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CRYSTAL STRUCTURES OF INTERMEDIATES IN A NEW SYNTHESIS OF ANTITUMOR DRUG CABOZANTINIB

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Abstract – The heterocyclic antitumor drug cabozantinib was synthesized by condensation of 4-(6,7-dimethoxyquinolin-4-yloxy)aniline and methyl 1-(4-fluorophenylcarbamoyl)cyclopropanecarboxylate in the presence of two equivalents of sodium methoxide and azeotropic removal of methanol. In turn, the intermediate methyl 1-(4-fluorophenylcarbamoyl)cyclopropanecarboxylate was prepared from 4-fluoroaniline and dimethyl 1,1-cyclopropanedicarboxylate in the presence of one equivalent of sodium methoxide. Four crystal structures of intermediates and a byproduct were determined.

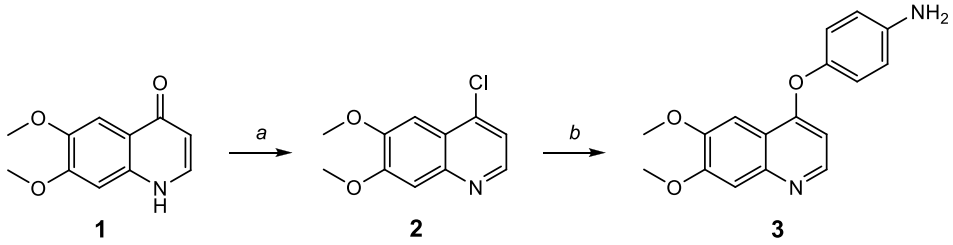
INTRODUCTION

Cabozantinib, a kinase inhibitor, displayed activity toward a broad range of tumor models.[1] The drug demonstrated promising activity in a clinical trial on metastatic prostate cancer.[2] Potent inhibitory effects were suggested in a colorectal cancer model.[3] Preclinical work showed that cabozantinib was effective for treatment of gastrointestinal stromal tumors.[4] Favorable results were also observed in thyroid carcinoma.[5] The drug is still under study for the evaluation of its efficacy and safety towards other types of solid tumors.[6] A new synthesis of this antitumor drug, other than the patented pathway, is reported. Several patents disclose processes for the preparation of the diamide, cabozantinib. The methods employed include standard coupling conditions of acid and amine,[7] acid chloride and amine,[8] or alternative pathways.[9] It was our intention to avoid obnoxious, toxic acid chlorides and expensive coupling reagents for the construction of the intermediate and target amides. Thus, we resorted to the methyl esters as building blocks and to inexpensive sodium methoxide as the sole reagent. In addition, the synthesis should be accomplished without chromatography. As may be expected, since we intended to start from known materials, some

should be accomplished without chromatography. As may be expected, since we intended to start from known materials, some reactants and intermediates remained the same as in the established syntheses. In addition, crystal structures of three intermediates (6,7-dimethoxyquinolin-4(1*H*)-one monohydrate, 4-(6,7-dimethoxyquinolin-4-yloxy)aniline and methyl 1-(4-fluorophenylcarbamoyl)cyclopropane-carboxylate) and a byproduct (*N*,*N*′-bis(4-fluorophenyl)cyclopropane-1,1-dicarboxamide) were determined by single crystal X-ray diffraction.

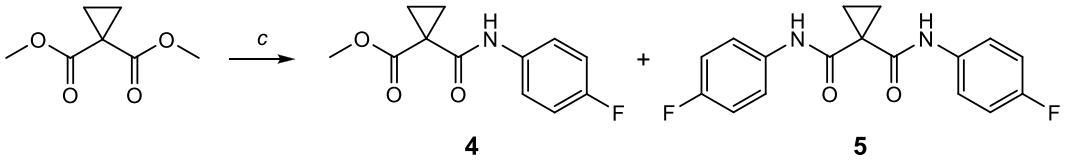
RESULTS AND DISCUSSION

Previously, the preparation of quinolinone **1** was reported by cyclization of suitable precursors and decarboxylation, requiring high temperatures.[10–12] A recent, elegant alternative route involves cyclization of ynones derived from anthranilic acid precursors.[13] We used a more convenient cyclization reaction starting from commercial 2-amino-4,5-dimethoxyacetophenone.[14,15] which, in turn, is available from veratrol by acetylation, followed by nitration and subsequent reduction.[16] The conversion of the quinolinone **1** to chloro derivative **2** has been repeatedly described in the literature.[11,12,15,17] In this case, we combined the advantageous aspects of the separate reports into one convenient procedure. Reaction of **2** with 4-aminophenol and NaH in DMSO,[12] provided 4-(6,7-dimethoxyquinolin-4-yloxy)aniline (**3**), as previously described (Scheme 1). This reaction has also been described using NaO*t*Bu in DMA,[18] although with lower yield.



