Electronic Supplementary Information

Construction of quinoline ring via a 3-component reaction in water: crystal structure analysis and H-bonding patterns of a 2-aryl quinoline derivative

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Table of contents

Experimental

Chemistry

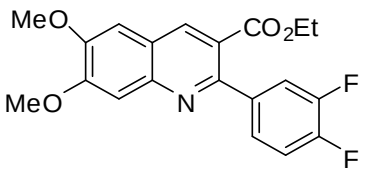
General methods: Unless stated otherwise, reactions were performed under nitrogen atmosphere using oven dried glassware. Reactions were monitored by thin layer chromatography (TLC) on silica gel plates (60 F254), visualizing with ultraviolet light or iodine spray. Flash chromatography was performed on silica gel (230-400 mesh) using distilled hexane, ethyl acetate, dichloromethane. ^{1}H NMR and ^{13}C NMR spectra were determined in $CDCl_3$ solution by using 400 or 100 MHz spectrometers, respectively. Proton chemical shifts (δ) are relative to tetramethylsilane (TMS, δ = 0.00) as internal standard and expressed in ppm. Spin multiplicities are given as s (singlet), d (doublet), t (triplet) and m (multiplet) as well as b (broad). Coupling constants (*J*) are given in hertz. Infrared spectra were recorded on a FT-IR spectrometer. Melting points were determined using melting point apparatus and are uncorrected. MS spectra were obtained on a mass spectrometer.

General procedure for the preparation of quinoline 4

A mixture of Montmorillonite K-10 (75 mg), an appropriate aniline **1** (0.98 mmol), ethyl 3,3-diethoxypropionate **3** (466 mg, 2.45 mmol) and an aldehyde **2** (1.07 mmol) in pure water (7.5 mL, 5 times Vol w. r. t. aniline) was stirred at 90 °C for the time mentioned in Table 2 in the presence of air. After completion of the reaction (indicated by TLC), the mixture was cooled to room temperature and filtered. The filtrate was extracted with EtOAc (3 x 5 mL). The organic layers were collected, combined, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using ethyl acetate-hexane to give the desired product.

Spectral data for the 2-aryl quinoline derivatives

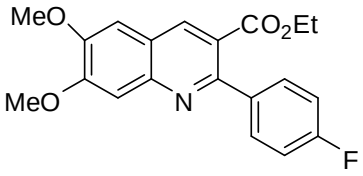
Ethyl 2-(3,4-difluorophenyl)-6,7-dimethoxyquinoline-3-carboxylate (4a)



Off white solid; mp 164-166 °C; IR (KBr) 1722, 1619, 1589, 1522, 1500, 1463, 1343, 1269,

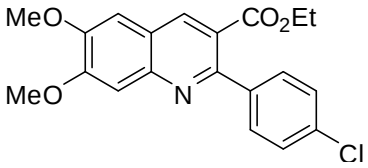
1203, 1158, 1096 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.18 (t, *J* = 6.8 Hz, 3H), 4.05 (s, 6H), 4.21 (q, *J* = 6.8 Hz, 2H), 7.14-7.16 (m, 2H), 7.42-7.45 (m, 1H), 7.47-7.50 (m, 2H), 8.56 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.8, 56.2, 56.3, 61.4, 105.2, 107.9, 116.7, 116.8, 117.8, 118.0, 121.7, 122.6, 124.9, 137.6 (2C), 145.8, 150.6, 154.2, 154.5, 167.4; HRMS: *m/z* calcd for $C_{20}H_{18}F_2NO_4$ (M+1) 374.1204; found 374.1206.

Ethyl 2-(4-fluorophenyl)-6,7-dimethoxyquinoline-3-carboxylate (4b)



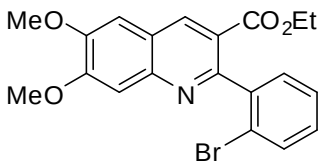
Light yellow solid; mp 165-166 °C; IR (KBr) 1714, 1618, 1498, 1454, 1431, 1393, 1351, 1269, 1237, 1158, 1029 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.11 (t, *J* = 7.2 Hz, 3H), 4.05 (s, 6H), 4.18 (q, *J* = 7.2 Hz, 2H), 7.14-7.26 (m, 3H), 7.48 (s, 1H), 7.54-7.58 (m, 2H), 8.54 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.8, 56.1, 56.3, 61.3, 105.2, 107.9, 114.8, 115.1, 121.5, 122.9, 130.3, 130.4, 137.4, 145.8, 150.4, 154.4, 155.4, 161.6, 164.1, 167.8; HRMS: *m/z* calcd for $C_{20}H_{19}FNO_4$ (M+1) 356.1298; found 356.1281.

