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SYNTHESIS OF NEW PYRAZOLE–METHYL-MALEOPIMARATE CONJUGATES

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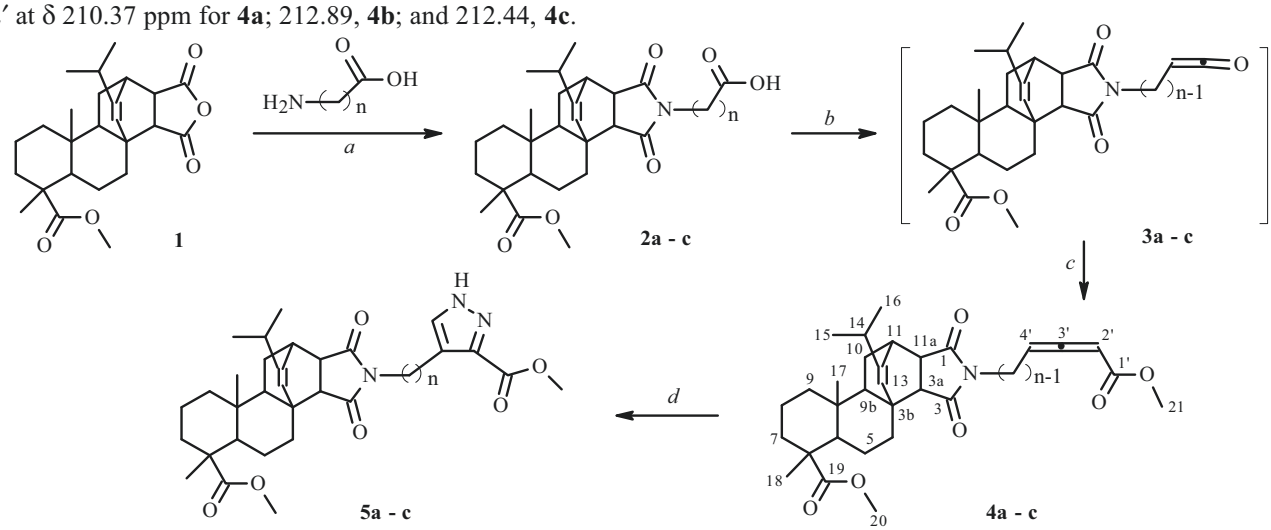
Regiospecific synthesis of conjugates containing a diterpenoid fragment and a pyrazole-ring pharmacophore by 1,3-dipolar cycloaddition of diazomethane to allenoates in the presence of Et_3N was demonstrated.

Keywords: methyl maleopimarate, diterpenoids, allene, pyrazoles, 1,3-dipolar cycloaddition, allenoates.

Pyrazoles are very important heteroaromatic compounds due to their broad distribution in natural products and pharmacologically active compounds [1–3]. Many pyrazole-containing compounds such as Celebrex [4], rimonabant [5], and Viagra [6] were successfully commercialized as drugs. Methyl maleopimarate (MEMPA) was obtained by the known method from levopimaric acid and maleic anhydride [7, 8] and is a convenient and available reagent for synthesizing compounds with anti-inflammatory, antiulcer, fungicidal, and other activities [9–12]. In continuation of research on potential biologically active compounds, we synthesized conjugates with a diterpene fragment and pyrazole-ring pharmacophore. The key reaction was 1,3-dipolar cycloaddition of diazomethane to allenoates.

Allenes **4a**–**c** were synthesized from *N*-substituted amino acids **2a**–**c**, which were obtained via condensation of MEMPA (**1**) with glycine, *β*-alanine, and *γ*-aminobutyric acid in refluxing DMF. The reaction of *N*-substituted amino-acid chlorides **2a**–**c** with Et_3N passed through ketenes **3a**–**c**, which reacted with methyl(triphenylphosphoranylidene)acetate to give allenoates **4a**–**c** in yields of 63, 67, and 70%, respectively [13] (Scheme 1). The structures of the synthesized allenes were proved by physicochemical analytical methods. Thus, ^{13}C NMR spectra were characterized by resonances for two terminal allene C atoms C-2′ and C-4′ at δ 96.13 and 91.17 ppm for **4a**; 90.16 and 89.7 ppm, **4b**; 91.86 and 88.56, **4c**; and also central C atom C-2′ at δ 210.37 ppm for **4a**; 212.89, **4b**; and 212.44, **4c**.