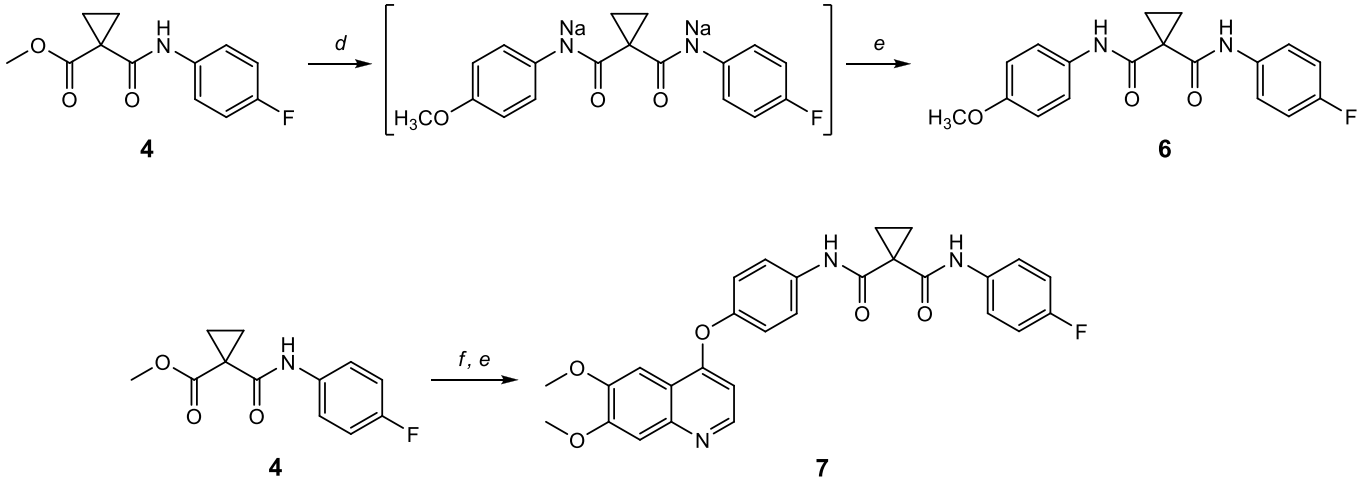
Scheme 1. Reagents and conditions: (*a*) $SOCl_2$, reflux; (*b*) NaH, DMSO, 4-aminophenol, 100 °C.

The second intermediate, methyl 1-(4-fluorophenylcarbamoyl)cyclopropanecarboxylate (**4**), was prepared from 4-fluoroaniline and dimethyl 1,1-cyclopropanedicarboxylate in the presence of one equivalent of sodium methoxide to generate the anilide anion (Scheme 2). A small excess of the base had a beneficial effect with regard to yield. Cyclohexane, tetrahydrofuran and toluene were examined as solvents suitable for azeotropic removal of methanol. The higher reaction temperature attained in toluene improved the yield significantly. *N*,*N*′-Bis(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (**5**) was identified as a byproduct, which was also prepared independently. Assessment of the product mixture was accomplished in a straightforward manner by inspection of the ^{1}H NMR spectra: the amide NH protons of **4** and **5** resonate at 10.34 and 10.07 ppm, respectively.



Scheme 2. Reagents and conditions: (*c*) NaOMe, 4-fluoroaniline, toluene, 63 °C.

The monoamide **4** was easily purified due to its solubility in *i*-pentane, whereas the diamide **5** could be separated due to insolubility in *t*-BuOMe. *N*-(4-Fluorophenyl)-*N*'-(4-methoxyphenyl)cyclopropane-1,1-dicarboxamide **(6)** was synthesized as a model compound (Scheme 3) in order to establish suitable reaction conditions and to avoid wasting the precious intermediate aniline **3**. It was observed that at least two equivalents of sodium methoxide were necessary for clean formation of the diamide. Using this essential information, **3** and **4** were coupled in the final key step to give the target product, cabozantinib (**7**), via the dianion (Scheme 3). Excess **4** was removed by simple washing and could be recycled,



Scheme 3. Reagents and conditions: (*d*) 2 NaOMe, 4-methoxyaniline, toluene, 63 °C; (*e*) H^+, H_2O; (*f*) 2 NaOMe, quinolinoxyaniline **3**, toluene, 63 °C.