Ethyl 2-(4-chlorophenyl)-6,7-dimethoxyquinoline-3-carboxylate (4c)



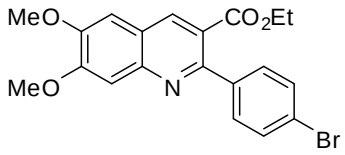
Yellow semi solid; IR (KBr) 1713, 1619, 1585, 1505, 1467, 1421, 1343, 1265, 1225, 1158, 1083 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.14 (t, *J* = 7.2 Hz, 3H), 4.07 (s, 6H), 4.21 (q, *J* = 7.2 Hz, 2H), 7.18 (s, 1H), 7.55-7.59 (m, 3H), 7.75-7.79 (m, 2H), 8.57 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.9, 56.2, 56.3, 61.4, 106.1, 107.8, 120.5, 123.0, 130.1, 130.5, 131.1, 131.4, 135.1, 145.8, 150.4, 154.4, 155.4, 161.6, 163.8, 168.8**;** HRMS: *m/z* calcd for $C_{20}H_{19}ClNO_4$ (M+1) 372.1003; found 372.1007.

Ethyl 2-(2-bromophenyl)-6,7-dimethoxyquinoline-3-carboxylate (4d)



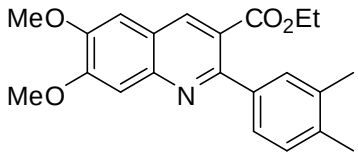
Yellow semi solid; IR (KBr) 1708, 1615, 1589, 1495, 1463, 1345, 1271, 1237, 1177, 1085 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.13 (t, *J* = 6.8 Hz, 3H), 4.04 (s, 6H), 4.21 (q, *J* = 6.8 Hz, 2H), 6.85-6.90 (m, 4H), 7.42-7.45 (m, 1H), 7.48 (s, 1H), 8.54 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.8, 56.1, 56.3, 61.3, 105.2, 107.9, 121.6, 122.5, 122.8, 130.2 (2C), 131.1 (2C), 137.5, 140.1, 145.9, 150.5, 154.4, 155.3, 167.6; HRMS: *m/z* calcd for $C_{20}H_{19}BrNO_4$ (M+1) 416.0497; found 416.0511.

Ethyl 2-(4-bromophenyl)-6,7-dimethoxyquinoline-3-carboxylate (4e)



Off white solid; mp 200-201 °C; IR (KBr) 1703, 1617, 1590, 1495, 1465, 1419, 1345, 1270, 1237, 1177, 1071 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.15 (t, *J* = 6.8 Hz, 3H), 4.04 (s, 6H), 4.21 (q, *J* = 6.8 Hz, 2H), 7.16 (s, 1H), 7.45-7.47 (m, 3H), 7.57-7.59 (m, 2H), 8.57 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.8, 56.1, 56.3, 61.3, 105.2, 107.9, 121.6, 122.5, 122.7, 130.2 (2C), 131.1 (2C), 137.4, 140.1, 145.8, 150.5, 154.4, 155.3, 167.6; HRMS: *m/z* calcd for $C_{20}H_{19}BrNO_4$ (M+1) 416.0497; found 416.0511.

