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SYNTHESIS OF AMINOMETHYL DERIVATIVES OF CHRYSIN

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Aminomethylation of chrysin through the action of aminals was studied. 6,8-Bis-substituted chrysin derivatives were synthesized.

Keywords: chrysin, electrophilic substitution, aminomethylation, aminal.

A promising route for creating modern anticancer drugs is the synthesis of analogs of rohitukine, a chromone alkaloid isolated from *Dysoxylum binectariferum* [1]. A series of 8-(4-piperidin-4-yl)- and 8-(3-pyrrolidin-3-yl)-5,7-dihydroxyflavones containing various substituents in ring B were synthesized. The inhibition of cyclin-dependent kinases (CDKs) by these compounds was studied [2–6]. The synthetic rohitukine derivative Flavopiridol is used in modern medical practice [7]. Also, 8-aminomethyl derivatives of isoflavones are effective CDK-2 inhibitors [8, 9]. Advantages of the latter over their regioisomers 8-(4-piperidin-4-yl)- and 8-(3-pyrrolidin-3-yl)-5,7-dihydroxyflavones are the simplicity of synthesizing them and the availability of the starting compounds.

The goal of our work was to study aminomethylation of chrysin (5,7-dihydroxyflavone) (**1**), which occurs in *Scutellaria discolor* [10] and *S. squarrosa* [11] in addition to many other plants and is the simplest and most available flavone with the phloroglucinol arrangement of hydroxyls. Several publications on chrysin aminomethylation have appeared. Thus, use of aminals for aminomethylation of phenols was proposed in one of the first reports where it was shown that 6-, 8-, or 6,8-bis-aminomethyl derivatives could form in this reaction [12]. However, conditions for regioselective aminomethylation were not found. It was shown in recent work [13] that use of an equivalent amount of an aminomethylating reagent (aldehyde and primary amine or 2-hydroxypiperidine) led to the formation of a mixture of the 6- and 8-aminomethyl derivatives with the 6-aminomethyl derivatives formed preferentially. Formation of 3-aminomethyl derivatives [14–17] where decarbonylation of 3-formylchromones was observed in several instances [18] is also an alternative version of the aminomethylation of 3-unsubstituted chromones.

According to our information, the reaction of chrysin with aminals obtained via condensation of formaldehyde with secondary amines is carried out most easily in dioxane. A mixture of several products is formed according to TLC data if an equivalent of aminomethylating reagent is added to the reaction. Apparently, this occurs because of the practically equally probable aminomethylation at the 6- and 8-positions. Furthermore, acid–base isomerization of the 5,7-dihydroxyflavone ring can happen in this instance. This prevents a single product from being isolated. Such behavior of 5,7-dihydroxyflavones substituted in ring A was shown earlier using regioisomeric chromone alkaloids as examples [19, 20].

Changing the reaction conditions (solvent, temperature, reaction time) also did not lead to regioselective aminomethylation. Increasing the amount of aminal to two equivalents produced 6,8-bis-aminomethyl derivatives **2**–**4**, indicating that the reactivities of the C-6 and C-8 atoms of the chromone ring toward the action of electrophilic reagents were practically identical. Apparently, the direction and nature of the aminomethylation of 5,7-dihydroxyflavones and isomeric 5,7-dihydroxyisoflavones were analogous both through the action of aminals [21, 22] and under classical Mannich-reaction conditions [23].

NMR spectroscopy was used to prove the structures of synthesized Mannich bases **2**–**4**. The disappearance in PMR spectra of H-6 and H-8 resonances and the appearance of resonances for two methylenes in addition to amines provided confirmation that the C-6 and C-8 bis-aminomethyl chrysin derivatives had formed.

