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Synthesis of 1,2-azole derivatives on the basis of α,β-unsaturated triterpene aldehydes

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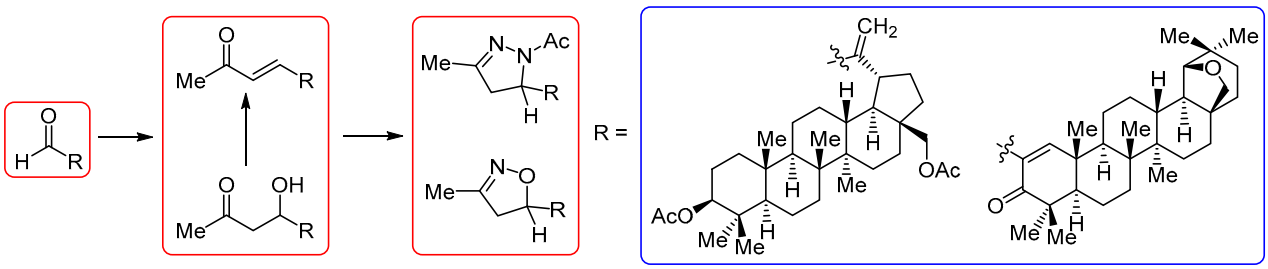


α,β-Unsaturated lupane and 19β,28-epoxy-18α-oleanane aldehydes were used in the synthesis of triterpenoids bearing substituted 1,2-azole moieties (1-acetyl-3-methyl-4,5-dihydro-1*H*-pyrazole and 3-methyl-4,5-dihydroisoxazole) at the rings A and E. The route of synthesis for these 1,2-azole derivatives of triterpenes included an aldol condensation of α,β-unsaturated aldehydes with acetone, the products of which (α,β-unsaturated methyl ketone and β-hydroxy ketone) underwent a further cycloaddition reaction with acetylhydrazide and hydroxylamine. Cytotoxic activity studies of the synthesized compounds against seven cancer cell lines (Hep-2, HCT116, MS, RD TE32, A549, MCF-7, and PC-3) showed that the highest cytotoxicity (IC_{50} 0.66–11.97 μM) against all tested cell lines was exihbited by 19β,28-epoxy-18α-oleanane aldehyde and the products of its condensation reactions with acetone and acetylhydrazide.

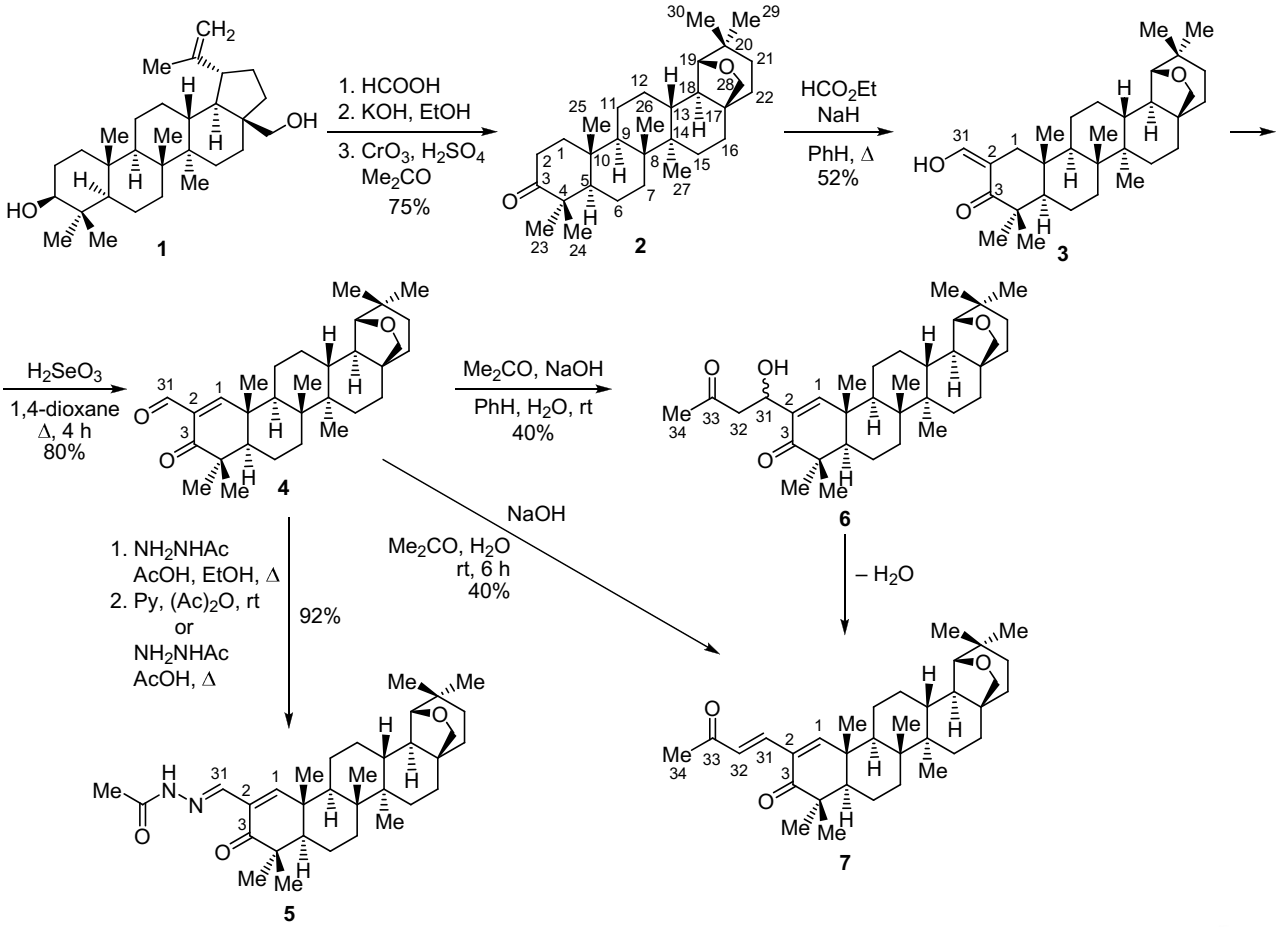
Keywords: 1,2-azoles, betulin, oxazoline, pyrazoline, triterpenoids, α,β-unsaturated aldehydes, aldol condensation, cytotoxic activity.

