Supporting Information

Article: Design, Synthesis and Biological Evaluation of Novel 3-aryl-4-(1*H*-indole-3yl)-1,5-dihydro-2*H*-pyrrole-2-ones as VEGF-R inhibitors

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Content:

1) IR-Data

2 ν_{max} 3344, 3222, 2931, 1666, 1618, 1578, 1496, 1403, 13362, 1238, 1118, 994, 748, 720, 658 cm^{-1}.

3 ν_{max} 3351, 3206, 1681, 1633, 1582, 1505, 1449, 1412, 1379, 1332, 1237, 1124, 1004, 753 cm^{-1}.

4 ν_{max} 3294-2823 (ν NH-C=O, OH, {O}CH3), 1666, 1238, 1119, 973, 738 cm^{-1}.

5 ν_{max} 3096, 2961, 2938, 2843, 1719, 1682, 1587, 1505, 1473, 1451, 1418, 1327, 1239, 1125 cm^{-1}.

6a ν_{max} 2888, 1668, 1626, 1571, 1502, 1458, 1406, 1320, 1230, 1126, 995, 730 cm^{-1}.

7 ν_{max} 3319, 3272, 2941, 2838, 1681, 1638, 1583, 1550, 1503, 1459, 1431, 1414, 1345, 1128 cm^{-1}.

8 ν_{max} 3397, 3176, 2931, 1653, 1624, 1587, 1542, 1521, 1440, 1409, 1329, 1240, 1134, 744 cm^{-1}.

9 ν_{max} 2911, 2606, 1680, 1586, 1504, 1416, 1330, 1319, 1172, 1126, 990, 833 cm^{-1}.

10 ν_{max} 3369, 2924, 2840, 1674, 1656, 1581, 1532, 1506, 1461, 1233, 1162, 1128, 998, 725 cm^{-1}.

11 ν_{max} 3393, 1655, 1595, 1550, 1502, 1457, 1415, 1342, 1242, 1174, 1127, 1105, 993, 801, 729 cm^{-1}.

12 ν_{max} 3288, 2937, 2839, 1731, 1644, 1589, 1505, 1456, 1422, 1327, 1231, 1121, 1001, 740 cm^{-1}.

13 ν_{max} 3304, 3188, 2937, 1653, 1616, 1587, 1539, 1507, 1458, 1436, 1312, 1238, 1131, 744 cm^{-1}.

14 ν_{max} 3344, 3200, 2936, 2833, 1634, 1596, 1565, 1508, 1458, 1424, 1335, 1244, 1120, 1101, 990, 735 cm^{-1}.

15 ν_{max} 3425, 2944, 2866, 1669, 1590, 1543, 1508, 1460, 1424, 1369, 1236, 1126, 1015, 881 cm^{-1}.

16 ν_{max} 3310, 2940, 1672, 1636, 1591, 1534, 1447, 1388, 1237, 1172, 1139, 1126, 1001, 729 cm^{-1}.

18 ν_{max} 3280, 2924, 1766, 1704, 1616, 1499, 1464, 1414, 1321, 1242, 1224, 1124, 1069, 832 cm^{-1}.

19 ν_{max} 3185, 3062, 2950, 1665, 1623, 1579, 1505, 1452, 1406, 1329, 1237, 1126, 1093, 834, 742 cm^{-1}.

20 ν_{max} 3310, 2924, 2852, 1667, 1579, 1501, 1448, 1407, 1325, 1235, 1119, 1050, 996, 744 cm^{-1}.

21 ν_{max} 2936, 2860, 2937, 1675, 1578, 1528, 1501, 1450, 1403, 1327, 1239, 1122, 1003, 913, 828, 744 cm^{-1}.

22 ν_{max} 3320, 3096, 2970, 1670, 1634, 1584, 1535, 1503, 1452, 1407, 1331, 1237, 1124, 1083, 994, 750 cm^{-1}.

23 ν_{max} 3171, 3094, 2955, 1670, 1616, 1578, 1499, 1455, 1405, 1326, 1295, 1239, 1118, 1077, 1000, 853, 752 cm^{-1}.

24 ν_{max} 3094, 2974, 1677, 1619, 1580, 1526, 1502, 1451, 1408, 1327, 1237, 1126, 1078, 1003, 845, 742 cm^{-1}.

25 ν_{max} 3511, 3372, 3183, 2935, 2834, 1682, 1661, 1582, 1500, 1455, 1386, 1337, 1237, 1170, 1122, 999, 745 cm^{-1}.

26 ν_{max} 3224, 2933, 1673, 1579, 1529, 1500, 1407, 1326, 1235, 1291, 1235, 1122, 1069, 1002, 740, 697 cm^{-1}.

27 ν_{max} 3282, 2921, 1840, 1681, 1654, 1636, 1589, 1556, 1530, 1507, 1464, 1426, 1383, 1328, 1231, 1119, 1074, 1013, 751 cm^{-1}.

28 ν_{max} 3243, 2986, 2937, 1673, 1579, 1502, 1466, 1450, 1382, 1332, 1234, 1122, 1004, 827, 733, 657 cm^{-1}.

29 ν_{max} 3448, 3346, 3151, 2939, 2830, 1669, 1528, 1469, 1385, 1291, 1236, 1181, 1127, 991, 737 cm^{-1}.

30 ν_{max} 3297, 2938, 2837, 1699, 1640, 1583, 1535, 1504, 1463, 1412, 1356, 1315, 1232, 1159, 1126, 993, 735 cm^{-1}.

31 ν_{max} 3199, 3078, 2937, 2836, 1695, 1574, 1504, 1413, 1326, 1243, 1126, 1001, 740 cm^{-1}.

32 ν_{max} 3368, 3254, 1678, 1644, 1595, 1509, 1461, 1355, 1259, 1238, 1167, 993, 835, 738, 662 cm^{-1}.

33 ν_{max} 3176, 3048, 1668, 1601, 1505, 1435, 1371, 1252, 1179, 1117, 1032, 831, 748 cm^{-1}.

34 ν_{max} 3343, 2932, 1682, 1640, 1602, 1515, 1424, 1359, 1244, 1217, 1184, 1016, 998, 837, 815, 734 cm^{-1}.

35 ν_{max} 3193, 3047, 1683, 1607, 1505, 1426, 1354, 1259, 1247, 1181, 1031, 826, 755, 741 cm^{-1}.

2) ^{1}H-and ^{13}C-NMR-Data

(**2**) 4-(1*H*-Indol-3-yl)-3-(3,4,5-trimethoxyphenyl)-1,5-dihydro-2*H*-pyrrole-2-one.

^{1}H-NMR (MeOD-d_3): δ [ppm] = 7.5 (s, 1 H, indole C-2), 7.39 (dd, 1 H, indole C-4), 7.1 (m, 1 H, indole C-5), 6.85 (d, 2 H), 6.75 (s, 2 H, Phe-H), 4.51 (s, 2 H, CH_2), 3.80 (s, 3 H, para-{O}CH_3), 3.60 (s, 6 H, meta-{O}CH_3).

^{13}C-NMR (MeOD-d_3): δ [ppm] = 174.48 (C=O), 152.1 (2 C, meta-PhC), 147.5 (C-4), 136.5 (indole C-7a), 135.98 (para-PhC), 127.97 (indole C-6), 125.2 (indole C-3), 123.36 (PhCquart.), 120.9 (indole C-2), 119.8 (indole C-5), 118.77 (indole C-4), 110.4 (indole C-3), 108.4 (indole C-7), 106.1 (2 C, ortho-PhC), 58.8 (para-{O}CH_3), 54.0 (2 C, meta-{O}CH_3), 47.9 (CH_2).

(**3**) 3-(1*H*-Indol-3-yl)-4-(3,4,5-trimethoxyphenyl)-1,5-dihydro-2*H*-pyrrole-2-one.

^{1}H-NMR (DMSO-d_6): δ [ppm] = 11.4 (bs, 1H, indole-NH), 8.4 (s, 1H, amide-NH), 7.6 (d, J = 2.64, 1H, indole-H), 7.4 (d, J = 8.06, 1H), 7.0 (t, J = 7.44, 1H), 6.8 (t, J = 7.41, 1H), 6.6 (m, 3H, indole-H, 2×ortho-Ph-H), 4.4 (s, 2H, CH_2), 3.6 (s, 3H, para-{O}CH_3), 3.3 (s, 6H, meta-{O}CH_3).

^{13}C-NMR (DMSO-d_6): δ [ppm] = 173.7 (C=O), 152.8 ($C_{quart.}$), 146.3 ($C_{quart.}$), 138.1 ($C_{quart.}$), 136.4 ($C_{quart.}$), 129.7 (CH), 127.3 ($C_{quart.}$), 125.7 ($C_{quart.}$), 125.0 ($C_{quart.}$), 121.4 (CH), 120.9 (CH), 118.9 (CH), 112.0 (CH), 106.5 ($C_{quart.}$), 105.5 (PH-CH), 60.4 (para-{O}CH_3), 55.6 (meta-{O}CH_3), 47.5 (CH_2).

(**4**) 5-Hydroxy-4-(1*H*-indol-3-yl)-3-(3,4,5-trimethoxyphenyl)-1,5-dihydro-2*H*-pyrrole-2-one.

480 mg (1.9 mmol) of compound 1 are added to a stirring solution of 620 mg (2.5 mmol) $CeCl_3$ and 150 mg $NaBH_4$ in 20 mL ethanol. The progress of the reaction was monitored by TLC. After completeness water was added, the mixture extracted by ethylacetate, the organic phase dried over Na_2SO_4 and evaporated. The product was purified by Flash-chromatography on silica gel. Yield 32 % (230 mg, 0.6 mmol).

^{1}H-NMR (acetone-d_6): δ [ppm] = 10.75 (s, 1 H, indole NH), 7.84 (d, 1 H, indole 2-H), 7.59 (s, 1 H, OH), 7.44 (d, 1 H, indole 7-H), 7.08 (m, 1 H, indole 6-H), 6.82 (s, 2 H, *ortho*-PhH), 6.79 (d, 1 H, indole 4-H), 6.76 (m, 1 H, indole 5-H), 5.96 (d, 1 H, 5-H), 5.12 (d, 1 H, pyrrole NH), 3.71 (s, 3 H, *para*-{O}CH_3), 3,47 (s, 6 H, *meta*-{O}CH_3).

^{1}H-NMR (MeOD-d_3): δ [ppm] = 7.75 (s, 1 H, indole 2-H), 7.37 (d, 1 H, indole 7-H), 7.04 (t, 1 H, indole 6-H), 6.74 (s, 2 H, *ortho*-PhH), 6.75 (d, 1 H, indole 5-H), 6.67 (t,1 H, indole 4-H), 5.93 (s, 1 H, 5-H), 3.70 (s, 3 H, *para*-{O}CH_3), 3,46 (s, 6 H, *meta*-{O}CH_3).

^{13}C-NMR (acetone-d_6): δ [ppm] = 173.4 (C-3), 154.5 (*meta*-PhC), 149.8 (C-4), 139.6 (indole C-7a), 138.6 (*para*-PhC), 130.3 (C-3), 129.7 (indole C-2), 127.6 (indole C-3a), 126.6 ($PhC_{quart.}$), 123.6 (indole C-7), 123.3 (indole C-6), 121.0 (indole C-4), 113.4 (indole C-7), 110.8 (indole C-3), 109.5 (2 C, *ortho*-PhC), 81.5 (C-5), 66.9 (*para*-{O}CH_3), 61.5 (2 C, *meta*-{O}CH_3).