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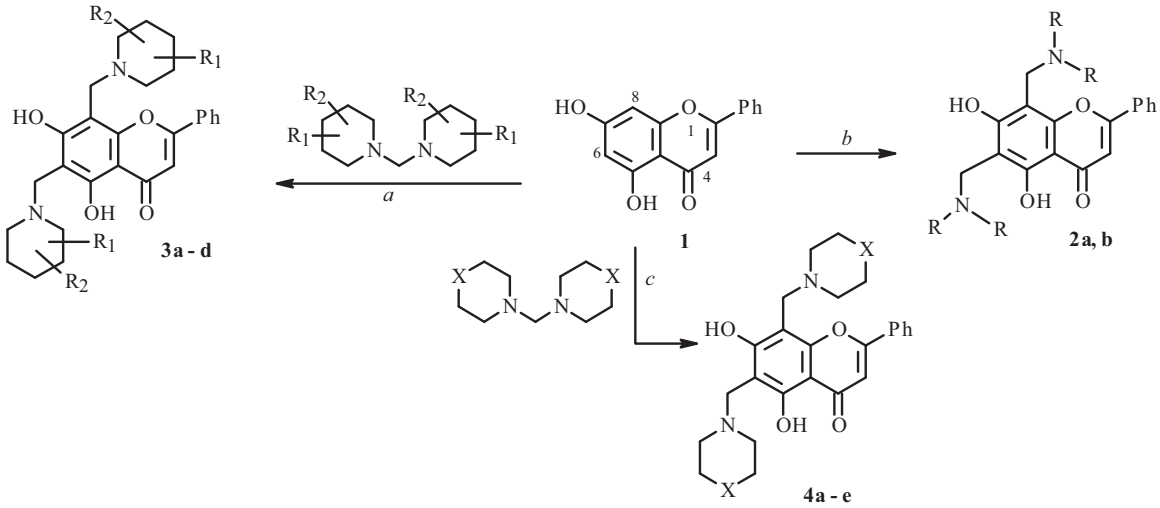

2a: R = Et; **2b:** R = $CH_2CH(CH_3)_2$; **3a:** $R_1 = R_2$ = H; **3b:** R_1 = H, R_2 = Me-3; **3c:** R_1 = H, R_2 = Me-4
3d: $R_1 = R_2$ = Me-3; **4a:** X = bond; **4b:** X = CH_2; **4c:** X = N-Me, **4d:** X = N-CH_2CH_2OH; **4e:** X = O

a. dioxane, 100°C, 3–5 h; *b*. $CH_2(N(R)_2)_2$, dioxane, 100°C, 2–3 h; *c*. dioxane, 100°C, 6–8 h.

The changes in the positions of the peaks for C-6 and C-8 in ^{13}C NMR spectra were consistent with substitution of H-6 and H-8. Thus, resonances for quaternary aromatic C-8 and C-6 at 101.40–103.48 and 103.96–105.24 ppm, respectively, were observed in spectra of synthesized derivatives **2**–**4** instead of peaks for CH atoms at 94 and 98 ppm [24]. Also, resonances for amine residues were observed as peaks with chemical shifts different by 0.02–0.06 ppm in PMR spectra and 0.02–2.20 ppm in ^{13}C NMR spectra. Even smaller differences of 0–0.06 ppm in PMR spectra and 0–2.06 ppm in ^{13}C NMR spectra were observed for the chemical shifts of CH_2-8 and CH_2-6 groups.

Thus, we studied aminomethylation of chrysin through the action of aminals. The reaction did not occur regioselectively although 6,8-bis-aminomethyl derivatives were formed with an excess of the aminomethylating reagent. A series of promising biologically active compounds that were analogs of chromone alkaloids were synthesized.

EXPERIMENTAL

The course of reactions and purity of products were monitored by TLC on Sorbfil UV-254 (Russia) and Merck (Germany) plates using $CHCl_3$:MeOH:Et_3N (190:9:1) and EtOAc as eluents. PMR spectra were measured in $CDCl_3$ relative to TMS (internal standard) on the δ-scale on a VXR-300 instrument (Varian, 300 MHz). ^{13}C NMR spectra were measured in $CDCl_3$ (δ 77.0, internal standard) on a Mercury 400 instrument (Varian, 400 MHz). Melting points were determined on a Buchi B-535 apparatus. Elemental analyses of all compounds corresponded to those calculated.

General Method for Synthesizing 2a–b, 3a–d, and 4a–e. A hot solution of chrysin (2 mmol) in dioxane (10 mL) was treated with the corresponding aminal (4.4 mmol), refluxed for 3-5 h (TLC monitoring), and cooled. The solvent was evaporated in vacuo. The residue was ground with Et_2O, dried, and crystallized from propanol-2:hexane.