Pentacyclic triterpenoids offer a great therapeutic potential and synthetic utility, and have been used for a long time by medicinal chemistry researchers as promising structural motifs for the design of compounds with high biological activity.[1–5] The introduction of nitrogen-, sulfur- or oxygen-containing heterocyclic substituents into the triterpene ring system can increase its biological activity and improve bioavailability.[6–10] Heterocyclic modifications of triterpenoids are often accomplished *via* classical synthetic reactions and reactive functional groups can be easily used for the purpose of adding a heterocyclic substituent to a triterpenoid molecule (for example, OH, >C=O, COOH, C=C etc.),[10–15] or else new reactive sites can be created in order to achieve heterocyclization.[16–21] Despite the great number of semisynthetic triterpenoids featuring various heterocyclic modifications of their molecular framework, it is still important to continue the development of new, practical, and effective methods for the synthesis of heterocycles on the basis of natural compounds.

Triterpene oxo derivatives, in particular aldehydes, are readily available, reactive substrates for the preparation of carbo- and heterocyclic structures with antiviral and cytotoxic activity, which we have demonstrated repeatedly with the examples of A-secotriterpene compounds bearing aldehyde and methyl ketone functionalities in the A-seco moiety.[22–26] Thus, by heterocyclization of the intermediate compound – the acetylhydrazone of 1-cyano-2,3-secolupane aldehyde, the cytotoxic (*R*)-1,3,4-oxadiazoline was obtained, which showed a proapoptotic effect against tumor cells.[22]

The goal of the current work was to study the possibility of synthesizing triterpene derivatives decorated with pyrazoline and isoxazoline rings by starting from α,β-unsaturated lupane and 18α-oleanane aldehydes.

Scheme 1



Allobetulone **2** was obtained on the basis of betulin **1** and further converted into 2-hydroxymethylidene-19β,28-epoxy-18α-oleanane derivative **3**,[27] the oxidation of which with H_2SeO_3 in 1,4-dioxane medium led to our previously described product – 2-formyl-19β,28-epoxy-18α-olean-1(2)-en-3-one (**4**)[28] (Scheme 1). The structure of aldehyde **4** was additionally confirmed by the X-ray structural analysis (Fig. 1).

Compound **4** crystallized in a noncentrosymmetric space group of monoclinic syngony. Molecular geometry verification using Mercury Mogul Geometry Check software[29] showed that all bond lengths and valence angles had values characteristic for the respective functionalities. The cyclohexenone ring A contains the C(4) and C(5) atoms in a twist boat conformation, which deviate from the plane defined by C(10)C(1)C(2)C(3) atoms by 0.59 and 0.98 Å, respectively. Despite the fact that the formyl substituent and the ketone carbonyl group are rotated at small angles relative to the C(1)=C(2) multiple bond (the torsion angles are the following: O(3)C(31)C(2)C(1) 10.7(5)°, O(2)C(3)C(2)C(1) 151.6(3)°), the conjugation between them is not strong. The 1.330(4) Å length of the C(1)=C(2) bond is characteristic for a regular localized double bond, while the lengths of the C(2)–C(3) and C(2)–C(31) bonds (1.478(4) and 1.483(5) Å, respectively) are insignificantly shortened compared to the length of a localized ordinary C–C bond. There is no specific shortened contacts in the crystal structure.

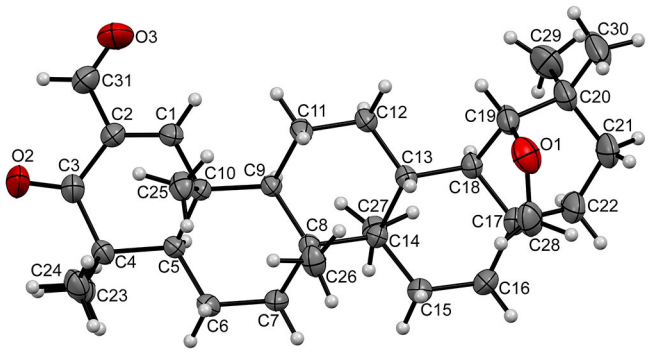


Figure 1. The molecular structure of compound **4** with atoms represented by thermal vibration ellipsoids of 50% probability.

The cycloaddition reactions between α,β-unsaturated carbonyl compounds and hydrazines have been widely used for the preparation of substituted 2-pyrazolines.[30] For example, various pyrazoline derivatives of steroids were obtained *via* a cycloaddition reaction of α,β-unsaturated ketones and acetic hydrazide in AcOH.[31,32] Two schemes have been proposed for the synthesis of pyrazoline derivatives of steroids. A two-step synthesis including 1) condensation of α,β-unsaturated steroid ketone with acetic hydrazide in EtOH under the conditions of acidic catalysis and 2) further cyclization of the formed

hydrazone, resulting in the formation of a pyrazoline ring, was performed at room temperature in a pyridine – acetic anhydride mixture.[31] In addition, a heterocyclization reaction of α,β-unsaturated ketone in AcOH was performed without isolation of the intermediate hydrazone.[32]

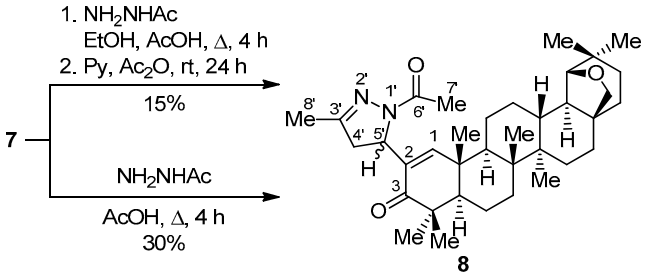
It was expected that the use of the aforementioned reaction conditions for the treatment of 19β,28-epoxy-18α-oleanane aldehyde **4** with acetic hydrazides should lead to the formation of pyrazoline that would be annulated at the C(1)–C(2) bond. However, under all of our explored reaction conditions, only the formation of the corresponding acetylhydrazone **5**[28] was observed, without its heterocyclization into pyrazoline (Scheme 1).

Since aldehyde **4** did not contain protons at the α-carbon atom relative to the aldehyde group, we used it in the aldol condensation reaction in the role of a carbonyl component for the introduction of an α,β-unsaturated methyl ketone moiety in the triterpene molecule. The condensation of aldehyde **4** with Me_2CO proceeded at room temperature in 2:1 PhH–Me_2CO mixture in the presence of NaOH, leading to the formation of β-hydroxy ketone **6** in 40% yield. The reaction progress was controlled by performing TLC analysis. The aldol reaction was stopped at the first signs of the presence of crotonic derivative **7**. The use of only Me_2CO as solvent led directly to α,β-unsaturated methyl ketone **7**. Aldol **6** was formed as a 7:3 diastereomer mixture, as indicated by the proton signal integrals in ^{1}H NMR spectrum: 1-CH (7.18 and 7.20 ppm), 31-CH (4.73 and 4.89 ppm), and 34-CH_3 (2.17 and 2.18 ppm).