(5) Oxo(3,4,5-trimethoxyphenyl)acetic acid. [48]

3,4,5-Trimethoxyacetophenone (4.2 g, 20 mmol) was dissolved and stirred in 50 mL $pyridine_{abs.}$ and 3.3 g (30 mmol) SeO_2 are added. The mixture was refluxed for 3 h and allowed to cool over night without stirring. The precipitated selene was filtered and pyridine was evaporated as an azeotrop by adding toluene. The residue was dissolved in ethylacetate and washed with saturated $NaHCO_3$ solution. The aqueous phase was extracted twice by ethylacetate. The combined organic phases were evaporated almost to dryness. By addition of diethylether the product precipitated as a bright white solid. Yield 80 % 3.84 g (16 mmol).

^{1}H-NMR (DMSO-d_6): δ [ppm] = 8.61 (s, 1 H, OH), 7.21 (s, 2 H, *ortho*-PhH), 3.84 (s, 6 H, *meta*-{O}CH_3), 3.78 (s, 2 H, *meta*-{O}CH_3).

^{13}C-NMR (DMSO-d_6): δ [ppm] = 187.9 (C-2), 166.3 (C-1), 153.0 (2 C, *meta*-PhC), 148.7 (*para*-PhC), 127.1 ($PhC_{quart.}$), 106.7 (2 C, *ortho*-PhC), 60.3 (*para*-{O}CH_3), 56.0 (2 C, *meta*-{O}CH_3).

(**6**) N-[2-(1*H*-Indol-3-yl)ethyl]-2-oxo-2-(3,4,5-trimethoxyphenyl)acetamide.

Compound **4** (2.1 g, 8.34 mmol) was dissolved in dichloromethane$_{abs.}$, 1.4 g CDI (carbonyldiimidazole) was added and the mixture stirred with a bubble counter for 1 h at room temperature. The reaction was warmed to 35°C when 1.335 g (8.33 mmol) tryptamine are added and stirred over night. The product was purified by silica gel Flash chromatography to yield 95 % (3.03 g, 7.91 mmol) of **6** as brownish oil which solidified slowly under vacuum.

^{1}H-NMR ($CDCl_3$): δ [ppm] = 8.27 (s, 1H, indole -NH), 7.74 (s, 2 H, *ortho*-PhH), 7.63 (d, J =7.3 Hz, indole 4-H), 7.35 (t, J = 7.3, indole 7-H), 7.25 (s, indole 2-H), 7.17 (t, 2 H, J = 7.8 Hz, indole 5-H, indole 6-H), 7.06 (s, 1 H, NH), 3.95 (s, *para*-{O}CH_3), 3.9 (s, 2 H, *meta*-{O}CH_3), 3.73 (q, J_{NH} = 6.4 Hz, J_{CH} = 6.5 Hz, H-1`), 3.08 (t, J = 6.5 Hz, H-2`).

^{13}C-NMR ($CDCl_3$): δ [ppm] = 185.8 (C-2), 161.9 (C-1), 152.7 (2 C, *meta*-PhC), 143.9 (*para*-PhC), 136.4 (indole C-7a), 128.2 ($PhC_{quart.}$), 127.1 (indole C-3a), 122.2 (indole C-6), 122.1(indole C-2), 119.5 (indole C-5), 118.6 (indole C-4), 112.3 (indole C-3), 111.3 (indole C-7), 108.7 (2 C, *ortho*-PhC)**,** 61.0 (*para*-{O}CH_3), 56.2 (2 C, *meta*-{O}CH_3), 39.5 (C-2`), 25.1(C-1`).

(**7**) N-[2-(1*H*-Indol-3-yl)-2-oxoethyl]-2-oxo-2-(3,4,5-trimethoxyphenyl)acetamide.

3.0 g of compound **6** (8 mmol) were dissolved in 200 mL THF and 20 mL water added. The mixture was cooled in an ice bath when 3.6 g (16 mmol) DDQ were added dropwise and the colour changed to deep red. After all DDQ had been added, the mixture was stirred for 2 hours in the ice bath. The organic solvent was carefully evaporated and the residue extracted by ethylacetate, the organic phase dried over Na_2SO_4 and evaporated. The product was purified by Flash-chromatography on silica gel to yield 49 % (1.55 g, 4.06 mmol) of **7** as a white solid.

^{1}H-NMR ($CDCl_3$): δ [ppm] = 12.1 (s, 1 H, indole NH), 9.24 (t, J = 5.7 Hz,1 H, indole 2-H), 8.52 (s, 1 H, indole 4-H), 8.15 (m, 1 H, indole 7-H), 7.57(s, 2 H, *ortho*-PhH), 7.51 (m, 1 H, NH), 7.23 (m, 2 H, Indole 5-H, 6-H), 4.69 (d, J = 5.81 Hz, 1 H, 2`-H), 3.93 (s, 6 H, *meta*-{O}CH_3), 3.80 (s, 3 H, *para*-{O}CH_3).

^{13}C-NMR ($CDCl_3$): δ [ppm] = 189.8 (C-1`), 189.1 (C-2), 166.3 (C-1), 152.9 (2 C, *meta*-PhC), 143.1 (2 C, *ortho*-PhC), 136.4 (indole C-7a), 133.9 (indole C-2), 128.1 ($PhC_{quart.}$), 125.3 (indole C-3a)**,** 123.0 (indole C-6), 122.0 (indole C-5), 121.0 (indole C-4), 113.8 (indole C-7), 112.2 (indole C-3), 107.4 (2 C, *meta*-PhC), 60.3 (*para*-{O}CH_3), 56.1 (2 C, *meta*-{O}CH_3), 45.42 (C-1´).

(**8**) N-[2-(1*H*-Indol-3-yl)-2-oxoethyl]-2-hydroxy-2-(3,4,5-trimethoxyphenyl)acetamide.

200 mg (0.5 mmol) of compound **7**, 1550 mg Ti (100 mesh, 32 mmol) and 3.94 mL TMSCl (32 mmol) were suspended in 25 mL dry THF and refluxed over night. The progress of the reaction was monitored by HPLC analysis. The solid was filtered off, washed with ethylacetate, and the combined organic phases evaporated. The product was purified by Flash-chromatography on silica gel to yield 45 % of **8** as a white solid (besides compound **8** an oily mixture of undefined polymers obtained).

^{1}H-NMR (DMSO-d_6): δ [ppm] = 12.0 (bs, 1H, indole NH), 8.41 (d, 1 H, CH), 8.25 (t, 1 H, amide NH), 8.15 (m, 1H, CH), 7.45 (m, 1H, CH), 7.20 (m, 2H, CH), 6.85 (s, 2 H, *ortho*-PhH), 6.25 (d, 1H, OH), 4.85 (d, 1H, CHOH), 4.45 (t, 2H, CH_2), 3.90 (s, 6 H, *meta*-{O}CH_3), 3.70 (s, 2 H, *meta*-{O}CH_3).

^{13}C-NMR (DMSO-d_6): δ [ppm] = 190.4 (C=O), 173.3, 152.8 (2 C, *meta*-PhC), 137.03, 136.78, 136.50, 133.74 (*para*-PhC), 125.4 ($PhC_{quart.}$), 123.6, 122.5, 121.33, 104.6 (2 C, *ortho*-PhC), 73.74 (1C, CH), 60.41 (*para*-{O}CH_3), 56.1 (2 C, *meta*-{O}CH_3), 45.5 (CH_2).

(**9**) 1-Bromo-2-oxo-2-(3,4,5-trimethoxyphenyl)ethanaminium bromide.

^{1}H-NMR (DMSO-d_6): δ [ppm] = 8.2 (bs, 3H, -$NH_3^{\oplus}$), 7.3 (s, 2H, ortho-Ph-H), 4.6 (bs, 2H, CH_2), 3.9 (s, 6H, meta-{O}CH_3), 3.8 (s, 3H, para-{O}CH_3).

^{13}C-NMR ($CDCl_3$): δ [ppm] = 192.2 (C=O), 153.3 (meta-Ph-C-O), 143.3 (para-Ph-C-O), 129.2 (Ph-$C_{quart.}$), 106.2 (Ph-CH), 60.6 (para-{O}CH_3), 56.6 (meta-{O}CH_3), 45.2 (CH_2).

(**10**) 2-(1*H*-Indol-3-yl)-N-[2-(3,4,5-trimethoxyphenyl)2-oxoethyl]acetamide.

Method A: In a three necked round bottom flask 1.0 g (3.3 mmol) **9**, 570 mg (3.3 mmol) indole-3-yl acetic acid and 500 mg (3.3 mmol) HOBt H_2O were evacuated. By the use of a septum 25 mL dry dichloromethane were added and the mixture cooled under argon in an ice bath. At this temperature, 880 mg (6.6 mmol) DCC dissolved in 5 mL dichloromethane were added dropwise. The reaction was allowed to stir at room temperature for 60 h when a fawn coloured suspension occurred. To this 850 mg (6.6 mmol) DIEA dissolved in 1 mL dry dichloromethane was dropped and allowed to stir for 24 h. The mixture was extracted by 50 mL dichloromethane, the organic phase washed with twice 20 mL 1 % HCl and brine. The organic phase was dried over Na_2SO_4 and evaporated. The product was purified by Flash-chromatography on silica gel to yield 79 % **10** as a yellow-white solid.

Method B: 175 mg (1 mmol) Indole-3-yl acetic acid were dissolved in 10 mL dry dichloromethane at room temperature when 210 mg (1 mmol PCl_5 are added and stirred for 30 min (colour changed to red). A suspension consisting of 300 mg (1 mmol) **9**, 155 mg pyridine (2 mmol) and 140 mg K_2CO_3 in 5 mL dry dichloromethane were added. Immediately an orange salt precipitates. After 24 h stirring at room temperature, further 155 mg pyridine are added and the mixture stirred for 140 h. 10 mL dichloromethane are added, the organic phase washed with twice 20 mL 1 % HCl and brine. The organic phase was dried over Na_2SO_4 and evaporated. The product was purified by Flash-chromatography on silica gel to yield 42 mg (0.11 mmol) of **10** as a white solid and 22 % 80 mg (0.22 mmol) of **11** as a brown solid.

^{1}H-NMR (DMSO-d_6): δ [ppm] = 10.9 (bs, 1H, indole-NH), 8.2 (t, J = 5.45, 1H, amide-NH), 7.5 (d, J = 7.60, 1H, indole-H), 7.4 (d, J = 7.68, 1H, indole-H), 7.3 (bs, 3H, indole-1H und Ph-2H), 7.1 (m, 1H, indole-H), 7.0 (m, 1H, indole-H), 4.7 (d, J = 5.45, 2H, CH_2), 3.8 (s, 6H, meta-{O}CH_3), 3.7 (s, 3H, para-{O}CH_3), 3.6 (s, 2H, CH_2).

^{13}C-NMR (DMSO-d_6): δ [ppm] = 194.7 (C=O), 17.,5 (amide-C=O), 153.2 ($C_{quart.}$), 142.5 ($C_{quart.}$), 136.5 ($C_{quart.}$), 130.6 ($C_{quart.}$), 127.6 ($C_{quart.}$), 124.3 (CH), 121.3 (CH), 119.1 (CH), 118.7 (CH), 111.7

(CH), 109.1 ($C_{quart.}$), 105.8 (CH), 60.5 (para-{O}CH_3), 56.4 (meta-{O}CH_3), 46.5 (CH_2), 32.9 (CH_2).

(**11**) 3-{[5-(3,4,5-Trimethoxyphenyl)-1,3-oxazol-2-yl]methyl}-1*H*-indole.

^{1}H-NMR: (DMSO-d_6) δ [ppm] = 11.0 (bs, 1H, indole-NH), 7.6 (d, J = 7.70, 1H, indole-H), 7.5 (s, 1H, oxazole-H), 7.4 (d, J = 8.11, 1H, indole-H), 7,3 (d, J = 2.47, 1H, indole-H), 7.1-7.0 (bm, 2H, indole-H), 6.9 (s, 2H, Ph-H), 4.3 (s, 2H, CH_2), 4.8 (s, 6H, meta-{O}CH_3), 4.7 (s, 3H, para-{O}CH_3).