5,7-Dihydroxy-6,8-bis[(diethylamino)methyl]-2-phenyl-4*H*-chromen-4-one (2a). Yield 68%, mp 95–96°C. $C_{25}H_{32}N_2O_4$. IR spectrum (KBr, cm^{-1}): 3424, 2963, 2828, 1657, 1628, 1580, 1358. ^1H NMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 1.10, 1.14 (6H, 6H, 2t, ^3J = 7.0, $NCH_2C\underline{H}_3$), 2.66, 2.71 (4H, 4H, 2q, ^3J = 7.0, $NC\underline{H}_2CH_3$), 3.88 (4H, s, CH_2-8 and CH_2-6), 6.63 (1H, s, H-3), 7.49–7.55 (3H, m, H-2′, H-4′, and H-6′), 7.88–7.95 (2H, m, H-3′ and H-5′). ^{13}C NMR spectrum (100 MHz, $CDCl_3$, δ, ppm): 10.73 (CH_3), 11.15 (CH_3), 46.17 (CH_2), 46.25 (CH_2), 47.66 (CH_2), 102.81 (C), 103.51 (C), 104.98 (C), 105.38 (CH),126.17 (CH), 128.88 (CH), 131.38 (CH), 131.80 (C), 155.16 (C), 158.42 (C), 163.06 (C), 166.40 (C), 182.38 (C).

5,7-Dihydroxy-6,8-bis[(di-*iso*-butylamino)methyl]-2-phenyl-4*H*-chromen-4-one (2b). Yield 54%, mp 131–133°C. $C_{33}H_{48}N_2O_4$. IR spectrum (KBr, cm^{-1}): 3449, 2954, 2785, 1688, 1588, 1366. ^1H NMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.78, 0.93 (12H, 12H, 2t, ^3J = 7.0, $CH(C\underline{H}_3)_2$), 1.71–1.85, 1.88–2.01 (2H, 2H, 2m, $C\underline{H}(CH_3)_2$), 2.20, 2.28 (4H, 4H, 2d, ^3J = 7.0, N-$C\underline{H}_2$CH), 3.80, 3.81 (2H, 2H, 2s, CH_2-8 and CH_2-6), 6.63 (1H, s, H-3), 7.47–7.57 (3H, m, H-2′, H-4′, and H-6′),

7.88–7.95 (2H, m, H-3′ and H-5′). ^{13}C NMR spectrum (100 MHz, $CDCl_3$, δ, ppm): 21.05 (CH_3), 21.08 (CH_3), 25.76 (CH_2), 26.47 (CH), 48.06 (CH), 50.12 (CH), 63.06 (CH_2), 63.81 (CH_2), 103.40 (C), 103.75 (C), 105.24 (C), 105.60 (CH), 126.40 (CH), 128.92 (CH), 131.44 (CH), 131.90 (C), 155.33 (C), 158.42 (C), 163.47 (C), 165.25 (C), 182.66 (C).

5,7-Dihydroxy-6,8-bis(piperidin-1-ylmethyl)-2-phenyl-4*H*-chromen-4-one (3a). Yield 82%, mp 171–172°C. $C_{27}H_{32}N_2O_4$. IR spectrum (KBr, cm^{-1}): 3449, 2938, 2851, 1647, 1587, 1361. ^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ, ppm): 1.34–1.77 (12H, m, $NCH_2C\underline{H}_2C\underline{H}_2$), 2.40–2.70 (8H, m, $NC\underline{H}_2CH_2$), 3.81 (4H, s, CH_2-8 and CH_2-6), 6.65 (1H, s, H-3), 7.49–7.59 (3H, m, H-2′, H-4′, and H-6′), 7.89–7.99 (2H, m, H-3′ and H-5′). ^{13}C NMR spectrum (100 MHz, $CDCl_3$, δ, ppm): 23.80 (CH_2), 24.15 (CH_2), 25.50 (CH_2), 25.86 (CH_2), 51.24 (CH_2), 52.85 (CH_2), 53.67 (CH_2), 54.24 (CH_2), 102.05 (C), 103.61 (C), 104.26 (C), 105.32 (CH), 126.21 (CH), 129.03 (CH), 131.52 (CH), 131.79 (C), 155.29 (C), 158.54 (C), 163.09 (C), 165.96 (C), 182.57 (C).