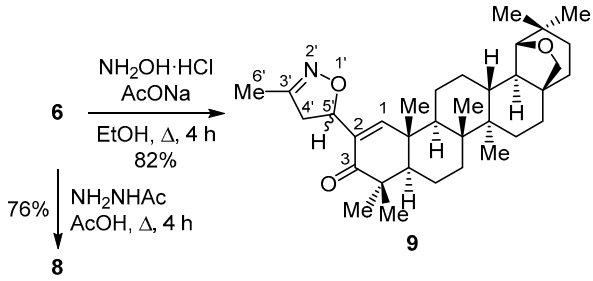
^{1}H NMR spectrum of α,β-unsaturated methyl ketone **7** showed that the 33-CH_3 protons of the methyl ketone moiety appeared as a singlet signal at 2.29 ppm, while two doublets in the region of 6.68 and 7.20 ppm were assigned to the olefinic protons of the C(31)−C(32) bond, with 16 Hz spin-spin coupling constant pointing to the *E*-configuration of double bond. ^{13}C NMR spectrum of compound **7** showed the signals of sp^2-hybridized carbon atoms in the range of 128.8–161.2 ppm, as well as the C-3 and C-33 carbonyl carbon atoms at 203.6 and 198.8 ppm, respectively.

In contrast to aldehyde **4**, the use of α,β-unsaturated methyl ketone **7** in the reaction with acetic hydrazide was found to be more successful and led to pyrazoline **8**, albeit in rather low yields – 15% or 30% (Scheme 2). At the same time, heating β-hydroxy ketone **6** at reflux temperature in AcOH with acetic hydrazide allowed to obtain pyrazoline **8** in 76% yield (Scheme 3). Pyrazoline **8**, regardless of the selection of compound **6** or **7** as starting material, was formed as a 7:3 mixture of diastereomers according to its ^{1}H NMR spectral data, and this mixture could not be separated chromatographically. ^{1}H NMR spectrum of the isomer mixture **8** contained signals that were assigned to the pyrazoline ring protons: the signals of 4'-CH_2 protons in the range of 2.41–2.58 ppm, 4'-CH_2 proton signals in the range of 3.11–3.19 ppm, and 5'-CH proton signals in the range of 5.00–5.01 ppm.

Scheme 2



Scheme 3

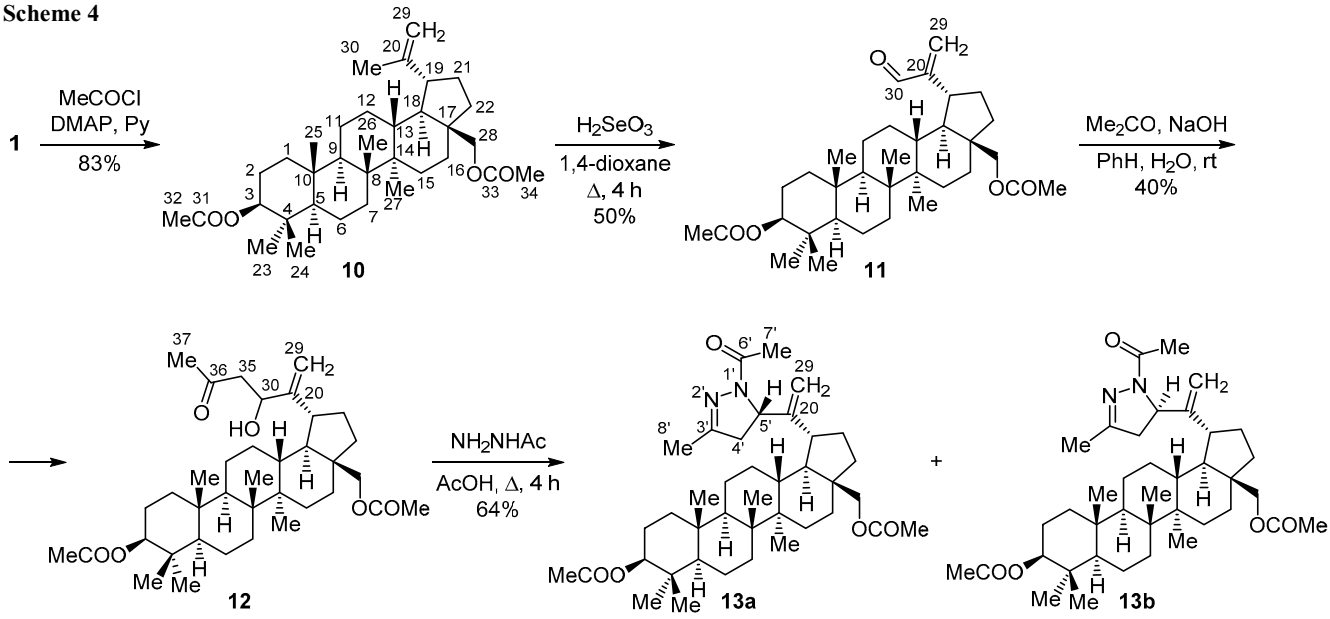


Heating β-hydroxy ketone **6** with hydroxylamine hydrochloride and AcONa at reflux temperature in EtOH provided isoxazoline **9** in 82% yield as a 7:3 mixture of diastereomers. ^{1}H NMR spectrum of product **9** contained a singlet signal of methyl group protons (at 1.90 ppm) and the signals of epimeric protons belonging to the heterocyclic moiety: 4'-CH_2 protons (2.32–2.34 and 2.47–2.61 ppm), as well as the 5'-CH protons (4.59–4.77 ppm).

Taking into account the observation that pyrazoline **8** was formed in the highest yield from β-hydroxy ketone **6**, the targeted aldol condensation reaction of lupane aldehyde **11**[33] (prepared from betulin 3,28-diacetate **10**[33]) with Me_2CO was performed under the optimal conditions for the synthesis of β-hydroxy ketone **6** (Scheme 4). Aldol **12** thus obtained was a 6:4 mixture of diastereomers, the ratio of which was determined from the ratio of ^{1}H NMR signal integrals for the 29-CH_2 group in the range of 4.91–5.09 ppm. During the synthesis of lupane pyrazoline derivative, compound **12** was refluxed with acetic hydrazide in AcOH for 4 h. TLC analysis indicated that the reaction mixture contained two products **13a** and **13b** (64% yield) with very close R_f values in a 6:4 ratio, which was determined on the basis of ^{1}H NMR spectrum (Scheme 4). Only isomer **13a** was successfully isolated from the mixture of products **13a**,**b** and characterized as an individual compound.