^{13}C-NMR (acetone-d_6) δ [ppm] = 163.1 (oxazole-$C_{quart.}$), 153.7 ($C_{quart.}$), 150.6 ($C_{quart.}$), 137.9 ($C_{quart.}$), 136.6 ($C_{quart.}$), 127.2 ($C_{quart.}$), 124.1 (CH), 123.6 ($C_{quart.}$), 122.6 (CH), 121.5 (CH), 119.0 (CH), 118.9 (CH), 111.9 (CH), 108.7 ($C_{quart.}$), 101.6 (CH), 60.5 (para-{O}CH_3), 56.4 (meta-{O}CH_3), 24.8 (CH_2).

(**12**) N-[2-(1*H*-Indol-3-yl)ethyl]-2-(3,4,5-trimethoxyphenyl)acetamide.

11.5 g (50 mmol) 3,4,5-Trimethoxyphenylacetic acid were dissolved in 300 mL dichloromethane and 10.5 g (65 mmol) CDI were added and the mixture was stirred for 1h. Then a solution of 8.0 g tryptamine in 100 mL dichloromethane was added and the reaction stirred for 2 h. The organic solvent was evaporated and the product purified by Flash-chromatography on silica gel to yield 98 % (18.4 g, 49.8 mmol) as a pale yellow oil which was dried under vacuum to a foamy brittle solid.

^{1}H-NMR ($CDCl_3$): δ [ppm] = 8.31 (s, 1 H, indole NH), 7.53 (d, 1 H, J = 7.7 Hz, indole 4-H), 7.34 (d, 1 H, J = 7.8 Hz, indole 7-H), 7.18 (m, 1 H, indole 6-H), 7.09 (m, 1 H, indole 5-H), 6.74 (d, 1 H, J = 2.1 Hz, indole 2-H), 6.31 (s, 2 H, *ortho*-PhH), 5.57 (s, 1 H, NH), 3.83 (s, 6 H, *meta*-{O}CH_3), 3.71 (s, 3 H, *para*-{O}CH_3), 3.53 (q, 1 H, J_{NH} = 5.9, J_{HH} = 6.4 Hz, 1`- H), 3.44 (s, 1 H, 2-H), 2.90 (t, 1 H, J = 6.4 Hz, 2`-H).

^{13}C-NMR ($CDCl_3$): δ [ppm] = 170.8 (C 1), 153.4 (2 C, *meta*-PhC), 136.9 (indole C-7a), 136.4 (*para*-PhC), 130.5 ($PhC_{quart.}$), 127.2 (indole C-2), 122.1 (indole C-3), 122.03 (indole C-6), 119.3

(indole C-5), 118.5 (indole C-4), 112.3 (indole C-3), 111.3 (indole C-7), 106.2 (2 C, *ortho*-PhC), 60.8 (*para*-C{O}CH_3), 56.00 (2 C, *meta*-C{O}CH_3), 44.1 (C-1`), 39.6 (C-2), 24.9 (C-2`).

(**13**) N-2-(1*H*-Indol-3-yl)-2-oxoethyl-2-(3,4,5-trimethoxyphenyl)acetamide.

18.3 g of compound **12** were dissolved in 300 mL THF, 30 mL water was added and the mixture cooled in an ice bath. At this temperature a solution of 19.2 g DDQ (1.7 equ.) dissolved in 50 mL THF was added dropwise. The colour turned to black-red and a precipitation occurs. After 2 h 100 mL water was added and the mixture kept in a freezer over night. The product was filtered off, washed with ethanol and diethylether to yield 58 % 11.12 g (29 mmol) of **13** as a white solid.

^{1}H-NMR (DMSO-d_6): δ [ppm] = 12.00 (s, 1 H, indole NH), 8.41 (s, 1 H, indole 2-H), 8.33 (m, 1 H, NH), 8.14 (m, 1 H, indole 4-H), 7.48 (m, 1 H, indole 7-H), 7.20 (m, 2 H, indole 5-H, 6-H), 6.67 (s, 2 H, *ortho*-PhH), 4.48 (d, 1 H, J = 5.7 Hz, 1`-H), 3.77 (s, 6 H, *meta*-{O}CH_3), 3.62 (s, 3 H, *para*-{O}CH_3), 3.47 (s, 1 H, 2-H).

^{13}C-NMR (DMSO-d_6): δ [ppm] = 190.2 (C=O), 170.3 (C-1), 152.5 (2 C, *meta*-PhC),136.3 (*para*-PhC), 135.9 (indole C-7a), 133.5 ($PhC_{quart.}$), 131.9 (indole C-2), 125.3 (indole C-3a), 122.8 (indole C-6), 121.4 (indole C-5), 121.0 (indole C-4), 113.9 (indole C-7), 112.1 (indole C-3), 106.3 (2 C, *ortho*-PhC), 59.9 (*para*-{O}CH_3), 55.7 (2 C, *meta*-{O}CH_3), 47.7 (C-1´), 42.4 (C-2).

(**14**) 3-[2-(3,4,5-Trimethoxybenzyl)-1,3-oxazol-5-yl]-1*H*-indole.

To 150 mg of compound **13** polyphosphoric acid (3 g, PPA) were added and the mixture heated in an oil bath to 100 °C (stirred mechanically). After 2 h the reaction was cooled in an ice bath and water was added carefully. The mixture was extracted by ethylacetate, the organic phase dried over Na_2SO_4 and evaporated. The product was purified by Flash-chromatography on silica gel to yield 58 % of **14** as a pale white solid.

^{1}H-NMR (DMSO-d_6): δ [ppm] = 11.5 (s, 1 H, indole NH), 7.8 (d, 1 H, indole 2-H), 7.7 (d, 1 H), 7.45 (d, 1 H, indole 4-H), 7.3 (s, 1 H, oxazole H), 7.15 (m, 2 H, indole 5-H, 6-H), 6.7 (s, 2 H, *ortho*-PhH), 4.1 (d, 2 H, CH_2), 3.75 (s, 6 H, *meta*-{O}CH_3), 3.65 (s, 3 H, *para*-{O}CH_3).

^{13}C-NMR (DMSO-d_6): δ [ppm] = 160.8, 153.1 (2 C, *meta*-PhC), 148.2, 136.4 (indole C-7a), 132.0 ($PhC_{quart.}$), 123.3, 120.7, 119.9, 112.23, 106.4, 103.8, 60.1 (*para*-{O}CH_3), 56.3 (2 C, *meta*-{O}CH_3), 34.2, CH_2).

(**15**) N-2-(N-[2-(1-{[2-(Trimethylsilyl)ethoxy]methyl}1*H*-indol-3-yl)-2-oxoethyl-2-(3,4,5-trimethoxyphenyl)acetamide. [38]

A dry 100 mL three necked round bottom flask was charged with 1530 mg (4 mmol) of compound **13** and 400 mg NaH (60 % dispersion) and cooled to -20 °C. At this temperature 50 mL dry THF was added to form a pale yellow suspension. Over 2 h the reaction was allowed to warm to room temperature and again cooled to -20 °C when 890 µl TIPSCl were added. The cooling was removed and the colour of the reaction changed to orange. After 1 h the reaction was quenched with saturated NH_4Cl solution, extracted with ethylacetate, the organic phase separated, dried over Na_2SO_4 and evaporated. The product was purified by Flash-chromatography on silica gel to yield 37 % of **15** as a solid.

^{1}H-NMR ($CDCl_3$): δ [ppm] = 7.75 (m, 1 H, indole 4-H), 7.45 (m, 1 H, indole 7-H), 7.12 (m, 2 H, indole 9-H, NH), 6.72 (d, J = 9.85 Hz, 1 H, 2´-H), 6.52 (s, 2 H, *ortho*-PhH), 3.88 (s, 6 H, *meta*-{O}CH_3), 3.86 (s, 3 H, *para*- {O}CH_3), 3.65 (s, 1 H, 2-H), 1.62 (m, 6 H, SiC<u>H</u>CH_3), 1.12 (s, 18 H, Ind.SiCH<u>CH_3</u>), 0.85 (s,18 H, 2`-SiCH<u>CH_3</u>).

(**16**) N-2-(1-Phenylsulfonyl-1*H*-indol-3-yl)-2-oxoethyl-2-(3,4,5-trimethoxyphenyl)acetamide.

In a 100 mL dry round bottom flask 1530 mg (4 mmol) of compound **13** were suspended in 50 mL absolute ethanol and 280 mg (5 mmol) KOH were added. The flask was connected to a rotating evaporator and rotated at 50 °C until a clear yellow solution occurs. The organic solvent was

evaporated to yield a bright yellow solid which was dissolved in dry acetone and 710 mg (4 mmol) of phenylsulfonylchloride was added. The reaction was stirred for 1 h and the organic solvent evaporated. The residue was extracted by ethylacetate, the organic phase dried over Na_2SO_4 and evaporated. The product was purified by Flash-chromatography on silica gel to yield 74 % of **16** as a pale yellow solid.

^{1}H-NMR ($CDCl_3$): δ [ppm] = 8.36 (s, 1 H, indole 2-H), 8.23 (m, 1 H, indole 7-H), 7.97 (m, 3 H, indole 4-H, 2 *ortho*-PhS-H), 7.53 (m, 3 H, indole 6-H, 2 *meta*-PhS.-H), 7.38 (m, 2 H, indole 5-H, *para*-PhS-H), 6.70 (t, 1H, NH), 6.58 (s, 2 H, *ortho*-PhH), 4.68 (d, 2 H, J = 4.7 Hz, 1`-H), 3.89 (s, 6 H, *meta*-{O}CH_3), 3.82 (s, 3 H, *para*-{O}CH_3), 3.63 (s, 2 H).

^{13}C-NMR ($CDCl_3$): δ [ppm] = 189.5 (C-2`), 171.1 (C-1), 153.5 (2 C, *meta*-PhC), 137.2 ($PhSC_{quart.}$), 137.1 (indole C-7a), 134.7 (*para*-PhSC),131.8 (indole C-2), 130.1 ($PhC_{quart.}$), 129.7 (2 C, *meta*-PhSC), 127.1 (2 C, *ortho*-PhSC), 127.0 (indole C-3a), 126.1 (indole C-2), 125.1 (indole C-5), 122.6 (indole C-6), 118.6 (indole C-3), 113.1 (indole C-7), 106.3 (2 C, *ortho*-PhC), 60.8 (*para*-{O}CH_3), 56.1 (2 C, *meta*-{O}CH_3), 46.7 (C -1`), 43.8 (C 2).

(**17**) 3-[1-(Phenylsulfonyl)-1*H*-indol-3-yl]-4-(3,4,5-trimethoxyphenyl)-1*H*-pyrrole-2,5-dione.

The compound was prepared from 140 mg 0.27 mmol of **16** following general procedure to yield **17** after Flash chromatography purification 60 % (0.17 mmol) as a deep red solid.

^{1}H-NMR (acetone-d_6): δ [ppm] = 8.84 (s, 1H, indole 2-H), 8.51 (m, 1 H, indole 7-H), 8.06 (m, 3 H, indole 4-H, ortho-PhSH), 7.68 (m, 3 H, indole 6-H, *meta*-PhSH), 7.45 (m, 2 H, indole 5-H, *para*-PhSH), 6.53 (s, 2 H, *ortho*-PhH), 5.92 (s, 1 H, NH), 3.58 (s, 3 H, *para*-{O}CH_3), 3.53 (s, 6 H, *meta*-{O}CH_3).

(**18**) N-(2-Oxo-2-(1-(2-trimethylsilyl)ethoxy)methyl)-1*H*-indol-3-yl)ethyl-2-(3,4,5-trimethoxyphenyl)acetamide.