n = 1 (**a**); 2 (**b**); 3 (**c**)

a. DMF, *b*. 1. $SOCl_2$, 2. Et_3N; *c*. $(Ph)_3P{=}CHCO_2Me$; *d*. CH_2N_2, CH_2Cl_2

Scheme 1

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An effective approach to the synthesis of substituted pyrazoles is 1,3-dipolar cycloaddition of diazo compounds to unsaturated compounds. Thus, reaction of allenoates **4a**–**c** with a five-fold excess of CH_2N_2 and an equimolar amount of Et_3N produced 3,4-disubstituted 1H-pyrazoles **5a**–**c** in yields of 39, 51, and 46%, respectively (Scheme 1). The reaction of CH_2N_2 with **4a**–**c** was regiospecific and formed a C-N bond in the α-position to the ester [14, 15]. The structures of the products were confirmed by physicochemical analytical methods.

Thus, NMR spectra (HMBC) of **5a** showed cross peaks for C-1″ methyl protons with C-1 and C-3 imide C atoms, C-3′ and C-4′ double-bond quaternary C atoms, and C-5′. The pyrazole proton resonating at 7.57 ppm coupled with C-3′ and C-4′ and the C-1″ methylene protons. The lack of correlation with C-6′ agreed with structure **5a**. Analogous cross peaks in HMBC mode were observed for **5b** and **5c**.

Therefore, a convenient synthesis of conjugates with an MEMPA moiety and pyrazole-ring pharmacophore by 1,3-dipolar cycloaddition of diazomethane to allenoates is proposed.

EXPERIMENTAL

IR spectra were recorded from thin layers or in mineral oil on an IR-Prestige-21 (FTIR Spectrophotometer, Shimadzu). NMR spectra were taken with TMS internal standard on a Bruker-AM 500 spectrometer at operating frequency 500.13 MHz for ^1H and 125.76 MHz for ^{13}C. Homo- and heteronuclear 2D correlation COSY, NOESY, HSQC, and HMBC methods were used for correct assignment of resonances in NMR spectra of reaction products. The course of reactions was monitored using TLC on Sorbfil plates (PTSKh-AF-A) with detection by UV light, I_2 vapor, and spraying with ninhydrin detector followed by heating at 100–120°C. Mass spectra were obtained on a LCMS-2010EV GC MS (Shimadzu) in chemical ionization at atmospheric pressure mode (APCI). Melting points were measured on a Boetius apparatus. Reaction products were isolated by column chromatography over silica gel (Chemapol, 40/100 and 100/160 μm).

General Method for Synthesizing MEMPA Imides 2a–c. A mixture of methyl maleopimarate (MEMPA, 10 mmol) and amino acid (15 mmol) in DMF (25 mL) was refluxed until the MEMPA disappeared (~5 h), cooled to room temperature, and treated with distilled H_2O. The resulting precipitate was filtered off, rinsed with distilled H_2O, dissolved in CH_2Cl_2, and dried over $MgSO_4$. The product was chromatographed using $CHCl_3$–Me_2CO (9:1).

[(3a*R*,6*R*,9a*R*,11a*R*)-6-(Methoxycarbonyl)-6,9a-dimethyl-1,3-dioxo-12-(propan-14-yl)tetrahydro-3b,11-ethenonaphtho[2,1-*e*]isoindol-2(1*H*)-yl]acetic Acid (2a). Yield 2.9 g (63%), white powder, mp 64°C. IR spectrum (ν, cm^{-1}): 2953, 1763, 1715, 1675, 1462, 1250, 1181. ^1H NMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.51 (3H, s, 17-CH_3), 0.95 (6H, m, CH_3-15, 16), 0.98, 1.43 (2H-gem, m, H-9), 1.17 (3H, s, CH_3-18), 1.22, 1.5 (2H-gem, m, H-5), 1.41–1.65 (2H, m, H-8), 1.29, 1.71 (2H-gem, m, H-10), 1.72, 2.52 (2H-gem, m, H-4), 1.41 (1H, m, H-9b), 1.55, 1.75 (2H-gem, m, H-7), 1.77 (1H, m, H-5a), 2.19 (1H, m, H-14), 2.54 (1H, d, J = 8.1, H-3a), 2.91 (1H, dd, J = 2.8, 8.1, H-11a), 3.08 (1H, m, H-11), 4.11 (2H, d, J = 9.6, H-2′), 3.68 (3H, s, CH_3-20), 5.4 (1H, s, H-13). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 15.65 (C-17), 16.72 (C-18), 17.02 (C-8), 19.77 and 20.57 (2C-15,16), 21.73 (C-5), 27.51 (C-10), 32.56 (C-14), 35.16 (C-4), 35.44 (C-11), 36.68 (C-7), 37.68 (C-9a), 38.07 (C-9), 38.87 (C-2′), 40.69 (C-3b), 45.25 (C-11a), 47.16 (C-6), 49.48 (C-5a), 52.08 (C-20), 52.54 (C-3a), 54.05 (C-9b), 124.37 (C-13), 146.86 (C-12), 171.41 (C-1′), 176.49 (C-1), 177,83 (C-3), 179.44 (C-19).