Known compounds **1**–**4** as well as the product **7** have not been fully characterized before, so we have included complete ^{13}C NMR and IR data in the Experimental Section. It must be noted that our experiments have been conducted on a small scale and are, therefore, not fully optimized. One alternative process, using the acid chloride instead of the methyl ester **4**, gave an almost quantitative yield of **7**.[17] Other pathways, also patented,[7,9] start from 1,1-cyclohexanedicarboxylic acid or from the monomethyl ester, and gave considerably lower yields.

A number of salts were discussed, and powder diffraction data of different crystalline forms of the malate salt were disclosed in the patent literature.[8]

6,7-Dimethoxyquinolin-4(1*H*)-one (**1**) crystallized as monohydrate (Figure 1). Stacks of the planar molecules are linked into a three-dimensional network of hydrogen bonds (H···acceptor and donor···acceptor distance, donor–H···acceptor angle): O4–H41···O3 (1.93 and 2.75(1) Å, 160°), O4–H42···O3 (1.96 and 2.81(1) Å, 171°), and N1–H···O4 (2.00(3) and 2.82(1) Å, 161(4)°). However, the bulk material gave a powder diffraction pattern different from the calculated one. Also the water content of the bulk was found to be only 3.1% by Karl-Fischer determination, whereas a monohydrate would require 8.1%. Therefore, the bulk material is definitely not a hydrate, but no single crystals of the anhydrous compound were obtained. The crystal structure of the chloro derivative **2** is known.[19]

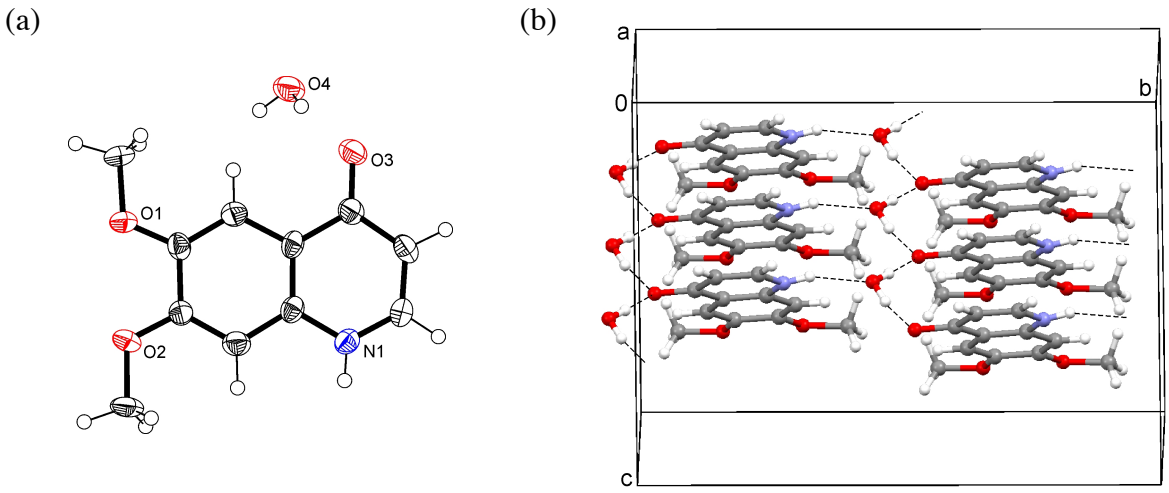


Figure 1. (a) ORTEP plot and (b) hydrogen bonding of 6,7-dimethoxyquinolin-4(1*H*)-one hydrate (**1**).

In the crystal structure of 4-(6,7-dimethoxyquinolin-4-yloxy)aniline (**3**), the molecules form chains by hydrogen bonding (Figure 2): N2–H···N1 (2.15(3) and 3.037(4) Å, 163(3)°). The angle between quinoline and phenyl ring planes was found to be 67.3°. An intramolecular hydrogen bond was observed in the structure of methyl 1-(4-fluorophenylcarbamoyl)cyclopropanecarboxylate (**4**): N1–H···O2 (1.94 and 2.681(2) Å, 144°). The molecule is located on a (010) mirror plane, only the C2 atoms of the cyclopropane ring are situated out of this plane (Figure 3). The asymmetric unit of *N*,*N*′-bis(4-fluoro-phenyl)cyclopropane-1,1-dicarboxamide (**5**) contains two independent molecules. Intermolecular hydrogen bonds in the direction of the *a* axis (Figure 4) create two independent chains of molecules: N1A–H···O2A (2.01(1) and 2.879(1) Å, 167(1)°), N2A–H···O1A (2.12(2) and 2.979(2) Å, 169(2)°), N1B–H···O2B (1.98(2) and 2.793(1) Å, 156°), and N2B–H···O1B (1.94(1) and 2.816(1) Å, 169(1)°). In repeated attempts, crystals of compound **6** exhibited severe disorder. No further efforts were undertaken to solve the structure. Finally, the crystal structure of the racemic malate of cabozantinib (**7**) was previously disclosed in the patent literature.[8]

