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Efficient one-pot synthesis of 2-(2-hydroxyaryl)-2,4,4-trimethylchromanes from 1-(2-hydroxyaryl)ethanones

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Contents

Experimental

General

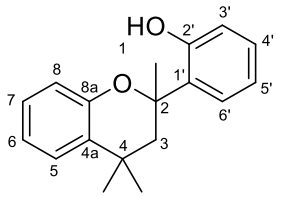
Commercially available reagents were used. Commercially available solvents were purified by standard procedures. All reactions were run under an argon atmosphere unless performed in aqueous solutions. NMR experiments were carried out on 400 MHz [400.1 MHz (^{1}H), 100.6 MHz (^{13}C)], 600 MHz [600.1 MHz (^{1}H), 150.9 MHz (^{13}C)] spectrometers. Chemical shifts are reported on the δ (ppm) scale relative to the residual ^{1}H and ^{13}C signal of $CDCl_3$ or DMSO-d_6. Coupling constants (*J*) are reported in Hertz and refer to apparent peak multiplications. The abbreviations s, d, t, q, and m stand for singlet, doublet, triplet, quartet, and multiplet in that order. The ESI MS measurements were performed using an Amazon X ion trap mass spectrometer (Bruker Daltonic GmbH, Germany) in the positive or negative mode in the mass range of 70–3000. IR spectra were recorded in KBr pellets. Compounds **2a,b** commercially available, compound **2c** were prepared as described early.[S1]

Representative procedure for the synthesis of chromanes **4a-c**

Magnesium turnings (0.32 g, 13.2 mmol) were added to a flame-dried two-necked flask equipped with a condenser, a rubber septum and a $CaCl_2$ drying tube on the top of the condenser and then activated with the small crystal of iodine under a stream of argon. Diethyl ether (5 ml) was added, and then MeI (0.82 ml, 1.87 g, 13.2 mmol) was added dropwise with a syringe at a rate to ensure gentle reflux. When the addition was complete and all magnesium turnings disappeared, a solution of the corresponding 2-hydroxyarylethanone **2** (4.4 mmol for **2a**,**b** and 3.2 mmol for **2c**) in Et_2O was added dropwise by syringe, and this was stirred at reflux for another 2 h. The mixture was allowed to cool to room temperature. It was hydrolyzed with water (2 ml) and then with 20% sulfuric acid (3 ml). The water layer was separated. The ether extract was dried over Na_2SO_4 and ether was removed on a rotary

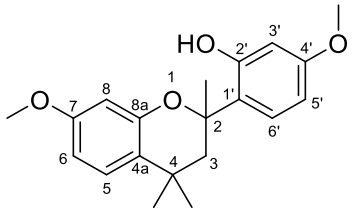
evaporator. Compound **4a**,**b** was isolated pure without additional purification. Compound **4c** was purified by flash chromatography (Silica gel Srlchem, 230-400 mesh, for flash chromatography; eluent EtOAc : hexane = 1 : 2).

2-(2-Hydroxyphenyl)-2,4,4-trimethylchromane (4a)



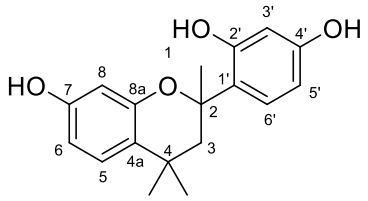
Yield 0.58 g (98%). Brown powder, mp 91–93 °C. IR: 3380, 3074, 3036, 3003, 2972, 2982, 2959, 2921, 2862, 2730, 2688, 2545, 2450, 2346, 2293, 2080, 1951, 1911, 1900,1869, 1830, 1813, 1785, 1735, 1699, 1686, 1655,1638, 1607, 1583, 1529, 1504, 1489, 1445, 1387, 1375, 1364, 1347, 1310, 1295, 1251, 1223, 1203, 1171, 1139, 1130, 1102, 1091, 1078, 1061, 1049, 979, 957, 926, 886, 871, 854, 830, 806, 762, 754, 712, 643, 602, 561, 541, 505, 481, 454, 412 cm^{-1}. ^1H NMR ($CDCl_3$), δ: 1.25 (s, 3H, *4^a-Me*), 1.52 (s, 3H, *4^e-Me*), 1.82 (s, 3H, *2-Me*), 2.19 (d, 1H, $^2J_{HH}$ 14.4 Hz, H^{3a}), 2.73 (d, 1H, $^2J_{HH}$ 14.4 Hz, H^{3e}), 6.95 – 6.90 (m, 2H, H$^{3'}$, H$^{5'}$), 7.04 (dd, 1H, $^3J_{HH}$ 8.1 Hz, $^4J_{HH}$ 1.4 Hz, H^8), 7.07 (td, 1H, $^3J_{HH}$ 7.4 Hz, $^4J_{HH}$ 1.4 Hz, H^6), 7.22 (m, 2H, $^4J_{HH}$ 1.7 Hz, H$^{4',6'}$), 7.27 (dd, 1H, $^3J_{HH}$ 7.8 Hz, $^4J_{HH}$ 1.5 Hz, H^5), 7.37 (dd, 1H, $^3J_{HH}$ 7.8 Hz, $^4J_{HH}$ 1.6 Hz, H^7), 8.17(br s, 1H, OH).^{13}C NMR ($CDCl_3$), δ: 28.25 (*2-Me*), 31.08 (C^4), 32.29 (*4-Me*), 32.80 (*4'-Me*), 47.48 (C^3), 81.46 (C^2), 117.77, 117.80 (C^8, C$^{3'}$), 119.90, 122.22 (C$^{5'}$, C^6), 126.69, 126.95(C^5, C^7), 127.46 (C^4), 128.91(C$^{6'}$), 129.95(C$^{1'}$), 132.02 (C^{4a}), 150.49 (C$^{2'}$), 154.42 (C^{8a}). ESI-MS, m/z: 267 [*M*-H]$^-$. Calcd for $C_{18}H_{20}O_2$. 268.36.