The analysis of ^{1}H NMR spectrum of compound **13a** allowed to assign two double doublet signals at 2.56 and 3.06 ppm to the 4'-CH_2 group protons, a double doublet at 4.78 ppm was assigned to the 5'-CH proton, while the two singlet signals at 2.00 and 2.25 ppm belonged to the methyl group at the C-3' carbon atom and the *N*-acetyl group. The characteristic ^{13}C NMR signals of the pyrazoline ring in compound **13a** were observed at 43.8 (C-4'), 61.0 (C-5'), 155.2 (C-3'), and 168.4 ppm (C-6'). The structural features of the heterocyclic system in compound **13a** were proved conclusively on the basis of two-dimensional COSY, ^{1}H–^{13}C HMBC, ^{1}H–^{13}C HSQC, and NOESY experiments.

Scheme 4



The proton signal assignments for compound **13a** were confirmed by using its COSY spectrum that showed coupling between the 4'-CH_2 and 5'-CH protons in the pyrazoline ring. The most informative cross peaks in $^{1}H–^{13}C$ HMBC spectrum (Fig. 2) were the following: between the proton signals of 29-CH_2 group and the signals of C-19 and C-5' carbon atoms, between the signals of 4'-CH and 5'-CH protons and the signals of C-20 and C-3' carbon atoms, between the signal of 7'-CH_3 protons and the signal of C-6' carbon atom, and between the signal of 8'-CH_3 protons and the signal of C-3' carbon atom. A NOESY experiment was used for determining the relative configuration of the C-5' carbon atom. The correlation between the 19-CH and 5'-CH protons in NOESY spectrum indicated that the product consisted of (5'*S*)-isomer (Fig. 2).

The *in vitro* cytotoxic activity of compounds **4**–**9**, **12**, **13a**,**b** was studied by using the cancer cell lines A549, Hep-2, HCT116, MS, PC-3, MCF-7, RD TE32, and the noncancer cell line HEK293 (Table 1). DMSO solutions were prepared using camptothecin as a positive control

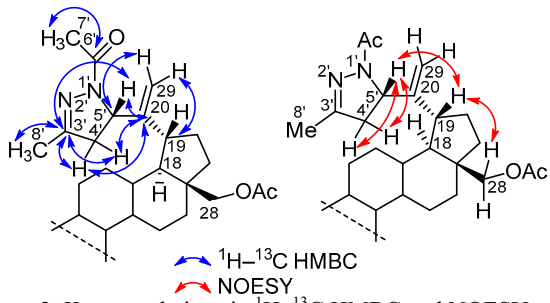


Figure 2. Key correlations in $^{1}H–^{13}C$ HMBC and NOESY spectra of compound **13a**.

compound, the study compounds **4**–**9**, **12**, **13a**, and the mixture of epimers **13a**,**b**. The DMSO solutions were subsequently diluted with the culture medium. Control cells were treated with the culture medium containing 1% DMSO.

According to the obtained data (Table 1), the heterocyclic derivatives **8**, **9**, **13a**, **13a**,**b** were less cytotoxic than the starting compounds **4**–**7**, **12**, which exhibited cyto-

Table 1. Cytotoxic activity (IC_{50}, μM) of compounds **4**–**9**, **12**, **13a**, **13a**,**b**

Compound	Cell lines							
	Hep-2	HCT116	MS	RD TE32	A549	MCF-7	PC-3	HEK293
4	2.23 ± 0.20	0.74 ± 0.06	2.35 ± 0.78	0.66 ± 0.05	1.32 ± 0.09	1.07 ± 0.12	1.32 ± 0.51	1.84 ± 0.095
5	1.36 ± 0.39	1.99 ± 0.2	2.24 ± 0.30	3.85 ± 1.63	2.37 ± 0.02	2.35 ± 0.16	1.08 ± 0.1	4.75 ± 0.34
6	7.74 ± 1.13	5.08 ± 0.23	4.68 ± 0.37	2.22 ± 0.34	5.91 ± 0.09	8.09 ± 0.32	5.59 ± 0.31	13.36 ± 0.56
7	11.97 ± 1.83	7.02 ± 0.23	9.45 ± 0.13	4.93 ± 0.74	8.56 ± 1.12	8.69 ± 1.33	7.10 ± 0.43	5.09 ± 0.24
8	–	55.89 ± 5.07	>100	–	–	52.71 ± 1.91	–	82.61 ± 4.44
9	–	55.89 ± 5.07	>100	–	–	52.71 ± 1.91	–	82.61 ± 4.44
12	–	11.84 ± 0.16	20.84 ± 1.65	–	–	12.41 ± 0.18	–	26.23 ± 4.76
13a	–	>100	97.70 ± 3.22	–	–	>100	–	>100
13a,**b**	–	37.31 ± 6.76	64.08 ± 14.93	–	–	22.18 ± 2.15	–	26.92 ± 2.12
Camptothecin	3.007 ± 0.166	1.883 ± 0.094	0.772 ± 0.337	1.716 ± 0.336	1.308 ± 0.025	0.036 ± 0.009	1.92 ± 0.06	1.61 ± 1.075

toxicity (IC_{50} 0.66–26.23 μM) against all tested cell lines. Moderate cytotoxicity against the MCF-7 cell line was shown by (5'*S*,*R*)-pyrazoline **13a**,**b**, while its (5'*S*)-isomer **13a** was not active, pointing to the (5'*R*)-epimer as the main contributor to the cytotoxic activity of (5'*S*,*R*)-isomer mixture.

Thus, we have developed an approach for the synthesis of triterpenoids bearing 1-acetyl-3-methyl-4,5-dihydro-1*H*-pyrazole and 3-methyl-4,5-dihydroisoxazole moieties, on the basis of a cycloaddition reaction between acetic hydrazide or hydroxylamine and the aldol condensation products obtained from α,β-unsaturated lupane and 19β,28-epoxy-18α-oleanane aldehydes with acetone.