In a dry 100 mL three necked round bottom flask 1530 mg (4 mmol) of compound **13** were suspended in 50 mL absolute THF and cooled to 0 °C. Through a septum 2 mL (4 mmol) of a 2 M sodium hexamethyl silylamide (NaHMDS) was added and the colour changed to brown. After 1 h stirring 700 mg (4 mmol) SEMCl was added. The progress of the reaction was monitored by TLC, after 2 h the reaction was quenched with a saturated NH_4Cl solution, extracted by ethylacetate, the organic phase separated, dried over Na_2SO_4 and evaporated. The product was purified by Flash-chromatography on silica gel to yield 84 % 1.74 g (3.4 mmol) of **18** as a white solid.

^{1}H-NMR ($CDCl_3$): δ [ppm] = 8.20 (s, 1 H, indole 4-H), 8.10 (s, 1 H, indole 2-H), 7.52 (d, 1 H, indole 7-H), 7.2-7.4 (m, 1H), 6.8-7.0 (m, 3 H, NH), 6.59 (d, 1H), 5.6 (s, 2 H, *ortho*-PhH), 3.88 (s, 3 H, *para*-{O}CH_3), 3.55 (s, 6 H, *meta*-{O}CH_3), 1.30 (m, 2 H, J = 8.1 Hz, 1``-H), 0.89 (t, 6 H, J = 8.1 Hz, 2``-H), 0.00 (s, 9 H, $SiCH_3$).

^{13}C-NMR ($CDCl_3$): δ [ppm] = 188.8 (C-2`), 180.0 (C-1), 153.5 (2 C, *meta*-PhC), 137.2 (indole C-7a), 136.7 (*para*-PhC), 134.1 (indole C-2), 130.2 ($PhC_{quart.}$), 126.3 (indole C-3a), 124.1 (indole C-6), 123.4 (indole C-4), 122.1 (indole C-5), 114.6 (indole C-3), 110.7 (indole C-7), 106.4 (2 C, *ortho*-PhC), 76.04 (indole NCH_2), 66.6 (C-1``), 60.8 (*para*-{O}$CH_3$), 56.1 (2 C, *meta*-{O}$CH_3$), 46.5 (C-1), 43.9 (C-2), 17.7 (C-2``), 0.00 (3 C, $SiCH_3$).

(**19**) 3-(3,4,5-Trimethoxyphenyl)-4-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-indol-3-yl)-1,5-dihydro-2*H*-pyrrole-2-one.

The compound was prepared from 260 mg 0.5 mmol of **18** following general procedure to yield 160 mg 66 % (0.33 mmol) of **19** as a bright white solid after Flash chromatography purification (chromatogram see supporting information).

^{1}H-NMR (DMSO-d_6): δ [ppm] = 8.34 (bs, 1 H, NH), 7.58 (d, 1 H, J = 8.3 Hz, indole 7-H), 7.3 (m, 2 H), 7,1 (m, 2 H, J = 7.2 Hz), 6.70 (s, 2 H, ortho-PhH), 5.4 (s, 2 H, NCH_2), 4.58 (s, 2H), 3.9 (s, 3 H, *para*-{O}CH_3), 3.7 (s, 6 H, *meta*-{O}CH_3), 3.45 (t, 2H, J = 7.8 Hz), 0.81 (t, 2 H, J = 7.8 Hz, 2´´-H), 0 (s, 9 H, $SiCH_3$).

^{13}C-NMR ($CDCl_3$): δ [ppm] = 176.3 (C-2), 154.8 (2 C, *meta*-PhC), 148.0 (C-4), 139.3 (indole C-3a), 138.1 (*para*-PhC), 130.3 (indole C-2), 129.3 (C-3), 127.2 ($PhC_{quart.}$), 124.5 (indole C-6), 122.9 (indole C-5), 122.7 (indole C-4), 112.0 (indole C-7), 111.4 (indole C-3), 108.2 (2 C, *ortho*-PhC), 77.1 (N-C), 67.66 (C-2´), 62.3 (*para*-{O}CH_3), 57.4 (2 C, *meta*-{O}CH_3), 50.6 (C-5), 19.1 (C-1´), 0.0 ($SiCH_3$).

(**19a**) 3-(3,4,5-Trimethoxyphenyl)-4-(1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-indol-3-yl)-1*H*-pyrrole-2,5-dione.

A dry 50 mL round bottom flask under argon was charged with 250 mg of **19**. Through a septum 2 mL of a 1M TBAF solution in THF was added when the colour immediately turned to deep red. After 3 min no starting material could be detected by TLC. Compound **19a** was isolated by Flash chromatography to yield 35 % of **19a** as an orange solid.

^{1}H-NMR ($CDCl_3$): δ [ppm] = 8.1 (m, 1 H), 7.95 (s, 1 H, NH), 7.49 (d, 1 H, J =8.2 Hz, indole 4-H), 7.19 (m, 1 H, J = 7.8 Hz, indole 5-H), 6.89 (m, 1 H, J = 7.8 Hz, indole 6-H), 6.81 (s, 2 H, *ortho*-PhH), 6.48 (m, 1 H, J = 8.2), 5.56 (s, 2 H, N-CH_2), 3.86 (s, 3 H, *para*-{O}CH_3), 3.54 (s, 6 H, *meta*-{O}CH_3), 3.4 (t, 2 H), 0.9 (t, 2 H), 0.00 (s, 9 H, $SiCH_3$).

^{13}C-NMR ($CDCl_3$): δ [ppm] = 172.6 (C-2), 172.3 (C-5), 153.8 (*meta*-PhC), 140.2 (C-3),137.7 (*para*-PhC), 134.6 (indole C-2), 132.4 (indole C-3a), 130.9 (C-4), 126.1 ($PhC_{quart.}$), 124.3 (indole C-5), 123.9 (indole C-4), 122.3 (indole C-6),111.6 (indole C-7), 108.9 (2 C, *ortho*-PhC), 106.5 (indole C-3), 77.2 (N-C), 67.4 (C-2´), 62.0 (*para*-{O}CH_3), 56.9 (2 C, *meta*-{O}CH_3), 18.75 (C-1´).

(**20**) 4-[1-(Hydroxymethyl)-1*H*-indol-3-yl]-3-(3,4,5-trimethoxyphenyl)-1,5-dihydro-2*H*-pyrrole-2-one.

In a 50 mL round bottom flask 200 mg of **19** and 0.5 mL HCl were heated in 10 mL ^{t}BuOH under reflux. The progress of the reaction was monitored by TLC, after 30 min the reaction was quenched with a saturated NaCl solution, extracted by ethylacetate, the organic phase separated, dried over Na_2SO_4 and evaporated. The product was purified by Flash-chromatography on silica gel

(chromatogram see supporting information) to yield 46 % of compound **20** (and 10 % of compound **2** and 16 % of compound **24**).

^{1}H-NMR ($CDCl_3$): δ [ppm] = 7.5 (d, 1 H, indole 7-H), 7.25 (m, 2 H, indole-H), 6.95 (m, 2H, indole-H), 6.70 (s, 2 H, ortho-PhH), 5.5 (s, 2 H, NCH_2), 4.37 (s, 2 H, CH_2), 3.8 (s, 3 H, *para*-{O}CH_3), 3.55 (s, 6 H, *meta*-{O}CH_3).

^{13}C-NMR ($CDCl_3$): δ [ppm] = 174.79 (C=O), 171.1 (C_q), 153.11, (2 CH, *meta*-PhC), 147.1 (C_q), 137.8 (indole CH), 136.0 (C_q), 128.6 (C_q), 127.8 (CH), 126.9 (C_q), 125.5 (C_q), 122.9 (indole CH), 121.2 (indole CH), 110.2 (C_q), 109.7 (indole CH), 106.8 (2 CH, *ortho*-PhC), 69.8 (CH_2), 60.8 (*para*-{O}CH_3), 55.9 (2 C, *meta*-{O}CH_3), 49.0 (CH_2).

(**21**) 4-[1-(Methoxymethyl)-1*H*-indol-3-yl]-3-(3,4,5-trimethoxyphenyl)-1,5-dihydro-2*H*-pyrrole-2-one.

In a 50 mL round bottom flask 290 mg of **19** and 100 µl HCl were heated in 20 mL metanol under reflux. The progress of the reaction was monitored by TLC, after 30 min the reaction was quenched with a saturated NaCl solution, extracted by ethylacetate, the organic phase separated, dried over Na_2SO_4 and evaporated. The product was purified by Flash-chromatography on silica gel to yield 61 % of compound **21** as a white solid.

^{1}H-NMR ($CDCl_3$): δ [ppm] = 7.47 (s, 1 H, indole 2-H), 7.21-7.07 (m, 4 H, NH, indole 7-, indole -6-H, indole 5-H), 6.75 (s, 2H), 5.37 (s, 2 H, NCH_2), 4.58 (s, 2 H), 3.85 (s, 3 H, *para*-{O}CH_3), 3.67 (s, 6 H, *meta*-{O}CH_3), 3.20 (s, 3 H, 1´-CH_3).

^{13}C-NMR ($CDCl_3$): δ [ppm] = 174.9 (C-2), 153.4 (2 C, *meta*-PhC), 146.5 (C-4), 137.8 (indole C-7a), 136.5 (para-PhC), 128.9 (indole C-6), 128.2 (indole C-3**)**, 125.9 ($PhC_{quart.}$)**,** 123.1 (indole C-2), 121.5 (indole C-5), 121.1 (indole C-4), 110.5 (indole C-3), 110.0 (indole C-7), 106.6 (2 C, *ortho*-PhC), 77 (NCH_2), 60.5 (*para*-{O}CH_3), 55.6 (2 C, *meta*-{O}CH_3), 49.1 (C-1´).

(**22**) 4-[1-(Ethoxymethyl)-1*H*-indol-3-yl]-3-(3,4,5-trimethoxyphenyl)-1,5-dihydro-2*H*-pyrrole-2-one.

In a 50 mL round bottom flask 290 mg of **19** and 100 µl HCl were heated in 20 mL ethanol under reflux. The progress of the reaction was monitored by TLC, after 75 min the reaction was quenched with a saturated NaCl solution, extracted by ethylacetate, the organic phase separated, dried over Na_2SO_4 and evaporated. The product was purified by Flash-chromatography on silica gel to yield 45 % of compound **22** as a white solid.

^{1}H-NMR (DMSO-d_6): δ [ppm] = 8.4 (bs, 1 H, pyrrole N-H), 7.8 (s, 1 H, indole 2-H), 7.5 (d, 1 H, indole 7-H), 7.15 (t, 1H, indole-6-H), 6.9 (m, 2H, indole 5/4-H), 6.6 (s, 2 H, Phe-CH), 5.5 (s, 2H, CH_2), 4.4 (s, 2H, CH_2), 3.65 (s, 3 H, *para*-{O}CH_3), 3.4 (s, 6 H, *meta*-{O}CH_3), 3.3 (q, 2H, CH_2), 1.0 (t, 3 H, CH_3).

^{13}C-NMR (DMSO-d_6): δ [ppm] = 184.8 (C=O), 173.2 (2 C_q, *meta*-PhC), 152.7 (C_q), 145.9 (C_q), 137.3 (indole C-7a), 136.8 (para-PhC), 130.1 (indole C-6), 128.8 (indole C-3**)**, 127.8, 125.3 ($PhC_{quart.}$)**,** 122.6 (indole C-2), 121.4 (indole C-5), 122.6 (indole C-4), 111.1 (indole C-3), 110.0 (indole C-7), 107.2 (2 C, *ortho*-PhC), 75.6 (NCH_2), 63.6 (CH_2), 60.4 (*para*-{O}CH_3), 55.8 (2 C, *meta*-{O}CH_3), 48.4 (CH_2), 15.05 CH_3).

(**23**) 4-[1-(Isopropoxymethyl)-1*H*-indol-3-yl]-3-(3,4,5-trimethoxyphenyl)-1,5-dihydro-2*H*-pyrrole-2-one.