3′-[(3a*R*,6*R*,9a*R*,11a*R*)-6-(Methoxycarbonyl)-6,9a-dimethyl-1,3-dioxo-12-(propan-14-yl)tetrahydro-3b,11-ethenonaphtho[2,1-*e*]isoindol-2(1*H*)-yl]propanoic Acid (2b). Yield 3.3 g (68%), white powder, mp 82°C. IR spectrum (ν, cm^{-1}): 3206, 1731, 1699, 1687, 1461, 1272, 1167. ^1H NMR spectrum ($CDCl_3$, δ ppm, J/Hz): 0.59 (3H, s, CH_3-17), 0.94 (6H, m, CH_3-15, 16), 0.96, 1.38 (2H-gem, m, H-9), 1.14 (3H, s, CH_3-18), 1.21, 1.46 (2H-gem, m, H-5), 1.41–1.65 (2H, m, H-8), 1.24, 1.63 (2H-gem, m, H-10), 1.69, 2.49 (2H-gem, m, H-4), 1.4 (1H, m, H-9b), 1.55, 1.72 (2H-gem, m, H-7), 1.77 (1H, m, H-5a), 2.16 (1H, m, H-14), 2.52 (2H, t, J = 7.6, H-2′), 2.43 (1H, d, J = 8.1, H-3a), 2.81 (1H, dd, J = 2.9, 8.1, H-11a), 3.06 (1H, m, H-11), 3.64 (2H, t, J = 7.6, H-3′), 3.68 (3H, s, CH_3-20), 5.39 (1H, s, H-13), 10.5 (1H, s, OH). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 15.64 (q, C-17), 16.74 (q, C-18), 17.03 (t, C-8), 19.97, 20.71 (each q, C-15, 16), 21.75 (t, C-5), 27.5 (t, C-10), 31.76 (t, C-2′), 32.62 (d, C-14), 33.56 (t, C-3′), 35.21 (t, C-4), 35.64 (d, C-11), 36.69 (t, C-7), 37.68 (s, C-9a), 38.1 (t, C-9), 40.73 (s, C-3b), 44.92 (d, C-11a), 47.15 (s, C-6), 49.49 (d, C-5a), 52.03 (q, C-20), 52.28 (d, C-3a), 54.13 (d, C-9b), 124.34 (d, C-13), 147.01 (s, C-12), 175.81 (s, C-1′), 177.03 (s, C-1), 178.4 (s, C-3), 179.31 (s, C-19).

4′-[(3a*R*,6*R*,9a*R*,11a*R*)-6-(Methoxycarbonyl)-6,9a-dimethyl-1,3-dioxo-12-(propan-14-yl)tetrahydro-3b,11-ethenonaphtho[2,1-*e*]isoindol-2(1*H*)-yl]butanoic Acid (2c). Yield 3.6 g (72%), white powder, mp 98°C. IR spectrum (ν, cm^{-1}): 2964, 1718, 1691, 1677, 1459, 1243, 1162. ^1H NMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.59 (3H, s, CH_3-17), 0.95