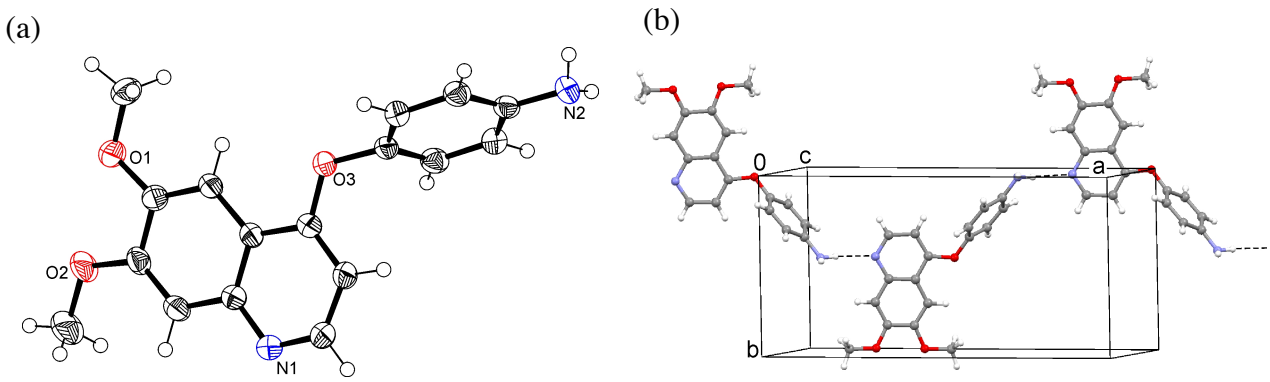


Figure 2. (a) ORTEP plot and (b) hydrogen bonding of **3**.

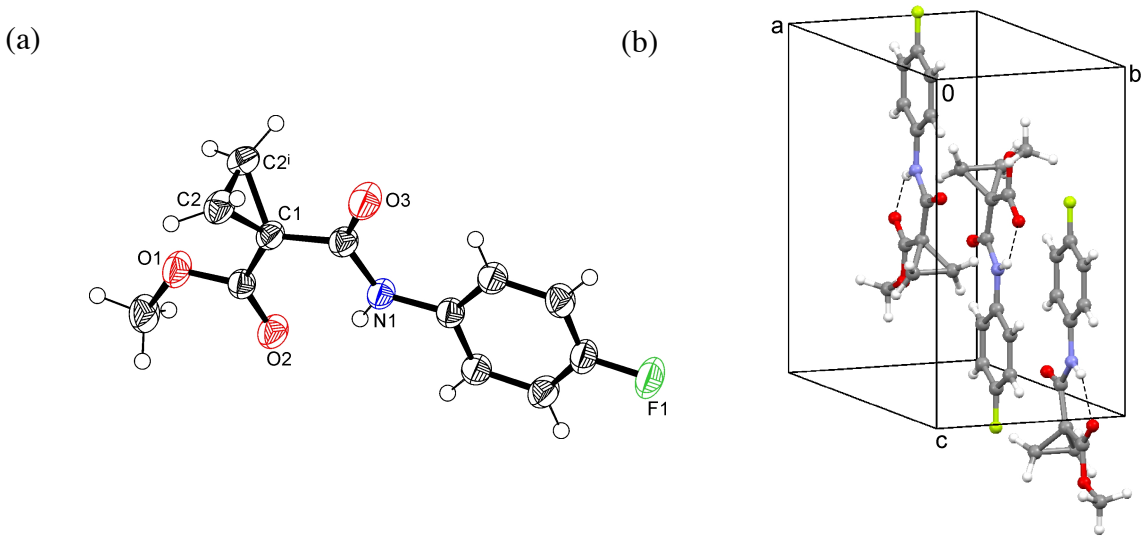


Figure 3. (a) ORTEP plot and (b) intramolecular hydrogen bonding of **4**; symmetry operation i: *x*, 1/2–*y*, *z*.