5-Methoxy-2-(7-methoxy-2,4,4-trimethylchroman-2-yl)phenol (**4b**)



Yield 0.70 g (97%). Red oil. IR: 3389, 2958, 2931, 2867, 2837, 1619, 1584, 1506, 1464, 1442, 1422, 1372, 1343, 1323, 1285, 1260, 1200, 1161, 1110, 1089, 1065, 1034, 987, 963, 836, 802, 733, 652, 634 cm^{-1}. ^1H NMR ($CDCl_3$), δ: 1.18 (s, 3H, *4^a-Me*), 1.41 (s, 3H, *4^e-Me*), 1.69 (s, 3H, *2-Me*), 2.03 (d, 1H, $^2J_{HH}$ 14.5 Hz, H^{3a}), 2.52 (d, 1H, $^2J_{HH}$ 14.5 Hz, H^{3e}), 3.76 (s, 3H, MeO), 3.78 (s, 3H, MeO), 6.39 - 6.43 (m, 2H, H$^{3'}$, H$^{5'}$), 6.47 (d, 1H, $^4J_{HH}$ 2.6 Hz, H^8), 6.59 (dd, 1H, $^3J_{HH}$ 8.6 Hz, $^4J_{HH}$ 2.6 Hz, H^6), 7.05 (d, 1H, $^3J_{HH}$ 9.3 Hz, H$^{6'}$), 7.18 (d, 1H, $^3J_{HH}$ 8.6 Hz, H^5), 8.16 (s, 1H, OH).^{13}C NMR ($CDCl_3$), δ: 28.22 (*4-Me*), 30.57 (C^4), 32.37 (*2-Me*), 32.89 (*4-Me*), 47.57 (C^3), 55.24 (MeO), 55.36 (MeO), 81.49 (C^2), 102.41 (C$^{3'}$), 102.84 (C^8), 105.93 (C^6), 109.06 (C$^{5'}$), 122.49 (C^{4a}), 124.11 (C$^{1'}$), 127.38 (C^5), 127.63 (C$^{6'}$), 151.32 (C$^{2'}$), 155.47 (C^{8a}), 158.90 (C$^{4'}$), 160.14 (C^7). ESI-MS, m/z 327 [*M*-H]$^-$. Calcd for $C_{20}H_{24}O_4$. 328.41.

4-(7-Hydroxy-2,4,4-trimethylchroman-2-yl)benzene-1,3-diol (**4c)**



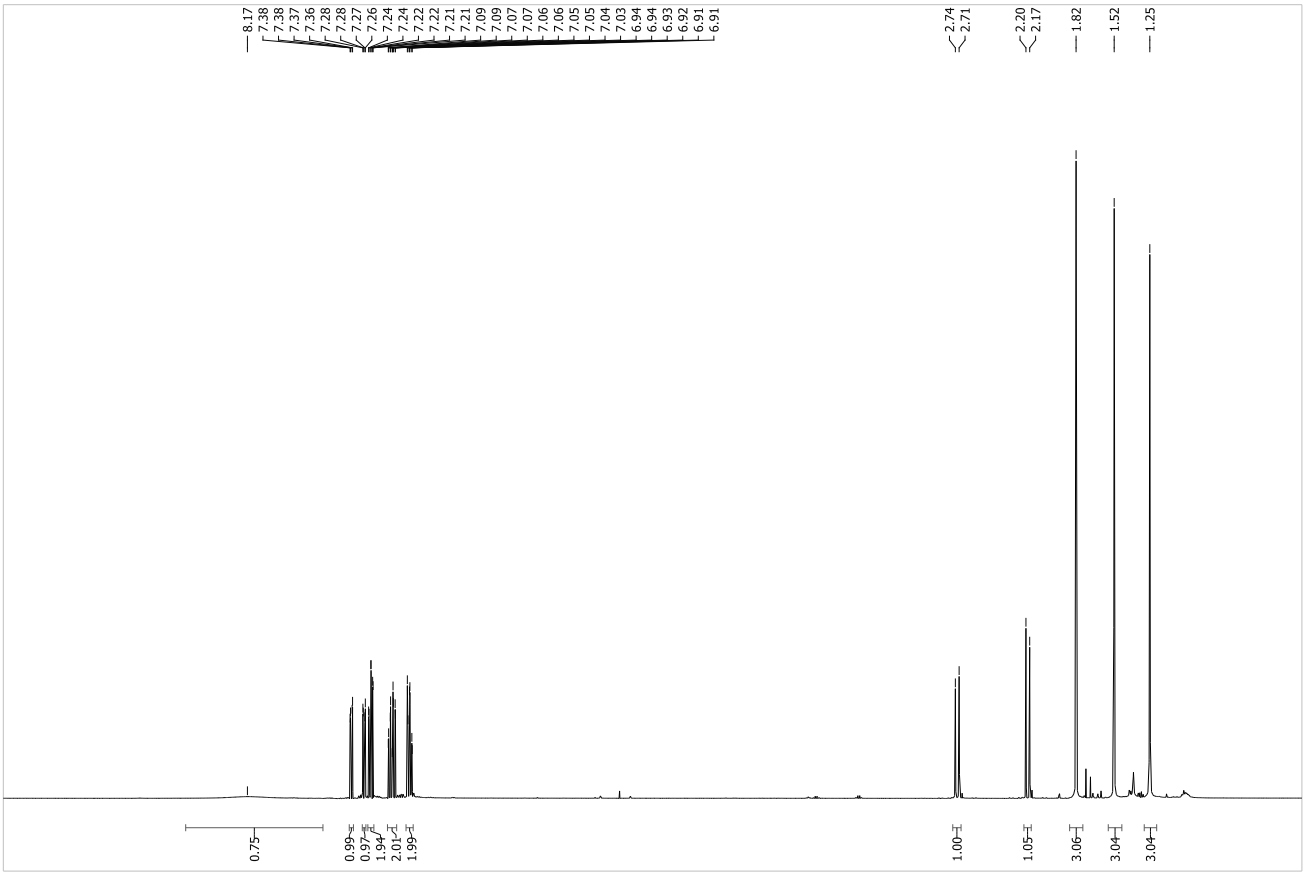
