrids **10** in excellent yields. The NOESY and chemical shift analysis of compounds **9g**,**k** and model compounds **11–14** confirmed our previous conclusions [48] that 3-substituted indazolones provide (*E*)-oxime derivatives selectively and 3-unsubstituted ones produce the (*Z*)-products predominantly. The stereochemical assignments obtained from NMR spectra were unambiguously confirmed by X-ray analysis of model compound (*E*)-**12** and its betulonic acid counterpart **9l**. Synthesis of enlarged combinatorial library of the title compounds and evaluation of their biological activities are in progress in our laboratories and will be reported elsewhere.

Acknowledgments

This work was supported by the Belarussian Foundation for Fundamental Research and GKNT grant X14LAT-002 (Belarus) and by Riga Technical University and Riga Stradins University co-project RTU/RSU-15 (PVS Nr. 2163) (Latvia). Dr. A. Mishnev is acknowledged for X-ray analysis of compound (*E*)-**12**.

References

[1] S.B. Tsogoeva. Recent progress in the development of synthetic hybrids of natural or unnatural bioactive compounds for medicinal chemistry, Mini-Rev. Med. Chem. 10 (2010) 773–793.

[2] L.F. Tietze, H.P. Bell, S. Chandrasekhar. Natural product hybrids as new leads for drug discovery, Angew. Chem. Int. Ed. 42 (2003) 3996–4028.

[3] G. Mehta, V. Singh. Hybrid systems through natural product leads: An approach towards new molecular entities, Chem. Soc. Res. 31 (2002) 324–334.

[4] K. Gademann. Natural product hybrids, Chimia. 60 (2006) 841–845.

[5] M. Decker. Hybrid molecules incorporating natural products: Applications in cancer therapy, neurodegenerative disorders and beyond, Curr. Med. Chem. 18 (2011) 1464–1475.

[6] R.A. Hill, J.D. Connolly. Triterpenoids, Nat. Prod. Rep., 30 (2013) 1028–1065.

[7] **S. Jäger, H. Trojan, T. Kopp, M.N. Laszczyk, A. Scheffler. Pentacyclic triterpene distribution in various plants – rich sources for a new group of multi-potent plant extracts,** *Molecules 14* **(2009)** 2016–2031.

[8] R.-Y. Kuo, K. Qian, S.L. Morris-Natschke, K.-H. Lee. Plant-derived triterpenoids and analogues as antitumor and anti-HIV agents, Nat. Prod. Rep. 26 (2009) 1321–1344.

[9] Huaming Sheng and Hongbin Sun. Synthesis, biology and clinical significance of pentacyclic triterpenes: a multi-target approach to prevention and treatment of metabolic and vascular diseases, Nat. Prod. Rep., 28 (2011) 543–593.

[10] M.K. Shanmugam, A.H. Nguyen, A.P. Kumar, B.K.H. Tan, G. Sethi. Targeted inhibition of tumor proliferation, survival, and metastasis by pentacyclic triterpenoids: Potential role in prevention and therapy of cancer, Cancer Lett. 320 (2012) 158–170.

[11] M.N. Laszczyk. Pentacyclic triterpenes of the lupane, oleanane and ursane group as tools in cancer therapy, Planta Med. 75 (2009) 1549–1560.

[12] **T.G. Tolstikova, I.V. Sorokina, G.A. Tolstikov, A.G. Tolstikov, O.B. Flekhter. Biological activity and pharmacological prospects of lupane terpenoids: I. Natural lupane derivatives,** Rus. J. Bioorg. Chem. 32 (2006) 37–49.

[13] A. Sami, M. Taru, K. Salme, Y.-K. Jari. Pharmacological properties of the ubiquitous natural product betulin, Eur. J. Pharm. Sci. 29 (2006) 1–13.

[14] M.G. Moghaddam, F.B.H. Ahmad, A. Samzadeh-Kermani. Biological activity of betulinic acid: A review, Pharmacol. Pharm. 3 (2012) 119–123.

[15] M. Kvasnica, M. Urban, N. J. Dickinson, J. Sarek. Pentacyclic triterpenoids with nitrogen- and sulfur containing heterocycles: synthesis and medicinal significance, Nat. Prod. Rep. 32 (2015) 1303–1330.

[16] a) **T.G. Tolstikova, I.V. Sorokina, G.A. Tolstikov, A.G. Tolstikov, O.B. Flekhter. Biological activity and pharmacological prospects of lupane terpenoids: II. Semisynthetic lupane derivatives,** Rus. J. Bioorg. Chem. 32 (2006) 291–276; b) S.-J. Yang, M.-C. Liu, Q. Z., D.-Y. Hu, W. Xue, S. Yang. Synthesis and biological evaluation of betulonic acid derivatives as antitumor agents, Eur. J. Med. Chem. 96 (2015) 58–65.