(6H, m, CH_3-15, 16), 0.98, 1.46 (2H-gem, m, H-9), 1.15 (3H, s, CH_3-18), 1.19, 1.49 (2H-gem, m, H-5), 1.41 (2H, m, H-8), 1.25, 1.65 (2H-gem, m, H-10), 1.67, 2.49 (2H-gem, m, H-4), 1.42 (2H, m, H-9b), 1.76 (2H, m, H-3′), 1.55, 1.72 (2H-gem, m, H-7), 1.79 (1H, m, H-5a), 2.18 (1H, m, H-14), 2.28 (2H, t, J = 7.5, H-2′), 2.44 (1H, d, J = 8.1, H-3a), 2.81 (1H, dd, J = 3, 8.1, H-11a), 3.07 (1H, m, H-11), 3.41 (2H, t, J = 7, H-4′), 3.68 (3H, s, CH_3-20), 5.4 (1H, s, H-13). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 15.65 (q, C-17), 16.73 (q, C-18), 17.03 (t, C-8), 19.85, 20.65 (each q, C-15, 16), 21.75 (t, C-5), 22.87 (t, C-3′), 27.49 (t, C-10), 31.18 (t, C-2′), 32.59 (d, C-14), 35.21 (t, C-4), 35.61 (d, C-11), 36.68 (t, C-7), 37.37 (t, C-4′), 37.67 (s, C-9a), 38.09 (t, C-9), 40.74 (s, C-3b), 44.93 (d, C-11a), 47.14 (s, C-6), 49.49 (d, C-5a), 52.02 (q, C-20), 52.24 (d, C-3a), 54.20 (d, C-9b), 124.28 (d, C-13), 147.07 (s, C-12), 177.46 (s, C-1), 177.9 (s, C-1′), 178,73 (s, C-3), 179.3 (s, C-19). Mass spectrum (ESI), *m/z* (I_{rel}, %): 500 [MH^+, 100], $C_{29}H_{41}NO_6$. Calcd M 499.64.

Method for Preparing Allenoates 4a–c by a Wittig Reaction. A suspension of acid (1 g) in anhydrous C_6H_6 (10 mL) was treated with a five-fold excess of $SOCl_2$ and refluxed with a $CaCl_2$ tube for 3 h. The solvent and excess of $SOCl_2$ were evaporated in a rotary evaporator. Then, the acid chloride was used without further purification. A solution of methyl(triphenylphosphoranylidene)acetate in CH_2Cl_2 was treated dropwise with an equimolar amount of Et_3N, chilled to –10°C, treated slowly dropwise with the cooled solution of *N*-phthalyl-substituted amino-acid chloride, stirred for 0.5 h, and stored at 0°C. The solvent was distilled off. The reaction products were isolated by column chromatography over silica gel (petroleum ether–EtOAc, 7:3).

Methyl 12-Isopropyl-2-(4′-methoxy-4′-oxobuta-1′,2′-dien-1′-yl)-6,9a-dimethyl-1,3-dioxohexadecahydro-3b,11-ethenonaphtho[2,1-*e*]isoindole-6-carboxylate (4a). Yield 0.68 g (63%), yellow oil. IR spectrum (ν, cm^{-1}): 2959, 2863, 1716, 1700, 1463. ^{1}H NMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.55 (3H, s, CH_3-17), 0.86 (6H, m, CH_3-15, 16), 0.88, 1.39 (2H-gem, m, H-9), 1.11 (3H, s, CH_3-18), 1.15, 1.47 (2H-gem, m, H-5), 1.41 (2H, m, H-8), 1.19, 1.68 (2H-gem, m, H-10), 1.63, 2.48 (2H-gem, m, H-4), 1.39 (2H, m, H-9b), 1.52, 1.71 (2H-gem, m, H-7), 1.74 (1H, m, H-5a), 2.16 (1H, m, H-14), 2.51 (1H, m, H-3a), 2.84 (1H, m, H-11a), 3.04 (1H, m, H-11), 3.62 (3H, s, CH_3-20), 3.69 (3H, s, CH_3-21), 5.41 (1H, s, H-13), 6.18 (1H, m, H-2′), 6.93 (1H, m, H-4′). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 15.54 (q, C-17), 16.72 (q, C-18), 17.00 (t, C-8), 20.19, 20.71 (each q, C-15, 16), 21.70 (t, C-5), 27.63 (t, C-10), 32.81 (d, C-14), 35.14 (t, C-4), 35.79 (d, C-11), 36.68 (t, C-7), 37.65 (s, C-9a), 38.09 (t, C-9), 40.83 (s, C-3b), 45.00 (d, C-11a), 47.08 (s, C-6), 49.43 (d, C-5a), 51.95 (q, C-20), 52.21 (q, C-21), 52.55 (d, C-3a), 53.66 (d, C-9b), 91.17 (d, C-4′), 96.13 (d, C-2′), 124.87 (d, C-13), 147.33 (s, C-12), 164.42 (s, C-1′), 173.94 (s, C-1), 175.03 (s, C-3), 179.12 (s, C-19), 210.37 (s, C-3′). Mass spectrum (ESI), *m/z* (I_{rel}, %): 510 [MH^+, 100], $C_{30}H_{39}NO_6$. Calcd M 509.63.