Yield 0.4 g (83%). Light-yelloy powder, mp 224–226 °C (lit. 223-224°C).[S2] IR: 3518, 3336, 3190, 3036, 2979, 2956, 2936, 2913, 2707, 2610, 2361, 2260, 2249, 2129, 1924, 1878, 1861, 1774, 1706, 1619, 1602, 1552, 1522, 1506, 1453, 1386, 1373, 1361, 1341, 1312, 1293, 1253, 1221, 1163,1137, 1102, 1088, 1074, 1060, 1044, 1024, 1013, 996, 980, 941, 855, 844, 837, 806, 765, 733, 710, 680, 659, 639, 621, 604 cm^{-1}. ^1H NMR ($CDCl_3$), δ: 0.84 (s, 3H, *4^a-Me*), 1.18 (s, 3H, *4^e-Me*), 1.56 (s, 3H, *2-Me*), 1.83 (d, 1H, $^2J_{HH}$ 14.2 Hz, H^{3a}), 2.65 (d, 1H, $^2J_{HH}$ 14.2 Hz, H^{3e}), 5.01 (br s, 3H, OH), 6.14 (dd, 1H, $^3J_{HH}$ 8.5 Hz, $^4J_{HH}$ 2.5 Hz, H$^{5'}$), 6.25 (d, 1H, $^4J_{HH}$ 2.5 Hz, H$^{3'}$), 6.34 (dd, 1H, $^3J_{HH}$ 9.3 Hz, $^4J_{HH}$ 2.5 Hz, H^6), 6.35 (brs, 1H, H^8), 6.89 (d, 1H, $^3J_{HH}$ 8.5 Hz, H$^{6'}$), 6.91 (m, 1H, $^3J_{HH}$ 8.4 Hz, H^5). ^{13}C NMR ($CDCl_3$/DMSO-d_6), δ: 28.72 (*2-Me*), 30.23 (*4-Me*), 31.61 (C^4), 32.55 (*4-Me*), 45.56 (C^3), 79.75 (C^2), 103.82 and 103.96 (C$^{3'}$ and C^8), 106.66 and 109.24 (C$^{5'}$ and C^6), 122.02 and 122.87 (C$^{1'}$ and C^{4a}), 127.25 and 128.23 (C^5 and C$^{6'}$), 152.11 (C$^{2'}$), 155.08 (C^{8a}), 156.0 (C$^{4'}$), 157.03 (C^7). ESI-MS, m/z: 299 [*M*-H]$^-$. Calcd for $C_{18}H_{20}O_4$. 300.35.