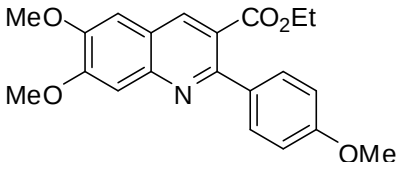
Ethyl 2-(3,4-dimethylphenyl)-6,7-dimethoxyquinoline-3-carboxylate (4f)



Yellow solid; mp 147-148 °C; IR (KBr) 1715, 1619, 1596, 1516, 1443, 1431, 1336, 1267, 1232, 1156, 1071 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.11 (t, *J* = 6.8 Hz, 3H), 2.31 (s, 6H), 4.04 (s, 6H), 4.21 (q, *J* = 6.8 Hz, 2H), 7.18-7.21 (m, 1H), 7.24-7.27 (m, 2H), 7.41 (s, 1H),

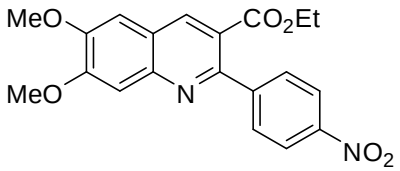
7.49 (s, 1H), 8.44 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.7, 19.5, 19.7, 56.0, 56.2, 61.1, 105.1, 108.0, 121.2, 123.3, 126.0, 129.2, 129.6, 136.1, 136.6, 136.9, 138.4, 145.7, 150.1, 154.0, 156.5, 168.2; HRMS: *m/z* calcd for $C_{22}H_{24}NO_4$ (M+1) 366.1705; found 366.1728.

Ethyl 6,7-dimethoxy-2-(4-methoxyphenyl)quinoline-3-carboxylate (4g)



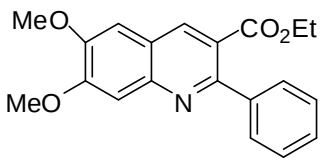
Yellow semi solid; IR (KBr) 1721, 1615, 1591, 1497, 1465, 1419, 1345, 1267, 1231, 1155, 1093 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.10 (t, *J* = 7.2 Hz, 3H), 4.08 (s, 9H), 4.21 (q, *J* = 7.2 Hz, 2H), 7.17-7.22 (m, 3H), 7.53 (s, 1H), 7.66-7.70 (m, 2H), 8.61 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.8, 56.0, 56.1, 56.3, 61.3, 105.8, 107.9, 114.2, 114.8, 120.5, 123.0, 129.3, 130.4, 138.1, 147.8, 150.4, 154.1, 155.4, 161.7, 164.1, 167.8; HRMS: *m/z* calcd for $C_{21}H_{22}NO_5$ (M+1) 368.1486; found 368.1484.

Ethyl 6,7-dimethoxy-2-(4-nitrophenyl)quinoline-3-carboxylate (4h)



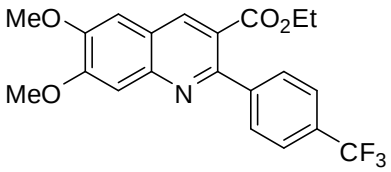
Light yellow solid; mp 173-174 °C; IR (KBr) 1720, 1619, 1598, 1511, 1462, 1435, 1352, 1269, 1228, 1160, 1094 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.15 (t, *J* = 7.2 Hz, 3H), 4.06 (s, 6H), 4.22 (q, *J* = 7.2 Hz, 2H), 7.17 (s, 1H), 7.48 (s, 1H), 7.72-7.75 (m, 2H), 8.31-8.35 (m, 2H), 8.65 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.9, 56.2, 56.4, 61.5, 105.2, 108.0, 122.1, 122.3 (2C), 123.2 (2C), 129.7 (2C), 137.9, 146.0, 147.8, 151.0, 154.4, 154.8, 168.8; HRMS: *m/z* calcd for $C_{20}H_{19}N_2O_6$ (M+1) 383.1243; found 383.1253.

Ethyl 6,7-dimethoxy-2-phenylquinoline-3-carboxylate[1] (4i)



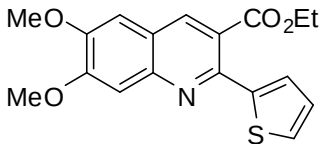
Off white solid; mp 140-141 °C; IR (KBr) 1706, 1592, 1496, 1445, 1415, 1376, 1342, 1272, 1235, 1160, 1008 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.05 (t, *J* = 6.8 Hz, 3H), 4.04 (s, 6H), 4.14 (q, *J* = 6.8 Hz, 2H), 7.14 (s, 1H), 7.41-7.57 (m, 4H), 7.58-7.61 (m, 2H), 8.52 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.6, 56.1, 56.7, 61.2, 105.2, 108.0, 121.5, 123.3, 127.4, 127.5, 128.0, 128.1, 128.5, 137.2, 141.1, 145.8, 150.3, 154.2, 156.5, 168.0; HRMS: *m/z* calcd for $C_{20}H_{20}NO_4$ (M+1) 338.1392; found 338.1390.