Methyl 12-Isopropyl-2-(5′-methoxy-5′-oxopenta-1′,2′-dien-1′-yl)-6,9a-dimethyl-1,3-dioxohexadecahydro-3b,11-ethenonaphtho[2,1-*e*]isoindole-6-carboxylate (4b). Yield 0.72 g (67%), yellow oil. IR spectrum (ν, cm^{-1}): 2950, 2869, 1967, 1770, 1694, 1436. ^{1}H NMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.56 (3H, s, CH_3-17), 0.89 (6H, m, CH_3-15, 16), 0.91, 1.24 (2H-gem, m, H-9), 1.12 (3H, s, CH_3-18), 1.15, 1.43 (2H-gem, m, H-5), 1.47 (2H, m, H-8), 1.19, 1.65 (2H-gem, m, H-10), 1.64, 2.5 (2H-gem, m, H-4), 1.39 (2H, m, H-9b), 1.53, 1.69 (2H-gem, m, H-7), 1.74 (1H, m, H-5a), 2.16 (1H, m, H-14), 2.42 (1H, m, H-3a), 2.78 (1H, m, H-11a), 3.04 (1H, m, H-11), 3.65 (3H, s, CH_3-20), 3.7 (3H, s, CH_3-21), 4.02 (2H, m, H-5′), 5.37 (1H, s, H-13), 5.65 (1H, m, H-2′), 5.52 (1H, m, H-4′). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 15.62 (q, C-17), 16.74 (q, C-18), 17.02 (t, C-8), 19.9, 20.68 (each q, C-15, 16), 21.74 (t, C-5), 27.52 (t, C-10), 32.67 (d, C-14), 35.23 (t, C-4), 35.45 (t, C-5′), 35.63 (d, C-11), 36.68 (t, C-7), 37.67 (s, C-9a), 38.1 (t, C-9), 40.72 (s, C-3b), 44.99 (d, C-11a), 47.12 (s, C-6), 49.49 (d, C-5a), 51.98 (q, C-20), 52.17 (q, C-21), 52.38 (d, C-3a), 54.06 (d, C-9b), 90.16 (d, C-2′), 89.7 (d, C-4′), 124.46 (d, C-13), 147.01 (s, C-12), 165.44 (s, C-1′), 176.51 (s, C-1), 177.69 (s, C-3), 179.2 (s, C-19), 212.89 (s, C-3′). Mass spectrum (ESI), *m/z* (I_{rel}, %): 524 [MH^+, 100], $C_{31}H_{41}NO_6$. Calcd M 523.66.

Methyl 12-Isopropyl-2-(6′-methoxy-6′-oxohexa-1′,2′-dien-1′-yl)-6,9a-dimethyl-1,3-dioxohexadecahydro-3b,11-ethenonaphtho[2,1-*e*]isoindole-6-carboxylate (4c). Yield 0.79 g (70%), yellow oil, mp 16–18°C. IR spectrum (ν, cm^{-1}): 2958, 2932, 1952, 1726, 1718. ^{1}H NMR spectrum ($CDCl_3$, δ, ppm): 0.59 (3H, s, CH_3-17), 0.94 (6H, m, CH_3-15, 16), 0.99, 1.44 (2H-gem, m, H-9), 1.14 (3H, s, CH_3-18), 1.18, 1.46 (2H-gem, m, H-5), 1.5 (2H, m, H-8), 1.22, 1.67 (2H-gem, m, H-10), 1.69, 2.5 (2H-gem, m, H-4), 1.41 (1H, m, H-9b), 1.55, 1.72 (2H-gem, m, H-7), 1.78 (1H, m, H-5a), 2.18 (1H, m, H-14), 2.28 (2H, m, H-5′), 2.47 (1H, m, H-3a), 2.83 (1H, m, H-11a), 3.03 (1H, m, H-11), 3.46 (2H, m, H-6′), 3.66 (3H, s, CH_3-20), 3.72 (3H, s, CH_3-21), 5.39 (1H, s, H-13), 5.62 (1H, m, H-2′), 5.51 (1H, m, H-4′). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 15.64 (q, C-17), 16.74 (q, C-18), 17.03 (t, C-8), 20.02, 20.73 (each q, C-15, 16), 21.75 (t, C-5), 25.73 (t, C-5′), 27.55 (t, C-10), 32.65 (d, C-14), 35.25 (t, C-4), 35.63 (d, C-11), 36.68 (t, C-7), 37.08 (t, C-6′), 37.67 (s, C-9a), 38.1 (t, C-9), 40.68 (s, C-3b), 44.95 (d, C-11a), 47.11 (s, C-6), 49.5 (d, C-5a), 51.95 (q, C-20), 52.03 (q, C-21), 52.3 (d, C-3a), 54.15 (d, C-9b), 91.86 (d, C-2′), 88.56 (d, C-4′),