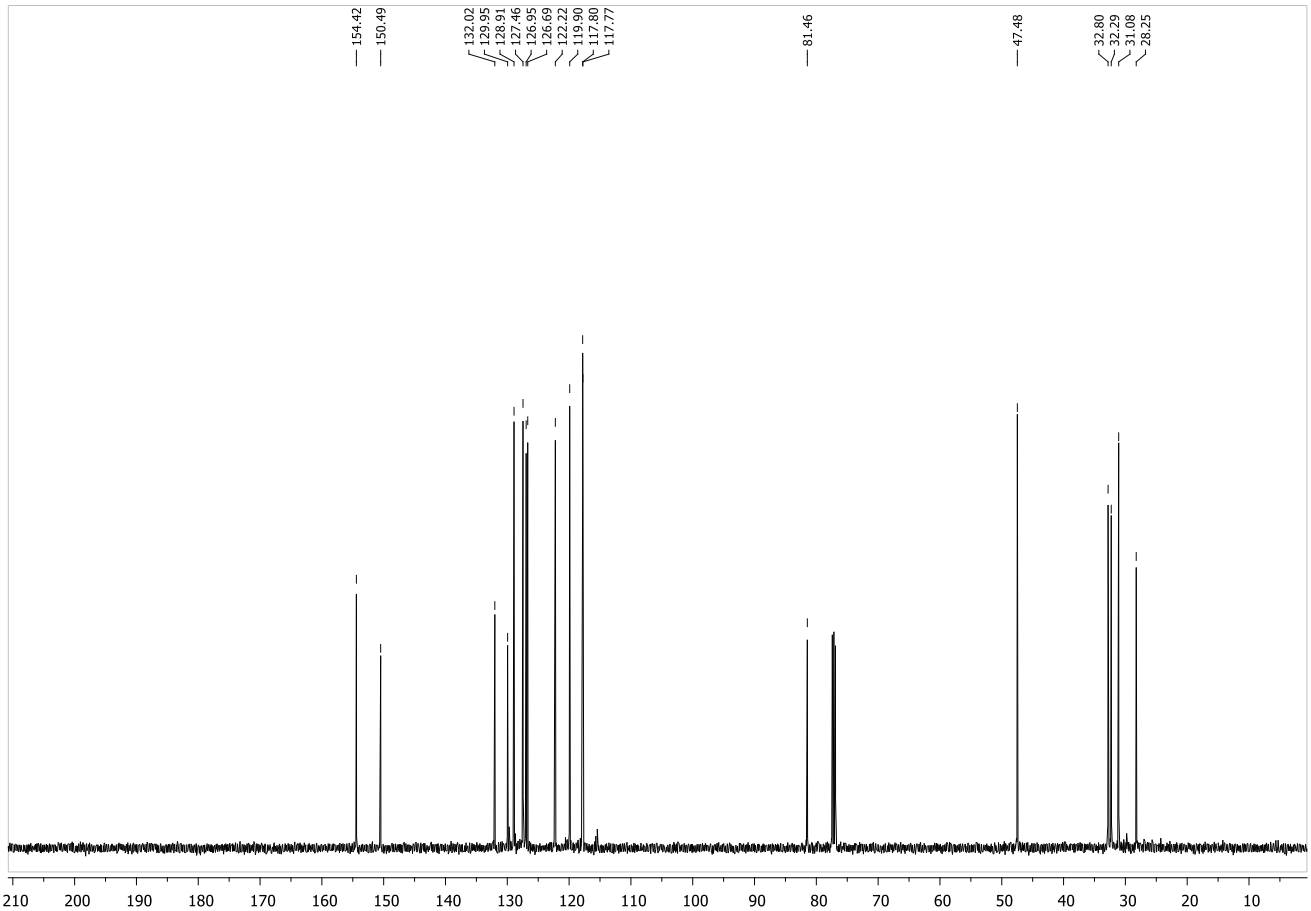
References

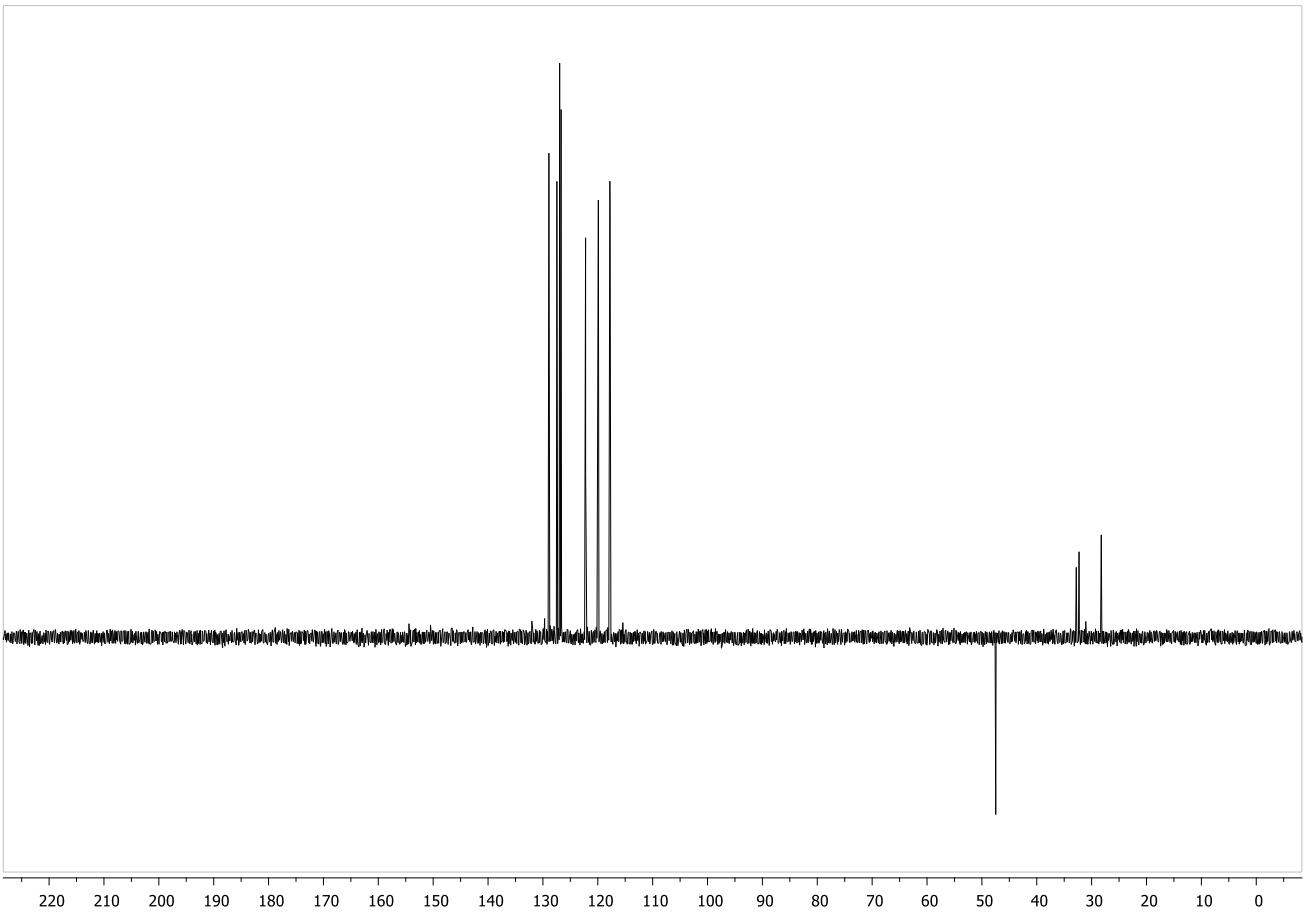
S1. C. Proença, H. M. T. Albuquerque, D. Ribeiro, M. Freitas, C. M. M. Santos, A. M. S. Silva and E. Fernandes, *Eur. J. Med. Chem.*, 2016, **115**, 381.
S2. S. I. Filimonov, N. G. Savinsky and E. M. Evstigneeva, *Mendeleev Commun.*, 2003, **13**, 194.