Experimental

IR spectra were recorded on a Bruker IFS 66/S FT-IR spectrometer for solutions in $CHCl_3$. ^1H and ^{13}C NMR spectra (400 and 100 MHz, respectively), as well as two-dimensional COSY, NOESY, ^1H–^{13}C HSQC, and ^1H–^{13}C HMBC spectra were acquired on a Bruker Avance II spectrometer for samples in $CDCl_3$ solutions, using HMDS as internal standard for ^1H NMR spectra (δ 0.06 ppm) and the $CDCl_3$ signal as internal standard for ^{13}C NMR spectra (δ 77.2 ppm). Chromato-mass spectroscopy analysis was performed on an Agilent Technologies 6890N instrument equipped with an HP-5ms capillary column, 15000 × 0.25 mm, evaporator temperature 240°C with temperature program in the range of 20–40°C/min, carrier gas – helium, EI ionization. High-resolution mass spectra for solutions of compounds **13a** and **13a**,**b** in MeCN were recorded on a Bruker maXis Impact HD instrument with electrospray ionization in positive ion mode, nitrogen flow 3.0 l/min, nebulizer pressure 0.3 bar, probe voltage 4.5 kV. Elemental analysis was performed using a vario EL cube elemental analyzer. Melting points were determined at a heating rate of 1°C/min on an OptiMelt MPA100 apparatus. The specific optical rotation values were measured for solutions in $CHCl_3$ on a PerkinElmer 341 polarimeter at 589 nm wavelength. Merck silica gel (60–200 μm) was used for column chromatography. Thin-layer chromatography was performed on Sorbfil plates, eluting with hexane–EtOAc system, visualization by treatment with 10% H_2SO_4 followed by heating at 95–100°C for 2–3 min.

Preparation of compounds 4 and 11 (General method). A solution of compound **3** (1.82 g, 4.0 mmol) or compound **10** (2.09 g, 4.0 mmol) in 1,4-dioxane (20 ml) was treated by the addition of H_2SeO_3 (0.9 g, 7 mmol). The reaction mixture was refluxed for 4 h, then washed with H_2O (50 ml) and extracted with EtOAc (2×50 ml). The organic layer was separated and dried over anhydrous $MgSO_4$, then the solvent was removed by distillation. The residue was purified by silica gel column chromatography. Eluent petroleum ether – EtOAc, 7:1 (for compound **4**) or 10:1 (for compound **11**).

2-Formyl-19β,28-epoxy-18α-olean-1(2)-en-3-one (4). Yield 1.50 g (80%), mp 172–176°C (mp 173.9°C[26]), $[\alpha]_D^{21}$–9.6° (*c* 0.6, $CHCl_3$). IR spectrum, ν, cm^{-1}: 1701, 1720 (C=O, HC=O). ^1H NMR spectrum, δ, ppm (*J*, Hz): 0.81–1.84 (20H, m, 4CH, 8CH_2); 0.84 (3H, s, CH_3); 0.94 (3H, s, CH_3); 0.97 (3H, s, CH_3); 1.10 (3H, s, CH_3); 1.12 (3H, s, CH_3); 1.17 (3H, s, CH_3); 1.18 (3H, s, CH_3); 3.48 (1H, d, *J* = 8.3) and 3.79 (1H, d, *J* = 8.3, 28-CH_2); 3.57 (1H, s, 19-CH); 7.90 (1H, s, 1-CH); 10.00 (1H, s, 31-CH). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 12.8; 13.5; 15.8; 18.3; 18.6; 20.7; 21.1; 24.0; 25.7; 25.9; 27.5; 28.3; 32.2; 32.6; 33.9; 35.8; 36.2; 39.4; 40.6; 41.0; 41.4; 44.0; 44.6; 46.2; 52.4; 70.7 (C-28); 87.4 (C-19); 131.0 (C-2); 165.2 (C-1); 189.8 (C-31); 203.1 (C-3).

3β,28-Diacetoxylup-20(29)-en-30-al (11). Yield 1.08 g (50%), mp 244–250°C (mp 246–248°C[31]). ^1H NMR spectrum, δ, ppm (*J*, Hz): 0.74–2.18 (24H, m, 4CH, 10CH_2); 0.82 (3H, s, CH_3); 0.83 (6H, s, 2CH_3); 0.93 (3H, s, CH_3); 1.02 (3H, s, CH_3); 2.02 (3H, s, 32(34)-CH_3); 2.05 (3H, s, 34(32)-CH_3); 2.80 (1H, td, *J* = 11.3, *J* = 5.3, 19-CH); 3.86 (1H, d, *J* = 11.1) and 4.27 (1H, d, *J* = 11.1, 28-CH_2); 4.44 (1H, dd, *J* = 10.8, *J* = 5.5, 3-CH); 5.91 (1H, s) and 6.25 (1H, s, 29-CH_2); 9.50 (1H, s, 30-CH). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 14.6; 16.0; 16.1 (2C); 16.4; 18.1; 20.8; 20.9; 21.2; 23.7; 27.0 (2C); 27.4; 27.9; 29.8; 34.1; 34.5; 37.0; 37.3; 37.8; 38.4; 40.9; 42.6; 46.6 (2C); 50.1; 55.4; 62.4 (C-28); 80.9 (C-3); 133.1 (C-29); 156.5 (C-20); 170.9; 171.3; 194.6 (C-30).

Preparation of compounds 6 and 12 (General method). A solution of aldehyde **4** (0.93 g, 2 mmol) or aldehyde **11** (1.08 g, 2 mmol) in a mixture of Me_2CO (5 ml) and PhH (10 ml) was treated by a dropwise addition of aqueous 10% NaOH solution (0.1 ml). The reaction mixture was stirred at room temperature, the reaction progress was controled by TLC. The reaction mixture was then washed with 10% HCl solution, extracted with PhH (2×10 ml), and washed with H_2O (2×10 ml). The organic layer was separated, dried over anhydrous $MgSO_4$, evaporated at reduced pressure, and the residue was purified by silica gel column chromatography. Eluent petroleum ether – EtOAc, 5:1 (for compound **6**) or 10:1 (for compound **12**).