Ethyl 6,7-dimethoxy-2-(4-(trifluoromethyl)phenyl)quinoline-3-carboxylate (4j)



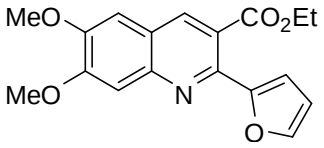
Yellow solid; mp 185-186 °C; IR (KBr) 1702, 1615, 1591, 1516, 1496, 1423, 1321, 1273, 1238, 1174, 1067 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.08 (t, *J* = 7.2 Hz, 3H), 4.08 (s, 6H), 4.20 (q, *J* = 7.2 Hz, 2H), 7.16 (s, 1H), 7.51 (s, 1H), 7.68-7.75 (m, 4H), 8.62 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.2, 55.7, 55.8, 60.8, 104.9, 107.4, 121.3, 122.0, 124.3, 124.6, 124.7, 128.5, 129.1, 129.5, 134.0, 137.2, 145.3, 150.2, 154.0, 154.5, 166.6; HRMS: *m/z* calcd for $C_{21}H_{19}F_3NO_4$ (M+1) 406.1266; found 406.1292.

Ethyl 6,7-dimethoxy-2-(thiophen-2-yl)quinoline-3-carboxylate (4k)



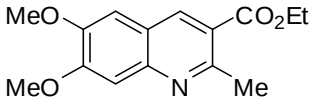
Light yellow solid; mp 155-156 °C; IR (KBr) 1708, 1615, 1583, 1500, 1467, 1421, 1341, 1263, 1223, 1156, 1086 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.26 (t, *J* = 7.2 Hz, 3H), 4.02 (s, 3H), 4.07 (s, 3H), 4.37 (q, *J* = 7.2 Hz, 2H), 7.05-7.09 (m, 2H), 7.35-7.37 (m, 1H), 7.43-7.46 (m, 2H), 8.35 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.9, 56.1, 56.3, 61.6, 105.0, 107.8, 121.3, 123.0, 127.3, 127.5 (2C), 136.4, 143.2, 145.6, 148.4, 150.3, 154.1, 168.4; HRMS: *m/z* calcd for $C_{18}H_{18}NO_4S$ (M+1) 344.0957; found 344.0966.

Ethyl 2-(furan-2-yl)-6,7-dimethoxyquinoline-3-carboxylate (4l)



Yellow liquid; IR (KBr) 1704, 1618, 1590, 1496, 1447, 1434, 1348, 1272, 1240, 1160, 1041 cm^{-1}; δ 1.13 (t, *J* = 7.2 Hz, 3H), 4.02 (s, 6H), 4.21 (q, *J* = 7.2 Hz, 2H), 7.25-7.27 (m, 2H), 7.40-7.43 (m, 1H), 7.75-7.78 (m, 2H), 8.56 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.8, 56.2, 56.3, 61.5, 105.0, 108.0, 121.4, 123.2, 127.1, 127.6, 127.6, 135.3, 143.2, 145.5, 148.3, 154.3, 157.3, 167.4; HRMS: *m/z* calcd for $C_{18}H_{18}NO_5$ (M+1) 328.1156; found 383.1166.

Ethyl 6,7-dimethoxy-2-methylquinoline-3-carboxylate[1] (4m)

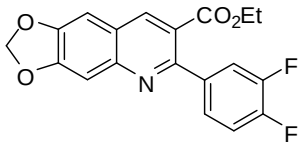


Yellow liquid; IR (KBr) 1717, 1619, 1592, 1447, 1336, 1272, 1237, 1164, 1083 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.08 (t, *J* = 7.2 Hz, 3H), 2.43 (s, 3H), 4.01 (s, 6H), 4.21 (q, *J* = 7.2 Hz, 2H), 7.21 (s, 1H), 7.24 (s, 1H), 8.54 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1, 25.5, 56.0, 56.2, 61.1, 105.1, 108.0, 122.0, 123.3, 136.5, 145.4, 150.1, 154.0, 156.5, 167.2; HRMS: *m/z* calcd for $C_{15}H_{18}NO_4$ (M+1) 276.1236; found 276.1243.