Copies of ^{1}H and ^{13}C NMR spectra

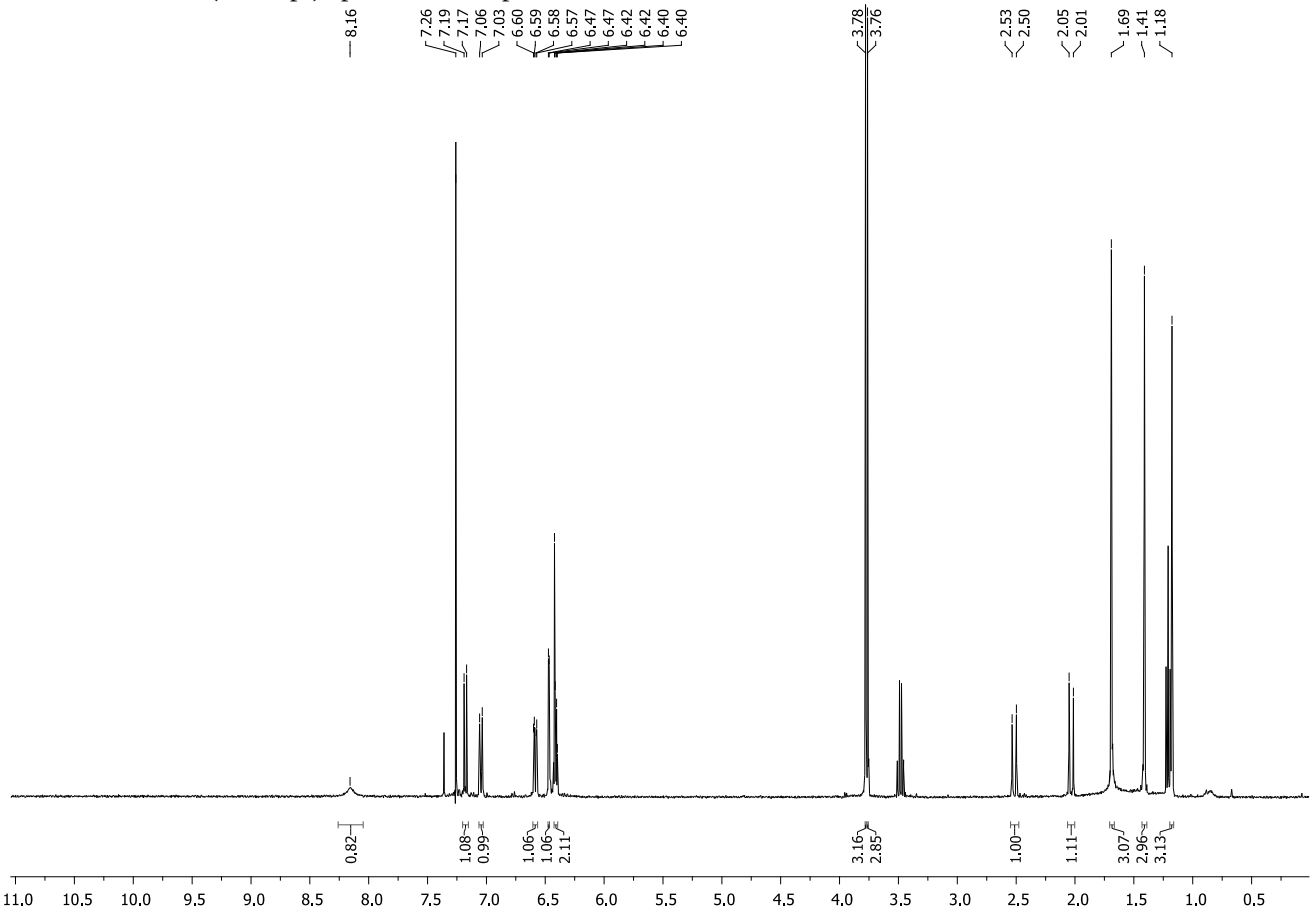
^{1}H and ^{13}C NMR (bb, dept) spectra of compound of **4a**