124.36 (d, C-13), 147.04 (s, C-12), 166.09 (s, C-1′), 177.26 (s, C-1), 178.46 (s, C-3), 179.15 (s, C-19), 212.44 (s, C-3′). Mass spectrum (ESI), *m*/*z* (I_{rel}, %): 538 [MH^+, 100], $C_{32}H_{43}NO_6$. Calcd M 537.69.

Method for Preparing Pyrazoles 5a–c. Solutions of allenoates (0.5 g) in CH_2Cl_2 (20 mL) were chilled to 0°C, treated with an equimolar amount of Et_3N and a five-fold excess of freshly prepared CH_2N_2 in CH_2Cl_2 in a single portion, warmed to room temperature, and stirred on a magnetic stirrer for 6 h. The solvent was distilled off. The reaction products were isolated by column chromatography over silica gel (petroleum ether–EtOAc eluent, 1:1).

Methyl 12-Isopropyl-2-{[3′-(methoxycarbonyl)-1*H*-pyrazol-4′-yl]methyl}-6,9a-dimethyl-1,3-dioxohexadecahydro-3b,11-ethenonaphtho[2,1-*e*]isoindole-6-carboxylate (5a). Yield 0.21 g (39%), yellow powder, mp 194–195°C. IR spectrum (ν, cm^{-1}): 3146, 1726, 1693, 1682, 1372, 1337, 1243, 1102. ^1H NMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.54 (3H, s, CH_3-17), 0.71 (3H, m, CH_3-15), 0.82 (3H, m, CH_3-16), 0.91, 1.39 (2H-gem, m, H-9), 1.11 (3H, s, CH_3-18), 1.19, 1.43 (2H-gem, m, H-5), 1.47 (2H, m, H-8), 1.21, 1.62 (2H-gem, m, H-10), 1.65, 2.49 (2H-gem, m, H-4), 1.35 (2H, m, H-9b), 1.52, 1.69 (2H-gem, m, H-7), 1.74 (1H, m, H-5a), 2.07 (1H, m, H-14), 2.43 (1H, d, J = 8.2, H-3a), 2.79 (1H, dd, J = 2.9, 8.2, H-11a), 3.02 (1H, m, H-11), 3.64 (3H, s, CH_3-20), 3.93 (3H, s, CH_3-21), 4.68, 4.79 (2H-gem, dd, J = 15.1, H-1″), 5.38 (1H, s, H-13), 7.57 (1H, s, H-5′), 11.3 (1H, s, NH-1′). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 15.63 (q, C-17), 16.72 (q, C-18), 17.01 (t, C-8), 19.73, 20.45 (each q, C-15, 16), 21.76 (t, C-5), 27.52 (t, C-10), 32.47 (t, C-1″), 32.53 (d, C-14), 35.25 (t, C-4), 35.36 (d, C-11), 36.67 (t, C-7), 37.66 (s, C-9a), 38.08 (t, C-9), 40.77 (s, C-3b), 45.05 (d, C-11a), 47.13 (s, C-6), 49.49 (d, C-5a), 51.96 (q, C-20), 51.98 (q, C-21), 52.30 (d, C-3a), 54.23 (d, C-9b), 118.37 (t, C-4′), 124.40 (d, C-13), 133.20 (d, C-5′), 137.78 (s, C-3′), 147.11 (s, C-12), 162.19 (s, C-6′), 176.96 (s, C-1), 178.01 (s, C-3), 179.23 (s, C-19). Mass spectrum (ESI), *m*/*z* (I_{rel}, %): 552 [MH^+, 100], $C_{31}H_{41}N_3O_6$. Calcd M 551.67.