General procedure for the preparation of quinoline 6

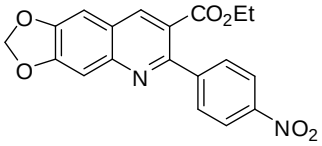
A mixture of Montmorillonite K-10 (75 mg), benzo[*d*][1,3]dioxol-5-amine (**5**, 0.98 mmol), ethyl 3,3-diethoxypropionate **3** (466 mg, 2.45 mmol) and aldehyde **2a** or **2h** (1.07 mmol) in pure water (7.5 mL, 5 times Vol w. r. t. aniline) was stirred at 90 °C for 5-6h in the presence of air. After completion of the reaction (indicated by TLC), the mixture was cooled to room temperature and filtered. The filtrate was extracted with EtOAc (3 x 5 mL). The organic layers were collected, combined, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using ethyl acetate-hexane to give the desired product.

Ethyl 6-(3,4-difluorophenyl)-[1,3]dioxolo[4,5-*g*]quinoline-7-carboxylate (6a)



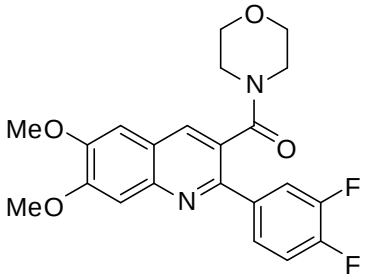
Yellow solid; mp 146-148 °C; IR (KBr) 1725, 1691, 1589, 1523, 1467, 1433, 1333, 1267, 1228, 1190, 1084 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.18 (t, *J* = 7.2 Hz, 3H), 4.24 (q, *J* = 7.2 Hz, 2H), 6.16 (s, 2H), 7.17-7.26 (m, 3H), 7.19-7.26 (m, 2H), 8.48 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.8, 61.5, 102.1, 102.9, 105.8, 116.7, 116.8, 117.8, 118.0, 122.8, 123.2, 124.9, 138.0, 148.7, 149.4, 151.7, 152.7, 154.1, 167.4; HRMS: *m/z* calcd for $C_{19}H_{14}NO_4F2$ (M+1) 358.0891; found 358.0883.

Ethyl 6-(4-nitrophenyl)-[1,3]dioxolo[4,5-*g*]quinoline-7-carboxylate (6b)



Light yellow solid; mp 212-214 °C; IR (KBr) 1722, 1599, 1587, 1512, 1462, 1435, 1349, 1258, 1231, 1175, 1083 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.15 (t, *J* = 6.8 Hz, 3H), 4.22 (q, *J* = 6.8 Hz, 2H), 6.18 (s, 2H), 7.18 (s, 1H), 7.43 (s, 1H), 7.73 (d, *J* = 4.8 Hz, 2H), 8.31 (d, *J* = 4.8 Hz, 2H), 8.58 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.8, 61.5, 102.3, 102.9, 105.9, 122.5, 123.1 (2C), 123.5, 129.7 (2C), 138.3, 147.3, 147.4, 147.5, 149.0, 153.0, 154.3, 166.8; HRMS: *m/z* calcd for $C_{19}H_{15}N_2O_6$ (M+1) 367.0930; found 367.0925.