5,7-Dihydroxy-6,8-bis[(3-methylpiperidin-1-yl)methyl]-2-phenyl-4*H*-chromen-4-one (3b). Yield 68%, mp 152–154°C. $C_{29}H_{36}N_2O_4$. IR spectrum (KBr, cm^{-1}): 3450, 2925, 2787, 1655, 1583, 1360. ^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ, ppm): 0.75–1.06 (8H, m, $C\underline{H}C\underline{H}_3$-3″), 1.52–1.88, 1.94–2.20 (10H, 2H, 2m, $NCH_2C\underline{H}_2$ and $NC\underline{H}_{2(\alpha)}CH_2$), 2.88–3.04 (4H, m, $NC\underline{H}_{2(\beta)}CH_2$), 3.81 (4H, s, CH_2-8 and CH_2-6), 6.65 (1H, s, H-3), 7.51–7.56 (3H, m, H-2′, H-4′, and H-6′), 7.90–7.95 (2H, m, H-3′, and H-5′). ^{13}C NMR spectrum (100 MHz, $CDCl_3$, δ, ppm): 19.50 (CH_3),19.74 (CH_3), 25.10 (CH_2), 25.47 (CH_2), 30.96 (CH), 31.09 (CH_2), 32.42 (CH), 32.79 (CH_2), 50.95 (CH_2), 52.58 (CH_2), 53.16 (CH_2), 53.18 (CH_2), 53.60 (CH_2), 53.65 (CH_2), 60.69 (CH_2), 61.65 (CH_2), 102.07 (C), 103.66 (C), 104.30 (C), 105.31 (CH), 126.19 (CH), 128.98 (CH), 131.49 (CH), 131.78 (C), 155.24 (C), 158.48 (C), 163.08 (C), 165.80 (C), 182.56 (C).

5,7-Dihydroxy-6,8-bis[(4-methylpiperidin-1-yl)methyl]-2-phenyl-4*H*-chromen-4-one (3c). Yield 68%, mp 174–176°C. $C_{29}H_{36}N_2O_4$. IR spectrum (KBr, cm^{-1}): 3449, 2920, 2795, 1650, 1586, 1361. ^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.90, 0.94 (3H, 3H, 2d, ^{3}J = 7.0, $CHC\underline{H}_3$-4″), 1.16–1.75 (10H, m, $NCH_2C\underline{H}_2$ and $C\underline{H}CH_3$-4″), 2.04–2.27 (4H, m, $NC\underline{H}_{2(\alpha)}CH_2$), 2.94–3.07 (4H, m, $NC\underline{H}_{2(\beta)}CH_2$), 3.81 (4H, s, CH_2-8 and CH_2-6), 6.64 (1H, s, H-3), 7.50–7.56 (3H, m, H-2′, H-4′, and H-6′), 7.89–7.96 (2H, m, H-3′, and H-5′). ^{13}C NMR spectrum (100 MHz, $CDCl_3$, δ, ppm): 21.58 (CH_3), 21.77 (CH_3), 30.36 (CH), 30.61 (CH), 33.77 (CH_2), 34.18 (CH_2), 50.90 (CH_2), 52.49 (CH_2), 53.14 (CH_2), 53.74 (CH_2), 102.17 (C), 103.60 (C), 104.35 (C), 105.29 (CH), 126.19 (CH), 129.01 (CH), 131.50 (CH), 131.77 (C), 155.23 (C), 158.47 (C), 163.06 (C), 165.86 (C), 182.55 (C).