In a 50 mL round bottom flask 250 mg of **19** and 100 µl HCl were heated in 20 mL isopropanol under reflux. The progress of the reaction was monitored by TLC, after 60 min the reaction was quenched with a saturated NaCl solution, extracted by ethylacetate, the organic phase separated, dried over Na_2SO_4 and evaporated. The product was purified by Flash-chromatography on silica gel (chromatogram see supporting information) to yield 83 % of compound **23** as a white solid.

^{1}H-NMR ($CDCl_3$): δ [ppm] = 7.5 (d, 1 H, indole H), 7.0-7.3 (m, 4 H, indole H), 6.7 (s, 2 H, Phe-CH), 5,45 (s, 2H, CH_2), 4.6 (s, 2H, CH_2), 3.9 (s, 3 H, *para*-{O}CH_3), 3.7 (s, 6 H, *meta*-{O}CH_3), 3.6 (q, 1H, 1´-CH), 1.0 (d, 6 H, 1´-CH_3).

^{13}C-NMR ($CDCl_3$): δ [ppm] = 174.9 (C=O), 153.3 (2 C_q, *meta*-PhC), 146.6 (C_q), 137.7 (C_q), 136.4 (indole C-7a), 128.7 (para-PhC), 128.2 (indole C-6), 127.9 (indole C-3**)**, 125.8, ($PhC_{quart.}$)**,** 122.9, indole C-H, 121.4 (indole C-H), 121.0 (indole C-H), 110.5 (indole C-3_q), 109.8 (indole C-H), 106.5 (2 C, *ortho*-PhC), 74.1 (NCH_2), 69.6 (CH), 60.7 (*para*-{O}CH_3), 55.9 (2 C, *meta*-{O}CH_3), 49.0 (CH_2), 21.8 (2 C, CH_3).

(**24**) 4-[1-(Tert-butoxymethyl)-1*H*-indol-3-yl]-3-(3,4,5-trimethoxyphenyl)-1,5-dihydro-2*H*-pyrrole-2-one.

^{1}H-NMR ($CDCl_3$): δ [ppm] = 7.5 (d, 1 H, indole H), 7.0-7.3 (m, 4 H, indole H), 6.7 (s, 2 H, Phe-CH), 4.95 (s, 2H, 1´-CH_2), 4.6 (s, 2H, pyrrole CH_2), 3.9 (s, 3 H, *para*-{O}CH_3), 3.7 (s, 6 H, *meta*-{O}CH_3), 1.2 (d, 9 H, 1´-CH_3).

(**25**) 4-[1-(Phenoxymethyl)-1*H*-indol-3-yl]-3-(3,4,5-trimethoxyphenyl)-1,5-dihydro-2*H*-pyrrole-2-one.

In a 50 mL round bottom flask 250 mg of **19** and 100 µl HCl were heated in 10 mL phenol under reflux. The progress of the reaction was monitored by TLC, after 60 min the reaction was quenched with a saturated NaCl solution, extracted by ethylacetate, the organic phase separated, dried over Na_2SO_4 and evaporated. The product was purified by Flash-chromatography on silica gel (for chromatogram see supporting information) to yield 87 % of compound **25** as a light brown solid.

^{1}H-NMR (DMSO-d_6): δ [ppm] = 9.8 (bs, 1H, pyrrole NH), 8.3 (s, 1H), 7.7 (s, 1H), 7.5 (m, 1 H), 7.0-7.2 (m, 2 H), 6.8 (m, 3 H), 6.6-6.7 (m, 4H), 5.25 (d, 2H, CH_2), 4.4 (s, 2H, CH_2), 3.6 (s, 3 H, *para*-{O}CH_3), 3.4 (s, 6 H, *meta*-{O}CH_3).

^{13}C-NMR (DMSO-d_6): δ [ppm] = 173.4 (C=O), 157.1, 155.1, 152.7 (2 C_q, *meta*-PhC), 146.3 (C_q), 137.2 (C_q), 136.7, 129.0, 128.7, 128.5, 126.9, 124.9, 123.7, 122.2, 121.4, 120.1, 119.3, 115.5, 111.0, 109.0 (Phe-C), 107.1 (Phe-C), 69.0 (NCH_2), 60.4 (*para*-{O}CH_3), 55.8 (2 C, *meta*-{O}CH_3), 48.3 (CH_2).

(**26**) 4-{1-[(Benzyloxy)methyl]-1*H*-indol-3-yl}-3-(3,4,5-trimethoxyphenyl)-1,5-dihydro-2*H*-pyrrole-2-one.

In a 50 mL round bottom flask 250 mg of **19** and 100 µl HCl were heated in 10 mL benzylalcohol under reflux. The progress of the reaction was monitored by TLC, after 20 min the reaction was quenched with a saturated NaCl solution, extracted by ethylacetate, the organic phase separated, dried over Na_2SO_4 and evaporated. The product was purified by Flash-chromatography on silica gel (for chromatogram see supporting information) to yield 93 % of compound **26** as a pale yellow solid.

^{1}H-NMR (DMSO-d_6): δ [ppm] = 8.35 (bs, 1H, pyrrole NH), 7.8 (s, 1H), 7.6 (d, 1H), 7.1-7.4 (m, 6 H), 6.75-6.9 (m, 2 H), 6.7 (s, 2H, PheH), 5.65 (d, 2H, CH_2), 4.3-4.5 (2#s, 4H, CH_2), 3.6 (s, 3 H, *para*-{O}CH_3), 3.35 (s, 6 H, *meta*-{O}CH_3).

(**27**) N-2-(N-[(2,2-Dimethyl-1,3-dioxolan-4-yl)methyl]-1*H*-indol-3-yl)-2-oxoethyl-2-(3,4,5-trimethoxyphenyl)acetamide.

In a dry 50 mL three necked round bottom flask 765 mg of **13** and 450 mg of 4-(bromomethyl)-2,2-dimethyl-1,3-dioxolane and 1000 mg K_2CO_3 were heated in 15 mL dry DMF under reflux. The progress of the reaction was monitored by HPLC, after 2h the reaction was quenched with a saturated NaCl solution, extracted by ethylacetate, the organic phase separated, dried over Na_2SO_4 and evaporated with toluol in order to remove DMF. The product was purified by Flash-chromatography on silica gel (for chromatogram see supporting information) to yield 48 % of compound **27** as brownish oil.

^{1}H-NMR ($CDCl_3$): δ [ppm] = 8.3 (m, 1 H), 8.0 (m, 3H), 7.9 (s, 1H, indole 2´H), 7.3-7.4 (m, 3 H, indole H), 6.9 (bs, 1H), 6.55 (s, 2 H, Phe-CH), 4.61 (s, 2H, CH_2), 4.5 (m, 1H, $CH_{aliphat.}$), 4.1-4.3 (m, 3H, $CH_{aliphat.}$), 3.9 (s, 6 H, *meta*-{O}CH_3), 3.8 (s, 3 H, *para*-{O}CH_3), 3.7-3.6 (m, 3H, $CH_{aliphat.}$, CH_2), 1.4 (s, 3 H, $CH_{3\ aliphat.}$), 1.3 (s, 3 H, $CH_{3\ aliphat.}$).

^{13}C-NMR ($CDCl_3$): δ [ppm] = 188.8 (C=O), 163.0 (C=O), 153.9 (2 C_q, *meta*-PhC), 137.6, 137.5 (C_q), 135.6 (indole CH), 130.7 (C_q), 126.4 (C_q), 124.2, 123.5, 122.7 (CH), 114.6, 110.7 (C_q), 110.3 (indole CH), 106.8 (2 C, *ortho*-PhC), 74.5 (CH), 66.9 (CH_2), 61.2 (*para*-{O}CH_3), 56.6 (2 C, *meta*-{O}CH_3), 49.6 (CH_2), 46.9 (CH_2), 44.3 (CH_2), 27.2 (CH_3), 25.6 (CH_3).

(28) 4-{1-[(2,2-Dimethyl-1,3-dioxolan-4-yl)methyl]-1*H*-indol-3-yl}-3-(3,4,5-trimethoxyphenyl)-1,5-dihydro-2*H*-pyrrole-2-one**.**

^{1}H-NMR ($DMSO-d_6$): δ [ppm] = 8.3 (bs, 1H, pyrrole-NH), 7.6 (s, 1H, indole-H), 7.5 (d, 1H), 7.1 (m, 1H), 6.9 (m, 2H), 6.6 (s, 2H, ortho-Ph-H), 4.4 (s, 2H, CH_2), 4.3-4.4 (m, 3H), 4.0 (t, 1H), 3,7 (s, 3H, para-{O}CH_3), 3.6 (m, 1H), 3.45 (s, 6H, meta-{O}CH_3), 1.2 (s, 6H, CH_3).

^{13}C-NMR ($DMSO-d_6$): δ [ppm] = 173.4 (C=O), 152.8 ($2C_{quart.}$), 146.1 ($C_{quart.}$), 137.2 ($C_{quart.}$), 137.1 ($C_{quart.}$), 136,4 ($C_{quart.}$), 130.7 (CH), 127,0 ($C_{quart.}$), 124.8 ($C_{quart.}$), 122.1 (CH), 121.3 (CH), 120.2 (CH), 110.96 (CH), 109.26 (PH-CH), 108.99, 107.1 (CH), 74.8 (CH), 66.3 (CH_2), 60,4 (para-{O}CH_3), 55,9 (meta-{O}CH_3), 48.5, 48.3 (CH_2), 26.8, 26.6 (CH_3).

(**29**) 4-[1-(2,3-Dihydroxypropyl)-1*H*-indol-3-yl]-3-(3,4,5-trimethoxyphenyl)-1,5-dihydro-2*H*-pyrrole-2-one.

In a 50 mL round bottom flask 250 mg of **28** were dissolved in 10 mL dichloromethane and 50 µl HCl were added. After 30 min a bulky white solid precipitated. The reaction was cooled after 3 h to complete the precipitation which was filtered off, washed with dichloromethane and diethylether to yield 96 % of **29** as a white solid.

^{1}H-NMR (DMSO-d_6): δ [ppm] = 7.7 (s, 1 H, indole 2´H), 7.5 (d, 1 H, indole 4´H), 7,1 (m, 1 H, indole 5´H), 6.8 (m, 2H, indole H), 6.7 (s, 2H, PheH), 6.5 (bs, 2H, OH), 4.4 (s, 2H, pyrrole CH_2), 4.3 (dd, $1H_{aliphat.}$), 4.0 (q, $1H_{aliphat.}$), 3.75 (m, $1H_{aliphat.}$), 3.6 (s, 3 H, *para*-{O}CH_3), 3.5 (s, 6H, *meta*-{O}CH_3), 3.3 (m, 2H, $CH_{2\ aliphat.}$).

^{13}C-NMR (DMSO-d_6): δ [ppm] = 173.47, 152.73 (2 C-O), 146.40 ($C_{quart.}$), 137.2, 137.1 ($C_{quart.}$), 131.1 (CH), 129.1, 126.5, 124.8 ($C_{quart.}$), 121.9 (CH), 121.3 (CH), 119.95 (CH), 110.99 (CH), 108.6 (2 CH, *ortho*-PhC), 107.27 (CH), 70.93 (CH), 63.61 (CH_2), 60.4 (*para*-{O}CH_3), 55.88 (2 C, *meta*-{O}CH_3), 49.5 (CH_2), 48.4 (CH_2).

(**30**) 2-(N-Methyl-1*H*-indol-3-yl)-*N*-[2-(3,4,5-trimethoxyphenyl)2-oxoethyl]acetamide.