2-((*S*,*R*)-4-Hydroxy-2-oxobutyl)-19β,28-epoxy-18α-olean-1(2)-en-3-one (6). Yield 0.42 g (40%), mp 136–139°C, $[\alpha]_D^{21}$ –9.00° (*c* 1.0, $CHCl_3$). IR spectrum, ν, cm^{-1}: 1712 (C=O), 3412 (OH). ^1H NMR spectrum, δ, ppm (*J*, Hz): 0.82 (3H, s, CH_3); 0.87–1.83 (20H, m, 4CH, 8CH_2); 0.93 (0.9H, s) and 0.94 (2.1H, s, CH_3); 0.95 (3H, s, CH_3); 1.05 (3H, s, CH_3); 1.06 (3H, s, CH_3); 1.10 (1.8H, s) and 1.11 (4.2H, s, 2CH_3); 2.17 (2.1H, s) and 2.18 (0.9H, s, 34-CH_3); 2.58 (0.3H, dd, *J* = 17.1, *J* = 8.9), 2.59 (0.7H, dd, *J* = 17.1, *J* = 8.9), 2.78 (0.7H, dd, *J* = 17.1, *J* = 4.0) and 2.95 (0.3H, dd, *J* = 17.1, *J* = 4.0, 32-CH_2); 3.47 (1H, d, *J* = 7.8) and 3.79 (1H, d, *J* = 7.8, 28-CH_2); 3.56 (1H, s, 19-CH); 4.73 (0.3H, dd, *J* = 8.8, *J* = 3.4) and 4.89 (0.7H, dd, *J* = 8.8, *J* = 3.4, 31-CH); 7.18 (0.7H, s) and 7.20 (0.3H, s, 1-CH). Mass spectrum, *m*/*z* (I_{rel}, %): 506 $[M-H_2O]^+$ (100). Found, %: C 78.02; H 9.81. $C_{34}H_{52}O_4$. Calculated, %: C 77.82; H 9.99.

30-((*S*,*R*)-4-Hydroxy-2-oxobutyl)lup-20(29)-ene-3β,28-diyl diacetate (12). Yield 0.45 g (40%), mp 152–154°C, $[\alpha]_D^{21}$ –9.2° (*c* 0.6, $CHCl_3$). IR spectrum, ν, cm^{-1}: 1733 (C=O), 3488 (OH). ^1H NMR spectrum, δ, ppm (*J*, Hz): 0.76–1.87 and 2.01–2.35 (25H, 2m, 5CH, 10CH_2); 0.82

(3H, s, CH_3); 0.84 (6H, br. s, $2CH_3$); 0.95 (1.8H, s), 0.98 (1.2H, s), 1.02 (1.8H, s) and 1.03 (1.2H, s, $2CH_3$); 2.02 (3H, s, 32(34)-CH_3); 2.05 (3H, s, 34(32)-CH_3); 2.19 (3H, s, 37-CH_3); 2.54–2.72 (2H, m, 19-CH, 35-CH_2); 2.86–2.94 (1H, m, 35-CH_2); 3.83 (0.6H, d, J = 11.0), 3.85 (0.4H, d, J = 11.0), 4.20 (0.6H, d, J = 11.0) and 4.23 (0.4H, d, J = 11.0, 28-CH_2); 4.43–4.50 (2H, m, 3-CH, 30-CH); 4.91 (0.4H, s), 4.95 (0.6H, s) 5.00 (0.4H, s), and 5.09 (0.6H, s, 29-CH_2). Mass spectrum, *m*/*z* (I_{rel}, %): 540 $[M–(CH_3)_2CO]^+$ (100). Found, %: C 74.47; H 9.93. $C_{37}H_{58}O_6$. Calculated, %: C 74.21; H 9.76.

2-((*E*)-2-Oxobut-3-enyl)-19β,28-epoxy-18α-olean-1(2)-en-3-one (7). Aqueous 10% NaOH solution (0.1 ml) was added to a solution of aldehyde **4** (0.93 g, 2 mmol) in Me_2CO (10 ml), then the reaction mixture was stirred for 6 h at room temperature. After diluting with 10% HCl solution, the reaction mixture was extracted with EtOAc (2×30 ml). The organic layer was separated, washed with H_2O, dried over $MgSO_4$, filtered, and evaporated to dryness. The residue was purified by silica gel column chromatography, eluent petroleum ether – EtOAc, 7:1. Yield 0.40 g (40%), mp 124–128°C, $[\alpha]_D^{21}$ +4.53° (*c* 0.8, $CHCl_3$). IR spectrum, ν, cm^{-1}: 1675 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.79–1.79 (20H, m, 4CH, 8CH_2,); 0.82 (3H, s, CH_3); 0.93 (3H, s, CH_3); 0.94 (3H, s, CH_3); 1.06 (6H, s, $2CH_3$); 1.11 (3H, s, CH_3); 1.15 (3H, s, CH_3); 2.29 (3H, s, 34-CH_3); 3.46 (1H, d, J = 7.8) and 3.77 (1H, d, J = 7.8, 28-CH_2); 3.55 (1H, s, 19-CH); 6.68 (1H, d, J = 16.3, 32-CH); 7.20 (1H, d, J = 16.3, 31-CH); 7.33 (1H, s, 1-CH). ^{13}C NMR spectrum, δ, ppm: 13.3; 16.2; 19.2; 19.3; 21.3; 21.7; 24.5; 26.2; 26.3; 26.4; 27.6; 28.5; 28.8; 32.7; 33.1; 34.5; 36.3; 36.7; 39.7; 41.1; 41.5; 41.6; 45.0; 45.3; 46.7; 52.6; 71.2 (C-28); 87.9 (C-19); 128.8; 130.9 (C-2); 138.8; 161.2 (C-1); 198.8 (C-33); 203.6 (C-3). Mass spectrum, *m*/*z* (I_{rel}, %): 506 $[M]^+$ (100). Found, %: C 80.70; H 10.01. $C_{34}H_{50}O_3$. Calculated, %: C 80.58; H 9.94.

2-((*S*,*R*)-1-Acetyl-3-methyl-4,5-dihydro-1*H*-pyrazol-5-yl)-19β,28-epoxy-18α-olean-1(2)en-3-one (8). Method I. A solution of compound **7** (0.20 g, 0.4 mmol) in EtOH (25 ml) was treated by the addition of acetic hydrazide (0.37 g, 5 mmol) and 5 drops of AcOH. The reaction mixture was refluxed for 4 h. The solvent was removed from the reaction mixture by evaporation at reduced pressure. The dry residue was dissolved with stirring in pyridine (5 ml) and acetic anhydride (5 ml), then left at room temperature for 24 h. The obtained reaction mixture was washed with 10% HCl solution until acidic pH, then extracted with EtOAc (2×10 ml) and washed with H_2O (5×10 ml) until neutral pH was achieved. The organic layer was separated, dried over anhydrous $MgSO_4$, evaporated at reduced pressure, the residue was purified by silica gel column chromatography, eluent petroleum ether – EtOAc, 1:1. Yield 34 mg (15%).

Method II. A solution of compound **7** (0.20 g, 0.4 mmol) in AcOH (25 ml) was treated by the addition of acetic hydrazide (0.37 g, 5 mmol). The reaction mixture was refluxed for 4 h, then extracted with EtOAc and washed with H_2O (5×10 ml). The organic layer was separated, dried over anhydrous $MgSO_4$, evaporated at reduced pressure, the residue was purified by silica gel column chromatography, eluent petroleum ether – EtOAc, 1:1. Yield 67 mg (30%).