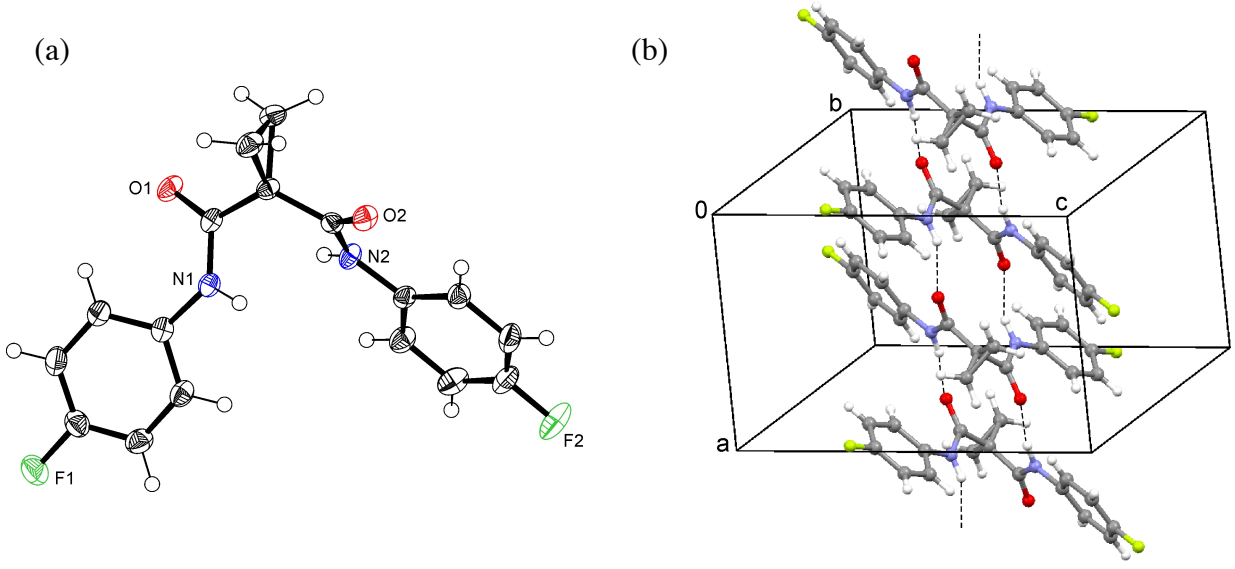


Figure 4. (a) ORTEP plot and (b) hydrogen bonding of **5**.

EXPERIMENTAL

Reagents and solvents were purchased from Sigma-Aldrich. NMR spectra were recorded with a Bruker Avance DPX 300 spectrometer. IR spectra were obtained with a Bruker Alpha FT instrument. High resolution mass spectra were measured with a Finnigan MAT 95 mass spectrometer. X-Ray diffraction data were collected with an Oxford Diffraction Gemini-R Ultra (for **1**, **4** and **5**) or Nonius KappaCCD (for **3**) diffractometer using Mo$K\alpha$ (λ = 0.7107 Å) or Cu$K\alpha$ radiation (λ = 1.5418 Å). CCDC 1419001–1419004 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

6,7-Dimethoxyquinolin-4(1*H*)-one (1).[14,15] Prepared as described previously; mp 250–254 °C (lit. 236–237 °C,[10] 224–225 °C[20]); IR (neat): 1602, 1494, 1440, 1269, 1238, 818 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.82 (s, 3H), 3.85 (s, 3H), 5.96 (d, J = 7.3 Hz, 1H), 6.99 (s, 1H), 7.44 (s, 1H), 7.78 (d, J = 7.3 Hz, 1H), 11.7 (br, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 55.5, 55.7, 99.2, 104.2, 107.7, 119.7, 135.7, 137.9, 148.5, 152.8, 175.7; HRMS (FAB) m/z 206.0835 (calcd 206.0812 for $C_{11}H_{12}NO_3$, $[M+H]^+$). Crystals were obtained from MeOH/H_2O. Single-crystal diffraction: T = 173(2) K; θ_{max} = 67.4°; Cu$K\alpha$ radiation; indices $-5 \le h \le 5$, $-19 \le k \le 19$, $-15 \le l \le 9$; D_x = 1.44 g cm^{-3}; 4219 reflections measured, 1221 independent with R_{int} = 0.030, $F(000)$ = 472, μ = 0.93 mm^{-1}. Crystal data for **1**, $C_{11}H_{11}NO_3 \cdot H_2O$ (M = 223.22 g mol^{-1}): monoclinic, Cc, a = 4.747(1), b = 16.504(1), c = 13.166(1) Å, β = 95.426(7), V = 1026.82(12) Å^3, Z = 4. R_1 = 0.052 and wR_2 = 0.154 for 1161 reflections with $I > 2\sigma(I)$, R_1 = 0.054 and wR_2 = 0.158 for all data; S = 1.07; $\Delta\rho_{max}$ = 0.45 and $\Delta\rho_{min}$ = –0.53 e Å^{-3}. CCDC reference number 1419001.