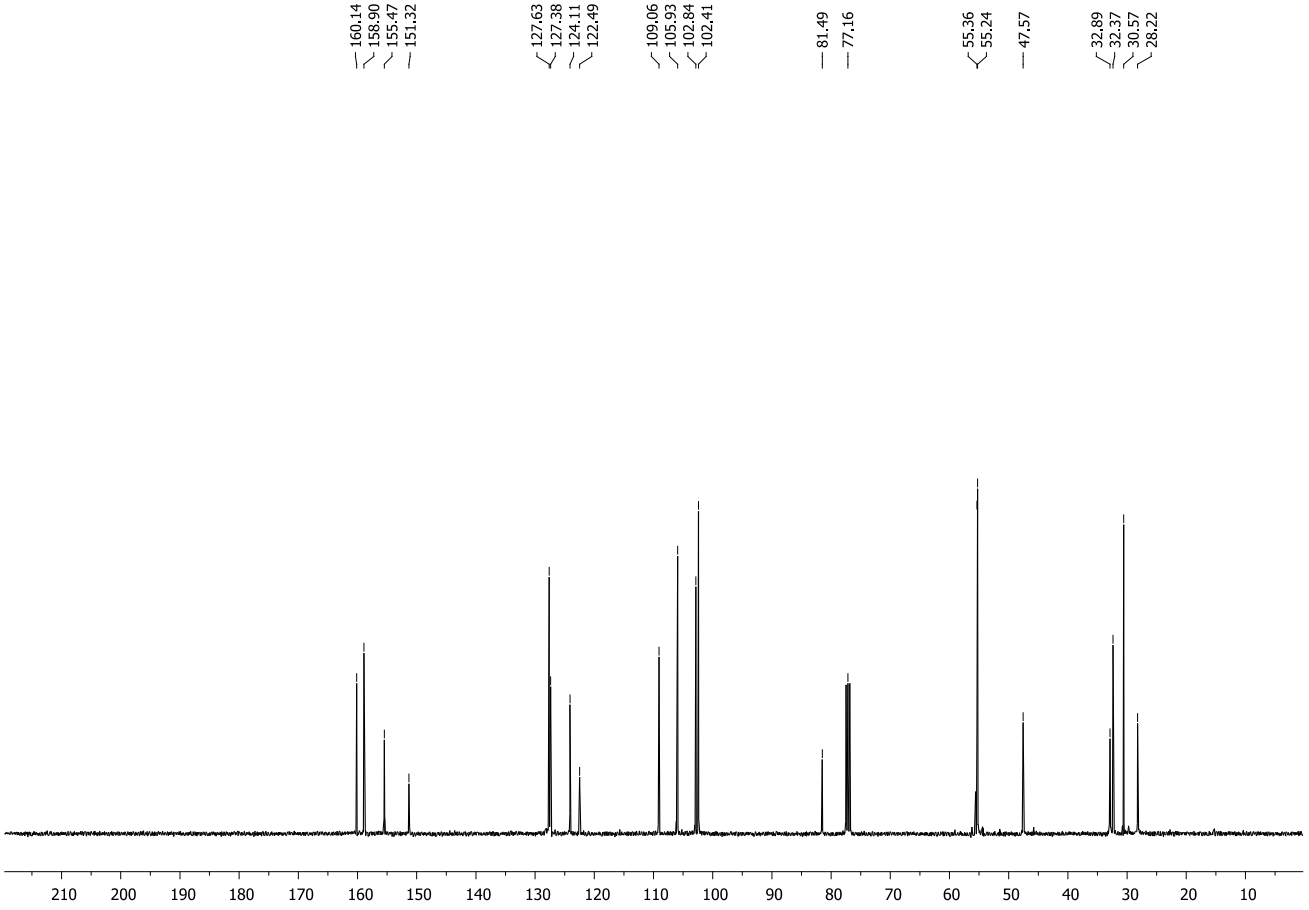






^{1}H and ^{13}C NMR (bb, dept) spectra of compound of **4b**

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