Supplementary Materials

Piplartine Synthetic Analogs: In Silico Analysis and Antiparasitic Study against *Trypanosoma cruzi*

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Abstract: Neglected tropical diseases (NTDs) cause thousands of deaths each year. Among these diseases, we find Chagas disease, whose etiologic agent is *Trypanosoma cruzi*. Piplartine is an alkamide present in various species of the genus *Piper* that possess trypanocidal activity. In this study, the antiparasitic potential of a collection of 23 synthetic analogs of piplartine against *Trypanosoma cruzi* was evaluated in vitro. The compounds were prepared via amidation and esterification reactions using 3,4,5-trimethoxybenzoic acid as starting material. The products were structurally characterized using ^{1}H and ^{13}C nuclear magnetic resonance, infrared spectroscopy, and high-resolution mass spectrometry. Of the twenty-three compounds tested in the cytotoxic activity assays, five presented good activity in the trypomastigote, epimastigote, and amastigote forms of *T. cruzi*, showing IC_{50} values ranging from 2.21 to 35.30 μM, 4.06 to 34.30 μM, and 1.72 to 5.72 μM, respectively. *N-iso*-butyl-3,4,5-trimethoxybenzamide (**17**) presented potent trypanocidal activity with an IC_{50} = 2.21 μM and selectively caused apoptosis (SI = 298.6). Molecular modeling experiments suggested the inhibitions of the histone deacetylase (HDAC) enzyme as the main trypanocidal mechanism of action of compound **17** in *T. cruzi*.

Keywords: piperlongumine; cytotoxicity; natural products; trypanocide; alkaloid; *Trypanosoma*; neglected diseases; antiparasitic activity

1. Experimental

1.1. Chemical Characterization Compounds 1-23

Methyl 3,4,5–trimethoxybenzoate (1): White crystalline solid; yield 94.9% (101.2 mg; 0.44 mmol); M.P.: 81–83 °C; TLC (8:2 Hexane/AcOEt), R*f* = 0.46; IR υmax (KBr, cm^{-1}): 3021, 2953; 1716, 1674, 1592 and 1467, 1338 and 1132, 1229 and 992, 863; ^{1}H NMR (400 MHz, $CDCl_3$,): δ 7.29 (*s*, 2H); 3.89 (*s*, 12H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.6; 152.8; 142.3; 125.2; 106.8; 60.9; 56.2; 52.2 [29].

Ethyl 3,4,5–trimethoxybenzoate (2): White solid; yield 94.6% (107.1 mg; 0.44 mmol); M.P.: 53–54 °C; TLC (8:2 Hexane/AcOEt), R*f* = 0.52; IR υmax (KBr, cm^{-1}): 3014, 2964, 1706, 1664, 1591 and 1456, 1332 and 1132, 1228 and 1042, 863; ^{1}H NMR (400 MHz, $CDCl_3$,): δ 7.29 (*s*, 2H); 4.39 (*q*, *J* = 7.1 Hz, 2H); 3.90 (*s*, 6H); 3.89 (*s*, 3H); 1.39 (*t*, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.2; 152.9; 142.1 125.4; 106.7; 61.1 ; 60.9; 56.4; 14.2 [28].

Propyl 3,4,5–trimethoxybenzoate (3): Propyl 3,4,5–trimethoxybenzoate (3): White crystalline solid; yield 99.1% (118.8 mg; 0.46 mmol); M.P.: 34–35 °C; TLC (8:2 Hexane/AcOEt), R*f* = 0.56; IR υmax (KBr, cm^{-1}): 3114, 2964, 1706, 1664, 1590 and 1459, 1333 and 1124, 1227 and 1008, 858; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 (*s*, 2H); 4.27 (*t*, *J* = 6.7 Hz, 2H); 3.93 (*s*, 9H); 1.79 (*sext*, *J* = 7.4 Hz, 2H); 1.02 (*t*, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.1; 152.6; 142.1; 125.4; 106.6; 66.6; 60.9; 56.1; 22.0; 10.4 [29].