4-Chloro-6,7-dimethoxyquinoline (2).[12] A mixture of **1** (1.0 g, 4.9 mmol) and $POCl_3$ (0.68 mL, 7.3 mmol) was heated at 130 °C (bath) for 1 h. The resulting liquid was allowed to cool and was stirred with CH_2Cl_2 (10 mL) and aqueous NH_3 (25%; 10 mL). The organic layer was washed with H_2O (10 mL), dried over $MgSO_4$ and the solvent removed. The residue was dissolved in a mixture of *t*-BuOMe (5 mL) and CH_2Cl_2 (2 mL) at 50 °C (bath), and the solution was kept at –30 °C overnight. The resulting crystals were collected and dried (0.65 g, 60%); mp. 132–133 °C (lit.[15,19] 130–131 °C); IR (neat): 1470, 1221, 1139, 1006, 853 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.02 (s, 3H), 4.03 (s, 3H), 7.33 (d, J = 4.9 Hz, 1H), 7.36 (s, 1H), 7.42 (s, 1H), 8.54 (d, J = 4.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 56.4, 56.5, 101.9, 108.1, 119.8, 122.3, 140.9, 146.1, 147.4, 151.0, 153.4; HRMS (FAB) m/z 224.0434 (calcd 224.0473 for $C_{11}H_{11}NO_2Cl$, $[M+H]^+$).

4-(6,7-Dimethoxyquinolin-4-yloxy)aniline (3).[12] Prepared as described previously; mp 214 °C; IR (neat): 1508, 1477, 1430, 1214, 847, 814 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.93 (s, 6H), 5.15 (s, 2H), 6.37 (d, J = 5.2 Hz, 1H), 6.67 (d, J = 8.8 Hz, 2H), 6.92 (d, J = 8.8 Hz, 2H), 7.36 (s, 1H), 7.50 (s, 1H), 8.42 (d, J = 5.2 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 55.7 (2C), 99.2, 102.3, 107.8, 114.9 (2C),

115.0, 121.8 (2C), 143.4, 146.3, 146.6, 148.8, 149.1, 152.4, 160.9; HRMS (FAB) *m/z* 297.1203 (calcd 297.1234 for $C_{17}H_{17}N_2O_3$, $[M+H]^+$). Single-crystal diffraction: T = 233(2) K; θ_{max} = 25.0°; Mo$K\alpha$ radiation; indices $-23 \le h \le 23$, $-11 \le k \le 11$, $-9 \le l \le 9$; D_x = 1.36 g cm^{-3}; 4441 reflections measured, 2492 independent with R_{int} = 0.022, $F(000)$ = 624, μ = 0.09 mm^{-1}. Crystal data for **3**, $C_{17}H_{16}N_2O_3$ (M = 296.32 g mol^{-1}): monoclinic, *Cc*, a = 19.831(1), b = 9.521(1), c = 7.680(1) Å, β = 92.652(3), V = 1448.54(13) Å^3, Z = 4. R_1 = 0.038 and wR_2 = 0.090 for 2254 reflections with $I > 2\sigma(I)$, R_1 = 0.043 and wR_2 = 0.093 for all data; S = 1.07; $\Delta\rho_{max}$ = 0.17 and $\Delta\rho_{min}$ = –0.15 e Å^{-3}. CCDC reference number 1419004.