Method III. A solution of compound **6** (0.21 g (0.4 mmol) in AcOH (25 ml) was treated by the addition of acetic hydrazide (0.37 g, 5 mmol). The reaction mixture was heated at reflux for 4 h. The reaction mixture was worked up in accordance with the method II. Yield 0.17 g (76%), mp 182–183°C, $[\alpha]_D^{21}$ +118.2° (*c* 0.7, $CHCl_3$). IR spectrum, ν, cm^{-1}: 1664 (C=O, C=N). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.80 (3H, s, CH_3); 0.82–1.73 (20H, m, 4CH, 8CH_2); 0.90 (2.1H, s) and 0.92 (0.9H, s, CH_3); 0.93 (3H, s, CH_3); 1.01 (3H, s, CH_3); 1.02 (3H, s, CH_3); 1.06 (2.1H, s) and 1.09 (0.9H, s, CH_3); 1.13 (3H, s, CH_3); 2.00 (2.1H, s) and 2.03 (0.9H, s, 8'-CH_3); 2.24 (0.9H, s) and 2.26 (2.1H, s, 7'-CH_3); 2.41 (0.7H, dd, J = 18.3, J = 5.3), 2.58 (0.3H, dd, J = 18.3, J = 5.3), 3.11 (0.3H, dd, J = 18.3, J = 11.6) and 3.19 (0.7H, dd, J = 18.3, J = 11.6, 4'-CH_2); 3.45 (1H, d, J = 7.8) and 3.77 (1H, d, J = 7.8, 28-CH_2); 3.54 (1H, s, 19-CH); 5.00 (0.3H, dd, J = 11.6, J = 5.3) and 5.01 (0.7H, dd, J = 5.3, J = 11.6, 5'-CH); 6.78 (0.7H, s) and 6.82 (0.3H, s, 1-CH). Mass spectrum, *m*/*z* (I_{rel}, %): 562 $[M]^+$ (100). Found, %: C 76.88; H 9.63; N 4.94. $C_{36}H_{54}N_2O_3$. Calculated, %: C 76.82; H 9.67; N 4.98.

2-((*S*,*R*)-3-Methyl-4,5-dihydroisoxazol-5-yl)-19β,28-epoxy-18α-olean-1(2)-en-3-one (9). A solution of compound **6** (0.21 g, 0.4 mmol) in EtOH (25 ml) was treated by the addition of AcONa (0.04 g, 0.5 mmol) and $NH_2OH·HCl$ (0.035 g, 0.5 mmol). The reaction mixture was heated at reflux for 4 h. The reaction mixture was extracted with EtOAc and washed with H_2O (2×10 ml). The organic layer was separated, dried over anhydrous $MgSO_4$, evaporated at reduced pressure, the residue was purified by silica gel column chromatography, eluent petroleum ether – EtOAc, 7:3. Yield 0.19 g (82%), mp 131–133°C, $[\alpha]_D^{21}$ +69.6° (*c* 0.6, $CHCl_3$). IR spectrum, ν, cm^{-1}: 1659 (C=N, C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.79–1.79 (20H, m, 4CH, 8CH_2); 0.81 (3H, s, CH_3); 0.92 (0.9H, s, CH_3); 0.93 (2.1H, s, CH_3); 0.94 (3H, s, CH_3); 1.03 (2.1H, s, CH_3); 1.04 (0.9H, s, CH_3); 1.05 (3H, s, CH_3); 1.08 (3H, s, CH_3); 1.09 (2.1H, s, CH_3); 1.11 (0.9H, s, CH_3); 1.89 (2.1H, s, 3'-CH_3); 1.90 (0.9H, s, 3'-CH_3); 2.32 (0.3H, dd, J = 15.2, J = 8.0), 2.34 (0.7H, dd, J = 15.2, J = 8.0), 2.47 (0.7H, dd, J = 15.0, J = 4.0) and 2.61 (0.3H, dd, J = 15.0, J = 4.0, 4'-CH_2); 3.46 and 3.78 (2H, 2d, J = 7.7, 28-CH_2); 3.55 (1H, s, 19-CH); 4.59 (0.3H, dd, J = 8.5, J = 4.0) and 4.77 (0.7H, dd, J = 8.5, J = 4.0, 5'-CH); 7.14 (1H, br. s, 1-CH). Mass spectrum, *m*/*z* (I_{rel}, %): 519 $[M–H_2]^+$ (100). Found, %: C 78.31; H 9.78; N 2.75. $C_{39}H_{51}NO_3$. Calculated, %: C 78.26; H 9.85; N 2.68.

3β,28-Diacetoxy-30-(1-acetyl-3-methyl-4,5-dihydro-1*H*-pyrazol-5-yl)lup-20(29)-enes 13a,b (a mixture of isomers). A solution of compound **12** (0.48 g, 0.8 mmol) in AcOH (20 ml) was treated by the addition of acetic hydrazide (0.74 g, 10 mmol) and heated at reflux for 4 h. The reaction mixture was extracted with EtOAc and washed with H_2O (2×10 ml). The organic layer was separated, dried over anhydrous $MgSO_4$, evaporated at reduced pressure, the residue was purified by silica gel

column chromatography, eluent petroleum ether – EtOAc, 5:1. Yield 0.33 g (64%), mp 140–144°C, $[\alpha]_D^{21}$ +5.2° (*c* 0.5, $CHCl_3$). IR spectrum, ν, cm^{-1}: 1664 (C=O, C=N). ^1H NMR spectrum, δ, ppm (*J*, Hz): 0.76–2.17 (25H, m, 5CH, $10CH_2$); 0.82 (3H, 3s, CH_3); 0.83 (3H, s, CH_3); 0.84 (3H, s, CH_3); 0.95 (1.8H, s) and 0.99 (1.2H, s, CH_3); 1.03 (3H, s, CH_3); 1.99 (1.2H, s) and 2.00 (1.8H, s, 8'-CH_3); 2.01 (3H, s, $OCOCH_3$); 2.04 (1.8H, s) and 2.05 (1.2H, s, $OCOCH_3$); 2.24 (1.8H, s) and 2.25 (1.2H, s, 7'-CH_3); 2.45–2.59 (1H, m) and 3.03–3.10 (1H, m, 4'-CH_2); 3.79 (0.6H, d, *J* = 10.9), 3.81 (0.4H, d, *J* = 10.9) and 4.24 (1H, d, *J* = 10.9, 28-CH_2); 4.45 (1H, dd, *J* = 10.4, *J* = 6.3, 3-CH); 4.65 (0.4H, s) and 4.74 (0.6H, s, 29-CH_2); 4.75–4.80 (1H, m, 5'-CH); 4.77 (0.4H, s) and 4.86 (0.6H, s, 29-CH_2). Found, *m*/*z*: 637.4569 $[M+H]^+$. $C_{39}H_{61}N_2O_5$. Calculated, *m*/*z*: 637.4575. Found, %: C 73.14; H 9.70; N 4.29. $C_{39}H_{60}N_2O_5$. Calculated, %: C 73.55; H 9.50; N 4.40.