Methyl 12-Isopropyl-2-{2″-[3′-(methoxycarbonyl)-1*H*-pyrazol-4′-yl]ethyl}-6,9a-dimethyl-1,3-dioxohexadecahydro-3b,11-ethenonaphtho[2,1-*e*]isoindole-6-carboxylate (5b). Yield 0.28 g (51%), mp 84–85°C. IR spectrum (ν, cm^{-1}): 3114, 1731, 1694, 1685, 1375, 1340, 1256, 1105. ^1H NMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.56 (3H, s, CH_3-17), 0.9 (3H, m, CH_3-15), 0.93 (3H, m, CH_3-16), 0.96, 1.38 (2H-gem, m, H-9), 1.14 (3H, s, CH_3-18), 1.17, 1.45 (2H-gem, m, H-5), 1.49 (2H, m, H-8), 1.19, 1.63 (2H-gem, m, H-10), 1.68, 2.49 (2H-gem, m, H-4), 1.38 (2H, m, H-9b), 1.53, 1.72 (2H-gem, m, H-7), 1.75 (1H, m, H-5a), 2.16 (1H, m, H-14), 2.39 (1H, d, J = 8.1, H-3a), 2.77 (1H, dd, J = 3, 8.1, H-11a), 2.88 (2H, m, H-2″), 3.04 (1H, m, H-11), 3.58 (2H, m, H-1″), 3.66 (3H, s, CH_3-20), 3.96 (3H, s, CH_3-21), 5.37 (1H, s, H-13), 7.59 (1H, s, H-5′), 10.4 (1H, s, NH-1′). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 15.64 (q, C-17), 16.75 (q, C-18), 17.04 (t, C-8), 19.98, 20.71 (each q, C-15, 16), 21.77 (t, C-5), 21.77 (t, C-2″), 27.56 (t, C-10), 32.67 (d, C-14), 35.29 (t, C-4), 35.62 (d, C-11), 36.68 (t, C-7), 37.68 (s, C-9a), 38.13 (t, C-9), 38.37 (t, C-1″), 40.70 (s, C-3b), 44.92 (d, C-11a), 47.15 (s, C-6), 49.51 (d, C-5a), 51.99 (q, C-20), 52.23 (q, C-21), 52.28 (d, C-3a), 54.15 (d, C-9b), 120.05 (s, C-4′), 124.36 (d, C-13), 133.23 (d, C-5′), 137.62 (s, C-3′), 146.98 (s, C-12), 162.09 (s, C-6′), 177.23 (s, C-1), 178.46 (s, C-3), 179.26 (s, C-19). Mass spectrum (ESI), *m*/*z* (I_{rel}, %): 566 [MH^+, 100], $C_{32}H_{43}N_3O_6$. Calcd M 565.70.

Methyl 12-Isopropyl-2-{3″-[5′-(methoxycarbonyl)-1′-methyl-1*H*-pyrazol-4′-yl]propyl}-6,9a-dimethyl-1,3-dioxohexadecahydro-3b,11-ethenonaphtho[2,1-*e*]isoindole-6-carboxylate (5c). Yield 0.25 g (46%), yellow powder, mp 81–82°C. IR spectrum (ν, cm^{-1}): 3185, 1728, 1694, 1683, 1439, 1377, 1245, 1100. ^1H NMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 0.57 (3H, s, CH_3-17), 0.89 (3H, m, CH_3-15), 0.95 (3H, m, CH_3-16), 0.93, 1.41 (2H-gem, m, H-9), 1.13 (3H, s, CH_3-18), 1.16, 1.45 (2H-gem, m, H-5), 1.49 (2H, m, H-8), 1.19, 1.64 (2H-gem, m, H-10), 1.68, 2.51 (2H-gem, m, H-4), 1.38 (1H, m, H-9b), 1.53, 1.71 (2H-gem, m, H-7), 1.73 (2H, m, H-2″), 1.76 (1H, m, H-5a), 2.16 (1H, m, H-14), 2.42 (1H, d, J = 7.9, H-3a), 2.68 (2H, m, H-3″), 2.78 (1H, dd, J = 2.4, 7.9, H-11a), 3.04 (1H, m, H-11), 3.38 (2H, m, H-1″), 3.67 (3H, s, CH_3-20), 3.92 (3H, s, CH_3-21), 5.37 (1H, s, H-13), 7.61 (1H, s, H-5′), 10.8 (1H, s, NH-1′). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 15.67 (q, C-17), 16.75 (q, C-18), 17.04 (t, C-8), 19.89, 20.69 (each q, C-15, 16), 21.68 (t, C-3″), 21.77 (t, C-5), 27.53 (t, C-10), 27.95 (t, C-2″), 32.64 (d, C-14), 35.30 (t, C-4), 35.68 (d, C-11), 36.70 (t, C-7), 37.69 (s, C-9a), 37.82 (s, C-1″), 38.12 (t, C-9), 40.74 (s, C-3b), 44.96 (d, C-11a), 47.15 (s, C-6), 49.52 (d, C-5a), 51.89 (q, C-20), 52.00 (q, C-21), 52.30 (d, C-3a), 54.21 (d, C-9b), 121.34 (s, C-4′), 124.30 (d, C-13), 133.74 (d, C-5′), 137.01 (s, C-3′), 146.98 (s, C-12), 161.99 (s, C-6′), 177.42 (s, C-1), 178.59 (s, C-3), 179.22 (s, C-19). Mass spectrum (ESI), *m*/*z* (I_{rel}, %): 580 [MH^+, 100], $C_{33}H_{45}N_3O_6$. Calcd M 579.73.