Isopropyl 3,4,5–trimethoxybenzoate (4): Light brown oil; yield 57.3% (68.6 mg; 0.26 mmol); TLC (8:2 Hexane/AcOEt), R*f* = 0.56; IR υmax (KBr, cm^{-1}): 3024, 2981, 1711, 1679, 1590 and 1461, 1327 and 1129, 1229 and 1007, 865; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28 (*s*, 2H); 5.24 (*sept*, *J* = 2.2 Hz, 1H); 3.90 (*s*, 6H); 3.89 (*s*, 3H); 1.36 (*d*, *J* = 6.3 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.7; 152.8; 142.0; 125.9; 106.7; 68.6; 60.9; 56.2; 21.9 [28].

Butyl 3,4,5–trimethoxybenzoate (5): Colorless oil; yield 99.6% (125.9 mg; 0.46 mmol); TLC (8:2 Hexane/AcOEt), R*f* = 0.64; IR υmax (KBr, cm^{-1}): 3006, 2961, 1716, 1655, 1590 and 1459, 1335 and 1129, 1225 and 1006, 865; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.29 (*s*, 2H); 4.31 (*t*, *J* = 6.7 Hz, 2H); 3.90 (*s*, 6H); 3.90 (s, 3H); 1.76 (*qu*, *J* = 6.7 Hz, 2H); 1.47 (*sext*, *J* = 7.4 Hz, 2H); 0.98 (*t*, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.4); 153.0 142.2; 125.7; 106.9; 65.3; 61.0; 56.4; 30.9; 19.4; 13.9 [28].

Isopentyl 3,4,5–trimethoxybenzoate (6): Brown oil, yield 45.3% (60.3 mg; 0.21 mmol); TLC (8:2 Hexane/AcOEt), R*f* = 0.60; IR υmax (KBr, cm^{-1}): 3002, 2959, 1717, 1655, 1590 and 1459, 1334 and 1129, 1225 and 1006, 865; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 (*s*, 2H); 4.34 (*t*, *J* = 6.8 Hz, 2H); 3.90 (*s*, 9H); 1.81-1.71 (*m*, 1H); 1.66 (*q*, *J* = 6.8 Hz, 2H); 0.98 (*d*, *J* = 6.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.5; 153.0; 142.3; 125.7; 107.0; 64.1 61.0; 56.4; 37.6; 25.5; 22.6 [11].

Pentyl 3,4,5–trimethoxybenzoate (7): White oil; yield 75.2% (100.1 mg; 0.35 mmol); TLC (8:2 Hexane/AcOEt), R*f* = 0.60; IR υmax (KBr, cm^{-1}): 3012, 2957, 1714, 1657, 1590 and 1461, 1335 and 1129, 1226 and 1006, 865; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 (*s*, 2H); 4.29 (*t*, *J* = 6.8 Hz, 2H); 3.89 (*s*, 9H); 1.75 (*qu*, *J* = 7.2 Hz, 2H); 1.44–1.34 (*m*, 4H); 0.92 (*t*, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.3 (C=O); 152.9 (C-3, C-5); 142.1 (C-4); 125.5 (C-1); 106.8; 65.3; 60.9; 56.2; 28.4; 28.2; 22.3; 14.0 [28].

Decyl 3,4,5–trimethoxybenzoate (8): Amorphous solid, yield 40.6% (67.4 mg; 0.19 mmol); M.P.: 49–50 °C; TLC (8:2 Hexane/AcOEt), R*f* = 0.64; IR υmax (KBr, cm^{-1}): 3015, 2956, 1709, 1672, 1590 and 1465, 1336 and 1131, 1226 and 990, 864; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 (*s*, 2H); 4.30 (*t*, *J* = 6.8 Hz, 2H); 3.90 (*s*, 9H); 1.80 (*qu*, *J* = 6.8 Hz, 2H); 1.42–1.26 (*m*, 14H); 0.87 (*t*, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.2; 152.6; 142.0; 125.4; 106.4; 65.3; 60.8; 56.2; 31.8; 29.5; 29.3; 29.3; 28.7; 26.0; 22.7; 14.1 [30].