6,8-Bis[(3,3-dimethylpiperidin-1-yl)methyl]- 5,7-dihydroxy-2-phenyl-4*H*-chromen-4-one (3d). Yield 68%, mp 155–156°C. $C_{31}H_{40}N_2O_4$. IR spectrum (KBr, cm^{-1}): 3440, 2947, 2862, 1648, 1585, 1361. ^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ, ppm): 0.90, 0.97 (6H, 6H, 2s, $C(CH_3)_2$-3″), 1.15–1.36, 1.50–1.74 (4H, 4H, 2s, $NCH_2C\underline{H}_2C\underline{H}_2$), 2,13–2.66 (8H, m, $NC\underline{H}_2CH_2$ and $NC\underline{H}_2C$), 3.72, 3.78 (2H, 2H, 2s, CH_2-8 and CH_2-6), 6.66 (1H, s, H-3), 7.49–7.56 (3H, m, H-2′, H-4′, and H-6′), 7.93–8.00 (2H, m, H-3′ and H-5′). ^{13}C NMR spectrum (100 MHz, $CDCl_3$, δ, ppm): 22.06 (CH_3), 22.58 (CH_3), 30.87 (C), 30.90 (C), 36.85 (CH_2), 37.46 (CH_2), 50.50 (CH_2), 53.14 (CH_2), 53.64 (CH_2), 53.89 (CH_2), 65.02 (CH_2), 66.01 (CH_2), 102.91 (C), 103.81 (C), 103.96 (C), 105.11 (CH), 126.29 (CH), 128.95 (CH), 131.51 (CH), 131.77 (C), 155.55 (C), 158.13 (C), 163.20 (C), 165.35 (C), 182.70 (C).

5,7-Dihydroxy-6,8-bis(pyrrolidin-1-ylmethyl)-2-phenyl-4*H*-chromen-4-one (4a). Yield 52%, mp 172–173°C. $C_{25}H_{28}N_2O_4$. IR spectrum (KBr, cm^{-1}): 3449, 2936, 2795, 1651, 1589, 1355. ^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ, ppm): 1.75–1.84, 1.83–1.91 (4H, 4H, 2m, $NCH_2C\underline{H}_2$), 2.61–2.70, 2.70–2.80 (4H, 4H, 2m, NCH_2CH_2), 3.96, 3.99 (2H, 2H, 2s, CH_2-8 and CH_2-6), 6.65 (1H, s, H-3), 7.50–7.57 (3H, m, H-2′, H-4′, and H-6′), 7.88–7.95 (2H, m, H-3′ and H-5′). ^{13}C NMR spectrum (100 MHz, $CDCl_3$, δ, ppm): 23.47 (CH_2), 23.58 (CH_2), 47.48 (CH_2), 49.69 (CH_2), 53.42 (CH_2), 53.79 (CH_2), 102.55 (C), 103.38 (C), 105.19 (C), 105.22 (CH), 126.06 (CH), 128.97 (CH), 131.45 (CH), 131.65 (C), 154.78 (C), 158.02 (C), 162.90 (C), 165.94 (C), 182.49 (C).

6,8-Bis(azepan-1-ylmethyl)- 5,7-dihydroxy-2-phenyl-4*H*-chromen-4-one (4b). Yield 64%, mp 134–136°C. $C_{29}H_{36}N_2O_4$. IR spectrum (KBr, cm^{-1}): 3446, 2926, 2851, 1651, 1585, 1361. ^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ, ppm): 1.51–1.80 (16H, m, $NCH_2C\underline{H}_2C\underline{H}_2C\underline{H}_2C\underline{H}_2$), 2.69–2.88 (8H, m, $NC\underline{H}_2CH_2$), 3.90, 3.93 (2H, 2H, 2s, CH_2-8 and CH_2-6), 6.64 (1H, s, H-3), 7.49–7.56 (3H, m, H-2′, H-4′, and H-6′), 7.92–7.98 (2H, m, H-3′ and H-5′). ^{13}C NMR spectrum (100 MHz, $CDCl_3$, δ, ppm): 26.75 (CH_2), 26.79 (CH_2), 27.05 (CH_2), 27.47 (CH_2), 50.06 (CH_2), 52.40 (CH_2), 54.81 (CH_2), 55.26 (CH_2), 103.48 (C), 104.60 (C), 105.21 (C), 105.24 (CH), 126.22 (CH), 128.97 (CH), 131.46 (CH), 131.84 (C), 155.50 (C), 158.35 (C), 163.03 (C), 166.78 (C), 182.51 (C).