Preparation of (2-(3,4-difluorophenyl)-6,7-dimethoxyquinolin-3-yl)(morpholino) methanone (8)



A reaction mixture of quinoline ester **4a** (100 mg, 0.27 mmol), morpholine **7** (27 mg, 0.32 mmol), 1, 2, 4-triazole (13.8 mg, 0.20 mmol) and DBU (30 mg, 0.20 mmol) was stirred at 90 ° C for 24 h under nitrogen. The reaction was monitored by TLC. After completion of the reaction

the mixture was cooled to room temperature and extracted with ethyl acete (3×5 mL). The organic layers were collected, combined, washed with water (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under low pressure. The residue was purified by chromatography on silica gel using EtOAc-hexane as eluent to afford the desired product as a yellow liquid (yield 75%); IR (KBr) 1689, 1618, 1591, 1531, 1499, 1471, 1345, 1273, 1215, 1165, 1083 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.45 (t, *J* = 5.6 Hz, 4H), 3.67 (t, *J* = 4.8 Hz, 4H), 4.03 (s, 3H), 4.05 (s, 3H), 7.18 (s, 1H), 7.21-7.23 (m, 1H) 7.30-7.25 (m, 1H), 7.42-7.48 (m, 2H), 8.57 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 46.1 (2C), 56.3 (2C), 66.4 (2C), 106.2, 107.9, 116.7 (2C), 117.8, 118.0, 121.7, 122.7, 124.9, 137.4, 140.6, 144.1, 150.6, 154.2, 154.5, 169.1; HRMS: *m/z* calcd for $C_{22}H_{21}F_2N_2O_4$ (M+1) 415.1443; found 415.1447.

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Single crystal X-ray data for compound 4j

Single crystals suitable for X-ray diffraction of (**4j**) was grown from methnol. The crystals were carefully chosen using a stereo zoom microscope supported by a rotatable polarizing stage. The data was collected at room temperature on Bruker's KAPPA APEX II CCD Duo with graphite monochromated Mo-Kα radiation (0.71073 Å). The crystals were glued to a thin glass fibre using FOMBLIN immersion oil and mounted on the diffractometer. The intensity data were processed using Broker's suite of data processing programs (SAINT), and absorption corrections were applied using SADABS.[1] The crystal structure was solved by direct methods using SHELXS-97 and the data was refined by full matrix least-squares refinement on F^2 with anisotropic displacement parameters for non-H atoms, using SHELXL-97.[2]

Crystal data of **4j**: Molecular formula = $C_{21}H_{18}F_3NO_4$, Formula weight = 405.37, Crystal system = Monoclinic, space group = $P2_1/c$, a = 13.624 (14) Å, b = 8.685 (8) Å, c = 17.083 (19) Å, V = 1861.5 (3) $Å^3$, T = 296(2) K, Z = 4, D_c = 1.450 Mg m^{-3}, μ(Mo-Kα) = 0.12 mm^{-1}, 18259 reflections measured, 4264 independent reflections, 3202 observed reflections [I > 2.0 σ (I)], R_1_obs = 0.043, Goodness of fit =1.02. Crystallographic data (excluding structure factors) for **4j** have been deposited with the Cambridge Crystallographic Data Center as supplementary publication number CCDC 864149.

Reference

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Pharmacology

Chorismate Mutase activity assay: Mycobacterium *tuberculosis* chorismate mutase (MtCM) gene was PCR amplified and cloned into expression vector pET22b. MtCM was purified from over expressed culture of BL21 (DE3) harboring pET22b/ MtCM by Ni-NTA affinity chromatography.

Activity of chorismate mutase enzyme is based on the direct observation of conversion of chorismate to prephenate Spectrophotometrically at OD_{274}. The reaction volume of 100 µl contained 50 mM Tris-HCl (pH 7.5), 0.5 mM EDTA, 0.1 mg/ml bovine serum albumin, and 10 mM β-Mercaptoethanol, and chorismic acid 4 mM. The reaction was started by adding 180 pmol of purified protein to the pre-warmed chorismic acid solution. Inhibitory screening of the test compounds against chorismate mutase activity was measured at 50 µM concentration of the effectors. The reaction was allowed to proceed at 37 °C and was terminated after 5 min with 100 µl of 1 N HCl. A blank with no enzyme for every reaction was kept as a control to account for the non enzymatic conversion of chorismate to prephenate.

The percentage of enzyme inhibition caused by the test compound is calculated by the following formula

% inhibition = 100 – residual activity of CM

$$\left[\text{Residual activity of CM} = \frac{(S + E + C) - (S + C)}{(S + E) - (S)} \times 100\right]$$

S = Substrate absorbance at 274 nm

E = Enzyme absorbance at 274 nm

C = Compound absorbance at 274 nm

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