4-Methoxy-benzyl 3,4,5–trimethoxybenzoate (10): White cristalline solid, yield 67.5% (105.7 mg; 0.32

mmol); M.P.: 83–84 °C; TLC (8:2 Hexane/AcOEt), R*f* = 0.36; IR υmax (KBr, cm^{-1}): 3008, 2944, 1711, 1670, 1589 and 1465, 1332 and 1126, 1228 and 1005, 864; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (*d*, *J* = 9.5 Hz, 2H); 7.31 (*s*, 2H, H-2); 6.91 (*d*, *J* = 8.8 Hz, 2H); 5.29 (*s*, 2H,); 3.89 (*s*, 9H); 3.81 (*s*, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.2; 159.6; 152.8, 142.1; 130.0; 128.2; 125.2; 113.9 ; 106.9; 66.7; 60.9; 56.1; 55.3 [11].

Benzyl 3,4,5–trimethoxybenzoate (12) White solid; yield 29.8% (84.9 mg; 0.28 mmol); M.P.: 91-92 °C; TLC (8:2 Hexane/AcOEt), R*f* = 0,38; IR υmax (KBr, cm^{-1}): 3006, 2944, 1698, 1634, 1583 and 1467, 1340 and 1128, 1249 and 1040, 818; ^{1}H NMR (400 MHz, $CDCl_3$,): δ 7.46 – 7.42 (*m*, 2H); 7.38 (*m*, 3H); 7.33 (*s*, 2H); 5.36 (*s*, 2H); 3.90 (*s*, 9H); ^{13}C NMR (100 MHz, $CDCl_3$,): δ 166.2; 153.0; 142.4; 136.2; 128.7; 128.3; 128.3; 125.2; 107.1; 66.9; 61.0; 56.4 [28].

4-Bromo-benzyl 3,4,5–trimethoxybenzoate (13): White cristalline solid, yield 55.0% (197.0 mg; 0.51 mmol); M.P.: 104–105 °C; TLC (8:2 Hexane/AcOEt), R*f* = 0.62; IR υmax (KBr, cm^{-1}): 3034, 2958, 1712, 1664, 1594 and 1454, 1334 and 1133, 1228 and 1010, 1070, 801; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.51 (*d*, *J* = 8.4 Hz, 2H); 7.32 (*d*, *J* = 8.4 Hz, 2H); 7.31 (s, 2H); 5.30 (s, 2H); 3.90 (*s*, 9H,); ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.1; 153.1; 142.7; 135.2; 131.9; 130.0; 125.0; 122.5; 107.2; 66.2; 61.1; 56.4 [11].

2-Methylnaphthalene 3,4,5–trimethoxybenzoate (14): White solid; yield 48.4% (160.9 mg; 0.45 mmol); M.P.: 84–85 °C; TLC (8:2 Hexane/AcOEt), R*f* = 0.58; IR υmax (KBr, cm^{-1}): 3002, 2936, 1714, 1670, 1590 and 1463, 1329 and 1129, 1225 and 1008, 864; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.91–7.85 (*m*, 4H); 7.55 (*dd*, *J* = 8.4 Hz; 1.6 Hz, 1H), 7.53–7.45 (m, 2H); 7.36 (s, 2H); 5,53 (s, 2H); 3.90 (*s*, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.3; 153.1; 142.5; 133.6; 133.3; 133.3; 128.6; 128.12 127.8; 127.5; 126.4; 126.4; 126.0; 125.2; 107.2; 67.1; 61.0; 56.4 [11].