In a dry 100 mL three necked round bottom flask 310 mg N-methyl-indolacetic acid, 500 mg **9** and 250 mg HOBt were dissolved in 5 mL dry dichloromethane and cooled in an ice bath. At this temperature a solution of 440 mg DCC in 5 mL dry dichloromethane was added dropwise and the reaction stirred for 60 h at room temperature. Then 420 mg DIEA in 2 mL dry dichloromethane was added dropwise and the reaction turned to orange-brown. After 4.5 h, the precipitation (dicyclohexylurea) was filtered off and washed with 20 mL dichloromethane. The filtrate was washed with 30 mL 1 % HCl, and brine. The organic phase was separated, dried over Na_2SO_4 and evaporated to yield 600 mg 93 % of **30** as a yellowish solid.

^{1}H-NMR (DMSO-d_6): δ [ppm] = 8.2 (t, J = 5.5, 1H, amide-NH), 7.6 (d, J = 7.55, 1H, indole-H), 7.4 (d, J = 7.98, 1H, indole-H), 7.24 (s, 2H, Ph-2H), 7.20 (s, 1H, indole-H), 7.1 (m, 1H, indole-H), 7.0 (m, 1H, indole-H), 4.6 (d, J = 5.33, 2H, CH_2), 3.8 (s, 6H, meta-{O}CH_3), 3.7 (d, 6H, para-{O}CH_3/N-CH_3), 3.6 (s, 2H, CH_2).

^{13}C-NMR (DMSO-d_6): δ [ppm] = 194.7 (C=O), 171.3 (Amid-C=O), 153.2 ($C_{quart.}$), 142.4 ($C_{quart.}$), 136.9 ($C_{quart.}$), 130.6 ($C_{quart.}$), 128.6 (CH), 127.9 ($C_{quart.}$), 121.4 (CH), 119.3 (CH), 118.7 (CH), 109.8 (CH), 108.3 ($C_{quart.}$), 105.8 (Ph-CH), 60.5 (para-{O}CH_3), 56.4 (meta-{O}CH_3), 46.4 (CH_2), 32.6 (CH_2 and N-CH_3).

(**31**) 3-(N-Methyl-1*H*-indol-3-yl)-4-(3,4,5-trimethoxyphenyl)-1,5-dihydro-2*H*-pyrrole-2-one.

^{1}H-NMR (DMSO-d_6): δ [ppm] = 8.4 (s, 1H, amide-NH), 7.7 (s, 1H, indole-H), 7.5 (d, J = 7,83, 1H, indole-H), 7.1 (t, J = 7.53, 1H, indole-H), 6.8 (t, J = 7.46, 1H, indole-H), 6.7-6.6 (m, 3H, indole-H and ortho-Ph-H), 4.4 (s, 2H, CH_2), 3.91 (s, 3H, N-CH_3), 3.7 (s, 3H, para-{O}CH_3), 3.4 (s, 6H, meta-{O}CH_3).

^{13}C-NMR (DMSO-d_6): δ [ppm] = 173.6 (C=O), 152.8 (C-O), 146.3 ($C_{quart.}$), 138.2 ($C_{quart.}$), 136.9 ($C_{quart.}$), 131.5 (CH), 129.7 ($C_{quart.}$), 125.3 ($C_{quart.}$), 121.5 (CH), 121.2 (CH), 119.1 (CH), 110.2 (CH), 105.64 ($C_{quart.}$), 105.60 (CH), 60.4 (para-{O}CH_3), 55.7 (meta-{O}CH_3), 47.5 (CH_2), 33.0 (N-CH_3).

(**32**) 2-(1*H*-Indol-3-yl)-N-[2-(4-methoxyphenyl)2-oxoethyl]acetamide.

In a dry 100 mL three necked round bottom flask 870 mg indolylacetic acid, 1000 mg 2-amino-1-(4-methoxyphenyl)ethanone hydrochloride and 760 mg HOBt were dissolved in 25 mL dry dichloromethane and cooled in an ice bath. At this temperature a solution of 1330 mg DCC in 15 mL dry dichloromethane was added dropwise and the reaction stirred for 1 h at 0°C and for 26 h at room temperature. Then 1280 mg DIEA in 2 mL dry dichloromethane was added dropwise and the colour turned to orange-brown. After 26 h, the precipitation (dicyclohexylurea) was filtered off and washed with 100 mL dichloromethane. The filtrate was washed with 30 mL 1 % HCl, and brine. The organic phase was separated, dried over Na_2SO_4 and evaporated. The product was purified by Flash-chromatography to yield 970 mg 61 % of **32** as a white solid.

^{1}H-NMR (DMSO-d_6): δ [ppm] = 10.9 (bs, 1H, indole-NH), 8.1 (t, J = 5.70, 1H, amide-NH), 7.9 (d, J = 9.01, 2H, ortho-Ph-2H), 7.6 (d, J = 7.69, 1H, indole-H), 7.3 (d, J = 8.01, 1H, indole-H), 7.2 (d, J = 2.17, 1H, indole-H), 7.1-6.9 (bm, 4H, indole-H and meta-Ph-H), 4.5 (d, J = 5.55, 2H, CH_2), 3.8 (s, 3H, para-{O}CH_3), 3.6 (s, 2H, CH_2).

^{1}H-NMR (acetone-d_6): δ [ppm] = 10.2 (bs, 1H, indole-NH), 7.9 (d, J = 9.00, 2H, ortho-Ph-H), 7.6 (d, J = 7.67, 1H, indole-H), 7.40 (m, 1H, indole-H), 7.36 (m, 1H, indole-H), 7.2-6.9 (bm, 5H,

amide-NH, indole-H and meta-Ph-H), 4.6 (d, J = 5.17, 2H, CH_2), 3.9 (s, 3H, para-{O}CH_3), 3.7 (s, 2H, CH_2).

^{13}C-NMR (acetone-d_6): δ [ppm] = 192.8 (CO), 170.7 (amide-CO), 163.8 ($C_{quart.}$), 136.7 ($C_{quart.}$), 129.9 (CH), 128.1 ($C_{quart.}$), 127.5 ($C_{quart.}$), 123.9 (CH), 121.3 (CH), 118.7 (CH), 118.6 (CH), 113.7 (CH), 111.2 (CH), 109.0 ($C_{quart.}$), 54.9 (para-{O}CH_3), 45.6 (CH_2), 32.7 (CH_2).

(**33**) 3-(1*H*-Indol-3-yl)-4-(4-methoxyphenyl)-1,5-dihydro-2*H*-pyrrole-2-one.

The compound was prepared from 400 mg (1.24 mmol) of **32** following general procedure. The product precipitated from ethylacetate solution and was washed with dichloromethane to yield 50 % 190 mg (0.62 mmol) of **33** as beige solid.

^{1}H-NMR (DMSO-d_6): δ [ppm] = 11.3 (bs, 1H, indole-NH), 8.3 (s, 1H, amide-NH), 7.6 (d, J = 2.30, 1H, indole-H), 7.4 (d, J = 7.95, 1H, indole-H), 7.3 (d, J = 8.83, 2H, ortho-Ph-H), 7.0 (m, 1H, indole-H), 6.8-6,7 (m, 4H, indole-H and meta-Ph-H), 4.4 (s, 2H, CH_2), 3.7 (s, 3H, para-{O}CH_3).

^{13}C-NMR (DMSO-d_6): δ [ppm] = 173.9 (C=O), 159.7 (C-O), 146.6 ($C_{quart.}$), 136.5 ($C_{quart.}$), 128.9 (orho-Ph-CH), 127.2 ($C_{quart.}$), 127.0 (CH), 125.3 ($C_{quart.}$), 124.6 ($C_{quart.}$), 121.3 (CH), 120.6 (CH), 119.0 (CH), 114.1 (meta-Ph-CH), 112.0 (CH), 106.6 ($C_{quart.}$), 55.5 (para-{O}CH_3), 47.7 (CH_2).

(**34**) 2-(N-Methyl-1*H*-indol-3-yl)-N-[2-(4-methoxyphenyl)2-oxoethyl]acetamide.

In a dry 100 mL three necked round bottom flask 300 mg N-methyl-indolylacetic acid, 320 mg 2-amino-1-(4-methoxyphenyl)ethanone hydrochloride and 240 mg HOBt were dissolved in 15 mL dry dichloromethane and cooled in an ice bath. At this temperature a solution of 430 mg DCC in 5 mL dry dichloromethane was added dropwise and the reaction stirred for 1 h at 0°C and for 60 h at room temperature. Then 410 mg DIEA in 1 mL dry dichloromethane was added dropwise and the colour turned to orange-brown. After 4 h, the precipitation (dicyclohexylurea) was filtered off and washed with 20 mL dichloromethane. The filtrate was washed with 20 mL 1 % HCl, and brine. The

organic phase was separated, dried over Na_2SO_4 and evaporated. The product was purified by Flash-chromatography to yield 460 mg 88 % of **34** as yellowish-white solid.

^{1}H-NMR (acetone-d_6): δ [ppm] = 8.0 (d, J = 8.94, 2H, ortho-Ph-H), 7.6 (d, J = 7.79, 1H, indole-H), 7.4 (dt, J = 8.09, J = 0.96, 1H, indole-H), 7.23 (s, 1H, indole-H), 7.22-6.9 (bm, 5H, amide-NH, indole-H and meta-Ph-H), 4.6 (d, J = 5.22, 2H, CH_2), 3.9 (s, 3H, para-{O}CH_3), 3.8 (s, 3H, N-CH_3), 3.7 (s, 2H, CH_2).

(**35**) 3-(N-Methyl-1*H*-indol-3-yl)-4-(4-methoxyphenyl)-1,5-dihydro-2*H*-pyrrole-2-one.

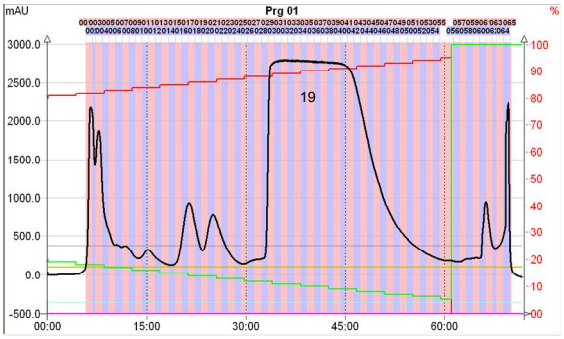
^{1}H-NMR (DMSO-d_6): δ [ppm] = 8.4 (s, 1H, amide-NH), 7.6 (s, 1H, indole-H), 7.4 (d, J = 7.83, 1H, indole-H), 7.3 (d, J = 7.75, 2H, ortho-Ph-H), 7.1 (t, J = 7.32, 1H, indole-H), 6.8-6.6 (m, 4H, indole-H and meta-Ph-H), 4.4 (s, 2H, CH_2), 3.8 (s, 3H, para-{O}CH_3), 3.7 (s, 3H, N-CH_3).

^{13}C-NMR (DMSO-d_6): δ [ppm] = 173.8 (C=O), 159.7 ($C_{quart.}$), 146.5 ($C_{quart.}$), 136.9 ($C_{quart.}$), 131.1 (CH), 129.0 (PH-CH), 127.2 ($C_{quart.}$), 125.6 ($C_{quart.}$), 124.1 ($C_{quart.}$), 121.4 (CH), 120.9 (CH), 119.2 (CH), 114.1 (PH-CH), 110.2 (CH), 105.7 ($C_{quart.}$), 55.5 (para-{O}CH_3), 47.7 (CH_2), 32.9 (N-CH_3).

3) Purification by Flash-chromatography

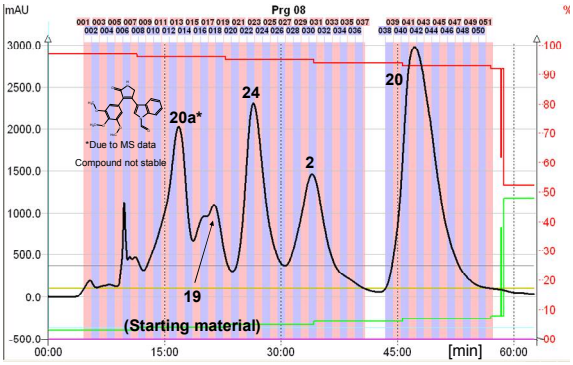
The graphic belongs to the purification of reaction mixture described for compound **19**.