3β,28-Diacetoxy30-((5*S*)-1-acetyl-3-methyl-4,5-dihydro-1*H*-pyrazol-5'-yl)-lup-20(29)-ene (13a). The mixture of isomers **13a**,**b** was purified by silica gel column chromatography, eluent petroleum ether – EtOAc, 5:1. Yield 0.13 g (40%), mp 119–122°C, $[\alpha]_D^{21}$ +26.2° (*c* 0.5, $CHCl_3$). IR spectrum, ν, cm^{-1}: 1664 (C=O, C=N). ^1H NMR spectrum, δ, ppm (*J*, Hz): 0.76–2.15 (25H, m, 5CH, $10CH_2$); 0.82 (3H, s, CH_3); 0.83 (3H, s, CH_3); 0.84 (3H, s, CH_3); 0.95 (3H, s, CH_3); 1.02 (3H, s, CH_3); 2.00 (3H, s, 8'-CH_3); 2.01 (3H, s, 32(34)-CH_3); 2.05 (3H, s, 34(32)-CH_3); 2.25 (3H, s, 7'-CH_3); 2.56 (1H, dd, *J* = 17.9, *J* = 4.7) and 3.06 (1H, dd, *J* = 17.9, *J* = 11.5, 4'-CH_2); 3.79 (1H, d, *J* = 11.0) and 4.24 (2H, d, *J* = 11.0, 28-CH_2); 4.45 (1H, dd, *J* = 9.4, *J* = 6.4, 3-CH); 4.74 (1H, 2s) and 4.86 (1H, s, 29-CH_2); 4.78 (1H, dd, *J* = 11.5, *J* = 4.7, 5'-CH). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 14.8; 16.1 (3C); 16.5; 18.2; 21.0; 21.1; 21.2; 21.9; 23.7; 27.0; 27.6; 28.0; 29.7; 29.8; 32.7; 34.2; 34.6; 37.1; 37.7; 37.8; 38.5; 41.0; 42.8 (C-19); 43.8 (C-4'); 46.2; 50.3; 51.5; 55.4; 61.0 (C-5'); 62.6 (C-28); 80.9 (C-3); 107.2 (C-29); 152.9 (C-20); 155.2 (C-3'); 168.4 (C-6'); 170.9 (C-31); 171.5 (C-33). Found, *m*/*z*: 637.4580 $[M+H]^+$. $C_{39}H_{61}N_2O_5$. Calculated, *m*/*z*: 637.4575. Found, %: C 73.10; H 9.69; N 4.33. $C_{39}H_{60}N_2O_5$. Calculated, %: C 73.55; H 9.50; N 4.40.

X-ray structural analysis of compound 4. Crystals suitable for X-ray structural analysis were obtained by slow evaporation of a solution of compound **4** in 5:1 hexane–EtOAc mixture. The X-ray structural analysis was performed on an Xcalibur Ruby automatic four-circle monocrystal diffractometer equipped with a CCD-detector according to the standard procedure (MoKα radiation, ω-scanning with a step of 1°) at 295(2) K. The absorption was accounted for empirically, using the SCALE3 ABSPACK algorithm.[34] The crystal ($C_{31}H_{46}O_3$, *M* 466.68) had monoclinic syngony, space group $P2_1$; *a* 8.7956(17), *b* 9.9842(15), *c* 15.227(2) Å; β 100.632(17)°; *V* 1314.2(4) $Å^3$; *Z* 2; d_{calc} 1.179 g/cm^3; μ 0.073 mm^{-1}. The structure was solved by using the Superflip software[35] and refined by full-matrix method of least squares by F^2 in anisotropic approximation for all non-hydrogen atoms with the SHELXL program[36] in combination with the OLEX2 graphical interface.[37] The atom positions were refined by using the riding model. The final parameters of refinement were the following: R_1 0.0526 (for 5360 reflections with $I > 2\sigma(I)$), wR_2 0.1388 (for all 6052 independent reflections), *S* 1.028. The complete X-ray structural analysis dataset for compound **4** was deposited at the Cambridge Crystallographic Data Center (deposit CCDC 1970634).

Biological activity study. The following cancer cell lines were selected for the study: human nonsmall cell lung cancer cell line A549, laryngeal carcinoma cell line Hep-2, human colorectal cancer cell line HCT116, human melanoma cell line MS, human prostate cancer cell line PC-3, human breast adenocarcinoma cell line MCF-7, human rhabdomyocarcoma cell line RD TE32, and the noncancer cell line HEK293, obtained from the Institute of Experimental Diagnostics and Therapy of Cancer at the N. N. Blokhin Russian Cancer Research Center of the Russian Academy of Medical Sciences (Moscow, Russia). The cells were inoculated on 96-well microplates and cultured in DMEM growth medium (for the cell lines RD TE32, A549, HCT116, PC-3, Hep-2, MCF-7, HEK293) or RPMI 1640 growth medium (in the case of the cell line MS) with the addition of fetal bovine serum (10%) and glutamine (0.3%) at 37°C under 5% CO_2 atmosphere in a Barnstead Isotemp CO_2 incubator. The study compounds were added to the microplate wells after 24 h as 100 μM solutions in DMSO, followed by serial dilution to 1.56 μM. The concentration of DMSO in the microplate wells did not exceed 1%. The survival rate of cells was determined after 72 h incubation of the cells with the study compounds by using MTT test[38] with a FLUOstar OPTIMA microplate reader (BMG Labtech GmbH, Germany). The IC_{50} values corresponding to 50% cell death were used as a quantitative criterion for the expression of cytotoxicity due to the test compounds. The control was assumed as 100%, in the case of cells incubated in the respective growth media with the addition of 1% of DMSO. The experiments were performed in triplicate.

Supplementary information file containing ^1H and ^{13}C NMR spectra and two-dimensional NMR spectra of the synthesized compounds is available at the journal website at http://link.springer.com/journal/10593.

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