Diphenyl 3,4,5–trimethoxybenzoate (15): Yellow solid; yield 41.5% (148.2 mg; 0.39 mmol); M.P.: 57–58 °C; TLC (8:2 Hexane/AcOEt), R*f* = 0.64; IR υmax (KBr, cm^{-1}): 3026, 2939, 1727, 1655, 1587 and 1456, 1338 and 1172, 1226 and 1127, 855; ^{1}H NMR (500 MHz, $CDCl_3$,): δ 7.59–7.47 (m, 12H); 7.44 (s, 1H); 4.06 (*s*, 9H); ^{13}C NMR (125 MHz, $CDCl_3$,): δ 165.3; 152.9; 142.5; 140.2; 128.6*; 128.5*; 128.0#; 127.5#; 127.1; 126.5; 125.2; 107.1; 77.6; 60.9; 56.3 [11].

***N*-Butyl-3,4,5–trimethoxybenzamide (16):** White solid; yield 89.1% (112.2 mg; 0.41 mmol M.P.: 115–116 °C; TLC (6:4 Hexane/AcOEt), R*f* = 0.36; IR υmax (KBr, cm^{-1}): 3294, 3017, 2932, 1681, 1634, 1583 and 1459, 1541 and 1506, 1236 and 1131, 843; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.98 (*s*, 2H); 6.22 (*s*, 1H); 3.87 (*s*, 6H); 3.86 (*s*, 3H); 3.43 (*q*, *J* = 5.8 Hz, 2H); 1.62 (*qu*, *J* = 7.2 Hz, 2H); 1.38 (*sext*, *J* = 7.5 Hz, 2H); 0.94 (*t*, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.3; 153.2; 140.8; 130.5; 104.5; 60.9; 56.3; 40.0; 31.9; 20.2; 13.9 [30].

***N*-Isobutyl-3,4,5–trimethoxybenzamide (17):** Yellow solid; yield 91.3% (115.0 mg; 0.43 mmol); M.P.: 118–119 °C; TLC (6:4 Hexane/AcOEt), R*f* = 0.36 ; IR υmax (KBr, cm^{-1}): 3307, 3015, 2955, 1687, 1634, 1583 and 1469, 1543 and 1504, 1237 and 1131, 842; ^{1}H NMR (500 MHz, $CDCl_3$,): δ 6.98 (*s*, 2H), 6.30 (*s*, 1H), 3.86 (*s*, 6H), 3.85 (*s*, 3H); 3.24 (*t*, *J* = 6.5 Hz, 2H), 1.92–1.84 (m, 1H), 0.95 (d, *J* = 6.7 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$,): δ 167.5; 153.3; 140.7; 130.4; 104.5; 60.9; 56.4; 47.6; 28.7; 20.2 [30].

***N*-Pyrrolidyl-3,4,5–trimethoxybenzoamide (18):** Yellow oil; yield 84,2% (105,3 mg; 0,39 mmol); TLC (1:9 Hexane/AcOEt), R*f* = 0,48; IR υmax (KBr, cm^{-1}):, 3038, 2971, 1657, 1621, 1582 and 1463, 1510 and 1417, 1239 and 1005, 843; ^{1}H NMR (400 MHz, $CDCl_3$,): δ 6.71 (*s*, 2H); 3.83 (*s*, 6H); 3.82 (*s*, 3H,); 3.59 (*t*, *J* = 6.1 Hz, 2H); 3.42 (*d*, *J* = 5.8 Hz, 2H); 1.92 (m, 2H); 1.86 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$,): δ 169.4; 152.9; 139.2; 132.1; 104.6; 60.8; 56.2; 49.8; 46.2; 26.3; 24.4 [31].