Methyl 1-(4-fluorophenylcarbamoyl)cyclopropanecarboxylate (4). A solution of 4-fluoroaniline (1.11 g, 10 mmol) and NaOMe (0.54 g, 10 mmol) in toluene (12 mL) was stirred under Ar at 100 °C (bath temperature), and the MeOH/toluene azeotrop was distilled off at 63 °C. In a stream of Ar, toluene (2 mL) was distilled to ensure complete removal of MeOH. To this mixture, dimethyl 1,1-cyclopropanedicarboxylate (1.58 g, 10 mmol) in toluene (5 mL) was added, and the heating was continued. Again, the MeOH/toluene azeotrop was distilled off, followed by toluene in a stream of Ar at a slightly higher bath temperature. The residue was allowed to cool and was stirred with H_2O (10 mL) and HCl (10 mL 1M), then extracted with CH_2Cl_2 (10 mL). The organic phase was dried over $MgSO_4$ and evaporated. The residue was repeatedly extracted with *i*-pentane (12 × 10 mL). The solvent was removed under reduced pressure at 50 °C to yield the crystalline product (1.32 g, 56%); mp 76 °C; IR (neat): 1705, 1659, 1550, 1506, 1443, 1205, 1151, 838, 716 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.38–1.42 (m, 4H), 3.68 (s, 3H), 7.11–7.17 (m, 2H), 7.60–7.65 (m, 2H), 10.34 (1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 16.3 (2C), 29.8, 52.4, 115.2 (d, J = 22.5 Hz, 2C), 121.1 (d, J = 7.9 Hz, 2C), 135.4, 158.1 (d, J = 239.6 Hz), 165.8, 171.8; HRMS (FAB) *m/z* 238.1128 (calcd 238.0874 for $C_{12}H_{13}FNO_3$, $[M+H]^+$). Single-crystal diffraction: T = 173(2) K; θ_{max} = 67.4°; Cu$K\alpha$ radiation; indices $-15 \le h \le 10$, $-8 \le k \le 5$, $-14 \le l \le 13$; D_x = 1.42 g cm^{-3}; 3313 reflections measured, 1077 independent with R_{int} = 0.026, $F(000)$ = 496, μ = 0.97 mm^{-1}. Crystal data for **4**, $C_{12}H_{12}FNO_3$ (M = 237.23 g mol^{-1}): orthorhombic, *Pnma*, a = 13.026(1), b = 6.998(1), c = 12.139(1) Å, V = 1106.63(11) Å^3, Z = 4. R_1 = 0.036 and wR_2 = 0.102 for 903 reflections with $I > 2\sigma(I)$, R_1 = 0.043 and wR_2 = 0.108 for all data; S = 1.06; $\Delta\rho_{max}$ = 0.19 and $\Delta\rho_{min}$ = –0.18 e Å^{-3}. CCDC reference number 1419002.

***N*,*N*'-Bis(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (5).** A solution of 4-fluoroaniline (2.22 g, 20 mmol) and NaOMe (1.08 g, 20 mmol) in cyclohexane (25 mL) was stirred under Ar at 75 °C (bath temperature), and the MeOH/cyclohexane azeotrop was distilled off at 55 °C. In a stream of Ar, cyclohexane (2 mL) was distilled to ensure complete removal of MeOH. To this mixture, dimethyl 1,1-cyclopropanedicarboxylate (1.58 g, 10 mmol) in cyclohexane (10 mL) was added, and the heating was continued. Again, the MeOH/cyclohexane azeotrop was distilled off, followed by cyclohexane in a

stream of Ar at a slightly higher bath temperature. The resulting oil was allowed to cool and was stirred with H_2O (20 mL) and HCl (20 mL 1M), then extracted with CH_2Cl_2 (40 mL). The organic phase was dried over $MgSO_4$ and evaporated. The residue was repeatedly stirred with *t*-BuOMe (5 × 10 mL), the insoluble product was collected by filtration and dried under reduced pressure to give a white powder (1.21 g, 39%); mp 187–189 °C; IR (neat): 1644, 1505, 1211, 829, 516 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.46 (s, 4H), 7.11–7.17 (m, 4H), 7.61–7.65 (m, 4H), 10.07 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 15.5 (2C), 31.4, 115.0 (d, J = 22.1 Hz, 4H), 122.4 (d, J = 8.0 Hz, 4H), 135.2 (2C), 158.3 (d, J = 240.4 Hz, 2H), 168.2 (2C); HRMS (FAB) m/z 317.1088 (calcd 317.1096 for $C_{17}H_{15}F_2N_2O_2$, $[M+H]^+$). Single-crystal diffraction: T = 173(2) K; θ_{max} = 25.4°; Mo$K\alpha$ radiation; indices $-10 \le h \le 10$, $-12 \le k \le 13$, $-18 \le l \le 19$; D_x = 1.40 g cm^{-3}; 9200 reflections measured, 5455 independent with R_{int} = 0.020, $F(000)$ = 656, μ = 0.11 mm^{-1}. Crystal data for **5**, $C_{17}H_{14}F_2N_2O_2$ (M = 316.30 g mol^{-1}): triclinic, $P\bar{1}$, a = 8.644(1), b = 11.247(1), c = 15.785(1) Å, α = 100.013(4), β = 94.434(4), γ = 93.114(4), V = 1503.12(12) $Å^3$, Z = 4. R_1 = 0.036 and wR_2 = 0.085 for 4585 reflections with $I > 2\sigma(I)$, R_1 = 0.046 and wR_2 = 0.091 for all data; S = 1.03; $\Delta\rho_{max}$ = 0.22 and $\Delta\rho_{min}$ = –0.22 e $Å^{-3}$. CCDC reference number 1419003.