[17] M. Willmann, V. Wacheck, J. Buckley, K. Nagy, J. Thalhammer, R. Paschke, T. Triche, B. Jansen, E. Selzer. Characterization of NVX–207, a novel betulinic acid-derived anti-cancer compound, Eur. J. Clin. Inv. 39 (2009) 384–394.

[18] O.B. Flekhter, E.I. Boreko, L.R. Nigmatullina, E.V. Tret'yakova, N.I. Pavlova, L.A. Baltina, S.N. Nikolaeva, O.V. Savinova, V.F. Eremin, F.Z. Galin, G.A. Tolstikov. Synthesis and antiviral activity of betulonic acid amides and conjugates with amino acids, Rus. J. Bioorg. Chem. 30 (2004) 89–98.

[19] I.D. Bori, H.-Y. Hung, K. Qian, C.-H. Chen, S.L. Morris-Natschke, K.-H. Lee. Anti-AIDS

agents 88. Anti-HIV conjugates of betulin and betulinic acid with AZT prepared via click chemistry, Tetrahedron Lett. 53 (2012) 1987–1989.

[20] C. Horwedel, S. B. Tsogoeva, S. Wei, T. Efferth. Cytotoxicity of artesunic acid homo- and heterodimer molecules toward sensitive and multidrug-resistant CCRF-CEM leukemia cells, J. Med. Chem. 53 (2010) 4842–4848.

[21] A.Yu. Spivak, R.R. Khalitova, Yu.P. Bel′skii, A.N. Ivanova, E.R. Shakurova, N.V. Bel′skaya, V.N. Odinokov, M.G. Danilets, A.A. Ligacheva. Synthesis of conjugates of lupane triterpenoids with chromane antioxidants and in vitro study of their influence on the production of nitrogen monoxide and on the arginase activity in activated macrophages, Rus. Chem. Bull. Int. Ed. 59 (2010) 2219–2229.

[22] H.-W. Cui, Y. He, J. Wang, W. Gao, T. Liu, M. Qin, X. Wang, C. Gao, Y. Wang, M.-Y. Liu, Z. Yi, W.-W. Qiu, Synthesis of heterocycle-modified betulinic acid derivatives as antitumor agents, Eur. J. Med. Chem. 95 (2015) 240–248.

[23] M. Urban, M. Vlk, P. Dzubak, M. Hajduch, J. Sarek, Cytotoxic heterocyclic triterpenoids derived from betulin and betulinic acid, Bioorg. Med. Chem. 20 (2012) 3666–3674.

[24] T.A.D. Thi, N.T.K. Tuyet, C.P. The, H. T. Nguyen, C. B. Thi, T. D. Duy, M. D'hooghe, T. V. Nguyen, Synthesis and cytotoxic evaluation of novel ester-triazole-linked triterpenoid-AZT conjugates, Bioorg. Med. Chem. Lett. 24 (2014) 5190–5194.

[25] D. D. Gaikwad, A.D. Chapolikar, C.G. Devkate, K.D. Warad, A.P. Tayade, R.P. Pawar, A.J. Domb. Synthesis of indazole motifs and their medicinal importance: An Overview, Eur. J. Med. Chem. 90 (2015) 707–731.

[26] M. Sapnakumari, B. Narayana, B.K. Sarojini, L.N. Madhu. Synthesis of new indazole derivatives as potential antioxidant agents, Med. Chem. Res. 23 (2014) 2368–2376.

[27] A. Thangadurai, M. Minu, S. Wakode, S. Agrawal, B. Narasimhan. Indazole: a medicinally important heterocyclic moiety, Med. Chem. Res. 21 (2012) 1509–1523.

[28] H. Cerecetto, A. Gerpea, M. González, V.J. Arán, C.O. de Ocáriz. Pharmacological properties of indazole derivatives: Recent developments, Mini-Rev. Med. Chem. 5 (2005) 869–878.

[29] J.R. Infante, G.L. Weiss, S. Jones , R. Tibes, T.M. Bauer , J.C. Bendell, J.M. Hinson Jr, D.D. Von Hoff, H.A. Burris, E.O. Orlemans, R.K. Ramanathan. Phase I dose-escalation studies of SNX-5422, an orally bioavailable heat shock protein 90 inhibitor, in patients with refractory solid tumours, Eur. J. Cancer. 50 (2014) 2897–2904.

[30] N. Reddy, P.M. Voorhees, B.E. Houk, N. Brega, J.M. Hinson Jr, A. Jillela. Phase I trial of the HSP90 inhibitor PF-04929113 (SNX5422) in adult patients with recurrent, refractory hematologic malignancies, Clin. Lymphoma Myeloma Leuk. 13 (2013) 385–91.