***N*-Cyclohexyl-3,4,5–trimethoxybenzamide (19):** White crystalline solid; yield 44.4% (61.4 mg; 0.21 mmol); M.P.: 179–180 °C; TLC (6:4 Hexane/AcOEt), R*f* = 2.2; IR υmax (KBr, cm^{-1}): 3468, 3077, 2871, 1677, 1621, 1582 and 1463, 1510 and 1417, 1239 and 1004, 844; ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.16 (*s*, 1H); 6.19 (*s*, 2H); 2.86 (*s*, 6H); 2.72 (*s*, 3H); 1.54 (*qu J* = 1.8 Hz, 1H); 0.88–0.76 (*m*, 4H); 0.67–0.62 (*m*, 2H); 0.36-0.32 (*m*, 4H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 164.9; 152.5; 139.8; 130.1; 104.9; 60.2; 56.1; 48.6; 32.6; 25.4; 25.1 [26].

***N*-4-Hydroxybenzyl-3,4,5–trimethoxybenzamide (20):** White solid, yield 57.1% (256.3 mg; 0.81 mmol); M.P.: 227–229 °C; TLC (5:5 Hexane/AcOEt), R*f* = 0.37; IR υmax (KBr, cm^{-1}): 3379 and 3314, 3346, 3019, 2099, 1634, 1611, 1574 and 1449, 1545 and 1499, 1414 and 1231, 1211 and 1122, 823; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8,40 (s, 1H); 7.99 (*t*, *J* = 5.7 Hz, 1H,); 6.35 (*s*, 2H); 6.24 (*d*, *J* = 8.5 Hz, 2H); 5.82 (*d*, *J* = 10.0 Hz, 2H); 3.48 (d, *J* = 5.7 Hz, 2H); 2.93 (s, 6H); 2.81 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 165.4; 156.3; 152.6; 139.9; 129.8; 129.6; 128.6; 115.0; 104.8; 60.1; 56.0; 42.3 [26].

***N*-Benzyl-3,4,5–trimethoxybenzamide (21):** White crystalline solid, yield 59.6% (84.6 mg; 0.27 mmol); M.P.: 138–139 °C; TLC (6:4 Hexane/AcOEt), R*f* = 0.38; IR υmax (KBr, cm^{-1}): 3305, 3028, 2942, 1655, 1625, 1580 and 1459, 1528 and 1499, 1237 and 1127, 840; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35–7.27 (*m*, 5H); 7.03 (*s*, 2H); 6.60 (s, 1H); 4.61 (*d*, *J* = 5,8 Hz, 2H); 3.86 (*s*, 3H); 3.85 (*s*, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.1; 153.3; 141.1; 138.2; 129.8; 128.8; 128.0; 127.7; 104.5; 61.0; 56.3; 44.3 [28].

***N*-(4-Fluorobenzyl)-3,4,5–trimethoxybenzamide (22):** White crystalline solid, yield 62.5% (90 mg; 0.28 mmol); M.P.: 131–132 °C; TLC (6:4 Hexane/AcOEt), R*f* = 0.34; IR υmax (KBr, cm^{-1}): 3288, 3012, 2947, 1672, 1634, 1585 and 1459, 1545 and 1508, 1280 and 1130, 1219 and 1098, 827; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29–7.27 (*m*, 2H); 7.01 (*s*, 2H); 6.98 (*d*, *J* = 8,7 Hz, 2H); 6.69 (s, 1H); 4.55 (*d*, *J* = 5,8 Hz, 2H); 3.85 (*s*, 6H); 3.84 (*s*, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.1; 163.5; 161.0; 153.3; 141.2; 134.0; 129.7; 129.6*; 129.5*; 115.7#; 115.5#; 104.5; 60.9; 56.3; 43.5 [11].
*, # Interchangeable.

***N*-4-Chlorobenzyl-3,4,5–trimethoxybenzamide (23):** White solid; yield 86.6% (137.0 mg; 0.41 mmol); M.P.: 157–158 °C; TLC (6:4 Hexane/AcOEt), R*f* = 0.34; IR υmax (KBr, cm^{-1}): 3254, 3004, 2946, 1653, 1629, 1582 and 1457, 1538 and 1498, 1235 and 1128, 1070 and 997, 816; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31 (*d*, *J* = 6.4 Hz, 2H); 7.28 (*d*, *J* = 6.4 Hz, 2H); 7.04 (*s*, 2H); 6.74 (s, 1H); 4.58 (*d*, *J* = 5,7 Hz, 2H); 3.88 (*s*, 3H); 3.87 (*s*, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.3; 153.1; 141.3; 136.9; 133.4; 129.0; 129.3; 128.9; 104.5; 61.0; 56.4; 43.5 [11].