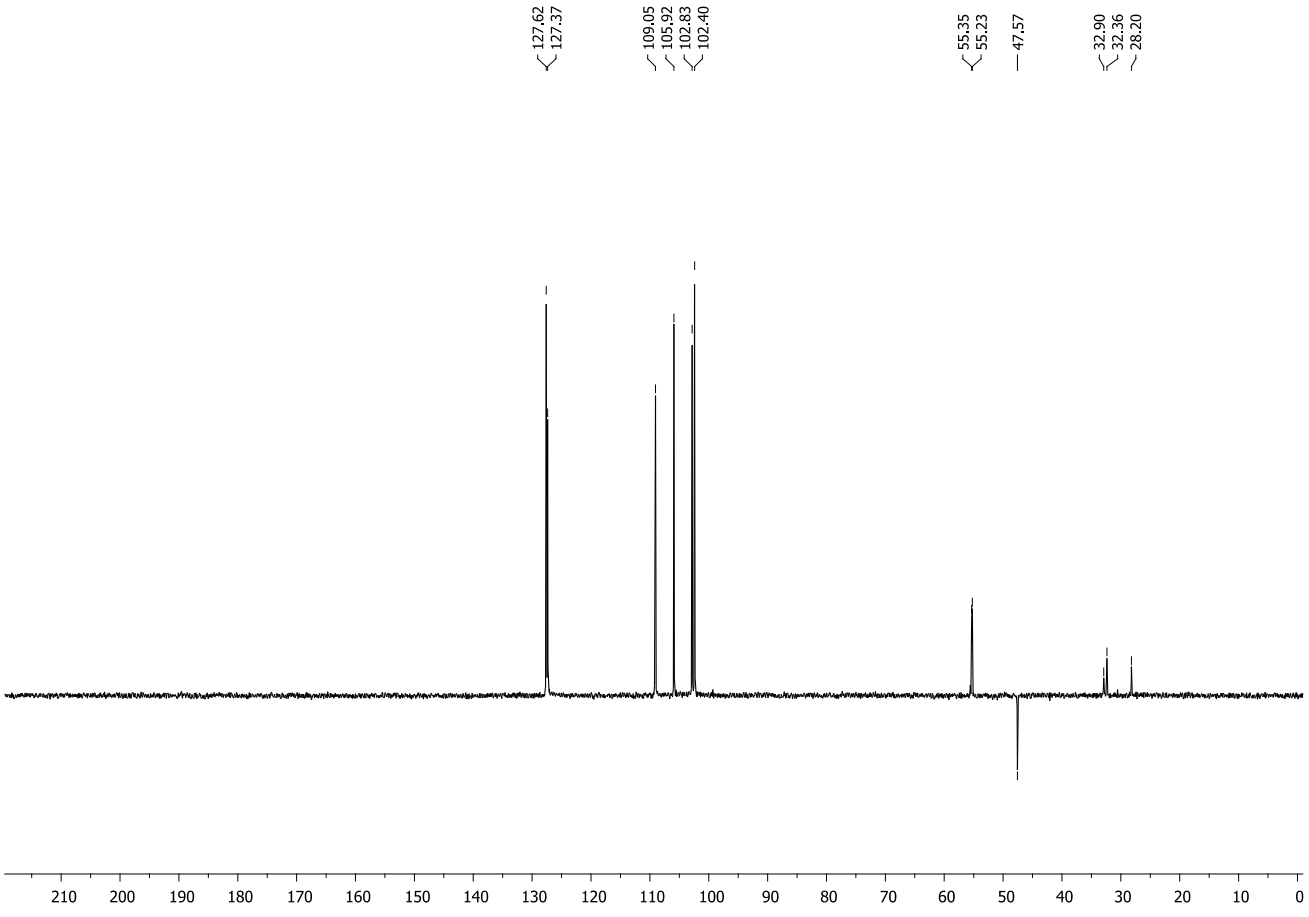
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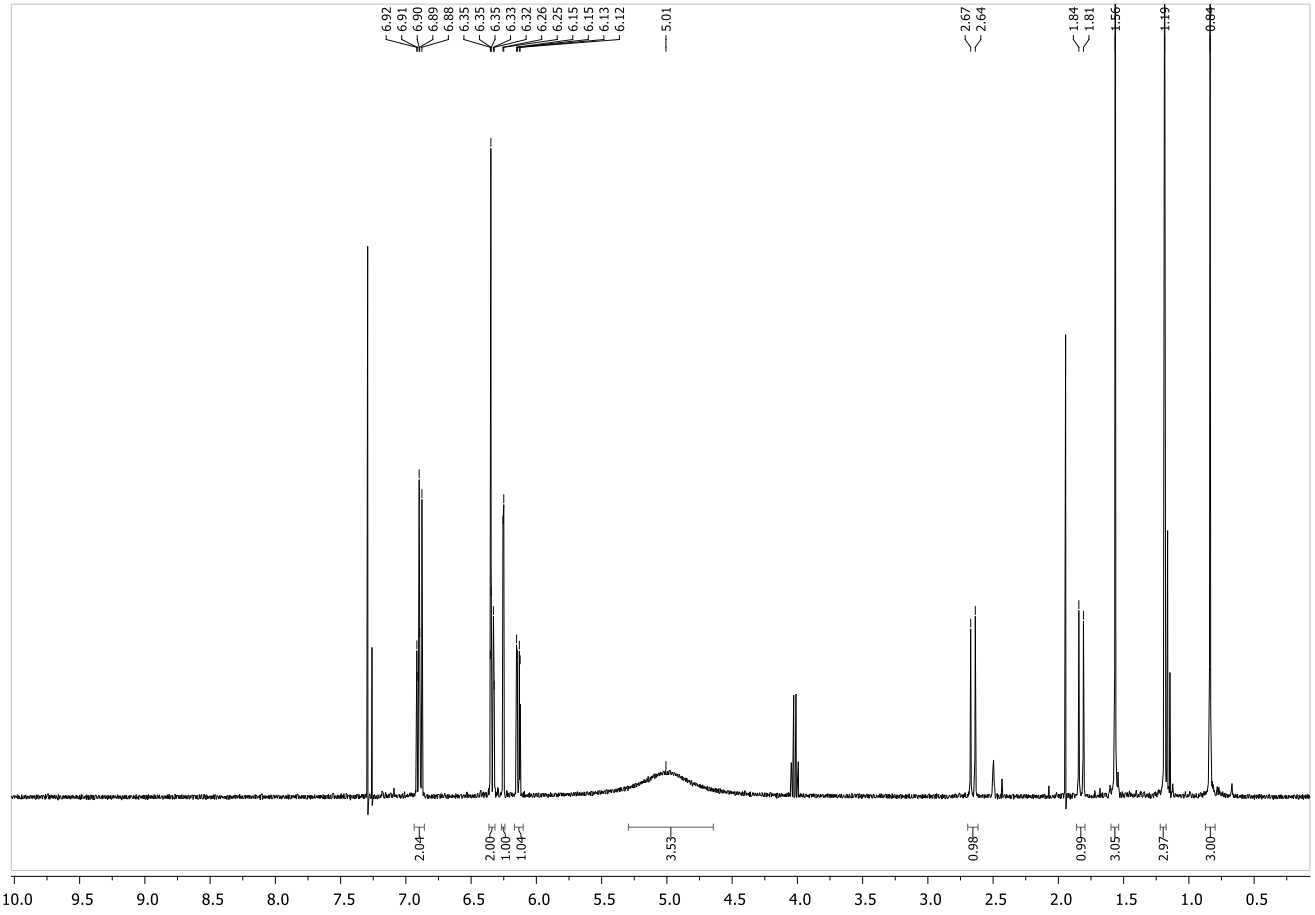
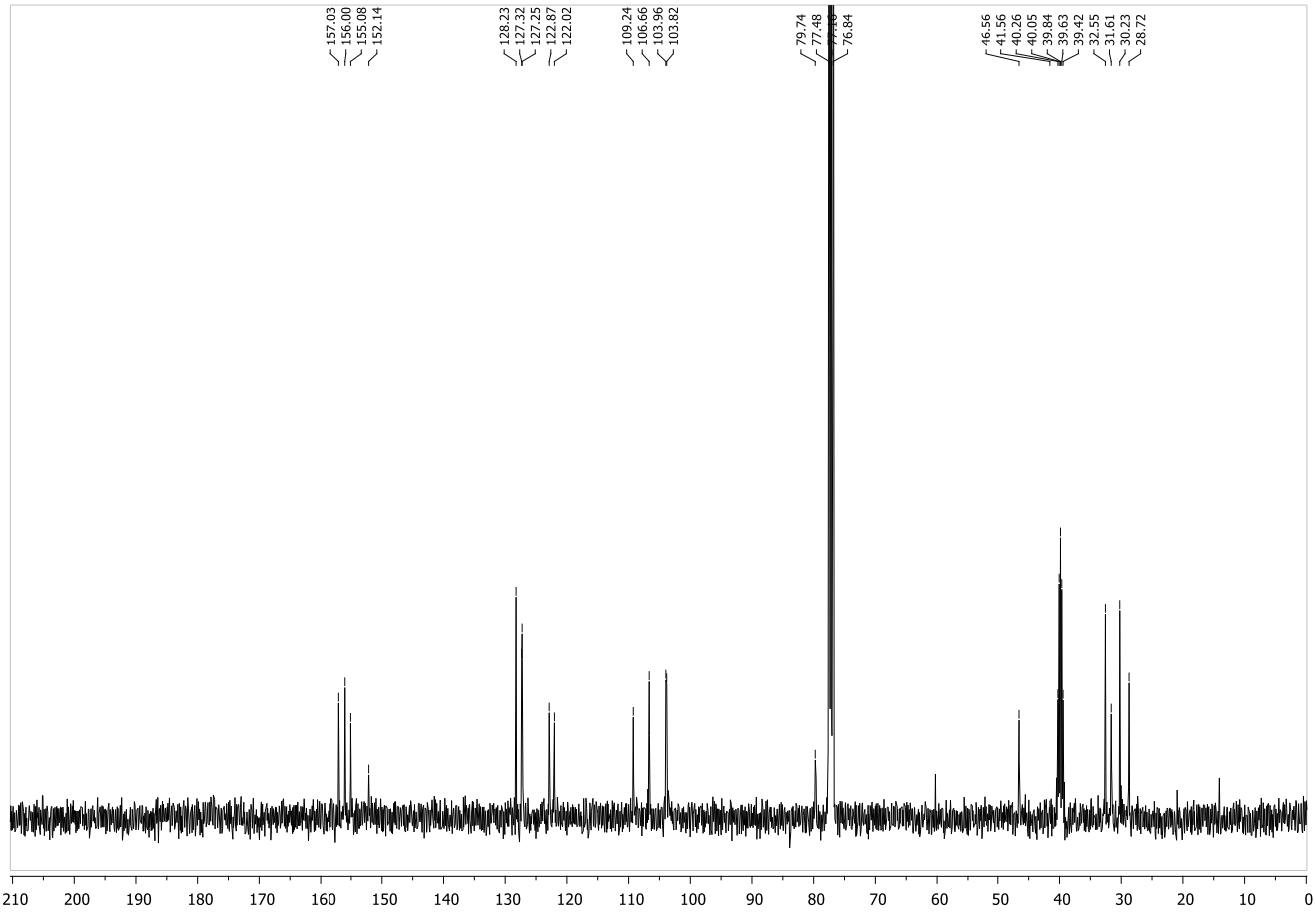