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REFERENCES

1. V. Kumar, K. Kaur, and A. K. Sharma, *Eur. J. Med. Chem.*, **69**, 735 (2013).
2. K. A. Krasnov, V. G. Kartsev, and S. F. Vasilevskii, *Chem. Nat. Compd.*, **41**, 446 (2005).
3. S. P. Bondarenko, M. S. Frasinyuk, V. I. Vinogradova, and V. P. Khilya, *Chem. Nat. Compd.*, **50**, 889 (2014).
4. L. M. Oh, *Tetrahedron Lett.*, **47**, 7943 (2006).
5. X. Deng and N. S. Mani, *Org. Lett.*, **10**, 1307 (2008).
6. N. K. Terrett, A. S. Bell, D. Brown, and P. Ellis, *Bioorg. Med. Chem. Lett.*, **6**, 1819 (1996).
7. X. Q. Liu, W. B. Xin, and J. W. Zhang, *Green Chem.*, **11**, 1018 (2009).
8. L. H. Zalkow, R. A. Ford, and J. P. Kutney, *J. Org. Chem.*, **27**, 3535 (1962).
9. O. B. Kazakova, E. V. Tret′yakova, O. S. Kukovinets, G. A. Tolstikov, T. I. Nazyrov, I. V. Chudov, and A. F. Ismagilova, *Bioorg. Khim.*, **36**, 762 (2010).
10. J. Wang, Y. P. Chen, K. Yao, P. A. Wilbon, W. Zhang, L. Ren, J. Zhou, M. Nagarkatti, C. Wang, F. Chu, X. He, A. W. Decho, and C. Tang, *Chem. Commun.*, **48**, 916 (2012).
11. G. Y. Yao, M. Y. Ye, R. Z. Huang, Y. J. Li, Y. T. Zhu, Y. M. Pan, Z. X. Liao, and H. S. Wang, *Bioorg. Med. Chem. Lett.*, **24**, 6755 (2013).
12. E. V. Tretyakova, I. E. Smirnova, O. B. Kazakova, G. A. Tolstikov, N. P. Yavorskaya, I. S. Golubeva, R. B. Pugacheva, G. N. Apryshko, and V. V. Poroikov, *Bioorg. Med. Chem.*, **22**, 6481 (2014).
13. I. M. Sakhautdinov, A. M. Gumerov, G. G. Gibadullina, O. V. Zakir′yanova, and M. S. Yunusov, *Chem. Nat. Compd.*, **51**, 332 (2015).
14. I. M. Sakhautdinov, A. M. Gumerov, I. R. Batyrshin, A. A. Fatykhov, K. Yu. Suponitsky, and M. S. Yunusov, *Heterocycles*, **89**, 641 (2014).
15. I. M. Sakhautdinov, I. R. Batyrshin, A. A. Fatukhov, V. M. Yumabaeva, K. Yu. Suponitsky, M. Yu. Antipin, and M. S. Yunusov, *J. Struct. Chem.*, **54**, 383 (2013).