Table S1. Predicted free energies of binding of compound **17** to its potential targets and its components according to the MM-PBSA method. Energy values are expressed in kcal/mol.

Target	Conformer	MM-PBSA Component							ΔG TOTAL
		VD WAALS	EEL	EPB	ENPOLAR	EDISPER	ΔG gas	ΔG solv.	
PPI-1	1	-26.27	-11.09	22.17	-21.32	34.07	-37.37	34.93	-2.44
	2	-24.81	-6.47	17.67	-20.05	32.35	-31.28	29.97	-1.32
	3	-27.55	-9.61	21.26	-22.36	35.68	-37.16	34.58	-2.58
PPI-2	1	-27.81	-6.67	16.97	-20.73	34.32	-34.48	30.56	-3.91
HDAC	1	-34.99	-69.76	56.70	-31.23	47.45	-104.75	72.92	-31.83
	2	-29.75	-72.57	55.11	-30.34	44.65	-102.31	69.42	-32.89

	3	-31.58	-79.12	62.66	-31.32	46.98	-110.70	78.32	-32.37
MAPK-1	1	-42.84	-25.04	49.09	-29.58	49.04	-67.88	68.55	0.67
MAPK-2	1	-33.18	-11.31	31.36	-25.17	43.21	-44.48	49.40	4.92
	2	-35.28	-21.90	40.14	-27.57	44.64	-57.18	57.21	0.03
	3	-33.03	-17.00	37.16	-26.20	43.98	-50.04	54.94	4.90
	4	-34.85	-30.36	48.42	-27.39	44.43	-65.21	65.47	0.26
IleRS	1	-42.36	-14.22	45.97	-29.00	50.09	-56.58	67.06	10.49
TUB	1	-41.78	-17.70	45.11	-29.34	50.14	-59.48	65.91	6.42
PDE	1	-35.10	-10.08	25.52	-27.37	43.94	-45.19	42.09	-3.09
	2	-39.00	-16.30	30.73	-29.48	47.72	-55.30	48.97	-6.32
DHFR-TS (folate site)	1	-34.62	-11.50	33.96	-26.30	43.97	-46.12	51.63	5.51
	2	-33.64	-11.21	31.63	-25.91	42.97	-44.85	48.70	3.85
DHFR-TS (dUMP site)	1	-28.99	-18.86	36.58	-22.87	39.28	-47.84	52.99	5.14
	2	-26.50	-9.58	22.43	-21.60	34.05	-36.07	34.87	-1.20

Figure S1. Infrared spectrum (KBr, cm-1) of N-Isobutyl-3,4,5–trimethoxybenzamide (**17**).