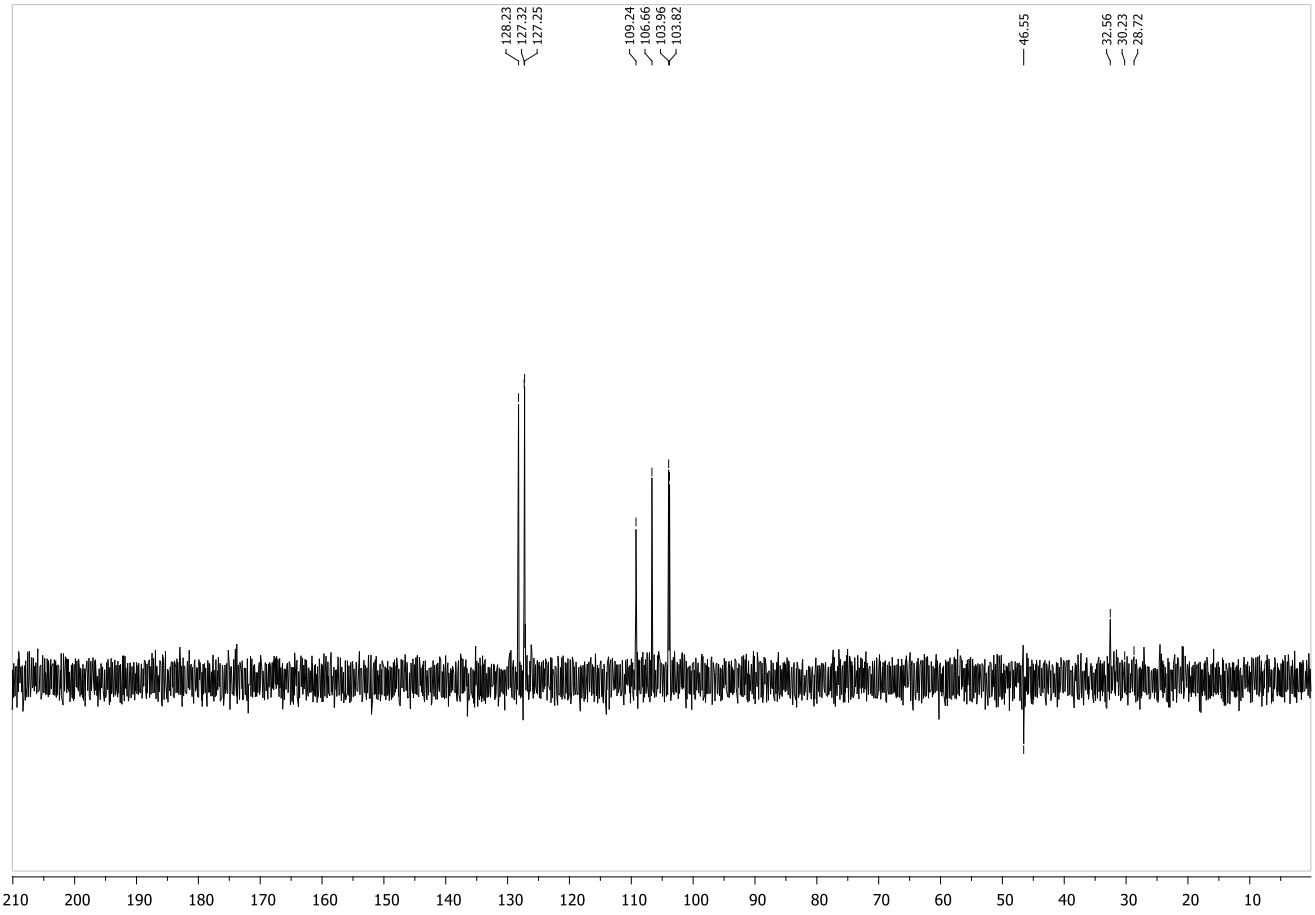
^{1}H and ^{13}C NMR (bb, dept) spectra of compound of **4c**



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