[31] K. Schiemann, D. Finsinger, F. Zenke, Tetrahydrobenzoisoxazole and tetrahydroindazole derivatives as modulators of the mitotic motor protein. PCT Int. Appl. (2008), WO2008080455 (A1), Chem. Abstr. 2008, 149, 153070.

[32] M. Xia, T. Zhang, Y. Wang, G. Xing. Tetrahydroindole derivatives and tetrahydroindazole derivatives, and use thereof. PCT Int. Appl. (2006) WO2006133634 (A1), Chem. Abstr. 2007,

146, 62711.

[33] P. Pevarello, M. Villa, M. Varasi, A. Isacchi, 4,5,6,7-Tetrahydroindazole derivatives and their preparation method and use in treating cell proliferative disorders or Alzheimer's disease. PCT Int. Appl. (2000), WO 2000069846 (A1), Chem. Abstr. 2000, 133, 362767.

[34] T.S. Khlebnicova, V.G. Isakova, F.A. Lakhvich. Reaction of 2-trifluoroacetylcyclohexane-1,3-diones and their enol ethers with phenylhydrazine, Dokl. Nats. Acad. Nauk Belarus, 51 (2007) 55–58.

[35] T.S. Khlebnikova, V.G. Isakova, A.V. Baranovskii, F.A. Lakhvich. Synthesis and spectroscopic investigation of the new polyfluoroalkyl-containing indazolones, Rus. J. Gen. Chem. 78 (2008) 1954–1963.

[36] T.S. Khlebnicova, V.G. Isakova, F.A. Lakhvich, P.V. Kurman. Regioselective synthesis of fluorine-containing indazolones from 2-acylcyclohexane-1,3-diones, Chem. Heterocycl. Comp. 44 (2008) 301−308.

[37] T.S. Khlebnikova, Yu.A. Piven, A.V. Baranovskii, F.A. Lakhvich. Regioselective Synthesis of polyfluoroalkyl-substituted 7-(1*H*-1,2,3-triazol-1-yl)-6,7-dihydro-1*H*-indazol-4(5*H*)-ones, Rus. J. Org. Chem. 48 (2012) 411–418.

[38] I. Strakova, M. Turks, A. Strakovs. Synthesis of triazole-functionalized tetrahydroindazolones by 1,3-dipolar cycloadditions between azides and alkynes, Tetrahedron Lett., 50 (2009) 3046-3049.

[39] M. Turks, I. Strakova, K. Gorovojs, S. Belyakov, Y. Piven, T. Khlebnikava, F. Lakhvich. A facile synthesis of 4-acylamino tetrahydroindazoles via the Ritter reaction, Tetrahedron 68 (2012) 6131−6140.

[40] I. Strakova, I. Kumpiņa, V. Rjabovs, J. Lugiņina, S. Belyakov, M. Turks, M. Resolution, absolute configuration and synthetic transformations of 7-amino-tetrahydroindazolones. Tetrahedron: Asymmetry, 22 (2011) 728−739.

[41] M. Turks, I. Strakova, K. Gorovojs, Y. Piven, T. Khlebnikava, F. Lakhvich, M. Golubeva, I. Kantrouskaya. Synthesis of biologically active 4-acylamino-4,5,6,7-tetrahydroindazoles, Latvian Patent (2012) LV14476, Chem. Abstr. 2012, 161, 216320.

[42] B. Bednarczyk-Cwynar, L. Zaprutko. Recent advances in synthesis and biological activity of triterpenic acylated oximes, Phytochem. Rev. 14 (2015) 203–231.

[43] Á. Berényi, R. Minorics, Z. Iványi, I. Ocsovszki, E. Ducza, H. Thole, J. Messinger, J. Wölfling, G. Mótyán, E. Mernyák, É. Frank, G. Schneider, I. Zupkó. Synthesis and investigation of the anticancer effects of estrone-16-oxime ethers in vitro, Steroids 78 (2013) 69–78.

[44] H.-E. Qu, R.-Z. Huang, G.-Y. Yao, J.-L. Li, M.-Y. Ye, H.-S. Wang, L. Liu. Synthesis and pharmacological evaluation of novel bisindole derivatives bearing oximes moiety: Identification of novel proapoptotic agents, Eur. J. Med. Chem. 95 (2015) 400−415.

[45] N.I. Petrenko, N.V. Elantseva, V.Z. Petukhova, M.M. Shakirov, E.E. Shul′ts, G.A. Tolstikov. Synthesis of betulonic acid derivatives containing amino-acid fragments, Chem. Nat. Comp. 38 (2002) 331–339.

[46] A. J. Nunn, F. J. Rowell, Semmler-Wolff aromatization and abnormal Beckmann and Schmidt reactions of 3-alkyl-4-oxo-1-phenyl-4,5,6,7-tetrahydroindazoles and their oximes in polyphosphoric acid. J. Chem. Soc., Perkin Trans. 1. 22 (1973) 2697–2703.