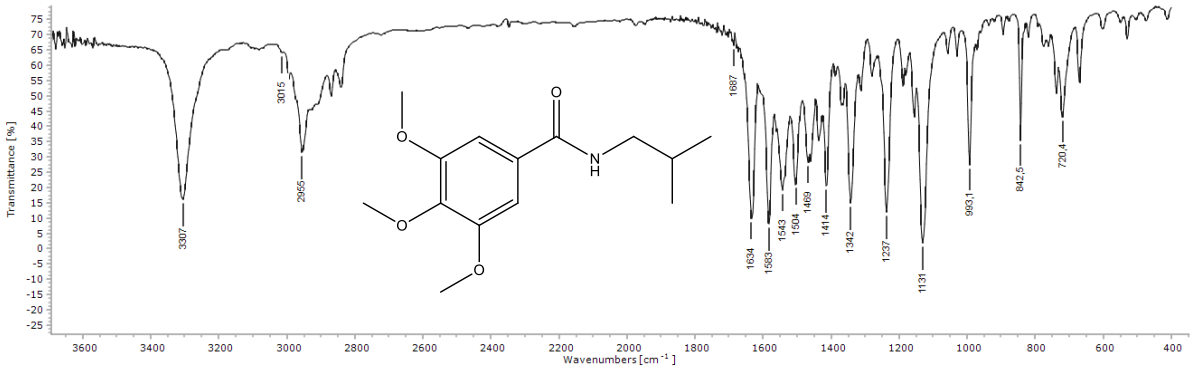

Figure S2. [1]H NMR spectrum of N-Isobutyl-3,4,5-trimethoxybenzamide (**17**), (CDCl3, 500 MHz).

Figure S3. [1]H NMR spectrum expansion of N-Isobutyl-3,4,5–trimethoxybenzamide (**17**), (CDCl3, 500 MHz).

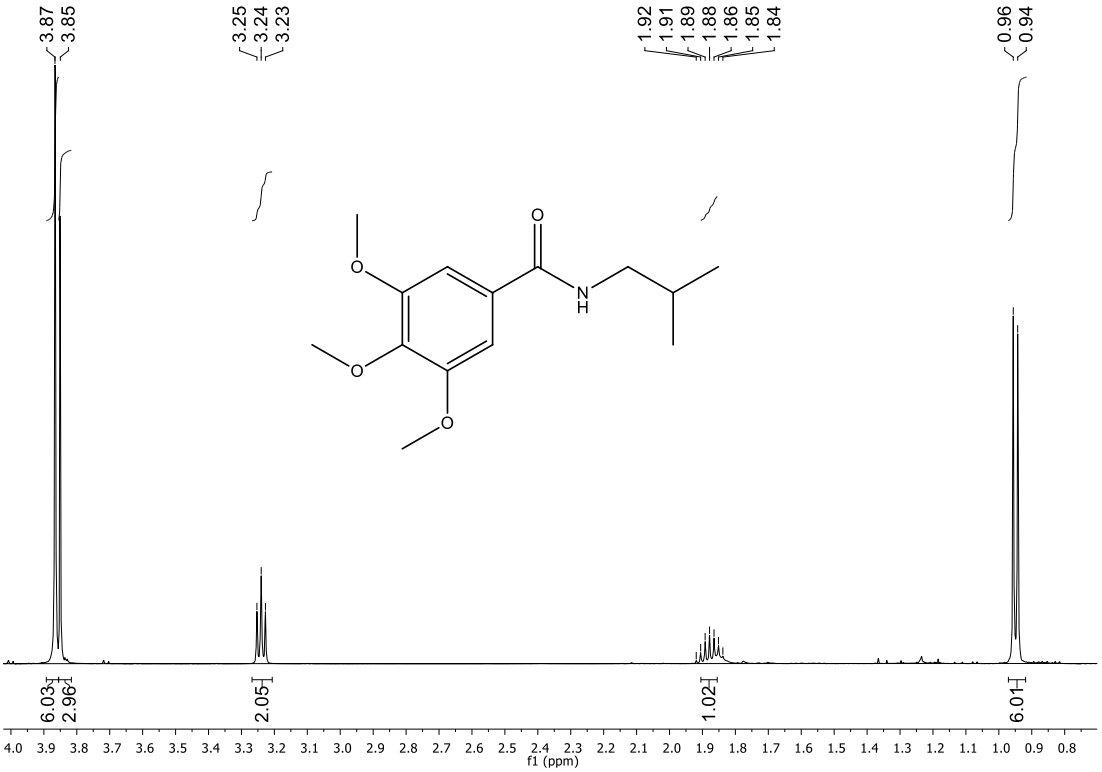

Figure S4. ^{13}C-APT NMR spectrum of N-Isobutyl-3,4,5-trimethoxybenzamide (**17**), (CDCl3, 100 MHz).