Flash purification. Gradient ethylacetate 20/ hexanes 20 to 100% ethylacetate



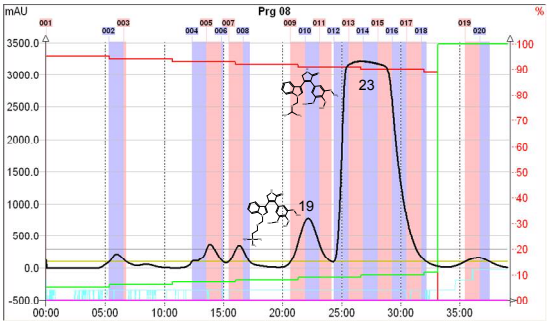
The graphic belongs to the purification of reaction mixture described for compound **20**.

Flash Gradient EE97/EtOH3 to EE90/EtOH10 over t = 80 min.
Flow = 25 ml/min



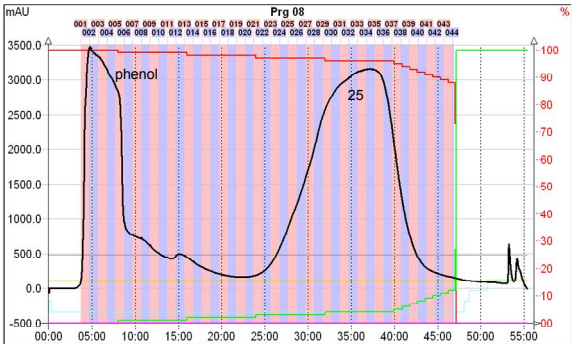
The graphic belongs to the purification of reaction mixture described for compound **23**.

Flash chromatogram ethylacetate/ethanol 97/3 gradient to 90/3



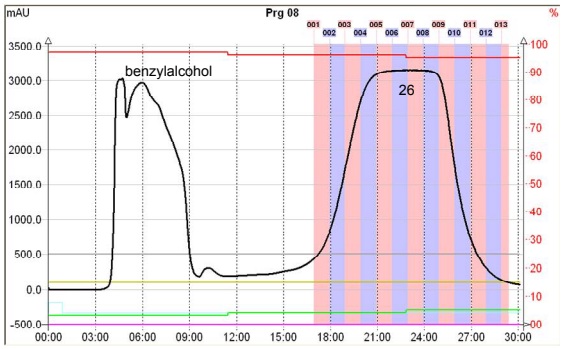
The graphic belongs to the purification of reaction mixture described for compound **25**.

Flash Gradient ethylacetate100% - ethylacetate 95% ethanole 5% over 40 min



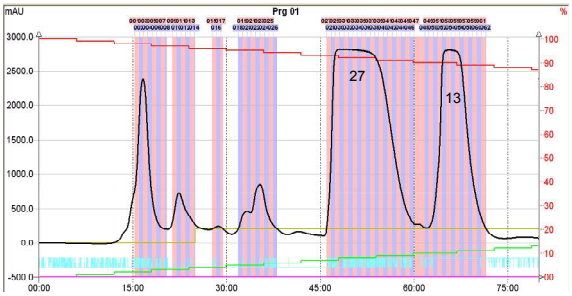
The graphic belongs to the purification of reaction mixture described for compound **26**.

Flash Gradient EE97%-EE95%EtOH5% over 40 min



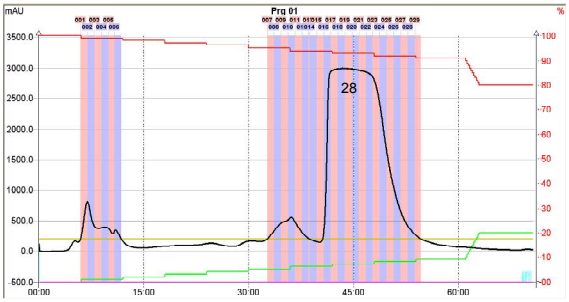
The graphic belongs to the purification of reaction mixture described for compound **27**.

Flash Gradient 100%EE to 20 %EtOH over 120 min.



The graphic belongs to the purification of reaction mixture described for compound **28**.

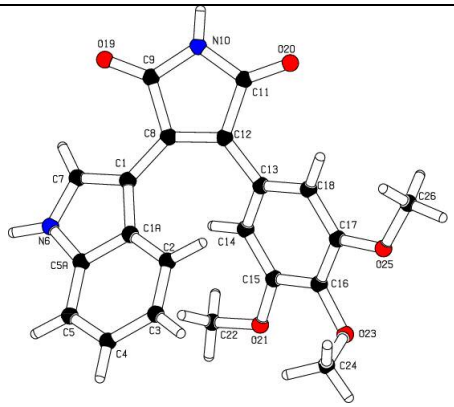
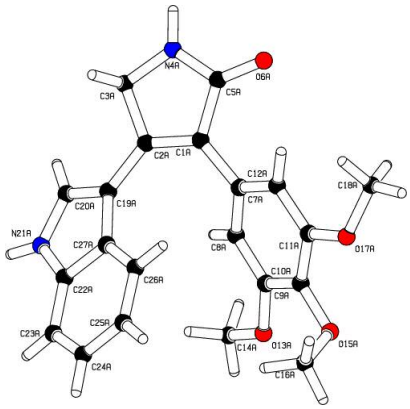
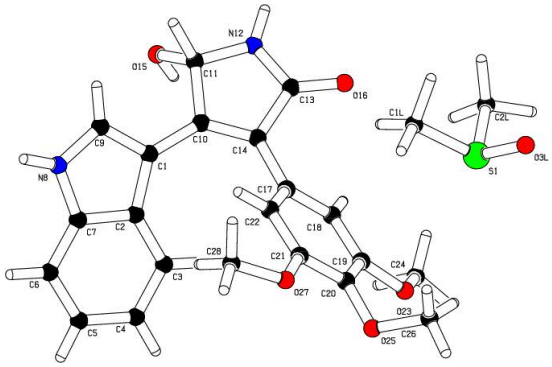
Flash. Gradient ethylacetate 100% to 20 % ethanol over 120 min flow 25 ml/min



4) Purity of key target compounds

Key compounds			tracings			
#	Rt [min]	%	Rt [min]	%	Rt [min]	%
1	7.882	98.7	9.841	1.3	-	-
2	5.199	97.9	5.969	2.1	-	-
3	5.285	97.5	7.729	2.5	-	-
4	5.356	98.0	10.656	2.0	-	-
11	9.100	98.8	11.573	1.2	-	-
14	8.767	100.0	-	-	-	-
19	10.782	98.6	7.747	1.4	-	-
21	7.763	100.0	-	-	-	-
22	8.428	97.3	6.464	2.7	-	-
23	9.036	98.5	10.360	1.5	-	-
24	9.500	98.8	10.845	1.2	-	-
25	9.204	76.5	8.582	23.5	-	-
26	9.772	98.2	10.225	0.9	10.880	0.9
28	8.579	98.4	10.308	1.6	-	-
29	5.790	97.1	4.232	2.9	-	-
31	7.908	97.4	7.058	2.6	-	-
33	7.816	97.9	7.107	2.1	-	-
35	8.854	100.0	-	-	-	-

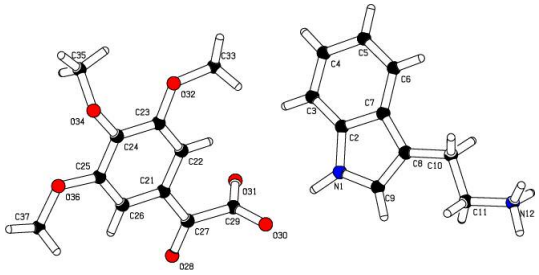
5) X-ray analysis

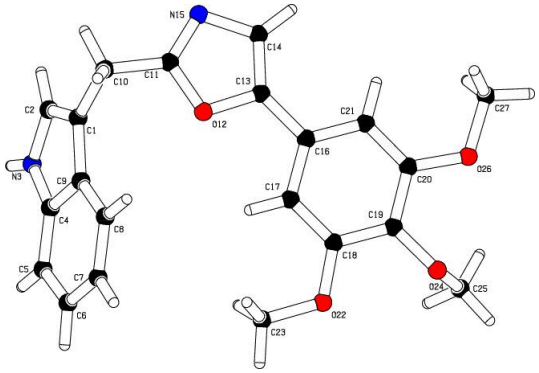
# Paper (test compounds indicated in bold letters)	Platon* plot showing the numbering scheme	CCDC-Nr. or Reference
1		Peifer, C., Schollmeyer, D. and Dannhardt, G. (2005): 3-(Indole-3-yl)-4-(3,4,5-trimethoxyphenyl)-1*H*-pyrrole-2,5-dione. Acta Cryst. E61, 721-723.
2		CSD Nr. 680816
4		CSD Nr. 680817

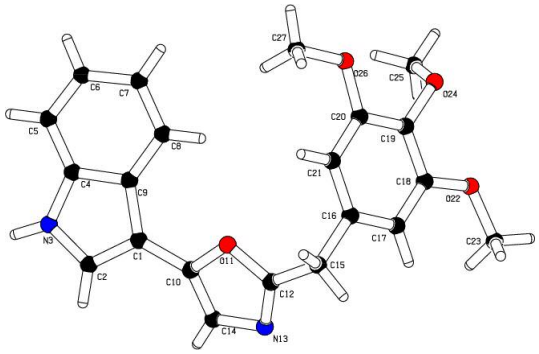
*Spek, A. L. (2003). J. Appl. Cryst. 36, 7–13.

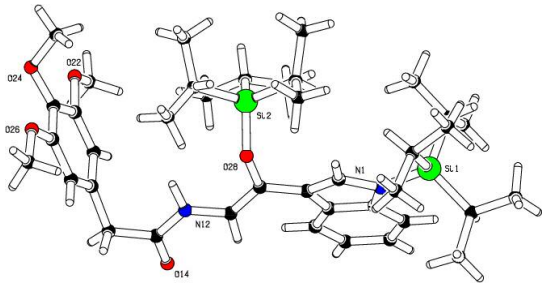
For clarity, only one enatiomer (C11)