5,7-Dihydroxy-6,8-bis[(4-methylpiperazin-1-yl)methyl]-2-phenyl-4*H*-chromen-4-one (4c). Yield 73%, mp 193–194°C. $C_{27}H_{34}N_4O_4$. IR spectrum (KBr, cm^{-1}): 3449, 2950, 2774, 1639, 1583, 1360. ^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ, ppm): 2.28, 2.31 (3H, 3H, 2s, $N'CH_3$), 2.35–2.81 (16H, m, $NC\underline{H}_2C\underline{H}_2N'$), 3.86 (4H, s, CH_2-8 and CH_2-6), 6.66 (1H, s,

H-3), 7.49–7.58 (3H, m, H-2′, H-4′, and H-6′), 7.89–7.95 (2H, m, H-3′ and H-5′). ^{13}C NMR spectrum (100 MHz, $CDCl_3$, δ, ppm): 45.83 (CH_3), 45.89 (CH_3), 50.39 (CH_2), 52.01 (CH_2), 52.35 (CH_2), 52.88 (CH_2), 54.65 (CH_2), 54.92 (CH_2), 101.78 (C), 103.79 (C), 104.08 (C), 105.38 (CH), 126.17 (CH), 129.11 (CH), 131.58 (C), 131.64 (CH), 155.25 (C), 158.78 (C), 163.24 (C), 165.00 (C), 182.59 (C).

5,7-Dihydroxy-6,8-bis{[4-(2-hydroxyethyl)piperazin-1-yl]methyl}-2-phenyl-4*H*-chromen-4-one (4d). Yield 68%, mp 170–171°C. $C_{29}H_{38}N_4O_6$. IR spectrum (KBr, cm^{-1}): 3423, 2941, 2813, 1654, 1579, 1359. ^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ, ppm): 2.39–2.85 (20H, m, NC$\underline{H}_2$C$\underline{H}_2$N′ and N′C$\underline{H}_2$CH_2OH), 3.54–3.67 (4H, m, N′CH_2C$\underline{H}_2$OH), 3.85, 3.87 (4H, 2s, CH_2-8 and CH_2-6), 6.67 (1H, s, H-3), 7.51–7.59 (3H, m, H-2′, H-4′, and H-6′), 7.87–7.95 (2H, m, H-3′ and H-5′). ^{13}C NMR spectrum (100 MHz, $CDCl_3$, δ, ppm): 50.54 (CH_2), 51.81 (CH_2), 52.45 (CH_2), 52.67 (CH_2), 52.85 (CH_2), 57.66 (CH_2), 57.71 (CH_2), 59.05 (CH_2), 101.40 (C), 103.91 (C), 104.22 (C), 105.45 (CH), 126.16 (CH), 129.13 (CH), 131.57 (CH), 131.71 (C), 155.19 (C), 158.93 (C), 163.26 (C), 164.86 (C), 182.60 (C).

5,7-Dihydroxy-6,8-bis(morpholin-4-ylmethyl)-2-phenyl-4*H*-chromen-4-one (4e). Yield 79%, mp 176–178°C. $C_{25}H_{28}N_2O_6$. IR spectrum (KBr, cm^{-1}): 3469, 2937, 2840, 1647, 1587, 1348. ^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ, ppm): 2.56–2.68 (8H, m, NC$\underline{H}_2$CH_2O), 3.68–3.81 (8H, m, NCH_2C$\underline{H}_2$O), 3.85, 3.86 (2H, 2H, 2s, CH_2-8 and CH_2-6), 6.68 (1H, s, H-3), 7.50–7.60 (3H, m, H-2′, H-4′, and H-6′), 7.88–7.96 (2H, m, H-3′ and H-5′). ^{13}C NMR spectrum (100 MHz, $CDCl_3$, δ, ppm): 50.99 (CH_2), 52.37 (CH_2), 52.85 (CH_2), 53.37 (CH_2), 66.63 (CH_2), 66.87 (CH_2), 101.25 (C), 103.91 (C), 104.00 (C), 105.49 (CH), 126.15 (CH), 129.14 (CH), 131.53 (C), 131.76 (CH), 155.30 (C), 159.08 (C), 163.33 (C), 164.55 (C), 182.60 (C).

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