[47] N. Melnikova, I. Burlova, T. Kiseleva, I. Klabukova, M. Gulenova, A. Kislitsin, V. Vasin, B. Tanaseichuk. A Practical Synthesis of Betulonic Acid Using Selective Oxidation of Betulin on Aluminium Solid Support, Molecules 17 (2012) 11849–11863.

[48] T.S. Khlebnikova, Yu.A. Piven, A.V. Baranovskii, F.A. Lakhvich. Synthesis and transformations of perfluoroalkyl-containing 6,7-dihydro-1*H*-indazol-4(5*H*)-one oximes, Rus. J. Org. Chem. 51 (2015) 650–656.

[49] G. M. Sheldrick. A short history of SHELX. Acta Crystallogr Sect A. 64 (2008) 112-122.

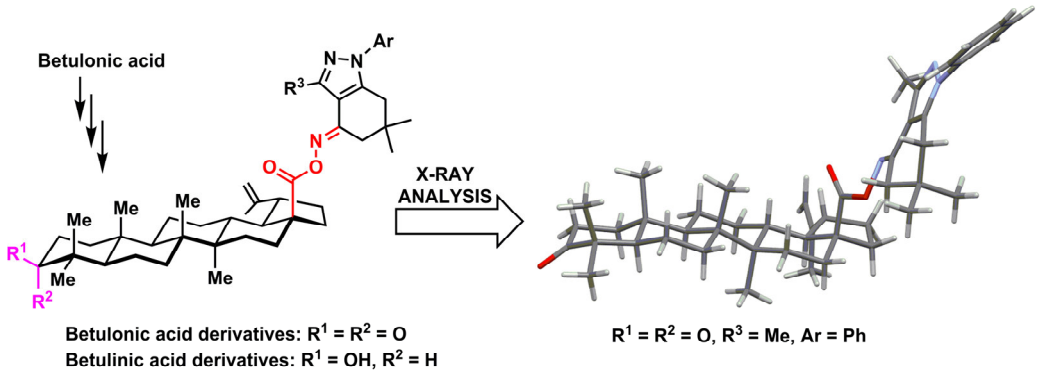
[50] M. C. Burla, R. Caliandro, M. Camalli, B. Carrozzini, G. L. Cascarano, C. Giacovazzo, M. Mallamo, A. Mazzone, G. Polidori, R. Spagna. SIR2011: A new package for crystal structure determination and refinement. J. Appl. Cryst. 45 (2012) 357–361.

[51] L. J. Farrugia. WinGX and ORTEP for Windows: An update, J. Appl. Crystallogr. 45 (2012) 849–854.

[52] J. M. Pezzuto, D. S. Kim. Methods of manufacturing betulinic acid, U.S. Patent (1998) 5804575 (A).

[53] E. Bębenek, E. Chrobak, J. Wietrzyk, M. Kadela, A. Chrobak, J. Kusz, M. Książek, M. Jastrzębska, S. Boryczka. Synthesis, structure and cytotoxic activity of acetylenic derivatives of betulonic and betulinic acids, J. Mol. Struct. 1106 (2016) 210–219

[54] V. A. Levdanskij, N. I. Polezhaeva, B. N. Kuznetsov. Method for preparing betulinic acid. Russ. Patent (2006) 2269541 (C1).



Graphical abstract

Synthesis of novel lupane triterpenoid–indazolone hybrids with oxime ester linkage

Tatyana S. Khlebnicova [a], Yuri A. Piven [a], Alexander V. Baranovsky [a], Fedor A. Lakhvich [a], Svetlana V. Shishkina[b], Daina Zicāne [c], Zenta Tetere [c], Irisa Rāviņa [c], Viktors Kumpiņš [c], Inese Rijkure [c], Inese Mieriņa [c], Uldis Peipiņš [c], Māris Turks [c,*]

[a] *Institute of Bioorganic Chemistry, National Academy of Sciences of Belarus, Acad. Kuprevicha Str. 5/2, 220141 Minsk, Belarus*

[b] *Institute for Single Crystals, National Academy of Sciences of Ukraine, pr. Lenina 60, Kharkiv, 61001 Ukraine*

[c] *Institute of Technology of Organic Chemistry, Faculty of Materials Science and Applied Chemistry, Riga Technical University, P. Valdena Str. 3, Riga, LV-1048, Latvia. E-mail: maris_turks@ktf.rtu.lv*

HIGHLIGHTS

* Novel lupane triterpenoid-indazolone hybrids with oxime linkage are obtained

* This is the first report on oxime esters derived from betulonic and betulinic acid at their C(28).

* X-ray structure of the hydrid molecule is reported

* Purification procedure for betulonic acid *via* its cyclohexylammonium salt is developed