***N*-(4-Fluorophenyl)-*N*'-(4-methoxyphenyl)cyclopropane-1,1-dicarboxamide (6).** A solution of 4-methoxyaniline (0.27 g, 2.2 mmol) and NaOMe (0.25 g, 4.6 mmol) in toluene (10 mL) was stirred under Ar at 100 °C (bath temperature), and the MeOH/toluene azeotrop was distilled off at 63 °C. In a stream of Ar, toluene (2 mL) was distilled to ensure complete removal of MeOH. To this mixture, methyl ester **4** (0.50 g, 2.1 mmol) in toluene (5 mL) was added, and the heating was continued. Again, the MeOH/toluene azeotrop was distilled off, followed by toluene in a stream of Ar at a slightly higher bath temperature. The residue was allowed to cool and was stirred with HCl (10 mL 1M), then extracted with EtOAc (10 mL). The organic phase was dried over $MgSO_4$ and evaporated. The residue was stirred with *t*-BuOMe (5 mL), the insoluble product was collected by filtration and dried under reduced pressure to yield a white powder (0.21 g, 30%); mp 165 °C; IR (neat): 1561, 1337, 1234, 1215, 834, 518 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.45 (s, 4H), 3.72 (s, 3H), 6.87 (d, J = 8.9 Hz, 2H), 7.14 (t, J = 8.8 Hz, 2H), 7.50 (d, J = 8.9 Hz, 2H), 7.63 (dd, J = 5.1 and 8.8 Hz, 2H), 9.85 (s, 1H), 10.13 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 15.5 (2C), 31.0, 55.2, 113.6 (2C), 115.0 (d, J = 22.3 Hz, 2C), 122.2 (2C), 122.3 (d, J = 8.0 Hz, 2C), 131.8, 135.3, 155.5, 158.2 (d, J = 239.8 Hz), 168.0, 168.4; HRMS (FAB) m/z 329.1277 (calcd 329.1296 for $C_{18}H_{18}FN_2O_3$, $[M+H]^+$).

Cabozantinib (7). A solution of aniline **3** (240 mg, 0.81 mmol) and NaOMe (115 mg, 2.1 mmol) in toluene (15 mL) was stirred under Ar at 100 °C (bath temperature), and the MeOH/toluene azeotrop was distilled off at 63 °C. In a stream of Ar, toluene (2 mL) was distilled to ensure complete removal of MeOH. To this mixture, methyl ester **4** (230 mg, 0.97 mmol) in toluene (15 mL) was added, and the

heating was continued. Again, the MeOH/toluene azeotrop was distilled off, followed by toluene in a stream of Ar at a slightly higher bath temperature. The residue was allowed to cool and was stirred with saturated aqueous NH_4Cl solution (30 mL), then extracted with EtOAc (30 mL). The organic phase was filtered, washed with ag. $NaHCO_3$ solution (10 mL), dried over $MgSO_4$ and evaporated. The residue was stirred with *t*-BuOMe (3 × 3 mL), the insoluble product was collected and dried under reduced pressure to yield an off-white powder (250 mg, 62%); mp 98 °C; IR (neat): 1504, 1477, 1211, 831, 516 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.49 (s, 4H), 3.93 (s, 3H), 3.94 (s, 3H), 6.43 (d, *J* = 5.2 Hz, 1H), 7.15 (t, *J* = 8.8 Hz, 2H), 7.22 (d, *J* = 8.9 Hz, 2H), 7.39 (s, 1H), 7.50 (s, 1H), 7.65 (dd, *J* = 5.1 and 8.8 Hz, 2H), 7.77 (d, *J* = 8.9 Hz, 2H), 8.46 (d, *J* = 5.2 Hz, 1H), 10.08 (s, 1H), 10.21 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 15.4 (2C), 31.5, 55.7 (2C), 99.1, 103.0, 107.8, 115.0 (d, *J* = 22.0 Hz, 2C), 121.2 (2C), 122.2, 122.4 (d, *J* = 7.9 Hz, 2C), 135.1, 135.2, 136.4, 146.4, 148.8, 149.3, 149.5, 152.6, 158.3 (d, *J* = 240.4 Hz), 160.0, 168.1, 168.2 ppm; HRMS (FAB) *m/z* 502.1827 (calcd 502.1778 for $C_{28}H_{25}FN_3O_5$, $[M+H]^+$).

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