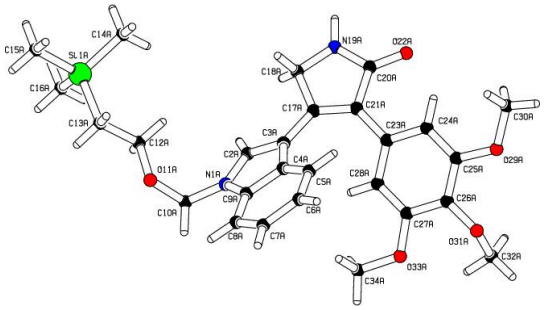
is shown

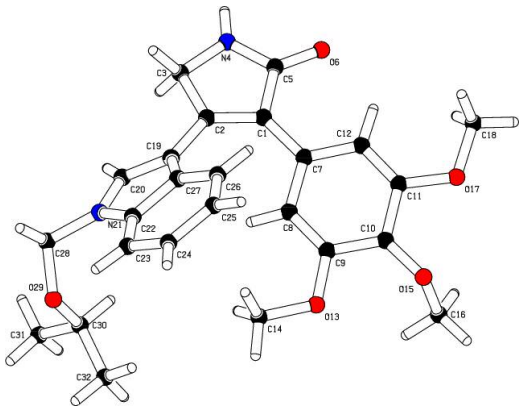
6a  CSD Nr. 680818

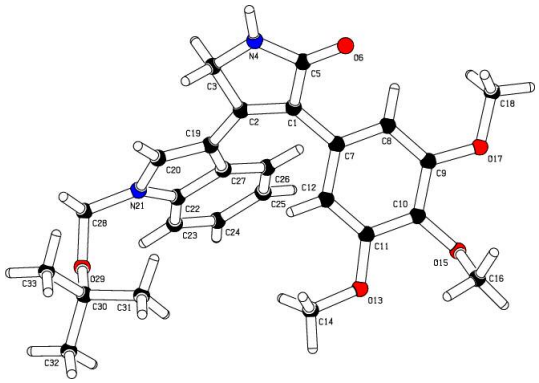
11  CSD Nr. 680819

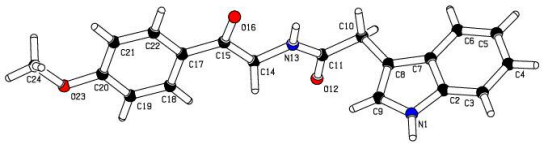
14  CSD Nr. 680820

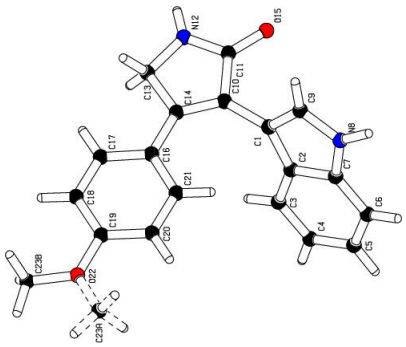
15  Peifer, C., Selig, R., Schollmeyer, D. and Laufer, S. (2007): *N*-{2-[1-(Triisopropylsilyl)-1*H*-indol-3-yl]-2-[(triisopropylsilyl)oxy]vinyl}-2-(3,4,5-trimethoxyphenyl)acetamide. Acta Cryst. E63, 1266-1268.

19  CSD Nr. 680821

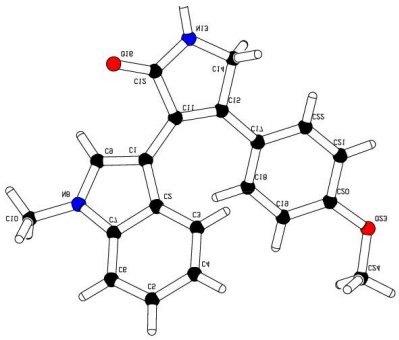
23  CSD Nr. 680822

24  CSD Nr. 680823

32  CSD Nr. 680824

33  CSD Nr. 680825

35



CSD Nr. 680826

6) Quality controls for selectivity profiling of compounds using 24 protein kinases

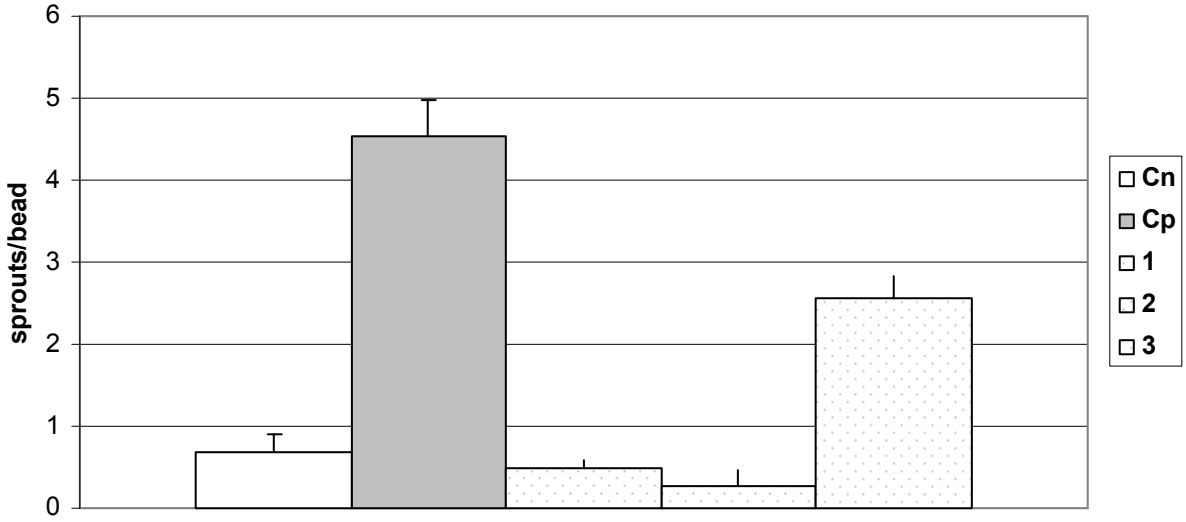
As a parameter for assay quality, the Z´-factor (Zhang et al. (1999). J. Biomol. Screen. 2: 67-73) for the low and high controls of each assay plate (n = 8) was used. ProQinases´s criterion for repetition of an assay plate is a Z´-factor below 0.4. Z´-factors in this project did not drop below 0.43 and exceeded 0.70 in most cases, indicating a good to excellent assay quality.

As an additional control, a 1 % DMSO plate (n = 88) was included for each enzyme as an indicator for putative washing and/or pipetting variations. For the 1 % DMSO plates the Z´-factor and the CV (%) (n = 88) was calculated. The CV of the 1 % DMSO plates did not exceed 14.77 % and were lower than 8 % in most cases.

Cpd #	AKT1	ARK5	AuroraA	AuroraB	B-RAF-VE	CDK2/CycA	CDK4/CycD1	CK2-A1	EGFR	EPHB4	ERB2	FAK	IGF1-R	SRC	VEGFR2	VEGFR3	FLT3	INS-R	MET	PDGFR-β	PLK1	SAK	TIE2	COT
1	-	4.3 E-5	5.4 E-6	1.7 E-5	4.0 E-5	6.9 E-6	1.4 E-5	-	1.6 E-5	5.1 E-6	2.6 E-5	6.5 E-7	1.3 E-5	2.1 E-5	2.5 E-9	5.0 E-9	2.7 E-7	1.6 E-5	3.5 E-5	6.8 E-7	-	9.9 E-7	7.4 E-7	6.4 E-5
2	-	-	1.6 E-5	4.6 E-5	-	6.6 E-5	5.6 E-5	-	2.3 E-5	5.3 E-5	5.1 E-5	9.5 E-6	2.2 E-5	1.4 E-5	3.1 E-8	3.7 E-8	6.1 E-6	4.3 E-5	6.0 E-5	1.1 E-5	-	1.0 E-5	5.2 E-6	3.2 E-5
3	-	1.8 E-6	3.2 E-6	2.1 E-6	-	9.8 E-5	3.0 E-5	-	-	-	7.6 E-5	-	9.1 E-5	4.1 E-5	1.1 E-5	9.4 E-6	2.2 E-6	-	-	-	-	7.7 E-6	3.4 E-5	-
4	-	7.5 E-5	-	-	-	-	-	-	-	-	-	-	-	-	5.9 E-6	3.4 E-6	4.4 E-5	-	-	5.5 E-5	-	-	-	-
19	-	-	-	-	-	-	-	-	2.2 E-5	4.4 E-5	6.1 E-5	7.9 E-5	8.7 E-6	4.5 E-6	3.1 E-6	5.6 E-6	3.4 E-5	-	-	7.1 E-5	-	-	2.6 E-5	-
21	-	-	6.1 E-5	-	-	9.9 E-5	8.6 E-5	-	-	-	-	3.5 E-5	-	7.0 E-5	2.3 E-6	3.2 E-6	2.5 E-5	-	-	5.2 E-5	-	5.5 E-5	2.5 E-5	-
22	-	-	2.9 E-5	-	-	-	9.6 E-5	-	-	-	-	2.8 E-5	-	4.0 E-5	5.3 E-6	3.6 E-6	5.6 E-5	-	-	7.4 E-5	-	3.5 E-5	2.4 E-5	-
23	-	-	3.3 E-5	-	-	-	-	-	-	-	-	2.7 E-5	-	2.9 E-5	5.2 E-6	5.3 E-6	-	-	-	-	-	4.4 E-5	1.1 E-5	-
24	-	9.8 E-5	3.0 E-5	4.3 E-5	3.8 E-5	2.3 E-5	2.7 E-5	-	9.0 E-6	2.0 E-5	2.5 E-5	2.8 E-5	7.7 E-6	4.4 E-6	4.4 E-6	4.8 E-6	2.0 E-5	2.7 E-5	2.9 E-5	3.8 E-5	-	2.8 E-5	1.1 E-5	9.6 E-6
25	-	-	6.5 E-6	2.0 E-5	5.1 E-5	2.0 E-5	4.4 E-5	-	-	-	3.7 E-5	4.3 E-5	-	4.9 E-5	1.5 E-6	2.5 E-6	5.8 E-5	4.4 E-5	4.5 E-5	8.0 E-5	-	9.0 E-6	1.7 E-6	4.0 E-5
26	-	-	-	-	-	1.0 E-4	-	9.3 E-5	1.4 E-5	3.7 E-5	3.6 E-5	4.0 E-5	1.8 E-5	9.1 E-6	1.6 E-6	1.7 E-6	3.6 E-5	8.1 E-5	-	5.6 E-5	-	-	1.1 E-5	6.3 E-5
28	-	-	-	-	-	-	-	-	9.4 E-5	-	-	7.7 E-5	-	5.7 E-5	8.0 E-6	3.2 E-6	7.8 E-5	-	-	-	-	2.3 E-5	3.1 E-5	-
29	-	3.4 E-5	4.7 E-5	-	-	6.0 E-5	8.2 E-5	-	5.8 E-5	-	-	5.7 E-5	-	-	4.2 E-6	2.5 E-6	3.0 E-6	-	-	4.0 E-5	-	1.6 E-5	2.5 E-5	-
31	-	4.9 E-6	3.2 E-6	9.8 E-6	5.0 E-5	4.2 E-5	4.0 E-5	-	-	-	7.7 E-5	5.0 E-5	7.0 E-5	5.7 E-5	1.5 E-5	1.1 E-5	5.0 E-6	4.7 E-5	-	4.5 E-5	-	9.2 E-6	7.0 E-5	-
33	-	2.0 E-6	1.6 E-5	4.9 E-6	-	-	3.5 E-5	-	7.2 E-5	-	-	-	-	-	1.3 E-5	8.7 E-6	9.9 E-6	-	-	-	-	1.2 E-5	5.7 E-5	-
35	-	3.6 E-6	1.0 E-4	5.7 E-5	7.6 E-5	-	-	-	-	-	-	-	-	3.9 E-5	3.1 E-5	1.8 E-5	1.4 E-5	-	-	-	-	4.6 E-5	4.8 E-5	-

IC_{50} values (M) of the test compounds in this study in an assay panel of 24 therapeutically relevant PK´s of the kinome.

7) HLMEC sprouting assay of compounds 1, 2 and 3 at a concentration of 2.6 µM



Antiangiogenic activity of compounds **1**, **2** and **3** at a concentration of 2.6 µM in the HLMEC sprouting assay presented as sprouts/bead ± SD (for each experiment n = 18). Compound **1**: 0.48 ± 0.1 sprouts/bead; Compound **2**: 0.27 ± 0.2 sprouts/bead; Compound **3**: 2.56 ± 0.27 sprouts/bead; **Cp** = control positive with 20 ng/ml VEGF stimulation: 4.54 ± 0.0.45 sprouts/bead; **Cn** = control negative without VEGF stimulation 0.69 ± 0.22 sprouts/bead. Statistical analysis was performed by using GraphPad InStat3 software. ANOVA, Tukey-Kramer test and Bonferroni test showed the results of compounds **1**, **2** and **3** to be highly significant compared to **Cp** (*** $p < 0.001$). Compound **1** *vs* **2** was not significant ($p > 0.05$). Compounds **1** and **2** *vs* **3** were highly significant (*** $p < 0.001$).